Using the Key Characteristics Framework to Identify Potential Breast Carcinogens

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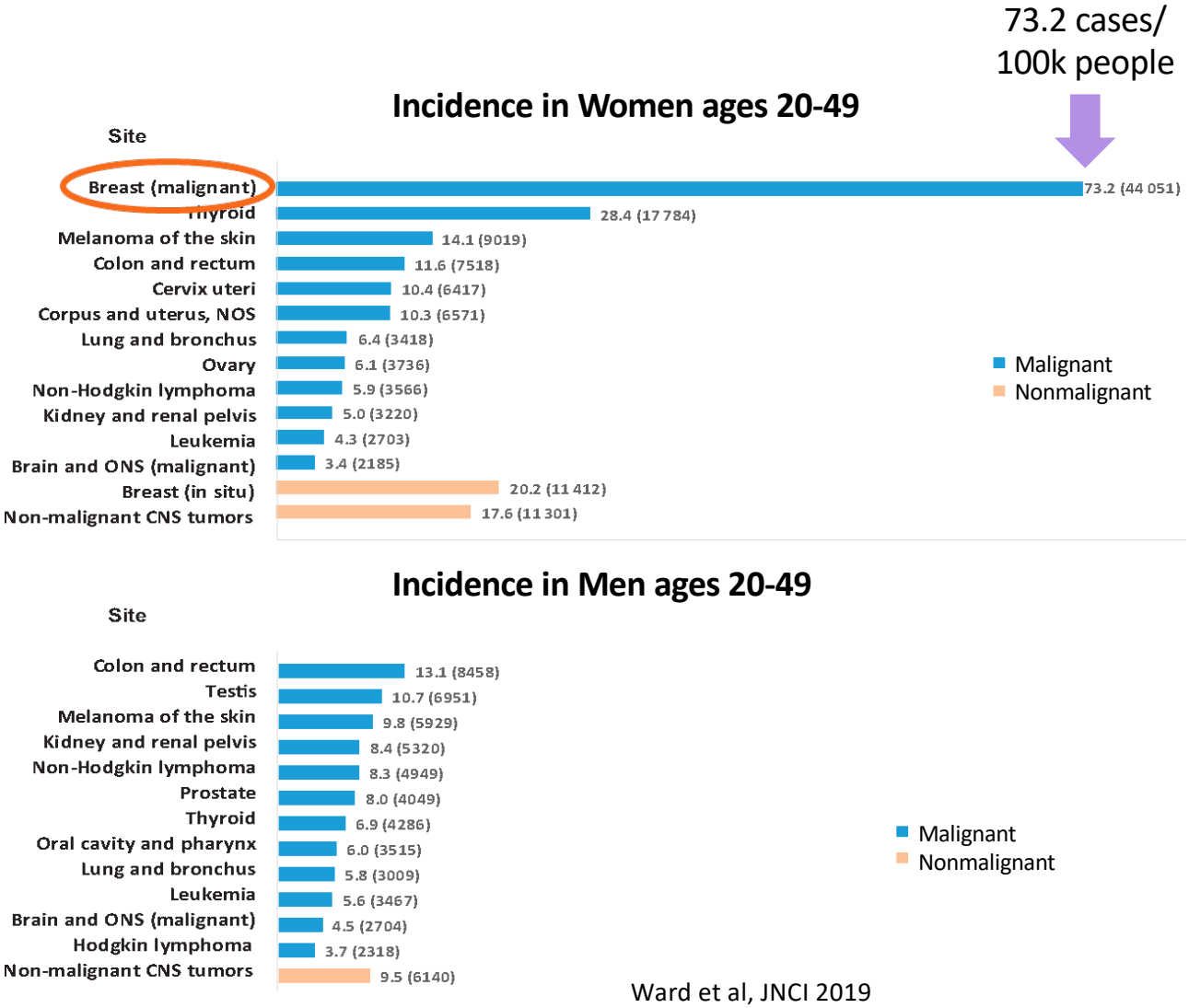
Breast Cancer:
a public health crisis

- #1 invasive cancer diagnosis in the US and worldwide
- 6x more prevalent than any cancer among men under age 50 in the US
- Rising in rate of diagnosis, esp. in younger women



Ward et al, JNCI 2019

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Objective

Demonstrate application of the **Key Characteristics framework to identify chemical risk factors** for human chronic diseases using breast cancer as an example

Key Characteristics (KCs) of Carcinogens

Describes features of exposures that cause cancer

Framework for evaluating potential carcinogens based on **mechanistic** effects (which can be measured quickly) rather than cancer (which takes a long time)

For breast cancer, focus on estrogen and progesterone

Key characteristic:	
1. Is electrophilic or can be metabolically activated	
2. Is genotoxic	AKA, damages DNA
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	

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

Outline

- How we identified breast cancer-relevant chemicals with Key Characteristics
  - Integrate *in vivo* cancer studies (in animals) and *in vitro* molecular effects (in cells) to identify chemical exposures that may increase breast cancer risk
- How we validated our approach
  - Demonstrate that endocrine and genotoxicity data can predict chemicals likely to increase breast cancer risk
- Chemical testing and regulatory decisions: what you need to know
  - The Endocrine Disruptor Screening Program and pesticides

Breast Cancer Etiology

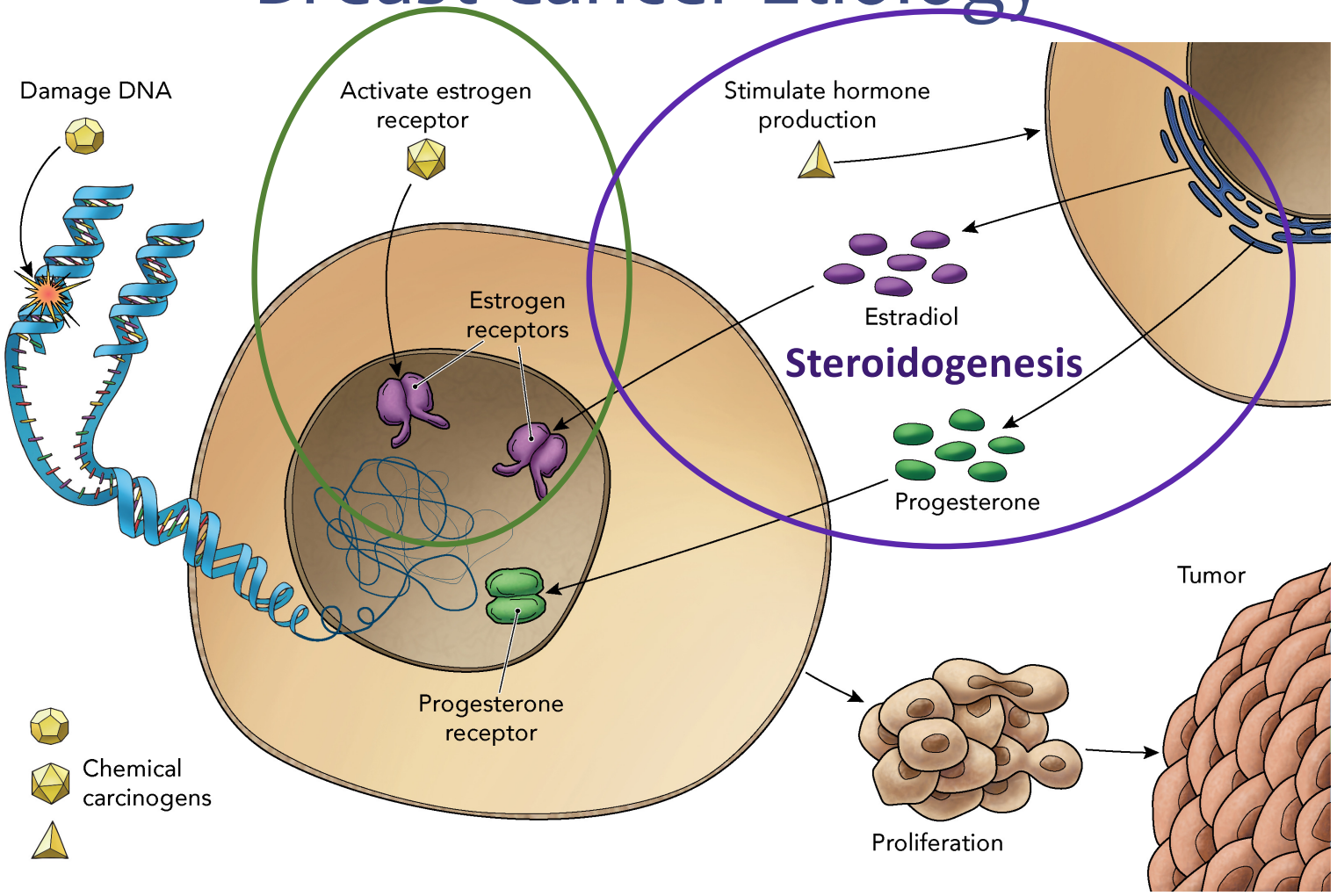
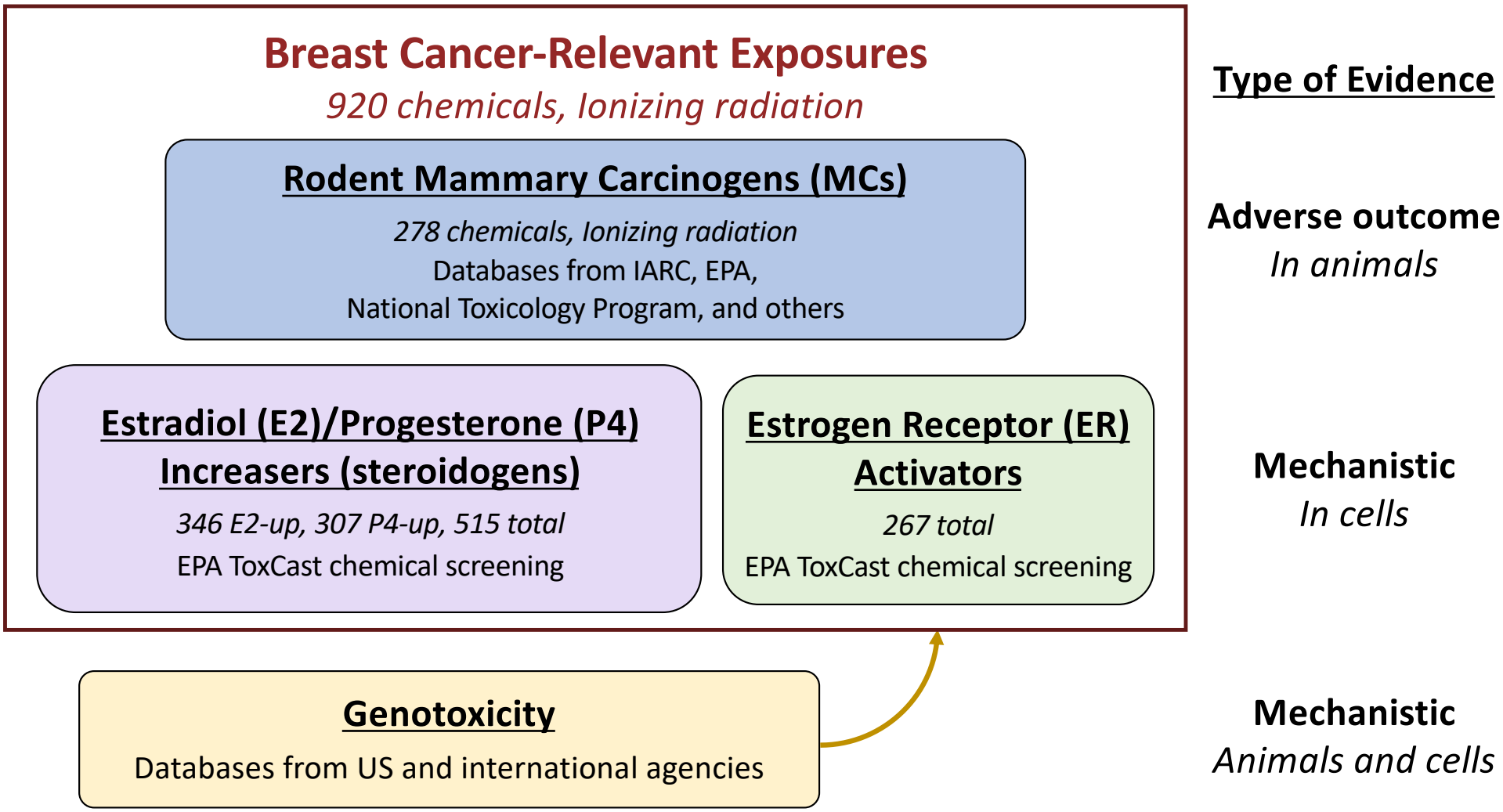
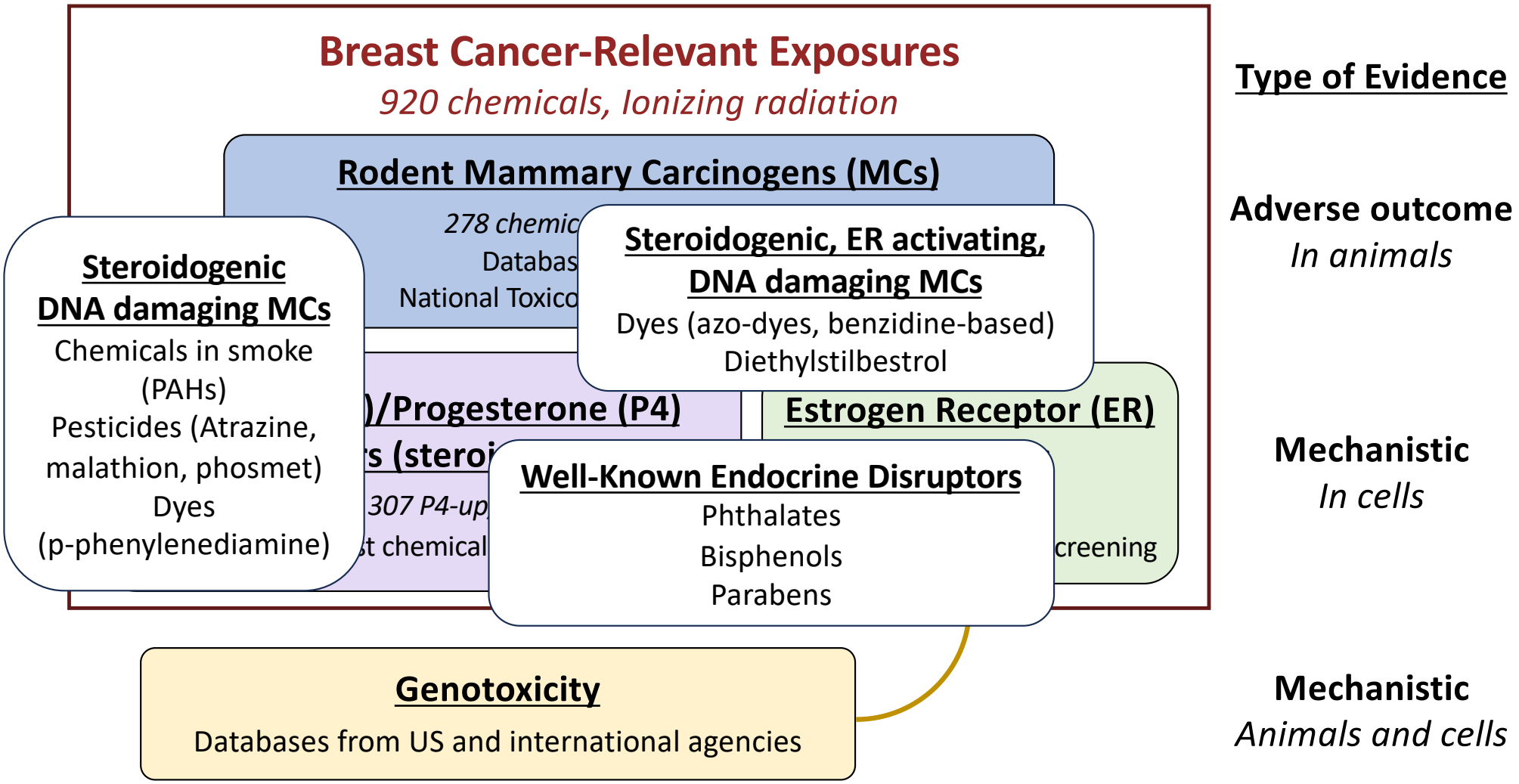


Image credit Jeff Dixon for Silent Spring



Kay et al., EHP 2024, DOI 10.1289/EHP13233



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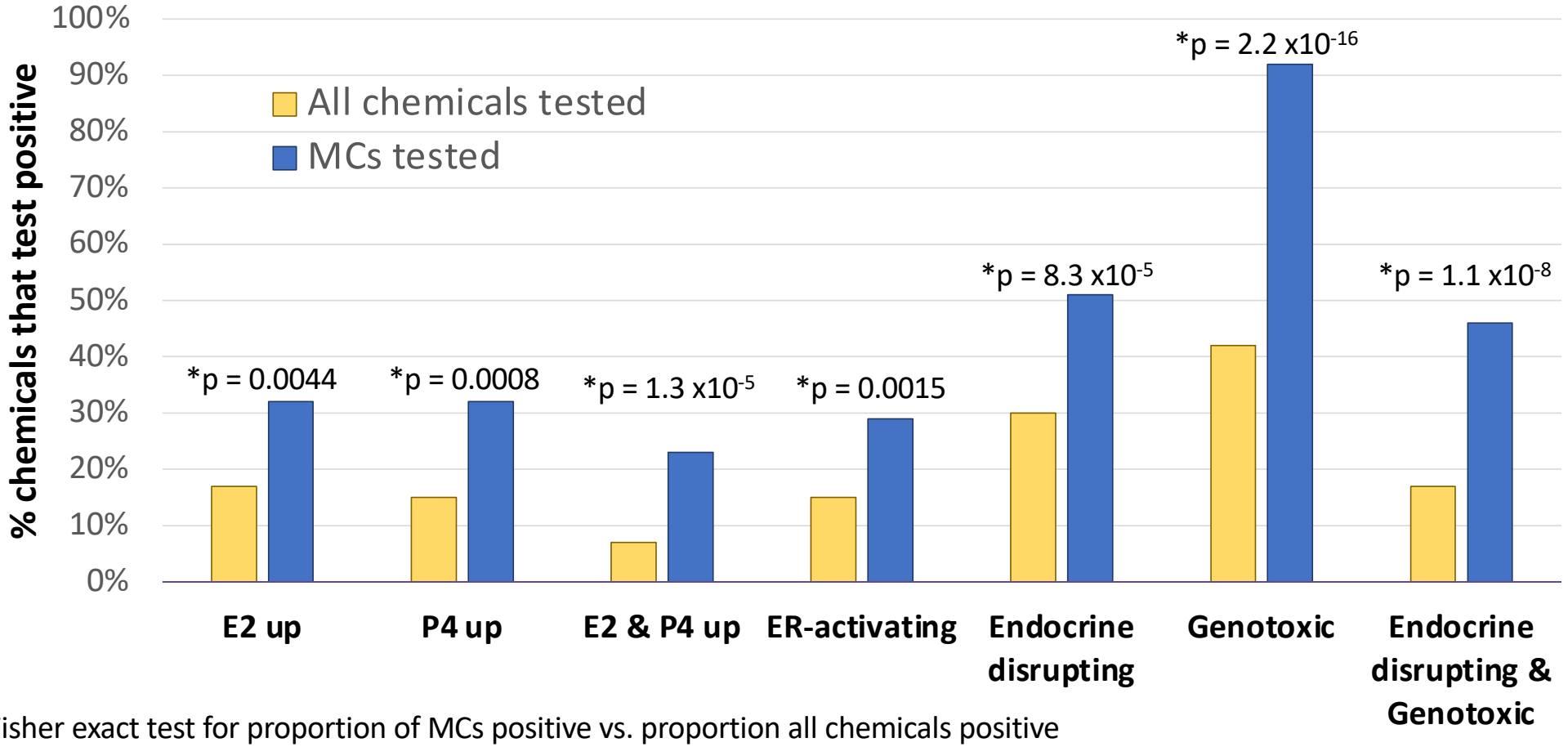
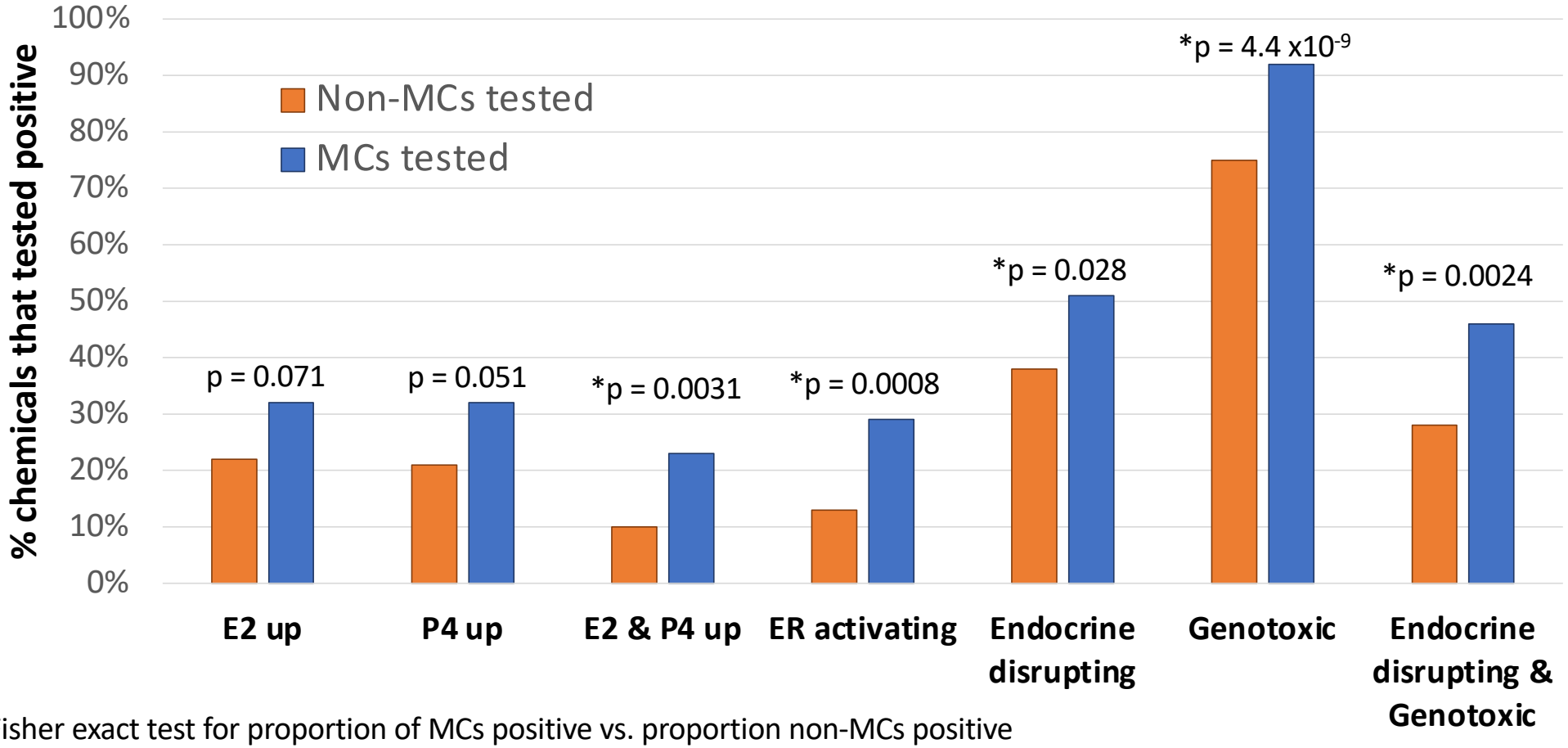
MCs are enriched for BC-relevant KCs



*Fisher exact test for proportion of MCs positive vs. proportion all chemicals positive

Kay et al., EHP 2024, DOI 10.1289/EHP13233

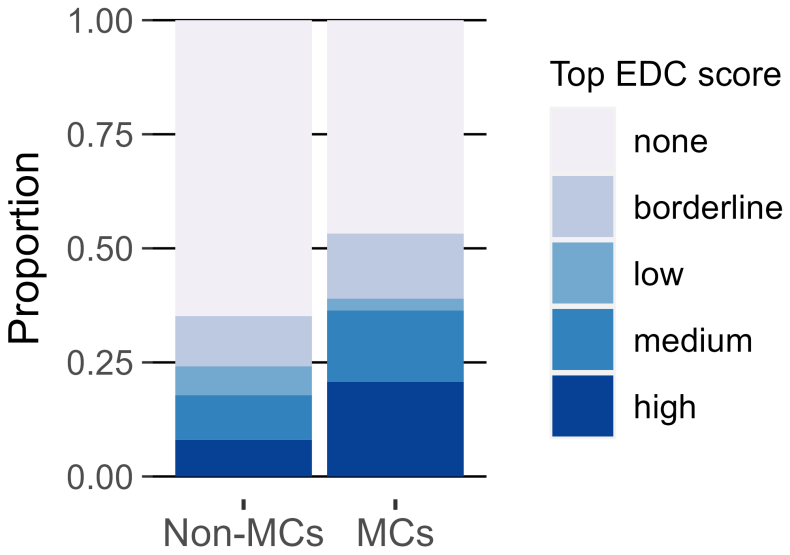
MCs are enriched for BC-relevant KCs vs. Non-MCs



*Fisher exact test for proportion of MCs positive vs. proportion non-MCs positive

Kay et al., EHP 2024, DOI 10.1289/EHP13233

MCs are more likely to be stronger EDCs



Top EDC score	# Non-MCs	% Non-MCs	# MCs	% MCs	Fold-diff	p-value
High	38	**8%**	16	**21%**	2.6	***0.0015**[a]
Medium	46	**10%**	12	**16%**	1.6	0.16[a]
Low	30	**6%**	2	**3%**	0.4	0.29[a]
Borderline	52	**11%**	11	**14%**	1.3	0.44[a]
None	306	**65%**	36	**47%**	0.7	***0.0033**[a]
Total	472		77			
Trend[b]						***2.1 E-4**[b]

[a]Fisher exact test for proportion of MCs positive vs. proportion non-MCs positive

[b]Two-sided Cochran-Armitage trend test for strength of endocrine activity in MCs vs. non-MCs

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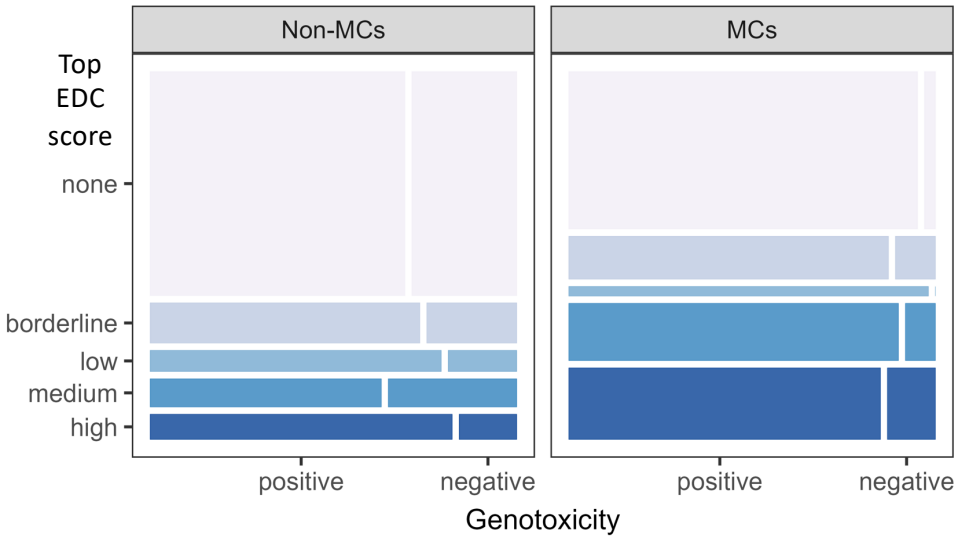
MCs are more likely to be stronger EDCs *and* genotoxic



Top EDC score	Gentox	# Non-MCs	% Non-MCs	# MCs	% MCs	Fold-diff	p-value
High	+	21	**6%**	13	**18%**	2.9	***0.0032**[a]
Medium	+	18	**5%**	11	**15%**	2.9	***0.0084**[a]
Low	+	17	**5%**	2	**3%**	0.6	0.55[a]
Borderline	+	30	**9%**	8	**11%**	1.3	0.51[a]
None	+	158	**47%**	32	**45%**	1	0.79[a]
Trend[b]	+						***0.0012**[b]
Total		336		71			

[a]Fisher exact test for proportion of MCs positive vs. proportion non-MCs positive

[b]Cochran-Armitage trend test for strength of endocrine activity in MCs vs. non-MCs

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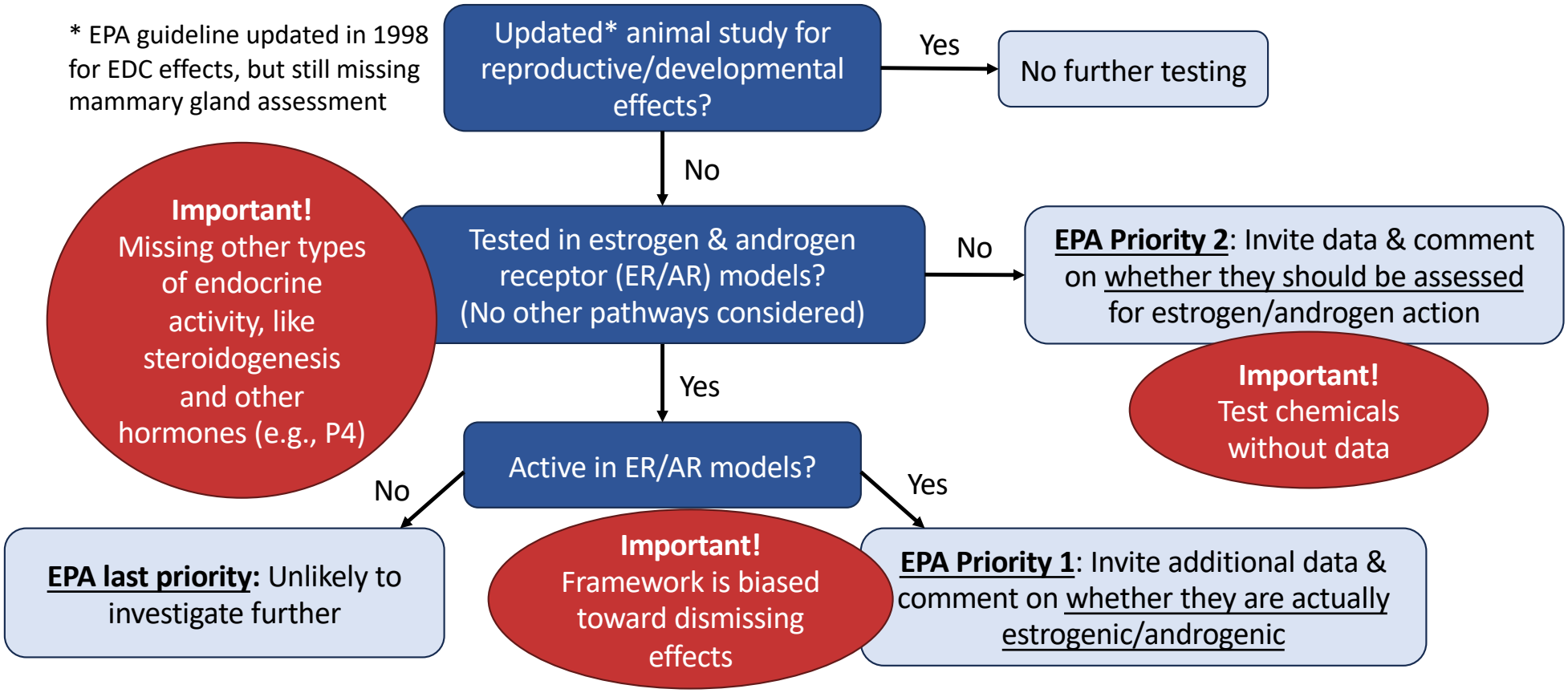
Conclusions

- We identified hundreds of chemicals that could increase breast cancer risk by combining traditional cancer studies with mechanistic data
- Rodent MCs are more likely to increase E2/P4 synthesis, activate the ER, and cause DNA damage vs. non-MCs
- Endocrine activity can flag likely MCs, but *lack of activity does not indicate the chemical is not an MC*
  - E2/P4 steroidogenesis and ER activation are important BC-relevant activities, but there are many others (and most lack methods to screen chemicals for them)
- Our study highlights ways regulatory chemical assessment can be strengthened to better protect human health

Endocrine Disruptor Screening Program: EPA's new proposal to prioritize pesticides

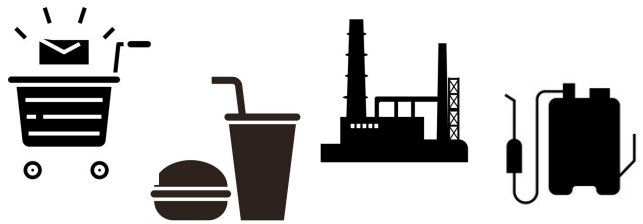


Coming soon!

We've identified many potential BC hazards – now what?

Further prioritize chemicals for reduction and research!

- Exposure sources
- Biomonitoring and predicted intake levels
- Environmental releases
- Current regulations



Thank you!

Application of the Key Characteristics Framework to Identify Potential Breast Carcinogens Using Publicly Available *in Vivo*, *in Vitro*, and *in Silico* Data
Jennifer E. Kay, Julia Green Brody, Megan Schwarzman, Ruthann A. Rudel

https://ehp.niehs.nih.gov/doi/10.1289/EHP13233

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