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

Supporting implementation

Education and training

Evaluating prevention

Establishing causes
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

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

Lorenzo Tomatis
1929-2007
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)

<table>
<thead>
<tr>
<th>Cancer in humans</th>
<th>Cancer in experimental animals</th>
<th>Mechanistic and other relevant data</th>
</tr>
</thead>
<tbody>
<tr>
<td>— Preamble Part B, Section 6(a)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Sufficient evidence</th>
<th>Evidence suggesting lack of carcinogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Causal relationship has been <strong>established</strong></td>
<td>□ 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</td>
</tr>
<tr>
<td>Chance, bias, and confounding <strong>could be ruled out with reasonable confidence</strong></td>
<td>Conclusion is limited to cancer sites and conditions studied</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Limited evidence</th>
<th>Inadequate evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Causal interpretation is <strong>credible</strong></td>
<td>Studies permit <strong>no conclusion</strong> about a causal association</td>
</tr>
<tr>
<td>Chance, bias, or confounding <strong>could not be ruled out</strong></td>
<td></td>
</tr>
</tbody>
</table>

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Evidence suggesting lack of carcinogenicity
Evaluating experimental animal data (Subgroup 3)

Cancer in experimental animals

— Preamble Part B, Section 6(b)

Mechanistic and other relevant data

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)

Data suggest a carcinogenic effect but: (e.g.) single study, benign tumours only, promoting activity only

Studies permit no conclusion about a carcinogenic effect

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

Evidence suggesting lack of carcinogenicity

Evidence suggesting lack of carcinogenicity

Evidence suggesting lack of carcinogenicity
The plenary sessions will combine the human and experimental evaluations

<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>Sufficient</td>
<td>Group 1 ((\text{carcinogenic to humans}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Group 2A ((\text{probably carcinogenic}))</td>
<td>Group 2B ((\text{possibly carcinogenic})) (exceptionally, Group 2A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>Group 2B ((\text{possibly carcinogenic}))</td>
<td>Group 3 ((\text{not classifiable}))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESLC</td>
<td>Group 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:**
- Sufficient evidence indicates that a substance is likely carcinogenic to humans.
- Limited evidence suggests a probable carcinogenic effect but with some uncertainty.
- Inadequate evidence indicates insufficient or contradictory data.
- ESLC (Evidence Supporting the Limitation of Claims) is used when carcinogenicity cannot be definitively established.

**Groups:**
- Group 1: Carcinogenic to humans
- Group 2A: Probably carcinogenic
- Group 2B: Possibly carcinogenic
- Group 3: Not classifiable
- Group 4: Other categories
Overall carcinogenicity evaluation

<table>
<thead>
<tr>
<th>EVIDENCE IN HUMANS</th>
<th>EVIDENCE IN EXPERIMENTAL ANIMALS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sufficient</strong></td>
<td><strong>ESLC</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Group 1</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Group 2A</strong></td>
</tr>
<tr>
<td><strong>Limited</strong></td>
<td><strong>Group 2B</strong> (exceptionally, Group 2A)</td>
</tr>
<tr>
<td><strong>Inadequate</strong></td>
<td><strong>Group 3</strong></td>
</tr>
<tr>
<td><strong>ESLC</strong></td>
<td><strong>Group 4</strong></td>
</tr>
</tbody>
</table>

- **Sufficient** evidence in exposed humans
- **Limited** evidence: 1 strong evidence in exposed humans
- **Inadequate** evidence: 3 strong evidence, mechanism does not operate in humans
- **ESLC** evidence: 4 consistently and strongly supported by a broad range of mechanistic and other relevant data

**Group 1**
- 2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A

**Group 2A**
- 2A belongs to a mechanistic class

**Group 2B**
- 2B with supporting evidence from mechanistic and other relevant data

**Group 3**
- 2B with strong evidence from mechanistic and other relevant data

**Group 4**
- 2B with strong evidence from mechanistic and other relevant data
Mechanisms Involved in Human Carcinogenesis

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.

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)
# 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 sufficient evidence in humans</th>
<th>Agents with limited evidence 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; chloromethylmethyl ether</td>
<td>Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work</td>
</tr>
<tr>
<td></td>
<td>methyl ether (technical grade)</td>
<td>Carbon electrode manufacture</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>
</tr>
<tr>
<td></td>
<td>Coal gasification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coal-tar pitch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coke production</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Engine exhaust, diesel</td>
<td></td>
</tr>
</tbody>
</table>
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).
### Selected topics from OHRNC 2015

<table>
<thead>
<tr>
<th>Agent</th>
<th>Evaluation</th>
<th>Cancer</th>
<th>Monograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ore Extraction Ni, CrVI, silica, radon,...</td>
<td>1</td>
<td>Lung, nasal cavities (Ni)</td>
<td>100C, 100D</td>
</tr>
<tr>
<td>Asbestos</td>
<td>1</td>
<td>Lung, mesothelioma, larynx, ovary</td>
<td>Color-rectum, pharynx, stomach</td>
</tr>
<tr>
<td>Beryllium</td>
<td>1</td>
<td>Lung</td>
<td>100C</td>
</tr>
<tr>
<td>Coal dust</td>
<td>3</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>Air pollution</td>
<td>1</td>
<td>Lung</td>
<td>109</td>
</tr>
<tr>
<td>Shift-work</td>
<td>2A</td>
<td>Breast</td>
<td>98</td>
</tr>
<tr>
<td>CNT</td>
<td>2B</td>
<td></td>
<td>111</td>
</tr>
</tbody>
</table>
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.
• 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
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).*
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.
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).
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 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

<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) and backward (afternoon/evening → morning → night)</td>
</tr>
<tr>
<td>Rate of rotation</td>
<td>Daily change, 2-3-4 day change, weekly, etc.</td>
</tr>
<tr>
<td>Morning shift</td>
<td># consecutive days of early morning shift (before 6 am)</td>
</tr>
<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>
<tr>
<td>Sleep</td>
<td>Sleep duration &amp;</td>
</tr>
<tr>
<td>Light at night</td>
<td>During sleep period</td>
</tr>
</tbody>
</table>

### Considerations of circadian impact for defining ‘shift work’ in cancer studies: IARC Working Group Report

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
• 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.

<table>
<thead>
<tr>
<th>Panel: Agents recommended by the IARC Advisory Group for assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High priority</strong></td>
</tr>
<tr>
<td>Acrylamide, furan, and 5-(hydroxymethyl) furfural—commonly found in cooked foods; cancer bioassay data are available</td>
</tr>
<tr>
<td>Aspartame and sucralose—widespread use and concern about their potential carcinogenicity</td>
</tr>
</tbody>
</table>

- 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
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)
- 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)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>Total</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>97.0</td>
<td>82.5</td>
<td>95.0</td>
</tr>
<tr>
<td>Sinonasal</td>
<td>48.0</td>
<td>20.1</td>
<td>34.4</td>
</tr>
<tr>
<td>Lung</td>
<td>22.2</td>
<td>5.5</td>
<td>15.2</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>11.1</td>
<td>2.5</td>
<td>8.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>7.2</td>
<td>1.9</td>
<td>5.4</td>
</tr>
<tr>
<td>Breast</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>NMSC</td>
<td>7.0</td>
<td>1.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Larynx</td>
<td>2.9</td>
<td>1.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>3.3</td>
<td>1.1</td>
<td>2.5</td>
</tr>
<tr>
<td>STS</td>
<td>3.4</td>
<td>1.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.0</td>
<td>0.3</td>
<td>2.0</td>
</tr>
<tr>
<td>NHL</td>
<td>2.1</td>
<td>1.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Melanoma (eye)</td>
<td>2.9</td>
<td>0.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Total</td>
<td>8.45</td>
<td>2.35</td>
<td>5.51</td>
</tr>
</tbody>
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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)

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
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

http://monographs.pubcan.org
Evaluating mechanistic and other data (Subgroup 4)

<table>
<thead>
<tr>
<th>Mechanistic and other relevant data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have the mechanistic events been established? Are there consistent results in different experimental systems? Is the overall database coherent?</td>
</tr>
<tr>
<td>Has each mechanism been challenged experimentally? Do studies demonstrate that suppression of key mechanistic processes leads to suppression of tumour development?</td>
</tr>
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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
## Tumour (Site) Concordance between Humans and Animals

| Site                          | Lip | Nose | Oral Cavity | Tongue | Pharynx | Larynx | Trachea | Larynx | Vocal Cord | Hypopharynx | Oesophagus | Stomach | Duodenum | Jejunum | Ileum | Colon | Rectum | Liver | Pancreas | Adrenal Gland | Parathyroid | Pituitary | Thyroid | Larynx | Trachea | Bronchus | Melanoma | Male Genital | Breast | Skin | Soft Connective Tissue | Bone | Cartilage | Glial Tumor | Hematopoietic | Digestive System | Urogenital System | All Cancers Combined |
|-------------------------------|-----|------|-------------|--------|---------|--------|---------|--------|------------|-------------|------------|---------|---------|---------|--------|-------|-------|--------|-------|---------|-------------|------------|----------|---------|--------|--------|---------|---------|-----------|--------|------|----------------------|------|-----------|-------------|-------------|-----------------|------------------|---------------------|
| agent                         |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Azathioprine                  |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Chlorambucil                  |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Combined oral contraceptives  |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Cyclophosphamide              |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Diethylstilbestrol            |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Estrogen only menopausal therapy|     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Methoxsalen in combination with UV | |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Phenacetin                    |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Plants containing aristolochic acid | |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Tamoxifen                     |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Thiopeta                      |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Arsenic and Arsenic Compounds |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Asbestos                      |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Berillium and Berillium compounds |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Cadmium and cadmium compounds |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Chromium (VI) compounds       |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Erionite                      |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Nickel and nickel compounds   |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Silica dust, crystalline (quartz or other) | |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Fission products including Sr-90 | |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Neutrons                      |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| Solar radiation               |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| X-rays, Gamma rays            |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| alpha particle emitters (Am-241) |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| alpha particle emitters (Ci-249) |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| alpha particle emitters (Ci-252) |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| alpha particle emitters (Cm-244 and Cm-244) | |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| alpha particle emitters (Np-237) |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |
| alpha particle emitters (Po-210) |     |      |             |        |         |        |         |        |             |             |            |         |         |         |        |       |       |        |       |        |              |            |          |         |        |         |         |         |           |        |      |                      |      |           |             |             |                 |                  |                     |

**Legend:**
- **Red** - Human S + Any Animal
- **Green** - Human L + Any Animal
- **Blue** - Human S but No Animal
- **Yellow** - Animal Only

*Source: International Agency for Research on Cancer, World Health Organization*
Group-1 agents with less than sufficient evidence in humans

- 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

• 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
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 \( \mu \text{m} \) 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.
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 Agency for Research on Cancer in Lyon to review the evidence on occupational exposures and cancer risk. So far, the most influential epidemiological studies assessing cancer risks were conducted among the 2.5 million workers exposed to diesel exhausts in the USA. These studies showed that the risk of lung cancer is doubled after 20 years of employment. With such large numbers of exposed workers, these findings are not easily explained by chance.

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

Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls

The carcinogenicity of outdoor air pollution
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).
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.
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.
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).
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).