NTP
National Toxicology Program

The Path to Converging on Cancer

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Outline

- Problem identification
  - Cancer and environmental chemicals
  - The Halifax Project
- Problem formulation
  - Key features
  - Groups involved in problem formulation
    - The National Toxicology Program
    - University of California, Berkeley Working Group
    - Converging on Cancer Workshop
- Implementation

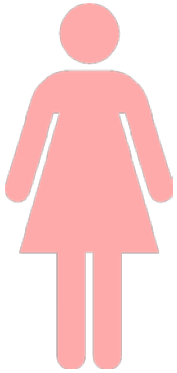
Problem Identification

Problem Formulation

Implementation/Testing

Public health burden of cancer

Leading Sites of New Cases



30%	Breast
13%	Lung & bronchus
7%	Colon & rectum
7%	Uterine corpus

19%	Prostate
14%	Lung & bronchus
9%	Colon & rectum
7%	Urinary bladder

From American Cancer Society

U.S. Cancer Statistics

1,735,350	Estimated new cancer cases diagnosed in 2018
609,640	Estimated 2018 cancer deaths
38.4	Percentage of people that will be diagnosed during their lifetime
147 billion	Estimated expenditures for cancer care in 2017

From National Cancer Institute

Environmental contribution to cancer

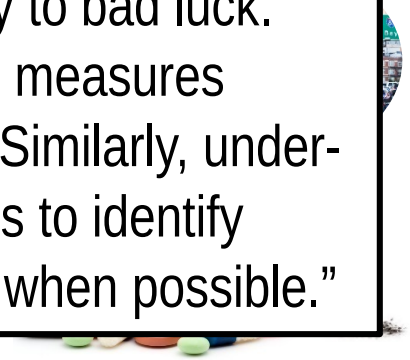
Intrinsic risk factors = random errors in DNA replication, aka ‘bad luck’ (unmodifiable)

Non-intrinsic risk factors

Endogenous risk factors (partially modifiable)

- Biologic aging
- Genetic

Exogenous risk factors (modifiable)

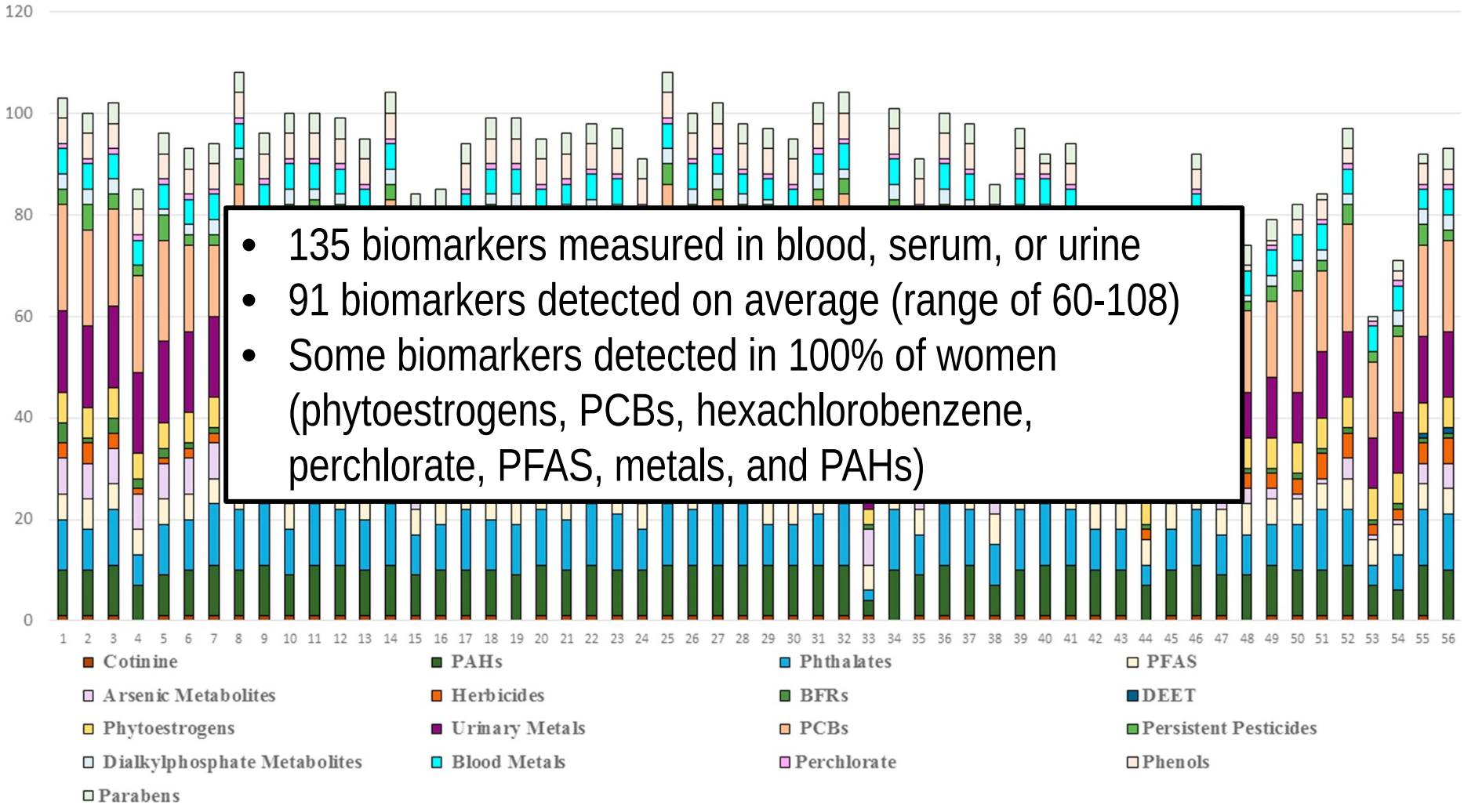


“it is detrimental to prevention and cancer control measures if the risk, especially for clinically significant cancers, is over interpreted to be due solely to bad luck. This underestimates the potential impact of prevention and control measures aimed at reducing or delaying incidence and death due to cancer. Similarly, under-estimating the fraction of preventable cancer risk impedes progress to identify modifiable exposures for cancer prevention and control measures when possible.”

Adapted from Wu et al. 2018

Exposure to a complex milieu of chemicals

Rosofsky et al. 2017

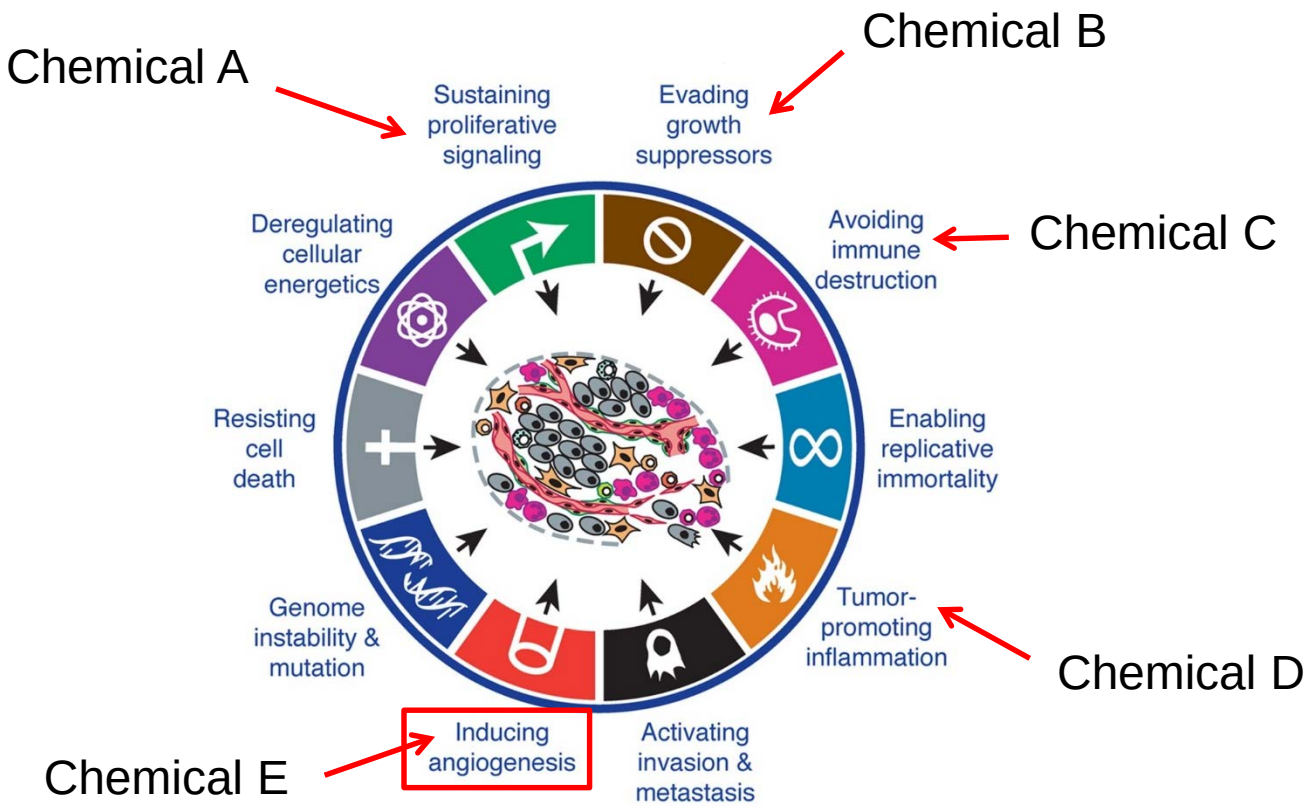


- 135 biomarkers measured in blood, serum, or urine
- 91 biomarkers detected on average (range of 60-108)
- Some biomarkers detected in 100% of women (phytoestrogens, PCBs, hexachlorobenzene, perchlorate, PFAS, metals, and PAHs)

Leroy Lowe (Getting to Know Cancer)

- Brought together cancer biologists and environmental toxicologists
- Teams formed to review the Hanahan and Weinberg (2000, 2011) hallmarks of cancer ‘pathways’ and identify 1) biomarkers and assays associated with each pathway and 2) environmental chemicals likely to interact with each pathway
- Underlying hypothesis: Environmentally-relevant levels of noncarcinogenic chemicals interact with hallmark pathways to contribute cumulatively to the development of cancer

Something from nothing

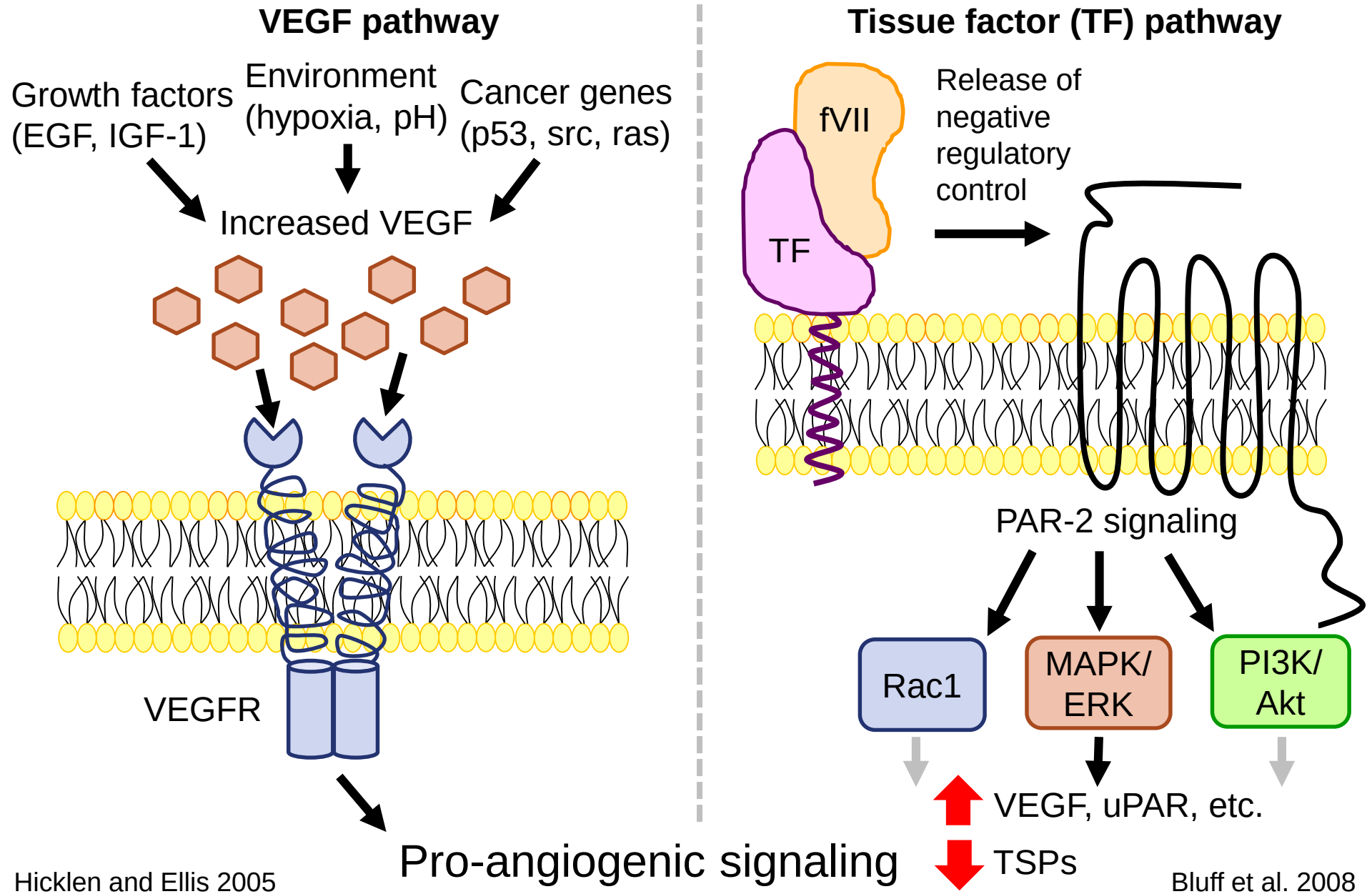


Hanahan and Weinberg 2011

Angiogenesis (Hu et al. 2015)

- Reviewed the key signaling pathways involved in angiogenesis
- Identified molecular markers associated with those signaling pathways
- Reviewed the pro-angiogenic action of environmental carcinogens (cigarette smoke, nicotine, and arsenic)
- Identified environmental chemicals predicted to act on the signaling pathways
  - Ubiquitous environmental chemicals
  - Shown to disrupt specific pathways
  - Not known to cause cancer
- Discussed cross-talk with other hallmarks

Key angiogenic pathways

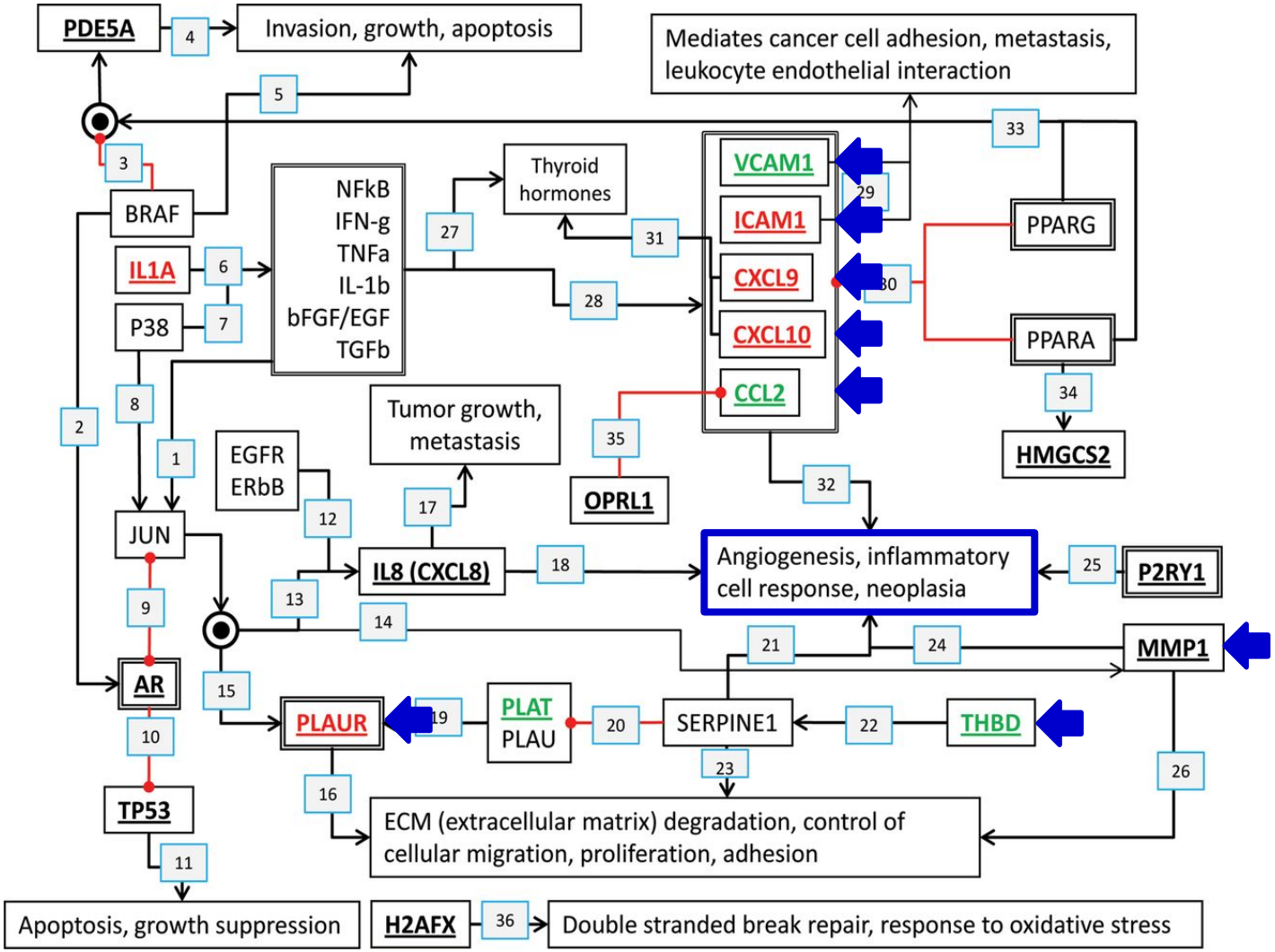


Hicklen and Ellis 2005

Bluff et al. 2008

Kleinstreuer et al. 2013

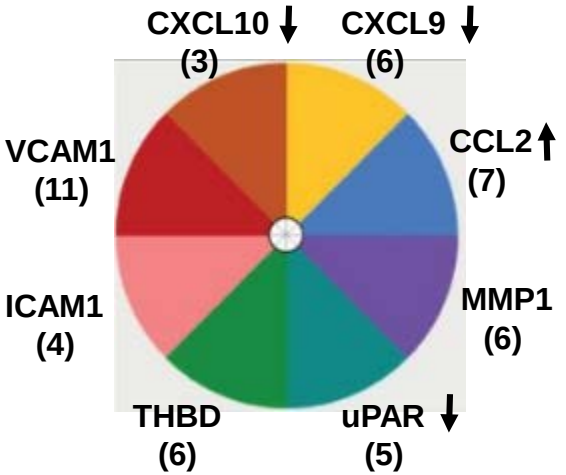
Identification of genes, pathways, and hallmark processes linked to EPA ToxCast assays (672 high throughput assays), which correlated to animal cancer data



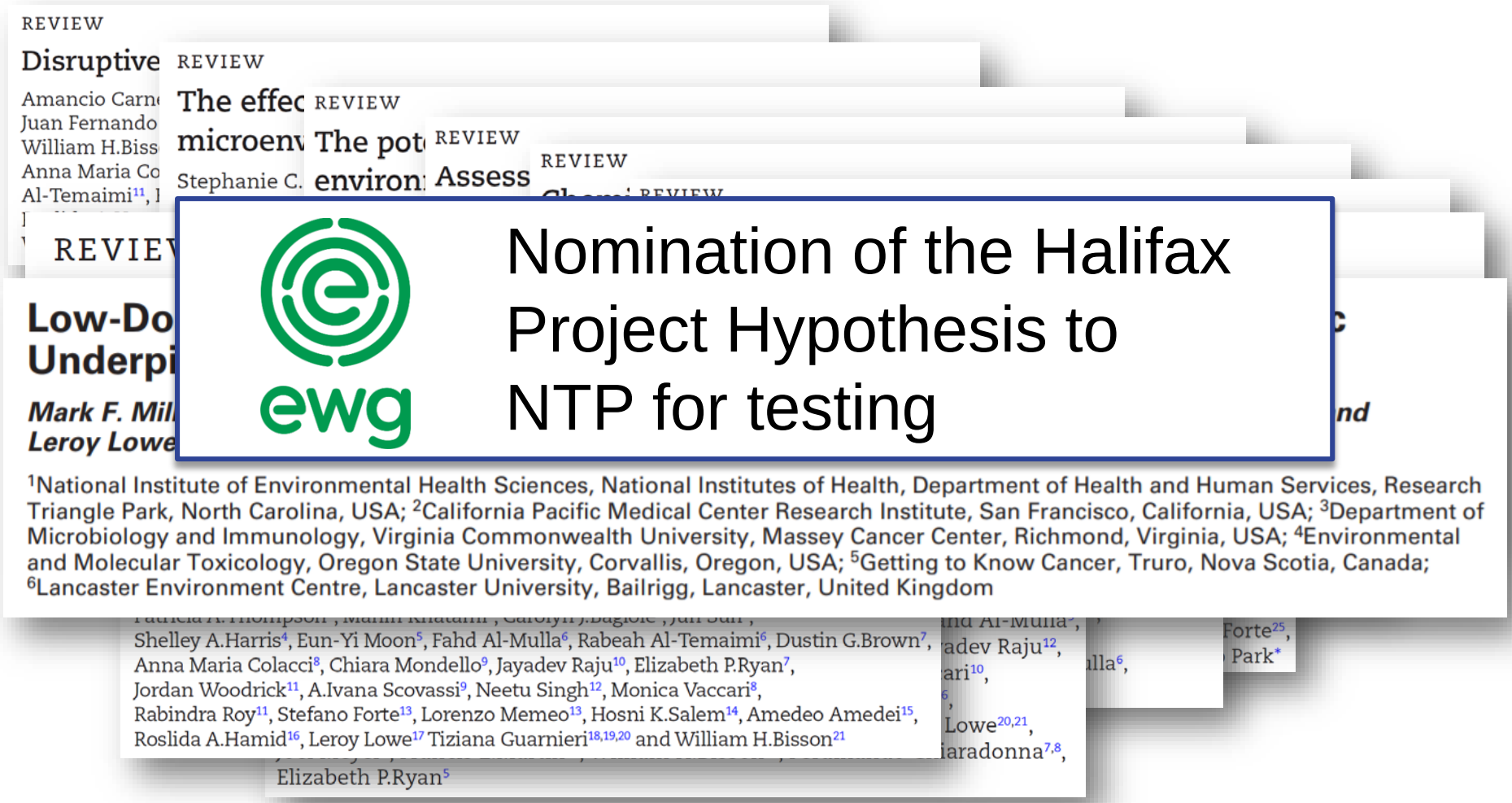
Environmental chemicals

Hu et al. 2015

- HPTE
- Bisphenol AF
- Chlorothalonil
- Diniconazole
- Biphenyl
- Ziram
- Methylene bis(thiocyanate)
- Tributyltin chloride
- C.I. solvent yellow 14
- PFOS

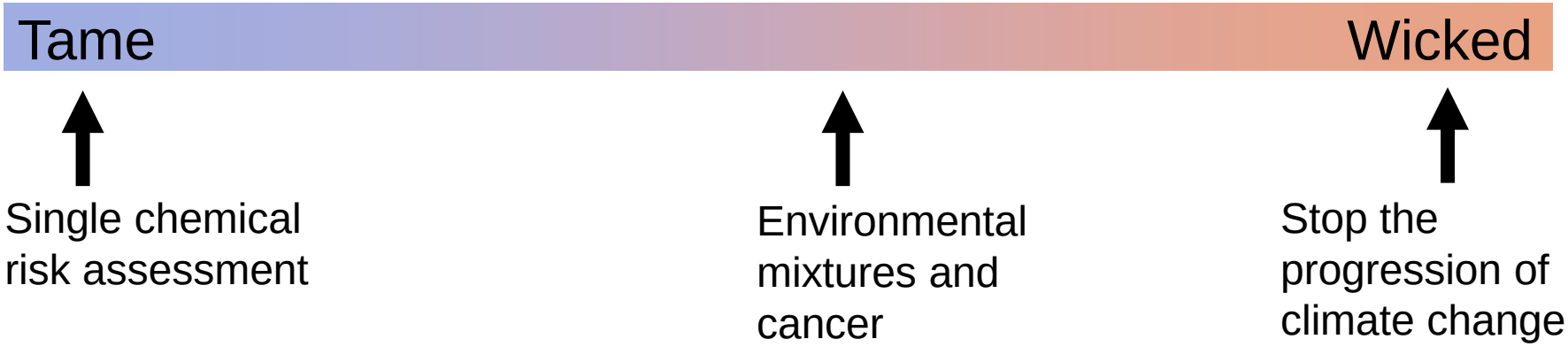


Halifax project output



Halifax problem statement

Low doses of environmental chemicals that target cancer pathways (but are not complete carcinogens) contribute cumulatively to the development of the disease and would not be accounted for in the current cancer risk assessment process.



Problem Identification

Problem Formulation

Implementation/Testing

Sauve-Ciencewicki et al. 2019

Process

- Evaluate available information
- Identify data needs
- Gain preliminary understanding of potential risks
- Develop hypotheses and conceptual models

Features

- Is systematic and iterative
- Involves stakeholders (including relevant experts)
- Incorporates experiential knowledge
- Includes logical and reasonable debate

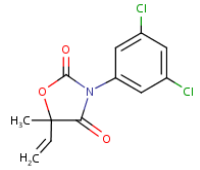
Evaluate available information

Incorporate experiential knowledge

- Understanding the underlying biology of cancer: Dean Felsher (Stanford University) and David Beebe (University of Wisconsin - Madison)
- Research programs that incorporate knowledge of biological systems to understand mixtures
  - EuroMix projects: Johanna Zilliacus (Karolinska Institutet):
    - Liver steatosis
    - Endocrine disruption of estrogen/testosterone balance leading to disruption of reproductive function
    - Skeletal malformations
  - Research on mixtures that disrupt male reproductive tract development: Earl Gray (US EPA)

Adverse Outcome Pathway network

Male reproductive tract development



Androgen Receptor Antagonism

Reduced AR dependent mRNA/protein

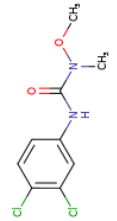
Abnormal cell apoptosis/ proliferation

Disruption of AR tissue development

Malformations

Decreased sperm

Impaired fertility

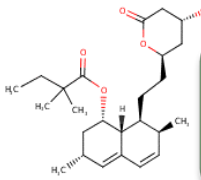


Inhibition of steroidogenic enzymes

Reduced T synthesis

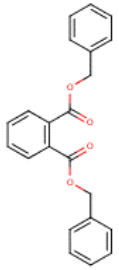
Suppressed development of gub. cords inguinalscrotal

Undescended testis



Inhibition of HMG-CoA reductase

Reduced cholesterol synthesis



Unknown

Decreased INSL3 synthesis

Abnormal cell apoptosis/ proliferation

Suppressed development of gub. cords transabdom.

Molecular Initiating Event

Key Event

Key Event

Key Event

Adverse Outcome

Adverse Outcome

Adapted with permission from Justin Conley (EPA)

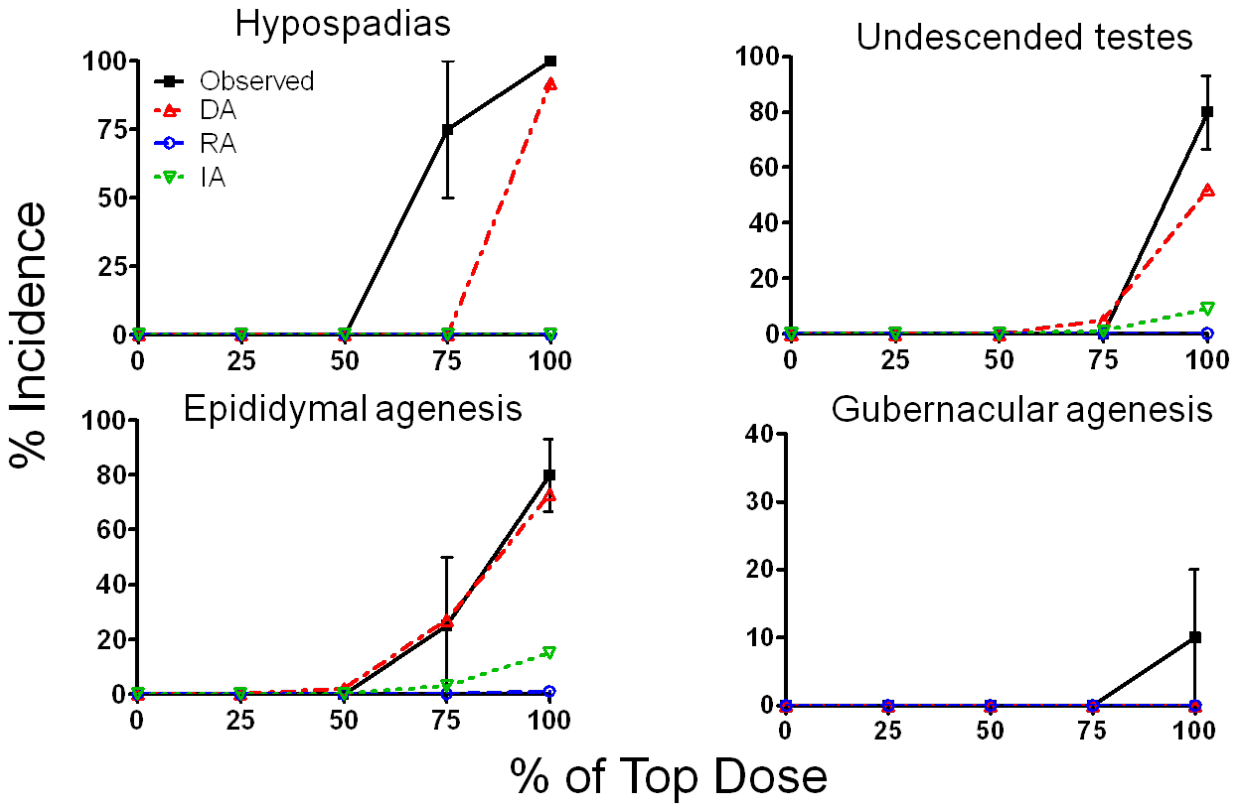
Evaluating mixtures

Rider et al. 2008

<u>Decrease testosterone</u>
DBP
BBP
DEHP

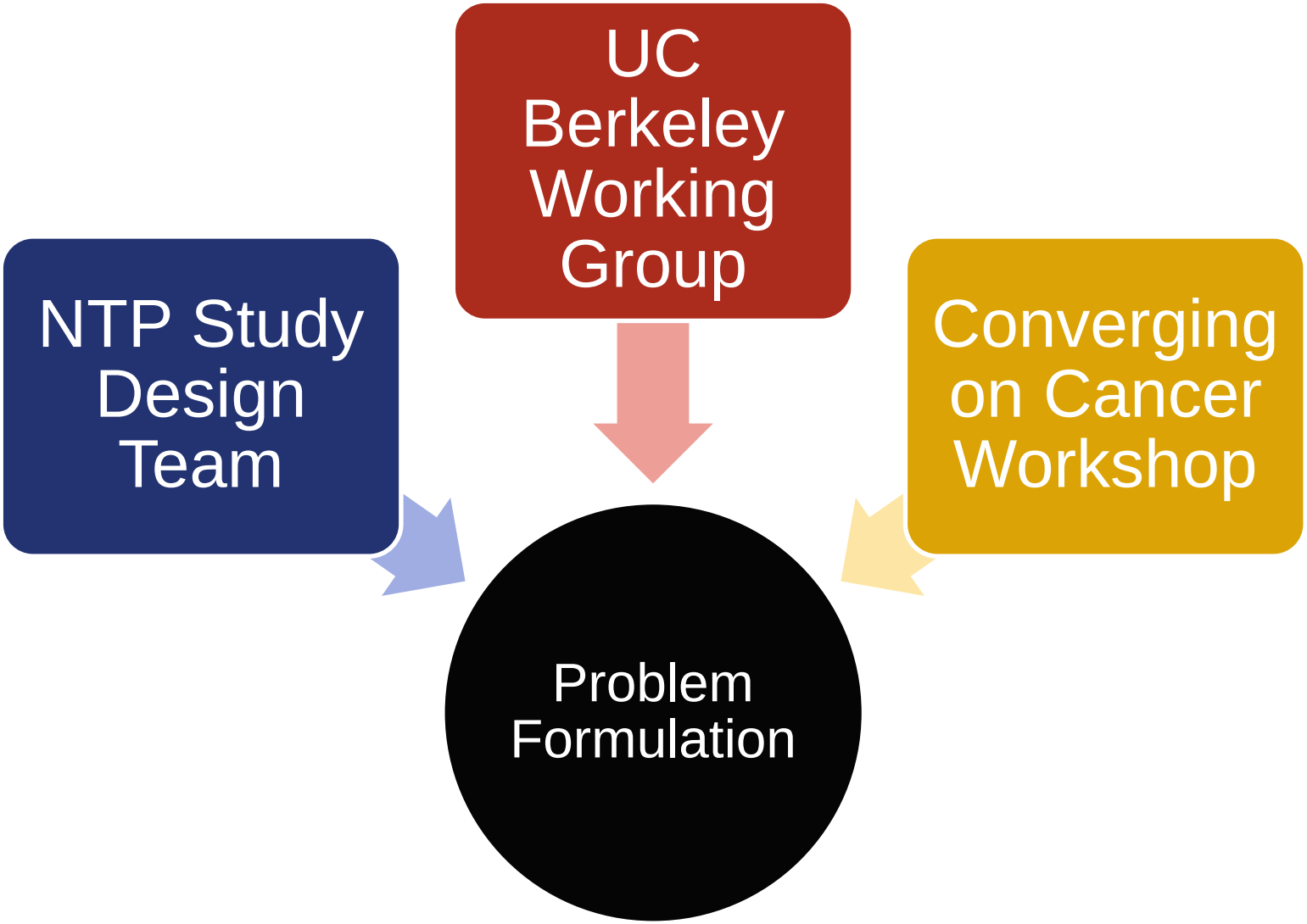
<u>AR antagonists</u>
Vinclozolin
Procymidone

<u>Mixed mechanism</u>
Prochloraz
Linuron



Implication of this work: Chemicals that do not act independently but contribute to toxicity in a dose additive manner should be considered in cumulative risk assessment in order to be health protective.

Groups that have been working on the problem



The National Toxicology Program

Mission: To improve public health through the development of data and knowledge that are translatable, predictive and timely

- Interagency program
  - Headquartered at NIEHS
- Research on nominated test articles
  - Thousands of agents evaluated in comprehensive toxicology studies
  - GLP compliant testing through government contracts
- Analysis activities
  - Report on Carcinogens (RoC)
  - Office of Health Assessment and Translation (OHAT)
  - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

Linda Birnbaum
Director, NIEHS & NTP

Brian Berridge
Associate Director, NTP

Environmental mixtures and cancer project

Mixtures toxicology

Cancer

In vitro/in silico/ mechanistic

Operational

UC Berkeley Working Group

Cancer and Environmental Mixtures

Martyn Smith
(UC Berkeley)

Lauren Zeise
(OEHHA)

- Refine the key characteristics with knowledge of cancer biology in mind (hallmarks)
- Develop a list of recommended assays that map to characteristics and hallmark pathways
- Formulate hypotheses and testing approaches related to environmental mixtures and cancer

Converging on Cancer Workshop

April 29-30, 2019

- Gather experts in cancer biology, *in vitro*/*in silico*, risk assessment, mixtures toxicology, methods development
- Present effort to date
  - Pre-meeting webinars
  - Presentations during meeting
- Further refine problem statement and develop a path forward for implementation
  - Identify key challenges
  - Get input on testing strategies

https://ntp.niehs.nih.gov/go/COC

Defining terms in the problem statement

- Low dose
  - Environmentally-relevant levels
  - Below NOAEL
  - Less concerned about low dose, more concerned about understanding the joint action of multiple chemicals that converge on pathways leading to cancer
- Mixtures
  - Focus on chemicals that have not been identified as carcinogens
  - Only include non-genotoxic chemicals
  - Identify chemicals based on pathways
- Cancer
  - *De novo* cancer
  - Priming the conditions for cancer (e.g., decreased time to cancer with genetic predisposition, lower dose of carcinogen required)
  - Cancer type-specific or generalizable to all cancers

Revisiting the problem statement

Cancers are a complex set of related diseases with wide ranging etiologies, and humans are exposed to a milieu of chemicals that may contribute to disease development. Can current knowledge of cancer hallmarks and key characteristics of carcinogens inform a new approach for assessing the carcinogenic risk posed by chemicals and mixtures?

Breakout session discussion

Questions

- What are the benefits and challenges to using mechanistic cancer data (e.g., key characteristics of carcinogens framework) in public health-based decision-making?
- Where along progression of cancer development would we be comfortable in predicting the eventual outcome of malignancy? What key events, individually or in combination, would be necessary/sufficient to indicate carcinogenicity?
- How might we detect those key events in an *in vivo* animal modeling system and *in vitro*/*in silico* modeling systems? Specifically, what are the existing technologies and platforms (*in vivo*, *in vitro*, and *in silico*) that should be applied to a human-relevant carcinogenicity evaluation strategy, and in what combinations?

Questions (continued)

- How would we go about building scientific confidence in new testing strategies? How can we better communicate the probabilistic nature of chemical carcinogenic risk?
- Should we be addressing the joint action of co-carcinogens below their individual cancer thresholds, or focusing on chemicals that are not carcinogens but target the Hallmarks/Key Characteristics and could contribute to cancer development jointly?
- Can mixtures hypotheses be generalizable across cancer types? When should they be specific to tumor types/incidence based on ADME principles and knowledge of key events for that cancer type?

Identifying data needs

- Use of data to identify cancer hazard
  - Organizations that synthesize bodies of evidence to determine the carcinogenic potential of substances
    - International Agency for Research on Cancer – Kate Guyton
    - NTP Report on Carcinogens – Amy Wang and Gloria Jahnke
  - Industries that use cancer data to inform product development
    - Syngenta – Doug Wolf
- Assessment of cancer risk from real-world exposures
  - Environmental Protection Agency – Glenn Rice
  - Food and Drug Administration - Tim McGovern
  - CalEPA Office of Environmental Health Hazard Assessment – Martha Sandy and Lauren Zeise

Problem Identification

Problem Formulation

Implementation/Testing

Requirements

- Tractable
  - Can be executed in a reasonable timeframe with a reasonable investment
- Interpretable
  - Upon completion of testing, knowledge is gained, regardless of outcome
- Impactful
  - Will either support current risk assessment paradigm as protective of human health or provide data to advance cancer risk assessment practice

Next webinars

Monday, April 22

12:00-12:30 pm

Carcinogenicity Health Effects Innovation: Modernizing the NTP Approach for Assessing Carcinogenic Risk from Environmental Exposures

Warren Casey (NIEHS/NTP)

12:30-1:00 pm

The Key Characteristics of Carcinogens: Integration with the Hallmarks of Cancer and Assays and Biomarkers to Measure Them

Mark Fielden (Amgen)

Acknowledgements

Nicole Kleinstreuer

UC Berkeley Working Group

Martyn Smith (UC Berkeley)

Lauren Zeise (OEHHA)

Cliona McHale (UC Berkeley)

Tom Webster (Boston University)

Workshop Steering Committee

Nicole Kleinstreuer (NIEHS/NTP; Co-chair)

Martyn Smith (UC Berkeley)

Leroy Lowe (Getting to Know Cancer)

Lauren Zeise (OEHHA)

Weihsueh Chiu (Texas A&M)

Bill Goodson (CPMCRI)

Olga Naidenko (EWG)

Johanna Congleton (EPA)

Danielle Carlin (NIEHS)

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Canden Byrd

Laura Thomas

Lindsey Green

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Brian Berridge

Warren Casey

June Dunnick

Nigel Walker

Scott Masten

Mark Miller

Amy Wang

Kembra Howdeshell

Matt Stout

Mary Wolfe

Mike DeVito

NTP study design team

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Problem Formulation

- Sauve-Ciencewicki et al. 2019. Regulatory Toxicology and Pharmacology 101, 187-193

Mixtures

- Rider et al. 2008. International Journal of Andrology 31, 249–262

Thank you!
Questions?