



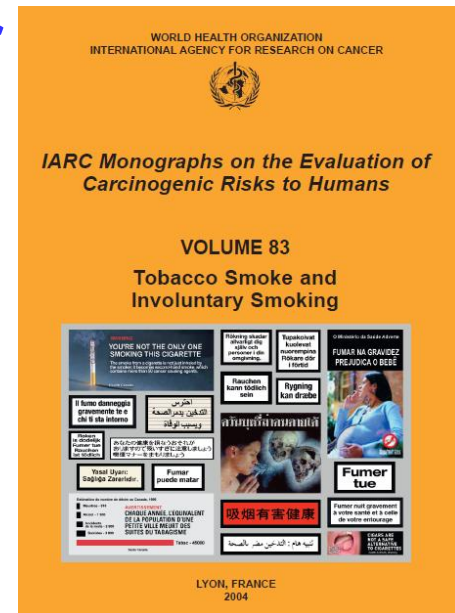
Scientific Insights Gained from Reviewing 100+ Human Carcinogens with a focus on those related to Mining

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International Agency for Research on Cancer
Lyon, France

International Scientific Symposium
Emerging Issues in Environmental and Occupational Health: Mining and
Construction in Transition Economies
April 22-23, 2013 in Yerevan, Armenia

Global burden and control of cancer

- Rising burden of cancer: estimates by 2030 22.2 million new cases/a compared to 12.7 million in 2008
- 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



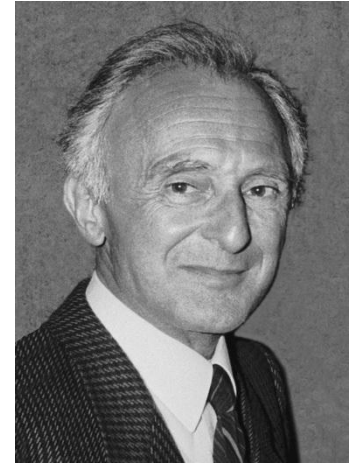
“The encyclopaedia of carcinogens”

The *IARC Monographs* evaluate

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

More than 950 agents have been evaluated

- 110 are *carcinogenic to humans* (Group 1)
- 65 are *probably carcinogenic to humans* (Group 2A)
- 274 are *possibly carcinogenic to humans* (Group 2B)



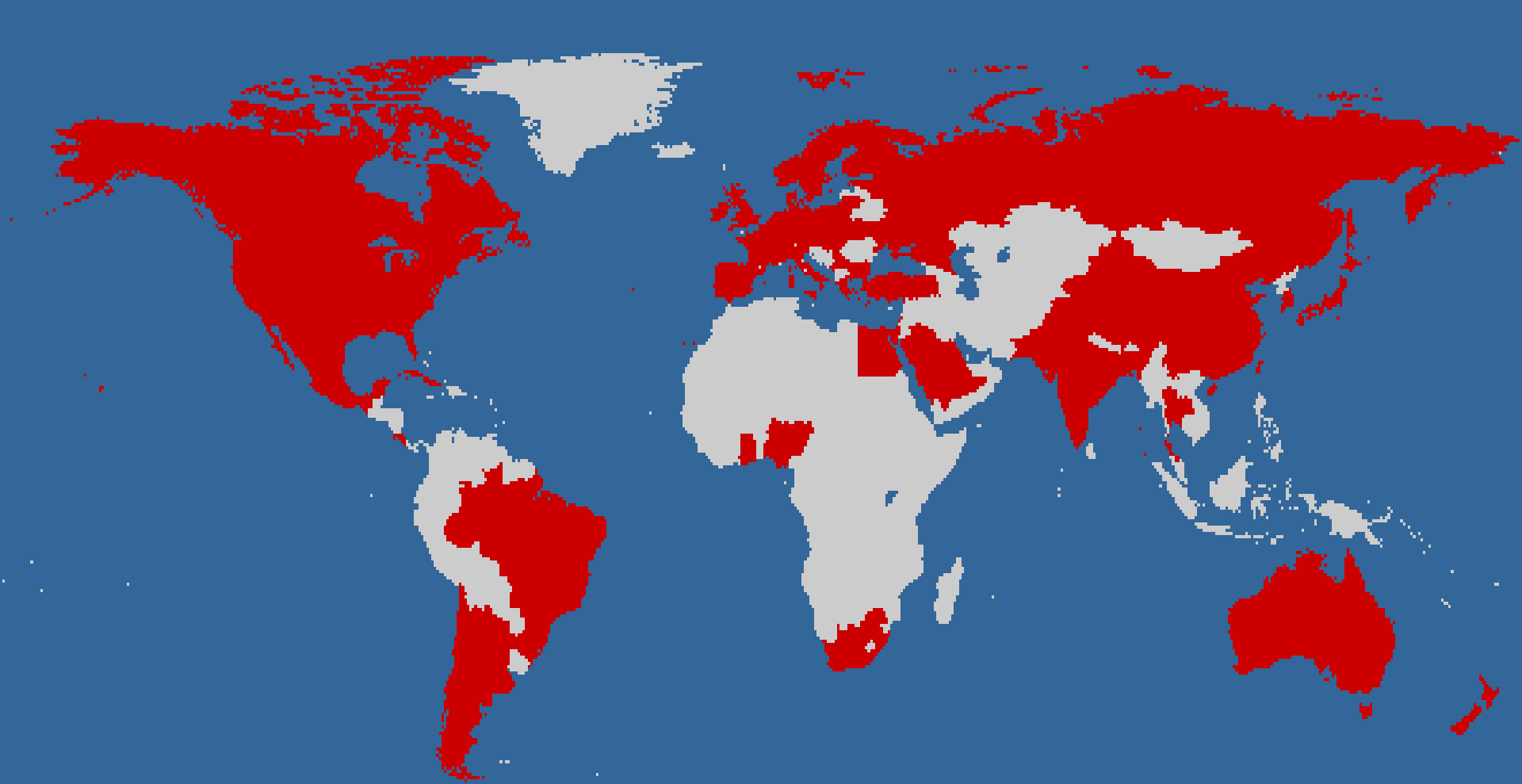
Lorenzo Tomatis
1929-2007

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



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



Overall carcinogenicity evaluation

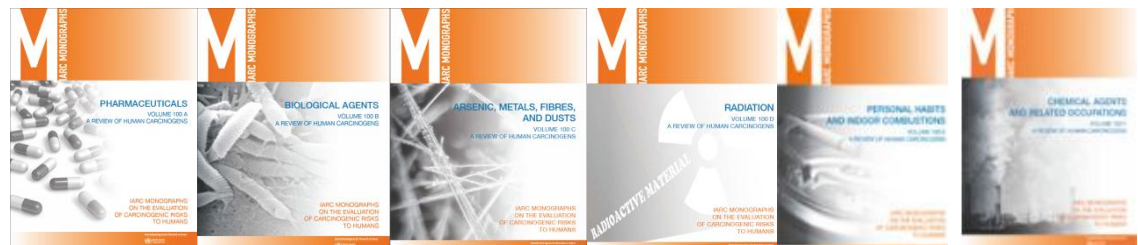
		EVIDENCE IN EXPERIMENTAL ANIMALS			
		<i>Sufficient</i>	<i>Limited</i>	<i>Inadequate</i>	<i>ESLC</i>
EVIDENCE IN HUMANS	<i>Sufficient</i>	Group 1			
	<i>Limited</i>	↑ 1 <u>strong evidence in exposed humans</u> Group 2A	↑ 2A belongs to a mechanistic class where other members are classified in Groups 1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

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



IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

AGENTS	Organs
Browse	
Combined search	liver adenocarcinoma
ORGAN SITE/CANCER	Liver
Browse	liver (HCC)
Combined search	
CATEGORIES	
Browse	
MONOGRAPHS	
Browse	



IARC Monographs on the Evaluation of Carcinogenic

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

Liver
 WHO Classification of tumours: **C22.0**
 Epidemiology (at Globocan)

Evidence for carcinogenicity at humans

Agent	Evidence	Remarks
Aflatoxins	sufficient	
Alcohol	sufficient	
Asbestos	sufficient	
Blotchy	sufficient	
Chronic hepatitis B virus	sufficient	
Chronic hepatitis C virus	sufficient	
Chronic liver disease	sufficient	
Chronic liver disease with cirrhosis	sufficient	
Chronic liver disease with cirrhosis and chronic hepatitis B virus	sufficient	
Chronic liver disease with cirrhosis and chronic hepatitis C virus	sufficient	
Chronic liver disease with cirrhosis and chronic hepatitis B virus and chronic hepatitis C virus	sufficient	
Chronic liver disease with cirrhosis and chronic hepatitis B virus and chronic hepatitis C virus and alcohol	sufficient	
Chronic liver disease with cirrhosis and chronic hepatitis B virus and chronic hepatitis C virus and alcohol and aflatoxins	sufficient	
Chronic liver disease with cirrhosis and chronic hepatitis B virus and chronic hepatitis C virus and alcohol and aflatoxins and nitrosamines	sufficient	
Chronic liver disease with cirrhosis and chronic hepatitis B virus and chronic hepatitis C virus and alcohol and aflatoxins and nitrosamines and aflatoxins	sufficient	
Chronic liver disease with cirrhosis and chronic hepatitis B virus and chronic hepatitis C virus and alcohol and aflatoxins and nitrosamines and aflatoxins and nitrosamines	sufficient	
Chronic liver disease with cirrhosis and chronic hepatitis B virus and chronic hepatitis C virus and alcohol and aflatoxins and nitrosamines and aflatoxins and nitrosamines and aflatoxins and nitrosamines	sufficient	

ogenicity at animals

Species	Remarks
Mouse	
Mouse	
Mouse	
Rat	
Mouse	
Tree Shrew	
Trout	
Rat	
Rat	
Mouse	
Rat	
Mouse	
beverages Rat	
beverages Mouse	
Rat	
Mouse	
Rat	
Mouse progeny	
Mouse	

At a glance

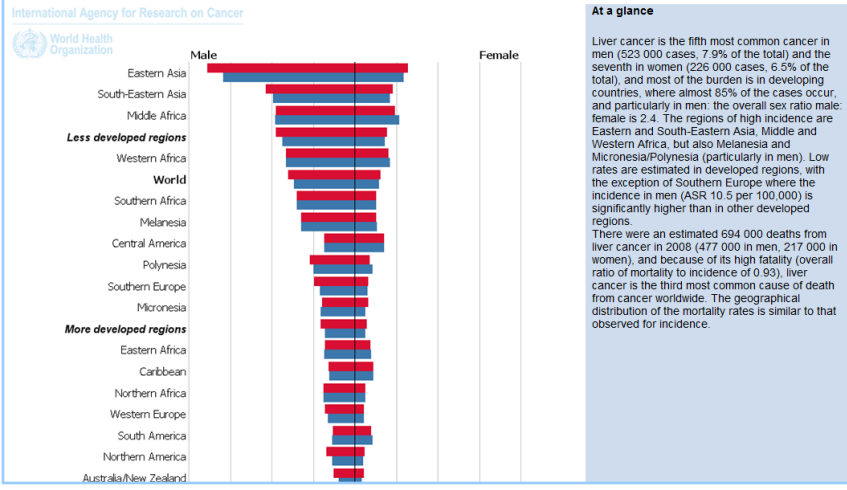
Liver cancer is the fifth most common cancer in men (523 000 cases, 7.9% of the total) and the seventh in women (226 000 cases, 6.5% of the total), and most of the burden is in developing countries, where almost 85% of the cases occur, and particularly in men: the overall sex ratio male:female is 2.4. The regions of high incidence are Eastern and South-Eastern Asia, Middle and Western Africa, but also Melanesia and Micronesia/Polynesia (particularly in men). Low rates are estimated in developed regions, with the exception of Southern Europe where the incidence in men (ASR 10.5 per 100,000) is significantly higher than in other developed regions. There were an estimated 694 000 deaths from liver cancer in 2008 (477 000 in men, 217 000 in women), and because of its high fatality (overall ratio of mortality to incidence of 0.93), liver cancer is the third most common cause of death from cancer worldwide. The geographical distribution of the mortality rates is similar to that observed for incidence.

GLOBOCAN 2008
 CANCER FACT SHEET
 International Agency for Research on Cancer

Incidence: [men](#)
 Mortality: [men](#)
 Incidence: [women](#)
 Mortality: [women](#)

Liver Cancer Incidence, Mortality and Prevalence Worldwide in 2008 Summary

Estimated numbers (thousands)	Men		Women		Both sexes	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
World	523	478	226	217	749	695
More developed regions	82	75	107	40	189	114
Less developed regions	440	402	325	177	765	581
WHO Africa region (AFRO)	29	28	19	14	48	42
WHO Americas region (PAHO)	31	28	26	21	57	49
WHO East Mediterranean region (EMRO)	9	9	5	4	14	12
WHO Europe region (EURO)	43	42	39	24	82	66
WHO South-East Asia region (SEARO)	46	42	27	20	73	62
WHO Western Pacific region (WPRO)	363	327	313	133	676	460
IARC membership (22 countries)	101	88	121	45	222	130
United States of America	15	12	14	6	29	17
China	292	266	219	105	511	371
India	14	12	6	5	20	17
European Union (EU-27)	32	30	30	15	62	45



WHO Classification of Tumours

- Digestive System
- Endocrine Organs
- Breast
- Female Genital Organs
- Head and Neck
- Skin
- Soft Tissue and Bone
- Urinary System and Male Genital Organs
- Nervous System
- Haematopoietic & Lymphoid Tissues
- Lung, pleura, thymus & heart

WHO Classification of Tumours of the Digestive System

C22 - Liver and intrahepatic bile ducts:

- Epithelial tumours
- Epithelial tumours: biliary
- Malignancies of mixed or uncertain origin
- Mesenchymal tumours
- Germ cell tumours
- Lymphomas
- Secondary tumours

Epithelial tumours

Non-neoplastic lesion

- Focal nodular hyperplasia (FNH)

Benign

- 8170/0 Hepatocellular adenoma

Malignant

- 8170/3 Hepatocellular carcinoma (HCC), NOS
- 8171/3 Hepatocellular carcinoma, fibrolamellar
- 8970/3 Hepatoblastoma
- 8020/3 Undifferentiated carcinoma

Epithelial tumours: biliary

Benign

- 8160/0 Bile duct adenoma
- 8202/0 Microcystic adenoma
- 9013/0 Biliary adenofibroma

Premalignant lesions

- 8148/2 Biliary intraepithelial neoplasia, grade 3
- 8503/0 Intraductal papillary neoplasm (IPN) with low- or intermediate-grade intraepithelial neoplasia
- 8503/2 Intraductal papillary neoplasm (IPN) with high-grade intraepithelial neoplasia
- 8470/0 Mucinous cystic neoplasm (MCN) with low- or intermediate-grade dysplasia
- 8470/2 Mucinous cystic neoplasm (MCN) with high-grade dysplasia

Malignant

- 8160/3 Intrahepatic cholangiocarcinoma
- 8503/3 Intraductal papillary neoplasm (IPN) with an associated invasive carcinoma
- 8470/3 Mucinous cystic neoplasm (MCN) with an associated invasive carcinoma

Malignancies of mixed or uncertain origin

- 8975/1 Calcifying nested epithelial stromal tumor
- 8980/3 Carcinosarcoma, NOS



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

Further research often finds additional cancer sites

- Burden of cancer: Alcohol drinking & breast and colorectal cancers
- Multiple mechanistic pathways: Formaldehyde and leukemia

Further research confirmed carcinogenic potential under conditions of lower exposure

- Radon: Vol 43, evaluation based on studies of miners, Vol 100, residential exposure & lung cancer.

Use of mechanistic data to identify carcinogens is accelerating

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

IARC Monographs, Vols 105–107

THE LANCET **Oncology**

News



Published Online
June 15, 2012

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

In June, 2012, 24 experts from seven countries met at the International Agency for Research on Cancer. The most influential epidemiological studies assessing cancer risks associated with diesel-engine exhausts with 20 years of employment roughly doubling the risk after adjusting for tobacco smoking. When this study

News

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

News

Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls



IARC MONOGRAPHS - MEETINGS

Upcoming Meetings

**Volume 108: Some drugs and herbal medicines
(4-11 June 2013)**

- [Preliminary List of Agents to be Reviewed](#)
- [Preliminary List of Participants](#)
- [Call for Data \(closes 4 May 2013\)](#)
- [Call for Experts \(closed 14 December 2012\)](#)
- [Request for Observer Status \(closed 4 February 2013\)](#)
- [WHO Declaration of Interests for this volume](#)

**Volume 109: Ambient air pollution
(8-15 October 2013)**

Advisory Group, June 2008

Volumes 101 and beyond

Acetaldehyde

Acrylamide and furan

Air pollution

Bitumen (Vol 103)

Carbon-based nanomaterials

Crystalline fibres other than asbestos

Growth hormone

Iron and iron oxides

Malaria (Vol 104)

Motor vehicle engine exhausts (V 105)

Nucleoside-analogue antiviral drugs

PFOA, other perfluorinated compounds

Polyomaviruses (SV40, BK, JC, Merkel cell virus) (Vol 104)

Radiofrequency electromagnetic fields and radar (includes mobile telephones) (Vol 102)

Sedentary work

Statins

Stress

Testosterone, other androgenic steroids

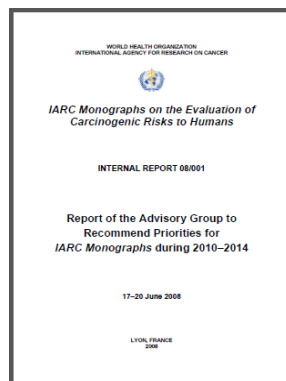
Ultrafine particles

Welding

Agents recently tested in experimental animals (Vol 101)

▶ Never before reviewed

International Agency for Research on Cancer



Ionising radiation, Vol 100D

- One of the best studied and most ubiquitous carcinogens in our general environment
 - Radon: high lung cancer rates in miners reported since 16th century
 - X-rays : first animal experiments: 1903-1904
 - Cancers among pioneer radiologists
 - Cancers among survivors of atomic bombs
- Evaluations of health effects
 - US NAS – BEIR / BEAR since 1956
 - IARC Monographs: radon (vol 43,1988),
external radiation(75,2000),
internally deposited radionuclide (78,2001)
 - IARC Monographs, Vol 100D, 2009

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

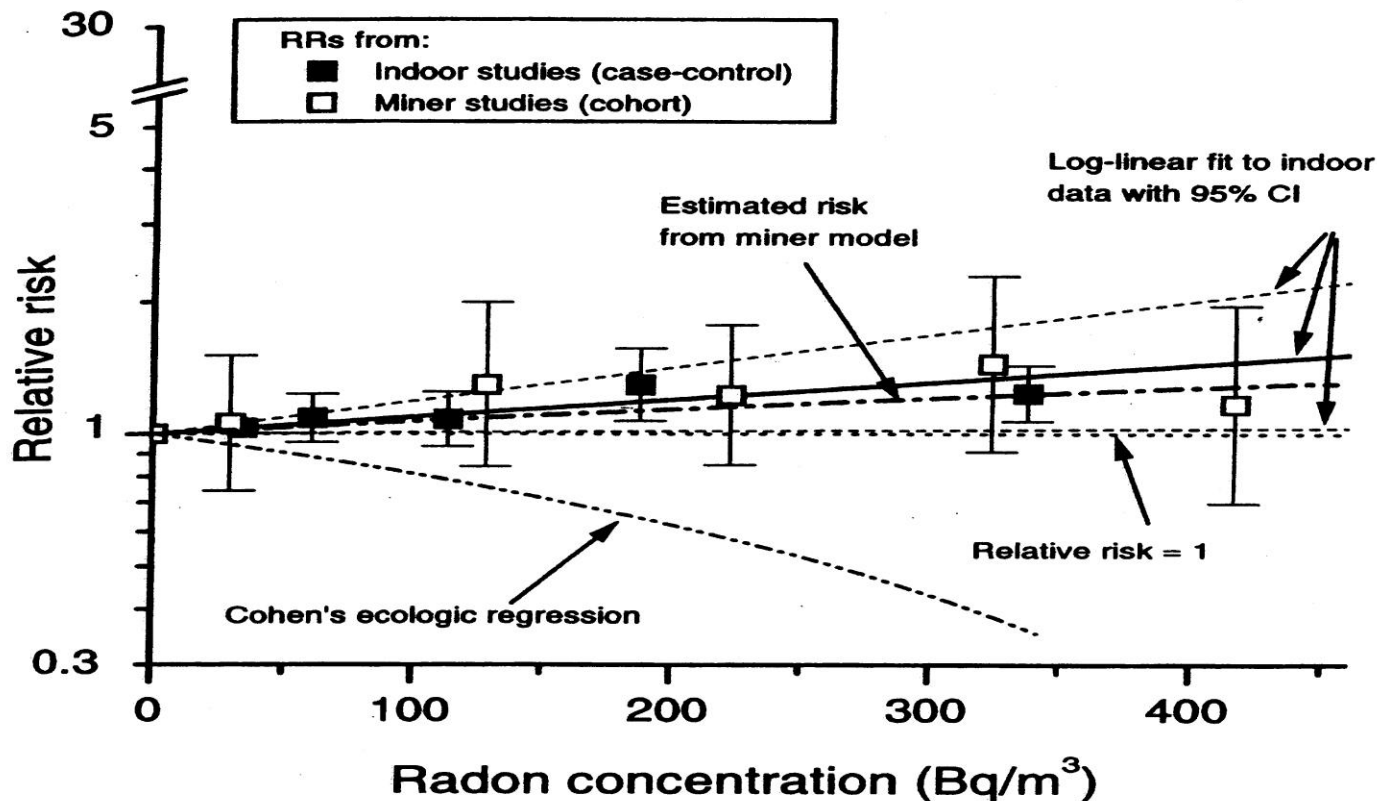


FIGURE 3-2 Summary relative risks (RR) from meta-analysis of indoor-radon studies and RRs from pooled analysis of underground-miner studies, restricted to exposures under 0.175 Jhm^{-3} (50 WLM). Included are RR of 1, fitted exposure-response and its 95% confidence interval from indoor-radon studies,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

Asbestos, Vol 100C: Carcinogenic to humans



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

Silica dust, Vol 100C

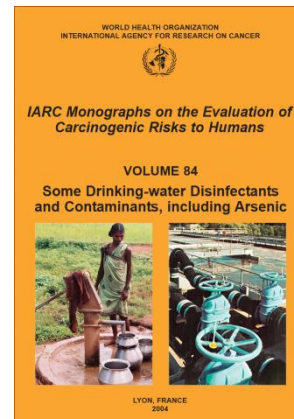
- There is *sufficient evidence in humans* for the carcinogenicity of silica dust.
Sufficient evidence: cancer of the **lung**;
- There is *sufficient evidence in experimental animals* for the carcinogenicity of quartz
- **Mechanistic data**: most genotoxicity studies negative; oxidative stress , inflammatory response, carcinogenicity may depend on inherent characteristics of the crystalline silica, or external factors affecting its biological activity

Overall evaluation

- Silica dust is *carcinogenic to humans (Group 1)*.

Arsenic and arsenic compounds, Vol 100C

- **Arsenic and inorganic arsenic compounds** are *carcinogenic to humans* (Group 1).
Sufficient evidence: cancer of **lung, urinary bladder, and skin**.
Limited evidence: cancer of the **kidney, liver, and prostate**.
- **Dimethylarsinic acid and monomethylarsonic acid** are *possibly carcinogenic to humans* (Group 2B).
- **Arsenobetaine and other organic arsenic compounds** not metabolized in humans, are *not classifiable as to their carcinogenicity* to humans (Group 3).
- Overall evaluation on arsenic and inorganic arsenic compounds based on the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and other relevant mechanistic data.
- The metabolite **monomethylarsonic** acid is extensively metabolized to dimethylarsinic acid.



Chromium(VI) compounds, V100C

- There is *sufficient evidence in humans* for the carcinogenicity of chromium (VI) compounds. Sufficient evidence: cancer of the **lung**; Limited evidence: **sinonasal cancer**
- There is *sufficient evidence in experimental animals* for the carcinogenicity of chromium (VI) compounds.

Overall evaluation

- Chromium (VI) compounds are *carcinogenic to humans (Group 1)*.

Cadmium and Cd compounds, V100C

- There is *sufficient evidence in humans* for the carcinogenicity of cadmium & Cd compounds. Sufficient evidence: cancer of the **lung**; Limited evidence: cancers of **prostate & kidney**
- There is *sufficient evidence in experimental animals* for the carcinogenicity of Cd compounds

Overall evaluation

- Cd and Cd compounds are *carcinogenic to humans (Group 1)*.

PAHs & Industrial Coal Tar-derived PAH-mixtures

WG for Vol 92 evaluated 59 PAH and 9 related industries

Occupational exposures to **benzo[a]pyrene** up to 100 $\mu\text{g}/\text{m}^3$ compared with levels in ambient air of a few ng/m^3

Highest reported levels of exposure to benzo[a]pyrene in the **aluminium production (Söderberg process)**

Diet is the major source of exposure to PAH in the non-smoking, non-occupationally exposed population

Meta-analysis: Exposure to PAH and lung cancer

- 39 cohort studies included
- Additional exposure assessment by industrial hygienists
- URR at 100 $\mu\text{g}/\text{m}^3$ *years B[a]p estimated

Industry	Studies (n)	B[a]p $\mu\text{g}/\text{m}^3$	URR (95% CI)
Coke ovens	10	0.5 – 20	1.17 (1.12-1.22)
Coal gasification	4	0.5 – 10	1.15 (1.11-1.20)
Alumimum	8	0.05 - 15	1.16 (1.05-1.28)

Polycyclic Aromatic Hydrocarbons, Vol 100F

Special Report: Policy

A review of human carcinogens—Part F: Chemical agents and related occupations

	Tumour sites or types with sufficient evidence in humans	Tumour sites or types with limited evidence in humans	Evidence of genotoxicity as the main mechanism
PAH-related exposures			
Benzo[a]pyrene	Strong*
Soot (chimney sweeping)	Skin, lung	Urinary bladder	Moderate
Coal gasification	Lung	..	Strong
Coal-tar distillation	Skin	..	Strong
Coke production	Lung	..	Strong
Coal-tar pitches (paving, roofing)	Lung	Urinary bladder	Strong
Aluminium production	Lung, urinary bladder	..	Weak/moderate†‡

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Acknowledgements



IARC MONOGRAPHS SECTION - STAFF

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

International Agency for Research on Cancer

Other carcinogens, other routes of exposure

- **Asbestos** (all forms), carcinogenic to humans, sufficient evidence for mesothelioma, cancers of lung, larynx, ovaries; limited evidence: cancers of colorectum, pharynx and stomach
- **Nickel**, carcinogenic to humans, sufficient evidence for cancers of lung and sinonasal cavities
- **Lead**, probably carcinogenic to humans, limited evidence for stomach cancer (lung cancer, glioma)
- **Cobalt**, possibly carcinogenic to humans, inadequate evidence in humans, sufficient evidence in bioassays
- WHO-FERG: Food-related burden of disease, **Arsenic** and cancer of the lung, skin and urinary bladder
Cadmium and kidney disease (lung cancer),
Lead and cognitive development, **methyl mercury**
- **Chromium** in drinking water, consultation Greek Minister of Environment – CAL-EPA