The IARC Monographs, Vol 100: A review and update on occupational carcinogens

Kurt Straif, MD MPH PhD

International Agency for Research on Cancer
Lyon, France

Carpi, 23 Oct 2010

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)

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**

Straif et al on behalf of the WHO IARC Working Group, Lancet Oncol, 2009
Baan et al on behalf of the WHO IARC Working Group, Lancet Oncol, 2009

Lung carcinogens, IARC Vol 100C

Agent	Human evidence	*Sufficient* human evidence	limited human evidence	*Sufficient* animal evidence
Arsenic and inorganic arsenic compounds	S	lung, bladder, skin	kidney, liver, prostate	inorganic compounds: lung, bladder, liver, adrenal
Beryllium and beryllium compounds	S	lung		inhalation, instillation: lung ingestion, local: bone
Cadmium and cadmium compounds	S	lung	prostate, kidney	Cd compounds: lung, testis, prostate,
Chromium (VI) compounds	S	lung	nose, nasal sinus	lung, oral cavity, GI tract, local-site
Nickel compounds	S	lung, nose, nasal sinus		lung, adrenal tumours, local-site
Asbestos, all forms of	S	lung, mesothelioma, larynx, ovary	colorectum, pharynx, stomach	lung, mesothelioma
Crystalline silica dust, quartz or crystobalite	S	lung		S: Quartz Lung (rats) Lymphomas (rats i.th, i.pl. i. p.; mice s.c.) L:Tridymite- and cristobalite

Lung carcinogens, IARC Vol 100F

Agent	Human evidence	*sufficient* human evidence	limited human evidence	Established mechanistic events
Soot (chimney sweeps)	§	Skin, lung.	Urinary bladder.	Genotoxic (moderate)
Coal gasification	§	Lung		Genotoxic (strong)
Coke production	§	Lung		Genotoxic (strong)
Coal-tar pitches	§	Lung	Bladder	Genotoxic
Aluminium production	§	Urinary bladder, lung.		Genotoxic (weak-to-moderate)
Iron and steel founding	§	Lung		Genotoxic (weak)
BCME, CMME	§	Lung		Genotoxic mechanism (moderate to strong)
Strong inorganic acid mists	§	Larynx	Lung	
Painting	§	Mesothelioma, urinary bladder, lung	Childhood leukaemia (maternal exposure)	Genotoxic (strong)
Rubber-mfctg industry	§	Leukaemia, lymphoma, urinary bladder, lung, stomach	Prostate, oesophagus, larynx	Genotoxic (strong)

Bladder carcinogens, IARC Vol 100F

Agent	Human evidence	*sufficient* evidence in humans	limited evidence in humans	*sufficient* evidence in animals
4-Aminobiphenyl	S	Urinary bladder		Mouse: liver (HCC), bladder, angiosarcoma (all sites). Dog: bladder.
Benzidine	S	Urinary bladder		Mouse: liver (HCC). Rat: mammary gland.
Dyes metabolized to benzidine	I	Inadequate evidence		Direct Black 38, Blue 6 Rat: liver (HCC)
MOCA	I	Inadequate evidence		Rat: lung, liver, mammary gland.
2-Naphthylamine	S	Urinary bladder		Mouse: liver. Rat: bladder. Dog: bladder. Monkey: bladder.
o-Toluidine	S	Urinary bladder		Mouse: haemangioma + haemangiosarcoma. Rat: urinary bladder, etc
Auramine production	S	Urinary bladder		-> auramine, Michler's ketone, Michler's base
Magenta production	S	Urinary bladder		-> CI Basic Red 9 (para-magenta) Mouse: liver (HCC). Rat: thyroid, Zymbal gland, lung, skin (fibroma).
Soot (as found in chimney sweeps)	S	Skin, lung.	Urinary bladder	-> PAHs
Coal-tar pitches	S	Lung	Urinary bladder	Mouse: skin
Aluminium production	S	Urinary bladder, lung.		-> PAHs
Painting	S	Mesothelioma, urinary bladder, lung	childhood leukaemia	-> individual agents
Rubber industry	S	Leukaemia, lymphoma, urinary bladder, lung, stomach	Prostate, oesophagus, larynx	-> individual agents

Upper respiratory tract, IARC Vol 100

Agent	*Sufficient* human evidence	Limited human evidence	*Sufficient* animal evidence
Nickel compounds	lung, nose, nasal sinus		lung, adrenal tumours
Cr (VI) compounds	lung	nose, nasal sinus	lung, oral cavity, GI tract
Wood dust, (Furniture & cabinet-making)	nasal sinus, nasopharynx		
Leather dust (Boot & shoe mfct & repair)	nasal sinus		
Formaldehyde	Nasopharynx, leukaemia.	Paranasal sinuses.	Rat: nasal cavity.
Isopropanolol mfctr	Nasal cavity		
Asbestos, all forms	lung, mesothelioma, larynx, ovary	colorectum, pharynx, stomach	lung, mesothelioma
Strong inorg. acid mists	Larynx	Lung	
Rubber industry	Leukaemia, lymphoma, bladder, lung, stomach	Prostate, oesophagus, larynx	

Boot & shoe mfct & repair, leather dust

Consistent and strong evidence from descriptive and case-control studies for increased risk of sinonasal cancer in the boot and shoe industry.

Very large excess risks particularly for sino-nasal adenocarcinoma.

Excess highest among workers with leather dust exposure.

Evaluation

There is sufficient evidence in humans for the carcinogenicity of leather dust. Leather dust causes sinonasal cancer.

There are no data in experimental animals for the carcinogenicity of leather dust.

Overall evaluation

Leather dust is carcinogenic to humans (Group 1).

Lymphohematopoietic cancer, IARC Vol 100

	Sufficient human evidence	limited human evidence	Established mechanistic events
Benzene	AML/ANLL	ALL, CLL, MM, NHL.	Genotoxic (strong)
1,3-Butadiene	Lymphohaematopoietic cancers		Genotoxic mechanism (strong)
Ethylene oxide		Lymphohaematopoietic cancers (specifically lymphoid tumours, ie, NHL, MM and CLL), breast cancer.	Genotoxic mechanism (strong)
Formaldehyde	Nasopharynx, Leukaemia.	Paranasal sinuses.	Nasal: genotoxic and cellular replication (strong). Leukaemia: genotoxic (moderate).
2,3,7,8-TCDD	All cancers combined	Soft-tissue sarcoma, non-Hodgkin lymphoma, lung	Receptor-mediated mechanism
Painting	Mesothelioma, urinary bladder, lung	Childhood leukaemia, maternal painting	Genotoxic (strong)
Rubber-mfctg industry	Leukaemia, lymphoma, urinary bladder, lung, stomach	Prostate, oesophagus, larynx	Genotoxic (strong)
HBV	hepatocellular carcinoma	cholangiocarcinoma, NHL	inflammation, liver cirrhosis, chronic hepatitis
HCV	hepatocellular carcinoma, NHL	cholangiocarcinoma	inflammation, liver cirrhosis, liver fibrosis

Formaldehyde and leukemia

IARC Monograph Volume 29 (1982)

Mortality study: in male pathologists a statistically significant increase in lymphatic and haematopoietic neoplasms was seen (8 cases observed, 3.3 expected) (Harrington & Shannon 1975)

IARC Monographs Supplement 7 (1987)

Mortality from leukaemia, predominantly of the myeloid type, has been found consistently to be higher in five studies of professional groups (embalmers, pathologists, anatomists). The absence of excesses for these cancers among industrial workers, however, argues against a role of formaldehyde.

Formaldehyde and leukemia (II)

IARC Monograph Volume 62 (1995)

Mortality study of 4000 embalmers/funeral directors. PMR for cancer of the lymphatic and haematopoietic system 1.3 (95% CI, 1.1–1.6; 100 deaths) (Hayes et al 1990)

IARC Monograph Volume 88 (2006)

Increased risks for leukaemia have been consistently observed in studies of professional workers (embalmers, funeral parlour workers, pathologists, anatomists) and in two of three of the most relevant studies of industrial workers.

Formaldehyde and leukemia (III)

IARC Working Group for Volume 88: there is *strong but not sufficient* evidence for a causal association between leukaemia and occupational exposure to formaldehyde. On the basis of the data available at this time, it is not possible to identify a mechanism for the induction of myeloid leukaemia in humans.

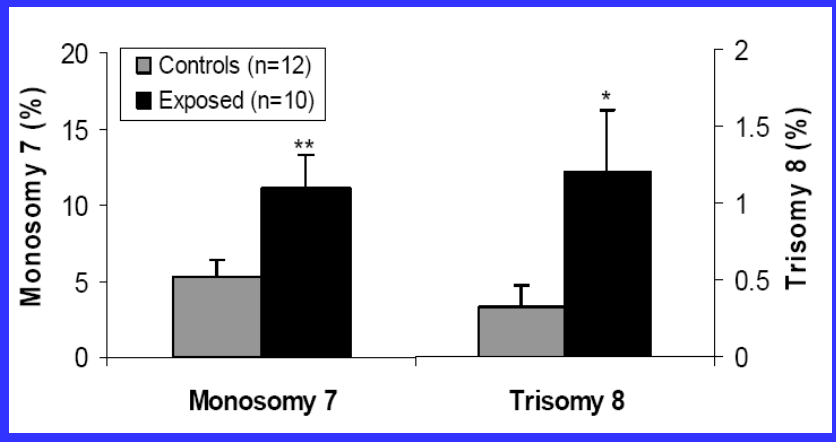
New epidemiological information: Mortality study among embalmers (Hauptmann *et al.*, *JNCI*, in press)

	OR (95% CI)	
Never	1.0	
Ever	11.2 (1.3–95.6)	
Years worked		
0	1.0	
0–20	5.0 (0.5–51.6)	
20–34	12.9 (1.4–117.1)	
>34	13.6 (1.6–119.7)	p for trend, 0.02

New mechanistic information (Zhang *et al*., *CEBP*, in press)

Molecular epidemiology study among formaldehyde-exposed workers and matched controls in China:

- total white blood cell counts and numbers of lymphocytes, granulocytes, platelets and red blood cells were lower in exposed workers; consistent with bone-marrow toxicity.
- haematopoietic progenitor cells of exposed workers showed monosomy of chromosome 7 and trisomy of chromosome 8; this type of aneuploidy is characteristic of leukemia.



Zhang *et al.*, Fig 4

Skin cancer, IARC Vol 100

Coal-tar distillation, soot , mineral oils, shale oils

- *Sufficient evidence* for skin cancer

Solar radiation

- BCC, SCC (accumulated solar skin damage)
- Melanoma (intermittent exposure)

Welders

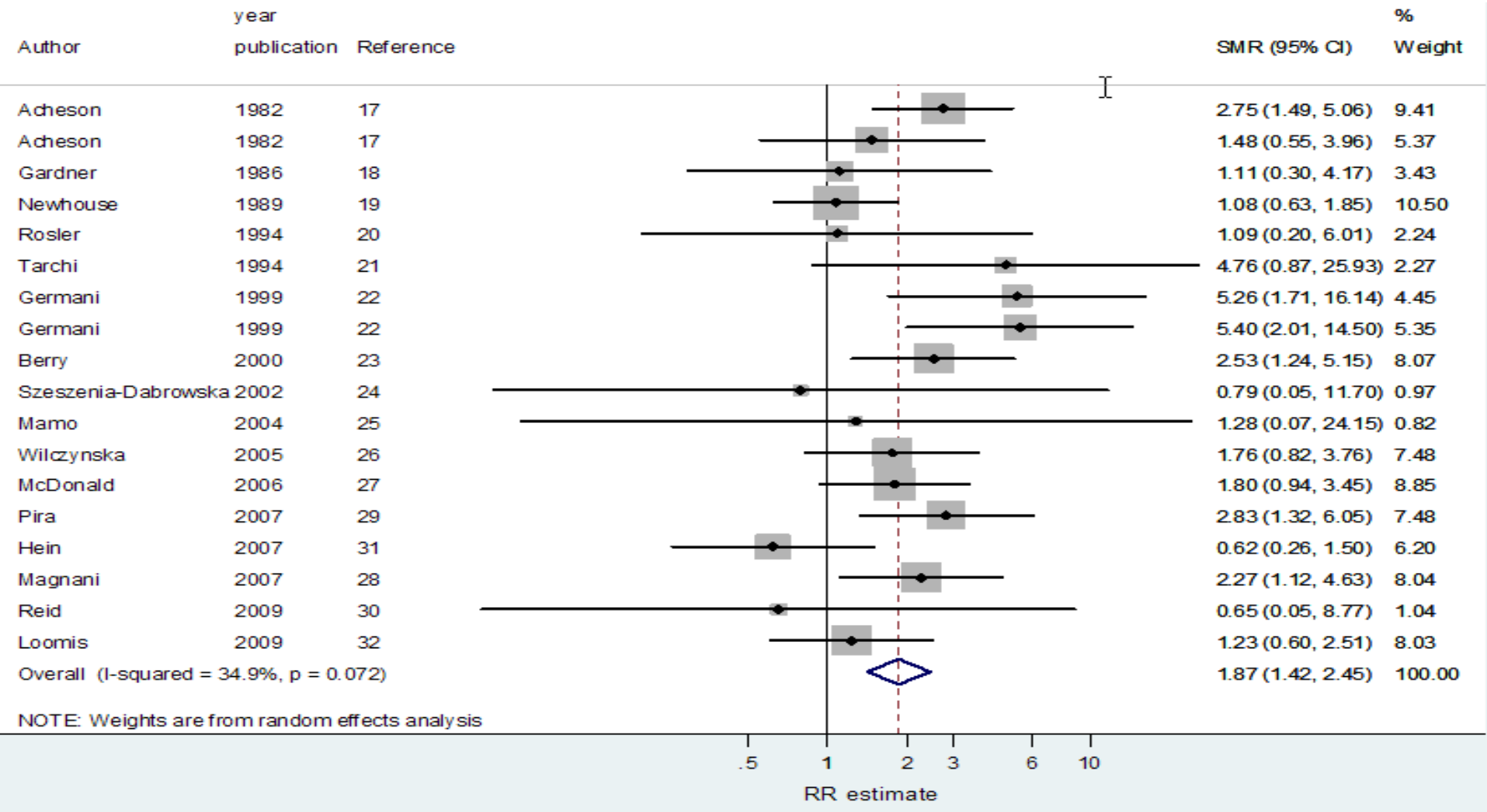
Six case-control studies reported on welding and ocular melanoma.

- All found a positive association, strong association in 3 studies, each of which related specifically to working as a welder or sheet metal worker
- Evidence of a dose-response relationship in 3 studies

Sufficient evidence for ocular melanoma in welders.

- Welders also exposed to other harmful agents, UV radiation?

Asbestos and Ovarian Cancer



Camargo et al (subm.)

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)

Neutrons (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 (2,3,7,8-TCDD), Vol 100F

Dioxin (2,3,7,8-TCDD) classified in Group 1 based on l*imited evidence* in humans, *sufficient evidence* in rodents, and strong evidence in humans and animals for a mechanism via initial binding to the aryl hydrocarbon receptor (AhR), which leads to changes in gene expression, cell replication, and apoptosis (Vol 69, 1997)

Now: Sufficient epidemiological evidence for all cancers combined (Vol 100F)

TCDD first agent classified initially in Group 1 based on mechanistic upgrade, to be later confirmed by increased cancer incidence in humans.

Like TCDD,

- 2,3,4,7,8-pentachlordibenzofuran and
- 3,3',4,4', 5-pentachlorobiphenyl (PCB-126) are
  - complete carcinogens in experimental animals,
  - extensive evidence for the same AhR-mediated mechanism.

The Working Group classified these two chemicals in Group 1

Volume 100 compiled information for subsequent scientific publications

- *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