The IARC Monographs Programme The identification of occupational carcinogens

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International Agency for Research on Cancer
Lyon, France

OHRNC, Irkutsk, 18 September 2015

IARC - priority areas for research

Describing occurrence

Establishing causes

Evaluating prevention

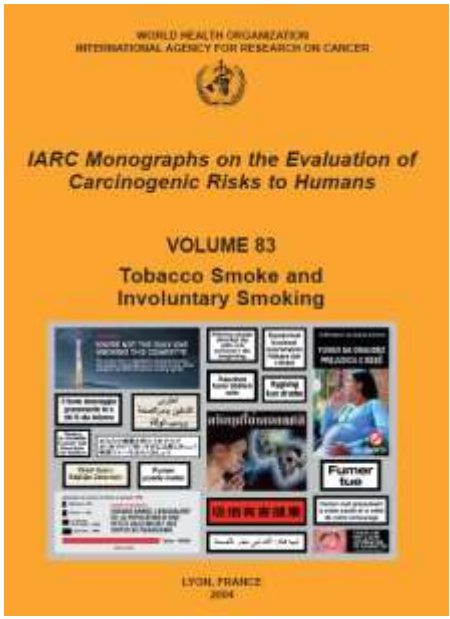
Supporting implementation

Education and training

International Agency for Research on Cancer

World Health Organization

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.
- First step in cancer prevention is to **identify what causes and what prevents cancer**

"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

- 117 are *carcinogenic to humans* (Group 1)
- 74 are *probably carcinogenic to humans* (Group 2A)
- 287 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

International Agency for Research on Cancer

World Health Organization

Since 1971 over 1000 scientists from over 50 countries have contributed their expertise to the IARC Monographs

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 ((http://monographs.iarc.fr/)
- In the published volume of *Monographs*

They are asked also to complete the conflict-of-interest form required by *The Lancet Oncology*

- IARC sends *TLO*'s form — not WHO's form — to *TLO;*
- *TLO* summarizes this information alongside IARC's summary

Evaluating human data (Subgroup 2)

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

☐*Sufficient evidence*	Causal relationship has been established Chance, bias, and confounding could be ruled out with reasonable confidence
☐*Limited evidence*	Causal interpretation is credible Chance, bias, or confounding could not be ruled out
☐*Inadequate evidence*	Studies permit no conclusion about a causal association
☐*Evidence suggesting lack of carcinogenicity*	Several adequate studies covering the full range of exposure levels are mutually consistent in not showing a positive association at any observed level of exposure Conclusion is limited to cancer sites and conditions studied

Evaluating experimental animal data (Subgroup 3)

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

☐*Sufficient evidence*	Causal relationship has been established through either: - Multiple positive results (2 species, studies, sexes of GLP) - Single unusual result (incidence, site/type, age, multi-site)
☐*Limited evidence*	Data suggest a carcinogenic effect but: (*e.g.*) single study, benign tumours only, promoting activity only
☐*Inadequate evidence*	Studies permit no conclusion 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

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

Overall carcinogenicity evaluation

EVIDENCE IN HUMANS	EVIDENCE IN EXPERIMENTAL ANIMALS: *Sufficient*	*Limited*	*Inadequate*	*ESLC*
Sufficient	Group 1			
Limited	↑1 strong evidence in exposed humans Group 2A	↑2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A Group 2B (exceptionally, Group 2A)		
Inadequate	↑1 strong evidence in exposed humans ↑2A strong evidence … mechanism also operates in humans Group 2B ↓3 strong evidence … mechanism does not operate in humans	↑2A belongs to a mechanistic class ↑2B with supporting evidence from mechanistic and other relevant data Group 3	↑2A belongs to a mechanistic class ↑2B with strong evidence from mechanistic and other relevant data Group 3	Group 3 ↓4 consistently and strongly supported by a broad range of mechanistic and other relevant data
ESLC	Group 3			Group 4

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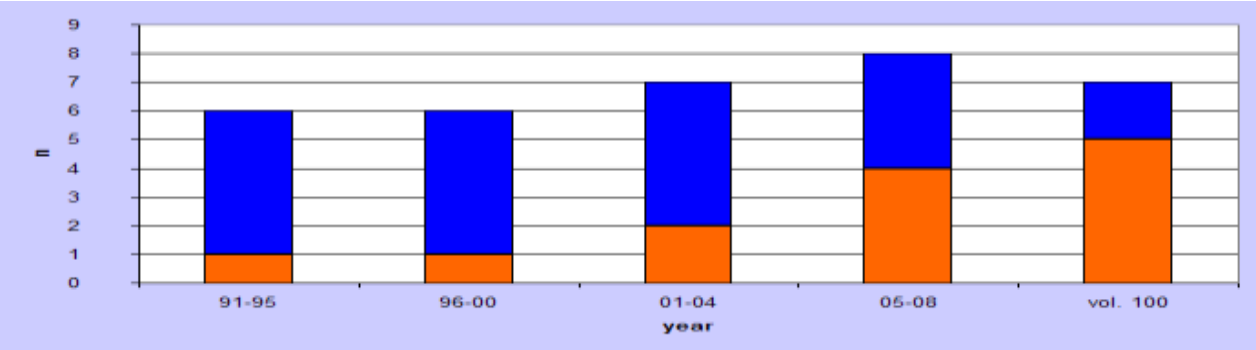
World Health Organization

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.

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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World Health Organization

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

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

IARC Monographs, Vol 113, June 2015

THE LANCET Oncology

News

Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid

In June, 2015, 26 experts from immunosuppressive effects that can

- Limited evidence in humans for the carcinogenicity of DDT (lymphoma, liver and testicular cancers)
- Sufficient evidence in experimental animals for the carcinogenicity of DDT and its metabolites DDE and DDD.
- Strong evidence that DDT affects several mechanisms that can operate in humans.
- DDT classified as "probably carcinogenic to humans" (Group 2A).

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Selected topics from OHRNC 2015

Agent	Evaluation	Cancer		Monograph
	Group	Sufficient	Limited	
Ore Extraction Ni, CrVI, silica, radon,...	1	Lung Nasal cavities (Ni)	Nasal cavities (Cr)	100C 100D
Asbestos	1	Lung, mesothelioma, larynx, ovary	Color-rectum, pharynx, stomach	
Beryllium	1	Lung		100C
Coal dust	3			68
Air pollution	1	Lung		109
Shift-work	2A		Breast	98
CNT	2B			111

IARC Monographs on Asbestos 2,1973; 14,1977; Suppl 7,1987; 100C, 2009

- All commercial forms of asbestos tested are carcinogenic in mice, rats, hamsters and rabbits
- Exposure to asbestos poses increased risks for asbestosis, lung cancer and mesothelioma in a dose-dependent manner.
- Mesotheliomas have occurred in individuals living in the neighborhood of asbestos factories and mines and in people living with asbestos workers
- No threshold has been identified for carcinogenic risks
- IARC Group 1 , human carcinogen, sufficient evidence in humans and sufficient evidence in animals

Volume 100C, Asbestos
Overall evaluations

- **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.**

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)

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)*.

IARC Monographs Vol. 111, CNT

Characterisation and exposure

- CNT may consist of
  - a single graphene cylinder (SWCNTs) with an outer diameter of 1–3 nm, or
  - multiple graphene cylinders arranged in concentric layers (MWCNTs) with diameters of 10–200 nm.
- CNTs are typically few micrometres in length, ranging from a few 100s of nanometers to several 10s of micrometers;
- Physical and chemical characteristics vary depending on the production technique.
- Applications include improving the structural properties of fabrics, plastics, rubbers, electronics, and composite materials.

IARC Monographs Vol. 111, CNT

Cancer in experimental animals, MWCNT-7

MWCNT-7 caused peritoneal mesotheliomas

- in male and female rats in one intraperitoneal injection study (Nagai et al., 2011)
- one intrascrotal injection study (Sakamoto et al., 2009),
- in male *p53*$^{+/-}$ mice in two intraperitoneal injection studies (Takagi et al., 2012).
- Inhalation of MWCNT-7 promoted 3-methylcholanthrene-initiated bronchioloalveolar adenoma and carcinoma in male mice (Sargent et al., 2014).

IARC Monographs Vol. 111, CNT

Cancer in experimental animals, other CNT

- Two other types of MWCNTs with physical dimensions similar to those of MWCNT-7 (length, 1–19 µm; diameter, 40–170 nm) caused mesotheliomas in male and female rats in one intraperitoneal study, (Nagai et al., 2011).
- Two studies with SWCNTs in rats were inconclusive.

Evaluation of of carcinogenicity in experimental animals

- *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.

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]

World Health Organization

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]

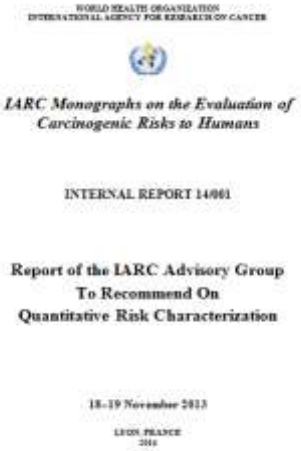
Acetaldehyde
Atrazine
Carbon black
Chloroform
Cobalt metal with tungsten carbide
Dichloromethane
Diesel engine exhaust
Di-2-ethylhexyl phthalate
Formaldehyde
Indium phosphide
Lead and lead compounds
Polychlorinated biphenyls (PCB)
Propylene oxide
Refractory ceramic fibers
Shiftwork that involves nightwork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

International Agency for Research on Cancer

World Health Organization

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

Lancet Oncol 2014
Published Online
May 6, 2014

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

- Beta-carotene
- Bisphenol A
- Disinfected water
- Dimethylformamide
- HCMV
- Indium-tin oxide
- Iron, dietary
- Coal mining

- MTBE, ETBE
- Nicotine
- Obesity , Physical inactivity
- Opium
- Phenyl and octyl tin compounds
- Pesticides
- Shift work
- Styrene
- Welding

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IARC MONOGRAPHS - MEETINGS

Upcoming Meetings

Meeting 114: Red Meat and Processed Meat (6-13 October 2015)

- Call for Data (closing date 11 September 2015)
- Call for Experts (closing date 6 February 2015)
- Request for Observer Status (closing date 5 June 2015)
- WHO Declaration of Interests for this volume
- Instructions for Authors

Meeting 115: Some Industrial Chemicals (2-9 February 2016)

- Preliminary List of Agents
- Call for Data (closing date 4 January 2016)
- Call for Experts (closing date 1 June 2015)
- Request for Observer Status (closing date 5 October 2015)
- WHO Declaration of Interests for this volume
- Instructions for Authors

Meeting 116: Coffee and Some Other Hot Beverages (24-31 May 2016)

International Agency for Research on Cancer

World Health Organization

Call for nominations of agents for review in future *IARC Monographs*

IARC encourages the general public, the scientific community, national health agencies, and other organizations, to nominate agents for review in future *IARC Monographs*. For details, please see: Information on nominations

UK HSE Burden of occupational cancer

Results

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 "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

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

Acknowledgements

The *IARC Monographs* and Handbooks 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)**
- **Institut National du Cancer (INCa), France**
- **U.S. Center for Disease Control (CDC)**

International Agency for Research on Cancer

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Spassiba

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

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

Cancer in humans

- ☐ *Sufficient evidence*
- ☐ *Limited evidence*
- ☐ *Inadequate evidence*
- ☐ *Evidence suggesting lack of carcinogenicity*

Cancer in experimental animals

- ☐ *Sufficient evidence*
- ☐ *Limited evidence*
- ☐ *Inadequate evidence*
- ☐ *Evidence suggesting lack of carcinogenicity*

Mechanistic and other relevant data

- Mechanistic data "weak," "moderate," or "strong"?
- Mechanism likely to be operative in humans?

Overall evaluation

☐ Group 1	*Carcinogenic to humans*
☐ Group 2A	*Probably carcinogenic to humans*
☐ Group 2B	*Possibly carcinogenic to humans*
☐ Group 3	*Not classifiable as to its carcinogenicity to humans*
☐ Group 4	*Probably not carcinogenic to humans*

From Recommended Priority to Publication of Monograph

IARC ad hoc Advisory Group Meeting

~ every 5 years, last in 2014

Human exposure; suspicion of carcinogenicity

Selection of topic(s) by IMO

~ 1 year before meeting; availability of key studies?

Overall management considerations

Preparation of meeting

Draft outline, selection of experts, writing assignments, conference calls, pre-meeting peer-review, working drafts

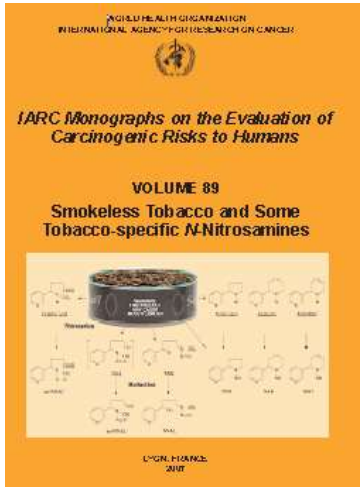
8-day Meeting at IARC

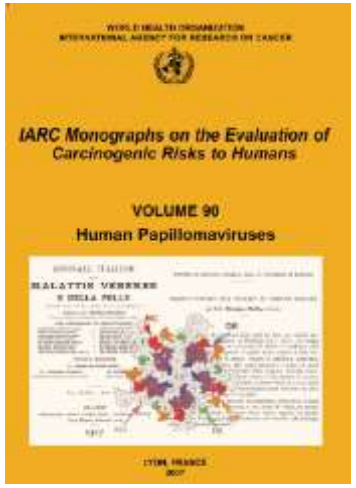
to reach consensus and make final evaluations

Lancet Oncology summary report

published shortly after the closing of the meeting

Publication of full-text Monograph, on-line (for free download) and in print; ~ 1 year after meeting





Dissemination of information

International Agency for Research on Cancer

World Health Organization

search

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

- AGENTS
  - Browse
  - Combined search
- ORGAN SITE/CANCER
  - Browse
  - Combined search
- CATEGORIES
  - Browse
- MONOGRAPHS
  - Browse
- DEVELOPMENT
  - Contributors

IARC Monographs

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed.

International Agency for Research on Cancer

World Health Organization

http://monographs.pubcan.org

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

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 carcinoi	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									0	0

Human S + Any Animal

Human L + Any Animal

Human S but No Animal

Animal Only

International Agency for Research on Cancer

World Health Organization

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)

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

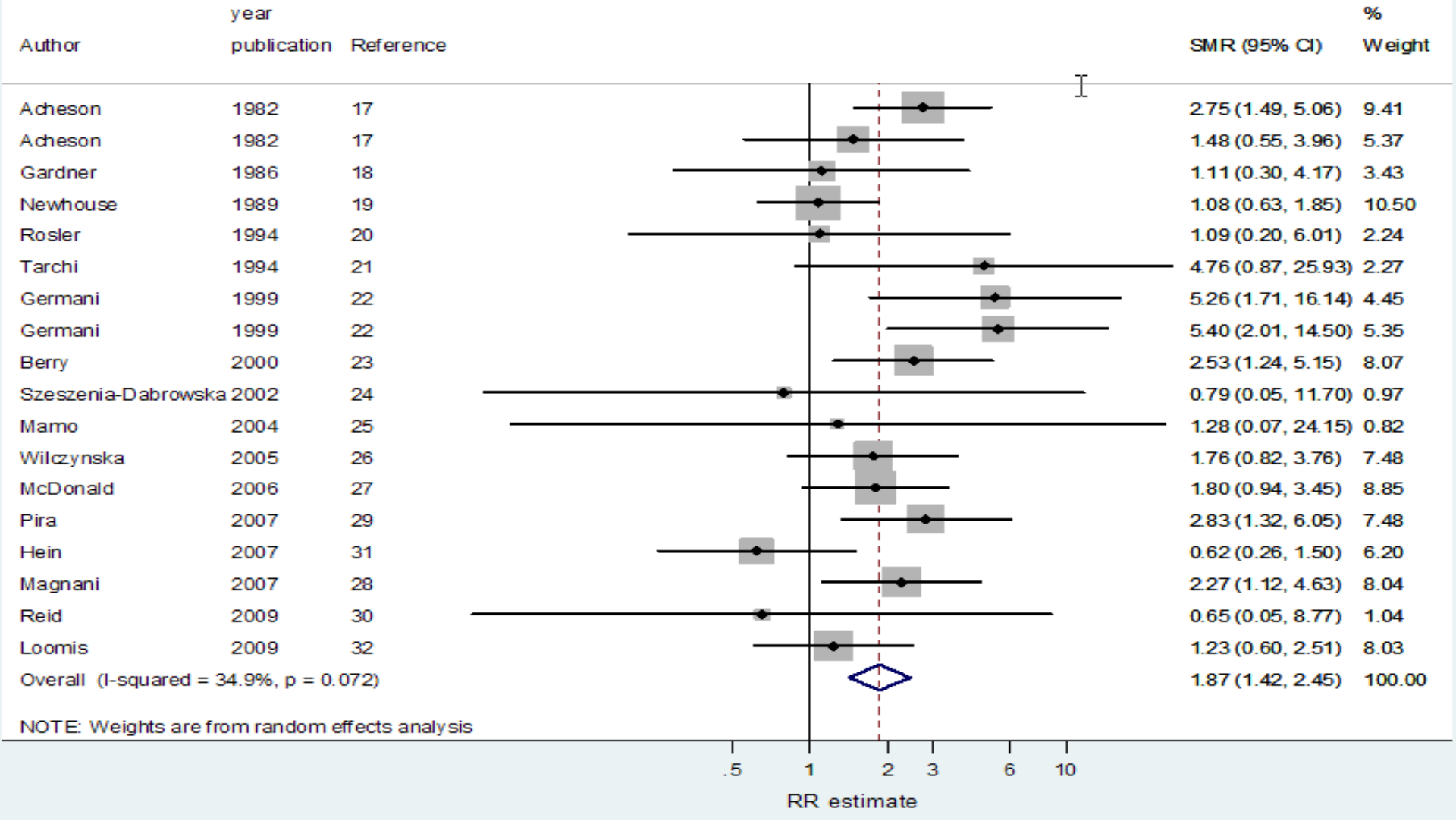
Asbestos: open questions

- 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.**

Asbestos and Ovarian Cancer



Camargo et al. Env Health Perspectives (2011)

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

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

News

World Health Organization

IARC Monographs, Vol 113, Lindane

- Lindane, (γ-isomer of hexachlorocyclohexane), used extensively for insect control in agriculture and for treatment of human ectoparasites;
- Now banned or restricted in most countries.

- The US Agricultural Health Study, a large prospective cohort study with detailed exposure assessment, reported statistically significant increases in NHL risk with increasing occupational exposure to lindane.

- Population-based case-control studies in the mid-western USA and Canada reported consistently positive associations.

IARC Monographs, Vol 113, Lindane

- Epidemiological cohort and case control studies of NHL in several countries provided sufficient evidence in humans for the carcinogenicity of lindane.

- Sufficient evidence in experimental animals for the carcinogenicity of lindane was provided by several studies of dietary administration in mice, with lindane consistently increasing the incidence of benign or malignant liver tumours.

- Strong evidence that lindane causes immunosuppressive effects that can operate in humans.

- Lindane classified as "carcinogenic to humans"(Group 1).

IARC Monographs, Vol 113, DDT

- DDT used for control of insect-borne diseases, particularly malaria and in agriculture. Most DDT uses banned >1970s, but human exposure to DDT and its metabolite (DDE) still occurs, mainly through diet.

- Liver cancer: Nested and population-based case-control studies in China reported strong dose-related associations with blood DDT (adjusted for potential confounders), no excess in cohort study of DDT sprayers (malaria control) in Italy.

- NHL: several positive cohort and case-control studies in North America and Europe, but other studies found no association.

- Testicular cancer: several case-control studies (USA, Europe) reported positive associations with DDT or DDE.

- Breast cancer: With > 40 studies no clear association with DDT or DDE; however, early-life exposure unresolved.

IARC Monographs, Vol 113, DDT

- Numerous positive cancer bioassays in mice, rats, and hamsters for DDT and its metabolites DDE and DDD.
- Immunosuppression consistently observed in numerous experimental systems, including human cells in vitro.
- DDT, DDD, and DDE increased oxidative stress in human blood mononuclear cells and stimulated human colon cancer and liver cancer cell proliferation.
- Oestrogenic effects and androgen-receptor antagonism in numerous experimental systems including human cells in vitro. Anti-oestrogens blocked oestrogenic effects of DDT in human breast cancer cells and in mice.

IARC Monographs Vol. 111, CNT

Characterisation and exposure

- The highest release of CNTs, usually as entangled agglomerates which can be respirable, is observed during production and handling, and in cleaning of the production reactor.
- Measurement of occupational exposure is limited, and consumer exposure was not quantified.

Cancer in humans

- No human cancer data were available to the Working Group.
- There is *inadequate evidence* for the carcinogenicity of CNTs in humans.

IARC Monographs Vol. 111, CNT

Mechanistic and other relevant data

- Evidence of translocation of three types of MWCNTs (including MWCNT-7) to the pleura (Mercer et al., 2013).
- Inhalation of some MWCNTs or SWCNTs induced acute or persistent pulmonary inflammation, granuloma formation, fibrosis, and bronchiolar or bronchioloalveolar hyperplasia in rodents (Shvedova et al., 2008; Pauluhn, 2010).

IARC Monographs Vol. 111, CNT

- The Working Group acknowledged that the above mechanisms are all relevant to humans.
- However, a majority did not consider the mechanistic evidence for carcinogenicity - especially concerning chronic endpoints – to be strong for any specific CNT.
- Furthermore, the lack of coherent evidence across the various distinct CNTs precluded generalisation to other types of CNTs.

Overall evaluation

- MWCNT-7 is *possibly carcinogenic to humans* (Group 2B);
- SWCNTs and MWCNTs excluding MWCNT-7 are *not classifiable as to their carcinogenicity to humans* (Group 3).