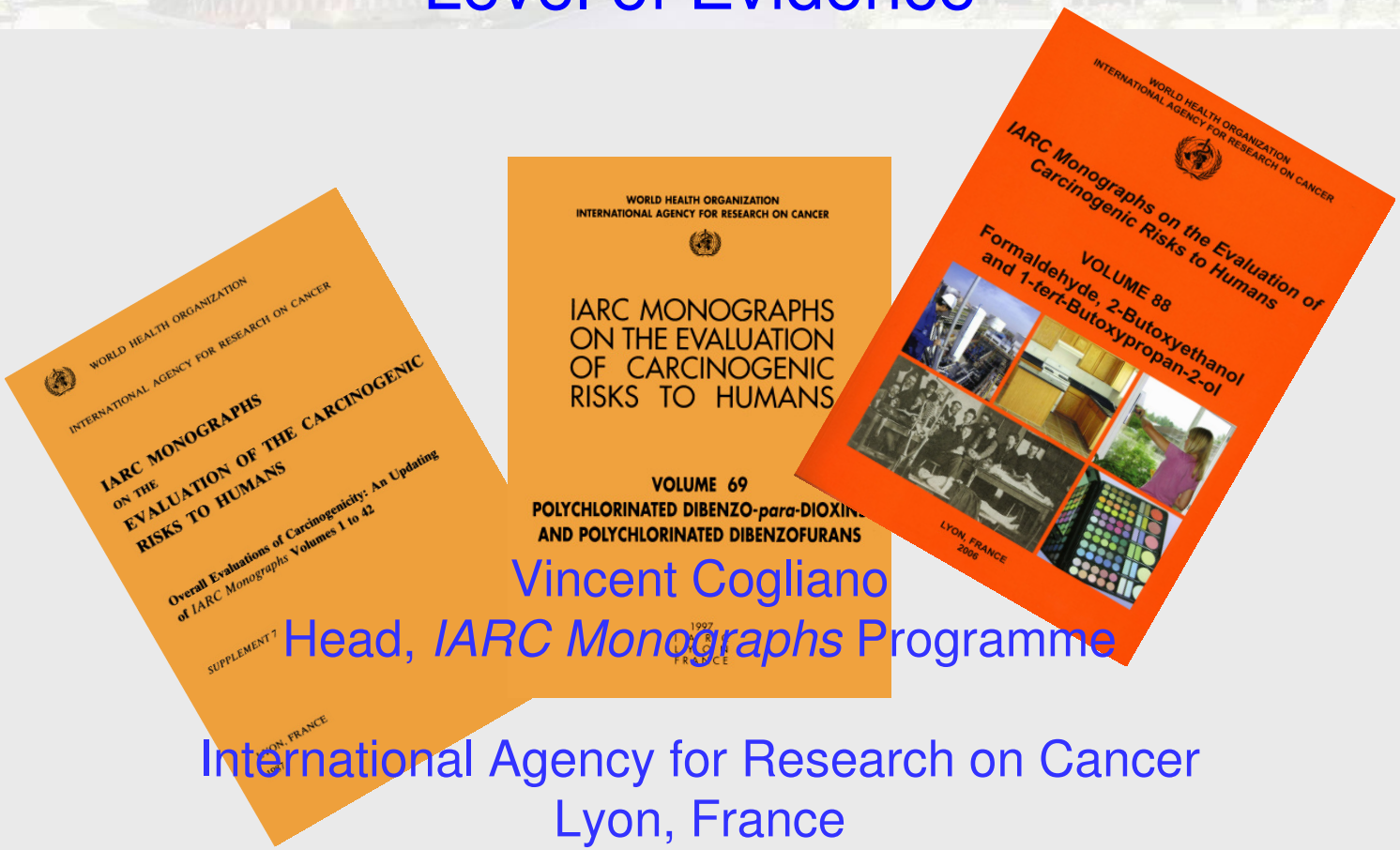
IARC's Approach to Assessing the Level of Evidence



Vincent Cogliano
Head, *IARC Monographs* Programme

International Agency for Research on Cancer
Lyon, France

The *IARC Monographs*

The *IARC Monographs* are a series of scientific reviews that identify environmental factors that can increase the risk of human cancer

Each *Monograph* includes

- Critical review of the pertinent scientific literature
- Evaluation of the weight of evidence that the agent can increase cancer risks

The *Monographs* strive to be authoritative

- Complete: all epidemiology studies, all animal bioassays, representative mechanistic data are considered
- Accurate: text and printed tables are verified by IARC scientists
- Trusted: impartial reviews, no conflicting interests, no interference

The *IARC Monographs* are unique in that they are developed by experts who conducted the original research

A worldwide endeavour that since 1971 has involved over 1200 scientists from 53 countries

International Agency for Research on Cancer

World Health Organization

Hazard and Risk

Cancer hazard: an agent that is capable of causing cancer

Cancer risk: a quantitative estimate of the carcinogenic effects of a cancer hazard

The *IARC Monographs* identify cancer hazards

- The *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher
- The *Monographs* may estimate dose-response relationships within the range of the available epidemiologic data
- The *Monographs* may compare the dose-response information from epidemiological or experimental studies

"The encyclopaedia of carcinogens"

The *IARC Monographs* evaluate

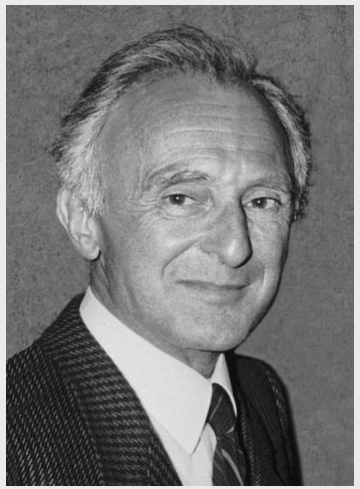
- Chemical agents and complex mixtures
- Occupational exposures
- Physical agents, biological agents
- Personal habits and household exposures

More than 900 agents have been evaluated

- 108 are *carcinogenic to humans* (Group 1)
- 59 are *probably carcinogenic to humans* (Group 2A)
- 248 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 these agents



Dr Lorenzo Tomatis
1929-2007
Founder of the *IARC Monographs*

Overview of the evaluation process

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

- Identify established and likely mechanistic events
- Determine whether each mechanism could operate 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 studies

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 human studies

Criteria for causality

- Strength of the observed association
- Consistency of the observed association
- Exposure-response relationship, including “natural experiments”
- Specificity (some agents cause one cancer type; others, multiple types)
- Temporal relationship
- Biological plausibility and coherence

Evidence of lack of carcinogenicity

- Consistent with an effect estimate of unity (1.0)
- Narrow confidence interval due to sufficient population size
- No individual study nor pooled results should show a consistent exposure-response relationship

Evaluating experimental animal bioassays

Cancer in humans	Cancer in experimental animals – Preamble Part B, Section 6(b)	Mechanistic and other relevant data

Sufficient evidence	Causal relationship has been established through either: - Multiple positive results (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 relevant data

Cancer in humans	Cancer in experimental animals	Mechanistic and other relevant data – Preamble Part B, Section 6(c)
– Identify established and likely mechanistic events		Are there consistent results in different experimental systems? Is the overall database coherent? Has each mechanism been challenged experimentally? Does suppression of key mechanistic processes lead to suppression of tumour development? Are there alternative explanations? Uneven support for different hypotheses may reflect only that uneven resources were devoted to their study
– Determine whether each mechanism could operate in humans		Could different mechanisms operate in different dose ranges, in humans and experimental animals, or in a susceptible group?

All studies contribute to the overall evaluation

Cancer in humans

- *Sufficient evidence*
- *Limited evidence*
- *Inadequate evidence*
- *Evidence suggesting lack of carcinogenicity*

Cancer in experimental animals

- *Sufficient evidence*
- *Limited evidence*
- *Inadequate evidence*
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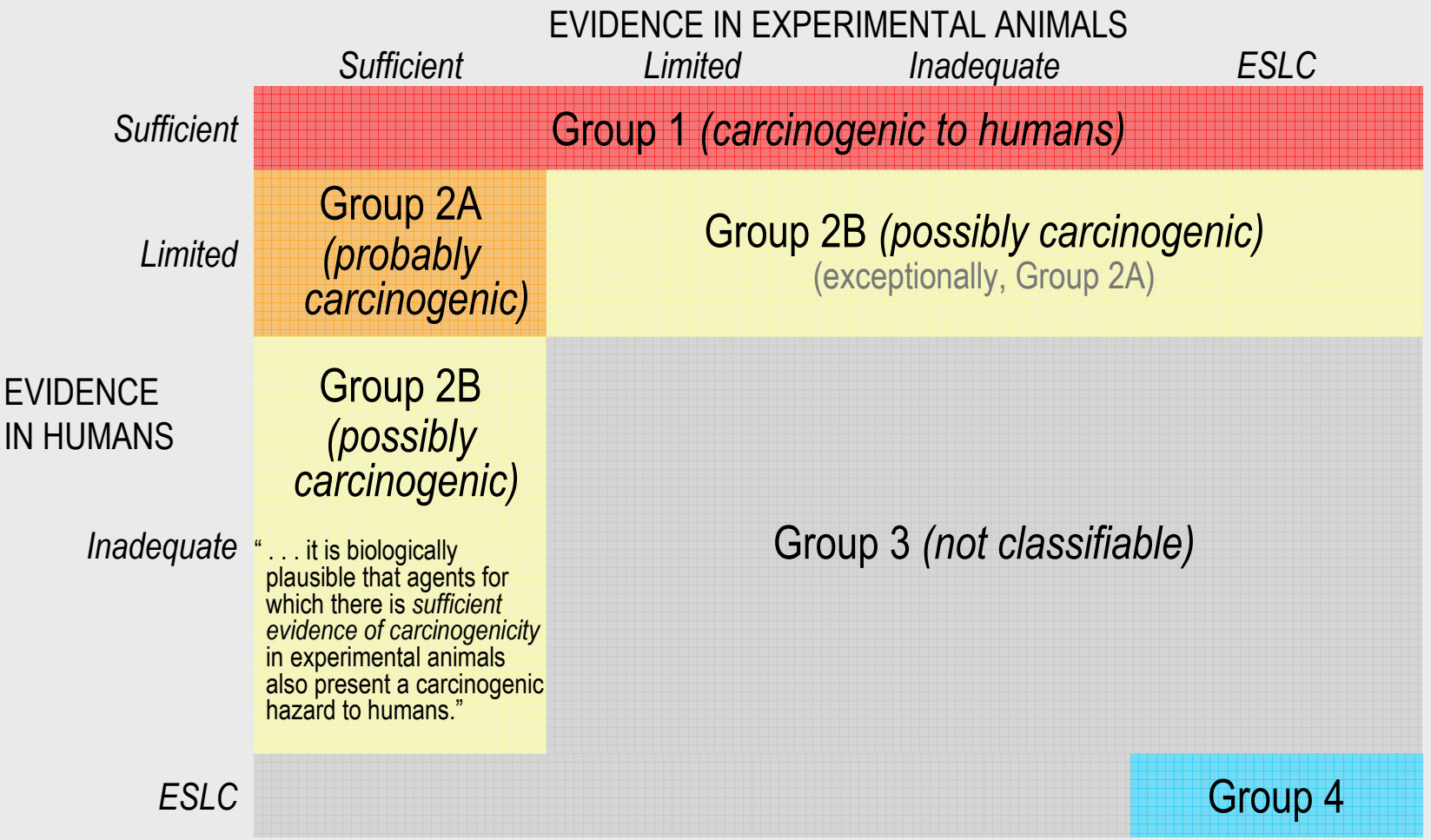
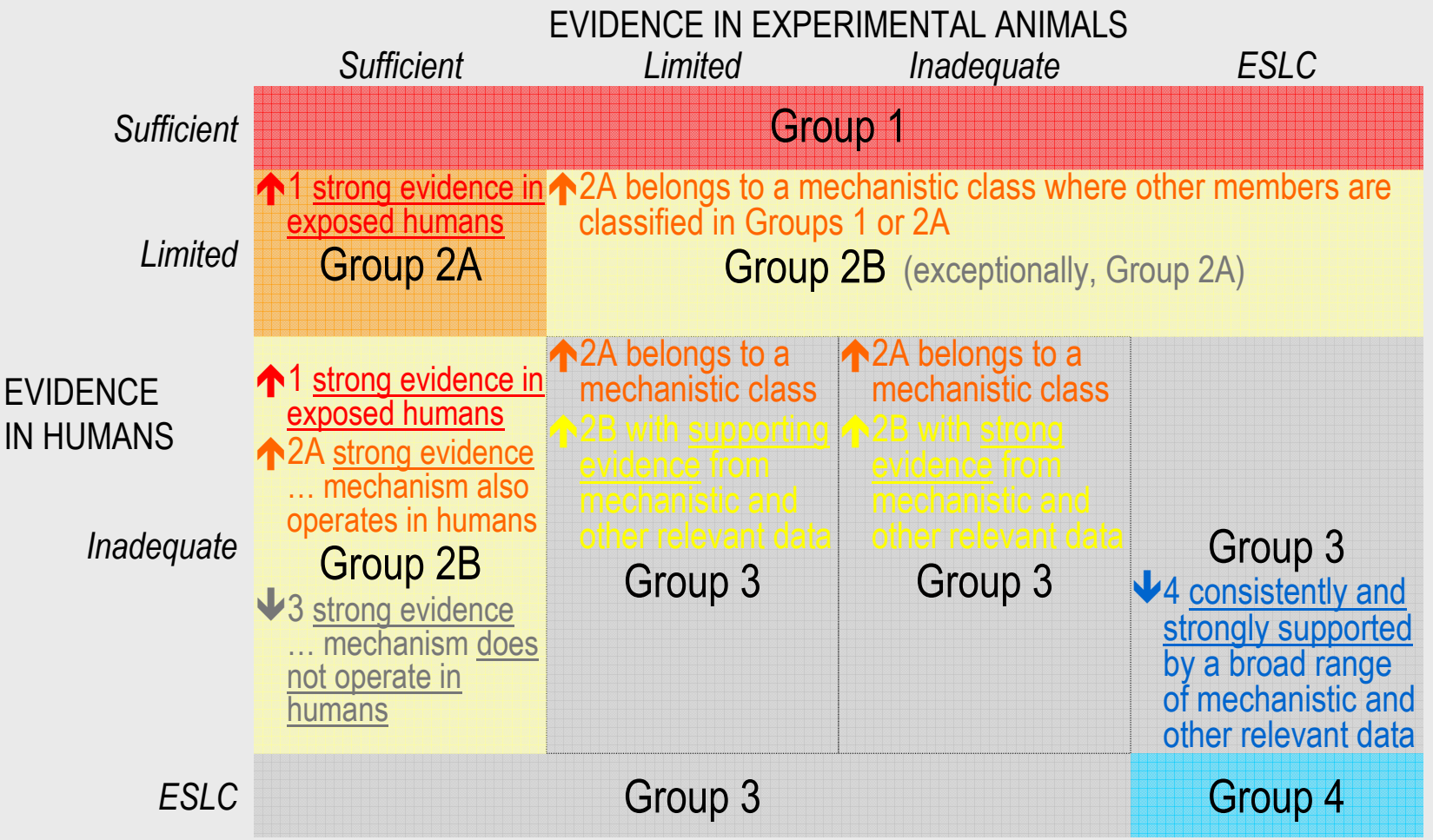
Overview of IARC classifications



Mechanistic data can be pivotal when the human data are not conclusive



"The categorization of an agent is a matter of scientific judgement . . ."

"It is recognized that the criteria for these evaluations cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate."

— Preamble, Part B, Section 6

"These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency)."

— Preamble, Part B, Section 6

"The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher."

— Preamble, Part A, Section 2

Volume 100:
A Review of Human Carcinogens

Objectives

- Update the critical review for each Group-1 carcinogen
- Identify tumour sites with *sufficient evidence*
- Identify established and likely mechanistic events

Volume 100 is being developed in six parts

A. *Pharmaceuticals* (Oct 2008)
B. *Biological Agents* (Feb 2009)
C. *Metals, Arsenic, Dusts and Fibres* (Mar 2009)
D. *Radiation* (June 2009)
E. *Personal Habits and Household Exposures* (Sept 2009)
F. *Chemical Agents and Related Occupations* (Oct 2009)

Volume 100:
Subsequent scientific publications

Volume 100 will provide information for two scientific publications that will promote new approaches to carcinogen identification

Tumour Concordance between Animals and Humans

- Increase understanding of the correspondence across species
- Where did animals provide an early warning about human carcinogens?

Mechanisms Involved in Human Carcinogenesis

- Increase understanding of how carcinogens act in the body
- Suggest susceptible populations and developmental stages
- Identify pre-cancerous biomarkers for preventive monitoring
- Identify mechanistic events that indicate a potential for carcinogenic activity
- How can we identify carcinogens without waiting until tumours have developed in humans?

Key points about IARC's approach

The *IARC Monographs* identify cancer hazards

- Hazard can be assessed with more confidence than risk
- Accurate estimation of risk can depend on understanding the role of multiple genetic and environmental risk factors and their interactions

The *IARC Monographs* use a graded approach to assessing the level of evidence

- This reflects how scientific evidence accumulates
- This is useful in communicating the level of evidence to general audiences

The *IARC Monographs* are encourage the use of mechanistic information

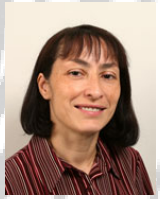
- Established and other likely mechanistic events are identified
- A cancer hazard can be identified based on mechanistic evidence alone

The *IARC Monographs* re-evaluate cancer hazards when new studies become available

Acknowledgements

IARC Monographs programme staff


Robert Baan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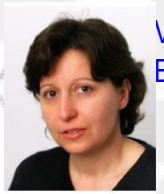
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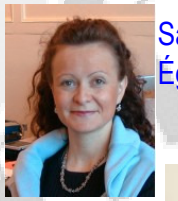
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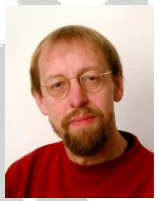
Kurt Straif

Other IARC scientists and support staff also contribute to the *Monographs*

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- European Commission, DG for Employment, Social Affairs and Equal Opportunities (since 1986)
- U.S. National Institute of Environmental Health Sciences (since 1992)
- U.S. Environmental Protection Agency (since 2001)