



*Beyond Key Characteristics of
Carcinogens (KCCs) :
An Improved Approach for
Integrating Mechanistic Data in
Cancer Risk Monographs*

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<https://lri.americanchemistry.com>

10/19/2023

Outline

1. Brief review of KCCs & how they are being used
2. Brief discussion of some of the problems with KCCs
3. Beyond KCCs - a proposal for an improved approach for incorporating mechanistic data
4. Discussion - your thoughts about this proposed improved approach

Table 1. The 10 key characteristics of carcinogens described by Smith et al., (2016) Used in IARC Monographs 112&113 etc., Table from Cox et al Reg Tox Pharm 90:185-196

Key Carcinogen Characteristic	IARC's Assignment and Use of ToxCast Data
1) Is Electrophilic or Can Be Metabolically Activated to Electrophiles	9 ToxCast assays associated with this characteristic ^a
2) Is Genotoxic	31 ToxCast assays associated with this characteristic
3) Alters DNA Repair or Causes Genomic Instability	No ToxCast assays could be associated with this characteristic
4) Induces Epigenetic Alterations	11 ToxCast assays associated with this characteristic
5) Induces Oxidative Stress	18 ToxCast assays associated with this characteristic

90:185-196 doi: 10.1016/j.yrtph.2017.08.021

Table 1. The 10 key characteristics of carcinogens described by Smith et al., (2016) Used in IARC Monographs 112&113 etc., Table from Cox et al Reg Tox Pharm 90:185-196

Key Carcinogen Characteristic	IARC's Assignment and Use of ToxCast Data
6) Induces Chronic Inflammation	45 ToxCast assays associated with this characteristic
7) Is Immunosuppressive	No ToxCast assays could be associated with this characteristic
8) Modulates Receptor-Mediated Effects	92 ToxCast assays associated with this characteristic
9) Causes Immortalization	No ToxCast assays could be associated with this characteristic
10) Alters Cell Proliferation, Cell Death or Nutrient Supply	68 ToxCast assays associated with this characteristic

IARC Monographs

Today

Key Characteristics of Carcinogens

The practice of using the Key Characteristics approach is now well-established at IARC Monographs and other government agencies ...

Ten Years of Using Key Characteristics of Human Carcinogens to Organize and Evaluate Mechanistic Evidence in IARC Monographs on the Identification of Carcinogenic Hazards to Humans: Patterns and Associations

Ivan Rusyn and Fred A. Wright

bioRxiv preprint doi: <https://doi.org/10.1101/2023.07.11.548354>; this version posted July 12, 2023. The copyright holder for this preprint was not certified by peer review) is the author/funder.

IARCs Use of KCCs

International Agency for Research on Cancer



World Health
Organization

*IARC Monographs on the Identification of
Carcinogenic Hazards to Humans*

<https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>

PREAMBLE

IARCs Use of KCCs

The IARC Monographs: Updated Procedures for Modern and Transparent Evidence Synthesis in Cancer Hazard Identification, Samet et al 2020 J Natl Cancer Inst 112:30-37. doi: 10.1093/jnci/djz169

The Monographs Programme of the International Agency for Research on Cancer: A brief history of its preamble, Baan and Straif 2022, ALTEX 39: 443-450. doi: 10.14573/altex.2004081.

“In the new Preamble, a prominent new paragraph in Section 4 on “Mechanistic evidence” deals with “evidence relevant to key characteristics of carcinogens”.

The strength of the mechanistic evidence is to be expressed as “strong”, “limited”, or “inadequate” (in contrast to “strong, moderate, weak”

And finally, in the Section on “Evaluation and rationale”, one of the elements that contribute to the classification “strong mechanistic evidence” is the finding of “Strong evidence that the agent exhibits key characteristics of carcinogens.” **However, the new Preamble does not specify criteria for evaluating mechanistic evidence, including how many and which of the ten characteristics constitute “strong evidence”** in this case. This is left to the judgement of the Working Group...”

Excerpt from the IARC Monograph Preamble

(b) Strong evidence that the agent exhibits key characteristics of carcinogens.

In this case, three descriptors are possible:

- (1) The strong evidence is in exposed humans. Findings relevant to a specific tumour type may be informative in this determination.
 - (2) The strong evidence is in human primary cells or tissues. Specifically, the strong findings are from biological specimens obtained from humans (e.g. ex vivo exposure), from human primary cells, and/or, in some cases, from other humanized systems (e.g. a human receptor or enzyme).
 - (3) The strong evidence is in experimental systems. This may include one or a few studies in human primary cells and tissues.
- (c) Strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Certain results in experimental animals (see Part B, Section 6b) would be discounted, according to relevant criteria and considerations in authoritative publications (e.g. Capen et al., 1999; IARC, 2003). Typically, this classification would not apply when there is strong mechanistic evidence that the agent exhibits key characteristics of carcinogens.

IARCs Use of KCCs

Excerpt from the IARC Monograph Preamble

Limited mechanistic evidence: The evidence is suggestive, but, for example, (a) the studies cover a narrow range of experiments, relevant end-points, and/or species; (b) there are unexplained inconsistencies in the studies of similar design; and/or (c) there is unexplained incoherence across studies of different end-points or in different experimental systems.

Inadequate mechanistic evidence: Common findings that lead to a determination of inadequate mechanistic evidence include: (a) few or no data are available; (b) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the studies; (c) the available results are negative.

Problems with the KCCs: Selected Citations

1. Klaunig (2022). Ten Characteristics of Carcinogens: Key to ? Society for Birth Defects Research and Prevention 62nd Annual Meeting
2. Becker et al. (2017) How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? Regul Toxicol Pharmacol. 2017 Nov;90:185-196.doi:10.1016/j.yrtph.2017.08.021.
3. Goodman and Lynch (2017) Improving the International Agency for Research on Cancer's consideration of mechanistic evidence. Toxicology and Applied Pharmacology, 319: 39-46 doi.org/10.1016/j.taap.2017.01.020.
4. Goodman et al. (2020) Recommendations for further revisions to improve the International Agency for Research on Cancer (IARC) Monograph program. Regul Toxicol Pharmacol. 2020 Jun;113:104639. doi: 10.1016/j.yrtph.2020.104639.
5. Borgert et al, (2015) Modernizing problem formulation for risk assessment necessitates articulation of mode of action. Regul. Toxicol. Pharmacol., 72 (3) (2015), pp. 538-551
6. Bus (2017) IARC use of oxidative stress as key mode of action characteristic for facilitating cancer classification: glyphosate case example illustrating a lack of robustness in interpretative implementation Regul. Toxicol. Pharmacol., 86 (2017), pp. 157-166
7. Smith et al. (2021) Categorizing the characteristics of human carcinogens: a need for specificity. Arch Toxicol 95, 2883-2889.
8. Ryman-Rasmussen (2022). [Do So-Called "Key Characteristics of Carcinogens" Meet TSCA's Scientific Standards? Flip a Coin!](#)
9. Meek and Wikoff (2023) The need for good practice in the application of mechanistic constructs in hazard and risk assessment. Toxicol Sci. 2023 Jun 28;194(1):13-22. doi: 10.1093/toxsci/kfad039. PMID: 37074944.

- Does not consider TK or dose-response
- Is the “burst phenomenon” - non-specific bioactivity - considered
- Does not consider reversibility of effect
- Non-specific nature of the KCCs
- Does not consider alternative modes of action
- Does not integrate evidence (does one just count the number of positives in each KCC assay?)

How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?

#777

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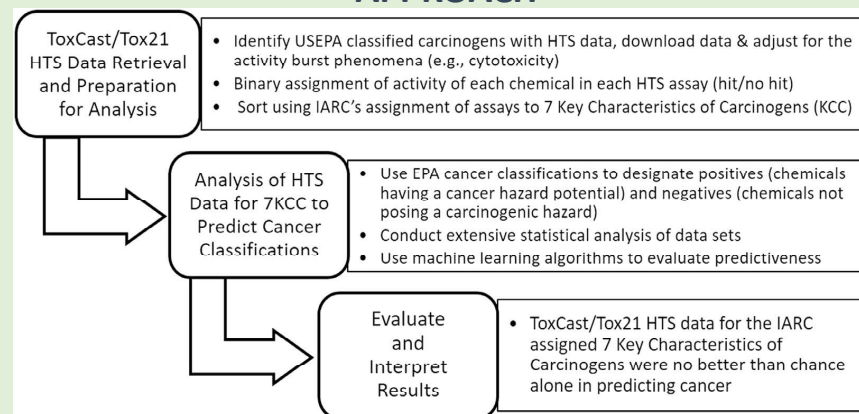
OBJECTIVES

- IARC's use of ToxCast/Tox21 data has followed implied/unverified inference, i.e., bioactivity patterns of substances in assays measuring such key characteristics distinguishes carcinogens from non-carcinogens.
- To evaluate this implied inference, we explicitly tested how well such ToxCast/Tox21 HTS data predict cancer classifications.

MAIN RESULTS

- ToxCast/Tox21 data were analyzed both with and without adjusting for the cytotoxicity burst effect .
- Assignment of ToxCast/Tox21 assays to the seven key characteristics of carcinogens was the same as IARC.
- The ability to predict cancer hazard for each key characteristic, alone or in combination, was found to be no better than chance.

APPROACH



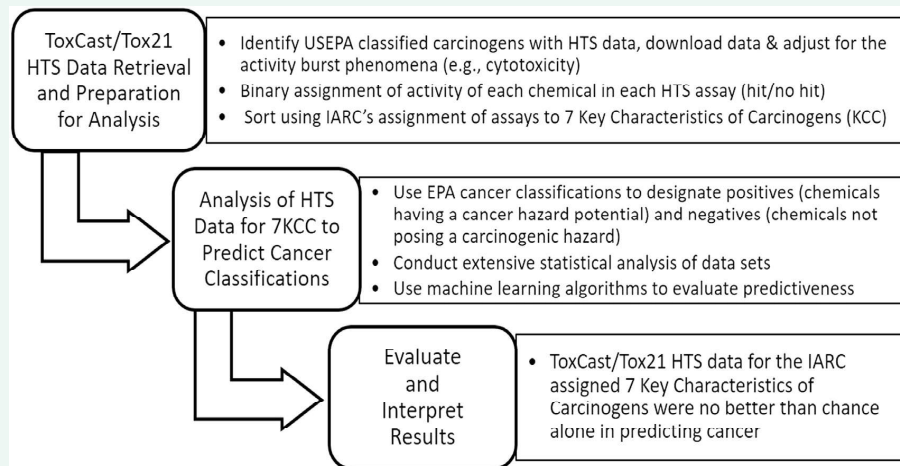
IMPACT/SIGNIFICANCE

- There is little scientific confidence in IARC's inference models derived from current ToxCast/Tox21 assays for the purported "key characteristics of carcinogens" to predict cancer.
- A more rigorous mode-of-action pathway-based framework to organize, evaluate, and integrate mechanistic evidence with animal toxicity, epidemiological investigations, and knowledge of exposure and dosimetry is needed to evaluate

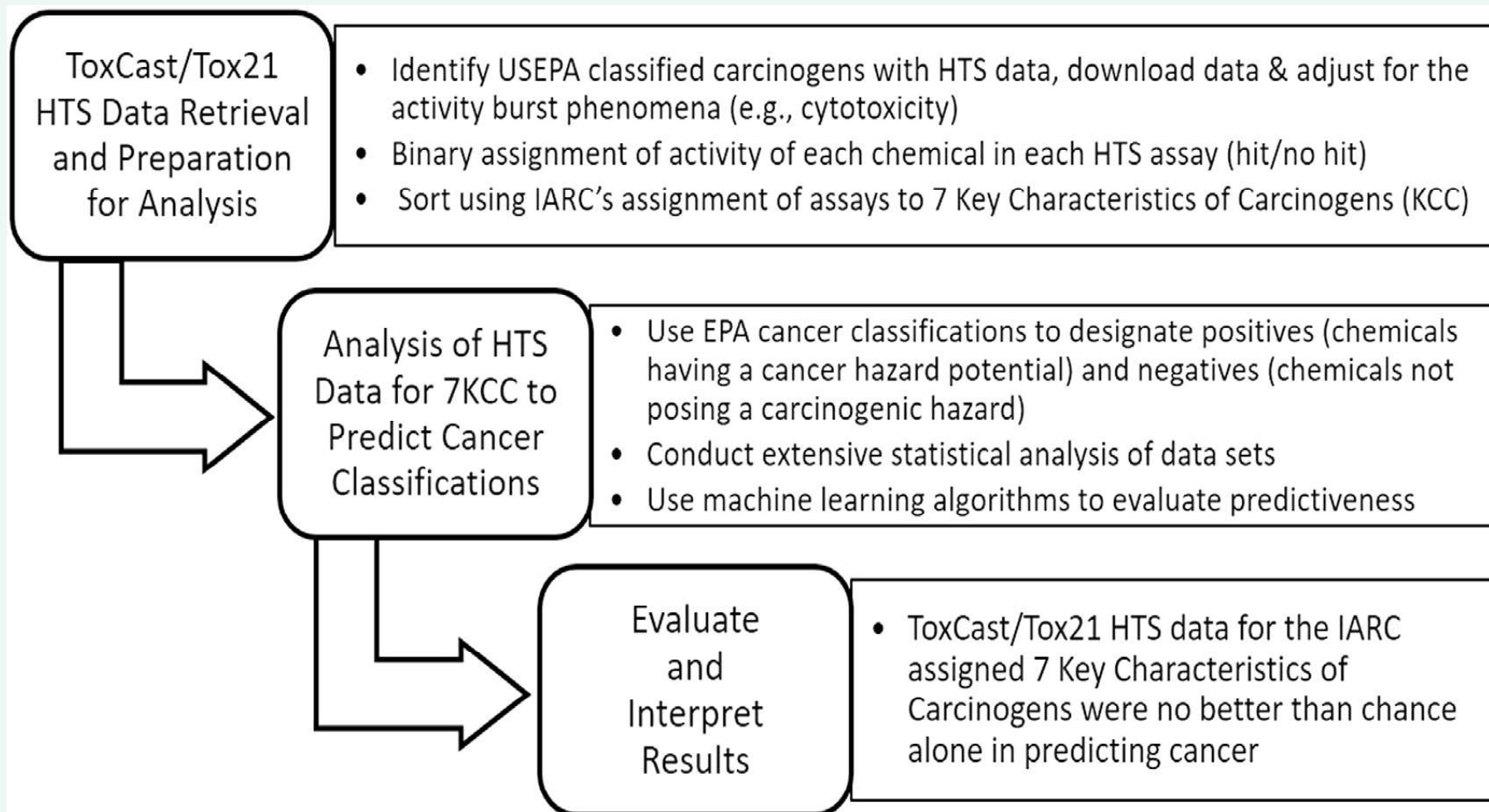
How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?

Regul Toxicol Pharmacol. 2017 Nov;90:185-196. doi: 10.1016/j.yrtph.2017.08.021. Epub 2017 Sep 1. PMID: 28866267

- **USEPA classified carcinogens and non-carcinogens with ToxCast HTS data were identified, and the HTS downloaded, and adjusted based on the activity burst phenomena.**
 - This adjustment accounts for cytotoxicity by selecting hits below the defined cytotoxicity threshold.
- **Activity of each chemical in each ToxCast HTS assay was assigned "hit" or "no hit."**
- **Data were sorted using IARC assignment of assays into the 7 Key Characteristics of Carcinogens.**
- **EPA cancer classifications were used to denote chemicals with and without cancer hazard potential.**
- **Statistical analysis of the data sets were performed and machine learning algorithms were used to evaluate predictiveness.**
 - Kolmogorov two-sample test: Used to compare the distribution of assay hits per chemical over all assays for substances with human cancer potential.
 - Cumulative distribution function plots: Used to explore differences between chemicals based on assay results.
 - Principal component analysis: Used to determine if differences between positive and negatives could be determined based on the 7 characteristics.
 - Jaccard similarity index: Used to explore differences of responses based on key characteristic and assay hit calls.
 - Logistic regression/correlation: Used to identify and quantify assay result and cancer classification dependencies.
 - Classification and regression trees: Used to identify and quantify assay result and cancer classification dependencies.



How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?



How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?

MAIN RESULTS

No statistically significant differences were found in ToxCast/Tox21 responses for the 7 IARC key characteristics of carcinogens for substances EPA-designated as posing cancer hazards to humans compared to EPA-designated non-carcinogens

ToxCast/Tox21 HTS data for the IARC 7 Key Characteristics of Carcinogens were no better than chance in cancer prediction

Statistical and Predictive Analysis Results	Significant	Non-Significant / No Predictiveness
Kolmogorov two-sample test: no significant differences between assay hit calls per chemical for positives and negatives		✓
Cumulative distribution function plots: the CDFs of non-carcinogens were not different from CDFs of carcinogens		✓
Principal component analysis: PCA could not clearly separate carcinogens from non-carcinogen into distinct groups		✓
Jaccard similarity index: no meaningful difference was noted between the ToxCast/Tox21 results for chemicals classified by EPA as having cancer hazard potential and substances EPA has determined do not pose a carcinogenic hazard		✓
Logistic regression/correlation: None of the key characteristics significantly correlated with chemicals classified as posing a cancer hazard		✓
Classification and regression trees: CART analysis (dependent variable = chemicals classified by EPA as having cancer hazard potential) did not identify any of the 7 key characteristics as a significant predictor of being classified as a carcinogen		✓
Bayesian networks: BN models developed from the ToxCast/Tox21 data for the 7 key characteristics not able to predict cancer hazard		✓
Random forest ensembles of CART trees: No predictive relationships observed, except a statistically significant association, threshold-like nonlinearity, between proliferation & probability of being a chemical classified by EPA as having cancer hazard		✓
Note: ToxCast/Tox21 data unadjusted for cytotoxicity <i>did</i> find marginal predictive power in identifying carcinogenicity based on oxidative stress in select analyses. However, these results were not maintained once the burst phenomenon was accounted for		

Since KCCs can't predict cancer classifications, how is “strong evidence” determined?

- **Recall:** “the new [IARC] Preamble does not specify criteria for evaluating mechanistic evidence, including how many and which of the ten characteristics constitute “strong evidence”
- Does one just count the number of positives in each KCC assay? This is not scientifically justified.

Where's the logic in IARC's Use of KCCs?

Another excerpt from the IARC Preamble:

“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” (National Academies of Sciences, Engineering, and Medicine, 2017)”

The logic in IARC's Use of KCCs?

Guyton et al. (2018) Application of the key characteristics of carcinogens in cancer hazard identification. Carcinogenesis. 2018 Apr 5;39(4):614-622. doi: 10.1093/carcin/bgy031

“Overall, we show that application of the KCs to hazard identification is a robust new approach to organizing and evaluating the mechanistic data related to carcinogenesis that avoids the need to identify, and thereby restrict attention to, specific pathways and hypotheses.”

“Because they are based on empirical observations of characteristics associated with known carcinogens, the KCs thus provide a more agnostic and unbiased survey of the mechanistic literature.”

The logic in IARCs Use of KCCs?

Maybe I'm overinterpreting --- but is hypothesis generation and evaluating data to see if a hypothesis is supported now considered a “biased” approach?

Excerpts from Ryan and O'Callaghan (2002). The Scientific Method, Extension | University of Nevada, Reno, FS-02-66.

- “Scientists seek to understand the relationships and intricacies between cause and effect in order to predict outcomes of future or similar events
- The Scientific Method is not the only way, but is the best-known way to discover how and why the world works, without our knowledge being tainted by religious, political, or philosophical values.
- The approach lends itself to answering questions in fair and unbiased statements, as long as questions are posed correctly, in a hypothetical form that can be tested”

An Improved Approach for Integrating Mechanistic Data in Cancer Risk Monographs



SOT | Society of
Toxicology
academic.oup.com/toxsci

Toxicological Sciences, 2023, 194(1), 13–22

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Forum

The need for good practice in the application of mechanistic constructs in hazard and risk assessment

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Abstract

A series of recent and proposed workshops address the interface between key characteristics and mechanistic pathway descriptions (adverse outcome pathways and mode of action) to identify commonalities and potential for complementary application. Informed by different communities, these constructs have collective potential to increase confidence to support the application of mechanistic data in hazard assessment. This forum article summarizes concepts, introduces evolving understanding, and invites future collaboration to contribute to better common understanding and development of good practice in the use of mechanistic data in hazard assessment.



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- Through increasing experience in the development and use of mechanistic constructs and their discussion at open science fora, it has become apparent that there has been miscommunication and misunderstanding of strengths and weaknesses of the application of KCs and pathway approaches in hazard identification as part of hazard characterization and risk assessment.
- **There is, seemingly, much to be learned in further collaboration to address the limitation that KCs represent heterogeneous data/endpoints across one or more levels of biological organization, precluding meaningful assessment of causality and perception that documented pathways are not sufficiently objectively inclusive of mechanistic data.**
- Increased communication, a better understanding of the nature of data which supports these constructs, and a common understanding of specific strengths and limitations which enable stepwise and complementary application of KC, AOP, and MOA constructs are critical components of developing good practice.
- A series of collaborative workshops to address the interface between mechanistic constructs and the path forward to development of good practice in their application is proposed.

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From Becker et al. (2017)

1. “Another reason the IARC approach falls short is that it does not explicitly incorporate understanding of the causal linkages of the sequence of key events and biological responses (including dose-response and temporal relationships) involved in carcinogenesis.
2. For incorporating mechanistic data into cancer hazard evaluations, we specifically recommend adoption of the AOP (OECD, 2016) or MOA framework (Meek et al., 2014) that articulates toxicity pathways comprised of sequences of key events, starting with an initial molecular event, followed by a series of key events linked to one another, ultimately resulting in a specific adverse outcome (Meek et al., 2013, Meek et al., 2014). “

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3. “Mechanistic and observational datasets can then be organized and aligned with corresponding key events and key event relationships, and defined Bradford Hill causal considerations can be applied to assess biological plausibility, essentiality and empirical evidence (Becker et al., 2017, Meek et al., 2013, Meek et al., 2014, OECD, 2016).”

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4. “Furthermore, adoption of the recently developed causal analysis scoring approach for evaluating the weight of evidence of potential cancer MOAs (Becker et al., 2017), built from the WHO/IPCS MOA framework, would provide a systematic and transparent approach for evaluating a chemical dataset, including mechanistic data, using hypothesized MOAs and the evolved Bradford Hill causal considerations for integrating evidence.

This quantitative confidence scoring approach facilitates side by side comparison of different hypothesized cancer MOAs and is useful in characterizing the likely operative MOA.”

Hypothesized Cancer MOAs to be Evaluated

Excerpts from Cohen et al (2019) Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans Reg Tox Pharm 103: 100-105, <https://doi.org/10.1016/j.yrtph.2019.01.017>

1. Cancer is due to mistakes occurring in the DNA (usually in somatic cells, but can be inherited through germ cells).
2. More than one mistake in the DNA is necessary.
3. All of the mistakes need to accumulate in a single cell (clonal origin of cancer).
4. The cell population at risk are the tissue pluripotent (stem) cells.
5. Every time DNA replicates, permanent mistakes could occur.
6. Carcinogenesis is a stochastic process.

Given this understanding, there are two fundamental ways to increase the risk of cancer by any agent, chemical or otherwise.

1. Damage DNA directly (Greenfield et al., 1984; Moolgavkar and Knudson, 1981) or
2. Increase the number of stem cell replications (Cohen, 1998a, 2010a, 1998b)."

Hypothesized Cancer MOAs to be Evaluated

1. Mutagenic MOA: a chemical (or metabolite) directly interacts with DNA cause mutations which can be carried forward in dividing cells.
2. Receptor-Mediated Induction of Proliferation MOA : (mitogenesis) a chemical (or metabolite) interacts with a receptor processes to induce cellular proliferation (at an intensity that exceeds homeostasis)
 - will not be carcinogenic at dose levels at which the increased cellular proliferation does not occur
3. Cytotoxicity MOA: a chemical (or metabolite) interacts with a receptor processes to induce cellular proliferation (at an intensity that exceeds homeostasis)
 - will have no effect on carcinogenicity at dose levels below which cytotoxicity occurs
4. Immunosuppression MOA: decrease in ability of immune system to fight infections that cause cancer (or impaired immune surveillance of neoplastic cells)

Hypothesized Cancer MOAs to be Evaluated

An understanding of the likely operative MOA is needed to develop risk assessments (e.g., to determine the most appropriate extrapolation method to be used to determine potential risks at relevant levels of exposure)

- Receptor-Mediated Induction of Proliferation MOA : will not be carcinogenic at dose levels at which the increased cellular proliferation does not occur
- Cytotoxicity MOA: will have no effect on carcinogenicity at dose levels below which cytotoxicity occurs
- Direct DNA reactive: in theory, cancer risk is only increased if rate of damage exceeds rate of repair

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Hypothesized MOA	Unique Key Events			Common Key Events	
Mutagenic MOA	KE #1 Activation and formation of chemical-specific pro-mutagenic DNA adducts	KE #2 Insufficient repair or mis-repair of pro-mutagenic DNA adducts	KE #3 Early induced critical mutations driving cancer	KE #4 Proliferation, clonal expansion of mutant cells, and progression	KE #5 Cancer
Cytotoxic MOA	KE #1 Direct cytotoxicity or metabolic activation to reactive metabolite leading to cytotoxicity	KE #2 Cytotoxicity in target tissues / cells	KE #3 Regenerative cell proliferation - with accompanying increase in spontaneous mutations		
Receptor Mediated MOA	KE #1 Direct interaction, or metabolism to molecule that binds to/activates a cellular receptor	KE #2 Interaction of the receptor in target tissues / cells	KE #3 Cell proliferation stimulus - increase in spontaneous mutations		
Immune Suppression MOA	KE #1 Reduced humoral or cellular immune response	KE #2 Reduced detection and destruction of pre-cancer and cancer cells or increased opportunistic or latent infections	KE #3 Survival of pre-cancer or cancer cells or increased inflammation due to infection or transcriptional reprogramming via oncogenic infection		

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Building from: Becker et al. 2017 Quantitative weight of evidence to assess confidence in potential modes of action. Regul Toxicol Pharmacol. 2017 Jun;86:205-220. doi: 10.1016/j.yrtph.2017.02.017. Epub 2017 Feb 20. PMID: 28232103.

Table 2. Sequence of steps for the quantitative confidence scoring method.

Step 1. Identify Postulated MOAs

Step 2: Summarize Pertinent Background Information

Step 3: Identify Key Events and Map Assays / Endpoints to Each Key Event

Step 4: Organize and Present MOA data within Modified Bradford Hill Framework

Step 5: Evaluate Empirical Support for each of the Key Events

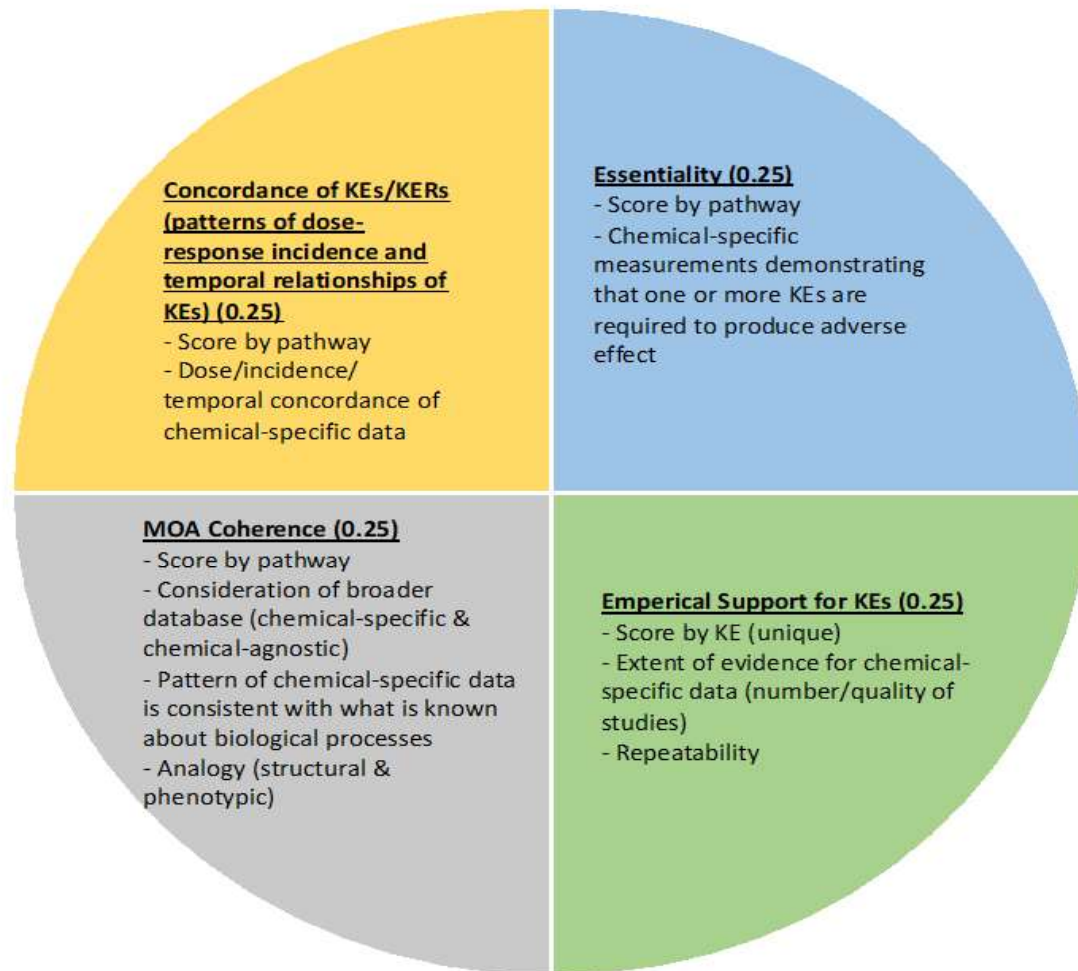
Step 6: Evaluate the Pattern of Evidence Across the Pathway to Derive a QMOA Confidence Score for Concordance of KEs/KERs

Step 7: Evaluate the Pattern of Evidence Across the Pathway to Derive a QMOA Confidence Score for the Criteria of Essentiality

Step 8: Evaluate the Pattern of Evidence Across the Pathway to Derive a QMOA Confidence Score for MOA Concordance

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- Bradford Hill Considerations (Hill, 1965)
- IPCS MOA/HR Framework (Boobis et al., 2006, 2008; Sonich-Mullin et al., 2001)
- EPA Cancer Guidelines (USEPA, 2005b)
- Evolved Bradford Hill Considerations (Meek et al., 2014)



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Table 7. Considerations in Assigning Scores for Empirical Support for KEs: Extent of Data for Each Key Event

High	3	Convincing evidence based on multiple studies and/or extensive data that demonstrates the substance causes the key event.
Moderate	2	Some evidence (direct or indirect) indicating the substance causes the key event, but scientific understanding is not yet completely established. Some studies may be equivocal or contradictory.
Low	1	Limited evidence (direct or indirect) that the substance causes the key event along this pathway. Scientific understanding of the key event is limited.
No Evidence	0	No data available or inconsistent and/or equivocal data to support or negate causation of this key event by the substance.
Low Counter Evidence	-1	Limited contradictory evidence (direct or indirect) that the substance does not cause this key event.
Moderate Counter Evidence	-2	Some evidence (direct or indirect) indicating that the key event is not caused by the substance, but scientific understanding is not completely established. Some studies may be equivocal.
High Counter Evidence	-3	Convincing evidence based on multiple studies and/or extensive data that shows the substance does not cause the key event.

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A MOA confidence score is calculated from the reviewer ratings using the following equation for combining the scores for the 4 criteria:

$$MOAScore = \frac{(E * WTe + MC * WTmc + C * WTc + \sum(KEs * WTes))}{MPS} \times 100$$

Where,

- E = Reviewer rating for Essentiality (-3 to +3)
- WTe = Weight assigned to Essentiality (0.25)
- MC = Reviewer rating for MOA Coherence (-3 to +3)
- WTmc = Weight assigned to MOA Coherence (0.25)
- C = Reviewer rating for Concordance of KEs/KERs (-3 to +3)
- WTc = Weight assigned to Concordance of KEs/KERs (0.25)
- KEes = Reviewer rating for KEs under Empirical Support (only unique KEs are included; -3 to +3)
- WTes = Weight assigned to Empirical Support (0.25)
- MPS = Maximum possible score (i.e., if all criteria received the highest rating of +3)

An Improved Approach for Integrating Mechanistic Data in Cancer Risk Monographs

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- MPS = Maximum possible score (i.e., if all criteria received the highest rating of +3)

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Example: clofibrate liver tumors in rodents (details in Becker et al., 2017): scores can range from -100 to +100 (higher the score, greater the confidence in that MOA)

- Mutagenic MOA Hypothesis the QMOA Confidence Score = -44
- Receptor Mediated Proliferation MOA (PPAR- α) the QMOA Confidence Score = +83

Conclusion: The confidence that clofibrate is operating via a PPAR α MOA to induce liver tumors in rodents is high

An Improved Approach for Integrating Mechanistic Data in Cancer Risk Monographs

Thoughts about this proposed improved approach?

- Why not try it? At its core is the fundamental principle of science - hypothesis generation & testing
 - articulate the biologically plausible MOAs that are to be evaluated and compared
 - organize and present the data to a group of risk assessment experts
 - have each individual expert assign scores using the criteria developed
 - aggregate the scores & evaluate results (statistically)
 - identify & communicate the likely operative MOA



Thanks for Your Attention

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