The *IARC Monographs* evaluate

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

More than 950 agents have been evaluated

- 118 are *carcinogenic to humans* (Group 1)
- 75 are *probably carcinogenic to humans* (Group 2A)
- 288 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
- 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)

Cancer in humans
— Preamble Part B, Section 6(a)

Cancer in experimental animals

Mechanistic and other relevant data

**Sufficient evidence**
- Causal relationship has been *established*
- Chance, bias, and confounding *could be ruled out with reasonable confidence*

**Limited evidence**
- Causal interpretation is *credible*
- Chance, bias, or confounding *could not be ruled out*

**Inadequate evidence**
- Studies permit **no conclusion** about a causal association

**Evidence suggesting lack of carcinogenicity**
- 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
- Conclusion is limited to cancer sites and conditions studied
Evaluating experimental animal data (Subgroup 3)

Cancer in experimental animals — Preamble Part B, Section 6(b)

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.
Evaluating mechanistic and other data (Subgroup 4)

Cancer in humans

• Are the mechanistic data “weak,” “moderate,” or “strong”?

Cancer in experimental animals

• Have the mechanistic events been established? Are there consistent results in different experimental systems? Is the overall database coherent?

• Has each mechanism been challenged experimentally? Do studies demonstrate that suppression of key mechanistic processes leads to suppression of tumour development?

Mechanistic and other relevant data

• Are there alternative explanations? Could different mechanisms operate in different dose ranges, in humans and experimental animals, or in a susceptible group?

Note: an uneven level of support for different mechanisms may reflect only the resources focused on each one.
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><strong>Sufficient</strong></td>
<td>Group 1 (<em>carcinogenic to humans</em>)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Limited</strong></td>
<td>Group 2A (<em>probably carcinogenic</em>)</td>
<td>Group 2B (<em>possibly carcinogenic</em>)</td>
<td>(exceptionally, Group 2A)</td>
<td></td>
</tr>
<tr>
<td><strong>Inadequate</strong></td>
<td>Group 2B (<em>possibly carcinogenic</em>)</td>
<td></td>
<td>Group 3 (<em>not classifiable</em>)</td>
<td></td>
</tr>
<tr>
<td><strong>ESLC</strong></td>
<td></td>
<td></td>
<td></td>
<td>Group 4</td>
</tr>
</tbody>
</table>
# 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>Sufficient</td>
<td></td>
<td></td>
<td>Group 1</td>
<td></td>
</tr>
<tr>
<td>Limited</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>Inadequate</td>
<td>↑1 strong evidence in exposed humans</td>
<td>↑2A belongs to a mechanistic class</td>
<td>↑2B with supporting evidence from mechanistic and other relevant data</td>
<td>Group 3</td>
</tr>
<tr>
<td></td>
<td>↑2A strong evidence ... mechanism also operates in humans</td>
<td>↑2B with strong evidence from mechanistic and other relevant data</td>
<td>Group 3</td>
<td></td>
</tr>
<tr>
<td>ESLC</td>
<td>↓3 strong evidence ... mechanism does not operate in humans</td>
<td>Group 3</td>
<td>Group 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group 4</td>
</tr>
</tbody>
</table>

International Agency for Research on Cancer

World Health Organization
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 <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</td>
</tr>
<tr>
<td></td>
<td>Asbestos (all forms)</td>
<td>pressed ware (manufacture of)</td>
</tr>
<tr>
<td></td>
<td>Beryllium and beryllium compounds</td>
<td>Biomass fuel (primarily wood),</td>
</tr>
<tr>
<td></td>
<td>Bis(chloromethyl)ether; chloromethyl methyl ether</td>
<td>indoor emissions from household</td>
</tr>
<tr>
<td></td>
<td>(technical grade)</td>
<td>combustion of</td>
</tr>
<tr>
<td></td>
<td>Cadmium and cadmium compounds</td>
<td>Bitumens, occupational</td>
</tr>
<tr>
<td></td>
<td>Chromium(VI) compounds</td>
<td>exposure to oxidized</td>
</tr>
<tr>
<td></td>
<td>Coal, indoor emissions from household combustion</td>
<td>bitumens and their</td>
</tr>
<tr>
<td></td>
<td>Coal gasification</td>
<td>emissions during roofing</td>
</tr>
<tr>
<td></td>
<td>Coal-tar pitch</td>
<td>Bitumens, occupational</td>
</tr>
<tr>
<td></td>
<td>Coke production</td>
<td>exposure to hard bitumens</td>
</tr>
<tr>
<td></td>
<td>Engine exhaust, diesel</td>
<td>and their emissions during</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mastic asphalt work</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbon electrode manufacture</td>
</tr>
</tbody>
</table>
• Employment in the boot and shoe industry is causally associated with the development of nasal adenocarcinomas; and relative risks well in excess of 10-fold have been reported in England and in Italy.

• It is most likely that exposure to leather dust plays a role in the association. There is also evidence that an increased risk may exist for other types of nasal cancers for employment in boot and shoe repairing shops.

• The occurrence of leukaemia and aplastic anaemia among shoemakers exposed to benzene is well documented (see also IARC, Vol 7, 1974)
Boot & shoe manufacturing & repair, Leather dust, Vol 100F

- 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).
Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposure as a painter.

- Occupational exposure as a painter causes cancers of the lung and urinary bladder.
- There is *limited evidence* in humans, based primarily on studies of maternal exposure, that painting is associated with childhood leukaemia.

Overall evaluation

Occupational exposure as a painter is *carcinogenic to humans (Group 1)*.
Classification of occupations

- Some occupations classified as carcinogenic to humans have had subsequent reviews attribute their carcinogenicity to specific chemical or physical agents.
- Examples are boot and shoe manufacture and repair (respiratory tract cancers are now attributed to leather dust; and leukemia, to benzene),
- These and other occupations should be regarded as carcinogenic to humans whenever there is exposure to the carcinogenic agents identified in those workplaces.
- Attributing carcinogenicity to specific agents helps national agencies develop regulations to prevent exposure to these agents wherever they are found, in the workplace or in the general environment.
Occupational exposure as a Firefighter (Vol 98)

Exposure

• Several types of firefighters exist, including municipal, wildland, industrial, aviation, and military firefighters.

• All fires generate an enormous number of toxic combustion products, including known and possible carcinogens, long-lived free radicals, and particulate matter. Smoke particles may serve as vehicles for adsorbed volatile organic compounds.
Occupational exposure as a Firefighter (Vol 98)

Exposure

- Peak exposures to some carcinogens may be very high, notably for benzene, 1,3-butadiene, and formaldehyde.
- The concentrations of respirable particulate matter to which firefighters may be exposed during overhaul can reach 50 mg/m3, or up to 1000 mg/m3, and above in the case of coarser particles.
Occupational exposure as a Firefighter (Vol 98)
Cancer in humans (I)

The Working Group reviewed

• 42 studies of cancer in firefighters that included 19 cohorts, 11 case–control studies, and 14 studies that used other designs.

• The studies that were most relevant to the assessment of the risk for cancer among firefighters were the larger historical cohort studies.
Occupational exposure as a Firefighter (Vol 98)

Cancer in humans (II)

- Although excesses of a variety of cancers have been observed in several studies, consistent patterns are difficult to discern due to the large variations of exposures.
- For intermittent but intense exposures to highly variable complex mixtures conventional measures such as years of employment or number of firefighting runs may be poor surrogates for exposure.
- The available epidemiological studies are inherently limited by this.
The Working Group up-dated a recent meta-analysis of cancer in firefighters (LeMasters et al, 2006).

For 3 types of cancer the RR were consistently increased and the average increase was statistically significant:

- Testicular cancer (all 6 studies showed increased risks, average relative risk 1.5), 1/3 with trend with duration
- Prostate cancer (increased risks in 18 of 21 studies, average relative risk 1.3), and
- non-Hodgkin lymphoma (increased risks in 5 of 6 studies, average relative risk 1.2).
Mechanisms of carcinogenicity

- The toxicokinetics of chemical mixtures are not well understood but are probably of significant importance because of the multiplicity of chemicals in smoke.
- For individual smoke components, inhalation was considered to be the major source of exposure; however, dermal absorption is also an important route of exposure for polycyclic aromatic hydrocarbons and polychlorinated biphenyls.
Occupational exposure as a Firefighter (Vol 98)

Mechanisms of carcinogenicity

• Studies to evaluate genotoxic effects in firefighters are few and not conclusive.

• Acute and chronic inflammatory respiratory effects observed in firefighters (Burgess et al, 1999) would provide a plausible mechanism for respiratory carcinogenesis.
There is limited evidence in humans that occupation as a firefighter is carcinogenic.

There is some evidence for an increased risk of testicular cancer, non-Hodgkin lymphoma and prostate cancer.

Occupation as a firefighter is possibly carcinogenic to humans (Group 2B).
### 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>
</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>
</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
- Formaldehyde
- Atrazine
- Indium phosphide
- Carbon black
- Lead and lead compounds
- Chloroform
- Polychlorinated biphenyls (PCB)
- Cobalt metal with tungsten carbide
- Propylene oxide
- Dichloromethane
- Refractory ceramic fibers
- Diesel engine exhaust
- Shiftwork that involves nightwork
- Di-2-ethylhexyl phthalate
- 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 importance.

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
- 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
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)

Danke !