The evidential role of the key characteristics of carcinogens

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KCCs are used by IARC to evaluate potential carcinogens.

But what are they, exactly, and how can they best be used?

EP: They should be interpreted as mechanism hypotheses, not as properties of carcinogens.

Contents

1 IARC


International Agency for Research on Cancer
World Health
Organization

Cancer kills ≈ 10 million people each year.

Nearly 1 in 6 deaths.

Causes include tobacco, obesity, alcohol, HPV, hepatitis and environmental and work-place exposures.

The International Agency for Research on Cancer (IARC) is the WHO body for cancer.

Set up in 1965, based in Lyon.

The IARC Monographs section evaluates potential carcinogens.

Since 1970, over a thousand agents have been evaluated.

The Preamble to the Monographs specifies the IARC Monographs methodology.

Potential carcinogens are classified as:

Group 1. The agent is carcinogenic to humans.

Group 2A. The agent is probably carcinogenic to humans.

Group 2B. The agent is possibly carcinogenic to humans.

Group 3. The agent is not classifiable as to its carcinogenicity to humans.

A review is carried out by a working group, which is divided into subgroups:

- Exposure characterization,
- Cancer in humans,
- Cancer in experimental animals,
- Mechanistic evidence.

The mechanistic subgroup looks for key characteristics of carcinogens . . .

2 Key characteristics of carcinogens

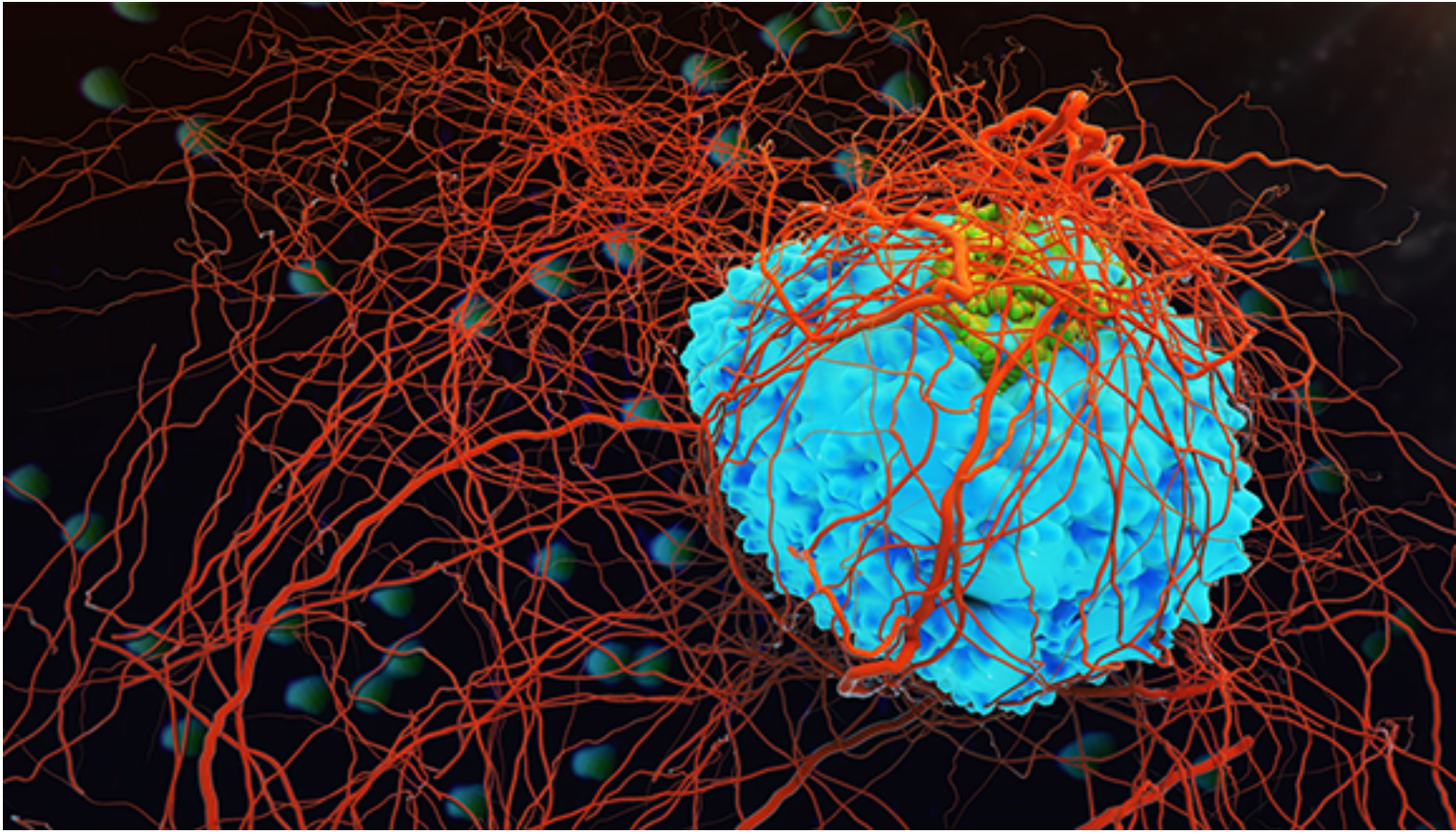


Table 1: The key characteristics of carcinogens described by Smith et al. (2016). From IARC (2019).

K_1	Is electrophilic or can be metabolically activated to an electrophile
K_2	Is genotoxic
K_3	Alters DNA repair or causes genomic instability
K_4	Induces epigenetic alterations
K_5	Induces oxidative stress
K_6	Induces chronic inflammation
K_7	Is immunosuppressive
K_8	Modulates receptor-mediated effects
K_9	Causes immortalization
K_{10}	Alters cell proliferation, cell death, or nutrient supply

The motivation behind the KCCs

KCCs are used to **guide the literature search**:

> 'there was no widely accepted method to search systematically for relevant mechanistic evidence, resulting in a lack of uniformity in the scope of mechanistic topics addressed across IARC Monographs evaluations.' (IARC, 2019, p. 26.)

Also for deciding whether **mechanistic evidence is strong**:

> 'For instance, ethylene oxide is genotoxic .... Evidence for a group of key characteristics can strengthen mechanistic conclusions (e.g. "induces oxidative stress" together with "is electrophilic or can be metabolically activated to an electrophile", "induces chronic inflammation", and "is immunosuppressive"); see, for example, 1-bromopropane.' (IARC, 2019, p. 29.)

Mechanistic evidence is classified as strong, limited or inadequate.

But what *are* the KCCs?

IARC is against thinking of KCCs as mechanism hypotheses:

> 'Key characteristics are distinct from the "hallmarks of cancer", which relate to the properties of cancer cells . . . . Key characteristics are also distinct from hypothesized mechanistic pathways, which describe a sequence of biological events postulated to occur during carcinogenesis. As such, the evaluation approach based on key characteristics, outlined below, "avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence."' (IARC, 2019, p. 27.)

Last year, IARC held a workshop on the KCCs, hoping to make their role more explicit.

Our view is that Evidential Pluralism can help to clarify their role . . .

3 Evidential Pluralism

Correlation is not Causation

A correlation between A and B (conditional on potential confounders) might be due to:

Causation. A is a cause of B.

Other causal explanations. Reverse causation, confounding, performance bias, detection bias, *. . .*

Statistical explanations. Chance, fishing, temporal trends.

Non-causal connections. Semantic, constitutive, mereological, logical, nomological or mathematical relationships between A and B.

If A is a cause of B, then there is some complex of mechanisms that:

Explains instances of B by invoking instances of A, and

Can account for the magnitude of the observed correlation.

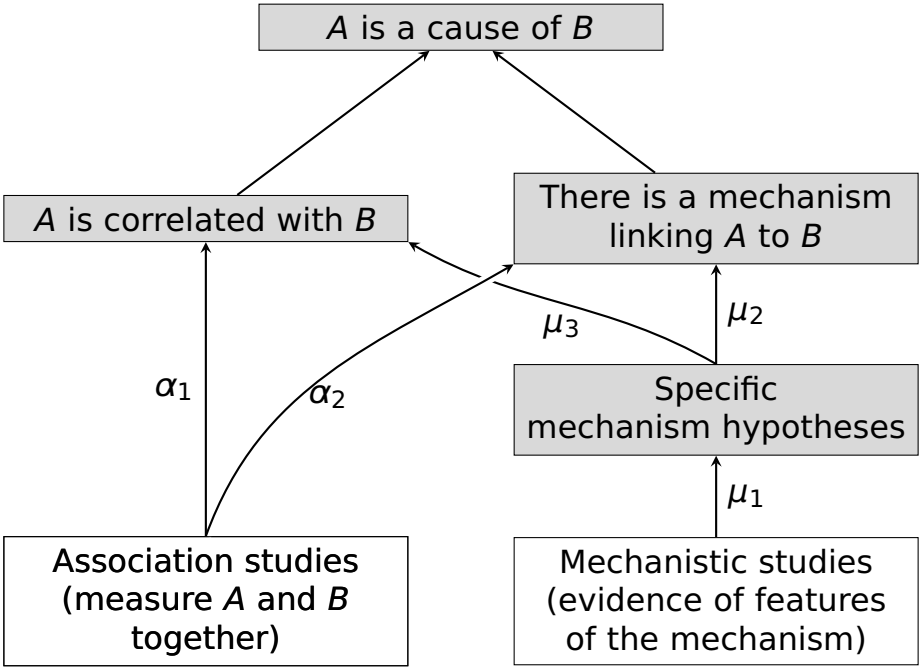
So, in order to establish causation one needs to establish two things:

Correlation. The existence of a correlation, conditional on potential confounders.

Mechanism. The existence of a mechanism that can explain that correlation.

(Russo, F. and Williamson, J. (2007). Interpreting causality in the health sciences. *International Studies in the Philosophy of Science*, 21(2):157–170.)

This observation motivates **Evidential Pluralism**, a theory of causal enquiry:

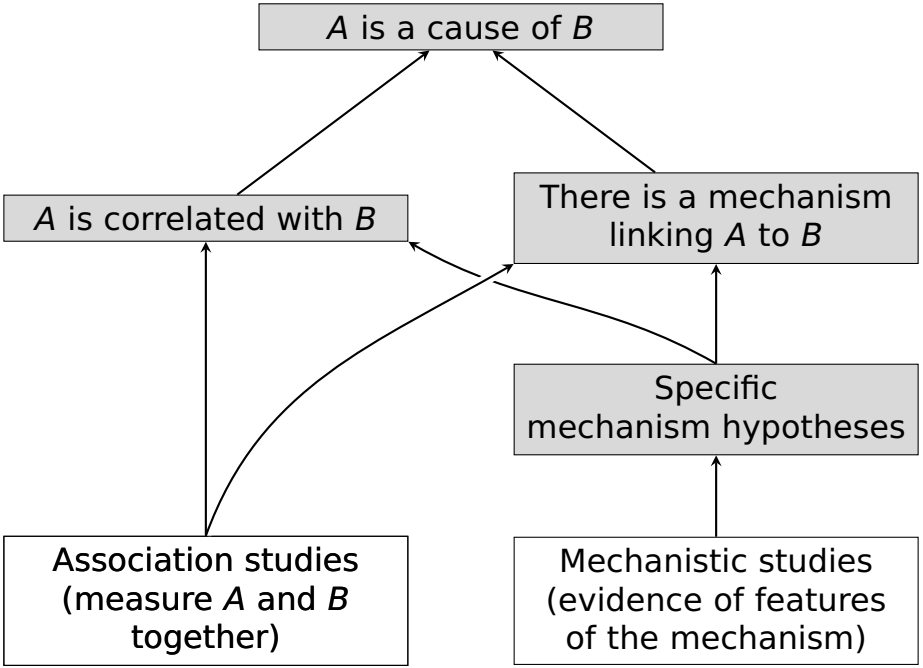


Object Pluralism. In order to establish a causal claim one normally needs to establish the existence of an appropriate conditional correlation and the existence of an appropriate mechanism complex.

Study Pluralism. So, when assessing a causal claim one ought to consider relevant association studies and mechanistic studies, where available.

EP contrasts with the standard approach to EBM & EBP:

Evidential pluralism: mechanistic studies are not inferior.

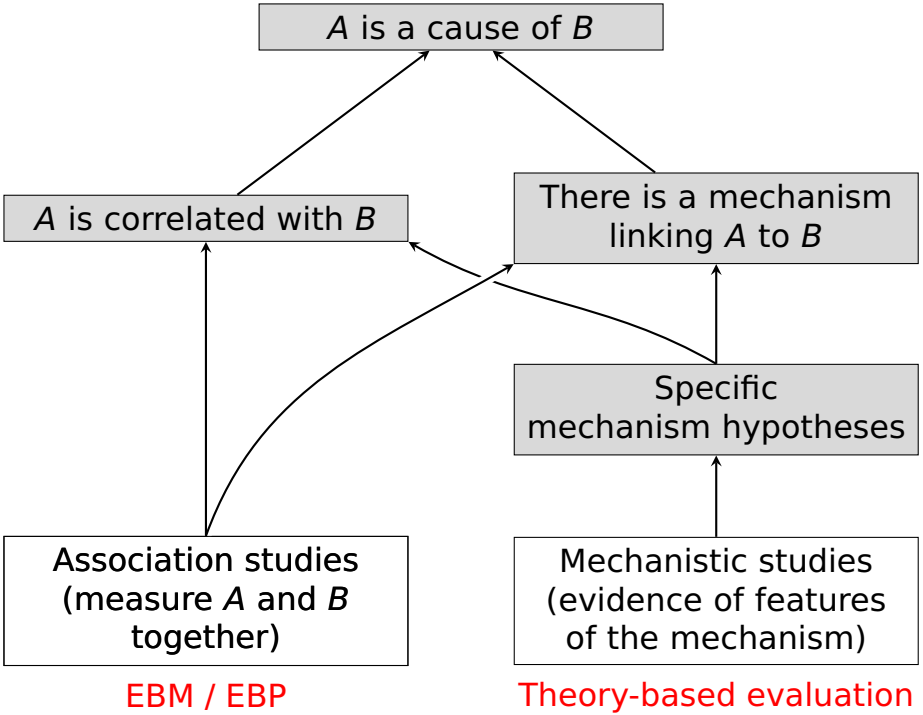


Reviews/meta-analyses
RCTs
Cohort studies
Case control studies
Case series
Case reports

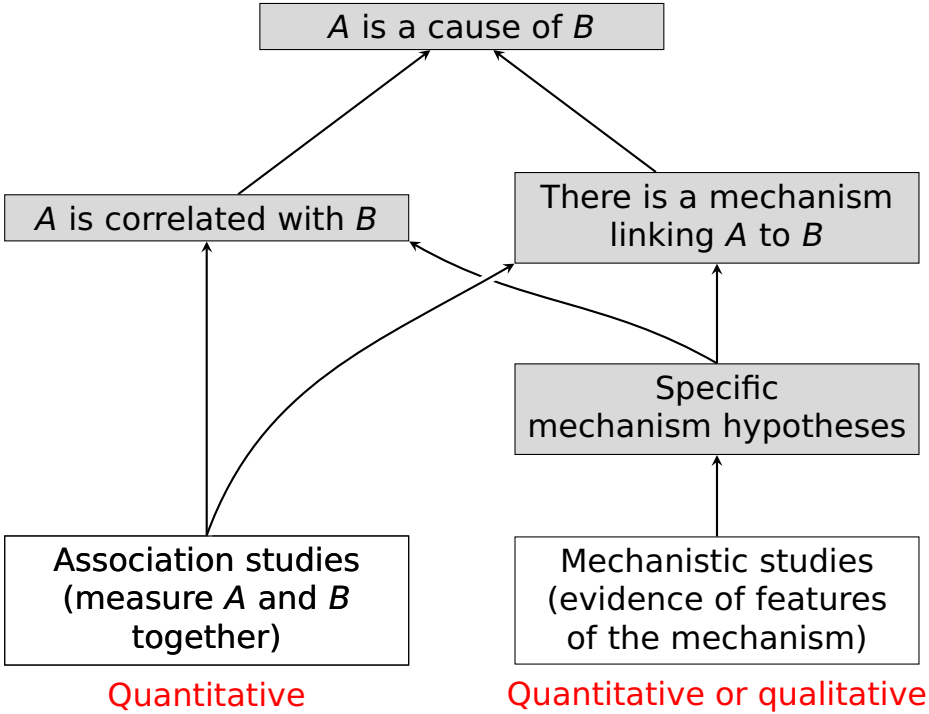
Manipulation: e.g., in *vitro*
Observation: e.g., imaging
Clinical studies: e.g., RCTs
Confirmed theory: e.g., immun.
Analogy: e.g., animal studies
Simulation: e.g., ABMs

Relation to other approaches

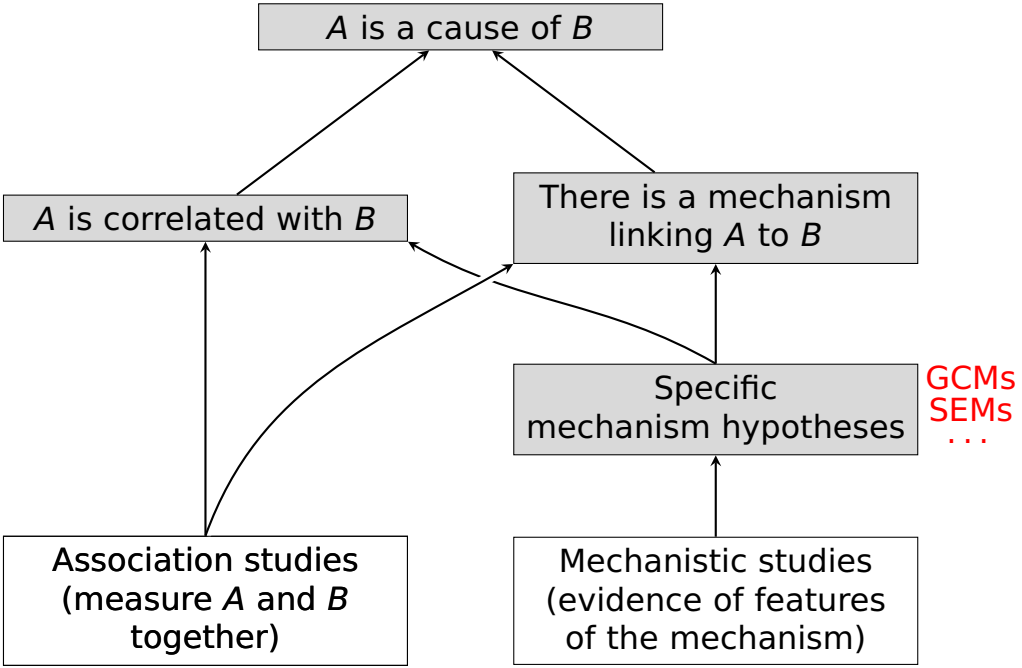
Evaluation approaches



Mixed-methods research

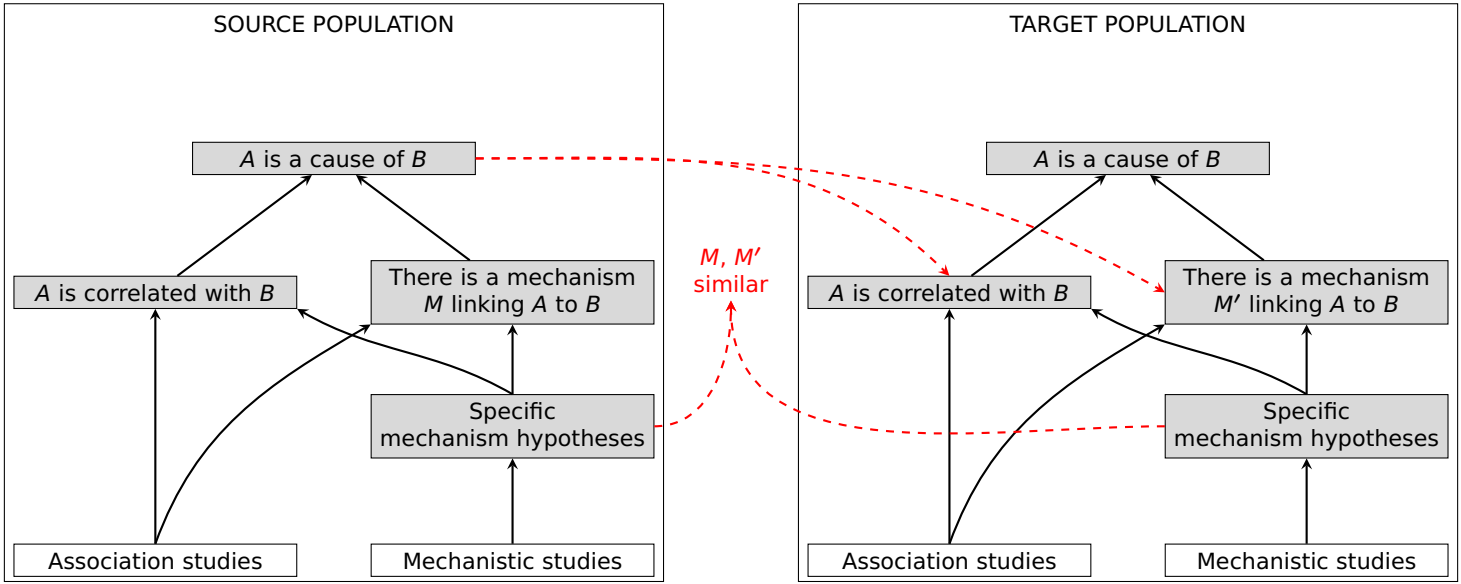


Causal modelling



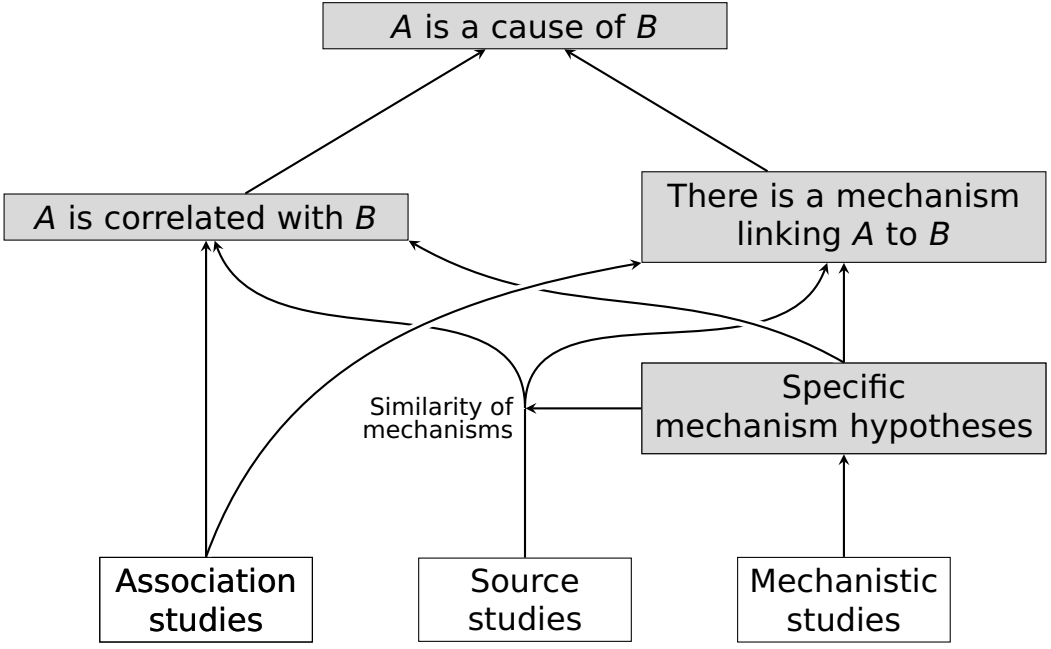
External validity

Evidential Pluralism also offers an account of extrapolating a causal claim to a new context:

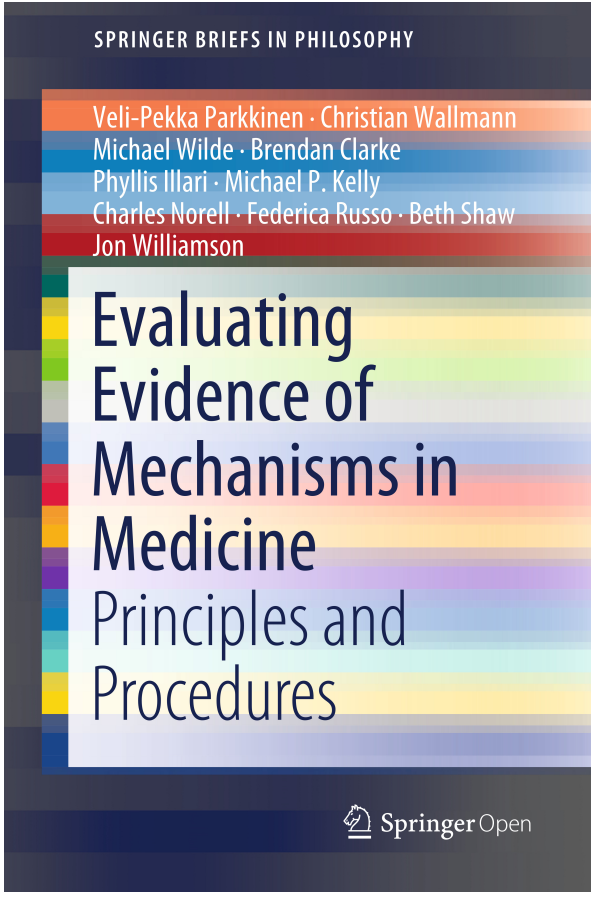


(Williamson, J. (2019a). Establishing causal claims in medicine. *International Studies in the Philosophy of Science*, 32(2):33–61.)

Bringing efficacy and external validity together:



EBM+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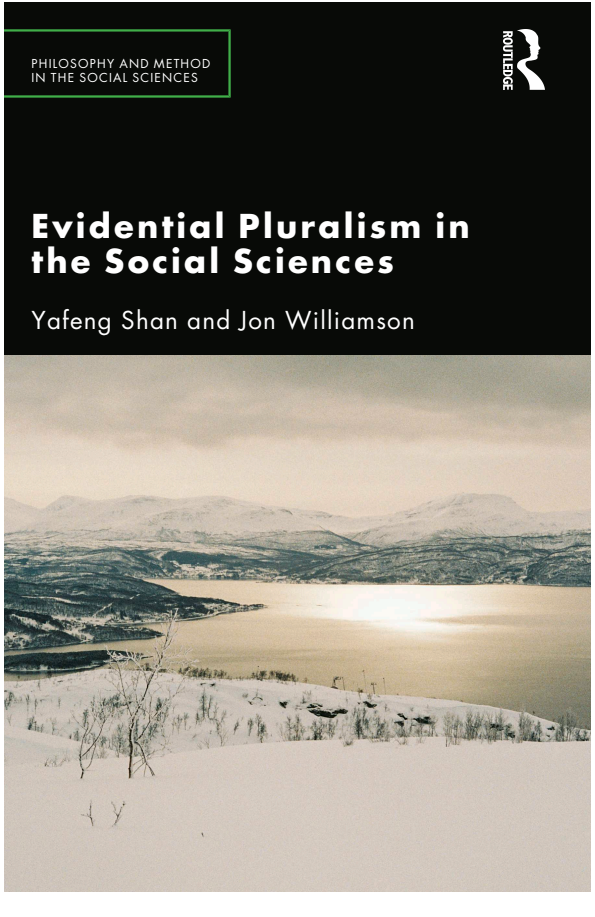
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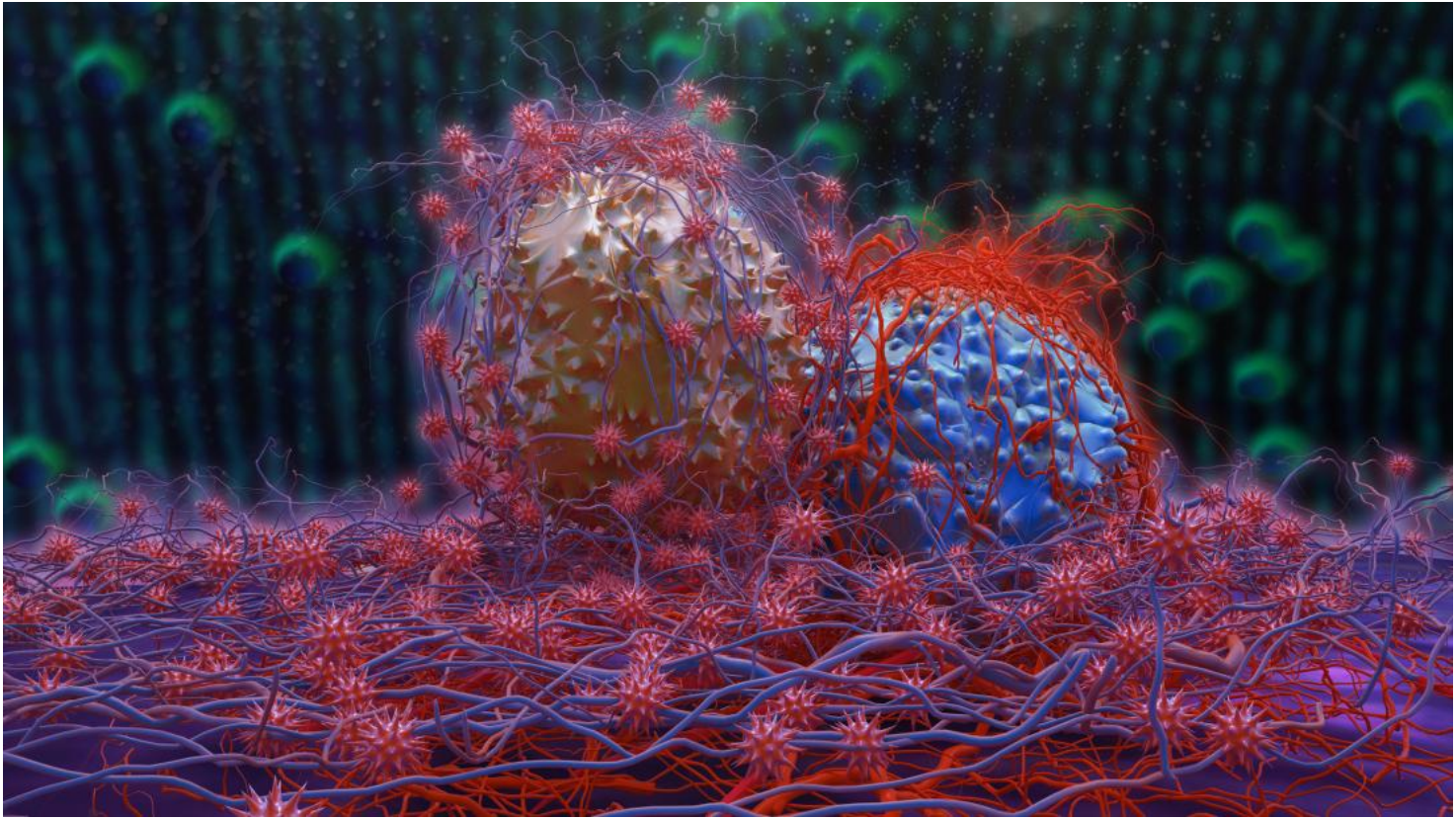
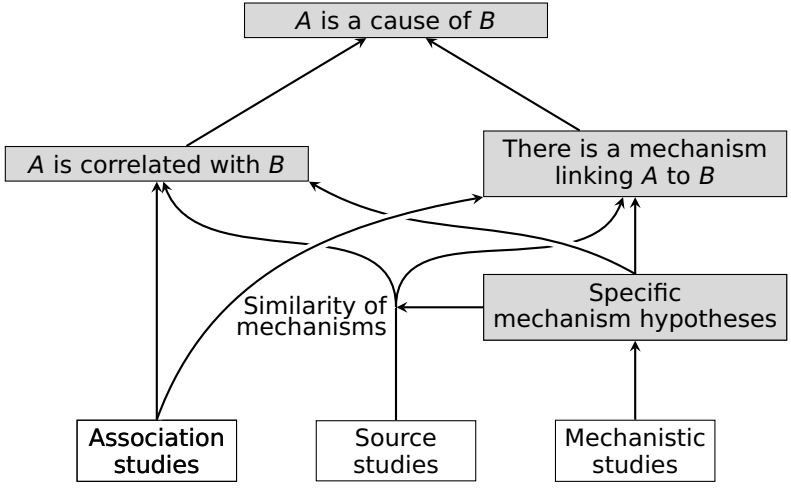
4 KCCs in the light of Evidential Pluralism





What does a working group need to do to conclude that an observed correlation is causal?

According to EP, it needs to determine the status of a general mechanistic claim:

> The claim that there exists some mechanism from exposure to cancer in humans that can account for the observed correlation.

This is informed by the evaluation of the mechanistic subgroup.

EP would view the KCCs as playing the role of specific mechanism hypotheses.

IE As hypothesised features of mechanisms.

Mechanistic studies are assessed to evaluate these specific mechanism hypotheses.

4.1 Justifying IARC's methods by appeal to EP

From this perspective, IARC conforms very closely to EP:

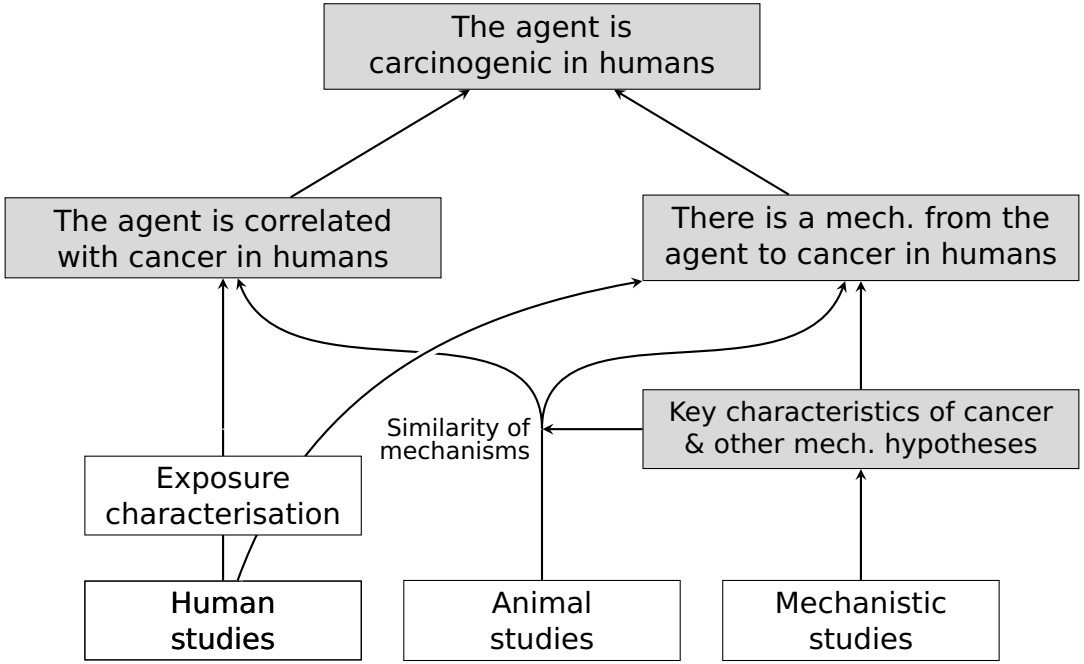


Table 2: Examples of IARC Monographs classifications based on mechanistic evidence; based on Benbrahim-Tallaa (2019)

Agent	Human evidence	Animal evidence	Mechanistic evidence (KCCs)	Eval.	Date (vol.)
d-Limonene	Inadequate	Sufficient	'the mechanism by which *d*-limonene increases the incidence of renal tubular tumours in male rats is not relevant to humans' (p.322)	3	1999 (73)
Simian virus (SV)40	Inadequate	Sufficient	No persuasive evidence that the mechanism of transformation in rodents is operative in humans	3	2014 (104)
1-Nitropyrene	Inadequate	Sufficient	Is genotoxic, induces oxidative stress (1,5)	2A	2014 (105)
1,3-Propane sultone	Inadequate	Sufficient	Is genotoxic (2)	2A	2017 (110)
Tetrabromo-bisphenol A	Inadequate	Sufficient	Modulates receptor-mediated effects, induces oxidative stress, is immunosuppressive (5, 7, 8)	2A	2018 (115)
3,3',4,4'-Tetrachloro-azobenzene	Inadequate	Sufficient	Belongs to a class of agents for which one or more members have been classified as carcinogenic or probably carcinogenic to humans	2A	2019 (117)

A first reason to interpret KCCs as specific mechanism hypotheses:

Justification. IARC evaluations can be justified as conforming to Evidential Pluralism.

4.2 Ontological considerations

KCCs as properties. 'Key characteristics *of carcinogens*'

It is not strictly correct to predicate KCCs of carcinogens:

> Many non-carcinogens also exhibit these characteristics.

Perhaps we can interpret KCCs as dispositional properties of agents or exposures?

> IARC is not really interested in dispositions.
>
> Suppose an agent has dispositions to genotoxicity and immunosuppression, but the circumstances don't obtain for one of these to manifest.
>
> > Then that unmanifested disposition is of no interest.
>
> Only dispositions that are manifested often enough to lead to significant population effects are of interest.
>
> IARC will only infer a KCC if it is manifested sufficiently often.

∴ It's not helpful to interpret KCCs as properties of agents at all.

KCCs as specific mechanism hypotheses. EP-motivated alternative:

> KCCs are best viewed as hypothesised features of mechanisms.
>
> The presence of such a feature is an (inconclusive) indicator that the mechanism leads to cancer.

This is not wholly incompatible with IARC's view of KCCs:

> 'human carcinogens often share one or more characteristics **that are related to the multiple mechanisms by which agents cause cancer**.' (IARC, 2019, p. 26.)

- KCCs are characteristics of mechanisms initiated by exposures.

So we have a second motivation for this interpretation:

Ontology. KCCs are features of mechanisms, not of carcinogens or even exposures.

4.3 IARC's objections to mechanism hypotheses

IARC views KCCs as a preferable alternative to mechanism hypotheses, because:

1. It is usually impossible to formulate detailed mechanism hypotheses before a literature search and review.

   This is a valid concern.

   But it is not a reason to resist interpreting KCCs as simple mechanism hypotheses. Distinguish:

   Coarse-grained mechanism hypotheses. Key features, e.g., KCCs.

   Fine-grained mechanism hypotheses. Rich and detailed.

2. It will be impossible to provide good evidence of all the steps of a mechanism.

   Evidence of **key features** is possible and can be confirmatory.

   KCCs are key features.

3. 'A hypothesis-based paradigm can introduce bias because focusing on a specific set of hypothesized key events inherently results in exclusion of data.'

   But this is exactly the role of the KCCs: to select (and exclude) data.

A third motivation:

Objections. This interpretation is not prone to IARCs worries about mechanism hypotheses.

4.4 The clarificatory role of mechanism hypotheses

Exposure E causes cancer C in virtue of key characteristic K_i:

Here the KCC:

> Cannot normally be construed as a single spatio-temporally located event that mediates between exposure and cancer.

∴ It should not be thought of as a mediating variable in that sense.

> Nevertheless, one can use a variable to represent a KCC.
>
> $K_i = 1$ if the KCC is present, $K_i = 0$ if it is absent.
>
> Thus one can use DAGs or their generalisations to represent KCCs.

Interpreting KCCs as features of mechanisms allows us to think in terms of (coarse-grained) mechanism hypotheses.

This has many advantages . . .

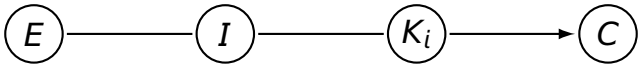
4.4.1 Indicators

Understanding KCCs as specific mechanism hypotheses can clarify the role of indicators such as biomarkers, assay endpoints and omic signatures.

Table 3: Examples of indicators (Smith et al., 2016, p.714)

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), 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)
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
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

Examples:

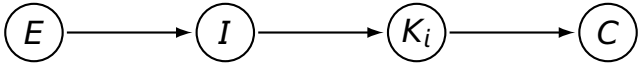


Evidence of association between the exposure E and the indicator I as well as between the indicator I and K_i.

This case provides evidence of correlation between E and K_i.

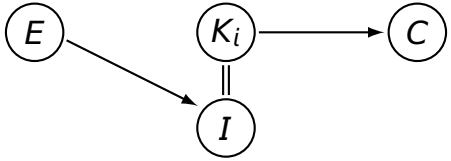
This helps to confirm the claim that there is a mechanism from E to C.

EG Tetrabromobisphenol A is correlated with immune system dysfunction (indicator), which is correlated with immunosuppression (K_7), which causes cancer.



In this case, I is established to be an intermediary on a mechanism from E with characteristic K_i.

This directly helps to establish a mechanism from E and C.

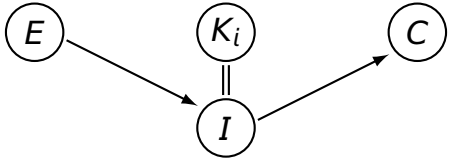


In this case, I is partly constitutive of K_i. It is also established to be an effect of E.

Again, this helps to establish a mechanism from E to C.

The more constitutive I is of K_i, the stronger the evidence of a mechanism from E to C.

EG Human papillomavirus 18 (HPV 18) inhibits senescence (indicator), which is partly constitutive of immortalization (K_9), which causes cancer.

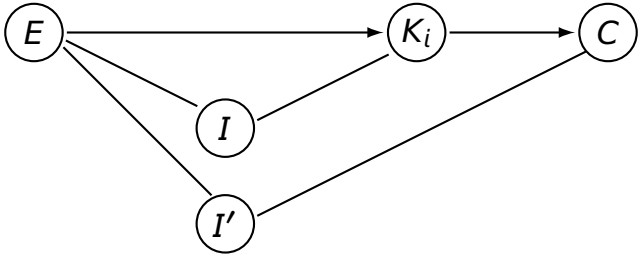


In some cases, there may be evidence that I itself is a cause of C.

EG DNA damage is a constitutive indicator of genotoxicity (K_2) and can directly cause cancer.

EG Reactive oxygen species levels (indicator) can provide better evidence for cancer than the KCC they are an indicator for, namely, oxidative stress (K_5).

Coarse-grained mechanism hypotheses can also elucidate the role of indicators other than indicators of KCCs.



EG The agent causes a disease that has previously been established to cause cancer (where there is no good KCC-related evidence).

EG IBS, diabetes.

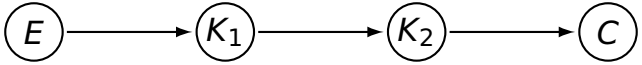
4.4.2 Connections between agents

Coarse-grained mechanism hypotheses can be used to connect agents.

EG Styrene causes cancer only via being metabolised to styrene-7,8-oxide.

Williamson, J. (2019b). Evidential Proximity, Independence, and the evaluation of carcinogenicity. *Journal of Evaluation in Clinical Practice*, 25(6):955–961

4.4.3 Connections between KCCs

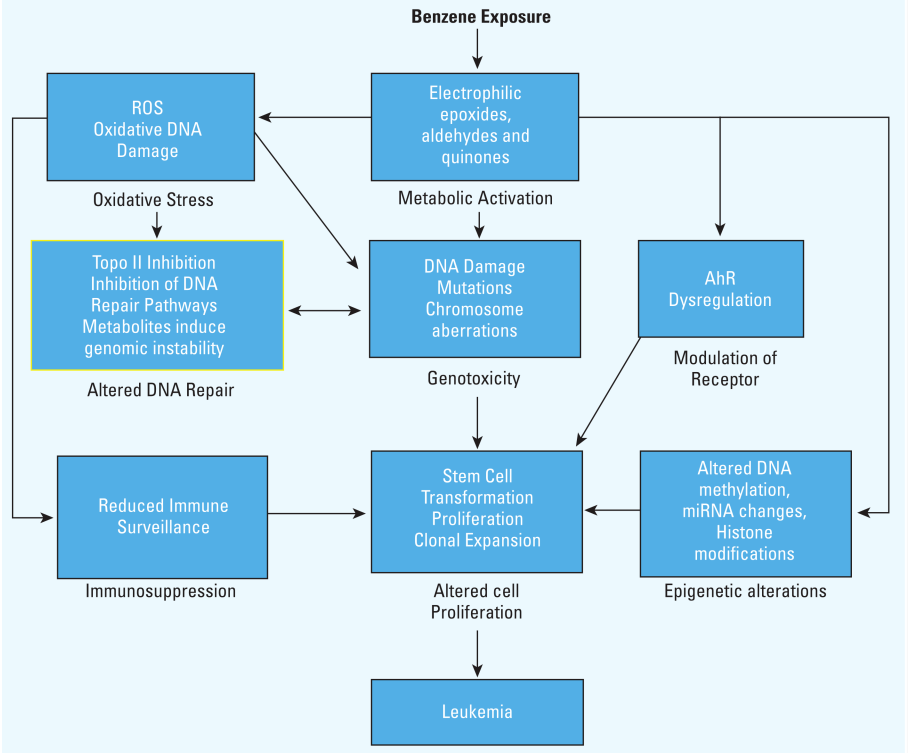


EG One often needs to show a link between K_1 and K_2: electrophilicity leads to DNA adducts, which in turn leads to DNA damage.

Coarse-grained mechanism hypotheses can help to avoid double-counting:

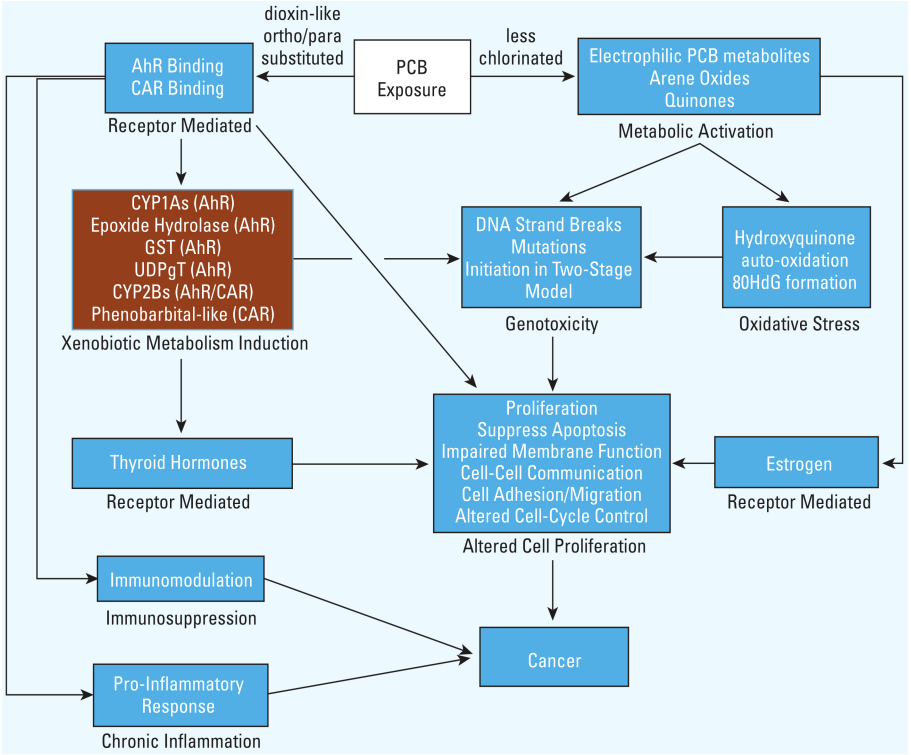
The presence of multiple KCCs may indicate a single path from exposure to cancer, or multiple paths, and it's important to distinguish the two.

EG Benzene exposure is linked to 8 of the 10 KCCs:



(Smith et al., 2016, p. 718)

EG PCB exposure is linked to 7 of the 10 KCCs:



(Smith et al., 2016, p. 719)

A fourth motivation:

Clarity. Thinking in terms of coarse-grained mechanism hypotheses provides clarity.

- EG Clarifying the roles of indicators.
- EG Clarifying connections between agents.
- EG Clarifying connections between KCCs.

5 Strength of mechanistic evidence

Preamble definition:

> ‘**Strong mechanistic evidence:** Results in several different experimental systems are consistent, and the overall mechanistic database is coherent. ’ (IARC, 2019, p. 33–34.)

What might it mean to say that ‘the overall mechanistic database is coherent’?

An EP-motivated account of overall coherence

It's important to emphasise that the $K_i \longrightarrow C$ link may be especially uncertain.

> KCCs are chosen on the grounds that that, frequently (in the reference class of all agents), mechanisms that exhibit a KCC lead to cancer.
>
> This frequency varies between KCCs: the $K_i \longrightarrow C$ link is more plausible for some KCCs than others.

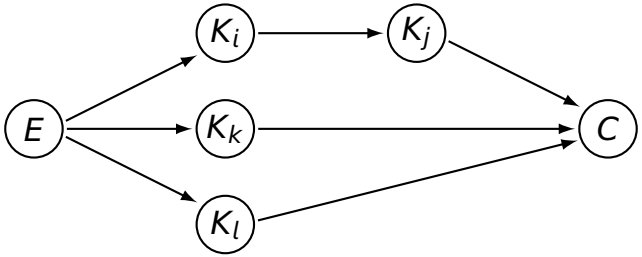
Evidence for a mechanism hypothesis exhibits **overall coherence** when either,

1. The hypothesised mechanism has some path for which each link in the path has strong evidence.

   ∴ One can be sufficiently confident that *that particular* path operates in humans.

2. The hypothesised mechanism has sufficiently many paths for which there is strong evidence for the $E \longrightarrow K_i$ link.

   ∴ One can be sufficiently confident that *some* path operates in humans.



NB Support for links can come from studies reviewed in the evaluation or from the link having been previously established in some relevant context which is plausibly mechanistically similar to the target context.

IE In some mechanistically similar population or mechanistically similar agent.

NB The hypothesised mechanism does not need to be specified in fine grain.

It could be as simple as $E \longrightarrow K_2 \longrightarrow C$.

What is important is that enough evidence is provided to be confident that at least one path is active in humans.

A fifth motivation:

Strength. This interpretation yields a natural account of strength of mechanistic evidence.

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6 Conclusion

EP can help us understand the role of KCCs in carcinogenicity assessment.

This requires interpreting KCCs as mechanism hypotheses.

Merits of this interpretation:

Justification. IARC evaluations can be justified as conforming to Evidential Pluralism.

Ontology. KCCs are features of mechanisms, not of carcinogens or even exposures.

Objections. This interpretation is not prone to IARCs worries about mechanism hypotheses.

Clarity. Thinking in terms of coarse-grained mechanism hypotheses provides clarity.

- EG Clarifying the roles of indicators.
- EG Clarifying connections between agents.
- EG Clarifying connections between KCCs.

Strength. This yields a natural account of strength of mechanistic evidence.

For more on Evidential Pluralism: jonwilliamson.uk/ep/

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