IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Advisory Group to Recommend an Update to the Preamble
Scientific Webinar, 15:00 – 18:00 (CEST), 17 September 2018

Compilation of presenters' slides

Agenda

15:00 – 15:05	Introduction from IARC Secretariat
15:05 – 15:15	Bice Fubini, University of Turin, Italy
15:15 – 15:25	Sabine Francke, U.S. Food and Drug Administration, USA
15:25 – 15:35	Nathaniel Rothman, National Cancer Institute (NCI), USA
15:35 – 15:45	Bernard Stewart, School of Women's & Children's Health, UNSW Australia Julie Goodman,
15:45 – 15:55	Gradient, USA
15:55 –16:05	Daniele Wikoff, ToxStrategies, USA
16:05 – 16:15	Jen Sass, Natural Resources Defence Council (NDRC), USA (oral presentation)
16:15 – 16:25	Tracey Woodruff, University of California, USA
16:25 – 16:35	Martyn Smith, University of California, Berkeley School of Public Health, USA
16:35 – 16:45	Elaine Faustman, Department of Environmental and Occupational Health Sciences, University of Washington, USA
16:45 – 16:55	David Christiani, Harvard Chan School of Public Health, United States [pre-recorded presentation]
16:55 – 17:05	Ron Melnick, NIEHS, USA
17:05 – 17:15	John E. French, UNC Gillings School of Global Public Health, University of North Carolina, USA
17:15 – 17:25	Paul Lambert, University of Wisconsin, USA
17:25 – 17:35	John Cherrie, Heriot-Watt University, United Kingdom
17:35 – 17:45	Paul Demers, Occupational Cancer Research Centre Toronto, Canada
17:45 – 17:50	Dana Loomis, University of Nevada, USA
17:50 – 18:00	Q & A and Wrap up

Please click on the name of the presenter to access the corresponding presentation

1 - Bice Fubini

IARC Preamble update

outline

Particles , fibers and foreign bodies

1 Peculiarity of agents acting in the solid state, particularly particles and fibers

Several chemical and physical properties to be indicated in section B1

2 Choice of the appropriate metric when comparing exposures in human data and doses in animal and in vitro cellular tests when comparing results obtained with different sources of the agent

The answer comes from mechanisms

3 Particles, dusts, fibers and foreign matter are not simple physical agents

4 Several physico chemical features and different reactive surface site involved in the carcinogenic mecchanism

Expected variability of hazard because of variability of all these features in different sources of the agent

# Particles , fibers and foreign bodies

Agents acting at the **solid state** – particles, fibers, foreign bodies - are different from chemical , physical or biological agents,   and should be mentioned separately in the list of agents (section B 1(a).

They act through their **exposed surface**, their **form/shape** end their **dimensions** Often all these factors contribute, at different stages of the pathogenic process, to the toxic response of cells and tissues.

Form, relative dimensions and, for particles and fibers, also **size distribution** and **specific surface** (extension of surface per unit mass), allow a precise definition of the agent. **Chemical composition** (s), whether mineral or material, mixture or single compound should be indicated
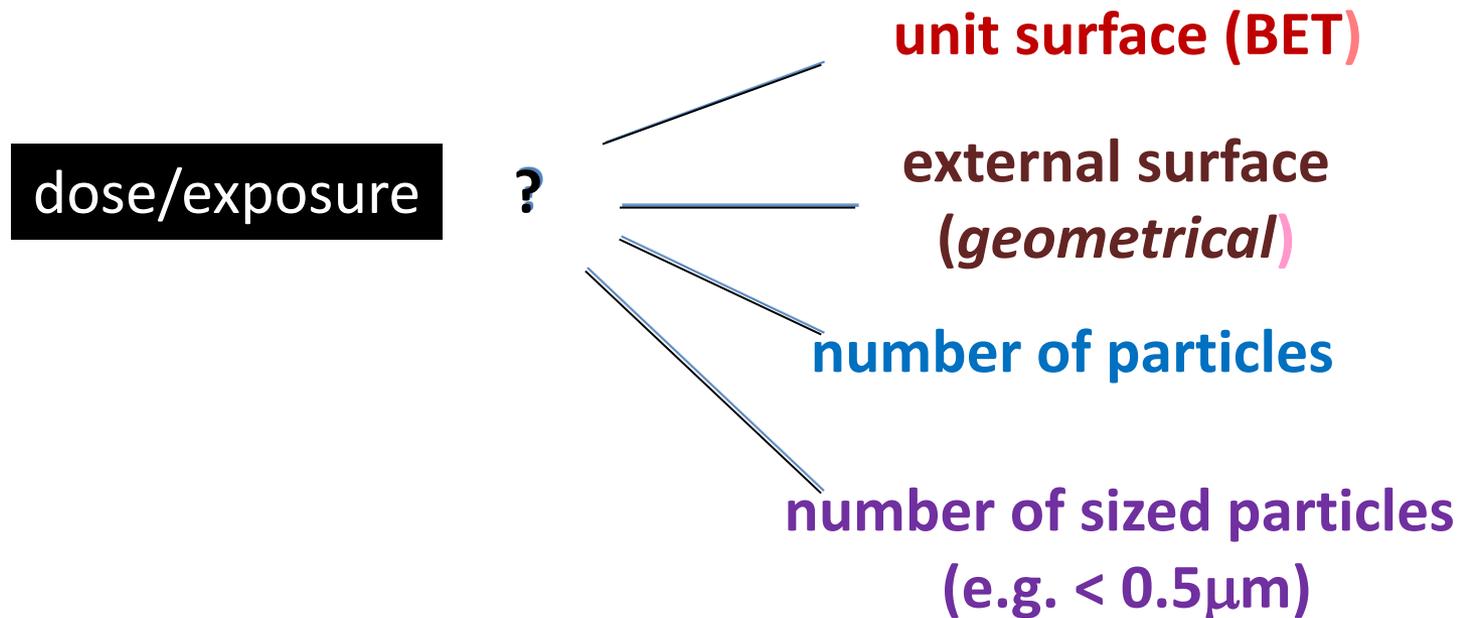
Particles and fibers mainly act as human carcinogens when inhaled, however when in the **nanosize range** penetrate through several body barriers, thus attaining various organs. The term *inhaled* in (section B 1(a) is thus presently too restrictive

Feedback from mechanisms for
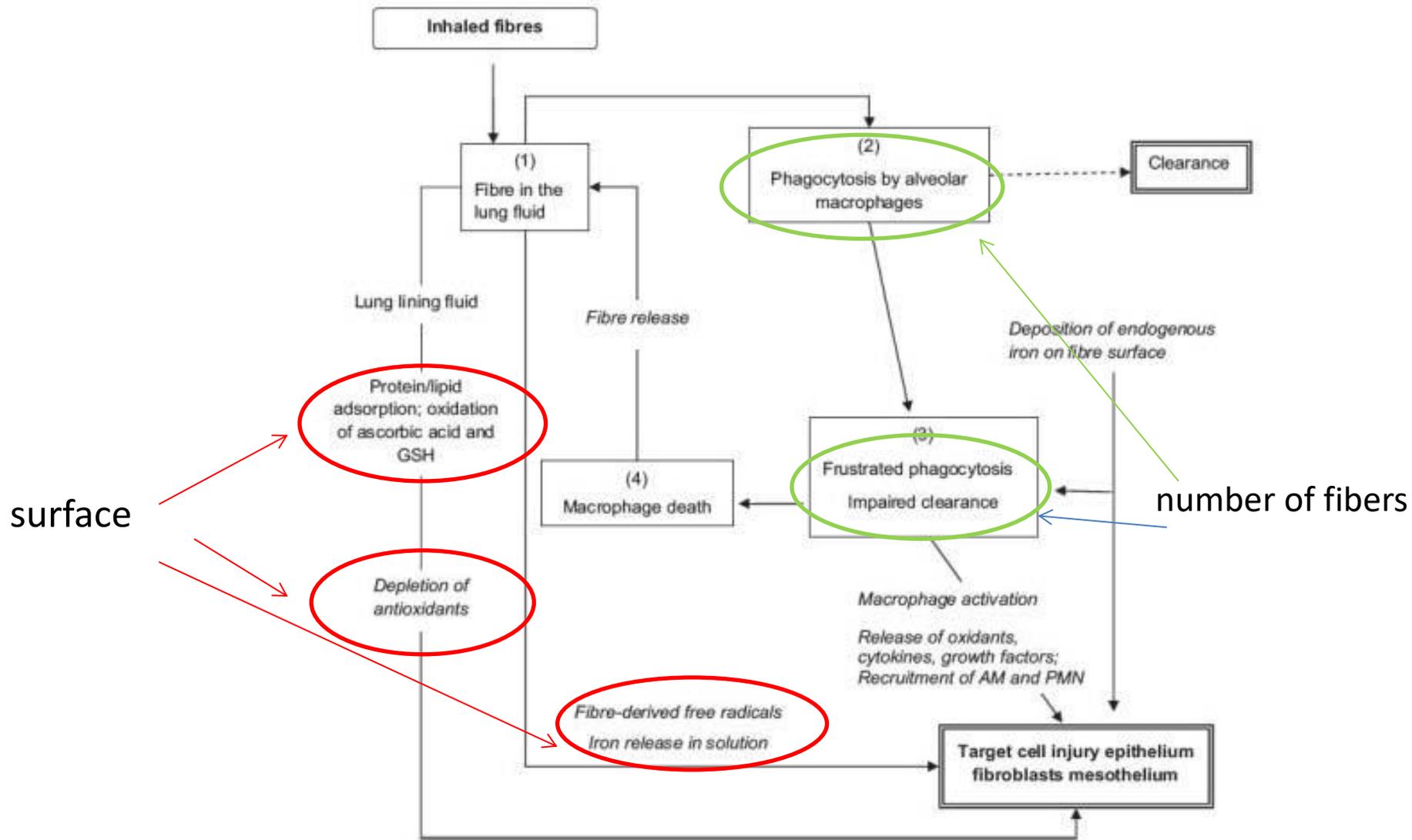dose evaluation in animal studies
and exposures in human studies
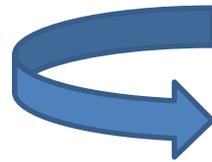
Particularly relevant
with nanomaterials

Metrics: which is the best unit to use when comparing **doses** (animal o in vitro cellular tests) or **exposures** (human data) of different sources of the agent? Mass?

dose/exposure ?

- unit surface (BET)
- external surface (*geometrical*)
- number of particles
- number of sized particles (e.g. < 0.5μm)

The mass is sufficient for "molecular" toxic agents but not for "particulate" toxic agents

asbestos

Inhaled fibres

(1) Fibre in the lung fluid

(2) Phagocytosis by alveolar macrophages → Clearance

Lung lining fluid

Fibre release

Protein/lipid adsorption; oxidation of ascorbic acid and GSH

(4) Macrophage death

(3) Frustrated phagocytosis — Impaired clearance

Deposition of endogenous iron on fibre surface

Depletion of antioxidants

Macrophage activation

Release of oxidants, cytokines, growth factors; Recruitment of AM and PMN

Fibre-derived free radicals — Iron release in solution

Target cell injury epithelium fibroblasts mesothelium

surface

number of fibers

IARC monograph 100c

A solid particle may comprise several characteristics – some chemical, some physical- which may act independently in different steps of the carcinogenic mechanism

From mechanisms the choice of the appropriate metric
for fibers and particles, often more than one has to be considered

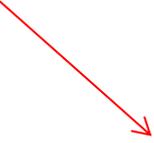3 Particles, dusts, fibers and foreign matter are not simple physical agents

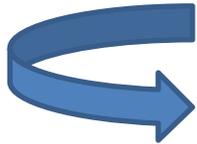The scientific community agrees that with particles and fibers three factors determine pathogenicity
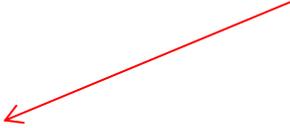
Size and shape   **Surface reactivity**   **Biopersistence**

Section 4, point (iii) " changes at the molecular level" page 25

*… Physical agents may also be considered to comprise foreign bodies …poorly soluble particles dust and particles….*

This limits the action to size and shape, without mentioning the chemical aspects linked to surface reactivity and biopersistence
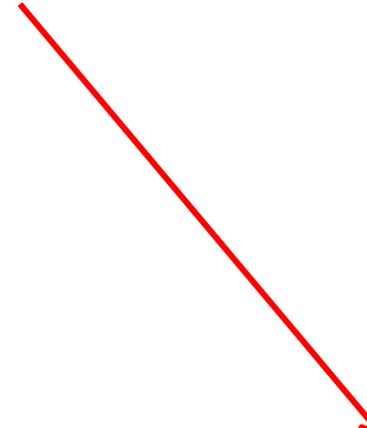
4 Hazard variability

adverse reactions originate at the **interface** between the surface of the agent and body fluids, cell membranes or tissues

The surface

The surface, two independent aspects: extention (physical feature) and surface reactivity, (chemical feature)
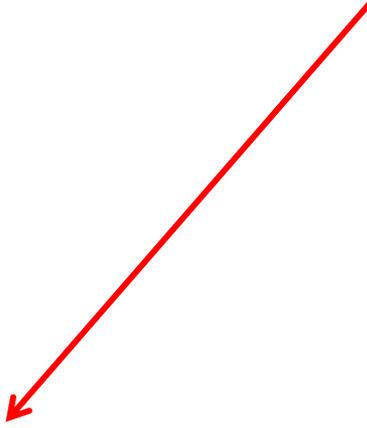
Specific surface: metric

Surface reactivity: generation of biochemical reaction upon contact with living matter

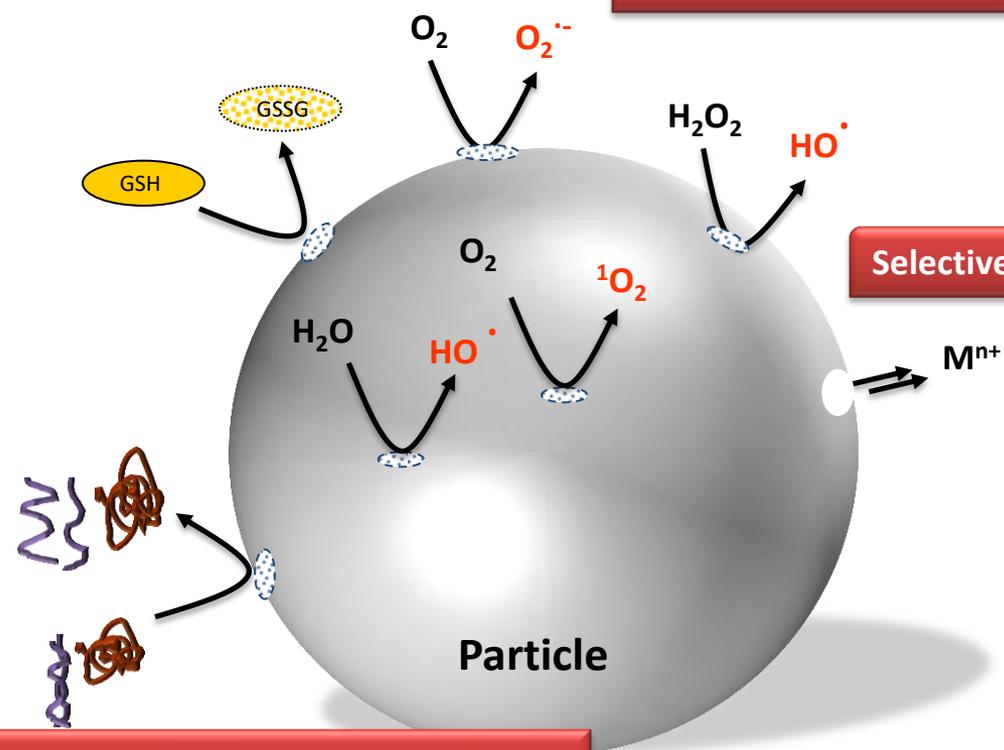On a single particle various kinds of reactive surface sites

Different surface sites give rise to different potentially adverse reactions
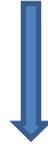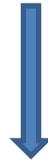
The relative abundance of surface sites may vary from one to another source
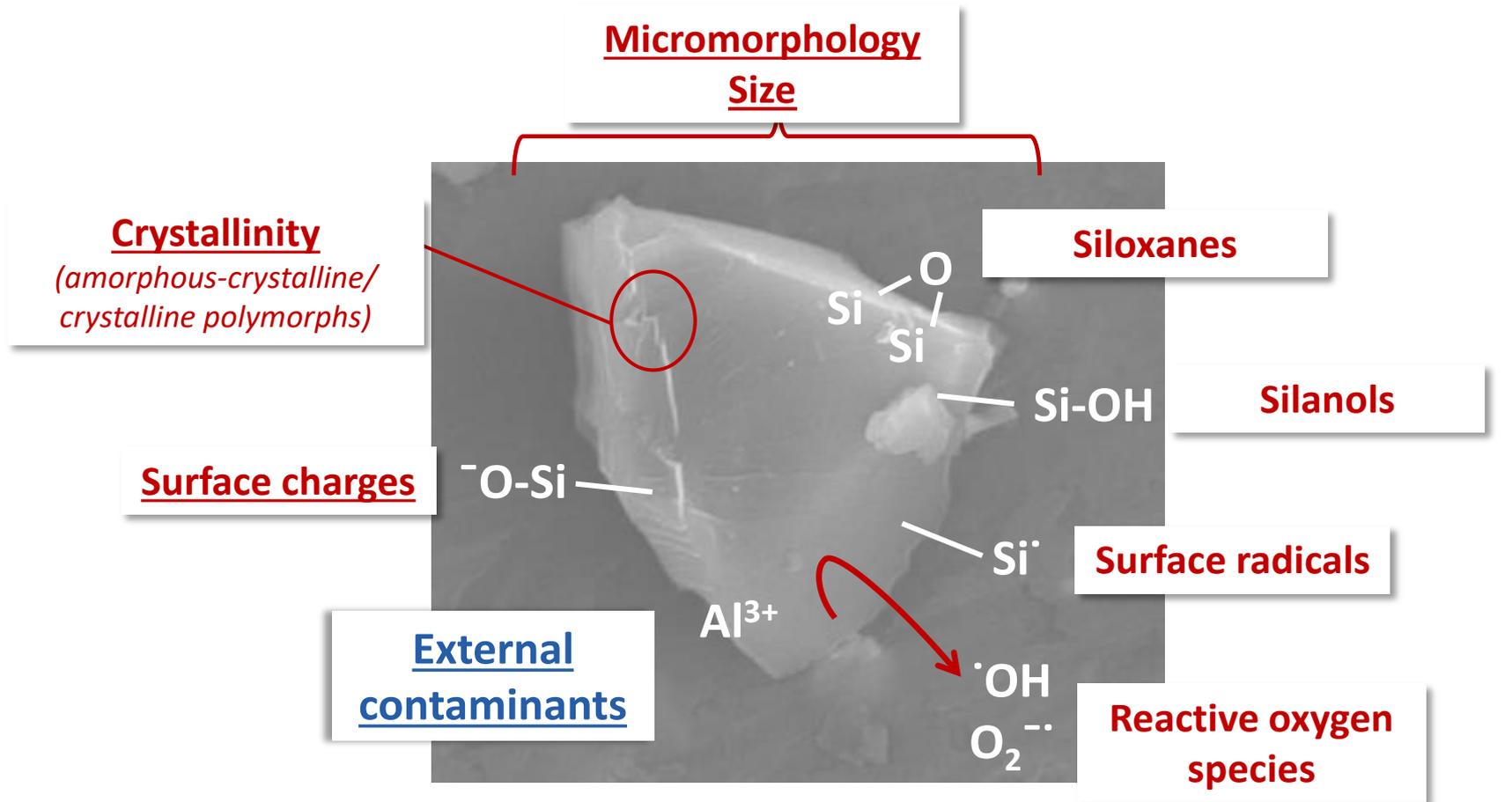
⬇

Great variability in the hazard related to solid agents

⬇

Take into account such possible differences when comparing studies

The physico-chemical bases of silica intrinsic variability

Large variety of physico-chemical features involved in the pathogenic process

Micromorphology
Size

Crystallinity
(amorphous-crystalline/
crystalline polymorphs)

Siloxanes

Silanols

Surface charges

Surface radicals

External contaminants

Reactive oxygen species

Variety of particles with different surface properties → reactivity → pathogenicity

Silica particles interact with living matter in several subsequent steps
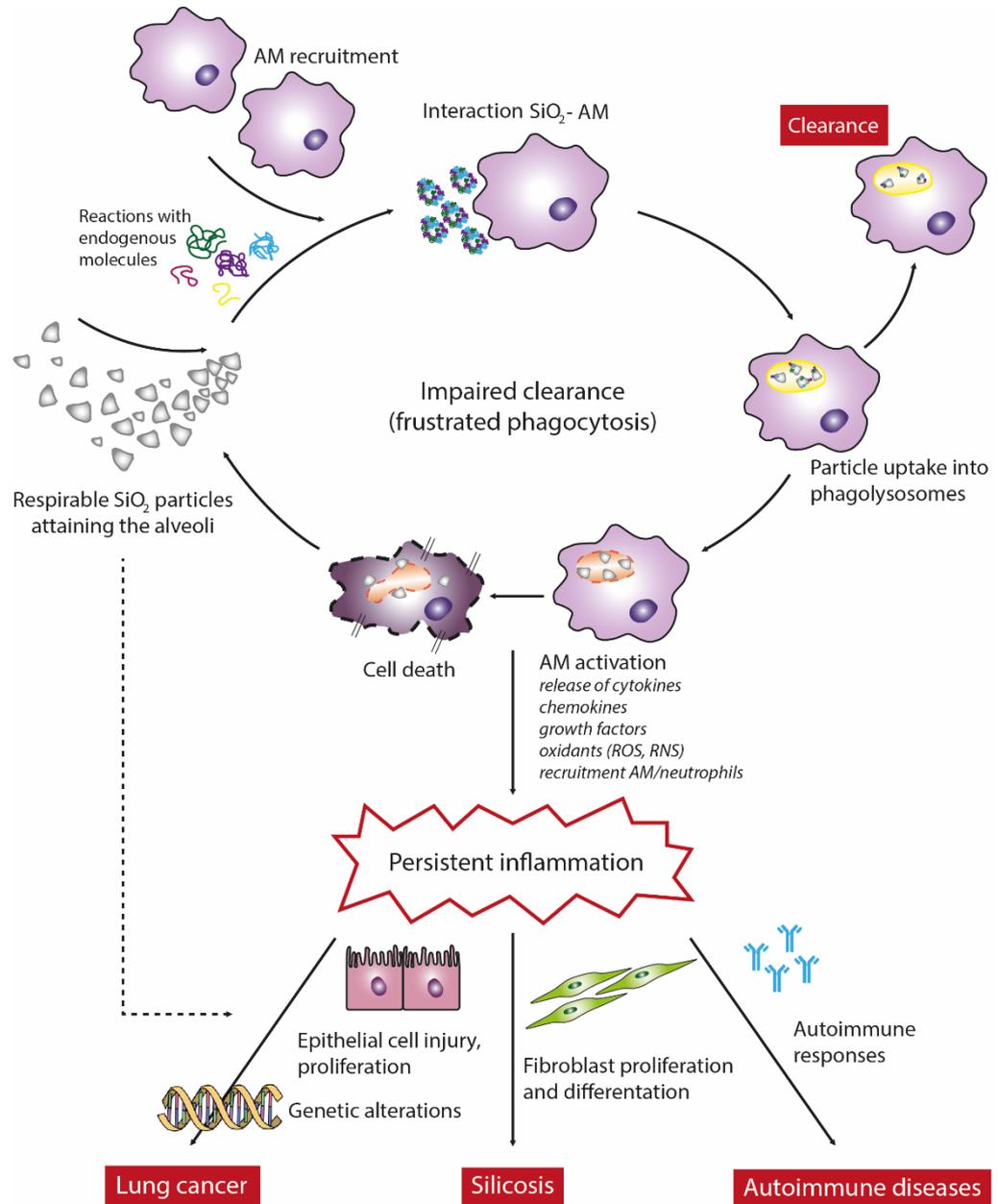
Redrawn from scheme in IARC monograph (*Vol. 100C, **2012***)
C. Pavan & B. Fubini, *Chem. Res. Toxicol. (2017)*

2 - Sabine Francke

Recommendations for an IARC Preamble Update from a regulatory pathology perspective

Sabine Francke, DVM, Dr.vetmed., PhD, DABT, Fellow IATP
Expert Toxicologic Veterinary Regulatory Review Pathologist

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Senior Science and Policy Staff

CFSAN Pathology

sabine.francke@fda.hhs.gov

1

U.S. Food and Drug Administration
Protecting and Promoting Public Health

IARC Preamble

- Thank you for the opportunity to speak
- We appreciate IARC's important work and its value to global regulatory decision making
- Specifically, the preamble contains many valuable considerations – still true despite rapidly changing science pertaining to carcinogenicity

US FDA CFSAN Pathology's Role in Cancer Risk assessment

=

Hazard identification

Reference: Bredfeldt and Arrieta, Hazard Identification in Toxicological Risk Assessment for Beginners; EditorsTorres and Bobst, Springer 2015, 19-41.

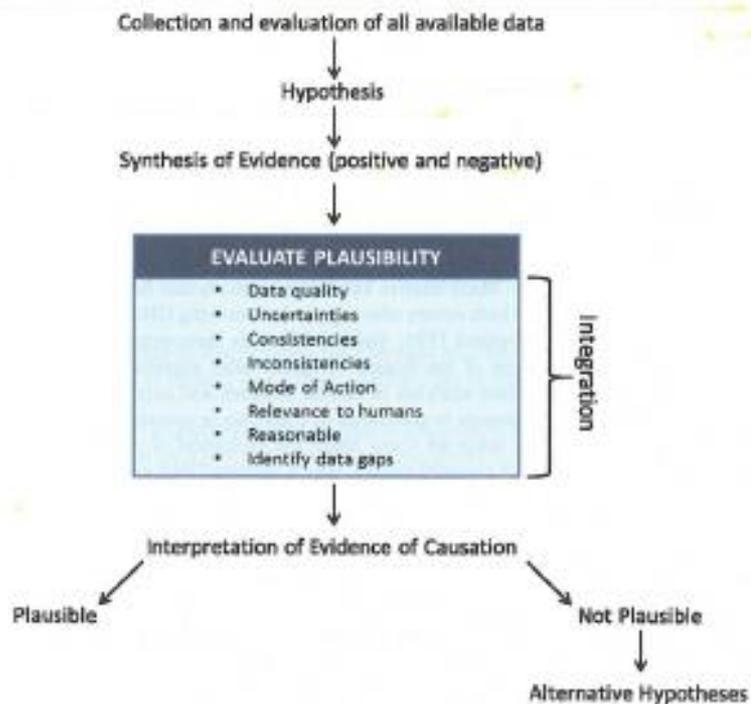# Hazard Identification
Its role within the Risk assessment process

Fig. 2.3 Illustrates the process of assessing and integrating evidence during hazard identification. The integration of various lines of evidence is sometimes called a weight of evidence analysis wherein available data is evaluated to determine if exposure to a chemical of concern causes the observed adverse effect(s).

4

Reference: Bredfeldt and Arrieta, Hazard Identification in Toxicological Risk Assessment for Beginners; EditorsTorres and Bobst, Springer 2015, 19-41.

US FDA's regulatory utility of the IARC monographs could improve if the following points would be considered while updating the IARC preamble

1. Shorten the preamble

– concisely state the IARC monograph's scope and objectives being restricted to only Hazard identification within the Risk assessment process

a. Clearly define all assessment related terminology

b. Highlight what falls in the scope and objectives

c. Emphasize that IARC does not conduct the risk assessment itself

b. Eliminate all information in the preamble that contradicts point 1) c.

2. Reword the Monograph conclusion categories so that they cannot be confused with risk assessment terminology

    a. Each category should include unequivocal terms that tie it specifically to Hazard identification (not risk assessment) and

    b. speak specifically to data quality pointing to an overall weight of evidence of

– positive,

– equivocal or

– negative carcinogenic test results.

2. cont. Reword the Monograph conclusion categories so that they cannot be confused with risk assessment terminology - Examples

- Quality and quantity (weight of evidence) of the materials evaluated point to overall positive test results pertaining to the carcinogenic potential of compound x

- Quality and quantity (weight of evidence) of the materials evaluated point to some positive test results and some negative test results pertaining to the carcinogenic potential of compound x – therefore, further studies are necessary and the compound will be re-evaluated in y amount of time

- Quality and quantity (weight of evidence) of the materials evaluated are overall inconclusive pertaining to the carcinogenic potential of compound x – therefore, an assessment cannot be made for the following reasons….

- Quality and quantity (weight of evidence) of the materials evaluated point to overall negative test results pertaining to the carcinogenic potential of compound x

8

3. Include statements addressing the Uncertainty in IARC's Hazard identification
(e.g. EFSA 2018 guidance)

GUIDANCE DOCUMENT

EFSA Journal

ADOPTED: 15 November 2017

doi: 10.2903/j.efsa.2018.5123

Guidance on Uncertainty Analysis in Scientific Assessments

EFSA Scientific Committee,
Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen,
Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci,
Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck,
Maged Younes, Peter Craig, Andrew Hart, Natalie Von Goetz, Kostas Koutsoumanis,
Alicja Mortensen, Bernadette Ossendorp, Laura Martino, Caroline Merten, Olaf Mosbach-Schulz
and Anthony Hardy

Abstract

Uncertainty analysis is the process of identifying limitations in scientific knowledge and evaluating their implications for scientific conclusions. It is therefore relevant in all EFSA's scientific assessments and also necessary, to ensure that the assessment conclusions provide reliable information for decision-making. The form and extent of uncertainty analysis, and how the conclusions should be reported, vary widely depending on the nature and context of each assessment and the degree of uncertainty that is present. This document provides concise guidance on how to identify which options for uncertainty analysis are appropriate in each assessment, and how to apply them. It is accompanied by a separate, supporting opinion that explains the key concepts and principles behind this Guidance, and describes the methods in more detail.

9

4. Update literature references

→ to current state of the science and professional best practices (consider Society of Toxicologic Pathology /European Society of Toxicologic Pathology best practice papers)

5. Mindfully nurture stakeholder confidence in the IARC assessment results

→ provide the greatest possible level of transparency during the monograph development by

→ publicly communicate changes to the monograph drafts and their scientific rationale, proactively as the changes occur.

– E.g. post session minutes that summarize the discussion points and committee agreements of each draft revision.[10]

Thank you for the opportunity to speak and

for your consideration of these comments.

3 - David Christiani (see video)

4 - Bernard W. Stewart

The IARC *Monograph* Preamble What's to be done in 2018?

Bernard W. Stewart

Faculty of Medicine, University of New South Wales

and

Cancer Control Program,

South Eastern Sydney Public Health Unit

Who's best informed?

Since 2006, at least 35 volumes of *Monographs* have been published

Some *Monograph* Programme staff members (including the Head) have probably participated in more that 30 meetings

By comparison, visiting scientists heavily engaged in the *Monographs* may have been involved in as many as six meetings.

IARC staff have greatest knowledge, but are limited in the extent of their participation.

The basis of previous updates

Typically, revisions of the Preamble have concerned changes necessary to incorporate new scientific insight or new procedures on the basis of

(1) IARC investigations achieved through Scientific Publications or Advisory Group meetings

Or

(2) Procedures seen to have been productive or necessary at one or more then-recent *Monograph* meetings

Recent IARC investigations

Recent *Monograph* Advisory Group meetings have concerned:

- Quantitative aspects of *Monograph* evaluations. Report addressed options but did not specify text changes to the Preamble.

- Concordance between tumour sites in humans and in animals following comparable carcinogen exposure: 'in press' as an IARC Scientific Publication

- Mechanisms of carcinogenesis: Peer review publication of the 'key characteristics'

Recent *Monograph* precedents

Recent *Monograph* Working Group meetings have resulted in decisions to:

- Accord greater confidence in cohort studies than in case-control studies for determining relevant associations

- Order 'key characteristic data' according to its relevant human cancer(s) rather than according to matters most studied.

- Determine matters to be subject to evaluation (apart from *Monograph* title), modify *Monograph* title and change the Volume title.

And what's new in 2018?

The *Monographs* are under attack.

Issues include (but are not limited to)

Reliance on 'experts who have a vested interest' (ie Working Group members are chosen specifically because of their contribution to the research being evaluated)

and

Reliance on peer-reviewed (journal) publications

Are any such matters to be affirmed or justified in the Preamble?

And what's new in 2018?

As originally envisaged both the Preamble and the *Monographs* themselves were 'scientist-to-scientist communications.

Not any more!!

Monograph evaluations are 'explained' by the media to the wider community.

The headlines include

Red meat 'probably' causes bowel cancer

Bacon, Hot Dogs: carcinogens from the corner store

WHO lists processed meat with asbestos and tobacco smoke

These statements cannot be dismissed as lies;

These statements require explanation, but relevant explanations are not achieved by quoting the corresponding IARC evaluations.

5 - Julie E. Goodman

Improving the Monograph Preamble

Julie E. Goodman, Ph.D., DABT, FACE, ATS

IARC Preamble Scientific Webinar
17 September 2018

Overview

- Current Preamble and Author Instructions, while providing useful information regarding general guidance, do not entirely conform to evidence-based systematic review methodology

- A thorough and comprehensive upgrade to the Monographs' guidance and procedures is needed to ensure they meet contemporary 21st century standards and best practices

- **Recommendations:** Include more specific guidance so all reviews are

  - Consistent
  - Systematic
  - Transparent
  - Comprehensive
  - Coherent

Systematic Review

- Detailed protocols for systematic review are needed
  - Could be in separate document and updated independently of the Preamble, as needed
  - Should be consistent across Monographs
  - Can be developed based on available methods
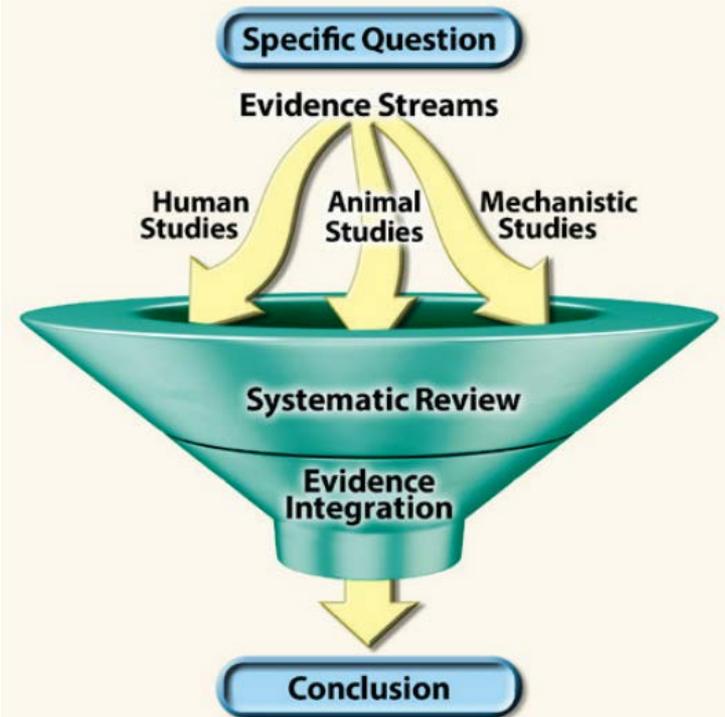
Study Quality

- Importance of study quality discussed in Preamble very broadly

- Should be expanded to include:
  - How factors that affect study quality impact the interpretation of study results
  - How results from low quality studies will be considered
  - How study quality information will be utilized when considering the body of literature as a whole.

- **Examples:** EFSA, US EPA, NTP, Texas Commission on Environmental Quality (TCEQ)

Evidence Integration

- Consider study quality

- Take into account null/negative associations

- Consider human relevance

- Adopt Mode of Action (MoA) as a central organizing principle

Problem Formulation
• Define the question(s) for assessment

▼

Weight of Evidence Assessment
1. Assemble the evidence
2. Weigh the evidence
3. Integrate the evidence

▶ *May occur at one or more points in the assessment, where evidence integration is needed*

▼

Uncertainty Analysis
• Assess and combine uncertainties from all parts of the overall assessment
• Identify data gaps

▼

Conclusion of Overall Assessment

Mechanistic and Mode-of-Action Evidence

- Current key-characteristics-of-carcinogens approach for mechanistic data is scientifically flawed
- Evaluate the totality of evidence (including high-throughput assay data) on plausible MoAs
- Consider study quality
- Determine the relevance of observed MoAs to humans
- Integrate equally and concurrently with other lines of evidence

Goodman, J; Lynch, H. 2017. "Improving the International Agency for Research on Cancer's consideration of mechanistic evidence." *Toxicol. Appl. Pharmacol.* 319 :39-46. doi: 10.1016/j.taap.2017.01.020.

Other Recommendations

- Consider experts from all sectors (balance of perspectives)
- Formalize chemical selection process
- Have MoA guiding principle for problem formulation
- Develop clear methodology for study selection
- Consider exposure route and dose in hazard assessment
- Formalize process for resolving conflicting opinions
- Make the decision-making process transparent
- Consider assessments by other scientific and regulatory bodies
- Consider public comments and independent peer reviews
- Improve hazard (*vs*. risk) communication

Questions?

Julie E. Goodman, Ph.D., DABT, FACE, ATS

Principal

jgoodman@gradientcorp.com
(617) 395-5525

The full set of comments can be accessed at:
https://www.americanchemistry.com/ACC-ASARP-IARC-Preamble-Comments-28-Aug-2018.pdf

6 - Daniele Wikoff

Submitted written comments for consideration

– Key comments summarized herein

Most comments reflect text that does not currently exist in the Preamble

– Difficult to use the template provided

ToxStrategies

Omit use of the term "risk" □ replace with "hazard"

The term "risk" should be replaced with the term "hazard" throughout the Preamble. It is important that authorities have clear definitions of what the output represents, such that they can appropriately use the Monographs in evaluations of risk. It is critical that the preamble reflect the underlying scientific process □ which is only of hazard identification (not risk).

- *Issues addressed:*
    - *Confusion regarding the use of the term "risk" continues to increase.*
    - *While the issue regarding the use of the term "risk" has been deliberated in the past, the IARC Monographs still retain the term "risk" in their title. The 2015 IARC Monographs Q&A points out their cancer classifications are hazards, not risks: "IARC classifies carcinogens in five categories ... The classification indicates the weight of the evidence as to whether an agent is capable of causing cancer (technically called 'hazard'), but it does not measure the likelihood that cancer will occur (technically called 'risk') as a result of exposure to the agent." The Preamble acknowledges, "The Monographs are used by national and international authorities to make risk assessments…" and, "these evaluations represent only one part of the body of information on which public health decisions may be based."*

ToxStrategies

The directives and role of the exposure working group should be clarified

Exposure information (i.e., the range of potential exposures currently summarized in IARC monographs) is not used in developing hazard classifications. While exposure information is useful to prioritization, the appropriateness of the exposure working group's role in evaluating evidence and voting on hazard classifications based on epidemiological, animal, and mechanistic studies is unclear.

- Available exposure information should be used solely to better understand context around exposure to the agent (e.g., route of exposure), not as a surrogate for agent identification and presumed risk characterization. This information *could* be used to inform appraisal criteria (particularly for epidemiological studies, i.e., has exposure been confidently characterized).

- Further clarification of the scientific principles and procedures associated with the evidence reviewed by the exposure group is needed given that exposure information is not used in the assessment of carcinogenicity hazard.
  - *Exposure information is not part of the evaluation of the potential for hazard.*
  - *The exposure working group's role in developing and voting on overall classifications is unclear. Rationale should be provided regarding the appropriateness of having exposure working group members vote on overall hazard classifications based epidemiological, animal, and mechanistic studies.*

ToxStrategies

Preamble should address the principles, *as well as the procedures* for carrying out the principles

Currently:

- *Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous Monograph meetings but remain, predominantly, the prerogative of each individual Working Group.*

Without specific guidance on procedures, working groups cannot consistently or transparently carry out the principles

The Preamble should be updated to reflect both principles and procedures

- Principles and procedures should integrate the practice of evidence-based reviews, allowing classifications and monographs to produced with increased rigor, transparency, and reproducibility

ToxStrategies

Use evidence-based methods: systematic review, meta-analysis to evaluate the totality of evidence

Systematic review: *"A scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies"* ☐ IOM, 2011

Suggest Preamble refinements that better reflect use of evidence-based systematic review methods:

– Emphasis on *a priori* identification of inclusion/ exclusion criteria for study selection, as well as determination of relevance and adequacy

– Incorporate formal study quality evaluation (i.e., critical appraisal of internal validity) by study type

– Implement *a priori* determination of topic-specific refinements for study quality and decision criteria (e.g., criteria specific to confounding and route of exposure for the agent under consideration) as part of considering the totality of evidence

Radboudumc

Patient care   Research   Education

SYstematic Review Center for Laboratory animal Experimentation
SYRCLE

OXFORD   SOT
www.toxsci.oxfordjournals.org

U.S. FOOD & DRUG ADMINISTRATION

Food

Labeling & Nutrition

Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final

FORUM ARTICLE

The Emergence of Systematic Review in Toxicology

Martin L. Stephens,[a,1] Kellyn
Kay Dickersin,[e] Suzanne Fitz
Thomas Hartung,[a,i] Jennifer M
Roberta W. Scherer,[e] Didier V

National Toxicology Program
U.S. Department of Health and Human Services

Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration

January 9, 2015

Office of Health Assessment and Translation (OHAT)

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

ToxStrategies

- Problem Formulation
- Protocol Development
- Identify Evidence Base
- Individual Study Assessment
- Body of Evidence Assessment
- Reporting

Structured guidance and formal criteria are needed: clarify process and procedures for what data are evaluated (i.e., relevant and adequate) and how *(= more detail than currently provided in Preamble)*

Study appraisal criteria need to be tailored to the agent *a priori (e.g., identification of specific confounding biases)*– including how such criteria will be considered in decision making

????

Approach must consider the totality of evidence (from all streams)

Refinements will aid in transparency, objectivity, and reproducibility

ToxStrategies

7

Increase transparency in the conduct and reporting of monograph reviews:

Government agencies, academic institutions, journals, and private entities using a variety of tools to transparently document assessments

IARC is *already using* some of these tools (HAWC, TableBuilder) ☐ additional transparency in conduct and reporting could be implemented easily

http://hawc.readthedocs.io/en/latest/index.html

Shapiro A, Lunn R, Jahnke G, Schwing P, Guyton K, Loomis D, Guha N. 2017 TableBuilder: A content management system for carcinogenicity health assessments for the IARC Monographs and the NTP Report on Carcinogens. Presented at: 4th International Symposium on Systematic Review and Meta-Analysis of Laboratory Animal Studies.

Consider the 2014 WHO Handbook when updating the Preamble

WHO
Handbook for Guideline Development

2nd edition

World Health Organization
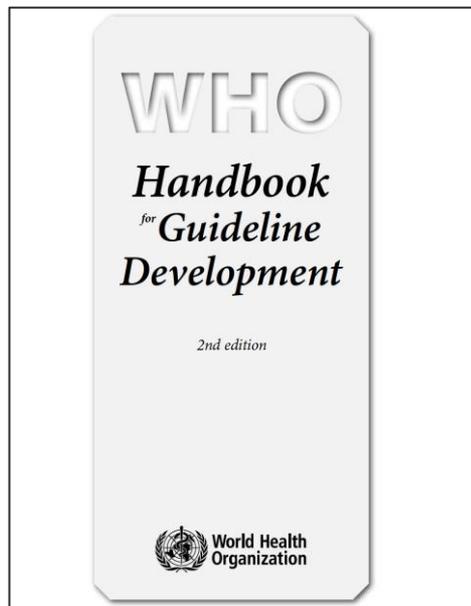
Declaration and management of interests

Formulating the review (including exposure)

Systematic review

Quality assessment

ToxStrategies

Consider (and actively manage) both financial and non-financial interests of working-group members

Conflict of Interest: "*circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest*" ▢ WHO 2014, IOM 2011, IOM 2009

- Secondary interests include not only financial interests but also other interests, such as the pursuit of professional advancement.

Example from WHO *Handbook for Guideline Development* (2014):

> "…[C]ertain individuals should not participate at all in the development of a guideline… those who have intellectual conflicts of interest that are severe and/or cannot be adequately managed at the group level … (such as) an author or co-author of one or more key studies within the body of evidence underpinning a recommendation, particularly if the body of evidence is limited… (see Section 6.10) (p.68)".

Current Preamble does not provide guidance as to how disclosures are to be evaluated and managed

- **It is well-recognized that <u>both financial and non-financial interests</u> need to be declared and appropriately managed**
- **IARC is strongly encouraged to follow the 2014 WHO *Handbook on Guideline Development,*** broadly speaking and as it pertains to disclosure and management of both financial and non-financial conflicts of interest, when refining the Preamble

WHO
Handbook for Guideline Development

2nd edition

World Health Organization
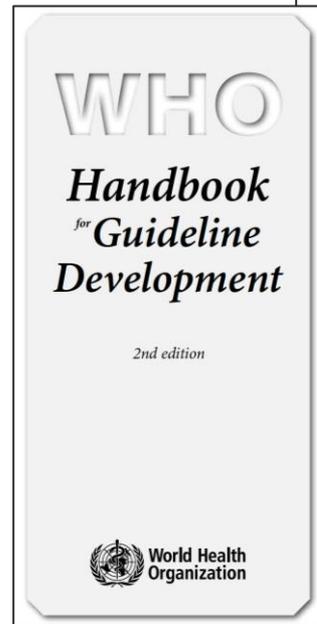
CONFLICT OF INTEREST
IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE

Bernard Lo and Marilyn J. Field, Editors

Committee on Conflict of Interest in Medical Research, Education, and Practice

Board on Health Sciences Policy

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ToxStrategies

Summary Themes of Comments

- Omit use of the term "hazard" and replace with "risk"
- Clarify principles and procedures related to exposure (e.g., priority setting primarily, as evaluations are hazard-based)
- Refine preamble to address the principles, as well as the procedures for carrying out the principles
- Use evidence-based methods (i.e., systematic review, meta-analysis)
  - Emphasis on *a priori* identification of inclusion/exclusion criteria for study selection, as well as determination of relevance and adequacy
  - Integrate formal study quality evaluation (i.e., critical appraisal of internal validity) by study type and structured decision criteria
- Increase transparency in the conduct and reporting of monograph reviews
  - Encourage use of tools already in practice to do so
  - Consider more public participation, including opportunities to comment (early and frequently) throughout monograph process
- Consider (and actively manage) both financial and non-financial interests of working-group members

ToxStrategies

Thank you for the opportunity to submit written comments and share verbal comments via webinar.

Remaining slides not presented during webinar; provided as support for key comments presented (additional details can also be found in the written submission).

ToxStrategies

Principles should be updated to be consistent with the WHO 2014 *Handbook for Guideline Development*

The Preamble should specifically identify multiple points in the update process when public and stakeholder comments will be collected, how they will be collected, and subsequently how they will be disseminated, evaluated, and integrated into the process. During this process, *all* comments should be considered.

- *Issues addressed: The current IARC preamble does not specifically address how and when public or stakeholder comments will be collected, considered, and reflected on in the monograph development process. Available materials suggest that only "pertinent" comments will be provided to the Advisory Group.*

The Preamble should include a mechanism that parallels *WHO's Handbook for Guideline Development,* by which both financial and non-financial conflicts of interest (COIs) for prospective IARC working-group experts can be evaluated and managed in a systematic manner. IARC is strongly encouraged to align its COI process relative to how COI will be evaluated and managed for full transparency in selection of working-group members, especially as it relates to invited experts, to the *2014 WHO Handbook for Guideline Development.*

- *Issues addressed:*
  - *The current Preamble briefly addresses disclosure of only financial conflicts (non-financial conflicts are not addressed). It provides no guidance as to how disclosures are to be evaluated and managed.*
  - *Criticism has been raised that some Working Groups are unbalanced and possibly prone to bias. It is well-recognized that both financial and non-financial bias need to be declared and appropriately managed. Criticisms received regarding unbalanced working groups could be addressed by revising the principles related to selection of working groups, including a more formalized plan for disclosure and management of financial and non-financial COI, consistent with globally accepted standard practice (NAS, 2013; WHO, 2014).*

ToxStrategies

Evidence-based principles *and procedures* should be implemented

In an effort to provide transparent, comprehensive, and consistent evaluations of potential human carcinogenicity, the Preamble should be updated to reflect the scientific principles, as well as the systematic procedures and decision criteria that are implemented to achieve the principles. Updates should reflect a more transparent and comprehensive statement of principles, decision criteria, and operating procedures.

- *Issues addressed: The current Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve <u>operations</u> that have been established as being effective during previous Monograph meetings but remain, predominantly, <u>the perogative of each individual Working Group</u>.*

The IARC Preamble scientific principles and procedures should be updated to integrate the practice of evidence-based reviews conducted systematically to provide evidence-based monographs produced with rigor, transparency, and reproducibility in the monograph process. Evidence-based practice involves systematic reviews and meta-analyses, as well as other "state-of-the-science" techniques, which utilize a predefined, multi-step process to identify, select, critically assess, analyze, and synthesize evidence from the totality of scientific studies to reach a conclusion.

- *Issues addressed:*
  - *The current Preamble does not fully employ evidence-based methods. Lack of such methods is associated with inconsistent evaluations, lack of transparency and reproducibility, and uncertainty in the underlying rigor.*
  - *The current Preamble indicates that only studies considered to be relevant are included. No principles or procedures are provided as to how such selections are made, suggesting that the evidence is not reviewed in totality.*

ToxStrategies

Emphasis should be placed on the need for *a priori* identification of criteria to select literature and determine relevance and adequacy

- **All data should be identified using a systematic approach that involves development and implementation of agent-specific protocols, in addition to refinement of principles and procedures in the Preamble. Pertinent epidemiological studies, cancer bioassays in experimental animals, other relevant data (including mechanistic data), and exposure studies, should be determined via implementation of processes developed *a priori* and documented in a protocol for each agent. As part of the protocol, a detailed search strategy will be developed, validated, and documented *a priori* by an Information Specialist. The search strategy should include syntax specific to each database (e.g., MeSH in PubMed), a list of databases (including grey literature sources if included), and dates of searching. The strategy should detail the process for screening titles and abstracts, as well as full text against inclusion/exclusion criteria. Such criteria should be developed to specifically characterize populations, exposures, comparators, and outcomes for inclusion/exclusion. These criteria should be developed *a priori* by the IARC Secretariat and reviewed and approved by working-group members prior to implementation.**
  - *Issue addressed: The Preamble is void of transparency principles and procedures related to systematic and objective identification of key studies.*
- **All available data that are identified during the literature search (which, by default, should capture data relevant to the evaluation if using an agent-specific protocol and search strategy) must be considered by the working group. That is, data sets should not be "cherry-picked." All data should be subjected to critical appraisal; criteria for critical appraisal (quality, adequacy) should be included in the Preamble and refined as warranted for each Agent.**
  - *Issues addressed:*
    - *The Preamble is currently void of scientific principles related to what is "relevant" or "adequate."*
    - *The Preamble does not address methods for identifying, selecting, evaluating, and integrating other relevant data, including for key characteristics of carcinogenesis*
    - *Each working group selects what they find to be relevant (which is not consistent with a systematic or evidence-based approach); clear and consistent criteria or descriptions are needed to inform working-group determinations of what constitutes exclusion based on inadequacy and/or irrelevance.*
    - *While the Preamble directs the Working Group to provide reasons for not giving consideration to a study in the "square brackets"; in practice, the monographs often do not provide clear or concise information as to the reason.*

ToxStrategies

Principles should include specific criteria for evaluation of study quality (adequacy) and procedures for evaluating and integrating considerations of quality as part of assessing the totality of evidence

The Preamble should be revised to include structured and defined criteria for evaluation of internal and external validity of study quality. An entire new section (is needed to describe these criteria. In addition to the definitions, the scientific principles for applying and integrating such data quality criteria should also be included. An entire section (not drafted as part of these comments) is needed to describe how to apply the data quality criteria.

- *Issues addressed:*
  - *While the Preamble alludes to evaluation of study quality, it does not provide clear criteria or principles to do so.*
  - *Because each set of evaluations is done by a different working group, and different staff within the IARC Secretariat, the preamble, having clear criteria for evaluation and integration of external validity as part of inclusion/exclusion, as well as the weight of the totality of the evidence, would improve the quality and consistency of the IARC monographs.*

The scientific principles for how bias domains (e.g., confounding, exposure, outcome, selection) are to be critically appraised <u>for every study</u> - as part of an evaluation of potential systematic error and, consequently, potential impact on direction, magnitude, consistency, and strength of results - need to be included, along with how study quality will be integrated into the weight-of-evidence assessment <u>when all data</u> are considered in totality.

- *Issues addressed:*
  - *The Preamble is void of principles and regarding how domains such as bias and chance should be assessed and subsequently weighted in evaluating the totality of the evidence.*
  - *The Preamble is a void of principles that clearly identify which bias domains should be evaluated for each study type, including, for example, agent-specific identification and evaluation of exposure and confounding biases in epidemiological studies as part of assessing the totality of the evidence.*
  - *The IARC Preamble indicates that evaluations consider studies that support a finding of cancer hazard, as well as studies that do not; however, there is no description of the scientific principles that describe how this is defined or implemented in practice.*

ToxStrategies

Clarification is needed for methods of identifying, selecting, evaluating, and integrating other relevant data, including information on key characteristics of carcinogenesis

The Preamble should be updated to reflect both the principles and the procedures related to the use of the "key characteristics of carcinogenesis" (KCC) approach for identifying and evaluating mechanistic data, as well as consideration of other possibly relevant data that are not considered KCC. Include descriptions of the principles and procedures as to what and how data organized by KCC (and "other" possibly appropriate characteristics) should be evaluated relative to up- and down-grading classifications in context of adverse outcome pathways _that are pertinent to the specific cancer type under evaluation._ It is also important that the Preamble consider "other" possibly appropriate characteristics that are not yet identified as KCC (i.e., characteristics of carcinogens that are not yet known).

- *Issues addressed:*
  - *The Preamble is void of reference to the KCC approach, despite numerous publications by IARC scientists and references to those in the Instructions to Authors*
  - *It is unclear how mechanistic data are identified, selected, evaluated, and integrated into IARC assessments, particularly KCC data*
  - *The preamble is currently void of discussion related to use of high-throughput screening (HTS) data as a source of information to be considered*

Paramount to the inclusion of KCC (and other relevant data), the Preamble must address how the collective mechanistic evidence (which is likely to include data demonstrating both activity and lack of activity) will be evaluated in the context of (a) adverse outcome pathways pertinent to specific cancer type(s) under evaluation, **and** (b) evidence from other streams (human, animal, exposure). The principles and procedures for considering study quality and relevance should be included in this update.

ToxStrategies

7 - Tracey Woodruff

Program on Reproductive Health and the Environment (PRHE)

Information for Families
Resources to help your family reduce their environmental exposures

Clinical Practice
Resources for health care professionals to promote environmental health

Research
Targeted research to inform clinical decision making and public policy

Policy
Resources to advance science-based policy solutions.

Mission: To create a healthier environment for human reproduction and development

by advancing scientific inquiry, clinical care, and health policies

that prevent exposures to harmful chemicals in our environment

UCSF
University of California
San Francisco

Outline

- Introduction of systematic reviews in environmental health
  - Development by universities (Navigation Guide) and government agencies (NTP/Office of Health Assessment and Translation (OHAT))
  - Reviews/recommendations by NAS
- Recommend using and applying new tools and methods to increase transparency and constancy
- Continue to support conflict of interest policies

Navigation Guide – 2009

THE COCHRANE COLLABORATION®

GRADE

National Toxicology Program
U.S. Department of Health and Human Services

BRIDGING CLINICAL & ENVIRONMENTAL HEALTH

By Tracey J. Woodruff, Patrice Sutton, and The Navigation Guide Work Group

An Evidence-Based Medicine Methodology To Bridge The Gap Between Clinical And Environmental Health Sciences

Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration

ABSTRACT Physicians and other clinicians could help educate patients about hazardous environmental exposures, especially to substances that could affect their reproductive health. But the relevant scientific evidence is voluminous, of variable quality, and largely unfamiliar to health professionals caring for people of childbearing age. To bridge this gap between clinical and environmental health, we created a methodology to

January 9, 2015
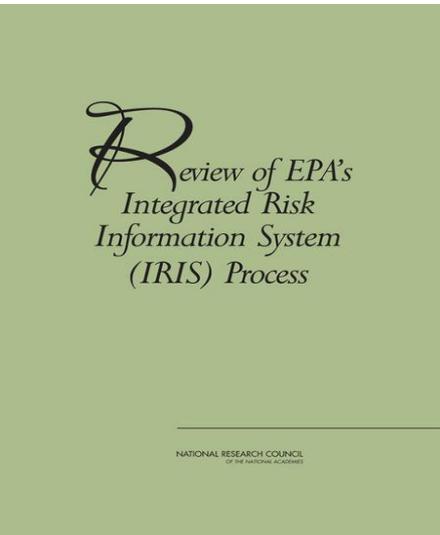
2014

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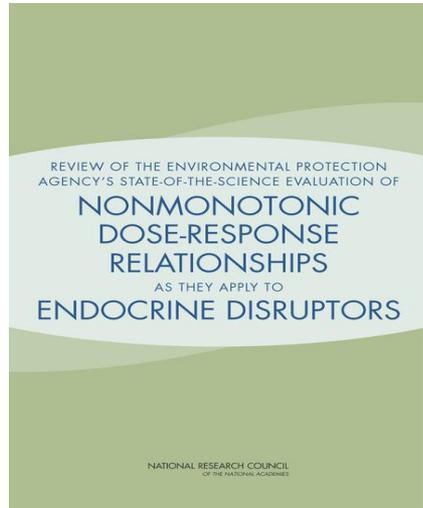
2017

2018

…**systematic-review standards** provide an approach that would substantially strengthen the IRIS process…"

"EPA should consistently use a more **systematic approach** to evaluating the literature ………."
NAS 2014

Systematic review process framework valuable for identifying, selecting, and evaluating evidence in a consistent and explicit manner

Using the Navigation Guide systematic review method for estimating the burden of work-related disease and injury

5

Systematic Review approach

A pre-specified analytic plan (protocol) is developed and applied consistently to the evidence.

Human Data

Non Human Data

"PECO" Statement → Systematic Search → Select Studies → Extract Data & Data Analysis → Evaluate Risk of Bias → Rate Quality → Rate Strength → Overall Conclusion

- Systematic, transparent, consistent, and reproducible

- Does not eliminate need for expert judgment, but outlines judgments made along the way

Recommendations

- Protocol
- Search
  - Work with a expert on search
  - Make transparent the search strategy and results of study inclusion/exclusion
- Continue to adopt the different steps of systematic reviews
- Recommend using and applying available tools and methods to increase transparency and constancy
  - Health Assessment Workspace Collaborative (HAWC)
- Continue to support conflict of interest policies
  - Evaluate financial conflicts as part of risk of bias

Support Infrastructure Development

Thank you!

UCSF
University of California
San Francisco

Program on Reproductive
Health and the Environment

Evaluate each evidence stream separately using systematic and transparent approaches
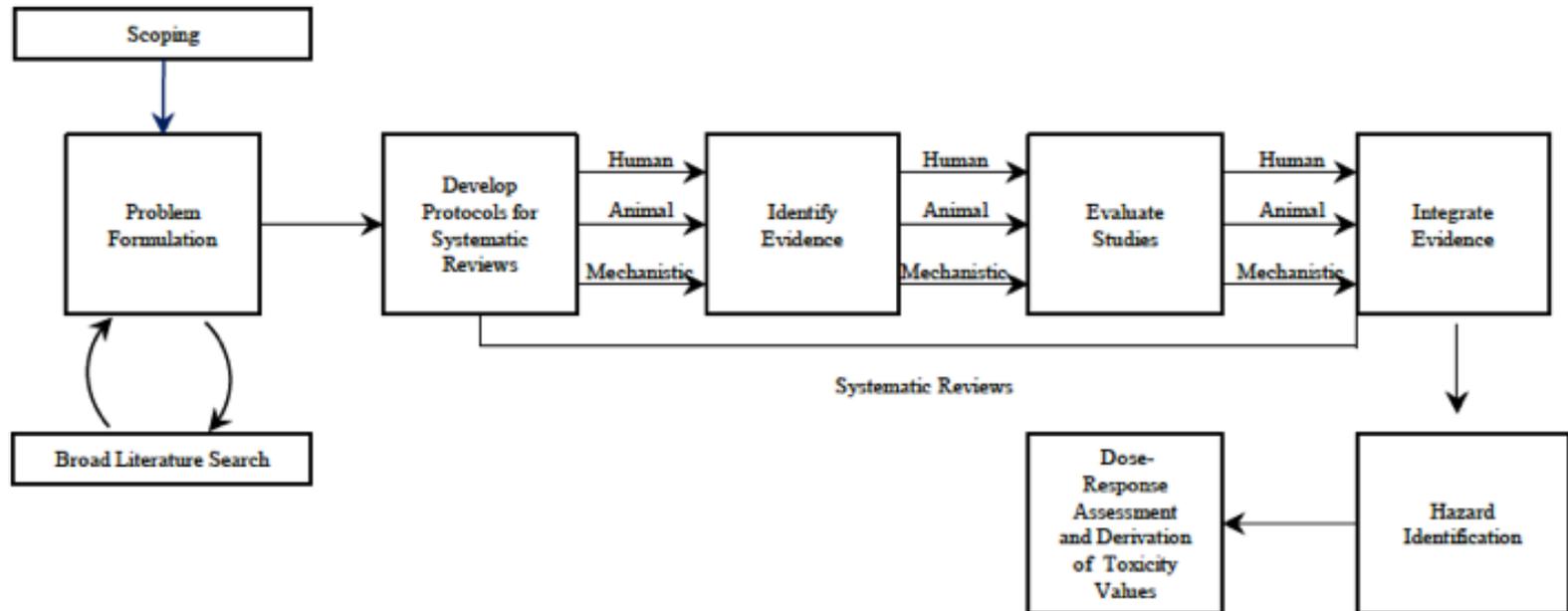
8 - Martyn Smith

The key characteristics approach to evaluating mechanistic data in carcinogen hazard identification

Martyn Smith

School of Public Health,
University of California, Berkeley CA, USA

martynts@berkeley.edu

MT Smith, UCB Sept 2018

http://superfund.berkeley.edu

How Mechanistic Evidence is Currently Evaluated?

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

—Part B, Section 6(c)

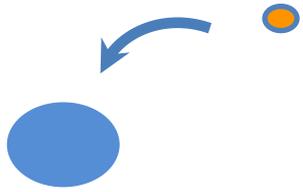| • Are the mechanistic data "weak," "moderate," or "strong"? | Have the mechanistic events been established? Are there <u>consistent</u> results in <u>different</u> experimental systems? Is the overall database <u>coherent</u>? |
	Has each mechanism been <u>challenged</u> experimentally? Do studies 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 <u>data from exposed humans</u> or human systems?
	Consider <u>alternative explanations</u> before concluding that tumours in experimental animals are not relevant to humans

The Key Characteristics of Human Carcinogens
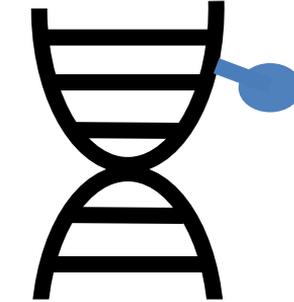
Courtesy of Amy Wang, NTP
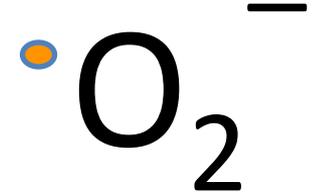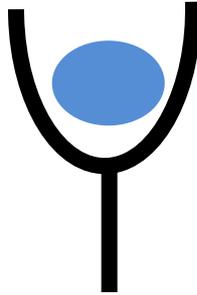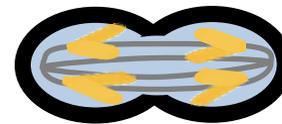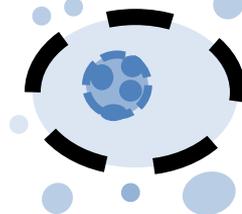
Characteristic	Examples of relevant evidence
1. Is Electrophilic or Can Be Metabolically Activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone, etc), formation of DNA and protein adducts.
2. Is Genotoxic	DNA damage (DNA strand breaks, DNA-protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei).
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces Epigenetic Alterations	DNA methylation, histone modification, microRNA expression
5. Induces Oxidative Stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)

Characteristic	Examples of relevant evidence
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is Immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes Immortalization	Inhibition of senescence, cell transformation, altered telomeres
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

A Hallmark *versus* a Key Characteristic

- A Hallmark describes what *IS*

- A Key Characteristic (KC) describes Something that makes "what is" happen

INTEGRATION OF THE KCs WITH HALLMARKS
Characteristics 1,2,4 and 8 can influence all Hallmarks

Key Characteristics

1. Is 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

Hallmarks

1. Genetic Instability
2. Sustained Proliferative Signalling
3. Evasion of Anti-growth Signalling
4. Resistance to Cell Death
5. Replicative Immortality
6. Dysregulated Metabolism
7. Immune System Evasion
8. Angiogenesis
9. Inflammation
10. Tissue Invasion and Metastasis

PLUS - Tumor Microenvironment

MT Smith, UCB Sept 2018

KCs act by disrupting Hallmark processes – Conclusion of Working Group convened in Berkeley, August 21-22, 2018

7

INTEGRATION OF THE KCs WITH HALLMARKS
Characteristics 3,5,6,7,9,10 influence specific Hallmarks

KC3: Alters DNA Repair or Causes Genomic Instability	(Hallmark) Genetic Instability
KC5: Induces Oxidative Stress	(Hallmark) Dysregulated Metabolism
KC6: Induces Chronic Inflammation	(Hallmark) Inflammation
KC7: Is Immunosuppressive	(Hallmark) Immune System Evasion
KC9: Causes Immortalization	(Hallmark) Replicative Immortality
KC10: Alters Cell Proliferation, Cell Death, or Nutrient Supply	(Hallmark) Sustained Proliferative Signalling (Hallmark) Evasion of Anti-growth Signalling (Hallmark) Resistance to Cell Death (Hallmark) Angiogenesis
NO KCs	(Hallmark) Tissue Invasion and Metastasis (Hallmark) Tumor Microenvironment

Several KCs act by disrupting specific Hallmark processes – From Leroy Lowe's presentation to Working Group convened in Berkeley, August 21-22, 2018

Application of the KCs at IARC

Use the KCs to:

- Identify the relevant mechanistic information
- Screen and organize the search results
- Evaluate quality of the identified studies
- Summarize the evidence for each KC as strong, moderate or weak and determine if it operates in humans or human in vitro systems

Systematic Approach
Using Key Characteristics of Carcinogens

Targeted searches for each key characteristic

Organize results by key characteristics, species, etc

Smith MT, Guyton KZ, Gibbons CF, Fritz JM et al.. *Env Health Persp.*, *124(6):713-21*
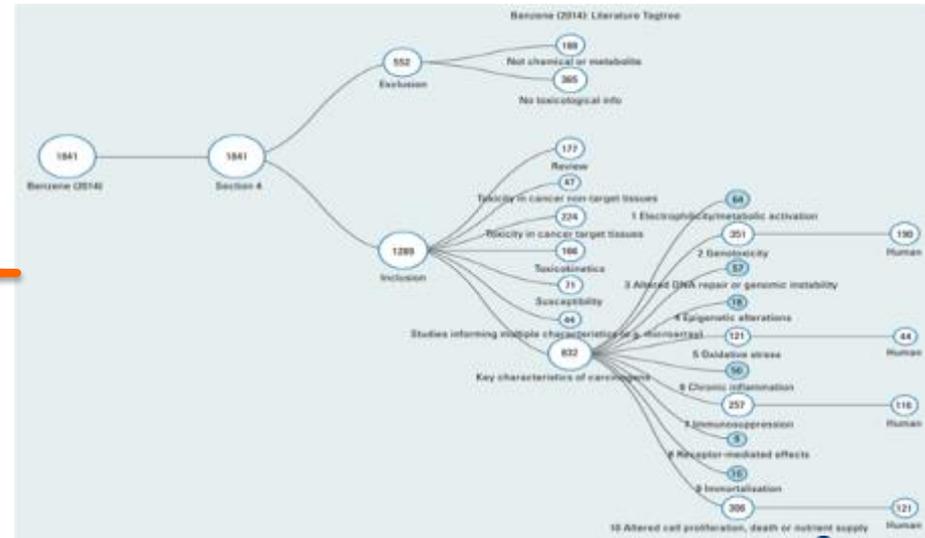
Use of KCs in Recent IARC Monographs Evaluations

Agent	Group	Cancer in humans	Cancer in animals	Strong mechanistic evidence (key characteristic)
Penta-chlorophenol	1	**Sufficient**	Sufficient	Is metabolically activated, is genotoxic, induces oxidative stress, modulates receptor-mediate effects, alters cell proliferation or death (1, 2, 5, 6, 8, 10)
Welding fumes	1	**Sufficient**	Sufficient	Are immunosuppressive, induce chronic inflammation (6, 7)
DDT	2A	**Limited**	**Sufficient**	Modulates receptor-mediated effects, is immunosuppressive, induces oxidative stress (5,7,8)
Dimethyl-formamide	2A	**Limited**	**Sufficient**	Is metabolically activated, induces oxidative stress, alters cell proliferation (1, 5, 10)
Tetrabromo-bisphenol A	2A*	Inadequate	**Sufficient**	**Modulates receptor-mediated effects, is immunosuppressive, induces oxidative stress (5, 7, 8)**
Tetrachloro-azobenzene	2A*	Inadequate	**Sufficient**	**Induces oxidative stress, is immunosuppressive, modulates receptor-mediated effects (6, 8, 10)**
ITO, melamine	2B	Inadequate	**Sufficient**	Induces chronic inflammation (8)
Parathion, TCP	2B	Inadequate	**Sufficient**	

*Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data

Guyton KZ et al. Carcinogenesis. 2018;39:614-622.

Key Characteristics with Strong Evidence across Multiple Evaluations (IARC Monographs Vol. 112-119)

Guyton KZ et al. Carcinogenesis. 2018;39:614-622.
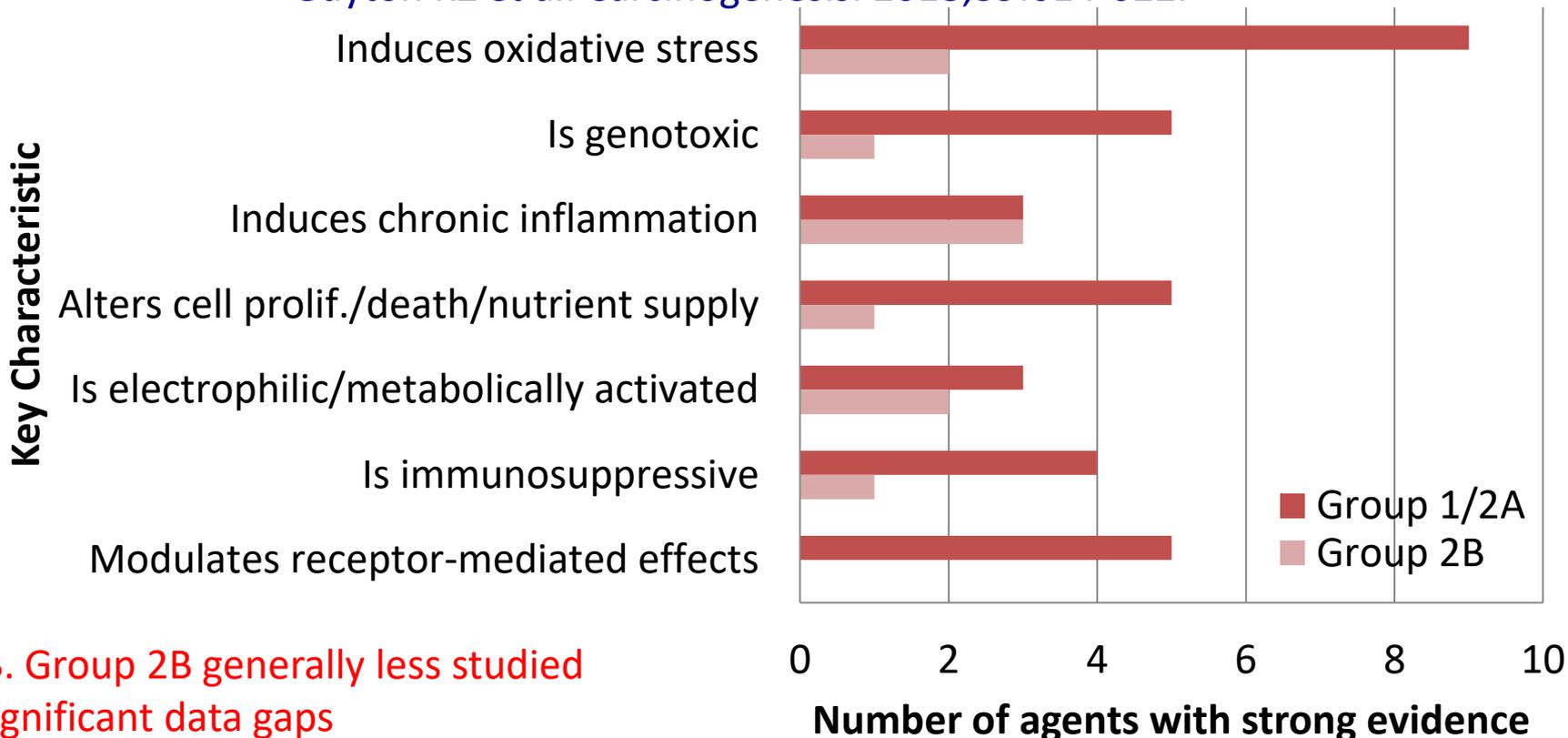
N.B. Group 2B generally less studied – significant data gaps

MT Smith, UCB Sept 2018

12

Key characteristics don't require risk assessor to guess the mechanism

- Mechanistic hypotheses in science are beneficial because if you test it and are wrong then you modify the hypothesis and get closer to the truth

- Mechanistic hypotheses in risk assessment are problematic because if you are wrong you may have made a bad risk decision that cannot easily be changed and may have caused medical or economic harm

National Academy of Sciences report released January 5, 2017

Using 21st Century Science to Improve Risk-Related Evaluations

The KC "approach avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence." (P.144)

AUTHORS

Committee on Incorporating 21st Century Science into Risk-Based Evaluations; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Academies of Sciences, Engineering, and Medicine

https://www.nap.edu/download/24635

Questions

- Does only 'Strong' evidence matter?
- How do we make 'Strong' consistent?
- How many strong KCs are needed?
- If a chemical possesses multiple KCs can we classify it as a possible/probable human carcinogen without any animal bioassay or epidemiological data?

9 - Elaine Faustman

- My comments are directed to:
- Maximizing this opportunity to update the Preamble and to
- Optimizing the use of new mechanistic and "other"
- types of "alternative" data to improve our assessments

- How have I interacted the IRAC monographs:
- I have been a consumer
- For risk assessments and evaluations on chemicals
- For exposure assessments
- For teaching
- I have been a participant
- I have been a working group member

Preamble:

The Preamble to the IARC Monographs describes the:
1) objectives and scope of the programme,
2) scientific principles and procedures used in developing a Monograph,
3) types of evidence considered and
4) scientific criteria that guide the evaluations.

From IARC preamble, 2006

- Of the four components of the Preamble I will focus on:

-

- Component 3: Increasing the types of information considered

-

- As a toxicologist and bench scientist as well as risk assessor I would

- Encourage IARC to look methodically at the types of new and
- alternative evidence that is rapidly becoming one of the largest
- categories of health and toxicology literature

- Build upon the white papers produced as products from a IARC
- Workshop held in Lyon to examine carcinogen mechanisms

- Example papers from these workshops built upon the Hallmarks of
- Cancer manuscripts and illustrated how a systematic method for
- identifying, organizing and summarizing mechanistic data could
- be developed. (For example Smith, et al 2016)
-
- This approach was applied to case studies, it addressed how biomarkers
- can inform our evaluations and also how time and how the various order
- of mechanistic signals may be working towards a common endpoint of
- cancer.
- Additional actions are needed to apply this more widely, add to the Preamble
- and ensure that it becomes standard practice.
-

- Why IARC?

- IARC is an internationally recognized and scientifically based agency that

- has over 40 years of successfully evaluated carcinogenic hazards for humans

- This has been done using a transparent and well-defined set of criteria for assessments as well as for defining participants and their roles in the workshop and monograph reports.

- Although many nations have capabilities to prepare assessments, IARC has this long history, successful partnerships and a context that has allowed for extra workshops that have facilitated new developments and set the standards within the discipline for assessment methods (for example applications of evidence for causality, quantitative dose-response evaluations, and epidemiology modeling to name a few in addition to the mechanistic workshops mentioned above).

- Additional research and systematic procedures are needed in considering the various types of alternative approaches such as in vitro, microfluidic platforms and also computational assessment. Just like the recent advances for assessing mechanistic data, IARC could help move forward systematic assessment of these methods for cancer hazard assessment.

- Exposure assessments have also been a key strength of IARC and the use of personal sensors linked with biomarkers of exposure could advance how such multiple pathway assessments are used especially for epidemiology studies but also in communicating potential for exposure.

- Keep the key strengths at IARC that have provided flexibility in looking at classes of chemicals by type and process and use. IARC is a "go to" source for this information.

▶ Kudos to IARC for over 40 years of carcinogen assessment. I look forward to the next decades and the innovations that IARC will make in integration of exposure and response for public and worker health.

10 - Nathaniel Rothman

Cross-sectional molecular epidemiology studies of humans exposed to suspect carcinogenic agents

- **Cross-sectional (*in vivo*) biomarker studies of humans exposed to potential carcinogenic agents will continue to play an important role in evaluating mechanistic data (Smith et al. 2016 EHP; Guyton et al. 2018 Carcinogenesis)**

- **In addition to standard epidemiological QC criteria, there are additional characteristics that need to be evaluated in these studies and should be addressed in revised sections B.2.a, B.2.e and B.4.**

Selected study design issues

- **Characterization of "exposed population"**

  - **Very recent as well as past quantitative exposure assessment**

  - **Range and relevance of exposure level**

  - **Current and past co-exposure characterization**

  - **Assessment of all important sources of exposure**

Selected study design issues

- **Characterization of control "unexposed" population**

    – **Comparability to exposed population by standard demographic characteristics**

    – **Comparability by SES, physical activity, work patterns, diet, other factors that could influence biomarker endpoints and may not be easily amenable to statistical adjustment**

Selected study design issues

- **Quality of biomarker data and analysis**

    – **Assay accuracy**

    – **Assay precision - CVs and especially ICCs critical**

    – **Important to incorporate assay precision into interpretation of results**

Evaluating relevance of exposure-biomarker association for a specific type of cancer

– Several million people enrolled into prospective cohorts/biobanks

– About to generate massive amount of omic data measured primarily in blood linked to future risk of developing specific cancers

– Can incorporate knowledge of this ongoing biomarker "validation" process in interpreting cross-sectional biomarker studies, which can provide biological plausibility to epidemiological observations made between an exposure and a specific cancer

Potential relationships between exposure, biomarker in specific tissue, and specific disease
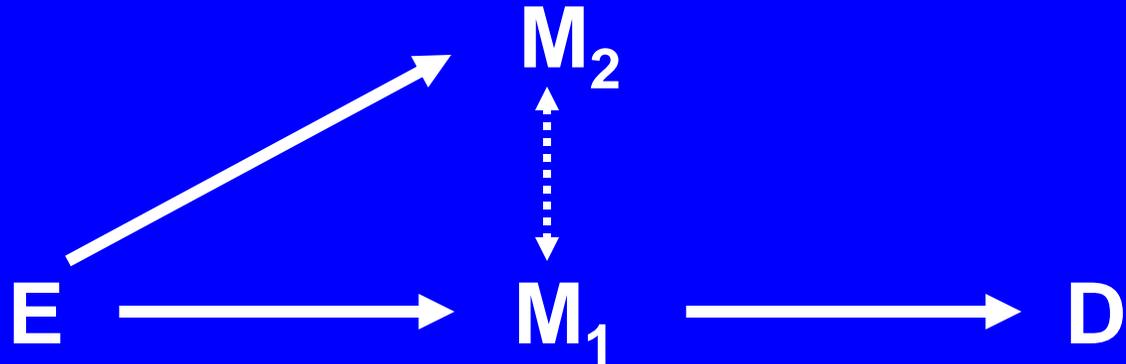
Potential relationships between exposure, biomarker in specific tissue, and specific disease
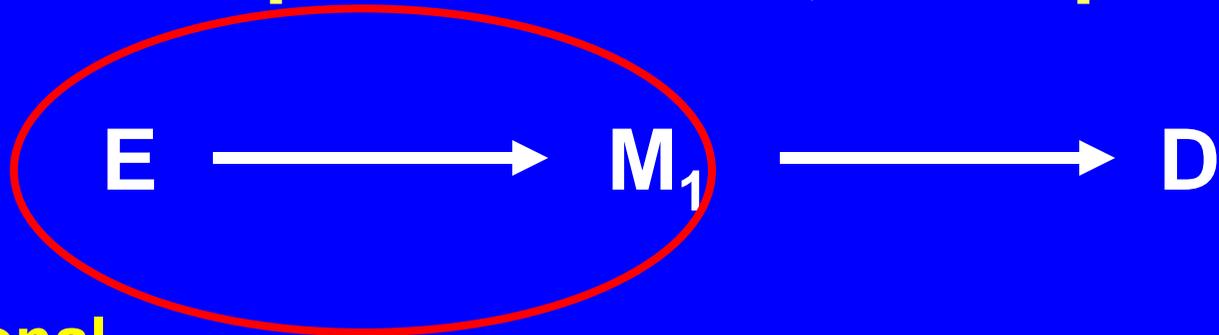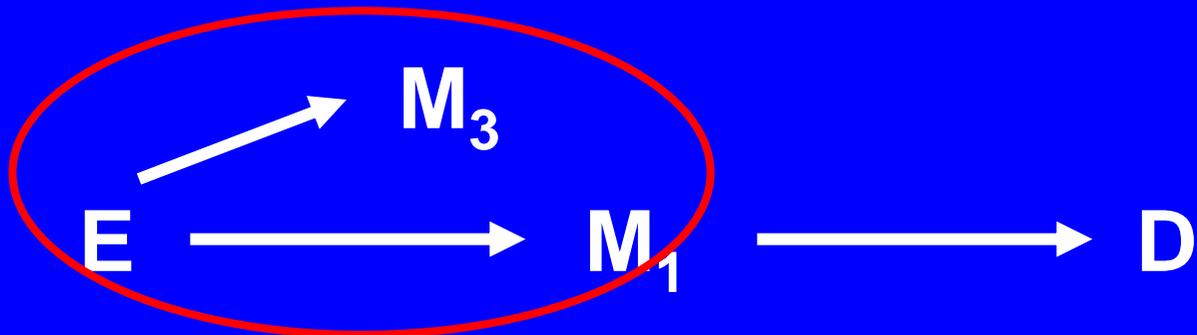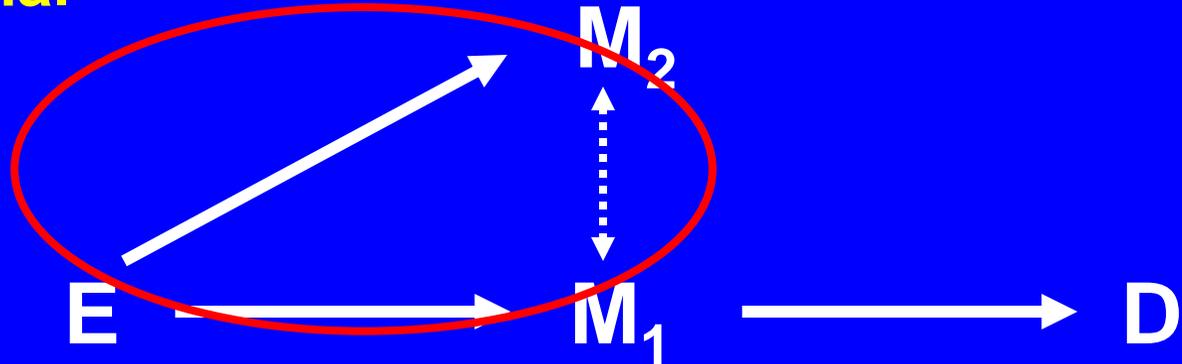
Potential relationships between exposure, biomarker in specific tissue, and specific disease
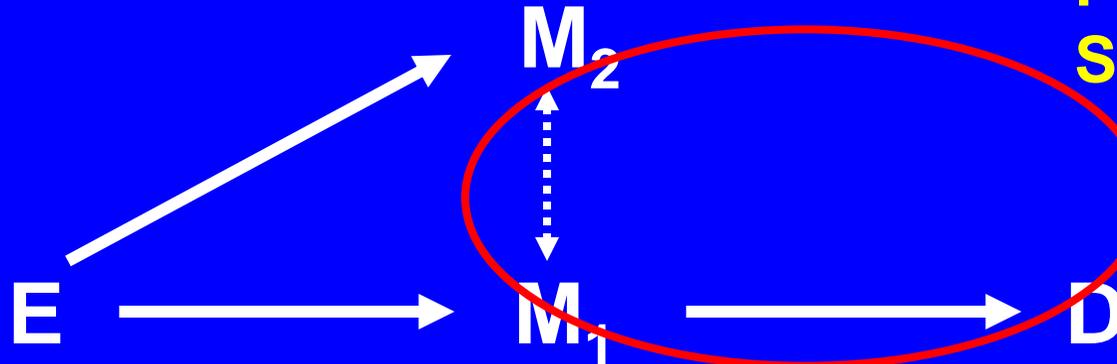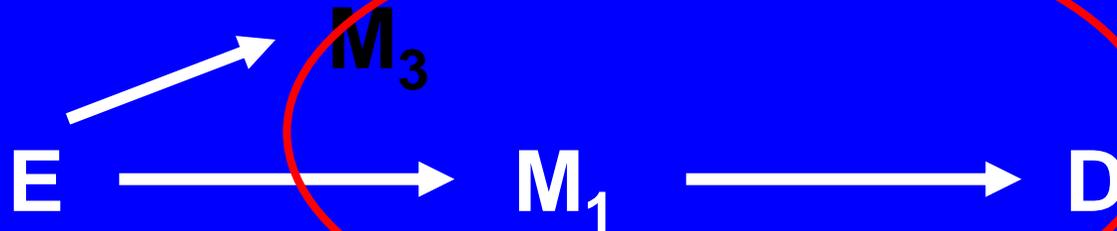
Summary

IARC review of cross-sectional biomarker studies of humans exposed to suspect carcinogenic agents can be improved by:

1) Formal definition of criteria for assessing molecular epidemiology cross-sectional study design quality and interpretation

2) Formal consideration of relevance of biomarker measured in a specific tissue for risk of specific types of cancer, informed by latest empirical results from prospective cohorts

11 - Ron Melnick

Comments on IARC Monographs Preamble

Ronald L. Melnick
Retired Toxicologist - NTP, NIEHS
Ron Melnick Consulting, LLC

IARC Public Webinar
17 September 2018

1. Cancer in Experimental Animals

Preamble needs to provide additional guidance on how working groups should judge adequacy and validity of experimental studies

1a. Aspects of Study Design

- **Basis for dose selection**
  - Adequately challenging to ID a cancer hazard
  - Characterize dose-response relationship

- **Study duration**
  - Sufficient to detect late developing tumors

- **Animal group size**
  - Large enough to detect rare or uncommon tumors

1b. Conduct of Studies

- **Agent**
  - **Purity**
  - **Stability in storage and in exposure medium**
  - **Exposure uniformity**

- **Compliance with GLP requirements**
  - **Non GLP studies should not be ignored if information is adequate to evaluate potential carcinogenicity**

- **Identification of lesions**
  - **Complete necropsy and histopathology**
  - **Extent of pathology review**

1c. Evaluation of Experimental Data

- **Reporting lesions**
  - Malignant and non-malignant lesions reported separately and combined
  - Incidence of preneoplastic lesions

- **Statistical analyses**
  - Trend and pairwise comparisons
  - Survival adjustment if differences in survival between controls and treatment groups

- **Use of historical control rates**
  - Most useful for rare or uncommon tumors
  - Most appropriate comparison is to the concurrent control group
  - For tumors with highly variable rates, account for variability in comparison to historical control rates

2. Overall Evaluation of Carcinogenicity

- **Application of mechanistic data, when less than sufficient evidence in humans:**
  - Current: upgrade to carcinogenic to humans if strong evidence in exposed humans
  - Suggested change: upgrade to carcinogenic to humans if strong evidence in exposed human cells or tissues

- **Downgrades to not classifiable (group 3)**
  - Current: strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans – Needs clarification
  - Cannot rely on inadequately tested mechanistic hypotheses

3. Confounding, Bias, and Follow-up

- **Chance, bias and confounding must be ruled out with reasonable confidence for sufficient evidence of carcinogenicity**

- **These criteria plus adequate follow-up need full written analyses before concluding there is *evidence suggesting lack of carcinogenicity***

12 - John E. French

Carcinogenic Hazard Identification using GEMM

John Edgar French, Ph.D.

UNC NRI & Gilling's School of Global Public Health – Chapel Hill, North Carolina USA

Formerly NIEHS, NTP

Research Triangle Park, North Carolina USA

Hypothesis

- An inducible proto-oncogene or inactivated tumor suppressor gene by itself increases susceptibility but does not cause cancer without activation or loss

- Exposure to a carcinogen will induce cancer with reduced latency due to additional genetic or epigenetic modifications

Criteria

- Broad range of susceptible tissues (**genetic background** dependent)

- Zero to low incidence of sporadic tumor incidence due to shortened latency

- Zero to low frequency of false negatives and false positives

- Mode or mechanism consistent with development of human cancers

Heterozygous *Trp53* deficient Mice

(Donehower et al., *Nature* 356:212, 1992)

Null (paternal C11)

6.5 kb

Wild-type (maternal C11)

16 kb

5 kb
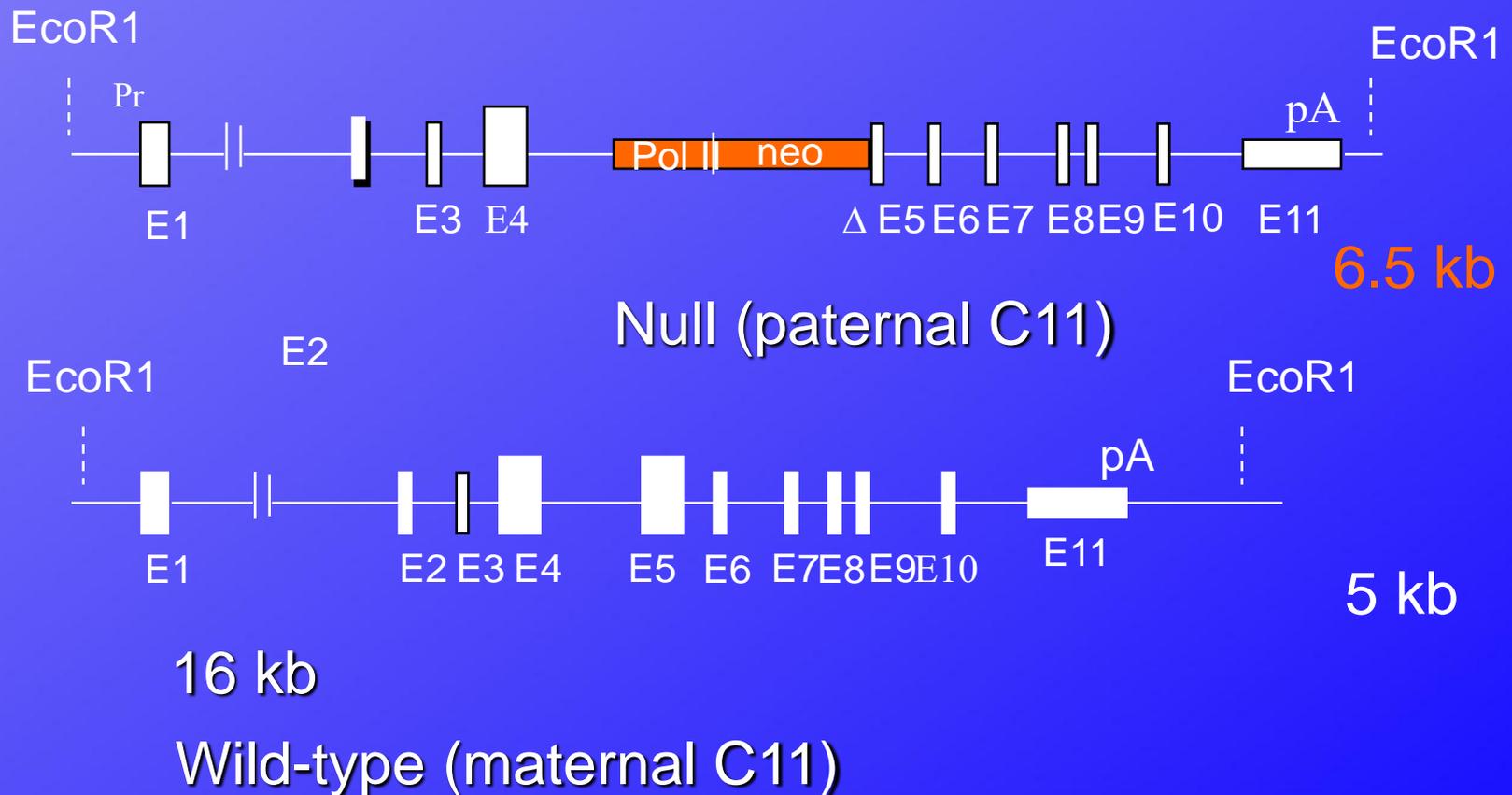
FVB/N-TgN(*v-Ha-ras*)^{Lep}(*Hras*)

- Tripartite construction
- Ectopic (integration site) expression
- Induced and/or clonally expanded
- Reporter phenotype
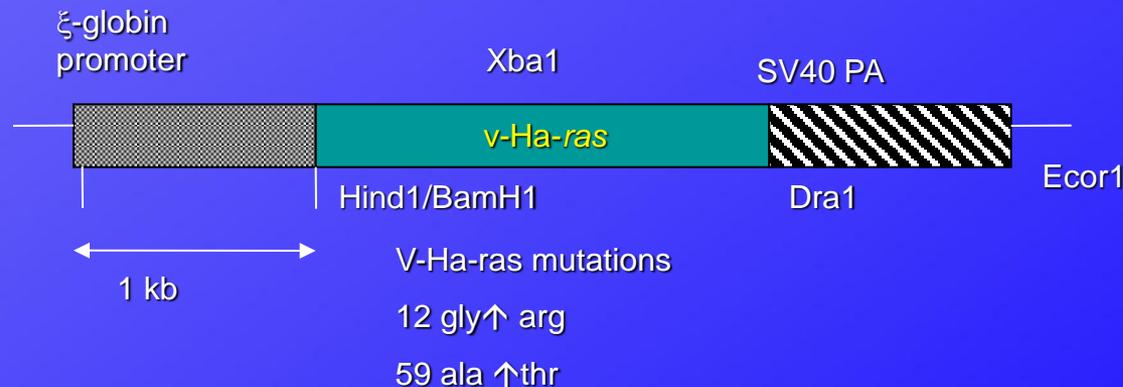
CB6F1-TgN(*RasH2*)^Sel
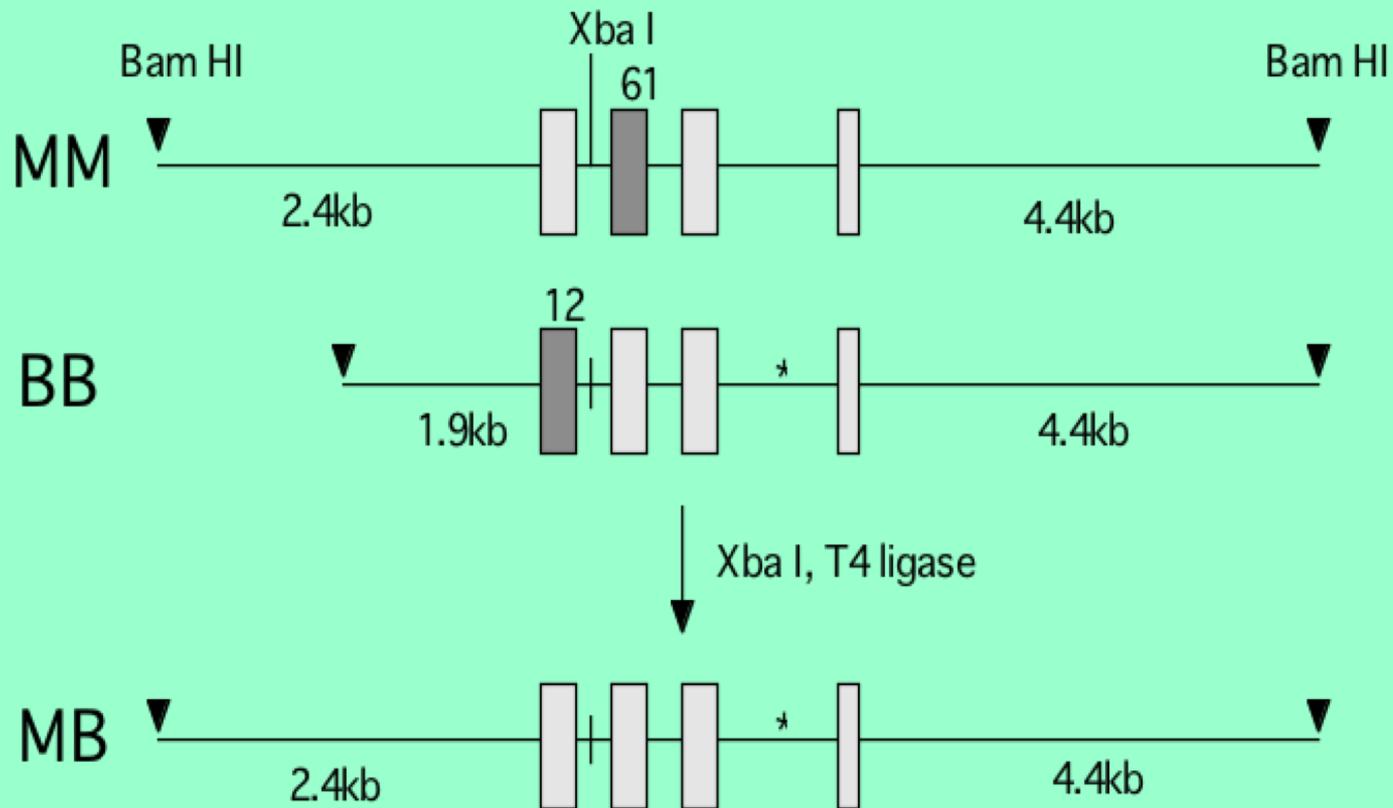
*: a point mutation in the last intron

Sekiya et al, Jpn. J. Cancer Res., 1985

GEMM Predictability

Data set for prediction (99 test chemicals)

| B6.129-Trp53^{tm1Brd} | FVB/N-TgN(v-ras$^{)Lep}$ | CB6F1-TgN(rasH2)^{Sel} |

[+] • 47 IARC Group1/2 NTP ROC - Known/Probable Human Carcinogens

[-] • 52 IARC Group 3/NTP ROC Least likely to be a human carcinogen

Pritchard et al. Environ Health Perspectives 111:444-54, 2003

Toxicologic Pathology 29 Issue 1_Suppl, 2001

GEMMs Predictability

Discrimination between
- known/probable human carcinogen
- least likely to be human carcinogen

1 = Trp53+/-
2 = Trp53-G
3 = Tg.AC
4 = RasH2
5 = p53-G/Ras-N
6 = p53-G/Ras-All
7 = p53-G/Tg.CA-N
8 = p53-G/Tg.AC-All
9 = NTP Rodent Bioassay
10 = Rat Bioassay Plus Tg.AC-N or Trp53-G
11 = Rat Bioassay Plus RasH2-N or Trp53-G
12 = Rat Bioassay Plus Genotoxicity
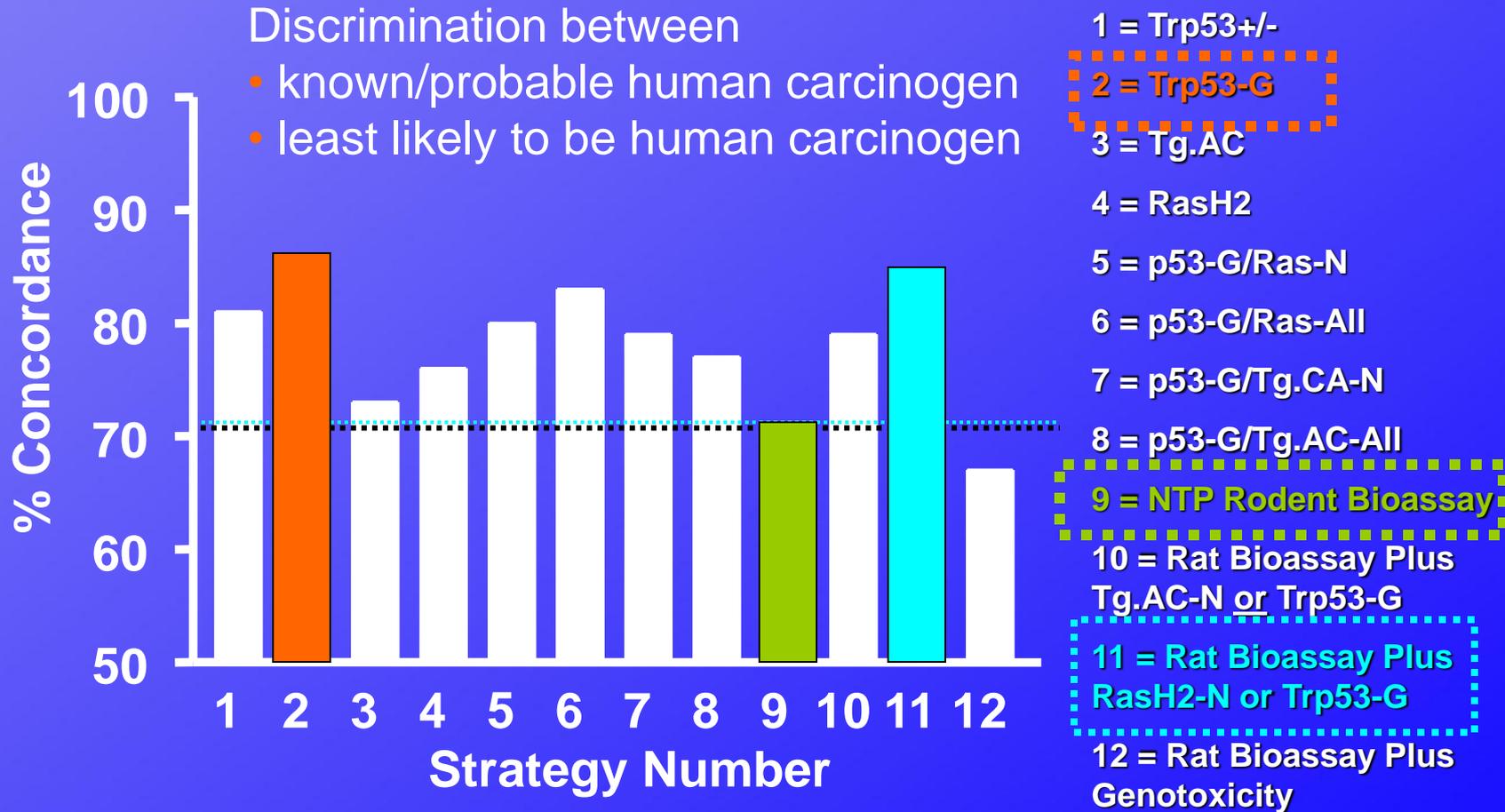
Pritchard et al. Environ Health Perspectives 111:444-54 (2003)

Conclusions

- Overall, GEMM performed well; issues of validation and standardization of protocols remain

- Combination of GEMM plus Rat (2-yr) bioassay missed no IARC Group 1/2 carcinogens and reduced the number of potential false positives for the expected human non-carcinogens (IARC Group 3)

- **Inclusion and elaboration in IARC Preamble warranted**

Population-based Mouse Models

GEMMs outcross to:

- homozygous inbred strains to create relevant population based models

- Collaborative-Cross Recombinant Inbred lines

- Diversity Outbred mice

for genome-wide analysis and mechanistic studies

Benzene induced myeloid leukemia in B6- & C3-*Trp53* heterozygous mice
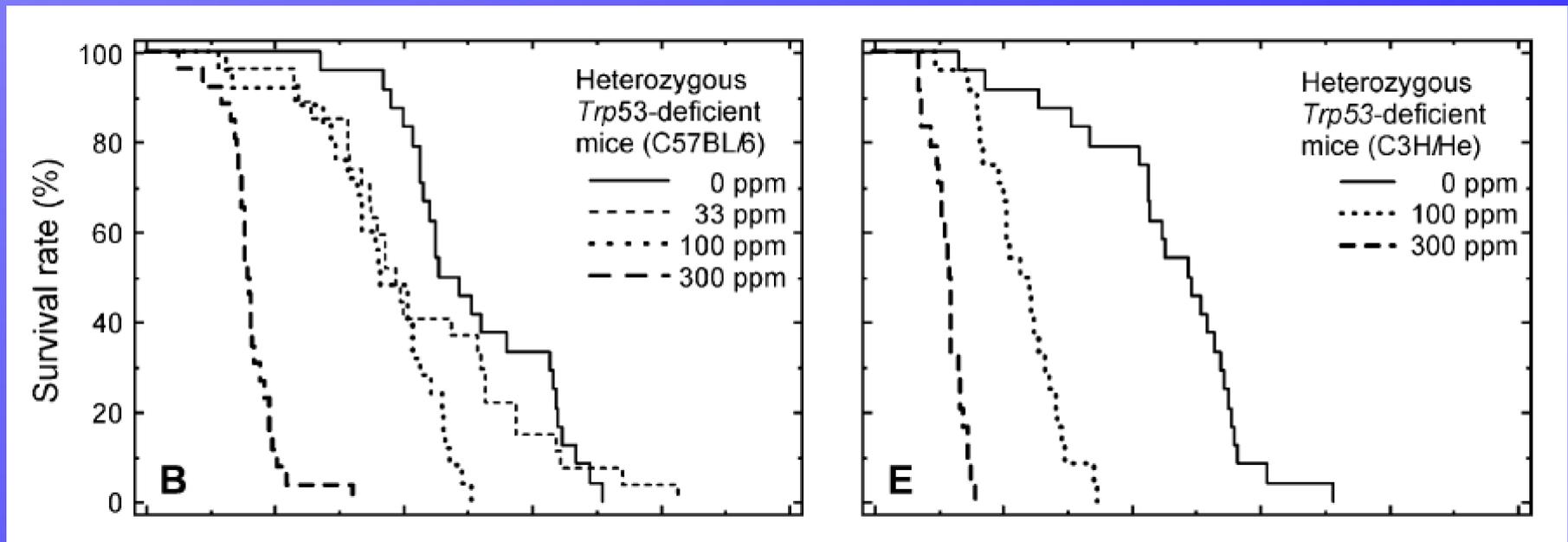
Myeloid leukemia: B6 (0, 0, 0, 2); C3 (2, 2, 9)

Survival (0, 3, or 6 Gy) *Trp53* def F1 Hybrids
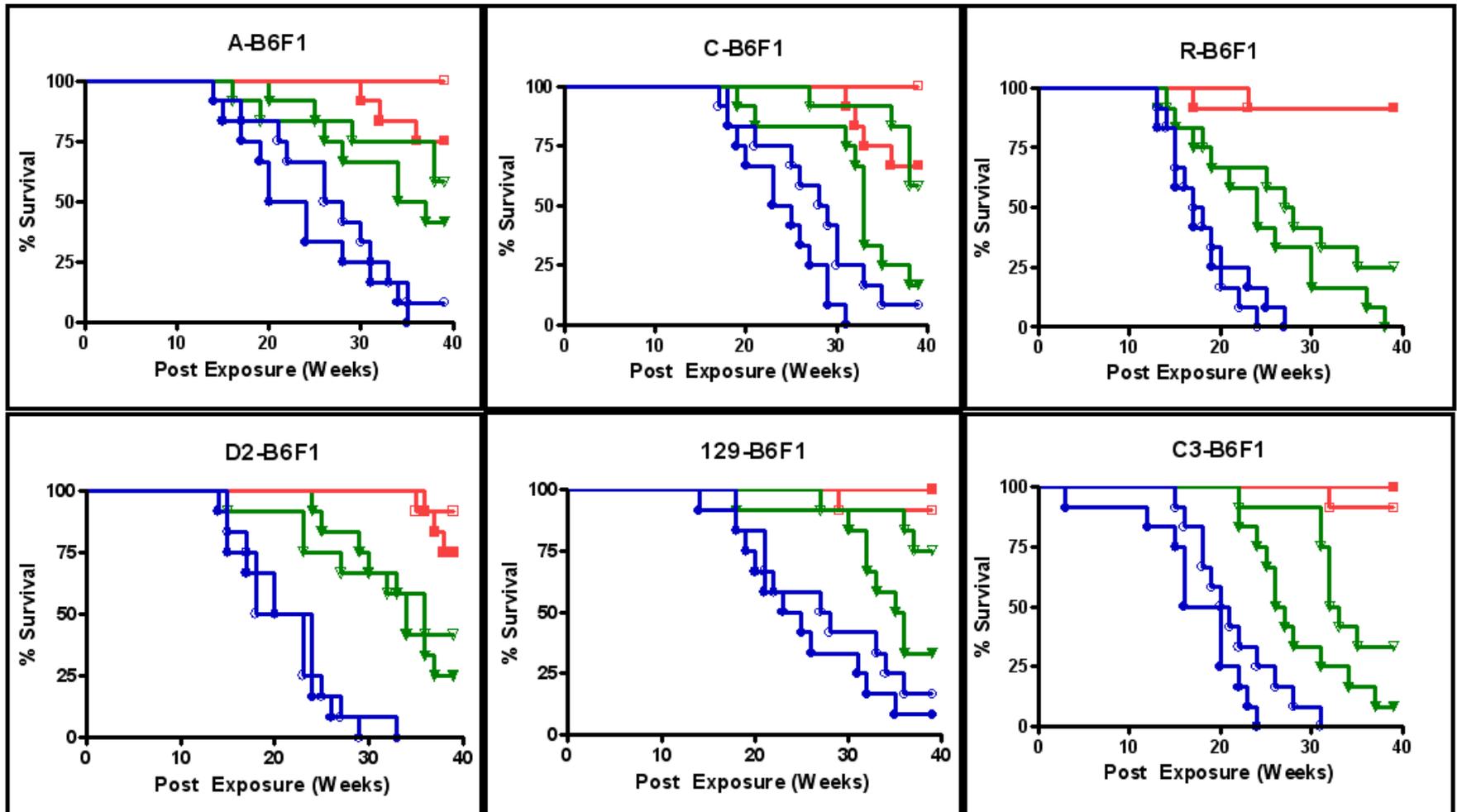
CB6.129F1-*Trp53*tm1Brd N12 Females

P = 0.00135

P = 0.0069

P = 0.0023

0 Gy   3 Gy   6 Gy

No. Mice with Tumor

Lymphoma, malignant
Leukemia, granulocytic
Histiocytic sarcoma
Salivary gland adenocarcinoma
Squamous cell carcinoma
Myoepithelial sarcoma
Adrenal cortical carcinoma
Rhabdomyosarcoma
Trichoepithelioma, malignant
Osteosarcoma
Alveolar/Bronchiolar carcinoma
Granuloasa cell tumor, ovary
Mammary gland adenocarcinoma

French et al. EHP 2015 Benzene induced micronuclei in Diversity Outbred Mice
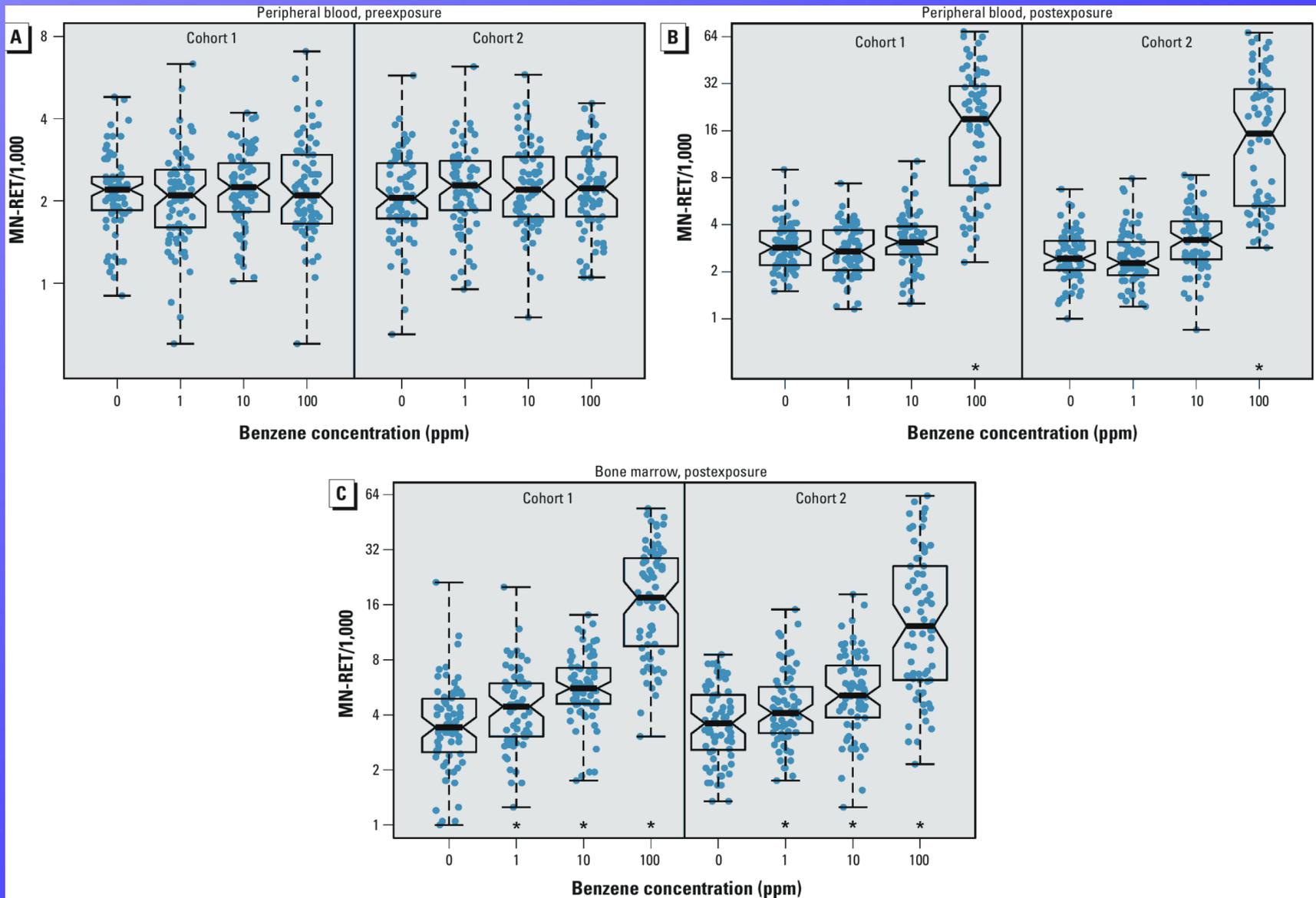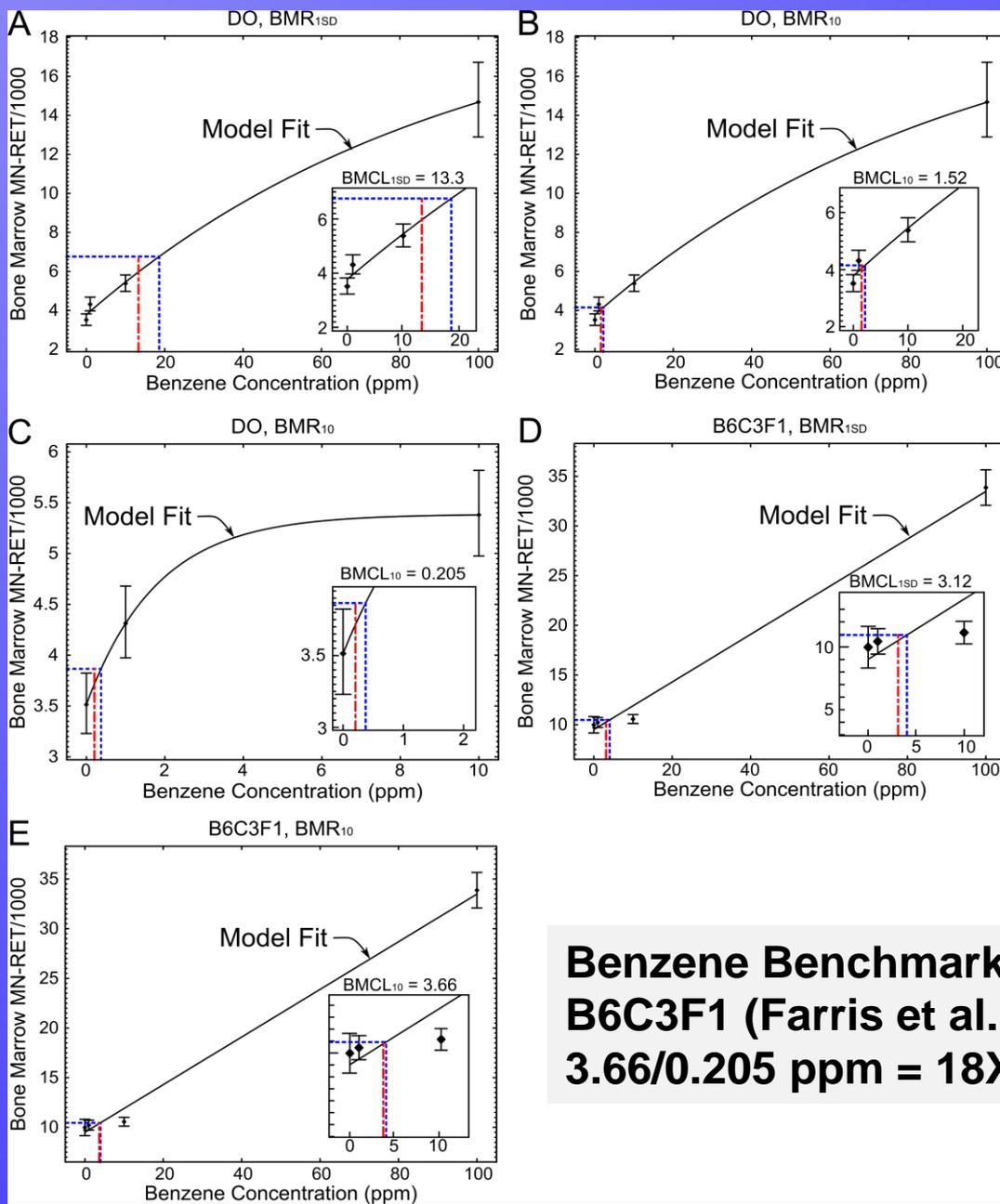
Benzene Benchmark Concentration Models B6C3F1 (Farris et al. 1996) and DO mice: 3.66/0.205 ppm = 18X difference

13 - Paul Lambert

Section 3: Animals testing of human viruses suspected of causing cancer

Cannot directly test human viruses in animals because they are species specific (i.e. they do not infect mice or other experimental animals).

Alternatives uses of animals for assessing the carcinogenicity of human viruses

1) Transgenic mice
2) Humanized mice

The absence of a Section 3 "Cancer in Experimental Animals" in the Monographs on viruses

The Working Group decided not to include in this Volume a separate section on "Cancer in experimental animals" in the *Monographs* on viruses, but rather to include description of such studies under Section 4 "Other Relevant Data" for the following reasons:

• The use of animals as surrogate hosts for the study of a human tumour virus is often problematic since species-specicity limits the feasibility of this approach for most of these viruses. HTLV-1 is one exception: this virus can infect several di erent animal species (rabbits, rats and monkeys) but does induce adult T-cell leukaemia/lymphoma in monkeys only. For some human tumour viruses (e.g. KSHV), the use of humanized SCID mice, in which the human target cell for the virus is placed into a mouse host context, can provide a platform for in- vivo infection. However, apart from EBV, which causes lymphoproliferative diseases in New World monkeys and humanized SCID mice, the use of surrogate hosts has not proven very useful for assessing the carcinogenicity of human viruses in humans.

• Cancer models for human tumour viruses that make use of animal viruses are very scarce. In fact, although many viruses that infect non-human primate species are related to the human tumour viruses, the incidence of cancer is low in these species – as it is in humans – which makes cancer studies costly and di cult. Moreover, animal tumour virus models in non-primate species often do not accurately reflect the mechanism of the disease caused by the cognate human tumour virus. For instance, woodchuck hepatitis virus induces HCC that is histopathologically very similar to that caused by HBV in humans, but it does so through a different mechanism.

• Transgenic mouse models provide powerful means for performing mechanistic studies to investigate the role of individual viral genes in cancer. Indeed, for many of the human tumour viruses described in this volume, transgenic mouse studies provide critical mechanistic evidence. However, such transgenic mouse models do not represent models for understanding the cancer etiology in the context of natural viral infections, and are therefore more appropriately discussed in Section 4.

HPV16 Transgenic Mice: Cervical Cancer

Chronic estrogen-induced cervical and vaginal squamous carcinogenesis in human papillomavirus type 16 transgenic mice.
Proc Natl Acad Sci U S A. 1996 93(7):2930-5. PMID: 8610145

Critical roles for non-pRb targets of human papillomavirus type 16 E7 in cervical carcinogenesis.
Cancer Res. 2006 66(19):9393-400. PMID: 17018593

The human papillomavirus E6 oncogene dysregulates the cell cycle and contributes to cervical carcinogenesis through two independent activities.
Cancer Res. 2007 67(4):1626-35. PMID: 17308103

A role for HPV16 E5 in cervical carcinogenesis.
Cancer Res. 2010 70(7):2924-31. PMID: 20332225

Human papillomavirus oncogenes reprogram the cervical cancer microenvironment independently of and synergistically with estrogen.
Proc Natl Acad Sci U S A. 2017 114(43):E9076-E9085. PMID: 29073104

Estrogen pellet

HPV16 Transgenic Mice: Head and Neck Cancer

[Identification of biomarkers that distinguish human papillomavirus (HPV)-positive versus HPV-negative head and neck cancers in a mouse model.](#)
Proc Natl Acad Sci U S A. 2006 103(38):14152-7. PMID: 16959885

[Role of Rb-dependent and Rb-independent functions of papillomavirus E7 oncogene in head and neck cancer.](#)
Cancer Res. 2007 67(24):11585-93. PMID: 18089787

[Human papillomavirus type 16 E6 and E7 oncoproteins act synergistically to cause head and neck cancer in mice.](#)
Virology. 2010 407(1):60-7. PMID: 20797753

HPV transgenic mouse

4NQO (16 weeks)

Cutaneous High Risk HPVs: Skin Cancer

Skin hyperproliferation and susceptibility to chemical carcinogenesis in **transgenic** mice expressing E6 and E7 of human papillomavirus type 38.
J Virol. 2005 79(23):14899-908. PMID: 16282489

Development of skin tumors in mice **transgenic** for early genes of human papillomavirus type 8.
Cancer Res. 2005 65(4):1394-400. PMID: 15735026

Spontaneous tumour development in human papillomavirus type 8 E6 **transgenic** mice and rapid induction by UV-light exposure and wounding.
J Gen Virol. 2009 90(Pt 12):2855-64. PMID: 19692543

Beta HPV38 oncoproteins act with a hit-and-run mechanism in ultraviolet radiation-induced skin carcinogenesis in mice.
PLoS Pathog. 2018 14(1):e1006783. PMID: 29324843

MCPyV: Merkel Cell Carcinoma

Merkel Cell Polyomavirus Small T Antigen Induces Cancer and Embryonic **Merkel Cell** Proliferation in a **Transgenic** Mouse Model.
PLoS One. 2015 Nov 6;10(11):e0142329. PMID: 26544690

Tumorigenic activity of merkel cell polyomavirus T antigens expressed in the stratified epithelium of mice.
Cancer Res. 2015 Mar 15;75(6):1068-79. PMID: 25596282

Merkel Cell Polyomavirus Small T Antigen Initiates **Merkel Cell** Carcinoma-like Tumor Development in Mice.
Cancer Res. 2017 ;77(12):3151-3157. PMID: 28512245

EBV and KSHV: Humanized mice

[Epstein-Barr virus type-2 infects T-cells and induces B-cell lymphomagenesis in **humanized mice**](#).
J Virol. 2018 Aug 8. pii: JVI.00813-18. PMID: 30089703

[An EBNA3C-deleted Epstein-Barr virus (**EBV**) mutant causes B-cell lymphomas with delayed onset in a cord blood-**humanized mouse model.**](#)
PLoS Pathog. 2018 Aug 20;14(8):e1007221. PMID: 30125329

[Persistent KSHV Infection Increases **EBV**-Associated Tumor Formation In Vivo via Enhanced **EBV** Lytic Gene Expression.](#)
Cell Host Microbe. 2017 Jul 12;22(1):61-73.e7. PMID: 28704654

[Latent Membrane Protein 1 (LMP1) and LMP2A Collaborate To Promote Epstein-Barr Virus-Induced B Cell Lymphomas in a Cord Blood-**Humanized** Mouse Model but Are Not Essential.](#)
J Virol. 2017 Mar 13;91(7). pii: e01928-16. PMID: 28077657

[Knockout of Epstein-Barr virus BPLF1 retards B-cell transformation and lymphoma formation in **humanized mice**](#).
MBio. 2015 Oct 20;6(5):e01574-15. PMID: 26489865

[An Epstein-Barr Virus (**EBV**) mutant with enhanced BZLF1 expression causes lymphomas with abortive lytic **EBV** infection in a **humanized mouse model.**](#)
J Virol. 2012 Aug;86(15):7976-87. PMID: 22623780

Suggested addition to section 3

In the case of human viruses, assessment of their carcinogenic properties cannot be carried out directly in animals because most of the relevant viruses only infect humans. Alternative uses of animals to assess the carcinogenicity of human viruses are therefore appropriate. These include the use of genetically engineered mice in which viral genes are targeted in their expression to the tissues that are normally infected by the virus in humans and from which cancers are known to arise, or use of humanized mice in which the human cells normally infected by the human virus are implanted into mice.

14 - John Cherrie

Exposure data…

- General information on the agent

- Production and use

- Methods of analysis and detection

- Occurrence, and sources

- Routes of human occupational and environmental exposures

- Regulations and guidelines

John Cherrie

Availability of exposure data…

- Problems getting data from outside USA and Northern Europe

- Mostly fairly recent with little contextual data

- Exposure levels (and prevalence) higher in the past

Creely KS *et al.* (2007) Trends in inhalation exposure--a review of the data in the published scientific literature. Ann Occup Hyg.; 51(8): 665-678.
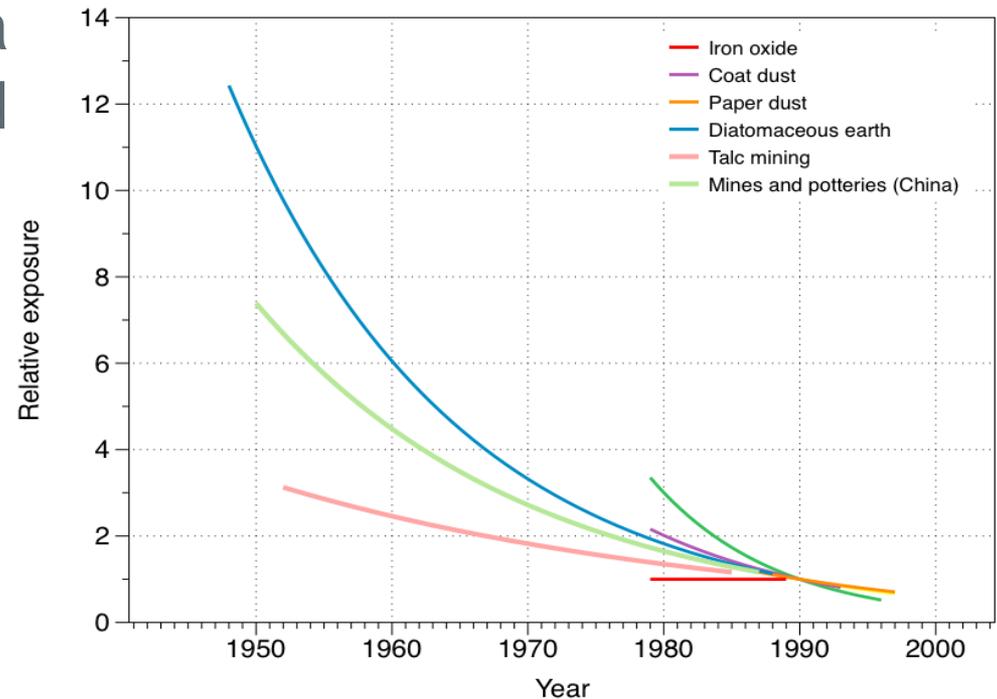
Availability of exposure data…

- Co-exposures often not clearly described

- Today, for workplace exposure, commercial companies hold the majority of data

- Perhaps use exposure modelling to estimate exposures

John Cherrie

Data on exposed population…

- Information on occurrence / production and use are insightful
  - However, data are often unavailable
  - Access to national/international databases, e.g. ECHA?
- Details of number of people exposed is mostly very limited
- Mostly little details of work or other activities where people may be exposed

John Cherrie

Measurement methods…

- Descriptive: no critical evaluation or recommendation of any method is meant or implied

- It's unclear what purpose this serves!

- Perhaps important to highlight the reliability of methods to assess exposure and how different approaches relate to each other, e.g. air sampling and biological monitoring

John Cherrie

Regulations and guidance…

- Workers, consumers and the environment
- Regulations are complex and vary between jurisdictions
- Impossible to give true international coverage
- Regulations and limit values frequently change
- Perhaps needs to highlight specific interventions, e.g. is the agent banned or is use restricted in specific countries

John Cherrie

Critical review of the epidemiological literature…

- Review exposure assessment methods of specific epidemiological studies identified collaboratively with the epidemiology group

- Past levels of exposure, reliability of assessments, inter-relationship of different measures

- Should highlight possible co-exposure to other risk factors

- Include in preamble

John Cherrie

15 - Paul Demers

Comments on the IARC Monographs Preamble

Paul A. Demers, Ph.D.
Director, Occupational Cancer Research Centre
Cancer Care Ontario, Toronto Canada
Professor, Dalla Lana School of Public Health,
University of Toronto

17 September, 2018

Areas I will comment on

- A general need for clarity/transparency
- Selection of the Working Group members
- Studies of Cancer in Humans
  - Selection of Studies
  - Quality of Studies considered
  - Criteria for Causality
- Evaluation

More Clarity Needed

"The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. <u>The procedures through which a Working Group implements these principles are not specified in detail.</u> They usually involve operations that have been established as being effective during previous Monograph meetings but remain, predominantly, the prerogative of each individual Working Group."

Preamble Page 1: 41 to 2:2.

More Clarity Needed

- Although I understand that there may be some variability, working procedures should be presented in greater detail for transparency.

- In addition, despite a section entitled "Working procedures," procedures are scattered throughout, even when related to the same topic

- For example, how are working group members (WG) chosen?

  - "participants are selected by IARC in consultation with other experts" (page 5: 30-31). Better detail on WG characteristics sought are provided on Page 4: 26-31.

Studies Considered by WG

- More clarity is needed in describing the selection of studies to be considered
  - IARC does an initial search using pubmed with other sources to supplement (page 5: 32-33)
  - After agents are assigned to WG, their responsibility to critically review and decide if any thing was missed and select the relevant data (4, 20-22)

- The basic criteria need to remain:
  - Published or accepted in the openly available literature and government reports

- IARC must consider all potentially relevant studies, even if some are given more weight in the evaluation

Quality of Studies Considered

- The quality issues currently described in the preamble are simple, but appropriate, although misclassification of exposure deserves more discussion.

- Various tools used for conducting systematic reviews and applying some type of quality screen would be inappropriate.

- Almost all studies considered by most WGs are observational in nature and must continue to examine the weight of the full body of epidemiologic evidence.

Criteria for Causality

- Under both Criteria for Causality (page 11) and Evaluation (page 16), the reader is reminded of the importance of chance, bias and confounding.

- Almost all observational studies have limitations which can result in bias.

- What is important is to consider is the direction and potential magnitude of those biases, which can help explain heterogeneity in study findings.

Procedures for Evaluation

- The reader gets very little sense of the formality of the WG plenary sessions or the rigour of the evaluation.

- The role of the epidemiology and animal studies sub-groups in proposing initial evaluations for their areas of responsibility does not seem to be mentioned.

- That their revised drafts are made available to the full WG prior to discussions in plenary should also be mentioned.

Preliminary Default Evaluation

Cancer in Experimental Animals

Cancer in Humans		Sufficient	Limited	Inadequate
	Sufficient	Group **1**	Group **1**	Group **1**
	Limited	Group **2A**	Group **2B** **Exceptionally: Group 2A**	Group **2B** **Exceptionally: Group 2A**
	Inadequate	Group **2B**	Group **3**	Group **3**

Strong mechanistic evidence can move an evaluation up or down a category

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

General Comments

- The working procedures need more clarity
  - For example, all WG meetings that I remember begin with a plenary session where the working procedures and the evaluation process are explained and issues such as conflict of interest are discussed
- Although nicely written prose, the Preamble is not the clearest document to find and locate information
- Better organization and a greater use of flow charts and other figures could help.

16 - Dana Loomis

Evaluating Epidemiologic Studies for the IARC Monographs

Dana Loomis, PhD

University of Nevada, USA

Declaration of Interests

- I have no financial interest related to the topic of this presentation or to the IARC Monographs

- I previously served as Senior Epidemiologist for the Monographs and Head of the IARC Monographs Group

Evaluation of evidence from epidemiologic studies

Searching and screening the literature

- Select potentially pertinent studies for further review

Evaluation of individual studies

- Identify the most informative studies

Evaluation of the body of evidence

- Sufficient
- Limited
- Inadequate
- ESLC

Overall evaluation
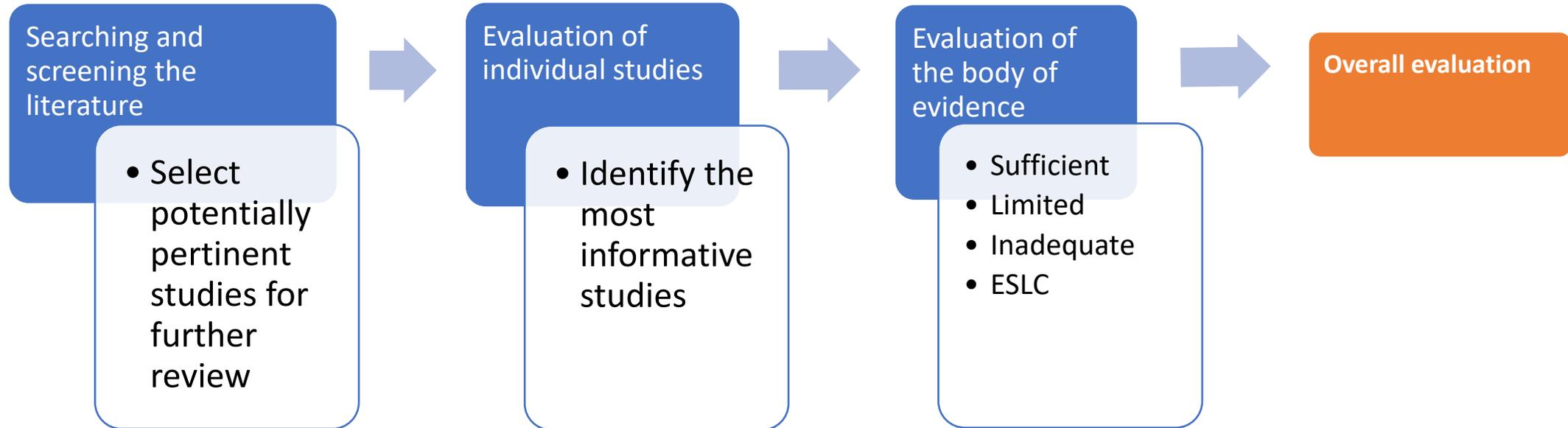
Evaluating epidemiologic studies: the purpose

- Why evaluate study quality?
  - To identify the most informative studies as a basis for hazard identification

- Other considerations
  - To assure the public that the informative studies have been considered and that strengths and limitations have been taken into account
  - To provide an trustworthy, understandable record of Working Groups' assessments of the evidence

Current practice: study selection

- Guidance from the Preamble
  - Only published/accepted reports are eligible (A.4)
  - "relevant sources of…data are gathered by IARC from recognized sources…including PubMed"
  - Working Groups "are expected to supplement IARC searches with their own searches" (A.6)
  - Studies of all types may be reviewed (B.2(a))
- Other procedures
  - IARC Secretariat conducts electronic searches, screens studies and documents results in HAWC
  - WGs may (or may not) conduct additional searches and add studies
  - Further inclusion/exclusion decisions are made in drafting and revision

Current practice: study quality

- Quality is formally evaluated and reported in the Monographs
- The Preamble gives specific guidance
- Consider "bias, confounding and chance" (B.2(b), specifically:
  - Definition of disease and exposure; potential for differential classification
  - Control of confounding; appropriate comparison groups in cohort studies
  - Presentation of "basic data" (numbers exposed & unexposed, observed & expected, etc)
  - Reporting of statistical methods
- Use square brackets to highlight any "important aspect of a study that directly impinges on its interpretation" (A.4, B)
- Further comments may be made in narrative descriptions or summaries

Liabilities of current practice

- Working Groups have wide discretion in study selection, evaluation and documentation
- However, the state of the art has evolved: transparency & accountability are expected
- The Preamble gives little guidance on how pertinent studies are found and none on documenting inclusion and exclusion; the term "*systematic review*" is not used
- IARC and WG search strategies and results are not published
- Inclusion/exclusion decisions are not consistently documented
- Evaluation of some key elements of quality (e.g., exposure assessment) is not specifically required
- Use of square brackets to note study limitations is inconsistent
- The studies found most influential are not always clearly identified

Alternatives: checklists, scores and algorithms

- Developed for reviews of RCTs, but increasingly adopted for environmental studies, notably by US government agencies
- Provide a formal structure:
  - Specifying which elements study quality are evaluated
  - Documenting how each element was assessed
- Some produce quality or "confidence" scores
- May be useful for non-expert reviewers
- Appearance of objectivity, yet many arbitrary elements
- Judgment still required
- "One-size-fits-all" approach
- Time consuming for reviewers

Alternatives: enhanced guidance and documentation

- Current practices and procedures usually provide robust results, but increased transparency would enhance public confidence

- Clarity and consistency also benefit the WG process

- Liabilities can be greatly reduced through improved instructions to Working Groups and clear, consistent documentation of study selection and evaluation

- Existing procedures (e.g., systematic searches) can be formalized by adoption into the Preamble

Recommendations

Study selection

- Amend the Preamble to specify systematic review methodology

- Publish search strategies (including WG searches) and numbers of studies included/excluded at each stage

- Document WG decisions to include/exclude studies within Monograph narratives

- Consider requiring explicit justification to include non-analytic studies, e.g., ecologic studies, case series, case reports

Recommendations

Study evaluation

- Revise Preamble language to clarify that potential for selection bias, information bias and confounding must be evaluated for every study

- Document specific concerns **or** absence of concern for every study in Monograph narratives

- Consider amending Preamble instructions to explicitly require evaluation of exposure assessment quality

- Amend Preamble instructions for study descriptions or summaries to ensure definitive studies are clearly identified

- *Do not adopt checklists, algorithms or scoring procedures*