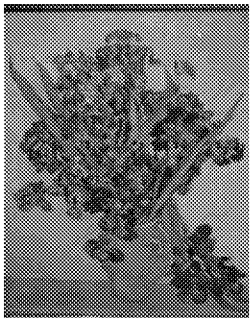
The Key Characteristics of Carcinogens



Vincent Cogliano

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Office of Research and Development
U.S. Environmental Protection Agency
Washington DC

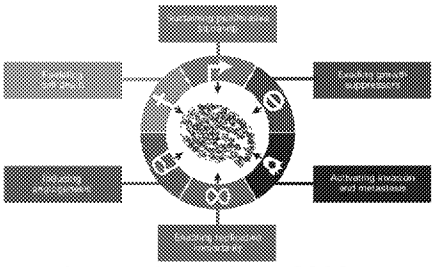
This talk does not necessarily represent the views or policies of the U.S. Environmental Protection Agency

Why Do We Need Key Characteristics?

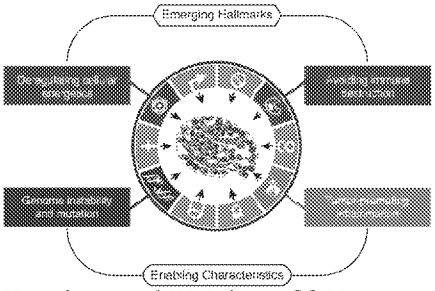
There is no broadly accepted systematic method for identifying, organizing, and summarizing mechanistic data

Mechanistic studies, compared to human and whole-animal studies, can be overwhelming in number

Hallmarks of Cancer (Cells)



Hanahan and Weinberg 2000



Hanahan and Weinberg 2011

Capabilities acquired by cancer cells that enable tumor growth and metastatic dissemination

- Sustaining proliferative signaling
- Evading growth suppressors
- Resisting cell death
- Enabling replicative immortality
- Inducing angiogenesis
- Activating invasion and metastasis

Emerging Hallmarks

- Reprogramming energy metabolism
- Evading immune destruction

Enabling Characteristics

- Genome instability and mutation
- Tumor-promoting inflammation

The Tumor Microenvironment

Cancer Cells . . . or Carcinogens?

The Hallmarks are characteristics of cancer cells, not of agents that cause cancer

It is useful to identify the characteristic properties of carcinogenic agents

IARC began this effort in 2012, building on the data for human carcinogens compiled and evaluated in *IARC Monographs* volume 100

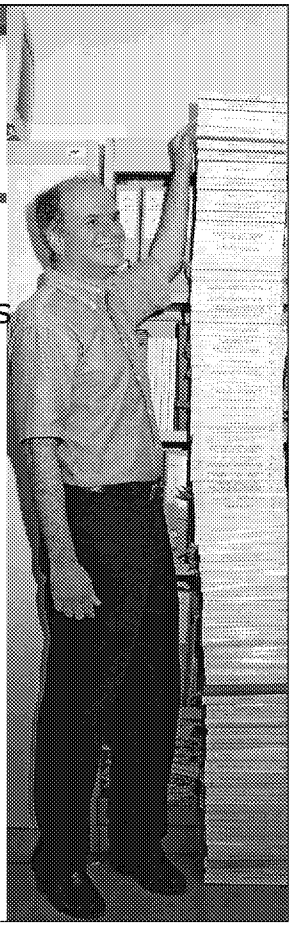
IARC Monographs Volume 100: *A Review of Human Carcinogens*

Objectives

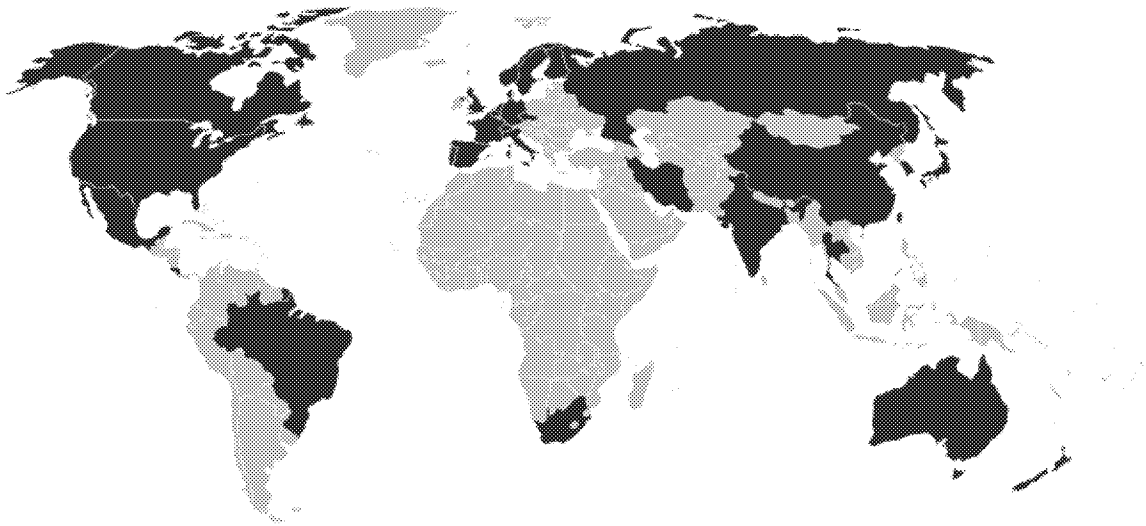
- Update reviews of the >100 human carcinogens
- Identify tumour sites with *sufficient evidence*
- Identify *established* & *likely* mechanistic events

Developed over six meetings, 160 scientists

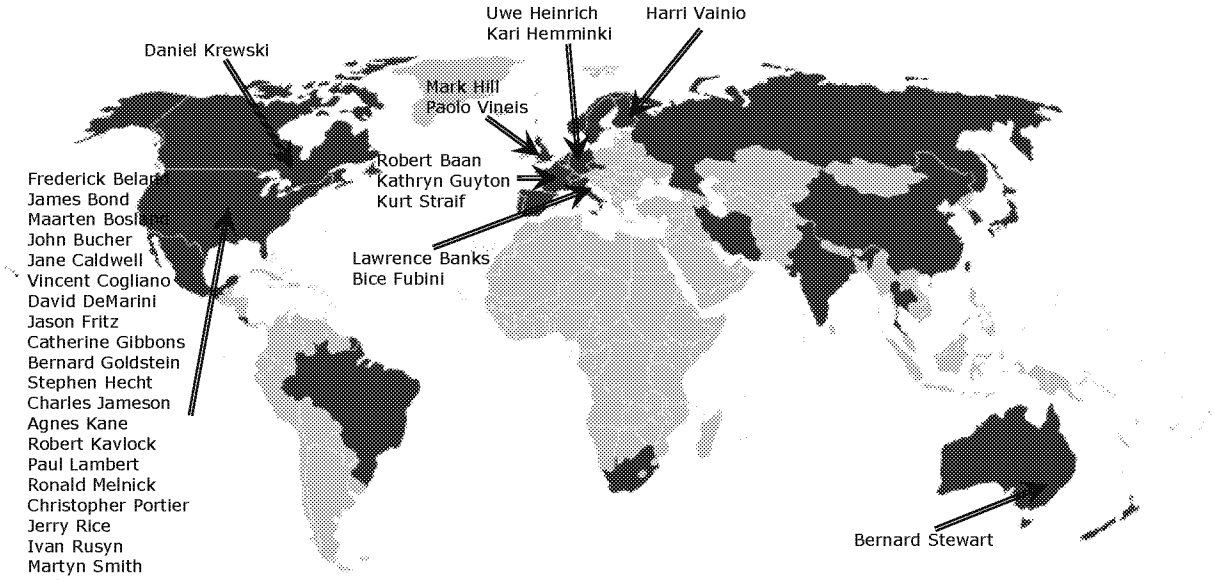
A. *Pharmaceuticals*
B. *Biological Agents*
C. *Metals, Dusts and Fibres*
D. *Radiation*
E. *Personal Habits and Household Exposures*
F. *Chemical Agents and Related Occupations*



Volume 100: 160 Scientists, 29 Countries

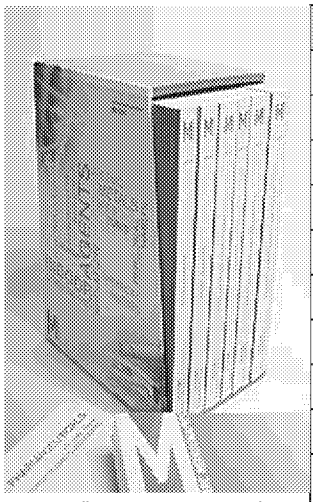


Key Characteristics: 36 Scientists, 8 Countries



Frederick Bela
James Bond
Maarten Bosla
John Bucher
Jane Caldwell
Vincent Cogliano
David DeMarini
Jason Fritz
Catherine Gibbons
Bernard Goldstein
Stephen Hecht
Charles Jameson
Agnes Kane
Robert Kavlock
Paul Lambert
Ronald Melnick
Christopher Portier
Jerry Rice
Ivan Rusyn
Martyn Smith
Leslie Stayner
Robert Ullrich
Michael Waalkes
Lauren Zeise

IARC's 10 Key Characteristics of Human Carcinogens

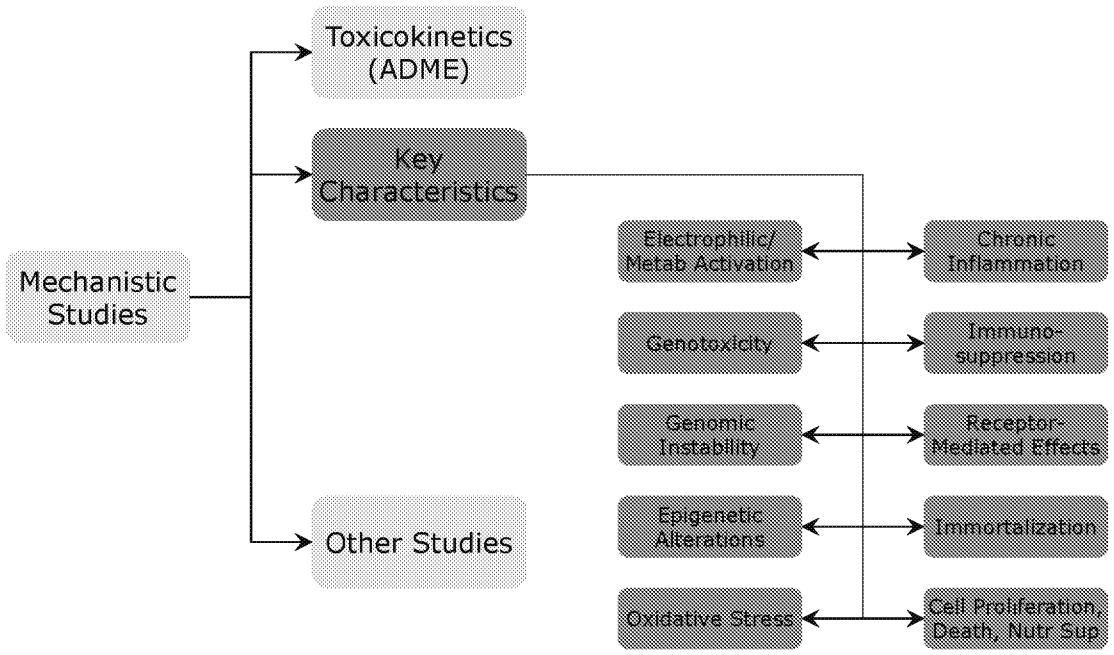


IARC Monographs
Volume 100

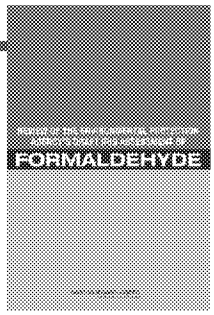
Key characteristic
1. Electrophilic or can be metabolically activated
2. Is genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces epigenetic alterations
5. Induces oxidative stress
6. Induces chronic inflammation
7. Is immunosuppressive
8. Modulates receptor-mediated effects
9. Causes immortalization
10. Alters cell proliferation, cell death, or nutrient supply

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K (2016) *Environmental Health Perspectives* 124(6): 713–721

1. Using the Key Characteristics To Search and Sort the Mechanistic Database



Systematic Review

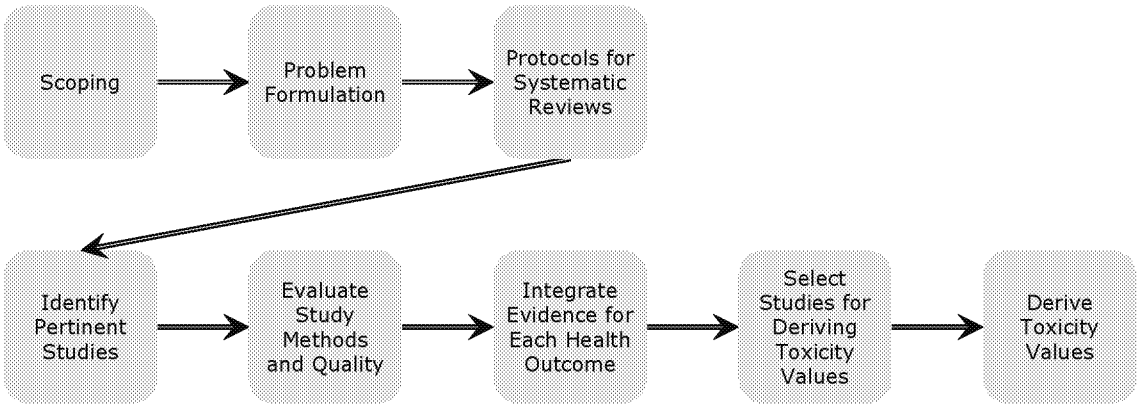


Systematic Review is an approach that promotes objectivity and transparency in syntheses of published research

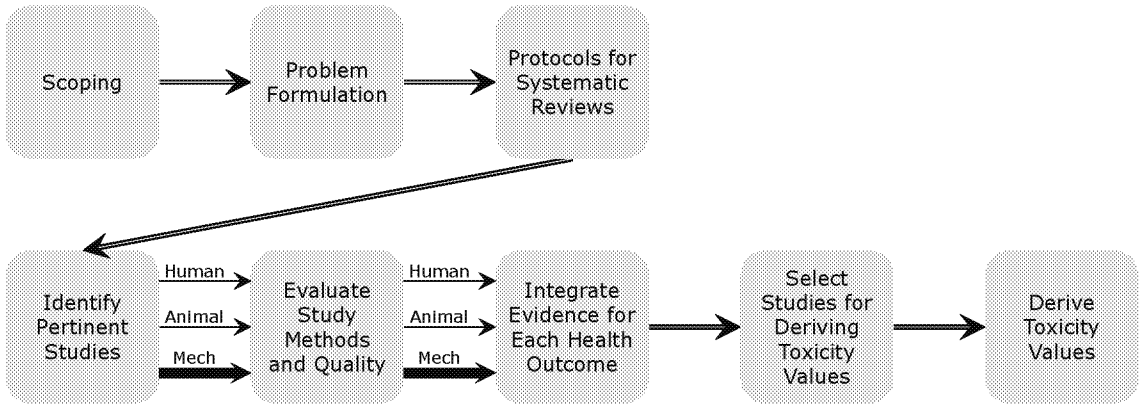
Identify Pertinent Studies → Evaluate Study Methods and Quality → Integrate Evidence for Each Health Outcome → Select Studies for Deriving Toxicity Values → Derive Toxicity Values

NRC (2011) *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*

Planning a Systematic Review

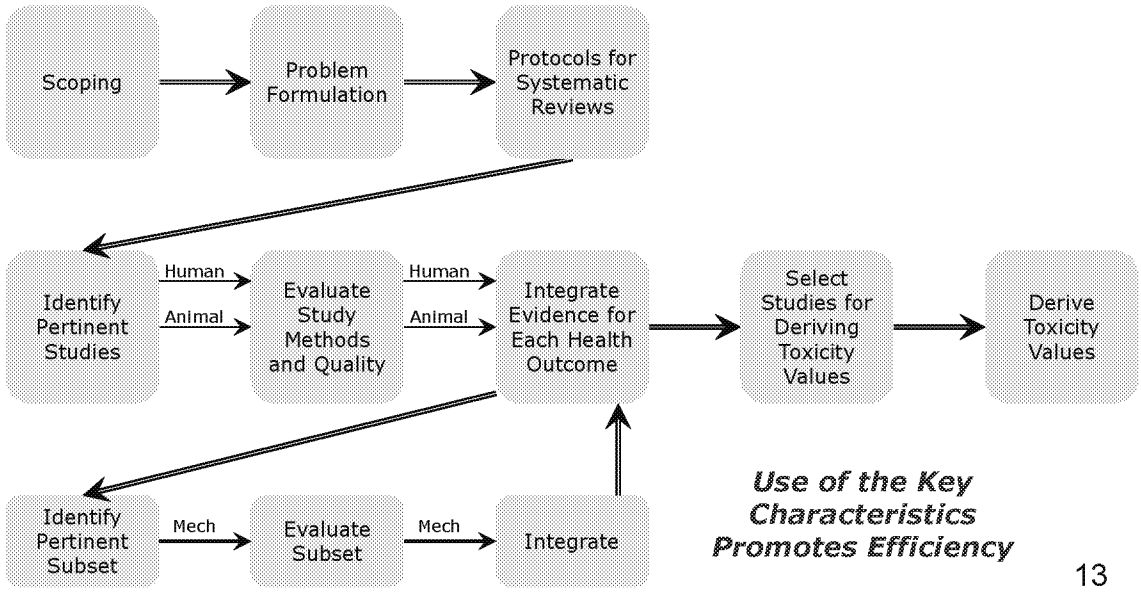


Critical Analysis of Available Information



Some Have Suggested That These Steps Proceed in Parallel for All Study Types

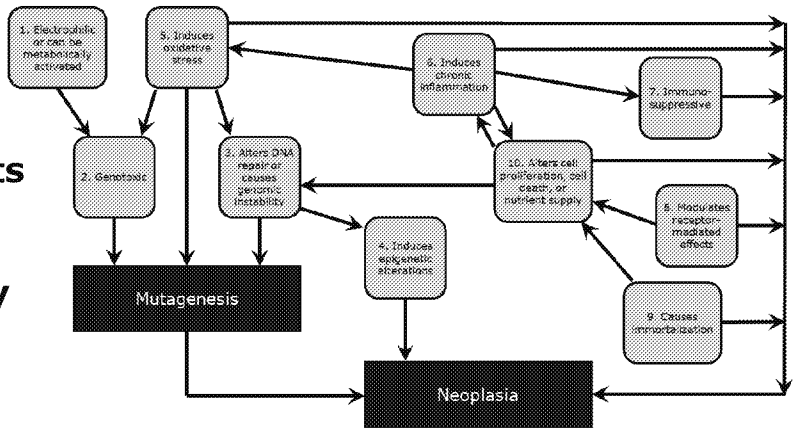
Pertinent Critical Analysis of ~~Available~~ Information



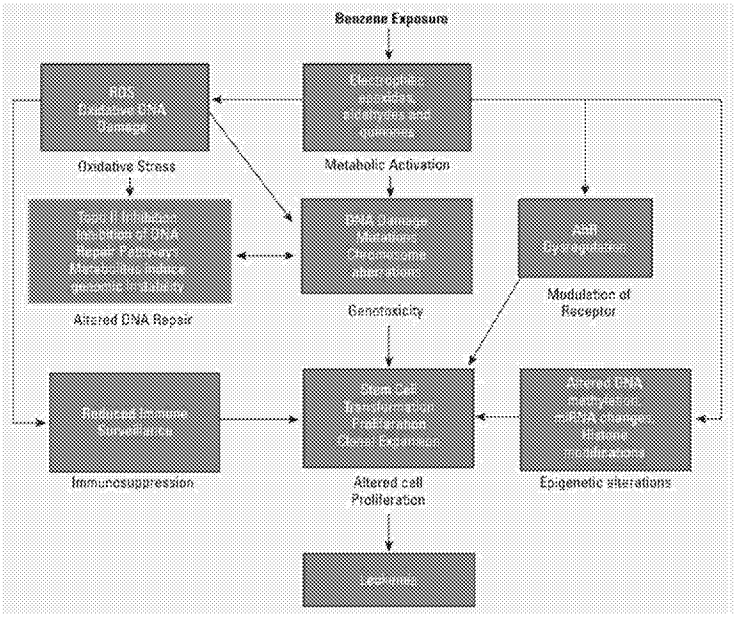
Use of the Key Characteristics Promotes Efficiency

2. Using the Key Characteristics To Identify Mechanistic Pathways

1. Identify pertinent studies
2. Screen and organize results
3. Synthesize the data to identify and evaluate pathways

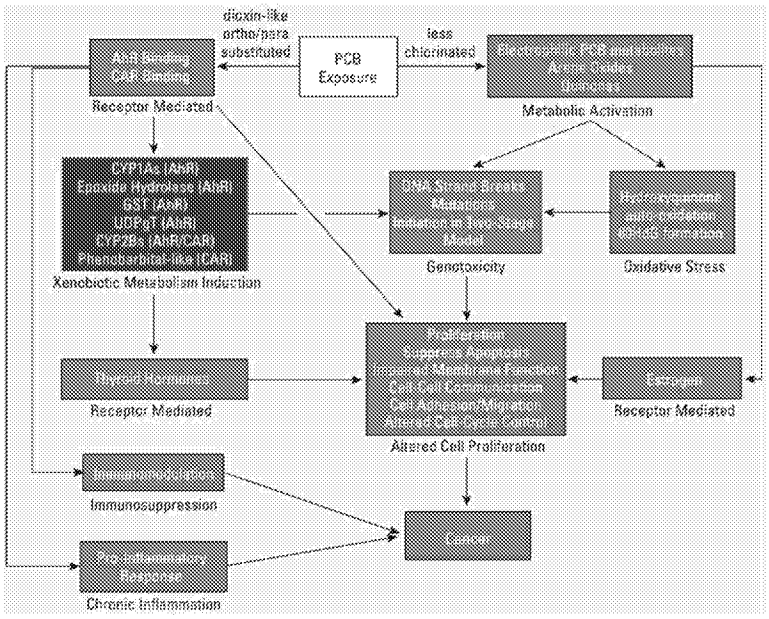


Example: Benzene



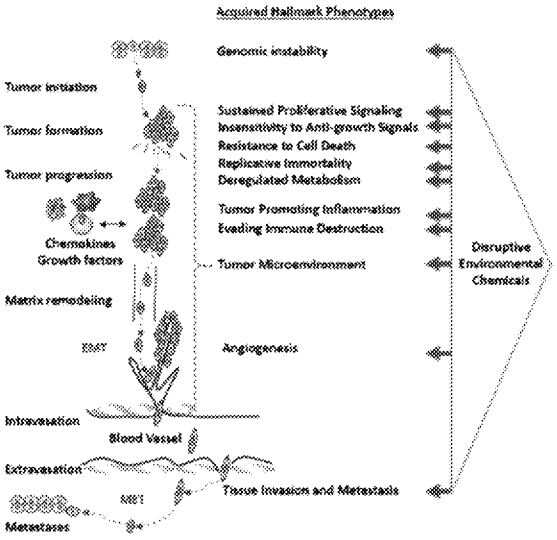
Smith MT et al (2016) *Environmental Health Perspectives* 124(6): 713–721

Example: PCBs



Smith MT et al (2016) *Environmental Health Perspectives* 124(6): 713–721

Pathways Can Involve Multiple Agents



Goodson WH III et al (2015) *Carcinogenesis* 36(suppl 1): S254–S296

" . . . some of the acquired hallmark phenotypes are known to be involved in many stages of disease development, but the precise sequencing of the acquisition of these hallmarks and the degree of involvement that each has in carcinogenesis are factors that have not yet been fully elucidated/defined."

" . . . a series of complementary exposures acting in concert might prove to be far more carcinogenic than predictions related to any single exposure might suggest. Interacting contributors need not act simultaneously or continuously, they might act sequentially . . ."

Some Closing Thoughts

The Key Characteristics provide an objective, systematic approach to

- Efficient sorting and analysis of mechanistic data
- Identification of mechanistic pathways

They show that carcinogens act through multiple mechanisms

Analysis of mechanistic pathways can identify data gaps that can be filled with high-throughput and other assays

Thank you!