Update of the scientific evidence on asbestos and cancer

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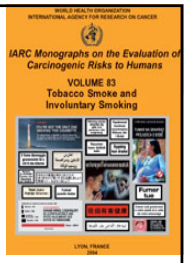
Asturias, 17 March 2011

The IARC Monographs



Consensus evaluations
of the weight of the evidence that an agent can increase the risk of cancer in humans

Approximately 900 agents evaluated since 1971

1 - carcinogenic to humans	110
2A - probably carcinogenic to humans	64
2B - possibly carcinogenic to humans	243

National and international health agencies use the *Monographs*

- As a source of information to identify potential carcinogens
- As scientific support for their actions to prevent cancer

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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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Special Report: Policy

A review of human carcinogens—Part C: metals, arsenic, dusts, and fibres

Group 1 agent	Tumour sites (or types) for which there is sufficient evidence in humans	Other sites with limited evidence in humans	Established mechanistic events
Arsenic and inorganic arsenic compounds	Lung, skin, urinary bladder	Kidney, liver, prostate	Oxidative DNA damage, genomic instability, aneuploidy, gene amplification, epigenetic effects, DNA-repair inhibition leading to mutagenesis
Beryllium and beryllium compounds	Lung	..	Chromosome aberrations, aneuploidy, DNA damage
Cadmium and cadmium compounds	Lung	Prostate, kidney	DNA-repair inhibition, disturbance of tumour-suppressor proteins leading to genomic instability
Chromium (VI) compounds	Lung	Nasal cavity and paranasal sinuses	Direct DNA damage after intracellular reduction to Cr(III), mutation, genomic instability, aneuploidy, cell transformation
Nickel compounds	Lung, nasal cavity, and paranasal sinuses	..	DNA damage, chromosome aberrations, genomic instability, micronuclei, DNA-repair inhibition, alteration of DNA methylation, histone modification
Asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite)	Lung, mesothelioma, larynx, ovary	Colorectum, pharynx, stomach	Impaired fibre clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signalling pathways, resistance to apoptosis
Erionite	Mesothelioma	..	Genotoxicity
Silica dust, crystalline in the form of quartz or crystobalite	Lung	..	Impaired particle clearance leading to macrophage activation and persistent inflammation
Leather dust	Nasal cavity and paranasal sinuses	..	..
Wood dust	Nasal cavity and paranasal sinuses, nasopharynx	..	..

Table: Metals, arsenic, dusts, and fibres assessed by the IARC Monograph Working Group

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Straif et al, Lancet Oncol, 2009

IARC Monographs on Asbestos

Asbestos

- **Serpentines Chrysotile (White asbestos)**
- **Amphiboles**
  - **Actinolit Tremolite (Brown asbestos)**
  - **Amosite (Brown asbestos)**
  - **Anthophyllite**
  - **Crocidolite (Blue asbestos)**

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IARC Monographs on Asbestos

Actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite

- Vol 2, 1973: sufficient evidence in humans, sufficient evidence in animals (1)
- Vol 14, 1977: sufficient evidence in humans, sufficient evidence in animals (1)
- Suppl 7,1987: sufficient evidence in humans, sufficient evidence in animals, 1

http://monographs.iarc.fr/

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Asbestos: Mesothelioma and lung cancer, V100C

- The epidemiologic evidence has only strengthened over time and there is currently overwhelming evidence that all commercial forms of asbestos fibers are causally associated with an increased risk of mesothelioma and lung cancer.
- There are still current controversies about the extent to which there are potency differences for the particular forms of asbestos (i.e. chrysotile versus amphiboles) and sizes (i.e. long and thin fibers). However, these issues do not alter the fundamental conclusion that the epidemiologic evidence indicates that all forms and sizes of commercial asbestos fibers are carcinogenic to humans.

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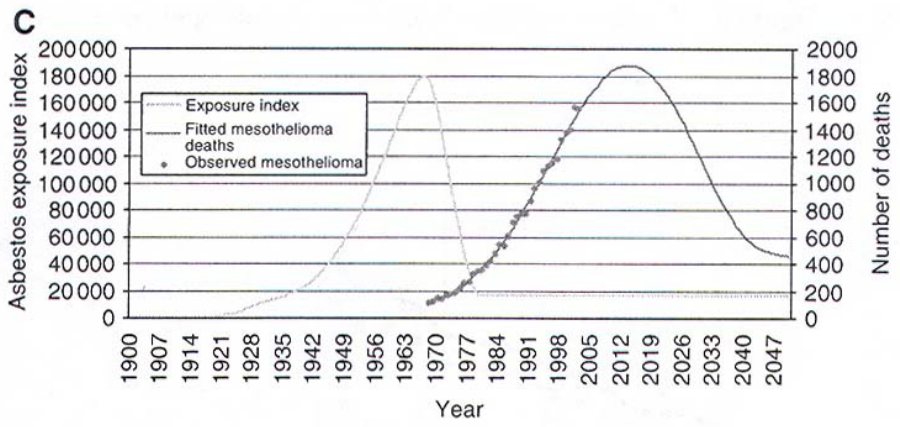
Exposure to asbestos and mesothelioma mortality in UK



Adapted from Hodgson et al, 2005

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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

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Chrysotile and cancer – recent epidemiological evidence

- Cohort of 5782 workers of 4 textile plants in NC, USA, followed-up 1950-2003. Lung cancer SMR 2.0 (95%CI 1.7-2.2), mesothelioma SMR 11.1 (95%CI 3.0-28.4); RR increased with time since first employment and duration of employment (Loomis et al, 2007)
- Cluster of 14 mesothelioma cases among workers who were active in the Balangero mine, Italy, and 13 among other people exposed to Balangero chrysotile adds further evidence to the carcinogenicity of tremolite-free chrysotile (Mirabelli et al, 2008).
- Cohort of 3072 workers of 1 textile plant in SC, USA, followed-up 1940-2001. Lung cancer was most strongly associated with exposure to thin (< 0.25 μm) and longer (> 10 μm) fibers (TEM) (Stayner et al, 2008)

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Asbestos: Laryngeal cancer, V100C

- Fairly consistent findings of both the occupational cohort studies as well as the case-control studies, plus the evidence for positive exposure-response relationships between cumulative asbestos exposure and laryngeal cancer that is reported in several the well conducted cohort studies.
- Meta-analyses of 29 cohort studies encompassing 35 populations and of 15 case-control studies of asbestos exposure and laryngeal cancer undertaken by the Institute of Medicine (2006).
- There is sufficient evidence to infer a causal relationship between asbestos exposure and laryngeal cancer.

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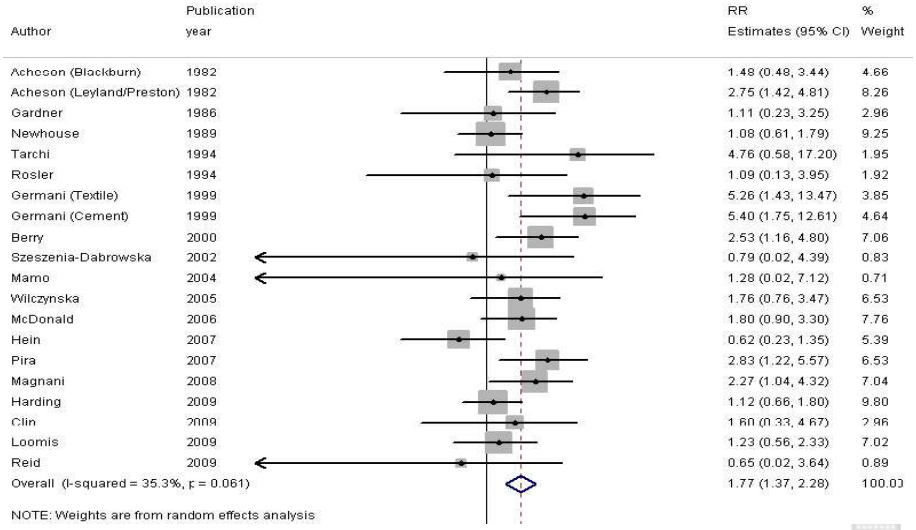
Asbestos and Ovarian Cancer



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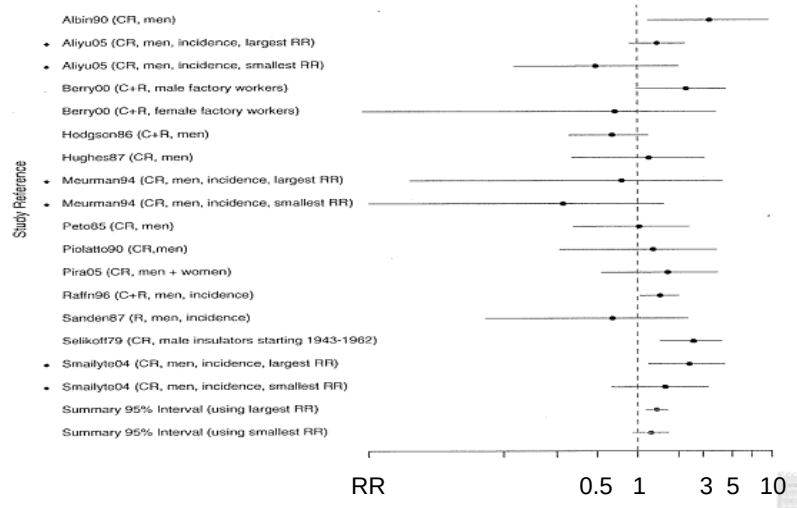
Camargo et al (subm.)

Asbestos: colorectal cancer, V100C



RR of colorectal cancer among people in highest exposure category compared to non-exposed

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Asbestos: mechanistic data, V100C

- The mechanistic basis for asbestos carcinogenicity is a complex interaction between these crystalline mineral fibres and target cells in vivo.
- The most important physicochemical properties of asbestos fibres related to pathogenicity are surface chemistry and reactivity, surface area, fibre dimensions, and biopersistence.
- Multiple direct and indirect mechanisms have been proposed based on numerous in-vitro cellular assays and acute and subchronic animal bioassays. These complex mechanisms most likely interact at multiple stages during the development of lung cancer and diffuse malignant mesothelioma.

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Asbestos: mechanistic data, V100C

Species differences

- There are significant species differences in the responses of the respiratory tract to inhalation of asbestos fibres.
- The biological mechanisms responsible for these species differences are unknown.
- Based on comparative animal experimental studies, there may be differences in deposition and clearance of fibres in the lungs, in severity of fibrosis, in kinetics of translocation of fibres to the pleura, and in levels or types of antioxidant defence mechanisms.

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Asbestos: Overall evaluations, V100C

- 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.

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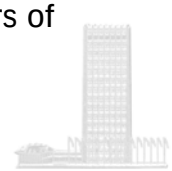

Burden of asbestos-related cancer

Recently, several new global and national estimates of attributable fractions (AF) for occupational cancer have been published
- Nurminen & Karjalainen, Finland (2001);
- Steenland et al, USA (2003);
- Driscoll et al, WHO GBD (2005);
- Rushton et al, UK (2008)

Used different methods to estimates asbestos-related lung cancer (based on mesothelioma mortality and mesothelioma/lung cancer ratio estimate; Levin's or Miettinen's equation)

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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

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Rushton et al, Occ Env Med; 2008.

Burden of asbestos-related cancer

85-90% of male mesothelioma cases due to occupational asbestos exposure

Among men, 17-29% of all lung cancer due to occupational exposure

Lung cancer accounted for 54-75% of occupational cancer

Asbestos accounted for ca. 50% of occupational lung cancer.

Straif, Occ Env Med, 2008

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