IARC Evaluation of PFOA carcinogenicity

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International Agency for Research on Cancer
Lyon, France

WORKSHOP

PROGETTARE UNO STUDIO EPIDEMIOLOGICO RELATIVO ALLA POPOLAZIONE DELLA REGIONE VENETO ESPOSTA A PFAS

Venice, 22–23 February 2017

Ospedale Civile SS. Giovanni e Paolo

International Agency for Research on Cancer

World Health Organization

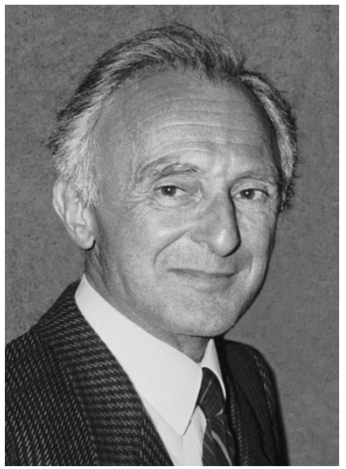
Conflict of Interest Statement

I declare no financial interests related to the subject matter of my presentation.

“The encyclopaedia of carcinogens”

The *IARC Monographs* evaluate

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



Lorenzo Tomatis
1929-2007

Almost 1000 agents have been evaluated

- 119 are *carcinogenic to humans* (Group 1)
- 81 are *probably carcinogenic to humans* (Group 2A)
- 292 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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How are Evaluations Conducted?

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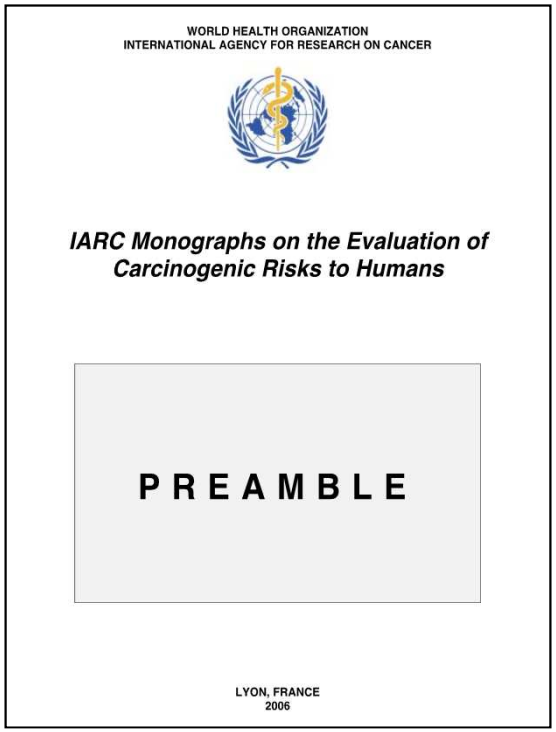


- Published guidelines for participant selection, conflict of interest & stakeholder involvement
- Criteria for data eligibility
- Guidelines for review of human, animal and mechanistic evidence
- Decision process for overall evaluations

http://monographs.iarc.fr/ENG/Preamble/index.php

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

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

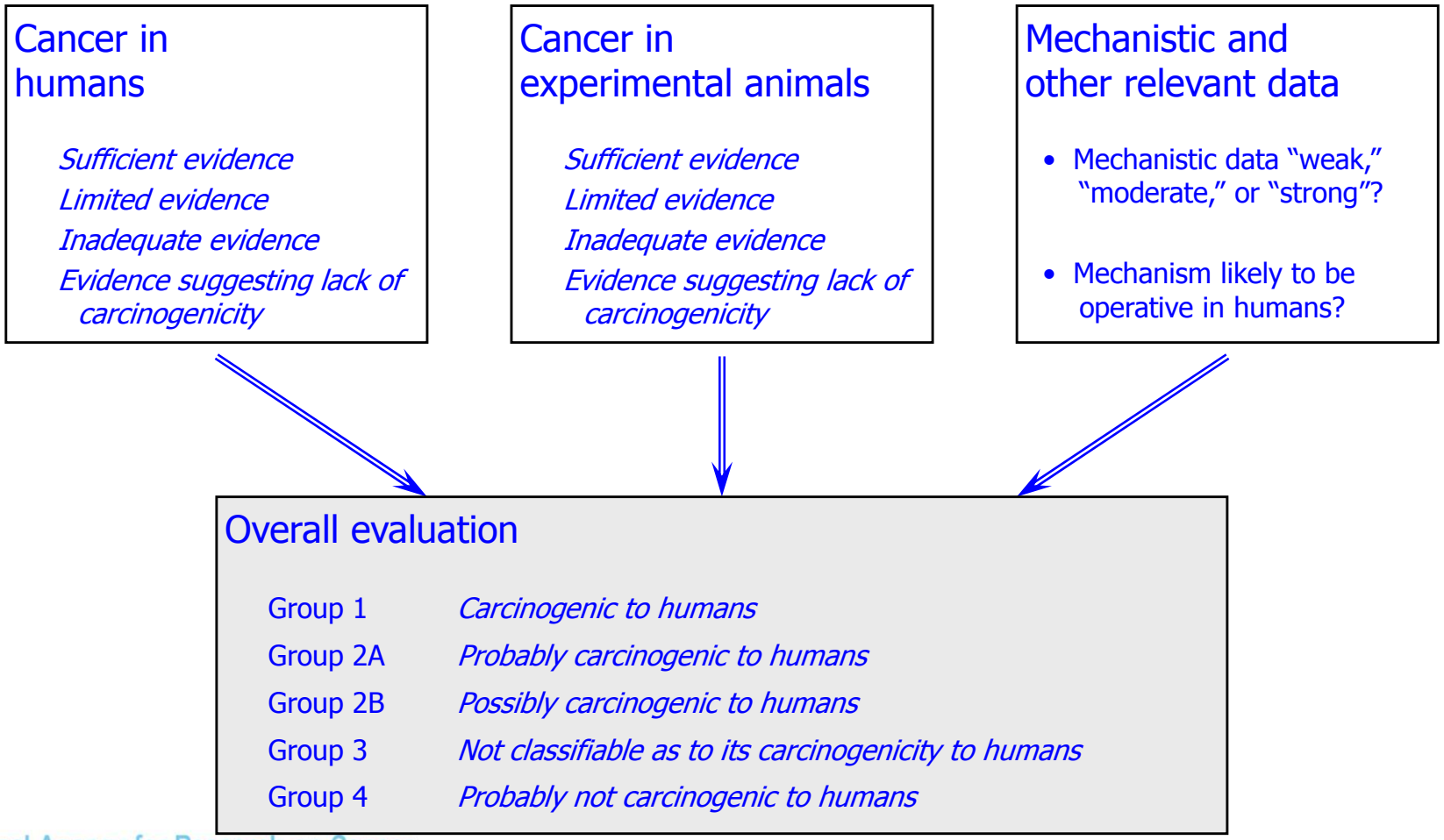
Representatives of national and international health agencies

Observers

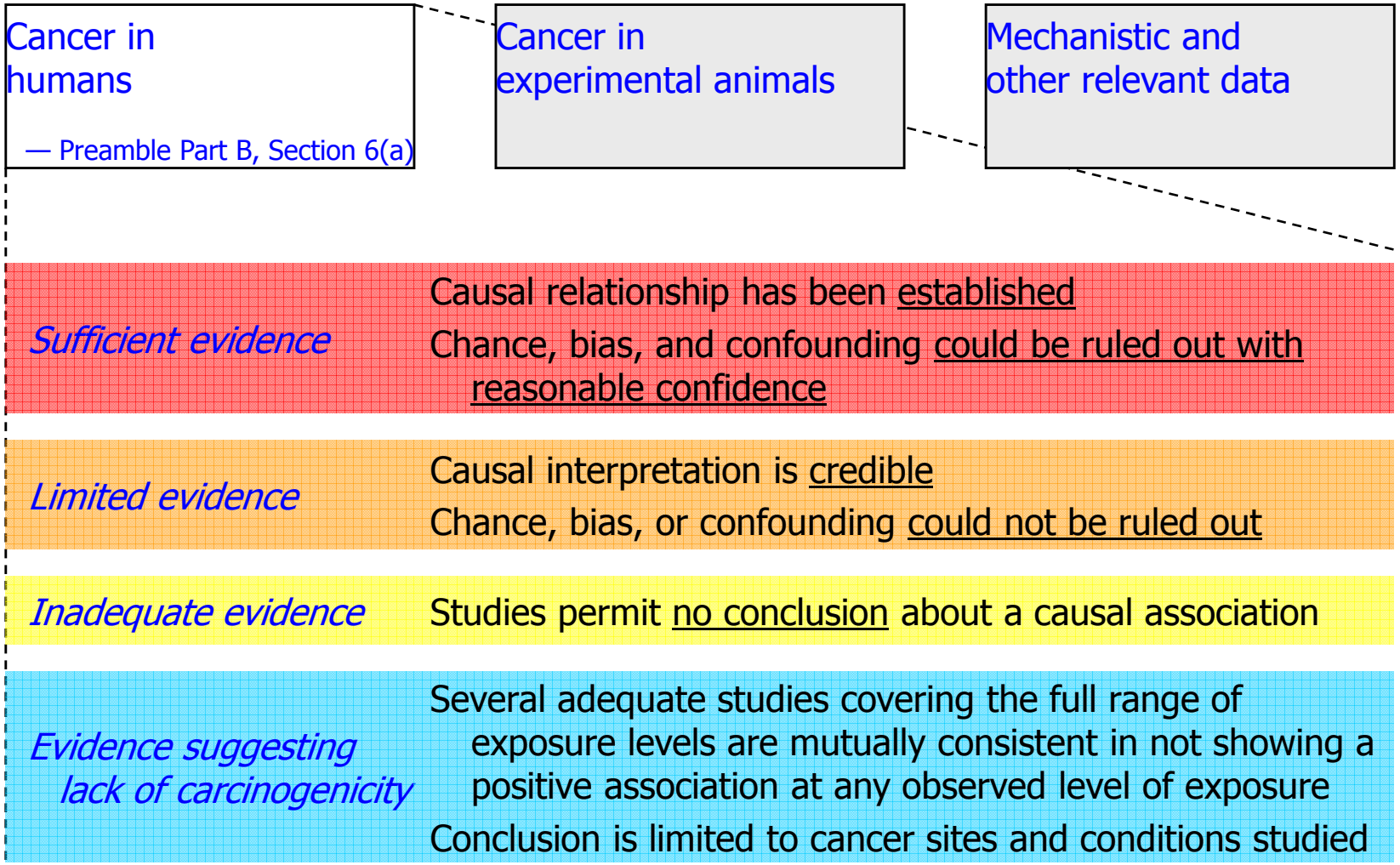
- Here to *observe* the meeting, *not to influence* its outcome
- All participants agree to respect the *Guidelines for Observers*

IARC Secretariat

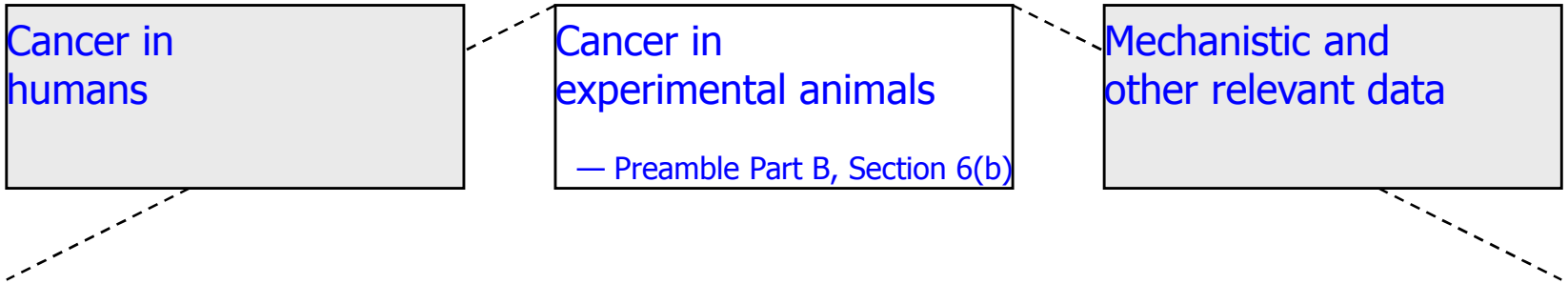
Subgroup work



Evaluating human data (Subgroup 2)

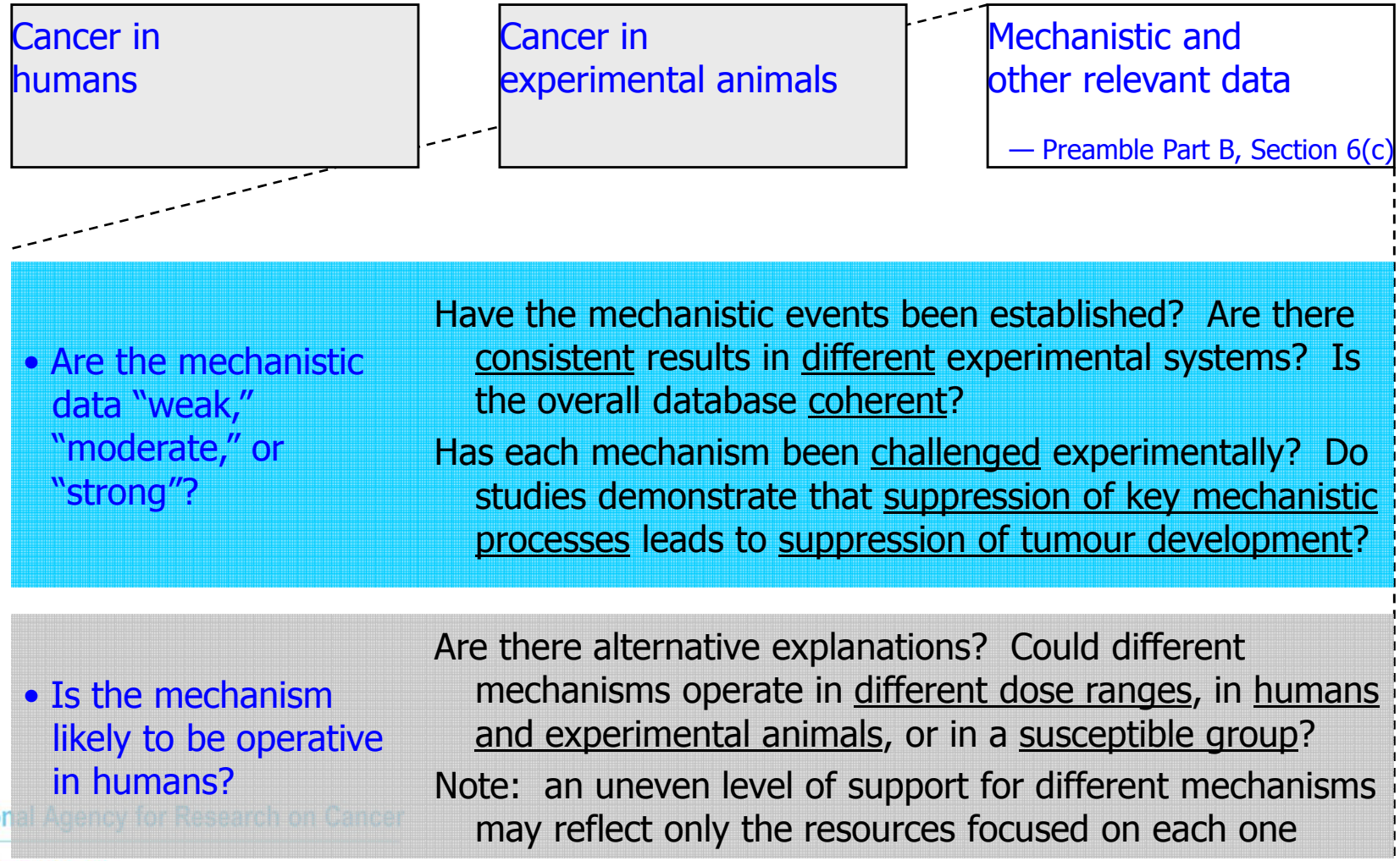


Evaluating experimental animal data (Subgroup 3)

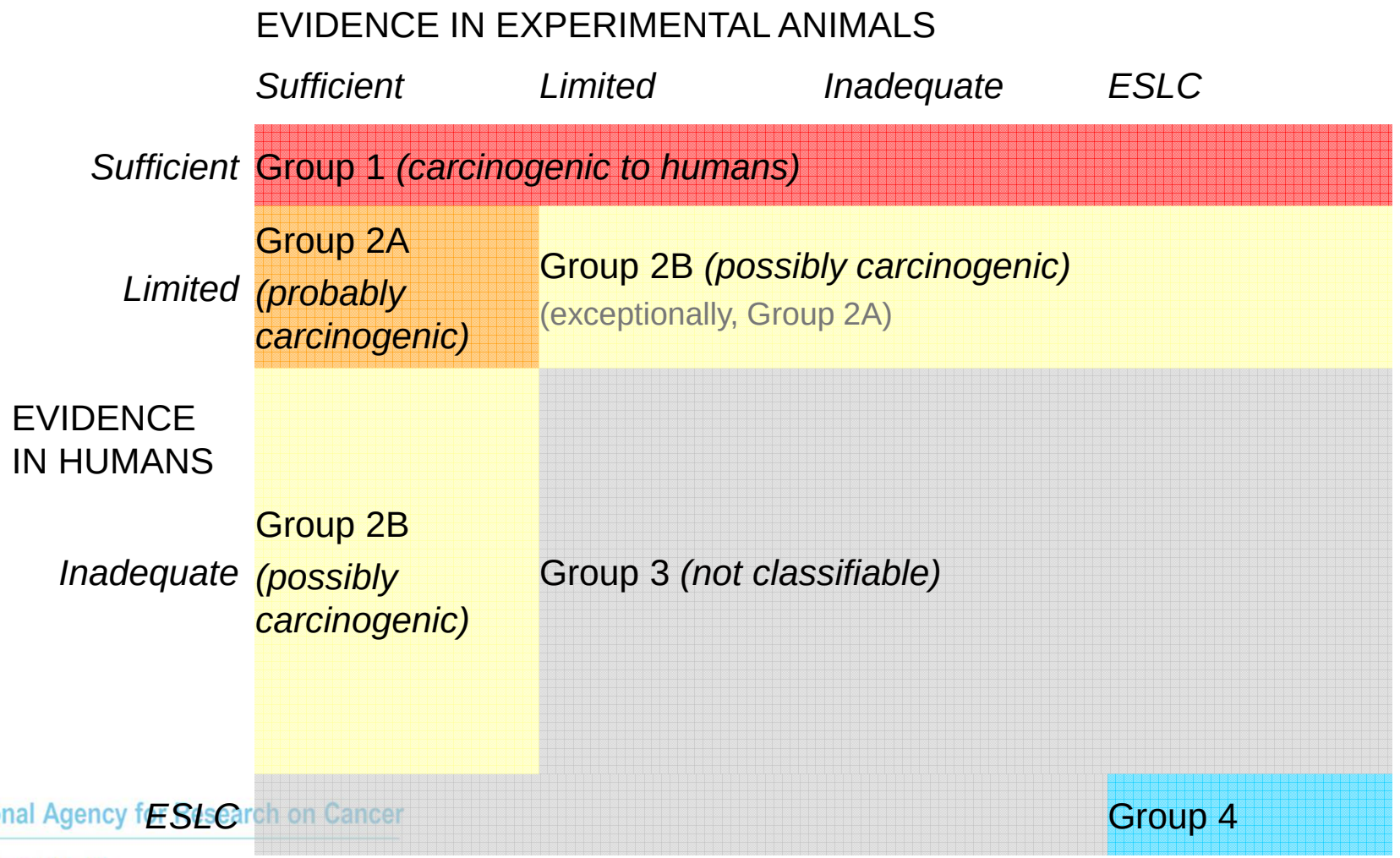


Sufficient evidence	Causal relationship has been established through either: - Multiple positive results (2 species, studies, sexes of GLP) - Single unusual result (incidence, site/type, age, multi-site)
Limited evidence	Data suggest a carcinogenic effect but: (*e.g.*) single study, benign tumours only, promoting activity only
Inadequate evidence	Studies permit no conclusion about a carcinogenic effect
Evidence suggesting lack of carcinogenicity	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

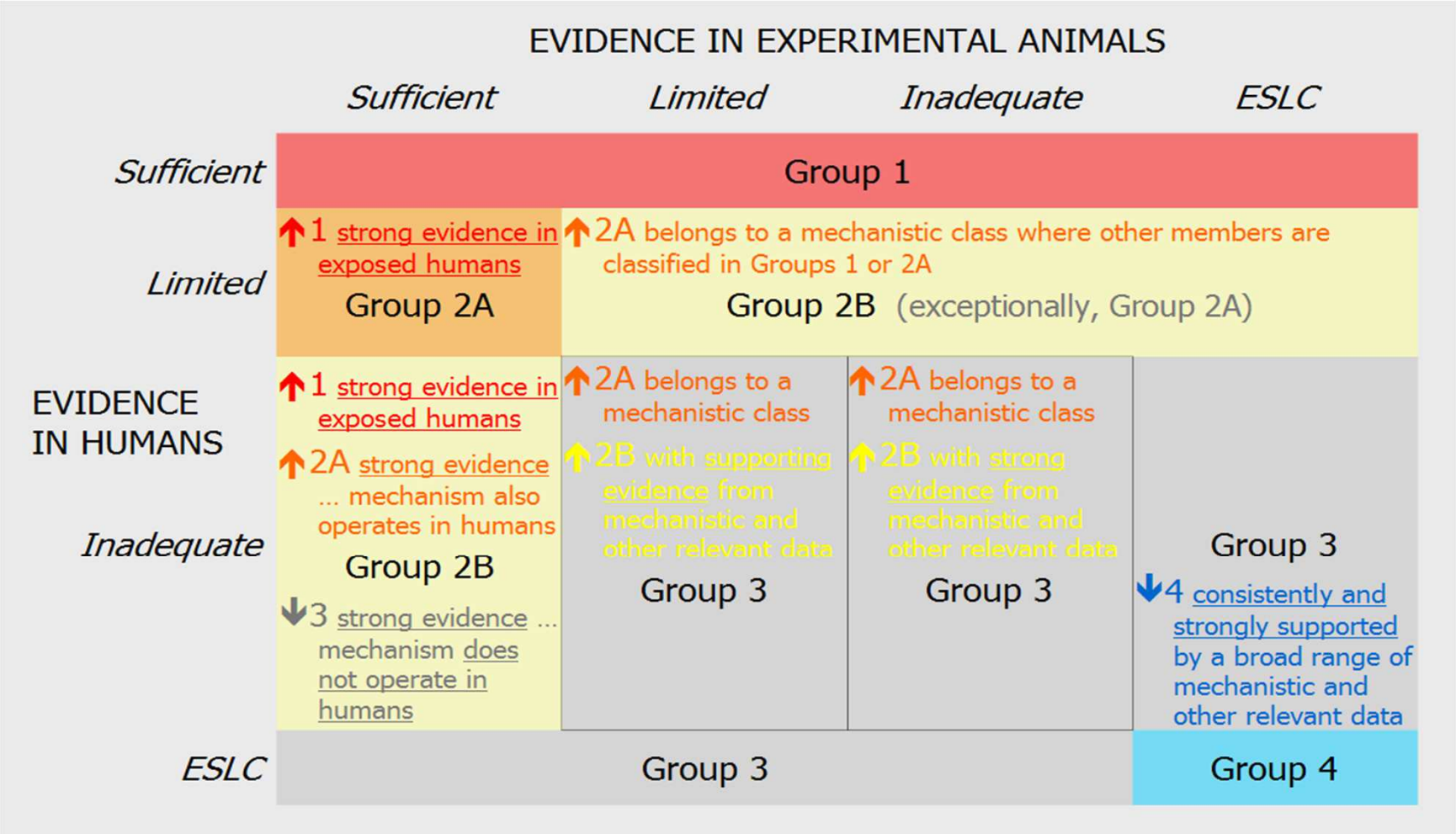
Evaluating mechanistic and other data (Subgroup 4)



The plenary sessions will combine the human and experimental evaluations



Overall carcinogenicity evaluation



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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)

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Preventable Exposures Associated With Human Cancers

Vincent James Cogliano, Robert Baan, Kurt Straif, Yann Grosse, Béatrice Lauby-Secretan, Fatiha El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Crystal Freeman, Laurent Galichet, Christopher P. Wild

Known and suspected causes of cancer

List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 110*

Cancer site	Carcinogenic agents with *sufficient evidence* in humans	Agents with *limited evidence* in humans
Kidney	Tobacco smoking X-radiation, gamma-radiation Trichloroethylene	Arsenic and inorganic arsenic compounds Cadmium and cadmium compounds Perfluorooctanoic acid Printing processes
Testis		DDT Diethylstilbestrol (exposure in utero) N,N-dimethylformamide Perfluorooctanoic acid

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

REVIEW

Preventable Exposures Associated With Human Cancers

Vincent James Cogliano, Robert Baan, Kurt Straif, Yann Grosse, Béatrice Lauby-Secretan, Fatiha El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Crystal Freeman, Laurent Galichet, Christopher P. Wild

Key Characteristics of Carcinogens (1)

- **Electrophilicty 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

Carcinogenesis vol.34 no.9 pp.1955–1967, 2013
doi:10.1093/carcin/bgt212
Advance Access publication June 7, 2013

REVIEW

Towards incorporating epigenetic mechanisms into carcinogen identification and evaluation

Zdenko Herceg*, Marie-Pierre Lambert, Karin van Veldhoven[1], Christiana Demetriou[1], Paolo Vineis[1], Martyn T.Smith[2], Kurt Straif and Christopher P.Wild

during development and contribute to the lineage-specific epigenome that is maintained over the lifetime of an organism.

Epigenetic mechanisms are essential for the stable propagation of

Key Characteristics of Carcinogens (2)

- **Receptor-mediated**
  - acts act 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

Special Report: Policy

Future priorities for IARC Monographs

An Advisory Group of 14 scientists from nine countries met in June, 2008, at the International Agency for Research on Cancer (IARC) to recommend topics for assessment in future IARC Monographs. IARC periodically convenes such Advisory Groups to ensure the

Panel: **Agents recommended by the IARC Advisory Group for assessment**

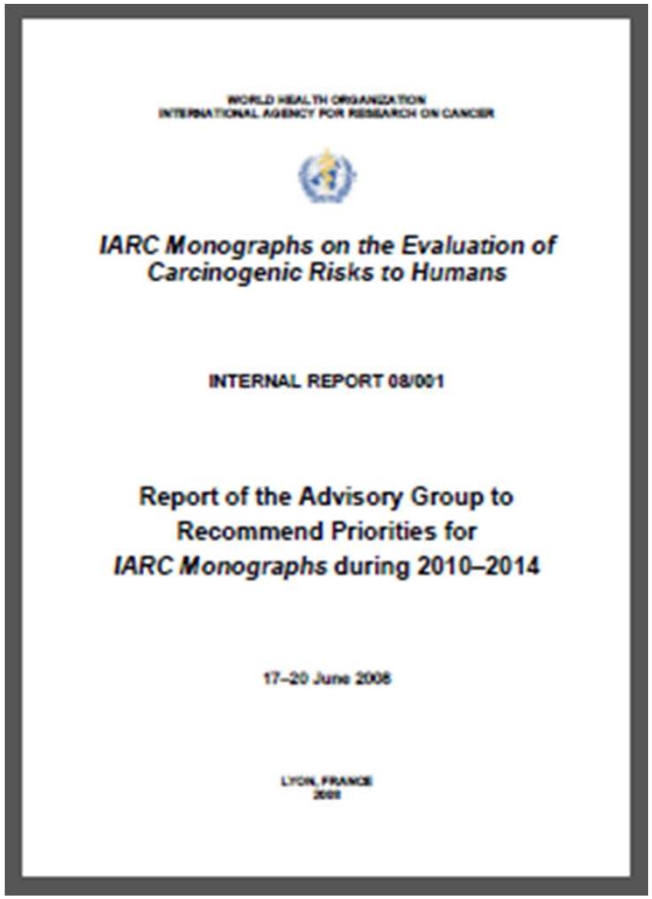
High priority

Acetaldehyde—derived from ethanol metabolism and has a role in oesophageal carcinogenesis; used as an industrial chemical and a food-flavouring agent

Acrylamide and furan—found in common cooked foods and are carcinogenic in animals

PFOA, High Priority

…PFOA has been associated with increased incidence of liver, Leydig cell and pancreatic acinar-cell tumours in rodent bioassays. It is currently being tested in two-year bioassays by the NTP.


WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

INTERNAL REPORT 08/001

Report of the Advisory Group to Recommend Priorities for *IARC Monographs* during 2010–2014

17–20 June 2008

LYON, FRANCE
2008

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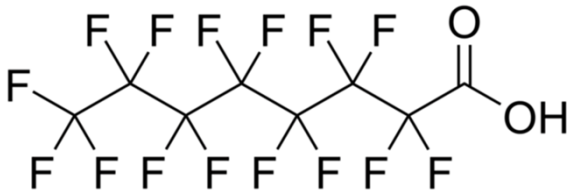
PFOA, Chemistry and Production

Perfluorooctanoic acid (PFOA):
Synthetic fluorinated carboxylic acid.



Two production methods:

- **Electrochemical fluorination** process results in a mixture of branched and straight-chain isomers of the ammonium salt,
- **Telomerization process** (used since early 2000s), results in an isomerically pure, straight-chain product.

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PFOA, Use

- PFOA and its salts mainly used as **emulsifiers** in the production of **fluoropolymers** such as polytetrafluoroethylene.
- PFOA has been used in metal cleaners, electrolytic-plating baths, self-shine floor polishes, cement, fire-fighting formulations, varnishes, emulsion polymerization, lubricants, gasoline, leather, and textile treatments and as non-stick coatings on cookware and in paper coatings such as food packaging.
- PFOA is **persistent in the environment** and has been detected in **air, water, dust, and food**.

PFOA, Exposure

- For general population, predominant sources of exposure are **food** (including transfer from **food packaging**) and **dust**.
- Serum concentrations of perfluorooctanoate of **<10 µg/L**, with **increase** over time **until about 2000**, and since constant or decrease.
- In people living near industrial sources of perfluoro-octanoate, mean serum concentrations from near-background concentrations to **> 200 µg/L**, with **drinking-water** as predominant route of exposure.
- Occupational exposure (inhalation and dermal), during **fluoropolymer production**, with mean serum concentrations in workers with highest exposure **>1000µg/L**.

PFOA, Cancer in Humans (1)

Few cancer epidemiology studies on PFOA in **3 types of populations**

- workers exposed in chemical plants producing or using PFOA,
- high-exposure communities (areas surrounding a plant with documented release of PFOA and contamination of water supplies),
- studies in the general population with background exposures.

Cancer of the testis

- informative results from 2 studies of cancer incidence in a high-exposure community setting in West Virginia and Ohio, USA (1 cohort study & 1 population-registry case–control study, some overlap in the cases),
- increased risk of incidence of cancer of the testis, with **3-fold increase in highest quartile of exposure** in both studies, **significant trend in the cohort study** (n/a in case–control study).

PFOA, Cancer in Humans (2)

Cancer of the kidney

3 studies in West Virginia, USA (occupational and community exposure), and one in a different occupational setting.

- exposure–response analysis of workers in West Virginia: 8/12 deaths from cancer of the kidney in highest exposure quartile, **elevated SMR and a significant trend**.
- other occupational cohort study: **no evidence** for increased incidence
- **modestly increased risk** in a community study with high exposure.
- study in somewhat overlapping population: elevated risks in high and very high exposure groups

Other cancer sites

- Some positive associations for cancers of the **bladder, thyroid, and prostate**, but inconsistent among studies and based on small numbers

PFOA, Cancer in exp. Animals

- PFOA was administered in the feed in one study of carcinogenicity in male and female rats, and in another study in male rats.
- PFOA increased the incidence of testi**cular Leydig cell adenoma** in males in both studies, and increased the incidences of hepatocellular adenoma and pancreatic acinar cell adenoma in the study in male rats only.
- PFOA was also shown to **promote hepatocarcinogenesis** in two feeding studies in male rats and two feeding studies in rainbow trout.

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PFOA, Mechanisms of Carcinogenicity

- Readily **absorbed via all routes** of exposure & excreted into the urine.
- **No metabolism** in experimental systems studied or in humans.
- **Humans unique** with highly efficient reabsorption of PFOA in kidneys, -> much longer retention and much greater body burden of PFOA
- *Strong* evidence that direct **genotoxicity is not** a mechanism of PFOA carcinogenesis.
- **Indirect DNA damage** may result from induction of oxidative stress
- In experimental animals, **liver** is well-established target for toxicity. **Potential mechanisms** for PFOA-induced toxicity and carcinogenicity in the liver include PPARα activation, other molecular pathways (i.e. constitutive androstane receptor, pregnane X receptor, estrogen receptor), and cytotoxicity.

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PFOA, Mechanisms of Carcinogenicity

- *Moderate* evidence for these mechanisms, largely from studies in rats and mice. Based on the available evidence, human relevance of the liver findings in rodents cannot be excluded.
- Studies in human cells, rodents, and fish, documented **perturbation of molecular pathways** involving **reproductive hormones and hormone receptors**, such as activation of estrogen receptor, interference with testosterone/estradiol balance, and induction of aromatase, and effects on reproductive organs consistent with **estrogenicity**.
- Although there is *moderate* evidence that PFOA affects reproductive-hormone pathways, there is *weak* evidence for their relevance to PFOA-associated carcinogenesis.
- **Overall**, there is *moderate* evidence for mechanisms of PFOA-associated carcinogenesis, including some evidence for these mechanisms being operative in humans.

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PFOA, Evaluation of Carcinogenicity

- Evidence for cancer of the **testis** considered credible and unlikely to be explained by bias and confounding, however, the estimate was based on small numbers.
- Evidence for cancer of the **kidney** was considered credible; however, chance, bias, and confounding could not be ruled out with reasonable confidence.

Evaluation

- *Limited evidence* in humans for the carcinogenicity of PFOA. A positive association was observed for cancers of the testis and kidney.
- *Limited evidence* in experimental animals for the carcinogenicity of PFOA

Overall evaluation

- PFOA is possibly carcinogenic to humans (Group 2B).

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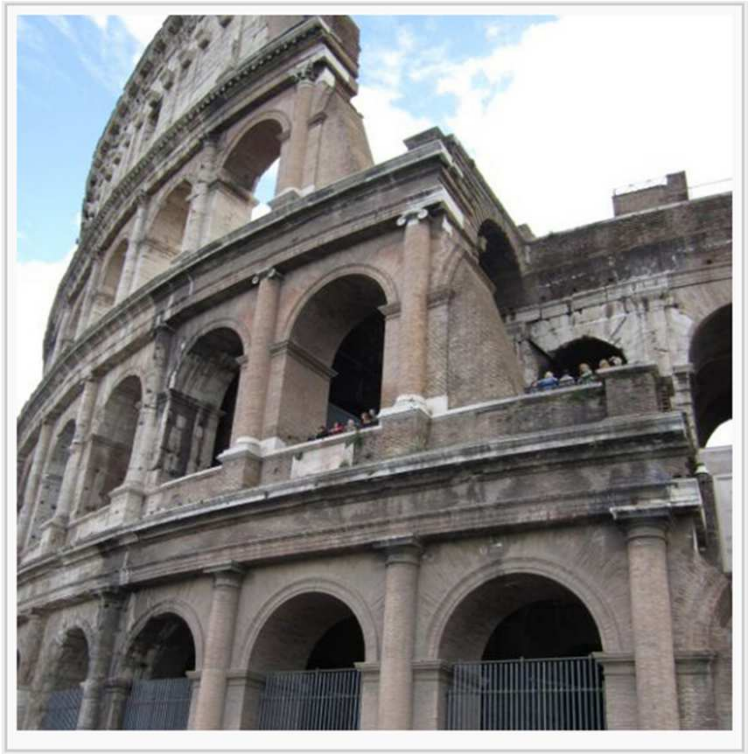
Twelfth meeting of the Persistent Organic Pollutants Review Committee (POPRC.12)

Rome, Italy, from 19 to 23 September 2016



- The Committee adopted the risk profile for PFOA, its salts and PFOA-related compounds, moving the chemicals to the next review stage, requiring a risk management evaluation that includes an analysis of possible control measures.
- The Committee endorsed the guidance on alternatives to PFOS and its related chemicals to assist countries in phasing-out of those chemicals listed under the Convention.

UNEP STOCKHOLM CONVENTION

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Team of the IARC Monographs & Handbooks of Cancer Prevention

Working Group for IARC Monographs Vol 110

Thank you - Grazie Mille

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- Institut National du Cancer (INCa), France
- The American Cancer Society, USA
- The Center for Disease Control, USA

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- European Commission (DG Employment, Social Affairs and Inclusion)