The IARC Monographs, Integrating mechanistic evidence in cancer hazard identification.

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Lyon, France

Mechanisms in medicine
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Outline of presentation

• Broader PH context, history and evolution of the IARC Monographs
• Evaluation of evidence of carcinogenicity in humans
• Mechanisms in overall evaluation
• Outlook and conclusions
Hazard Identification, Risk Assessment and Risk Management

Source: EPA Office of Research and Development.

International Agency for Research on Cancer

World Health Organization
“The encyclopaedia of carcinogens”

The *IARC Monographs* evaluate

- Chemicals
- Complex mixtures
- Occupational exposures
- Physical and biological agents
- Personal habits

More than 1000 agents have been evaluated

- 118 are *carcinogenic to humans* (Group 1)
- 81 are *probably carcinogenic to humans* (Group 2A)
- 299 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

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Lorenzo Tomatis
1929-2007
<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol 1, 1971</td>
<td>Evaluation of strength of evidence for carcinogenicity (hazard, not potency)</td>
</tr>
<tr>
<td>Vol 17, 1977</td>
<td>Use of standard terms for separate evaluation of human and animal evidence, <em>causality</em>, free wording of overall evaluation,</td>
</tr>
<tr>
<td>Suppl 1, 1979 (Vol 1-20)</td>
<td>Defined groups for overall evaluation (1, 2 high or low, 3); Annex: listing of target organs</td>
</tr>
<tr>
<td>Suppl 4, 1982 (Vol 1-29)</td>
<td>Results from short-term tests used for up-grade Group 1, 2A, 2B, 3</td>
</tr>
<tr>
<td>Suppl 7, 1987</td>
<td>Overall evaluation Vol 1-42, <em>Criteria for causality</em> Group 4 (probably not carcinogenic to humans)</td>
</tr>
<tr>
<td>Vol 43, 1987</td>
<td>Concurrent overall evaluation</td>
</tr>
<tr>
<td>Vol 54, 1991</td>
<td>Allow data on mechanisms for up/downgrade</td>
</tr>
</tbody>
</table>
Evidence of carcinogenicity in humans derived from 3 types of study, first 2 usually provide only suggestive evidence: 1) case reports 2) descriptive epidemiological studies 3) analytical epidemiological studies.

- An analytical study that shows a positive association between an agent and a cancer may be interpreted as implying causality to a greater or lesser extent, if the following criteria are met:
  - 1) there is no identifiable positive bias
  - 2) The possibility of positive confounding has been considered
  - 3) The association is unlikely to be due to chance alone.
  - 4) The association is strong.
  - 5) there is a dose-response relationship.
  - 6) convincing evidence of causality when several independent studies done under different circumstances result in 'positive' findings.

Analytical epidemiological studies that show no association between an agent and a cancer should be interpreted according to criteria analogous to those listed above.
In making their judgement, the Working Group considers several criteria for causality.

- **Strong association** more likely to indicate causality than a weak association, although recognized that relative risks of small magnitude do not imply lack of causality.
- Associations **replicated in several studies** … more likely to represent a causal relationship… If inconsistent results among investigations, possible reasons are sought.
- **Risk of the disease in question increases with the amount of exposure** considered to be a strong indication of causality, although absence of a graded response is not necessarily evidence against a causal relationship.
- Demonstration of a **decline in risk after cessation** of or reduction in exposure … also supports a causal interpretation of the findings.
- Although the same carcinogenic agent may act upon more than one target, the **specificity of an association** adds plausibility to a causal relationship.
- Although rarely available, results from **randomized trials** showing different rates among exposed and unexposed individuals provide particularly strong evidence for causality.
How are Evaluations Conducted?

- Published guidelines for participant selection, conflict of interest & stakeholder involvement
- Criteria for data eligibility
- Guidelines for review of human, animal and mechanistic evidence
- Decision process for overall evaluations

http://monographs.iarc.fr/ENG/Preamble/index.php
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
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
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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EVIDENCE IN HUMANS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>Group 2B (possibly carcinogenic)</td>
<td>Group 2B (possibly carcinogenic)</td>
<td>Group 3 (not classifiable)</td>
<td>Group 4</td>
</tr>
</tbody>
</table>
Preamble 2006, Criteria for Causality, I

**Strong association** more likely to indicate causality, small relative risks don’t imply lack of causality

**Replication** in several studies, using same design or different epidemiological approaches, different circumstances; reasons for inconsistent results sought, high quality studies given more weight

**Dose-response relationship** strong indication of causality; absence not necessarily evidence against; decline of risk after cessation of exposure supports causal interpretation

**Specificity** adds plausibility to causality, but carcinogen may act upon more than one target

**RCTs** rarely available, particularly strong evidence for causality

**Evidence suggesting lack of carcinogenicity**: caution
Preamble 2006, Criteria for Causality, II

- **Temporality**: The effect has to occur after the cause.
- **Plausibility**: A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism may be limited by current knowledge).
- **Coherence**: Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".
- **Analogy**: Group 2A (Preamble 2006)
  “An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.” Preamble 2006
Strong association
Cholangiocarcinoma among workers in the printing industry

- 16 cases of intrahepatic or extrahepatic cholangiocarcinoma among male (former) employees in a printing plant (around 70 workers) in Osaka, Japan
- Age range of 16 cases: 20 to 49 years
  - no chronic biliary inflammation such as primary cirrhotic cholangitis, intrahepatic cholelithiasis and liver fluke infection,
  - no chronic hepatitis B nor C
  - no malfusion of pancreaticobiliary ducts.
- SIR for biliary tract cancer ~1200 (95%CI 714-1963)
- Kumagai et al, Short report published in OEM-online 3/2013
- Suspected chemicals: 1,2-dichloropropane & dichloromethane
Not so strong association
IARC Monographs Vol 83, 2002
Lung Cancer Risk in Involuntary Smokers

- **Spouses** of smokers who had never smoked had a significant and consistent increase in lung cancer risk when exposed to second-hand tobacco smoke.

- **Husbands** of women who smoked experienced a 30% increase in risk of lung cancer.

- **Wives** of men who smoked experienced a 20% increase in risk of lung cancer.

- Risk increased with increasing exposure.
Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity. The advantages of combined analyses are:

- **Increased precision** due to increased sample size and
- The opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail.

A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies.

-> Straif et al, Use of Meta-analyses by IARC Working Groups. EHP 2012
Dose-response relationship
Breast cancer and alcohol consumption

Pooled analysis of data available worldwide in 2002 (> 58 000 women with breast cancer)
Fluoro-edenite fibrous amphibole first identified around Etna volcano, Biancavilla, Italy; similar mineral reported from the Kimpo volcano in Japan.

Unpaved roads made from local quarry products from Biancavilla, since the 1950s,

Several surveillance studies reported excess of mesothelioma in region of Biancavilla (Bruno et al., 2014).

Rate ratios for mesothelioma large & stable,

Excess similar in men and women, most prominent in young adults, suggesting environmental cause.

Increased incidences of mesotheliomas observed in male and female rats given fibrous fluoro-edenite by i.p. & i. pl. injection (Belpoggi et al., 2011).

Fluoro-edenite classified as carcinogenic to humans (Group 1)
Specificity?

Sentinel events,
- Vinyl chloride and angiosarcoma of the liver
- Asbestos and mesothelioma
RCTs

- Usually, ethically not acceptable in epidemiological studies of environmental risk factors
- RCTs for intervention studies after identification of carcinogenic hazards (Gambia Hepatitis Intervention Study, HPV vaccination)
- Evaluation of cancer protective factors (IARC Cancer Prevention Handbooks)
- WHI, estrogens-progestogen menopausal therapy and breast cancer in postmenopausal women
- Used in IARC Monographs to assess cancer bioassays and some mechanistic studies
For arsenic in drinking-water, ecological studies provide important information on causal inference, because of

- large exposure contrasts and limited population migration.
- As a consequence of widespread exposure to local or regional water sources, ecological measures provide a strong indication of individual exposure.
- Moreover, in the case of arsenic, the ecological estimates of relative risk are often so high that potential confounding with known causal factors cannot explain the results."
Plausibility


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

There is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. On the basis of the data available at this time, it is not possible to identify a mechanism for the induction of myeloid leukaemia in humans.
Silicon carbide (SiC) occurs in several forms: particles, fibres, and whiskers.

SiC whiskers; intentionally produced as durable industrial substitutes for asbestos; physically homogeneous and monocrystalline, with dimensions similar to asbestos amphiboles.

Mesotheliomas observed in 3 studies in female rats treated by intrapleural implantation, intrapleural injection, or intraperitoneal injection, and 1 inhalation study in rats

Sufficient evidence for the carcinogenicity of SiC whiskers in experimental animals

SiC whiskers classified as probably carcinogenic to humans (Group 2A) on the basis that physical properties of the whiskers resemble those of asbestos and erionite fibres.
The plenary sessions will combine the human and experimental evaluations.

<table>
<thead>
<tr>
<th>Evidence in Experimental Animals</th>
<th>Evidence in Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>Group 1 (carcinogenic to humans)</td>
</tr>
<tr>
<td>Limited (probably carcinogenic)</td>
<td>Group 2A</td>
</tr>
<tr>
<td>Limited (possibly carcinogenic)</td>
<td>Group 2B (possibly carcinogenic) (exceptionally, Group 2A)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Group 2B (possibly carcinogenic)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Group 3 (not classifiable)</td>
</tr>
<tr>
<td>ESOLC</td>
<td>Group 4</td>
</tr>
</tbody>
</table>

International Agency for Research on Cancer
World Health Organization
Evaluating mechanistic and other data (Subgroup 4)

<table>
<thead>
<tr>
<th>Cancer in humans</th>
<th>Cancer in experimental animals</th>
<th>Mechanistic and other relevant data</th>
</tr>
</thead>
</table>

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

  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?

- **Is the mechanism likely to be operative in humans?**

  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.
# 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>Group 1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sufficient</td>
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<td></td>
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<tr>
<td>Group 2A</td>
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<tr>
<td>1 strong evidence in exposed humans</td>
<td></td>
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<tr>
<td>Group 2B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 strong evidence in exposed humans</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Group 2B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 strong evidence in exposed humans</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2A belongs to a mechanistic class</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2B with supporting evidence from mechanistic and other relevant data</td>
<td></td>
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<tr>
<td>Group 3</td>
<td></td>
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<tr>
<td>1 strong evidence in exposed humans</td>
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</tr>
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<td>2A belongs to a mechanistic class</td>
<td></td>
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</tr>
<tr>
<td>2B with strong evidence from mechanistic and other relevant data</td>
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</tr>
<tr>
<td>Group 4</td>
<td></td>
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<tr>
<td>4 consistently and strongly supported by a broad range of mechanistic and other relevant data</td>
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</tr>
</tbody>
</table>

*International Agency for Research on Cancer*
IARC Monographs, Volume 100
A Review of Human Carcinogens

• 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)

• Volume 100 Workshops
  - Tumour (Site) Concordance between Humans and Animals
  - Mechanisms Involved in Human Carcinogenesis
## Ten Key Characteristics of Carcinogens

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Examples of relevant evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is Electrophilic or Can Be Metabolically Activated</td>
<td>Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone, etc), formation of DNA and protein adducts.</td>
</tr>
<tr>
<td>2. Is Genotoxic</td>
<td>DNA damage (DNA strand breaks, DNA-protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei).</td>
</tr>
<tr>
<td>3. Alters DNA repair or causes genomic instability</td>
<td>Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)</td>
</tr>
<tr>
<td>4. Induces Epigenetic Alterations</td>
<td>DNA methylation, histone modification, microRNA expression</td>
</tr>
</tbody>
</table>
Ten Key Characteristics of Carcinogens

Figure 3. An overview of how polychlorinated biphenyls (PCBs) may induce seven key characteristics.
Group-1 agents with less than sufficient evidence in humans

- Ethylene oxide (vol 60, 1994, Vol 97, 2007)
- 2,3,7,8-Tetrachlorodibenzo-para-dioxin (vol 69, 1997)
- Neutron radiation (vol 75, 2000)
- Areca nut (Vol 85)
- Gallium Arsenide (Vol 86, 2003)
- Tobacco-specific nitrosamines NNN and NNK (Vol 85)
- Benzo[a]pyrene (vol 92, 2005)
- Ethanol in alcoholic beverages
- Dyes metabolized to benzidine (Vol 99, 2007)
- MOCA (Vol 99, 2007)
- Aristolochic acid (Vol 100A)
- Acetaldehyde associated with consumption of alcoholic beverages (Vol 100E)
- pentachloro-dibenzofuran and pentachloro-biphenyl (Vol 100F, 2009), Dioxin-like PCBs (Vol 107)
Mechanisms Involved in Human Carcinogenesis

Use of mechanistic data to identify carcinogens is accelerating

Types of mechanistic upgrades

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

**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.
## 1. Cancer in humans and animals

<table>
<thead>
<tr>
<th></th>
<th>Benzo[a]pyrene</th>
<th>Dibenzo[a,h] anthracene</th>
<th>Benzo[a] anthracene</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiological data</strong></td>
<td>inadequate</td>
<td>inadequate</td>
<td>inadequate</td>
</tr>
<tr>
<td><strong>Cancer bioassays</strong></td>
<td>sufficient</td>
<td>sufficient</td>
<td>sufficient</td>
</tr>
<tr>
<td><strong>Preliminary evaluation</strong></td>
<td></td>
<td></td>
<td>2B</td>
</tr>
</tbody>
</table>
### 2. Mechanistic data in experimental animals

<table>
<thead>
<tr>
<th></th>
<th>Benzo[a]pyrene</th>
<th>Dibenzo[a,h] anthracene</th>
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<td>sufficient</td>
<td>sufficient</td>
</tr>
<tr>
<td><strong>2B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diol-epoxide</td>
<td>Strong (lung + skin)</td>
<td>Moderate (lung + skin)</td>
<td>Moderate (lung + skin)</td>
</tr>
<tr>
<td>Radical cation</td>
<td>Strong (skin)</td>
<td></td>
<td>_</td>
</tr>
<tr>
<td>Potential additional mechanisms</td>
<td>7,8-quinone/ROS, AhR, immunology</td>
<td>_</td>
<td>3,4-quinone /ROS</td>
</tr>
</tbody>
</table>
### 3. Mechanistic data in human cells

<table>
<thead>
<tr>
<th></th>
<th>Benzo[a]pyrene</th>
<th>Dibenzo[a,h]anthracene</th>
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</tr>
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<td>_</td>
<td>3,4-quinone/ROS</td>
</tr>
<tr>
<td>data in human cells in vitro</td>
<td>BPDE-DNA adducts in lung explants and mammary epithelial cells</td>
<td>DNA adduct profiles in skin cells similar to those in mouse <em>in vivo</em></td>
<td>_</td>
</tr>
</tbody>
</table>

2A 2B
## 4. Overall evaluation

<table>
<thead>
<tr>
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<td>—</td>
</tr>
</tbody>
</table>

### 2A

| **Data from exposed humans** | BPDE adducts (coke-oven workers, chimney sweeps) | Mutations in Ki-ras | — | — |
| Classification               | **Group 1** | **Group 2A** | **Group 2B** |
Evaluated in category of higher concern on the basis of mechanistic data:

**Sufficient evidence in experimental animals and mechanistic upgrade**
- Benzo[a]pyrene  
  Group 1
- Cyclopenta[cd]pyrene  
  Group 2A
- Dibenzo[a,h]anthracene  
  Group 2A
- Dibenzo[a,l]pyrene  
  Group 2A

**Limited evidence in experimental animals and mechanistic upgrade**
- Benz[j]aceanthrylene  
  Group 2B
- Benzo[c]phenanthrene  
  Group 2B
Aristolochic acid

IARC Monograph Vol 82, 2002

- Case reports: 2 Belgium, 1 Taiwan, 1 U.K.
- Among 10 renal-grafted Chinese herb nephro-pathy patients 4 cases of multifocal carcinoma in situ
- Among 39 patients with end-stage renal disease 18 cases of urothelial carcinomas

Herbal remedies containing plant species of the genus Aristolochia, Group 1
Aristolochic acid, Group 2A

IARC Monograph Vol 100A, 2008
DNA adducts and A:T→T:A transversions in TP53 identified aristolochic acid as the carcinogen in herbal remedies

Aristolochic acid Group 1
5.5 Evaluation
There is sufficient evidence in experimental animals for the carcinogenicity of melamine.

Overall evaluation
In making its overall evaluation, the Working Group noted that the non-DNA reactive mechanism by which melamine produced urinary bladder tumours in male rats occurred only under conditions in which calculi were produced.

Melamine is not classifiable as to its carcinogenicity to humans (Group 3).
Melamine, Vol 119

• Chinese children exposed in 2008 to infant milk formula adulterated with melamine

• Urinary tract precipitates and inflammation occurred in human beings and rodents exposed to high levels. In exposed infants, stones consisting mainly of melamine and uric acid in the kidney, ureter, and urinary bladder, and renal inflammation were reported.

• In chronic bioassays, rats and mice developed urinary tract inflammation. Male rats developed stones composed mainly of melamine and uric acid in the urinary bladder, and the incidence of stones correlated with carcinoma occurrence.

Melamine is probably carcinogenic to humans (Group 2B).
7 criteria that need to be met for considering the induction of kidney tumours to occur by an α2u-globulin-associated response

3 criteria have been met, specifically:

- induction of the characteristic sequence of histopathological changes associated with α2u-globulin accumulation;
- identification of the accumulating protein as α2u-globulin
- absence of genotoxicity

However, 4 of these criteria have not been met

- male rat specificity for nephropathy and renal tumourigenicity (also seen in female rats);
- reversible binding of the chemical or metabolite to α2u-globulin
- induction of sustained increase in cell proliferation in the renal cortex
- similarities in dose–response relationships of the tumour outcome with histopathological endpoints associated with α2u-globulin nephropathy
Discovery exploits the rapid expansion of human high dimensional molecular data

Rapid growth in genome-wide association studies

Innovation is not the use of GWAS data for genetic insights, but its large-scale exploitation for causal inference on modifiable exposures

≈2500 studies in 2015
≈1500 unique traits in 2015

Causal inference research

https://www.genome.gov/gwastudies/
Genetic instruments proxy a wide variety of modifiable exposures

Environmental factors
Alcohol, fatty acids, sun exposure, physical activity, resting energy expenditure, nutrients

Early life factors
Birthweight, child obesity, age at puberty onset

Endogenous biomarkers
Glycaemia, insulinaemia, IL-6, IGF, CRP, sex hormones, vitamin D, adiponectin

Metabolomics
Metabolites

Drug targets
Statins, aspirin

Epigenetics
DNA methylation
miRNAs

Mendelian randomization
Mendelian Randomisation informing evidence synthesis process

Body Fatness and Cancer — Viewpoint of the IARC Working Group

Beatrice Lauby-Secretan, Ph.D., Chiara Scoccianti, Ph.D., Dana Loomis, Ph.D., Yann Grosse, Ph.D., Franca Bianchini, Ph.D., and Kurt Straif, M.P.H., M.D., Ph.D., for the International Agency for Research on Cancer Handbook Working Group

Current paradigm

Exposure → Single cancer → Confounders

Future

Exposure → Cancer 1 → Cancer 2 → Cancer N

- CVD
- T2D
- Other

International Agency for Research on Cancer
Conclusions

• Evolution of evaluation criteria to recognize increased confidence in GLP studies and mechanistic data
• Use of mechanistic data in causal inference on cancer in humans (observational epidemiology, BH: no algorithm)
• Use of mechanistic data in making overall evaluation (mechanistic up- or downgrades); almost sole use of mechanistic evidence
• Mutagenicity vs genotoxicity vs 10 Key characteristics (KC) of carcinogens
• Further guidance for evaluation of mechanistic data (characterization of evidence: weak, moderate, strong)
• Outlook, new methods and tools (GWAS, HTP) for Mendelian randomisation (causal and mechanistic inference) and data on mechanisms (10 KC)
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Thank you