The key characteristics (KCs) approach to hazard identification

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SCIENCE FOR A SAFER WORLD

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Conflict of Interest Statement

- I am retained as a consultant and potential expert witness in U.S. litigation involving chemical exposures and disease outcomes, including cancer, on behalf of plaintiffs.
- I have no formal association with IARC, US EPA or CalEPA, but have an ongoing contract with OEHHA (Cal EPA) to further develop the key characteristics approach.
- The views expressed are solely my own.

Summary of today's talk

- Scientific findings providing insights into mechanisms of toxicity play an increasingly important role in hazard identification
- The key characteristics (KCs) provide the basis for a knowledge-based, objective approach to evaluating mechanistic data in hazard evaluations that contrasts with and compliments the reductive MOA/AOP approach
- Recent IARC Monograph, EPA, CalEPA and NTP evaluations have illustrated the applicability of the KC approach
- Key characteristics for reproductive toxicants, endocrine disruptors, neurotoxicants, cardiotoxicants and immunotoxicants have or are being developed
- A comprehensive set of biomarkers and assays are needed to measure the KCs

Need KCs for Evidence Integration in Identifying Chemical Hazards

- Human studies – epidemiology
- Animal studies – usually in rodents –acute, subchronic and chronic studies
- In vitro studies – e.g. HTS: Tox21/Toxcast
- Mechanistic data in humans (biomarkers), animals and in vitro – Provides biological plausibility, is increasing in importance, and KCs could enlighten approaches to testing

Mechanistic Data: *Challenges*

IARC Monographs
Volume 100

- How to search systematically for relevant mechanisms?
- How to bring uniformity across assessments?
- How to analyze the voluminous mechanistic database efficiently?
- How to avoid bias towards favored mechanisms?

The Classical Approach to Mechanistic Data has been Hypothesis Driven

Analysis of mechanistic data for hazard identification and risk assessment has typically involved developing a mode of action (MOA) or more recently an Adverse Outcome Pathway (AOP)

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

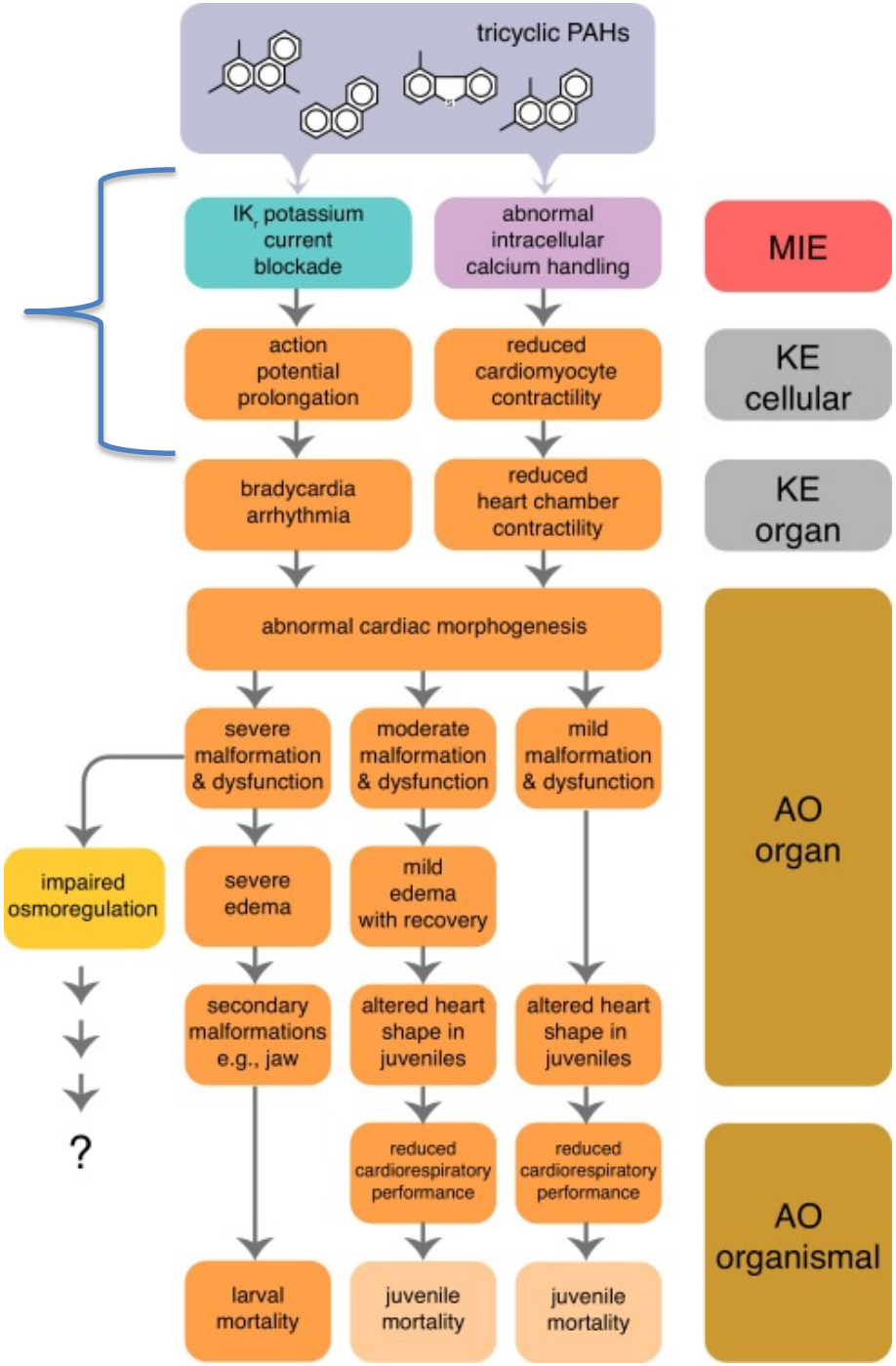
- Mechanistic hypotheses in science are beneficial because if you test it and are wrong then you modify the hypothesis and get closer to the truth

- 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

Limitations of MOA/AOP Approach

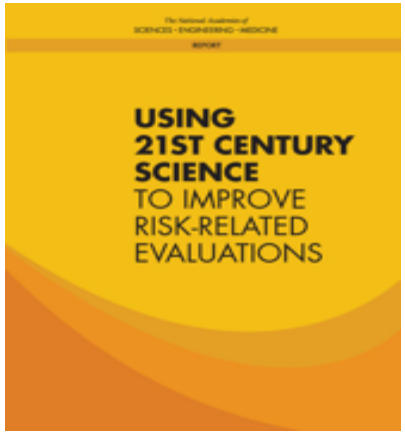
- Focus on ‘favorite’ mechanism may introduce bias, especially on committees and public databases
- MOA/AOP may be incomplete or wrong [e.g. DEHP – Rusyn and Corton (2012)]
- How many ‘validated’ AOPs needed for 100K chemicals producing 100s of adverse outcomes in different ways?
- KCs can help build unbiased MOA/AOPs if needed

Existing AOPs may also inform future KCs



JP Incardona, NL Scholz (2016) The influence of heart developmental anatomy on cardiotoxicity-based adverse outcome pathways in fish, Aquatic Toxicology, 177, 515-525

National Academy of Sciences report released January 5, 2017



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

Using 21st Century Science to Improve Risk-Related Evaluations

260 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-45348-6 | DOI: 10.17226/24635

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

2017 NAS Report "Using 21st Century Science to Improve Risk-Related Evaluations" – Comments on the Key Characteristics Approach

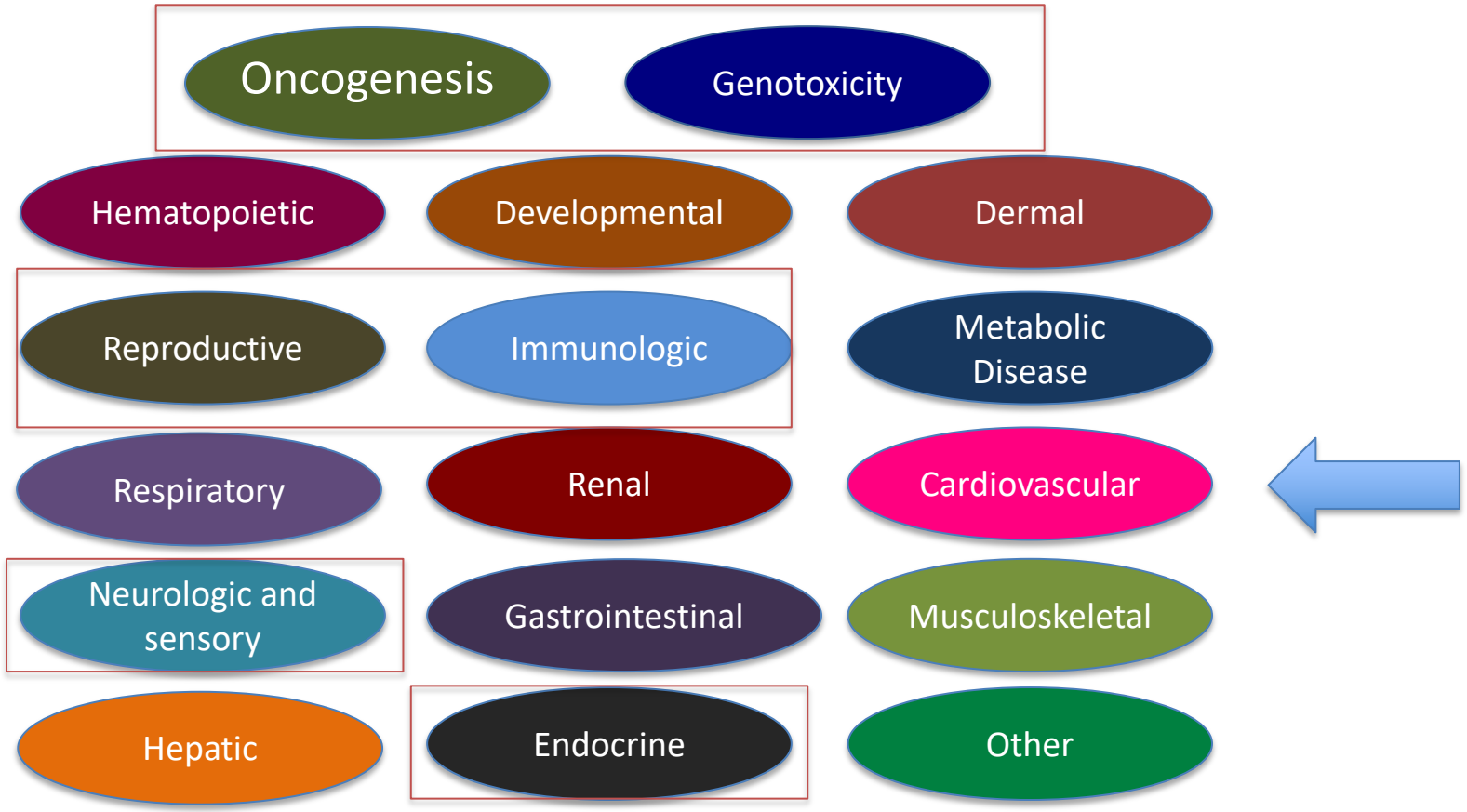
- The "approach avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence." (p.144)
- "The committee notes that key characteristics for other hazards, such as cardiovascular and reproductive toxicity, could be developed as a guide for evaluating the relationship between perturbations observed in assays, their potential to pose a hazard, and their contribution to risk." (p.141)

California's Hazard Traits

Hazard Traits

- Term in California legislation
- Coverage: "All of the health end points that are relevant to the people of the state in the design and implementation of programs for toxic chemicals."
- Properties of chemicals

CA Toxicological Hazard Traits



Key Characteristics of Human Carcinogens

Key characteristic:
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

Evidence that these characteristics are observed, especially in humans or as intermediate biomarkers in human specimens can provide biological plausibility for epidemiological findings and/or early warning if no epidemiology exists

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

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)

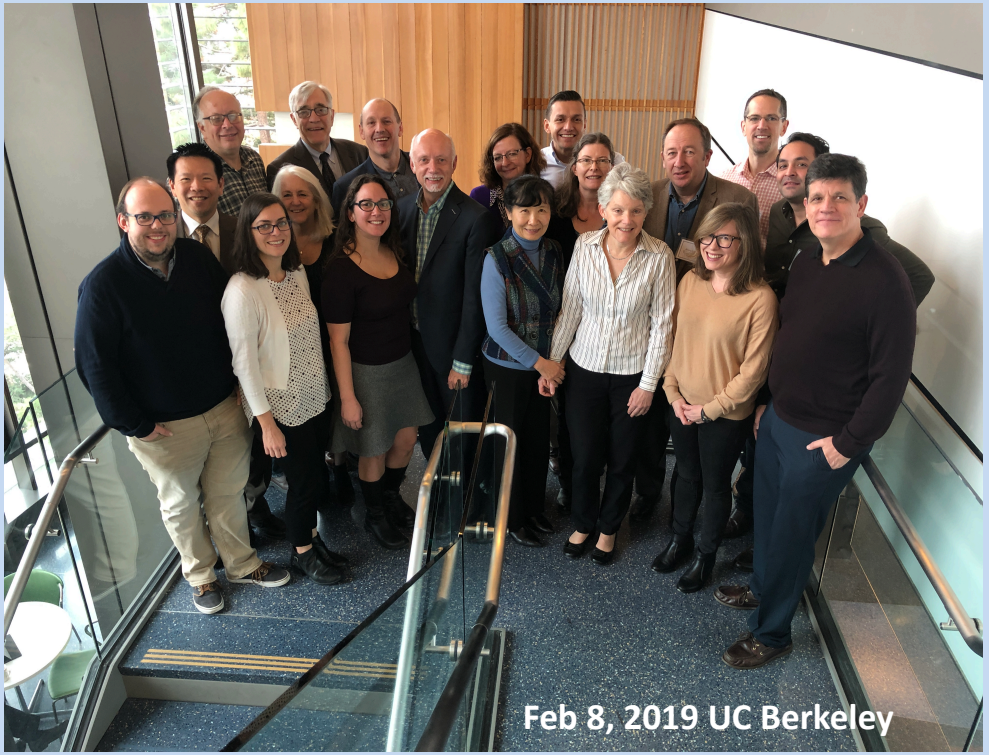
Characteristic	Examples of relevant evidence
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is Immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor 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

Published papers on KCs of carcinogens

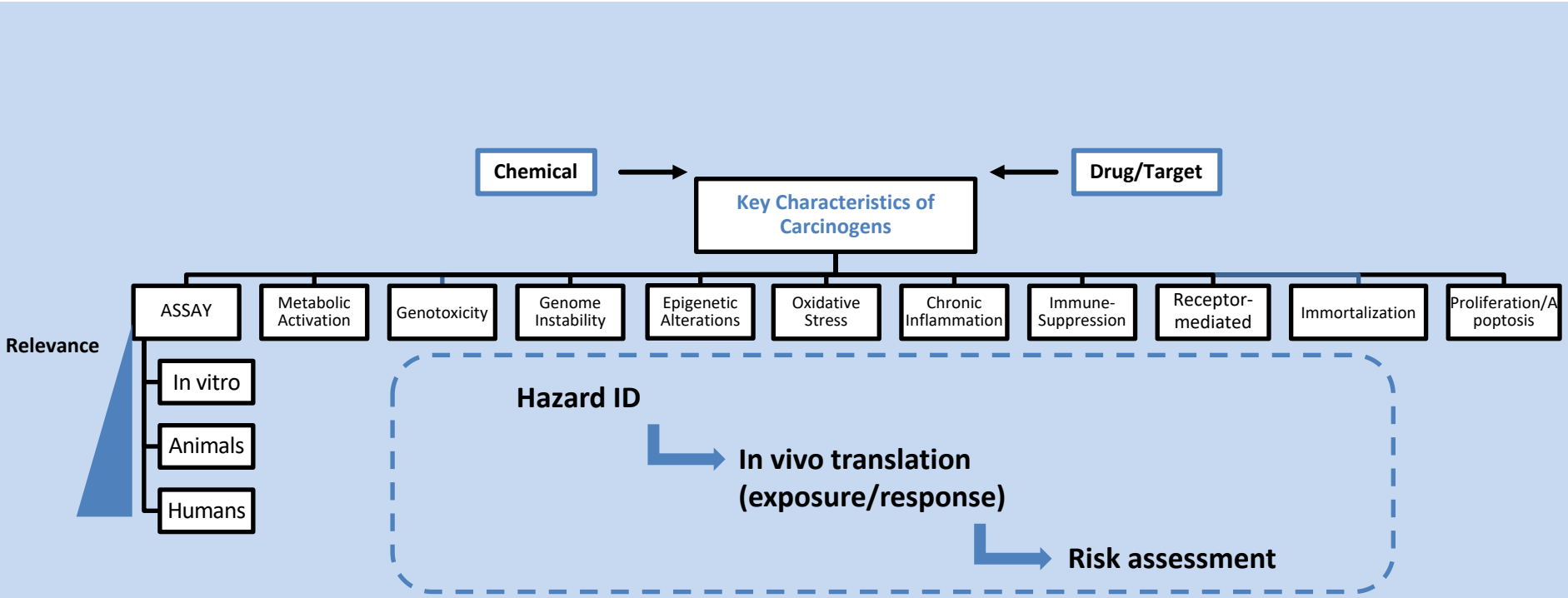
- Smith MT, et al. (2016) “Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis.” Environ Health Perspect. 124(6): 713-721. PMCID: PMC4892922.
- Guyton, K Z et al. (2018) "Key Characteristics Approach to Carcinogenic Hazard Identification." Chem Res Toxicol. 31(12):1290-1292. PMID: 30521319
- Smith MT, et al. (2020) “The Key Characteristics of Carcinogens: Relationship to the Hallmarks of Cancer, Relevant Biomarkers and Assays to Measure Them.” Cancer Epidemiol Biomarkers Prev. 2020 Mar 9. [Epub ahead of print] PMID: 32152214

How do we measure the KC's?

- KC Working Group: Goal was to outline well established in vitro and in vivo assays/biomarkers to assess the KC's, and highlight the gaps in the toolbox
- To facilitate research in the advancement of tools to aid in cancer hazard identification
- Goal eventually will be to identify all useful assays and biomarkers



How can the KC's be used? Toolbox to improve predictive toxicology and aid risk assessment



Key Characteristics of Carcinogens can be used to define a toolbox to assess new/untested chemicals or agents for carcinogenic hazards

From: Fielden MR, Ward LD, Minocherhomji S, Nioi P, Lebrec H, Jacobson-Kram D., Modernizing Human Cancer Risk Assessment of Therapeutics. *Trends Pharmacol Sci.* 2018; 39(3):232-247

Representative assays that measure the KCs

- Efforts underway to develop a complete list of assays and biomarkers on the web

Endpoint	In vivo assay in experimental animals	Biomarker assay in humans
KC 1: Is Electrophilic		
Protein adducts	Protein adduct measurement by LC/Mass spectrometry (PMID:27097313) *Chemoproteomics (PMID:26647369) Hemoglobin or albumin adducts in blood (PMID:12376136) Protein adductomics* (PMID:30857166)	
DNA adducts	DNA adductomics (PMID:29084424, 24437709) Nuclease P1-enhanced (32)P-postlabeling method (PMID:11559540) Mass spectrometry (PMID: 29889312)	
KC 2: Is Genotoxic		
Mutation/single nucleotide variants	Transgenic rodent assay (eg. Big Blue®) (OECD 488) Pig-a assay (PMID: 20857433)	HPRT mutation assay (PMID: 8829195)
Structural chromosome alterations/DNA strand breaks (clastogenicity, aneugenicity)	Alkaline comet assay (OECD 489; 16623855) Bone marrow micronucleus assay (OECD 474/487) Micronucleus assay in exfoliated cells (PMID: 29152700) Chromosome aberration (PMID: 21787692) Interphase and metaphase FISH (PMID: 23179826)	

Working Group on KCs of Endocrine Disruptors and Reproductive Toxicants

Berkeley CA, March 7-8, 2018

Three papers on KCs of reproductive toxicants and endocrine disruptors

1) Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment

Xabier Arzuaga, Martyn T. Smith… and Gail S. Prins, *Environ. Health Perspect*., 127 (6), 65001, 2019

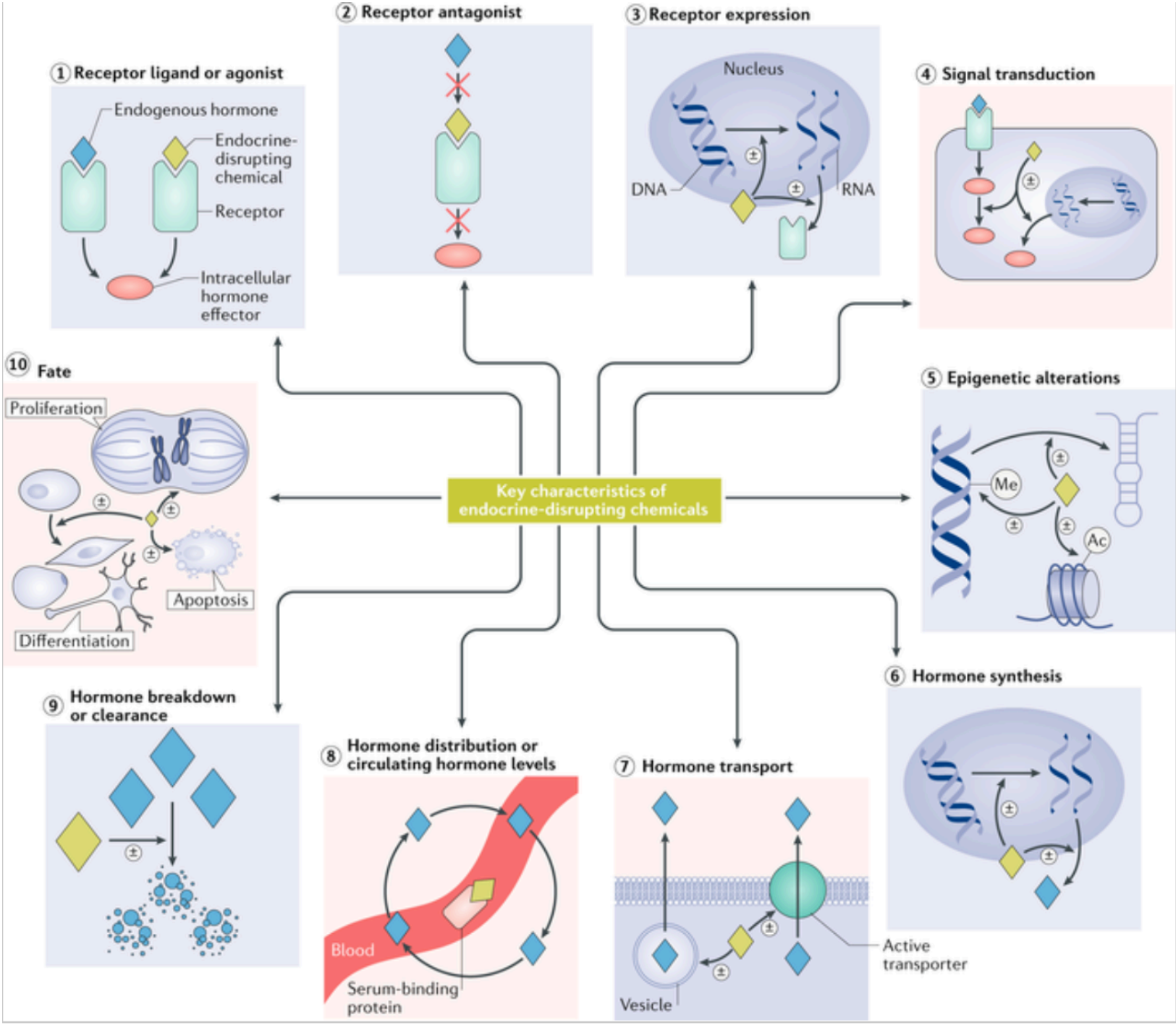
2) Proposed Key Characteristics of Female Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment

Ulrike Luderer, Brenda Eskenazi, Russ Hauser, et al. *Environ. Health Perspect*. 127 (7), 75001, 2019

3) Key Characteristics of Endocrine-Disrupting Chemicals as a Basis for Hazard Identification

Michele A. La Merrill, Laura N. Vandenberg, Martyn T. Smith, William Goodson, et al. *Nature Rev. Endocrinol.* 2020 Jan;16(1):45-57. doi: 10.1038/s41574-019-0273-8. PMID: 31719706

KCs of EDCs



La Merrill MA et al, Nature Reviews Endocrinology 2020

Universal EDC Key Characteristics

EDC Characteristic	Examples of relevant evidence
1. Interacts with or activates hormone receptors	Binding or agonism of hormone receptors
2. Antagonizes hormone receptors	Antagonism of nuclear or cell surface hormone receptors
3. Alters hormone receptor expression	Abundance, distribution and degradation of hormone receptors
4. Alters signal transduction in hormone responsive cells	Abundance of post-translational modifications, co-factors, transcription factors and transcripts and activity of associated enzymes
5. Induces epigenetic modifications in hormone producing or responsive cells	Chromatin modifications, DNA methylation, and non-coding RNA expression

Universal EDC Key Characteristics

EDC Characteristic	Examples of relevant evidence
6. Alters hormone synthesis	Expression or activity of enzymes or substrates in hormone synthesis
7. Alters hormone transport across cell membranes	Intracellular transport, vesicle dynamics or cellular secretion
8. Alters hormone distribution or circulating hormone levels	Blood protein expression and binding capacity, blood levels of pro-hormones and hormones
9. Alters hormone metabolism or clearance	Inactivation, breakdown, recycling, clearance, excretion or elimination of hormones
10. Alters fate of hormone producing or responsive cells	Atrophy, hyperplasia, hypertrophy, differentiation, migration, proliferation or apoptosis

Key Characteristics of Neurotoxicants and Developmental Neurotoxicants as a Basis for Organizing Data on Mechanisms of Neurotoxicity

Neurotoxicants

- Pamela Lein (UC Davis) (Chair)
- Aaron Bowman (Purdue)
- Zhengyu Cao (China Pharmaceutical University)
- Monica Carson (UC Riverside)
- Bill Slikker (US FDA NCTR)
- Dan Qiao (CalEPA)

DNTs

- Thomas Hartung (Johns Hopkins) (Chair)
- Brenda Eskenazi (UC Berkeley)
- Ellen Fritsche (IUF, Düsseldorf)
- Jean Harry (NIEHS)
- Tim Shafer (USEPA)
- Patty Wong (CalEPA)

Meeting held September 17-18, 2019

PARTICIPANTS for KCs of Cardiotoxicants	AFFILIATION
Smith, Martyn	UC Berkeley
Lind, Lars	Uppsala Univ.
Chiu, Weihsueh	Texas A&M
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Belcher, Scott	NCSU
Berridge, Brian	NTP
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Vargas, Hugo	Amgen
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Zeise, Lauren	OEHHA
Zhou, Changcheng	UC Riverside
Contract support:	
Elmore, Sarah	OEHHA

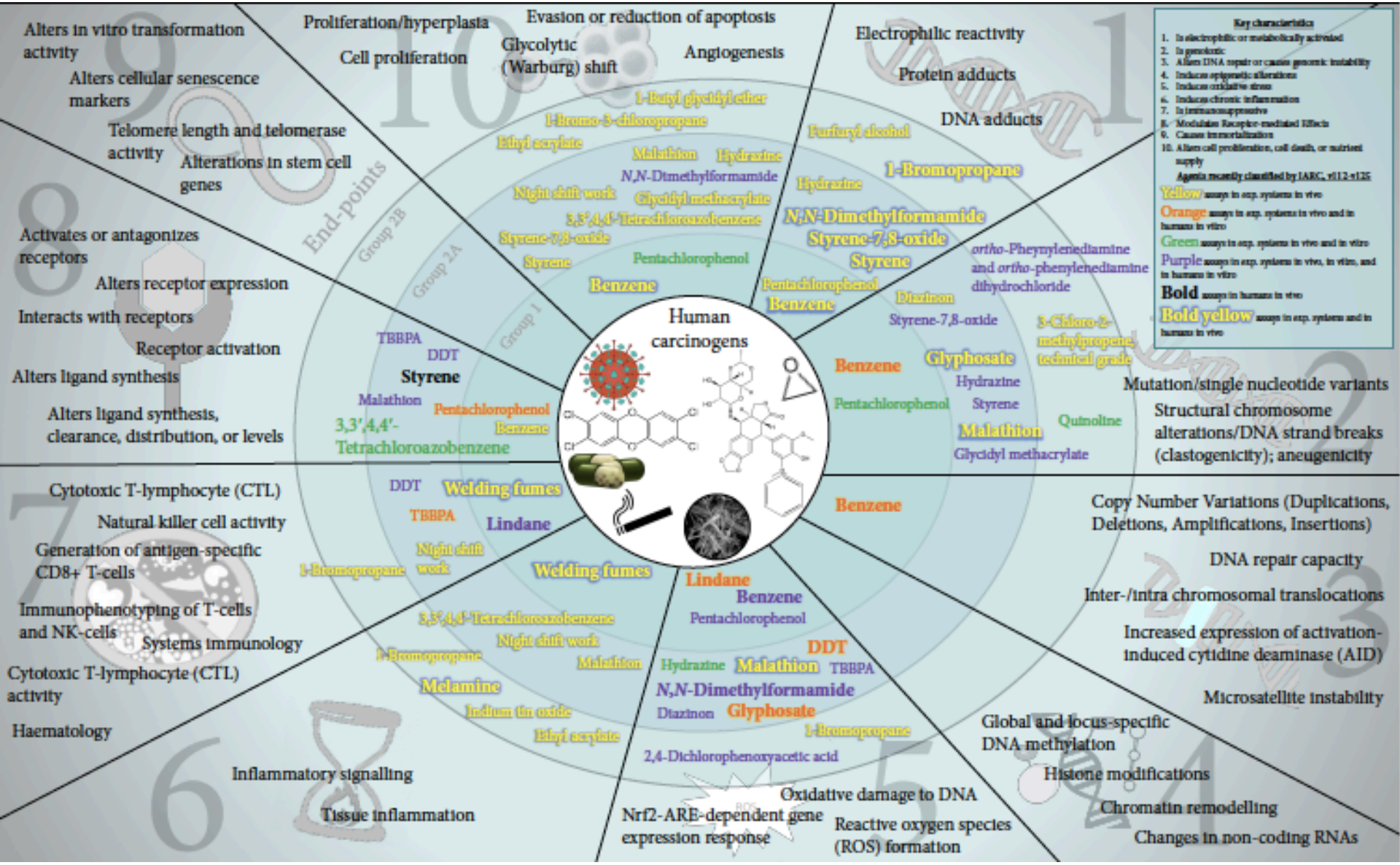
How are the KCs used?

Who is using them?

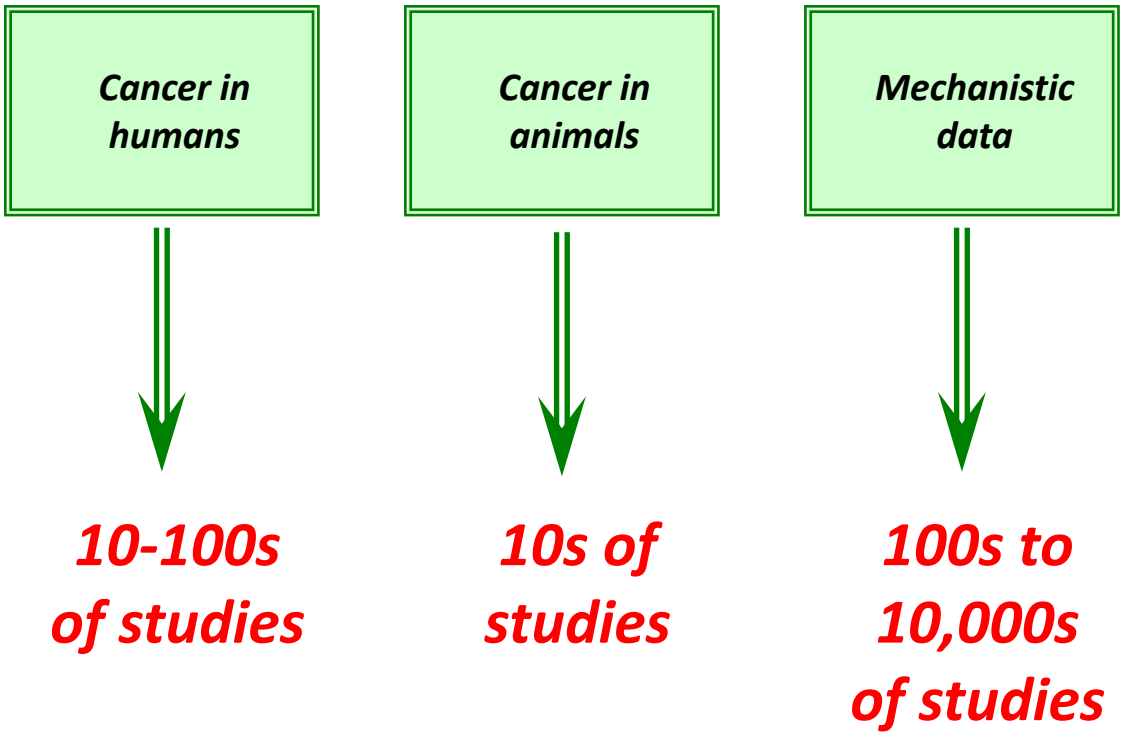
Application of the KC approach by IARC, NTP, Toxstrategies & EWG

- Guyton, K. Z., et al. (2018). "Application of the key characteristics of carcinogens in cancer hazard identification." Carcinogenesis **39**(4): 614-622. (see also IARC Preamble)
- Atwood, S. T., et al. (2019). "New Perspectives for Cancer Hazard Evaluation by the Report on Carcinogens: A Case Study Using Read-Across Methods in the Evaluation of Haloacetic Acids Found as Water Disinfection By-Products." Environ Health Perspect **127**(12): 125003.
- Chappell, G. A., et al. (2019). "Lack of potential carcinogenicity for sucralose - Systematic evaluation and integration of mechanistic data into the totality of the evidence." Food Chem Toxicol: 110898.
- Temkin, A.M. et al. (2020) “Application of the key characteristics of carcinogens to Per and Polyfluoroalkyl substances.” Int J Environ Res Public Health. Mar 4;17(5). pii: E1668. PMID: 32143379

KCs used in IARC Monographs 112-125



So Many Studies, So Little Time…



- How to search systematically for relevant mechanisms?
- How to bring uniformity across assessments?
- How to analyze the voluminous mechanistic database efficiently?
- How to avoid bias towards favored mechanisms

Systematic Approach
Using Key Characteristics of Carcinogens

Targeted searches for each key characteristic

Is Genotoxic (#2)

Actions

Description	First three characteristics
Search type	Search
Search database	PubMed
Search text	Benzene[Mesh] AND ("Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Mutagens"[Mesh] OR "Oncogenes"[Mesh] OR "Genetic Processes"[Mesh] OR "genomic instability"[MeSH] OR chromosom* OR clastogen* OR "genetic toxicology" OR "strand break" OR "unscheduled DNA synthesis" OR "DNA damage" OR "DNA adducts" OR "SCE" OR "chromatid" OR micronucle* OR mutagen* OR "DNA repair" OR "UDS" OR "DNA fragmentation" OR "DNA cleavage")

Induces Epigenetic Alterations (#4)

Actions

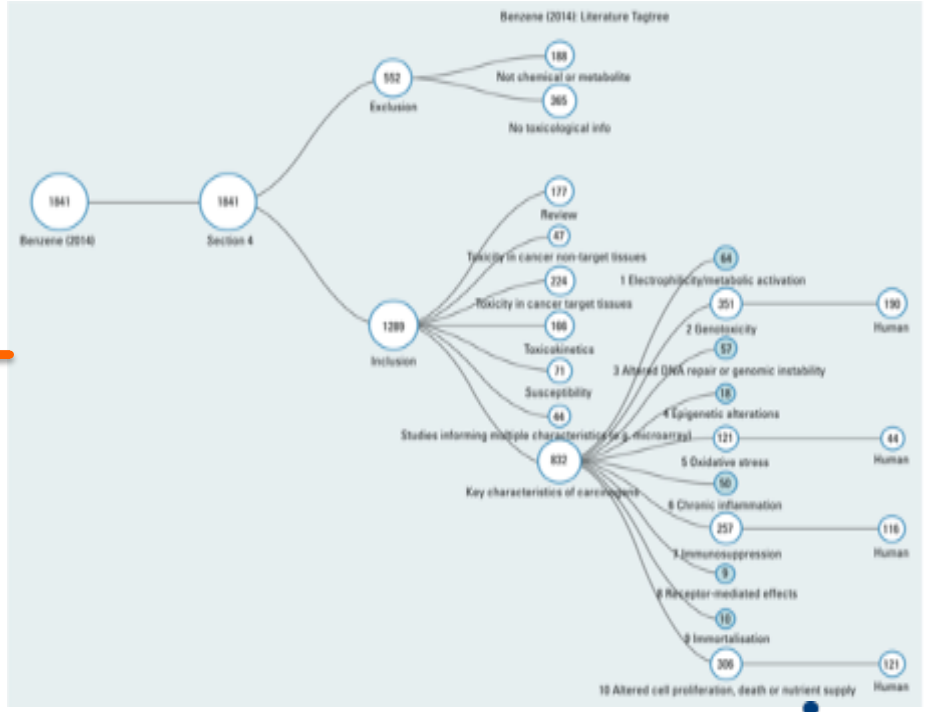
Description	Epigenetics
Search type	Search
Search database	PubMed
Search text	Benzene[Mesh] AND ("rna"[MeSH] OR "epigenesis, genetic"[MeSH] OR rna OR "rna, messenger"[MeSH] OR "rna" OR "messenger rna" OR mrna OR "histones"[MeSH] OR histones OR epigenetic OR miRNA OR methylation)

Induces oxidative stress (#5)

Actions

Description	Oxidative stress
Search type	Search
Search database	PubMed
Search text	Benzene[Mesh] AND ("reactive oxygen species"[MeSH] OR "reactive nitrogen species"[MeSH] OR "reactive oxygen species" OR "oxygen radicals" OR "oxidative stress"[MeSH] OR oxidative OR "oxidative stress" OR "free radicals")

Organize results by key characteristics, species, etc



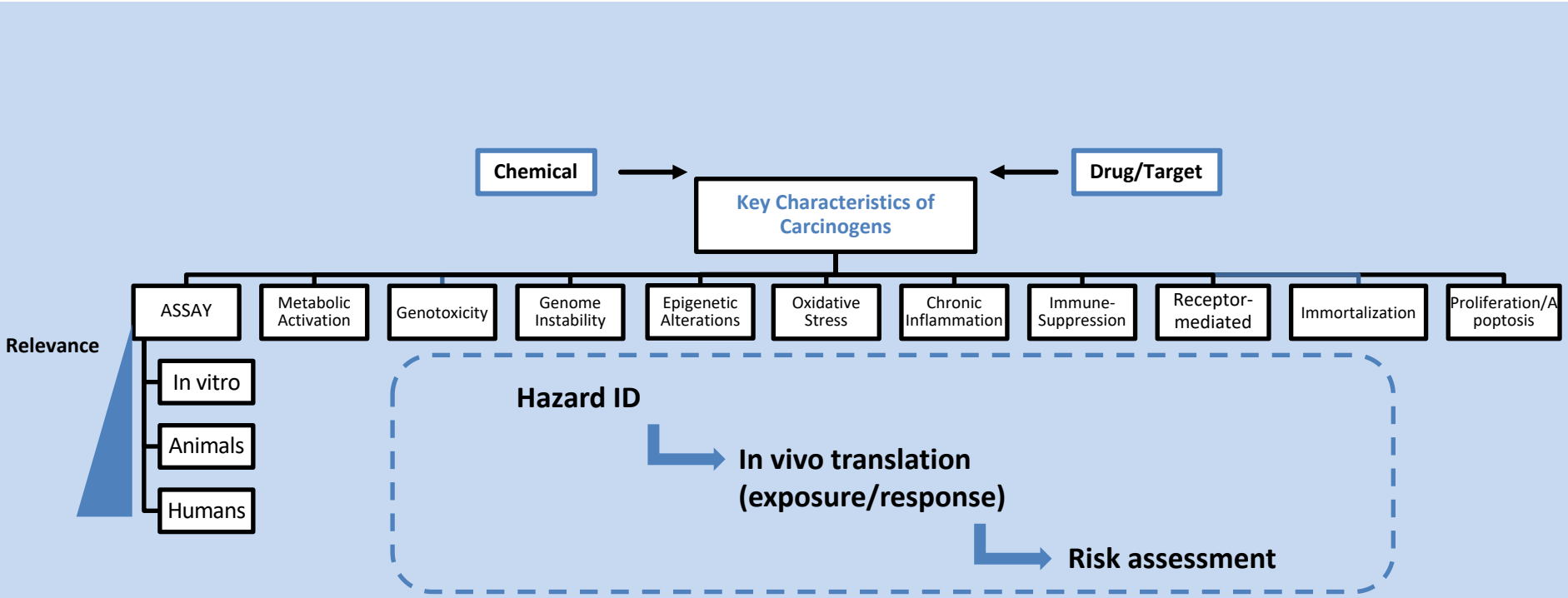
HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

Smith MT, Guyton KZ, Gibbons CF, Fritz JM et al.. *Env Health Persp.*, *124(6):713-21*

Applications of the KCs

- Facilitate systematic review of mechanistic data and identify data gaps
- Replace or Assist in Development of MOA/AOPs or networks
- Improve predictive toxicology and molecular epidemiology for disease prevention

How can the KC's be used? Toolbox to improve predictive toxicology and aid risk assessment



Key Characteristics of Carcinogens can be used to define a toolbox to assess new/untested chemicals or agents for carcinogenic hazards

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Comparison of Key Characteristics for Different Toxicants

Key Characteristics - Carcinogens	Male Repro	Female Repro	EDC	Neurotox
1. Is electrophilic or metabolically activated	-	-	-	-
2. Is genotoxic	X (5)	X (2)	-	X (10)
3. Alters DNA repair or genomic instability	-	-	-	-
4. Induces epigenetic alterations	X (6)	X (3)	X (5)	X (10)
5. Induces oxidative stress	X (7)	X (5)		X (8)
6. Induces chronic inflammation	X (8)	X (6)	-	X (12)
7. Is immunosuppressive	-	X (6)	-	-
8. Modulates receptor-mediated effects	X (4)	X (1)	X (1, 2, 3, 4)	X (2)
9. Causes immortalization	-	-	-	-
10. Alters cell proliferation, cell death, or nutrient supply	X (1)	X (9)	X (10)	X (1)

There may be key characteristics of bioactive hazardous chemicals

Thank you for listening!

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Thanks to All the KC Working Group Participants

90 people; 43 Institutions; 11 Countries to date

Last Name	First Name	Institution	KC Group(s)
Araujo	Jesus	UCLA	Cardiotox
Arzuaga	Xabier	U.S. EPA (IRIS)	Male repro
Baan	Robert	IARC (retired)	Carcinogens
Barchowsky	Aaron	Uni. Pittsburgh	Cardiotox
Beland	Frederick	FDA (NCTR)	Carcinogens
Belcher	Scott	N. Carolina State Uni.	Cardiotox
Berridge	Brian	NIEHS, NTP	Cardiotox
Beverly	Brandy	NIEHS, NTP	Male repro
Borrel	Alexandre	NIEHS, NTP	Assays & Hallmarks
Bowman	Aaron	Purdue Uni.	Neurotox
Browne	Patience	OECD	EDCs
Bucher	John	NIEHS, NTP	Carcinogens
Caldwell	Jane	US EPA (retired)	Carcinogens
Cao	Zhengyu	China Pharmaceutical Uni.	Neurotox
Cardenas	Andres	UC Berkeley	Assays & Hallmarks
Carson	Monica	UC Riverside	Neurotox
Chen	Tracy	FDA	Cardiotox
Chiamvimonvat	Nipavan	UC Davis	Cardiotox
Chiu	Weihsueh	Texas A&M Uni.	Carcinogens; Assays & Hallmarks; Cardiotox
Christiani	David	Harvard Uni.	Carcinogens
Cogliano	Vincent	OEHHA	Carcinogens; EDCs; Cardiotox
Cooper	Ralph	U.S. EPA (retired)	Female Repro
Corpet	Denis	Université de Toulouse	Carcinogens
DeMarini	David	U.S. EPA	Carcinogens
Elmore	Sarah	OEHHA	Cardiotox
Eskenazi	Brenda	UC Berkeley	Female Repro; Neurotox
Farraj	Aimen	U.S. EPA	Cardiotox
Felsher	Dean	Stanford Uni.	Assays & Hallmarks
Fielden	Mark	Amgen	Assays & Hallmarks
Fritsche	Ellen	IUC, Düsseldorf	Neurotox
Fritz	Jason	U.S. EPA	Carcinogens
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Gomes	Aldrin	UC Davis	Cardiotox
Goodson	William	UCSF	EDCs; Assays & Hallmarks
Gore	Andrea	Uni. Texas, Austin	EDCs
Guyton	Kathryn	IARC	Carcinogens; EDCs; Assays & Hallmarks
Harry	Jean	NIEHS	Neurotox
Hartung	Thomas	Johns Hopkins	Neurotox
Hauser	Russ	Harvard	Female Repro; Male Repro
Hecht	Stephen	Uni. Minnesota	Carcinogens
Hotchkiss	Andrew	U.S. EPA, NTP	Male repro
Houck	Keith	U.S. EPA	Assays & Hallmarks
Kavlock	Robert	U.S. EPA	Carcinogens
Kleinstreuer	Nicole	U.S. EPA, NTP	Assays & Hallmarks
Korach	Kenneth	NIEHS	EDCs; Female Repro; Male Repro
Kortenkamp	Andreas	Brunel Uni. London	EDCs
La Merrill	Michele	UC Davis	EDCs; Assays & Hallmarks
Lambert	Paul	Uni. Wisconsin	Carcinogens
Lebrec	Herve	Amgen	Assays & Hallmarks
Lein	Pamela	UC Davis	Neurotox
Lind	Lars	Uni. Uppsala	Cardiotox
Lowe	Leroy	Getting to Know Cancer	Assays & Hallmarks
Luderer	Ulrike	UC Irvine	Female Repro
McHale	Cliona	UC Berkeley	Female Repro; Assays & Hallmarks
Meyer	Kathleen	Sangamo Therapeutics	Cardiotox
Minocherhomji	Sheroy	Amgen, SSF	Assays & Hallmarks
Moran	Pancho	OEHHA	Female Repro
Pagani	Rodrigo	Uni. Illinois, Chicago	Male repro
Patisaul	Heather	N. Carolina State Univ.	EDCs
Portier	Christopher	Maastricht Uni.	Carcinogens
Posnack	Nikki	George Washington Uni.	Cardiotox
Prins	Gail	Uni. Illinois	Male repro
Rider	Cynthia	NIEHS, NTP	Assays & Hallmarks
Rieswijk	Linda	UC Berkeley (now at Maastricht Uni.)	Carcinogens; EDCs; Female Repro; Assays & Hallmarks
Ross	Matthew	Mississippi State Uni.	Carcinogens
Rusyn	Ivan	Texas A&M, College Station	Carcinogens
Sandy	Martha	OEHHA	Male repro; Assays & Hallmarks
Schrader	Steve	NIOSH (ret.)	Male repro
Shafer	Tim	U.S. EPA	Neurotox
Skakkebaek	Niels	Copenhagen Uni.	Male repro
Slikker	Bill	FDA, NCTR	Neurotox
Smith	Martyn	UC Berkeley	Carcinogens; EDCs; Female Repro; Male Repro; Cardiotox; Neurotox; Assays & Hallmarks
Solomon	Gina	UCSF, Public Health Inst.	Female Repro
Sone	Hideko	NIES Japan	EDCs; Assays & Hallmarks
Stewart	Bernard	Uni. New South Wales	Carcinogens
Straif	Kurt	IARC	Carcinogens
Udagawa	Osamu	NIES Japan	Female Repro
van den Berg	Martin	Utrecht Uni. (IRAS)	Carcinogens
Vandenberg	Laura	Uni. Massachusetts, Amherst	EDCs
Vargas	Hugo	Amgen	Cardiotox
Wang	Amy	NIEHS, NTP	Carcinogens; Assays & Hallmarks
Webster	Thomas	Boston Uni.	Assays & Hallmarks
Woodruff	Tracey	UCSF	EDCs
Yang	Xi	FDA	Cardiotox
Yost	Erin	NIEHS, NTP	Male repro
Zeise	Lauren	OEHHA	EDCs; Female Repro; Male Repro; Cardiotox; Neurotox; Assays & Hallmarks
Zhang	Luoping	UC Berkeley	Female Repro; Assays & Hallmarks
Zhou	Changcheng	UC Riverside	Cardiotox
Zlatnik	Marya	UCSF	Female Repro
Zoeller	Thomas	Uni. Massachusetts, Amherst	EDCs