The IARC Monographs Programme
The Identification of Human Carcinogens
Kurt Straif, MD PhD MPH

International Agency for Research on Cancer
Lyon, France

WCC, Melbourne, 4 Dec 2014
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**
“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

- 114 are *carcinogenic to humans* (Group 1)
- 69 are *probably carcinogenic to humans* (Group 2A)
- 283 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

Lorenzo Tomatis
1929-2007
You are part of a worldwide endeavour that since 1971 has involved over 1000 scientists from over 50 countries.
### Overall carcinogenicity evaluation

<table>
<thead>
<tr>
<th>Evidence in Experimental Animals</th>
<th>Sufficient</th>
<th>Limited</th>
<th>Inadequate</th>
<th>ESLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sufficient</strong></td>
<td></td>
<td></td>
<td>Group 1</td>
<td></td>
</tr>
<tr>
<td><strong>Limited</strong></td>
<td></td>
<td>2A</td>
<td>Group 2B</td>
<td></td>
</tr>
<tr>
<td>Group 2A</td>
<td>≥1 strong evidence in exposed humans</td>
<td>2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A</td>
<td>Group 2B (exceptionally, Group 2A)</td>
<td></td>
</tr>
<tr>
<td><strong>Inadequate</strong></td>
<td>≥1 strong evidence in exposed humans</td>
<td>≥2A belongs to a mechanistic class with supporting evidence from mechanistic and other relevant data</td>
<td>≥2A belongs to a mechanistic class with strong evidence from mechanistic and other relevant data</td>
<td>Group 3</td>
</tr>
<tr>
<td>Group 2B</td>
<td>≥2A strong evidence ... mechanism also operates in humans</td>
<td>≥2B with supporting evidence from mechanistic and other relevant data</td>
<td>≥2B with strong evidence from mechanistic and other relevant data</td>
<td>Group 3</td>
</tr>
<tr>
<td><strong>ESLC</strong></td>
<td></td>
<td>Group 3</td>
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<td>Group 4</td>
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</tbody>
</table>

### Observations

- Group 2B (exceptionally, Group 2A): For substances that are considered to be of uncertain carcinogenicity based on the interpretation of the available evidence.
- Group 3: For substances with sufficient evidence of carcinogenicity in experimental animals and in humans, with strong evidence of mechanistic relevance.
- Group 4: For substances with no evidence of carcinogenicity in humans or in experimental animals, but with strong evidence of mechanistic relevance.

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International Agency for Research on Cancer

World Health Organization
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)
## Known and suspected causes of cancer

### List of Classifications by cancer sites with *sufficient* or *limited* evidence in humans, Volumes 1 to 108*

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Carcinogenic agents with <em>sufficient evidence</em> in humans</th>
<th>Agents with <em>limited evidence</em> in humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Aluminum production</td>
<td>Acid mists, strong inorganic</td>
</tr>
<tr>
<td></td>
<td>Arsenic and inorganic arsenic compounds</td>
<td>Art glass, glass containers and pressed ware (manufacture of)</td>
</tr>
<tr>
<td></td>
<td>Asbestos (all forms)</td>
<td>Biomass fuel (primarily wood), indoor emissions from household combustion of</td>
</tr>
<tr>
<td></td>
<td>Beryllium and beryllium compounds</td>
<td>Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing</td>
</tr>
<tr>
<td></td>
<td>Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade)</td>
<td>Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work</td>
</tr>
<tr>
<td></td>
<td>Cadmium and cadmium compounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chromium(VI) compounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coal, indoor emissions from household combustion</td>
<td></td>
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<tr>
<td></td>
<td>Coal gasification</td>
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<tr>
<td></td>
<td>Coal-tar pitch</td>
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<td></td>
<td>Coke production</td>
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<td></td>
<td>Engine exhaust, diesel</td>
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<tr>
<td></td>
<td></td>
<td>Carbon electrode manufacture</td>
</tr>
</tbody>
</table>
Dissemination of information

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Organs
- liver adenocarcinoma
- Liver
- liver (HCC)

http://monographs.pubcan.org/organ.php
Mechanisms Involved in Human Carcinogenesis

New research continues to find additional human carcinogens & Use of mechanistic data to identify carcinogens is accelerating

Types of mechanistic upgrades

**Ethylene oxide**: Dose-related increase in the frequency of SCE, CA, and MN in lymphocytes of exposed workers.

DNA adducts and A:T→T:A transversions in TP53 identified **aristolochic acid** as the carcinogen in herbal remedies -> environmental exposures: cereal fields in the Balkans where *Aristolochia* plants grow as weeds

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

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

In June, 2012, 24 experts from seven countries met at the International Epidemiological Studies Assessing Cancer Risks with 20 Years of Employment Roughly Doubling the Risk after Adjusting for

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

Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls

The carcinogenicity of outdoor air pollution
Diesel engine exhaust: exposure (1)

- Diesel engines are used for on-road and non-road transport (e.g., trains, ships) and (heavy) equipment in various industrial sectors (e.g., mining, construction), and in electricity generators, particularly in developing countries.
- Emissions from these engines are complex, with varying composition.
- 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.
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.
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.
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.

Overall evaluation
• Diesel engine exhaust is carcinogenic to humans (Group 1).
Research Recommendations for Selected IARC-Classified Agents


- 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
IARC Workshop: Defining ‘Shift Work’ for epidemiological Studies of Cancer

<table>
<thead>
<tr>
<th>Working time</th>
<th>Workhours/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night work</td>
<td>At least 3 hrs of work between midnight and 5 am</td>
</tr>
<tr>
<td>Duration</td>
<td>Years employed in non-day shift work</td>
</tr>
<tr>
<td>Intensity</td>
<td>Number of non-day shifts per month/year</td>
</tr>
<tr>
<td>Cumulative exp.</td>
<td>Duration times intensity over the work history</td>
</tr>
<tr>
<td>Permanent shift</td>
<td># consecutive days of night work, followed by # days off</td>
</tr>
<tr>
<td>Rotating type</td>
<td>Continuous (365 days/year) or dis-continuous</td>
</tr>
<tr>
<td>Direction of rotation</td>
<td>Forward (morning → afternoon/evening → night) \ backward (afternoon/evening → morning → night)</td>
</tr>
<tr>
<td>Rate of rotation</td>
<td>Daily change, 2-3-4 day change, weekly, etc.</td>
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<tr>
<td>Morning shift</td>
<td># consecutive days of early morning shift (before 6 am)</td>
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<tr>
<td>Start/end time</td>
<td>Displacement from solar day, duration of the working hours</td>
</tr>
<tr>
<td>Rest after shift</td>
<td>Number of rest-days after night shifts</td>
</tr>
<tr>
<td>Jetlag</td>
<td>No of time zones crossed; eastward vs. westward</td>
</tr>
</tbody>
</table>

| Sleep                | Sleep duration & |
| Light at night       | During sleep period |
| Characteristics of the individual | Diurnal type (mor |
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.
Future priorities for the IARC Monographs

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 priority.

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
- Mate & coffee drinking
- MTBE, ETBE
- Nicotine
- Obesity, Physical inactivity
- Opium
- Phenyl and octyl tin compounds
- Pesticides
- Shift work
- Styrene
- Welding
Upcoming Meetings

Meeting 111: Some Nanomaterials and Some Fibres
(30 September - 7 October 2014)

Preliminary List of Agents
Call for Data (closing date 3 September 2014)
Preliminary List of Participants
Call for Experts (closed 30 January 2014)
Request for Observer Status (closed 3 June 2014)
WHO Declaration of Interests for this volume

Meeting 112: Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate,
Malathion, Parathion, and Tetrachlorvinphos
(3-10 March 2015)

Call for Data (closing date 3 February 2015)
Call for Experts (closing date 30 July 2014)
Request for Observer Status (closing date 3 November 2014)
WHO Declaration of Interests for this volume

Meeting 113: Some Organochlorine Insecticides and Some Chlorphenoxy Herbicides
(2-9 June 2015)
The *IARC Monographs* 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)
IARC - priority areas for research

Describing occurrence

Supporting implementation

Education and training

Establishing causes

Evaluating prevention
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
## Tumour (Site) Concordance between Humans and Animals

<table>
<thead>
<tr>
<th>Agent</th>
<th>Human S</th>
<th>Any Animal</th>
<th>Human L</th>
<th>Any Animal</th>
<th>Human S but No Animal</th>
<th>Animal Only</th>
</tr>
</thead>
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<td>Chromium (VI) compounds</td>
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</table>

*Note: The table represents the concordance between tumour sites in humans and animals. The codes (Z1 to Z39) correspond to specific sites or categories as detailed in the International Agency for Research on Cancer's guidelines.*
Key Characteristics of Carcinogens

• Electrophilicity 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
Key Characteristics of Carcinogens (2)

- Receptor-mediated
  - acts 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
Mechanisms of Carcinogenesis in Future Cancer-Hazard Evaluations

• Link between concordance of tumours and mechanisms of carcinogenesis
  ✓ Concordance confirmed by mechanistic data
  ✓ Discordance explained by mechanistic data
• Use of mechanistic data can help identify additional cancer sites
• Use of mechanistic data can help identify whether the carcinogenic potential is limited to certain dose levels
• Mechanistic data may help understand interactions of multiple factors acting jointly, and thus may help identify new carcinogens
• Identify populations and developmental stages that may be more susceptible
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
- $\text{PM}_{2.5}$ global range of annual average concentrations from $<10$ to $>100 \ \mu g/m^3$.
- In many areas WHO and national air quality guidelines for $\text{PM}_{2.5}$ 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$^3$
• 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 2\textsuperscript{nd} 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 3\textsuperscript{rd} evaluation was based on findings of studies in experimental animals exposed to polluted outdoor air (Sao Paolo) in conjunction with updating and confirming previous pertinent evaluations.
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.
- Atmospheric mutagenic activity varies > 5 orders of magnitude across locations and increased activity is quantitatively related to increased levels of atmospheric PM.
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.
Asbestos exposure index and observed and fitted mesothelioma mortality in Great Britain

Adapted from Hodgson et al, 2005
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.
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.
Ionising radiation

- 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).
Occupational exposure as a painter (Vol 100F)

Meta-analysis on lung cancer (Guha et al, EHP, 2010)

Cohort and linkage studies mRR, 1.36 (18 studies, 95% CI, 1.29-1.44)
Case-control studies mRR, 1.35 (29 studies, 95% CI, 1.22-1.51)
Pop.-based Case-control, smoking adjusted, mRR, 1.41 (95%CI, 1.23-1.61)
Among never & non-smokers, mRR, 1.96 (4 studies, 95%CI, 1.15-3.35)

Suggestive trend by duration of exposure
  <20 years (mRR, 1.37; 95%CI, 0.89-2.13)
  >20 years (mRR, 2.00; 95%CI, 1.01-3.92)

No particular causative agent could be identified from the available epidemiological studies

Increased mortality from mesothelioma noted in several studies.
Cancer in humans: Sufficient evidence

- 5 EU and US cohort studies
- 4 studies reported highly elevated risk of bladder cancer
- confounding by other bladder carcinogens eliminated

Cancer in experimental animals: Sufficient evidence

Mechanistic data

- Acute toxicity and genotoxicity in mammalian systems in vitro and in vivo
- Haemoglobin adducts in prilocaine-treated patients (o-toluidine-based anesthetic)

Overall evaluation: Group 1
1,3-Butadiene (Vol 97)

Overall Evaluation

• Group 1 (*carcinogenic to humans*)
• *sufficient evidence* in humans that exposure to 1,3-butadiene causes an increased risk for leukaemias
• The Working Group refrained from mentioning a particular histological subtype of lymphatic and haematopoietic neoplasm because of the changes in coding and diagnostic practices that have occurred during the course of the epidemiological investigations
• *sufficient evidence* in experimental animals for the carcinogenicity of 1,3-butadiene and D,L-diepoxybutane
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).
• TCE was widely used for degreasing metal parts until the 1990s, and in dry cleaning from the 1930s to 1950s, main current use is in chlorinated chemical production.

• A French case-control study in an area with high prevalence of occupational exposure to TCE, OR 2.16 (95% CI 1.02–4.60) for people with high cumulative exposure after adjusting for smoking and body-mass index (Charbotel 2006)

• In an eastern European study, OR 1.63 (95% CI 1.04–2.54) for any exposure to TCE and 2.34 (1.05–5.21) in the highest category of exposure intensity (Moore, 2010)

• Consistent with the importance of glutathione conjugation for kidney carcinogenesis, TCE-exposed people with an active GSTT1 enzyme had an increased risk (OR 1.88, 95% CI 1.06–3.33), but people without GSTT1 activity did not (0.93, 0.35–2.44) (Boice, 2006)

• A meta-analysis also reported significant RRs of kidney cancer; 1.3 overall and 1.6 for high-exposure groups (Scott, 2011)

Sufficient evidence for carcinogenicity, Group 1
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**Vol 107, PCBs, Nomenclature**

- 209 congeners

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*International Agency for Research on Cancer*
Cancer in humans

• Excess risks for melanoma were noted consistently in occupational studies in different industries in North America and Europe, in studies of the general population, and with cohort and case-control designs.
• Excess risks for melanoma were reported in several cohort studies of workers in the manufacture of capacitors and transformers, and in electric power and equipment maintenance.
• A significant linear exposure–response trend was noted in the largest study.
• In a population-based case-control study that assessed exposure with PCB serum levels, the association persisted after control for sun sensitivity and exposure.

There is sufficient evidence in humans for the carcinogenicity of PCBs. There is limited evidence for non-Hodgkin lymphoma and breast cancer.
Mechanisms, “Dioxin-like” PCBs

- 12 PCBs with a Toxicity Equivalency Factor (TEF) according to WHO: PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189
- PCB 126 classified in Group 1 in vol. 100F (IARC, 2012)
- Sufficient evidence of carcinogenicity in experimental animals (PCB 118, 126, 118 + 126)
- Activity identical to 2,3,7,8-TCDD for every step of the mechanism described for TCDD-associated carcinogenesis in humans:
  - Receptor binding activity
  - Changes in gene expression
  - Changes in protein activity
  - Increased cellular replication
  - Oxidative stress
  - Promotion in initiation-promotion studies
  - Complete carcinogens
## Overall evaluations

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<td>Polychlorinated biphenyls, dioxin-like, with a Toxicity Equivalency Factor (TEF) according to WHO (PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189) (NB: Overall evaluation upgraded to Group 1 with strong supporting evidence from other relevant data)</td>
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<td>(NB: Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data, namely mechanistic similarity with polychlorinated biphenyls classified in Group 1)</td>
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Cancer sites in experimental bioassays

- **Agents:** individual PCBs, binary mixtures, or fresh commercial products

- **Target organs (p<0.05 in at least one experiment):**
  - Rat: liver, biliary tract, thyroid gland, lung, oral mucosa, uterus
  - Rat offspring: mammary gland (benign + malignant)
  - Mouse: liver, lung, skin (topical)
  - Mouse offspring: lung (promotion)
**Carcinogenic mechanisms of PCBs**

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<th>Metabolic activation</th>
<th>Carcinogenic pathway</th>
<th>AhR</th>
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<td>Receptor affinity</td>
<td>AhR</td>
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<td>CYP2B1/2</td>
<td>Induction of xenobiotic metabolizing enzymes</td>
<td>CYP1A1</td>
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<tr>
<td>Mutations, DNA strand-breaks, X aberrations</td>
<td>Genetic and related effects</td>
<td>DNA adduct formation</td>
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<td>Liver</td>
<td>Organ toxicity</td>
<td>Liver, skin</td>
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<td>Other, including metabolic activation</td>
<td>Immunotoxicity</td>
<td>AhR mediated</td>
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<td>Driven by hydroxylated metabolites</td>
<td>Endocrine effects</td>
<td>AhR mediated (steroid hormones)</td>
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<td>Initiator</td>
<td>Initiation/promotion potential</td>
<td>Promoter</td>
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Outdoor Air Pollution is Highly Variable

Association of Lung Cancer and PM-2.5

International Agency for Research on Cancer
Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)

Ole Raaschou-Nielsen, Zorana J Andersen, Rob Beelen, Evangelia Samoli, Massimo Stafoggia, Gudrun Weinmayr, Barbara Hoffmann, Paul Fischer,

International Agency for Research on Cancer
Evaluation: Cancer in humans

• There is *sufficient evidence* in humans for the carcinogenicity of *outdoor air pollution*. Outdoor air pollution causes cancer of the lung. A positive association has been observed for cancer of the urinary bladder.

• There is *sufficient evidence* in humans for the carcinogenicity of *particulate matter in outdoor air pollution*. Particulate matter in outdoor air pollution causes cancer of the lung.
Cancer in experimental animals

• Mice exposed to traffic-related outdoor air pollution from São Paulo showed an increase in the incidence of lung adenoma, promotion of urethane-induced adenomas and tumour multiplicity in a dose-dependent manner (Several studies in mice s.c. injected with organic solvent-extracted material from particles collected from outdoor air pollution showed increased incidences of injection site tumours, and pulmonary adenoma or adenocarcinoma
Pre- and post-Monograph meeting analyses of pooled datasets and meta-analyses

- 16 case-control studies from 16 countries
- 19,369 lung cancer cases; 23,670 controls
- SYN-JEM, routine measurement data for PAH asbestos, crystalline silica, chromium/nickel
- Lifetime smoking and occupational histories
- ~1,000 never smoking lung cancer cases
- ~20% Women

- Research platform for occupational lung cancer research
- Diesel engine exhaust: Olsson et al, 2011
- Meta-consortium with ILCCO: alcohol drinking & lung cancer?
Occupational cancer: AF

- Very divergent estimates <1% to 40%
  Prevalence of risk factor & exposure level
  Strength of evidence for causal association
- Doll & Peto 1981 4% of US cancers
- Simonato et al, 1988: 0.6 – 40% of lung cancers
- Leigh et al, 1997 „WHO Global Burden of Disease“ direct & indirect methods: 6-10%
- Nurminen & Karjalainen, 2001: 8% of cancers in Finns
- Steenland et al 2003: 2.4 – 4.8% of US cancers
- Rushton et al 2008, UK....
“Occupational cancer, moreover, tends to be concentrated among relatively small groups of people among whom the risk of developing the disease may be quite large, and such risks can usually be reduced or even eliminated, once they have been identified. The detection of occupational hazards should therefore have a higher priority in any program of cancer prevention than their proportional importance might suggest.”

Doll & Peto, 1981
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)

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Impact of Monograph evaluations
Collaboration of IMO 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
• European Parliament, Debate on UV Radiation and Cancer
• National Agencies, e.g. NTP Report on Carcinogens, ANSES
Monographs 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)