Identifying Chemicals That Cause Breast Cancer:

An International Perspective

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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

- Critical review of all pertinent epidemiologic studies and animal bioassays, plus representative mechanistic data
- Evaluation 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
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 established and likely 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

- 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

<table>
<thead>
<tr>
<th>Cancer in humans</th>
<th>Cancer in experimental animals</th>
<th>Mechanistic and other relevant data</th>
</tr>
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<td>– Preamble Part B, Section 6(b)</td>
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### Causal relationship has been established through either:
- **Sufficient evidence**
  - Multiple positive results (2 species, studies, sexes of GLP)
  - Single unusual result (incidence, site/type, age, multi-site)

### Data suggest a carcinogenic effect but:
- **Limited evidence**
  - (e.g.) single study, benign tumours only, promoting activity only

### Studies permit no conclusion about a carcinogenic effect
- **Inadequate evidence**

### Adequate studies in at least two species show that the agent is not carcinogenic
- **Evidence suggesting lack of carcinogenicity**
  - Conclusion is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied
Evaluating mechanistic and other data

Identify established and likely mechanistic events:

- 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

— Preamble Part B, Section 6(c)
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
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- Inadequate evidence
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An overview of IARC’s classifications

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<tr>
<th>Evidence in Experimental Animals</th>
<th>Sufficient</th>
<th>Limited</th>
<th>Inadequate</th>
<th>ESLC</th>
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<tr>
<td>Sufficient</td>
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</tr>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Group 2A (probably carcinogenic)</td>
<td></td>
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<tr>
<td>Group 2B (possibly carcinogenic)</td>
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Mechanistic data can be pivotal when the human data are not conclusive.

**EVIDENCE IN EXPERIMENTAL ANIMALS**

- **Sufficient**
  - Group 1
    - 1 strong evidence in exposed humans
    - 2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A

- **Limited**
  - Group 2A
    - 1 strong evidence in exposed humans
    - 2A belongs to a mechanistic class
  - Group 2B (exceptionally, Group 2A)
    - 2A with supporting evidence from mechanistic and other relevant data

- **Inadequate**
  - Group 2B
    - 1 strong evidence in exposed humans
    - 2A with supporting evidence from mechanistic and other relevant data
    - 3 strong evidence... mechanism also operates in humans

- **ESLC**
  - Group 3
    - 1 strong evidence in exposed humans
    - 2A with strong evidence from mechanistic and other relevant data
  - Group 4
    - 4 consistently and strongly supported by a broad range of mechanistic and other relevant data

**EVIDENCE IN HUMANS**

- **Sufficient**
  - Group 2A
    - 1 strong evidence in exposed humans
    - 2A belongs to a mechanistic class

- **Limited**
  - Group 2B
    - 1 strong evidence in exposed humans
    - 2A with supporting evidence from mechanistic and other relevant data

- **Inadequate**
  - Group 3
    - 1 strong evidence in exposed humans
    - 2A with supporting evidence from mechanistic and other relevant data
    - 3 strong evidence... mechanism does not operate in humans

- **ESLC**
  - Group 4
    - 4 consistently and strongly supported by a broad range of mechanistic and other relevant data
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

- Is there concordance for each structure or mechanistic event?
- If so, how do rates compare between animals and humans?
Start with an hypothesized mechanism for tumours in animals

Look for concordance (or lack) between animals and humans

- 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

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Sequence of key events for stealing from a bank vault

- Enter building
- Disable alarm system
- Find vault room
- Enter vault room
- Open vault
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Sequence of key events

<table>
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<th>Event</th>
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<tbody>
<tr>
<td>Enter building</td>
<td>✓</td>
</tr>
<tr>
<td>Disable alarm system</td>
<td>✓</td>
</tr>
<tr>
<td>Find vault room</td>
<td>✓</td>
</tr>
<tr>
<td>Enter vault room</td>
<td>✓</td>
</tr>
<tr>
<td>Open vault</td>
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(How can) these events not be relevant?
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 faster and less expensive 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

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?*
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