Identifying Chemicals That Cause Breast Cancer:

An International Perspective

Vincent James Cogliano, PhD

Head, *IARC Monographs* programme
International Agency for Research on Cancer
Lyon, France
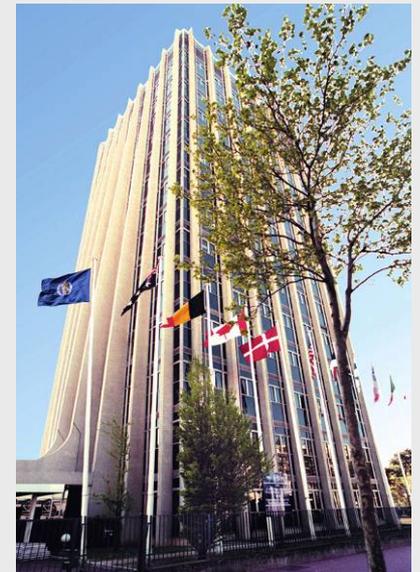
Overview

➢ The *IARC Monographs'* approach to identifying carcinogens

➢ How data on cancer mechanisms have been misused

➢ Some trends in cancer research and their implications for identifying chemicals that can cause breast cancer

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

➢ <u>Critical review</u> of all pertinent epidemiologic studies and animal bioassays, plus representative mechanistic data

➢ <u>Evaluation</u> of the weight of the evidence that the agent can alter the risk of cancer in humans

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

➢ Experts are selected based on knowledge and experience, and absence of conflicting interests

➢ No interference is tolerated at *Monograph* meetings

The *Monographs* are a worldwide endeavour that since 1971 has involved over 1000 scientists from 51 countries

"The encyclopaedia of carcinogens"
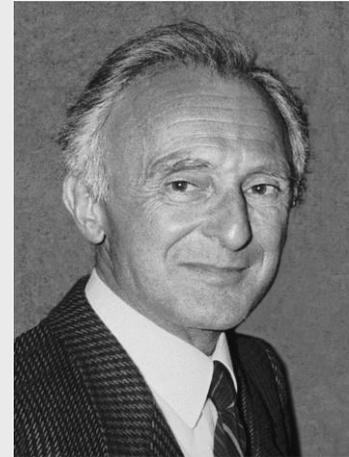
The *IARC Monographs* evaluate

> ➢ Chemicals agents and complex mixtures
> ➢ Occupational exposures
> ➢ Physical and biological agents
> ➢ Lifestyle factors

More than 900 agents have been evaluated

> ➢ 107 are *carcinogenic to humans* (Group 1)
> ➢ 61 are *probably carcinogenic to humans* (Group 2A)
> ➢ 247 are *possibly carcinogenic to humans* (Group 2B)

National and international health agencies use the *Monographs*

> ➢ As a source of information on known or suspected carcinogens
> ➢ As scientific support for their actions to prevent exposure to known or suspected carcinogens

Dr Lorenzo Tomatis
Founder, *IARC Monographs*
1929-2007

Evaluation of the weight of the evidence

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 <u>established</u> and <u>likely</u> mechanistic events:

- 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

Cancer in humans	Cancer in experimental animals	Mechanistic and other relevant data

– Preamble Part B, Section 6(a)

☐ *Sufficient evidence* — Causal relationship has been <u>established</u>
Chance, bias, and confounding <u>could be ruled out with reasonable confidence</u>

☐ *Limited evidence* — Causal interpretation is <u>credible</u>
Chance, bias, or confounding <u>could not be ruled out</u>

☐ *Inadequate evidence* — Studies permit <u>no conclusion</u> 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

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

Sufficient evidence
Causal relationship has been <u>established</u> through either:
- <u>Multiple positive results</u> (2 species, studies, sexes of GLP)
- <u>Single unusual result</u> (incidence, site/type, age, multi-site)

Limited evidence
Data <u>suggest</u> a carcinogenic effect but: *(e.g.)* single study, benign tumours only, promoting activity only

Inadequate evidence
Studies permit <u>no conclusion</u> 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

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

Identify <u>established</u> and <u>likely</u> mechanistic events:

– Are the mechanistic data "weak," "moderate," or "strong"?

Have the mechanistic events been established? Are there <u>consistent</u> results in <u>different</u> experimental systems? Is the overall database <u>coherent</u>?

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

– Is the mechanism likely to be operative in humans?

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

Note: an uneven level of support for different mechanisms may reflect only the resources focused on each one

All data 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*
- *Evidence suggesting lack of carcinogenicity*

Mechanistic and other relevant data

Identify <u>established</u> and <u>likely</u> mechanistic events:

- 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*

An overview of IARC's classifications

	EVIDENCE IN EXPERIMENTAL ANIMALS			
	Sufficient	*Limited*	*Inadequate*	*ESLC*
Sufficient	Group 1 *(carcinogenic to humans)*			
Limited	Group 2A *(probably carcinogenic)*	Group 2B *(possibly carcinogenic)* (exceptionally, Group 2A)		
Inadequate	Group 2B *(possibly carcinogenic)*	Group 3 *(not classifiable)*		
ESLC				Group 4

EVIDENCE IN HUMANS

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

EVIDENCE IN EXPERIMENTAL ANIMALS

	Sufficient	Limited	Inadequate	ESLC
Sufficient	Group 1			
Limited	↑1 <u>strong evidence in exposed humans</u> Group 2A	↑2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A Group 2B (exceptionally, Group 2A)		
EVIDENCE IN HUMANS **Inadequate**	↑1 <u>strong evidence in exposed humans</u> ↑2A <u>strong evidence</u> … mechanism also operates in humans Group 2B ↓3 <u>strong evidence</u> … mechanism <u>does not operate in humans</u>	↑2A belongs to a mechanistic class ↑2B with <u>supporting evidence</u> from mechanistic and other relevant data Group 3	↑2A belongs to a mechanistic class ↑2B with <u>strong evidence</u> from mechanistic and other relevant data Group 3	Group 3 ↓4 <u>consistently and strongly supported</u> by a broad range of mechanistic and other relevant data
ESLC	Group 3			Group 4

Organising mechanistic data: one proposed "Human Relevance Framework"

Start with an hypothesized mechanism for tumours in animals

Look for concordance (or lack) between animals and humans

| Bioassay exposure | → | Dose to target cells | → | Response at target cell | → | Later event | → | Later event | → | Animal tumour |

⇕ ⇕ ⇕ ⇕ ⇕

| Human exposure | → | Dose to target cells | → | Response at target cell | → | Later event | → | Later event | → | Human tumour ? |
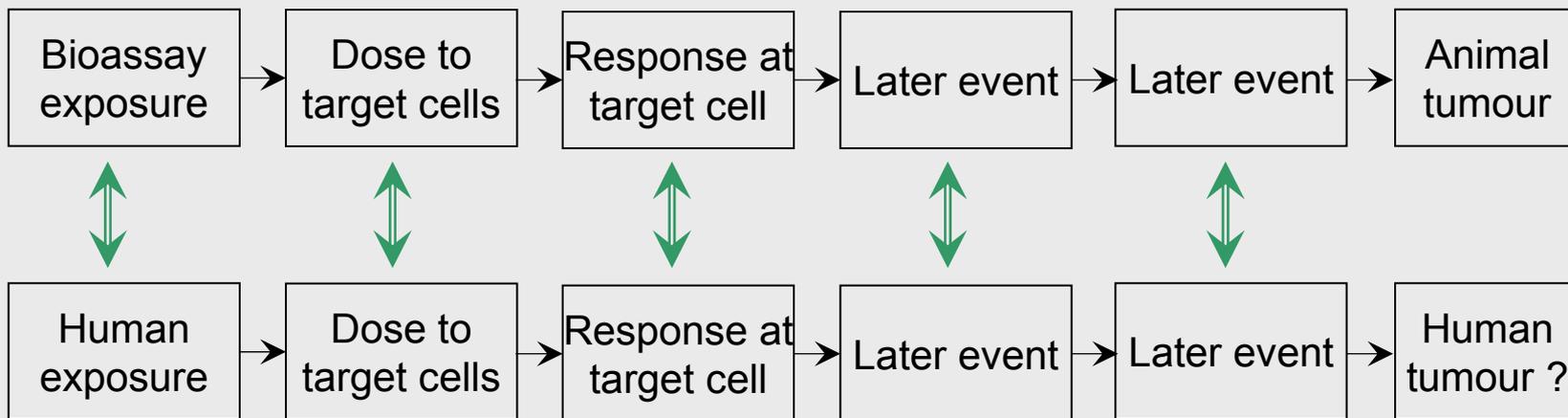
➢ Is there concordance for each structure or mechanistic event?
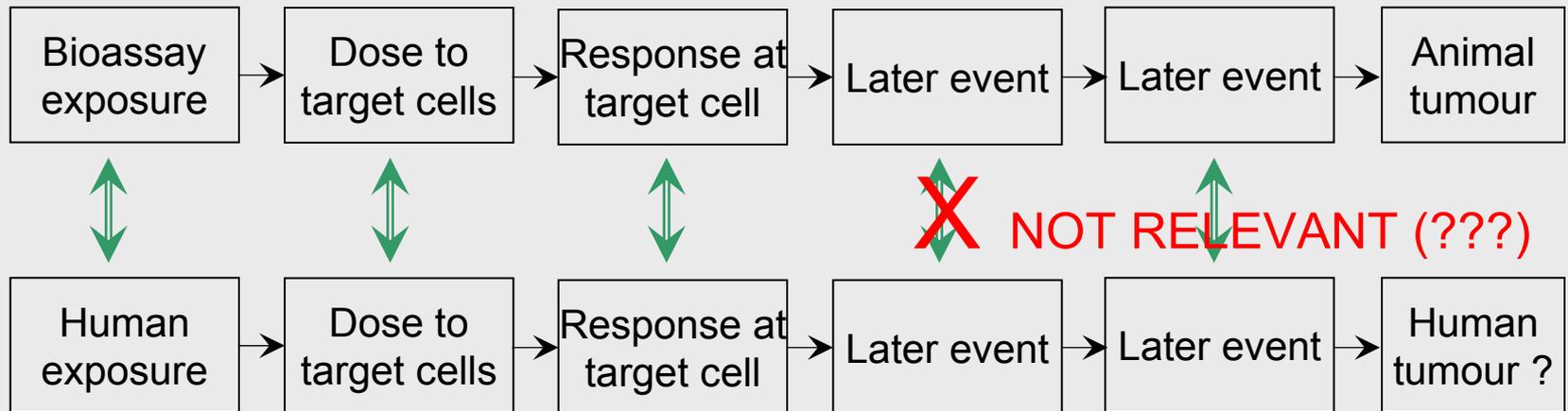➢ If so, how do rates compare between animals and humans?

Organising mechanistic data: one proposed "Human Relevance Framework"

Start with an hypothesized mechanism for tumours in animals

Look for concordance (or lack) between animals and humans

| Bioassay exposure | → | Dose to target cells | → | Response at target cell | → | Later event | → | Later event | → | Animal tumour |

✗ **NOT RELEVANT (???)**

| Human exposure | → | Dose to target cells | → | Response at target cell | → | Later event | → | Later event | → | Human tumour ? |

➤ Is there concordance for each structure or mechanistic event?

➤ If so, how do rates compare between animals and humans?

Discount relevance to humans if there is any lack of concordance!!!
– This goes beyond a framework . . . it's a biased decision rule –

We don't tolerate such faulty reasoning in other domains . . . an example

Objective: obtain a diamond pendant

There are several possible "modes of action"

- ➤ Buy one
- ➤ Find somebody who can buy one, then ask for it as a gift
- ➤ Find somebody wearing one, then steal it
- ➤ Steal one from a bank vault

We don't tolerate such faulty reasoning in other domains . . . an example

Objective: obtain a diamond pendant

There are several possible "modes of action"

➢ Buy one
➢ Find somebody who can buy one, then ask for it as a gift
➢ Find somebody wearing one, then steal it
➢ Steal one from a bank vault

Sequence of key events for stealing from a bank vault

– Enter building
– Disable alarm system
– Find vault room
– Enter vault room
– Open vault

We don't tolerate such faulty reasoning in other domains . . . an example

Objective: obtain a diamond pendant

There are several possible "modes of action"

- ➤ Buy one
- ➤ Find somebody who can buy one, then ask for it as a gift
- ➤ Find somebody wearing one, then steal it
- ➤ Steal one from a bank vault

Sequence of key events	Concordance with reality
– Enter building	√
– Disable alarm system	√
– Find vault room	√
– Enter vault room	√
– Open vault	X

We don't tolerate such faulty reasoning in other domains . . . an example

Objective: obtain a diamond pendant

There are several possible "modes of action"

- ➢ Buy one
- ➢ Find somebody who can buy one, then ask for it as a gift
- ➢ Find somebody wearing one, then steal it
- ➢ Steal one from a bank vault

Sequence of key events	Concordance with reality	
– Enter building	√	) How can
– Disable alarm system	√	) these events
– Find vault room	√	) not be
– Enter vault room	√	) relevant?
– Open vault	X	

Some trends in cancer research

The number of cancer bioassays has been falling

They are being replaced by shorter-term assays that study mechanistic events that may lead to cancer

Epidemiologic studies, too, are increasingly studying mechanistic events that precede the appearance of tumours

Such studies are both <u>faster</u> and <u>less expensive</u> than cancer bioassays or epidemiologic studies of cancer

And politically . . . pressures to reduce animal testing

- ➢ Ban on animal testing for cosmetic products in the EU
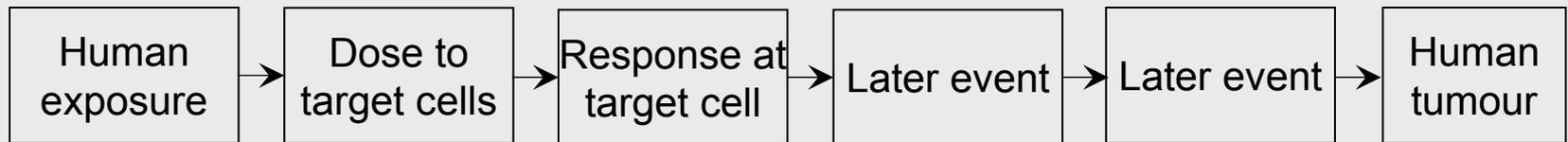- ➢ The REACH programme of the EU

A new paradigm for carcinogen identification

We must use mechanistic data to identify carcinogens and other health hazards

 ➢ Identify mechanistic events involved in human carcinogenesis
 ➢ Test to identify agents that can play a role in these events

| Human exposure | → | Dose to target cells | → | Response at target cell | → | Later event | → | Later event | → | Human tumour |

This raises the question, "What is a human carcinogen?"

 ➢ An agent that has been observed to cause human cancer?
　　　— OR —
 ➢ An agent that can increase the incidence of human cancer?

Can we identify carcinogens through mechanistic data alone . . . YES!

"In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of carcinogenicity in experimental animals."

— IARC Scientific Publication 147 (1999)

IARC has modified its guidelines to allow an agent to be classified as *possibly carcinogenic to humans* (Group 2B) solely on the basis of strong mechanistic evidence.

— Preamble to the *IARC Monographs* (2006)

What else must be done to get there?

New mechanistic approaches will need to be developed and validated

➢ Should these approaches try to predict animal bioassay results, or can we try to predict human carcinogenicity directly?

➢ What are the rates of false positives and false negatives?

New approaches will need to gain acceptance for use as support for regulatory actions – before phasing out current approaches

IARC Monographs Volume 100: *A Review of Human Carcinogens*

Objectives

➢ Update the critical review for each carcinogen in Group 1

➢ 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. *Lifestyle Factors* (Sept 2009)

F. *Chemicals and Related Occupations* (Oct 2009)

IARC Monographs Volume 100:
two subsequent scientific publications

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

Tumour Concordance between Animals and Humans

- ➤ Increase understanding of the correspondence across species
- ➤ Where could animal models have provided an early warning about human carcinogens?

Mechanisms Involved in Human Carcinogenesis

- ➤ Increase understanding of how carcinogens act in the body
- ➤ Identify pre-cancerous biomarkers for preventive monitoring
- ➤ Suggest susceptible populations and developmental stages
- ➤ How can we identify new carcinogens without waiting for tumours to develop in exposed humans?

What chemicals has IARC identified as causes of breast cancer?

Sufficient evidence for breast cancer in humans

- ➢ Estrogen-progestogen menopausal therapy
- ➢ Estrogen-progestogen contraceptives
- ➢ Diethylstilbestrol (DES)
- ➢ Alcoholic beverages

Limited evidence for breast cancer in humans

- ➢ Estrogen-only menopausal therapy

And interestingly . . .

- ➢ Shiftwork that includes nightwork (*limited evidence* in humans)

We must use mechanistic studies to identify other causes of breast cancer

These agents generally act through hormonal mechanisms

- ➢ DES
- ➢ Estrogen
- ➢ Progestogens

Alcohol's effect on breast cancer is thought to be hormonal rather than due to formation of acetaldehyde, the metabolite implicated in cancers of the oral cavity and esophagus

Nightwork leads to suppression of melatonin production and disregulation of circadian genes

How will we identify other hormonally active chemicals with a potential to contribute to breast cancer development?

Acknowledgements

IARC Monographs programme staff
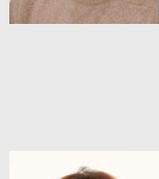
Robert Baan

Lamia Benbrahim-Tallaa

Véronique Bouvard

Sandrine Égraz

Fatiha El Ghissassi

Crystal Freeman

Laurent Galichet

Yann Grosse

Neela Guha

Anne-Sophie Hameau

Helene Lorenzen-Augros

Dorothy Russell

Béatrice Secretan

Kurt Straif

The *IARC Monographs* are supported by grants from

➢ U.S. National Cancer Institute (since 1982)

➢ European Commission, Employment and Social Affairs (since 1986)

➢ U.S. National Institute of Environmental Health Sciences (since 1992)

➢ U.S. Environmental Protection Agency (since 2001)