Identifying Potential Breast Carcinogens and Characterizing Sources in Consumer Products

Jennifer Kay, PhD

Silent Spring Institute

Northern California Genetic and Environmental Toxicology Association Symposium

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Researching the Environment and Women's Health

Silent Spring Institute

- Massachusetts Breast Cancer Coalition founded Silent Spring Institute in 1994
- Our goal: prevent cancers by reducing people's exposure to harmful chemicals where they live, work, and play

"A lab of our own"

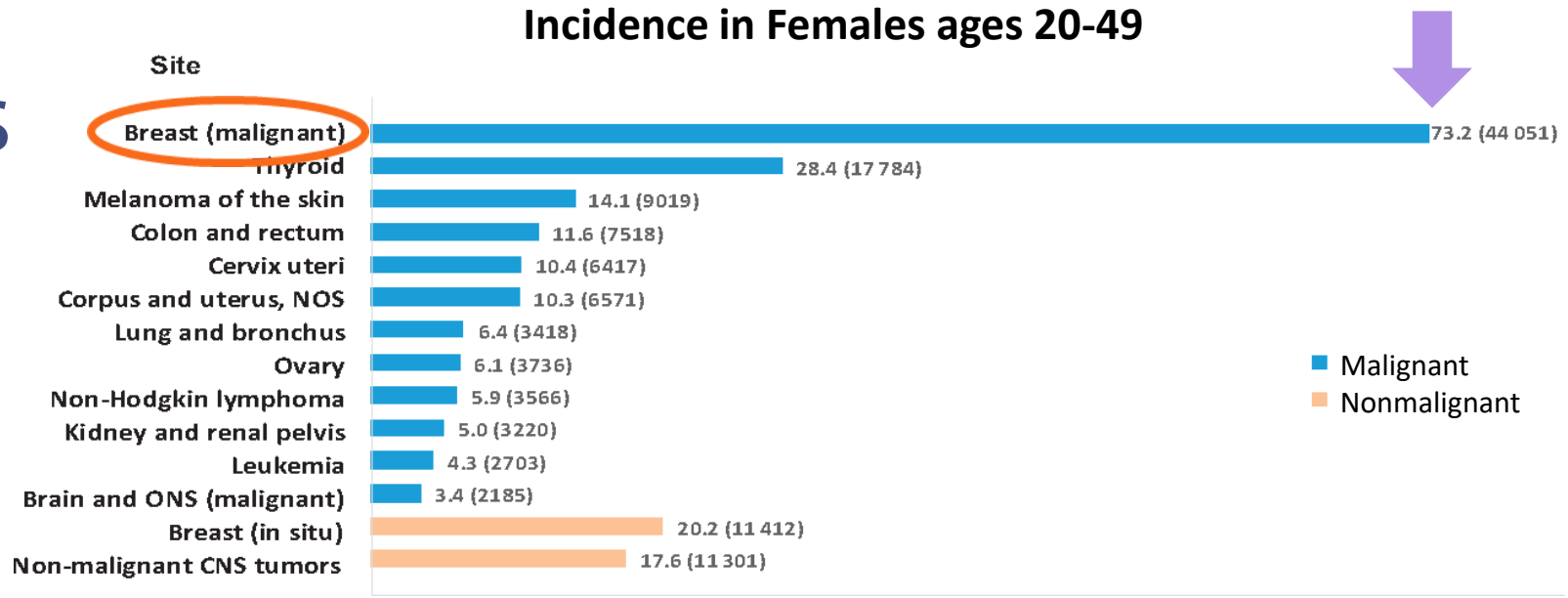
Who we are

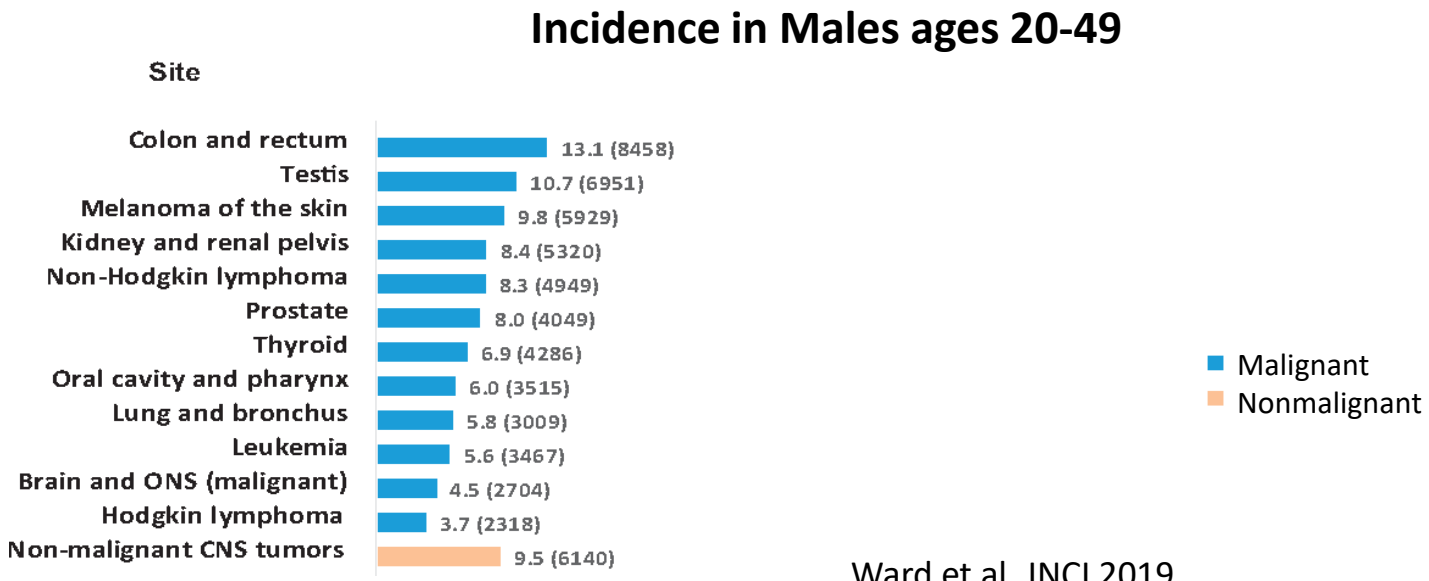
Silent Spring Institute is a mission-driven scientific research organization dedicated to uncovering the environmental causes of breast cancer.

Breast Cancer: a public health crisis

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

73.2 cases/ 100k people





Ward et al, JNCI 2019

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Outline

- Breast cancer-relevant chemicals (BCRCs) identified using the Key Characteristics of breast carcinogens

- Characterizing BCRC exposure sources and levels to prioritize research and action

ehp Environmental Health Perspectives

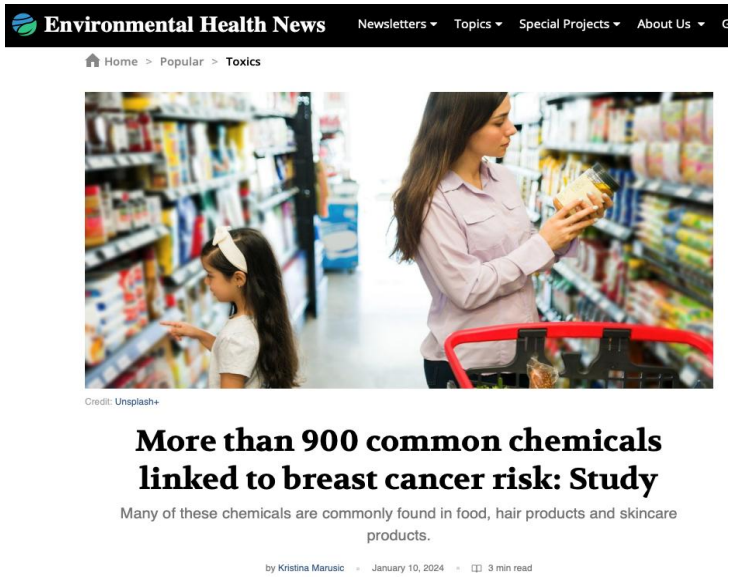
| Research Article | 10 January 2024

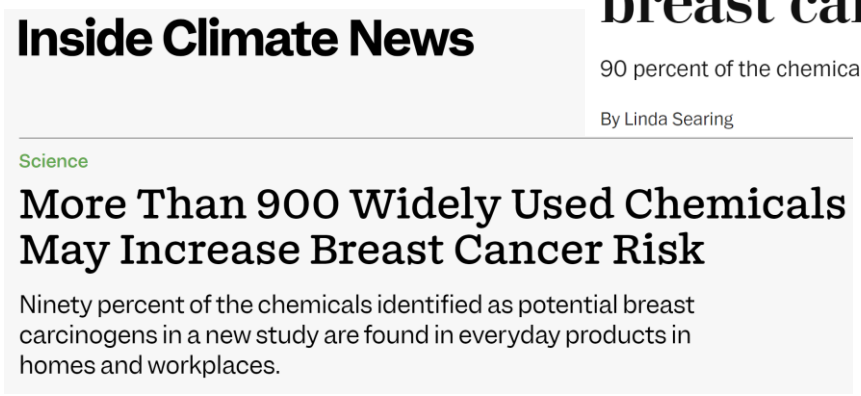
Application of the Key Characteristics Framework to Identify Potential Breast Carcinogens Using Publicly Available *in Vivo*, *in Vitro*, and *in Silico* Data

This article accompanies **INVITED PERSPECTIVE: NEW MOTIVATIONS AND FUTURE DIRECTIONS FOR INVESTIGATING ENVIRONMENTAL RISK FACTORS FOR BREAST CANCER.**

Authors: Jennifer E. Kay, Julia Green Brody, Megan Schwarzman,, and Ruthann A. Rudel | AUTHORS INFO & AFFILIATIONS

Publication: Environmental Health Perspectives • Volume 132, Issue 1 • CID: 017002 • https://doi.org/10.1289/EHP13233





Key Characteristics (KCs) of Carcinogens

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*

Breast Cancer Etiology

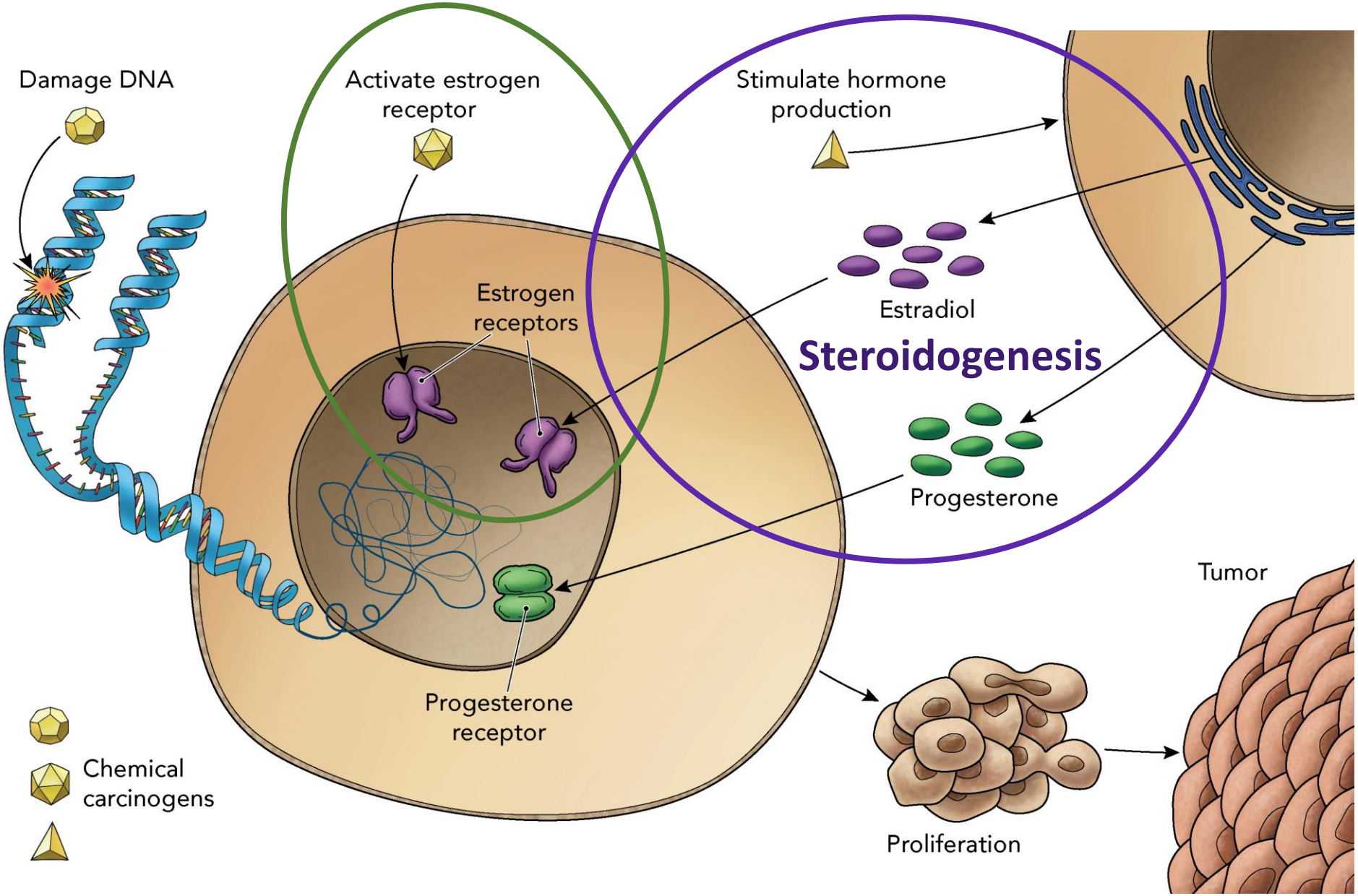
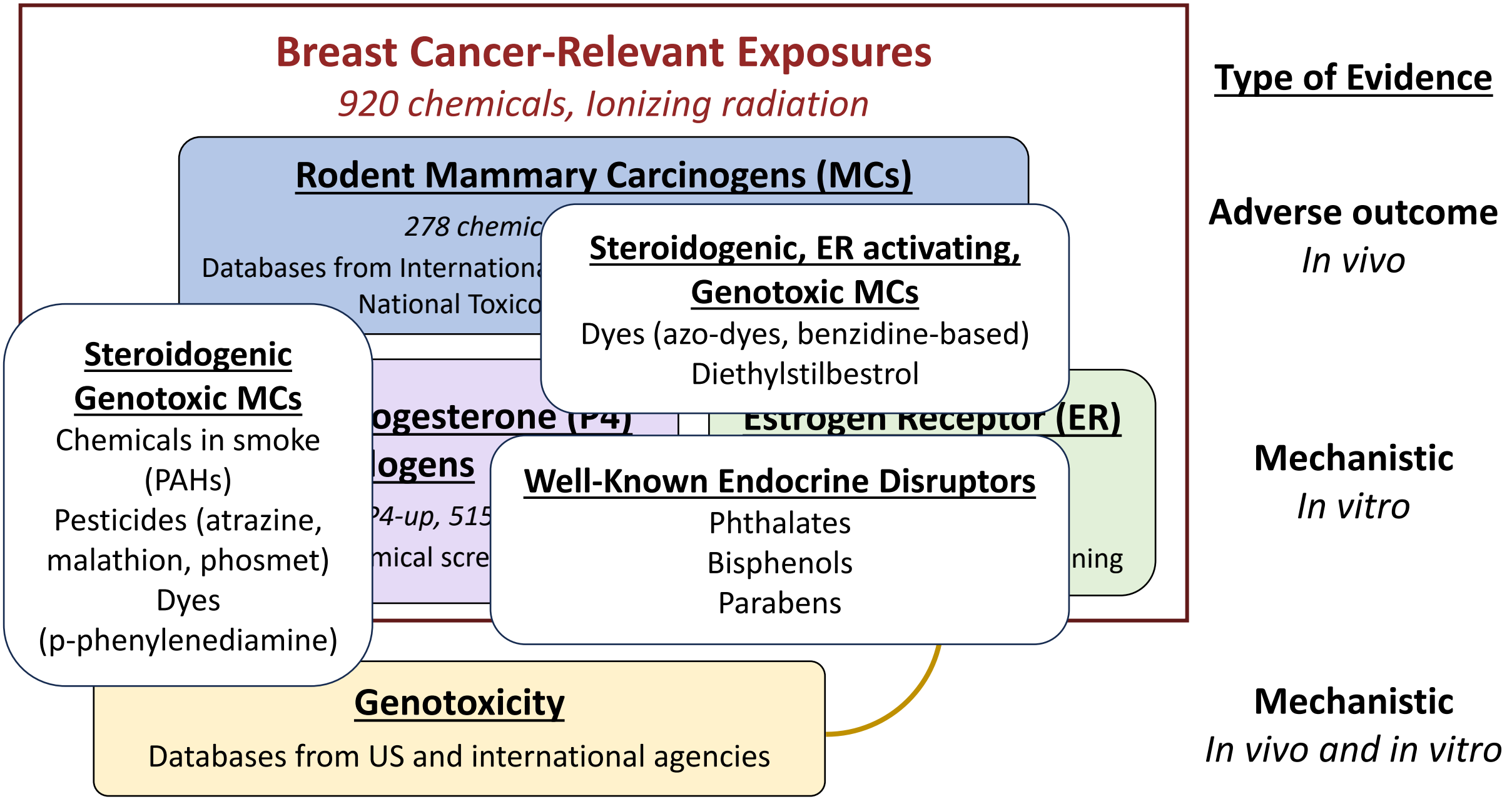


Image credit Jeff Dixon for Silent Spring



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

A comparison group:

Putative Non-Mammary Carcinogens

NTP and EPA cancer bioassay databases

- 850 chemicals tested in a 2-year cancer bioassay with no mammary tumor induction reported
- Why “putative”?
  - Some may have had mammary tumors inappropriately dismissed, as we found for 28 MCs we flagged previously
  - Some may have only been tested in mice, which rarely develop mammary tumors
  - The 2-year bioassay design has weaknesses for detecting mammary carcinogens, especially for endocrine disruptors…

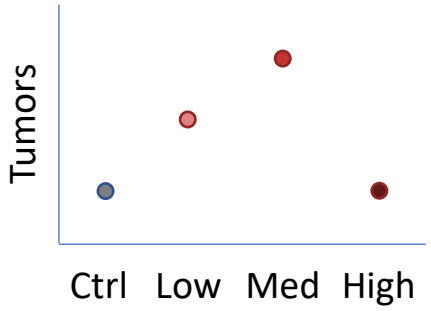
What bioassays miss

What we **need** to look at

Exposure *in utero* and in adults

Large (longitudinal) cross section from every animal

All dose groups



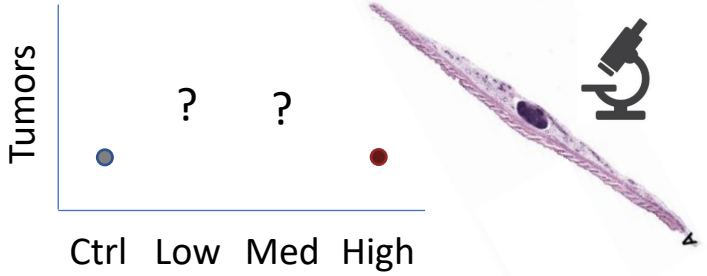
What we **do** look at

EPA

Exposure in adults

Macroscopic (visible) tumors from all groups

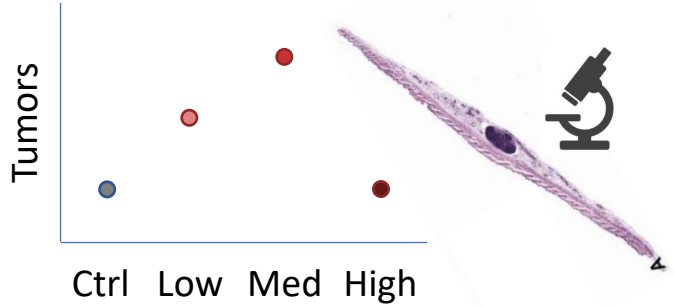
Tiny (transverse) cross section in ctrl and high dose, sometimes others



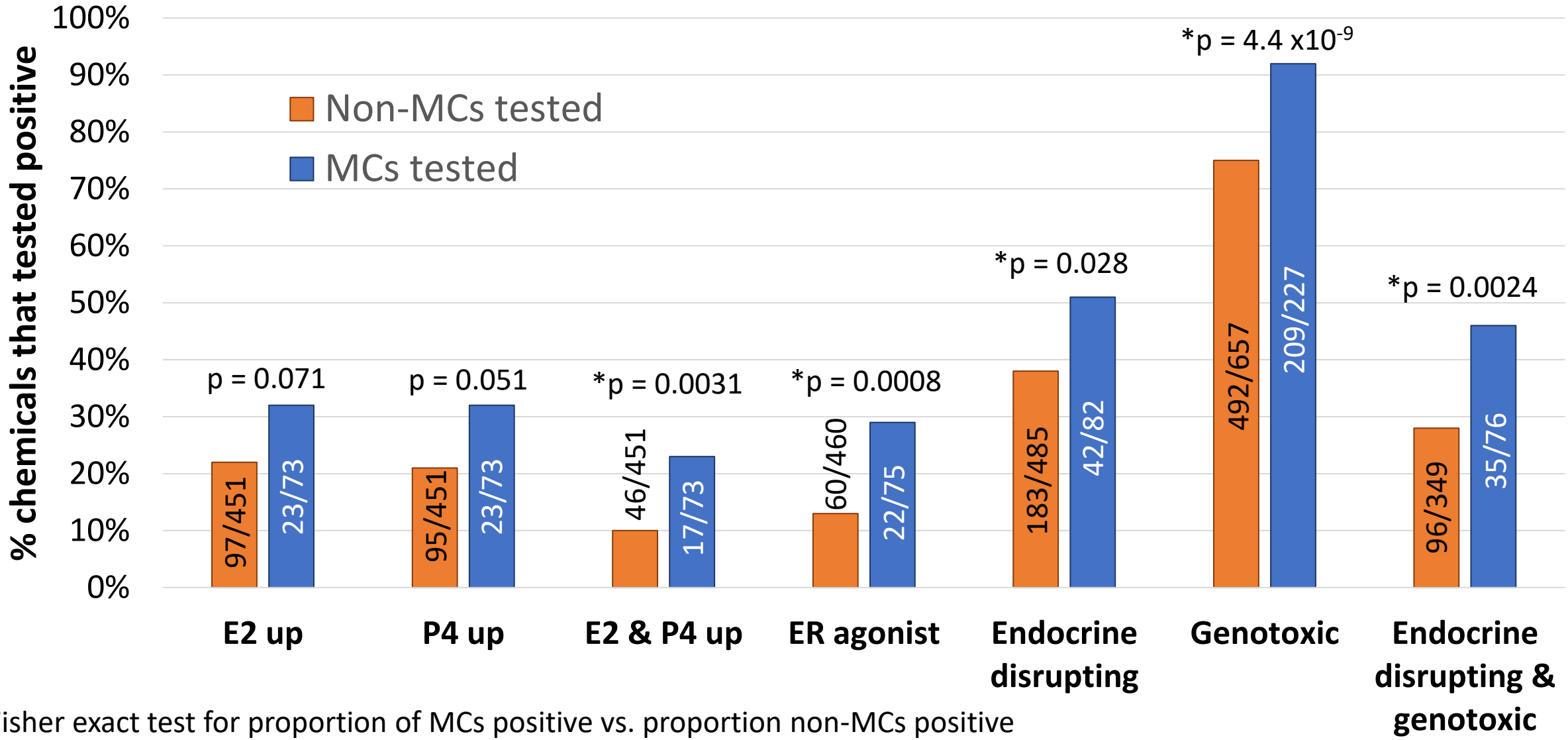
NTP

Exposure in adults, sometimes *in utero*

Tiny (transverse) cross section from all dose groups



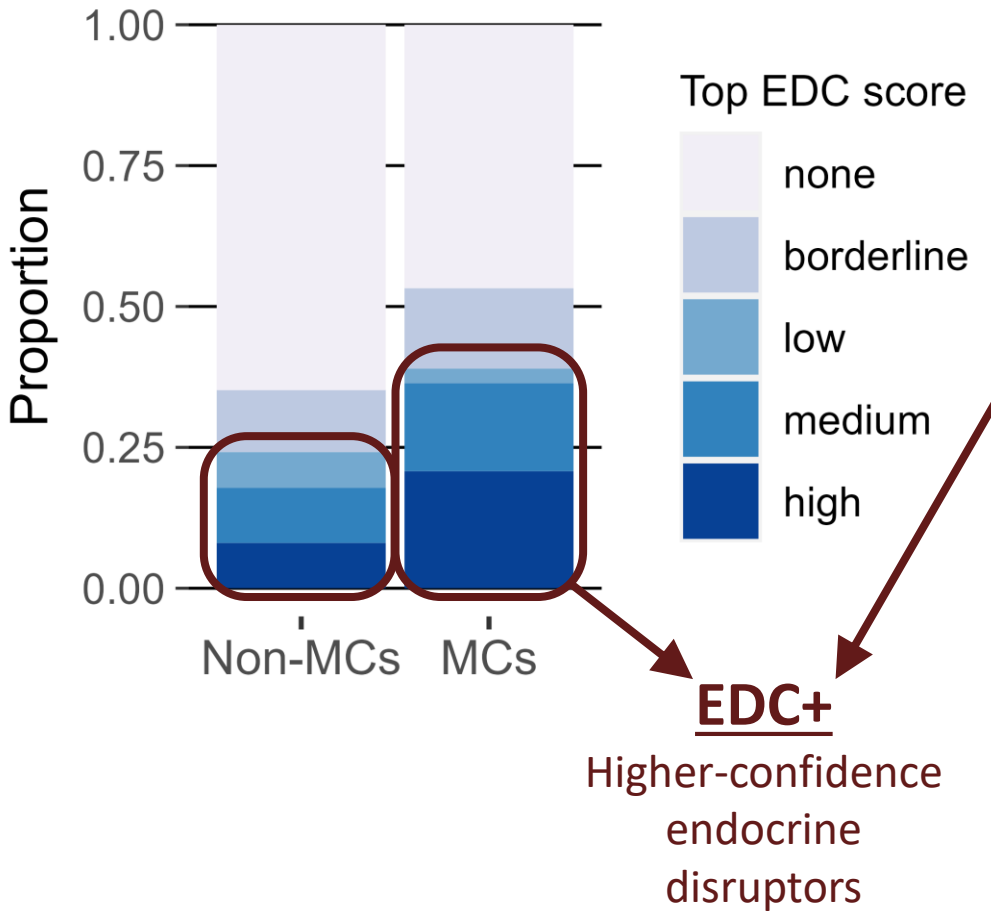
MCs are enriched for BC-relevant KCs vs. Non-MCs



*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



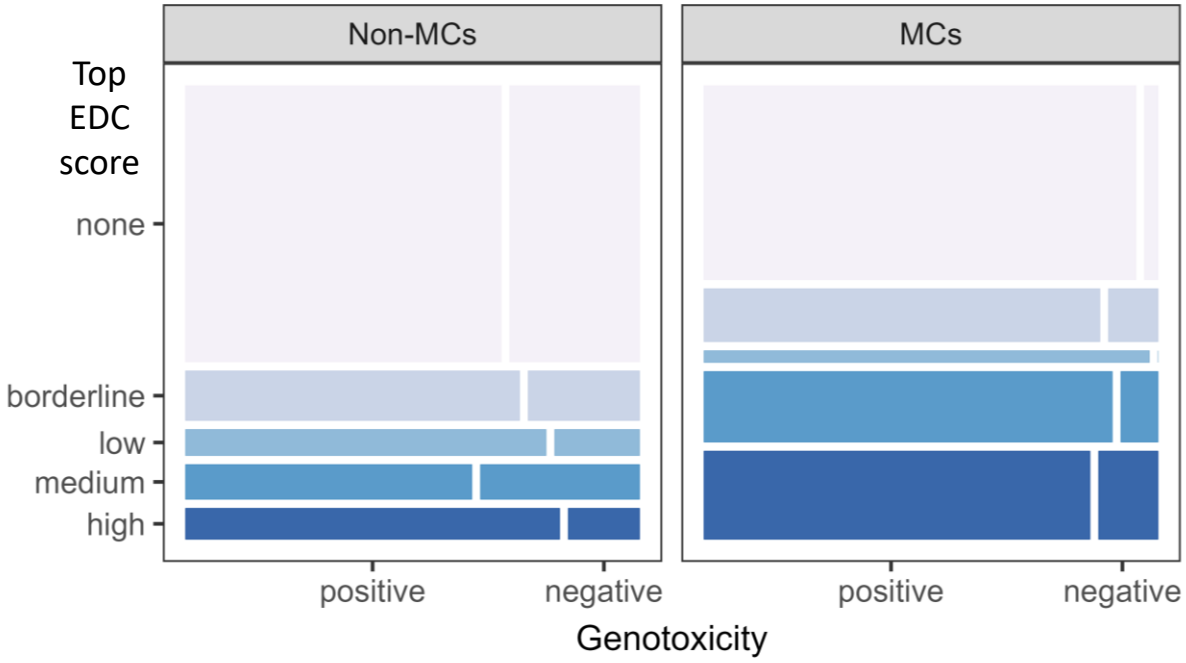
Top EDC score	# Non-MCs	% Non-MCs	# MCs	% MCs	Fold-diff	p-value
High	38	**8%**	16	**21%**	2.6	***0.0015**[a]
Medium	46	**10%**	12	**16%**	1.6	0.16[a]
Low	30	**6%**	2	**3%**	0.4	0.29[a]
Borderline	52	**11%**	11	**14%**	1.3	0.44[a]
None	306	**65%**	36	**47%**	0.7	***0.0033**[a]
Total	472		77			
Trend[b]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

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

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]
High	-	3	**1%**	2	**3%**	3.2	0.21[a]
Medium	-	10	**3%**	1	**1%**	0.5	0.7[a]
Low	-	4	**1%**	0	**0%**	0	1[a]
Borderline	-	10	**3%**	1	**1%**	0.5	0.7[a]
None	-	65	**19%**	1	**1%**	0.07	***2.6 E-5**[a]
Trend[b]	-						***0.0024**[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

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

Conclusions, part 1

- We identified hundreds of potential breast carcinogens by combining traditional cancer studies with *in vitro* screening data
- Rodent MCs are more likely to increase E2/P4 synthesis, activate the ER, and cause DNA damage vs. non-MCs
  - Stronger *in vitro* activity → higher likelihood of cancer risk
- 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)
- Work ongoing to identify the most important exposures and target for reduction

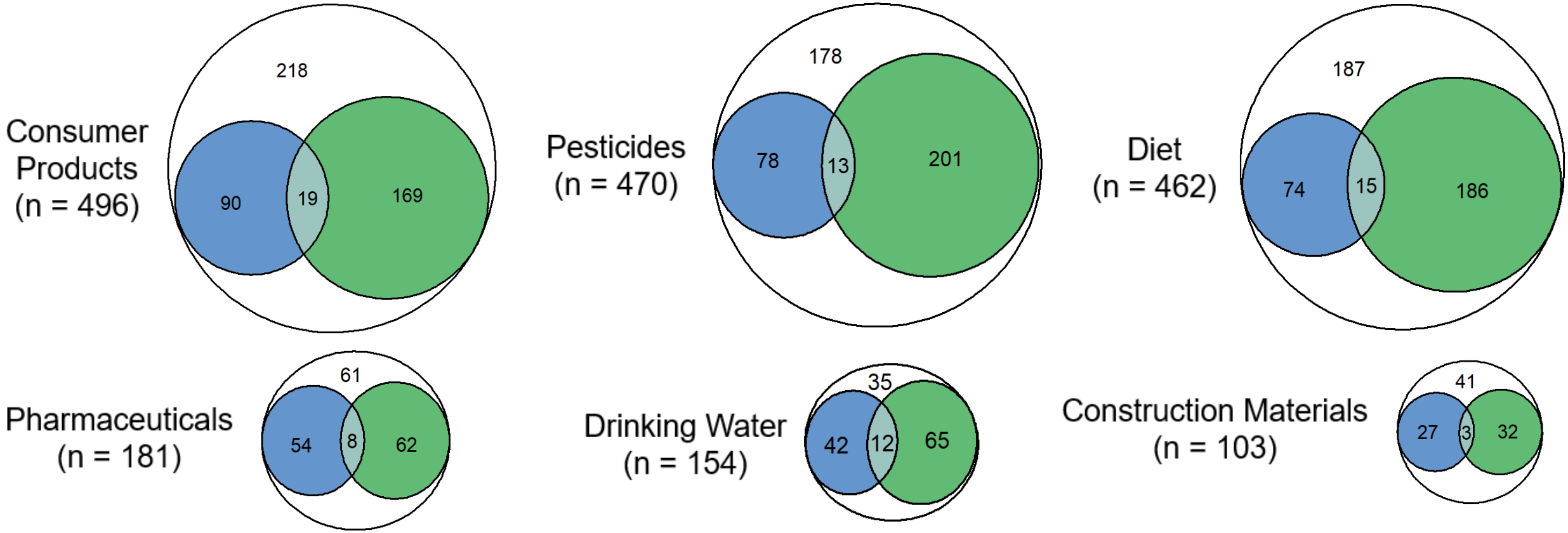
Coming soon!

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

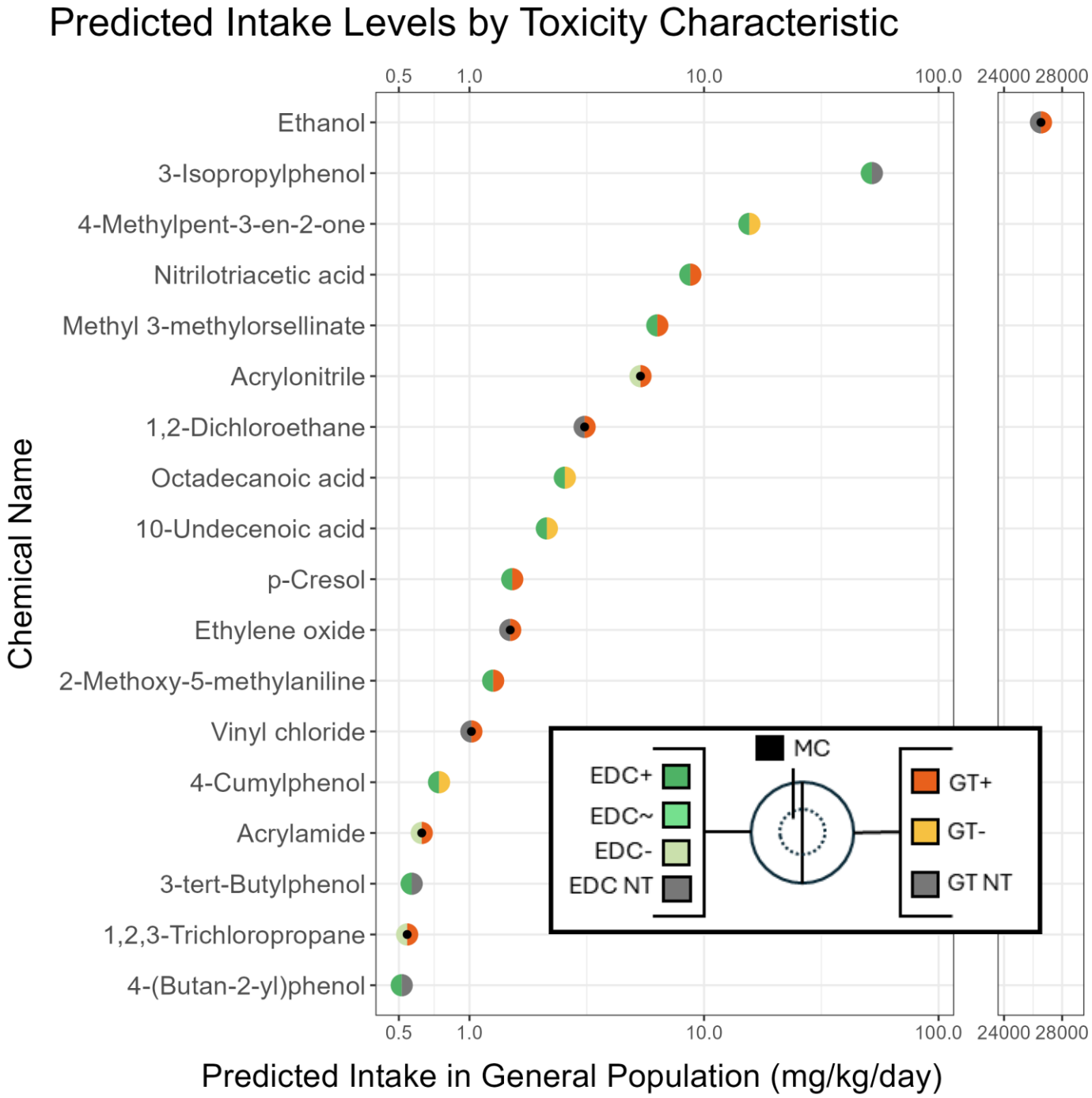
Further prioritize them for reduction and research!

- Exposure sources
- Biomonitoring and predicted intake levels
- Annual production and environmental releases
- Current regulations

Exposure sources of BCRCs



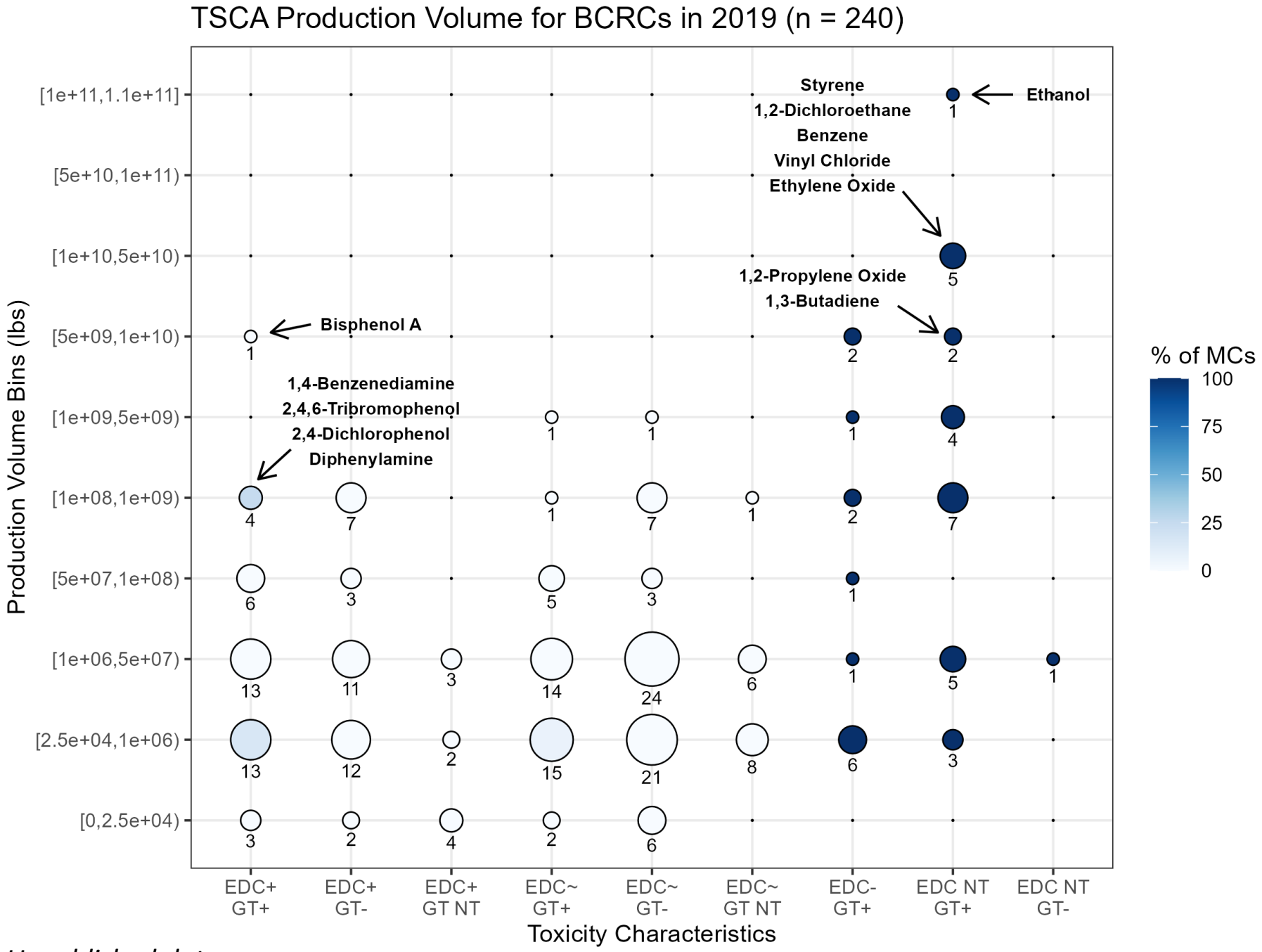
Unpublished data



Predicted daily intakes

- Predicted daily intake levels according to EPA modeling (high end of prediction)
- BCRCs in consumer products that are MC/EDC+, with intake > 0.5 mg/kg/day

Unpublished data



Production Volume

- Reported under Toxic Substances Control Act
- Lbs of chemicals produced or imported in 2019 (most recent available)

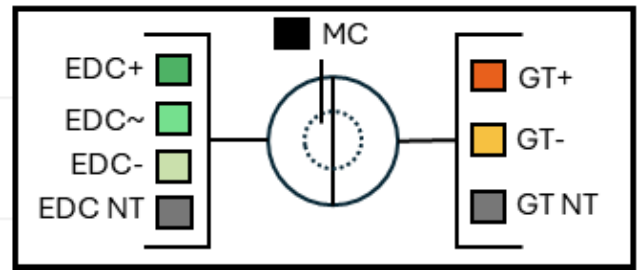
Unpublished data

Chemical Name	Toxicity Characteristics	Exposure Sources	Predicted Intake (mg/kg/d)	Production Volume (millions of lbs/y)
1,1-Dichloroethane			0.1823	100– <1000
1,2,3-Trichloropropane			0.5424	1– <20
1,2-Dichloroethane			3.097	30000– <40000
1,2-Dichloropropane			0.4597	100– <1000
1,2-Propylene oxide			0.1063	1000– <5000
1,3-Dichloropropene			0.4908	20– <100
11-Aminoundecanoic acid			0.9536	1– <20
2,4,6-Tribromophenol			1.112	20– <100
2,4-Dichlorophenol			0.8411	20– <100
2,4-Dimethylphenol			0.1526	10– <50

Integrating BCRC exposure data

Prioritize by

- Biological effect
- Uses
- Intake levels
- Production volumes
- (and more)



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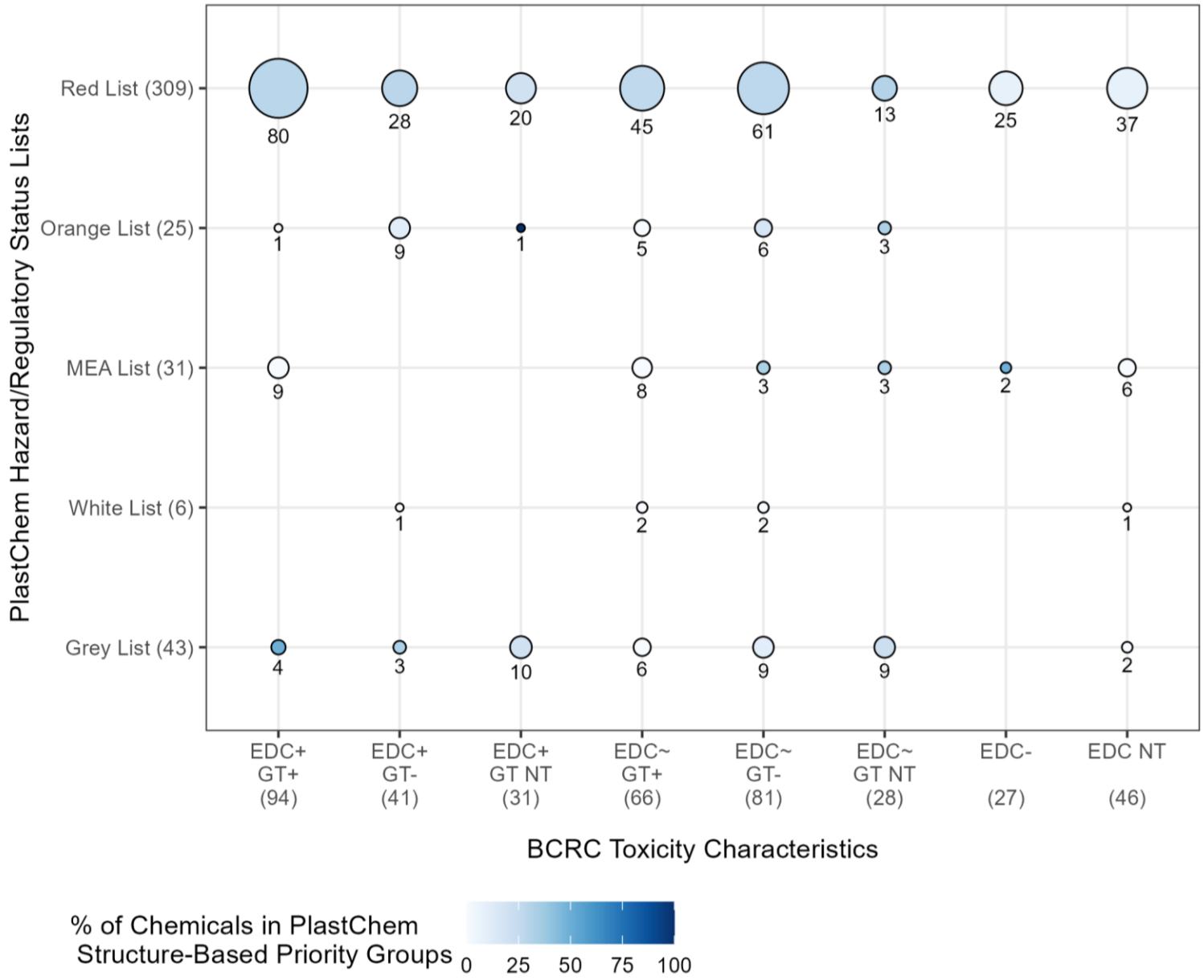


PlastChem Hazard/Regulatory Status Lists
Red List contains chemicals classified as hazardous and not regulated by multilateral environmental agreements (MEAs); Orange List = classified as less hazardous and/or proposed for regulation, MEA List = regulated under MEAs, White List = classified as not hazardous, Grey List = no hazard data

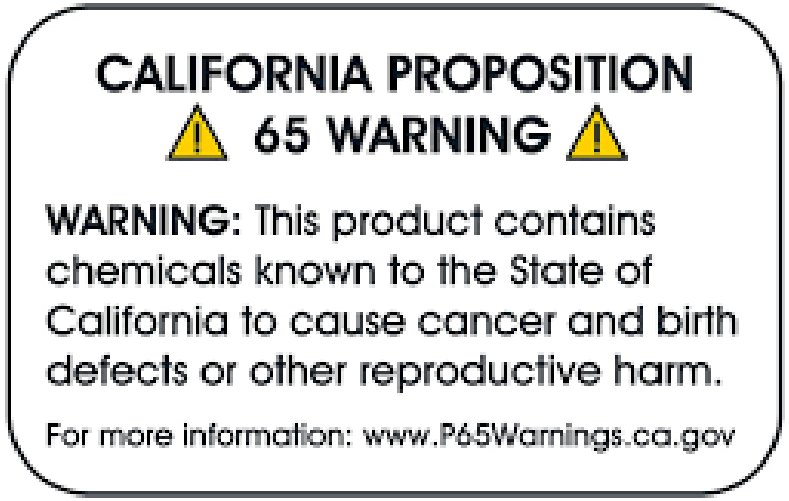
Potential Breast Carcinogens in Plastics

- Crossed our list with PlastChem Database
- Found 414 BCRCs in plastics
  - 98 MCs
  - 94 genotoxic EDC+
  - 88 in prioritized hazardous structural groups

Shakti et al., ES&T Letters 2024, DOI: 10.1021/acs.estlett.4c00942

Proposition 65

- California's Safe Drinking Water and Toxics Enforcement Act (aka, Prop 65)
  - List of carcinogens and reproductive/developmental toxicants identified from authoritative lists & scientific committee review
  - Prohibits discharge of listed chemicals
  - Requires notice of potentially harmful chemicals in products
- Implications
  - Consumer right-to-know
  - Basis for chemical restrictions (in- and out-of-state)
  - Promote use of safer alternatives



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Article

Identifying Toxic Consumer Products: A Novel Data Set Reveals Air Emissions of Potent Carcinogens, Reproductive Toxicants, and Developmental Toxicants

Kristin E. Knox,* Robin E. Dodson, Ruthann A. Rudel, Claudia Polsky, and Megan R. Schwarzman

Cite This: https://doi.org/10.1021/acs.est.2c07247

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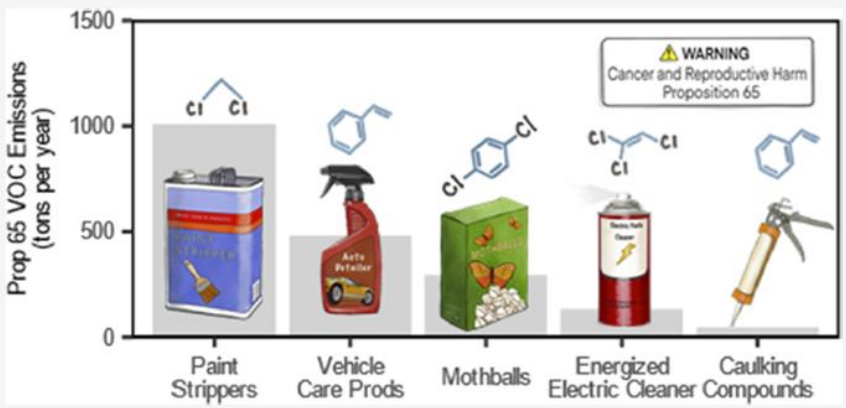
ABSTRACT: Consumer products are important sources of exposure to harmful chemicals. Product composition is often a mystery to users, however, due to gaps in the laws governing ingredient disclosure. A unique data set that the California Air Resources Board (CARB) uses to determine how volatile organic chemicals (VOCs) from consumer products affect smog formation holds a partial solution. By analyzing CARB data on VOCs in consumer products, we identified and quantified emissions of volatile chemicals regulated under the California Safe Drinking Water and Toxic Enforcement Act ("Prop 65"). We here highlight individual chemicals as well as consumer product categories that people are likely to be exposed to as individual consumers, in the



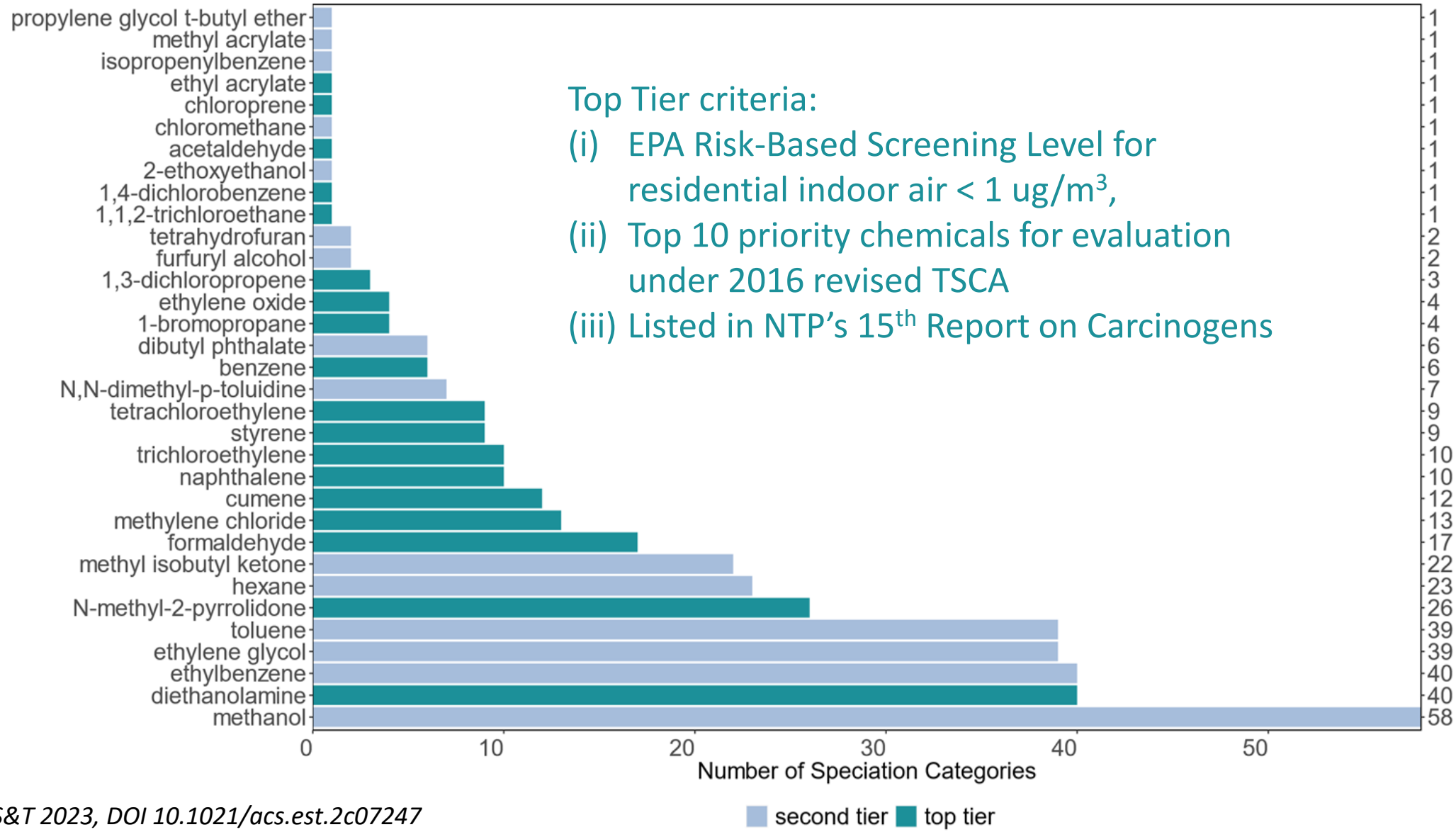
California Air Resources Board (CARB) chemical emissions from products

- CARB goal: mitigate smog-forming pollutants
- Based on surveys of CA manufacturers:
  - Collects volatile organic compound (VOC) **ingredients** in consumer and commercial products
  - Groups products into general **product categories**
  - Generates **emissions estimates** using fate and transport assumptions

Using CARB data to understand hazardous emissions from products

- Cross CARB emissions data with Prop 65 list of cancer and reproductive/developmental hazards
- Highlight chemical **ingredients** and **product categories**
- Identify and quantify **emissions**

33 Prop 65 VOCs in 105 Product Categories



Top Tier criteria:

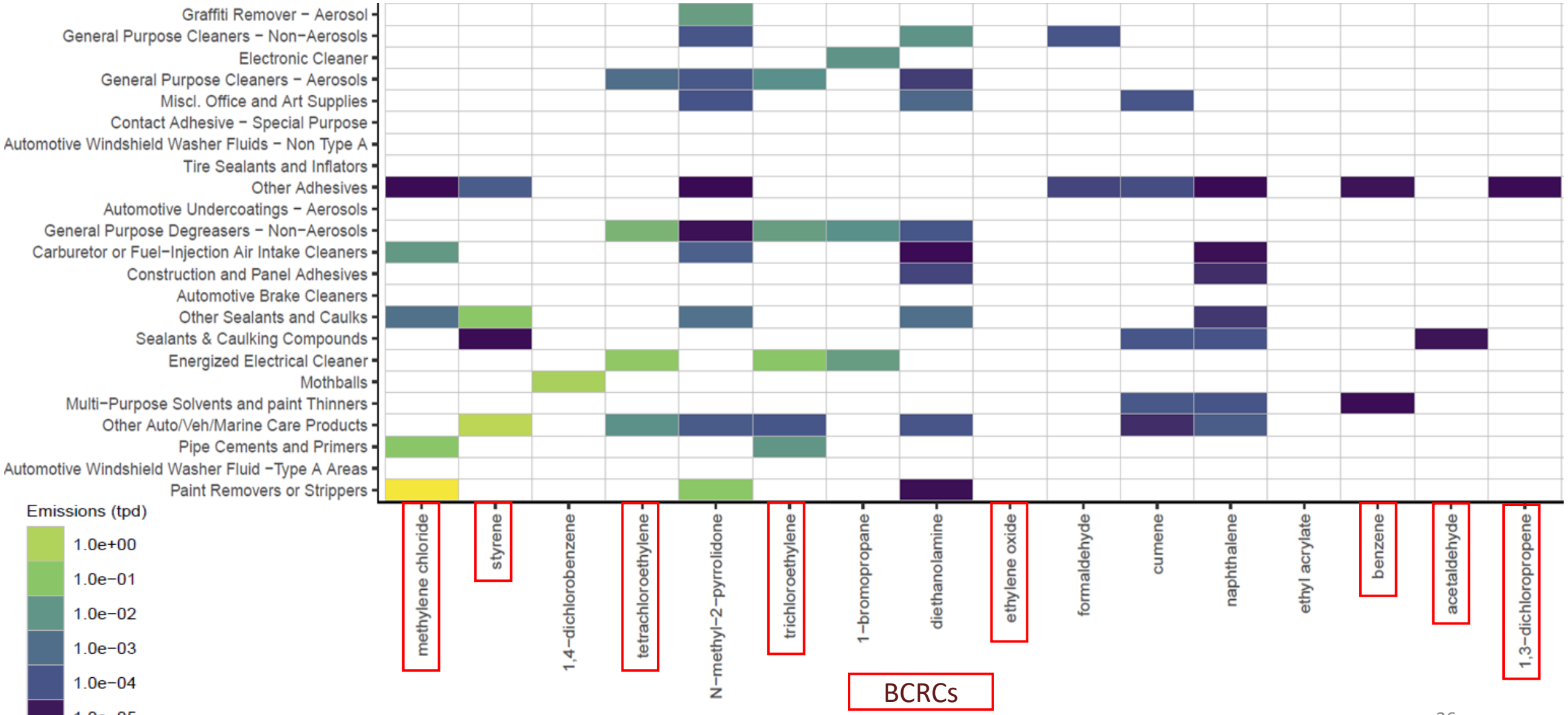
(i) EPA Risk-Based Screening Level for residential indoor air < 1 ug/m^3,

(ii) Top 10 priority chemicals for evaluation under 2016 revised TSCA

(iii) Listed in NTP's 15th Report on Carcinogens

Knox et al., ES&T 2023, DOI 10.1021/acs.est.2c07247

5,000 tons of Prop 65 chemicals emitted from CA products



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BREAST CANCER RELEVANT CHEMICALS (BCRCs)

+

CARB PRODUCT INGREDIENT DATA

=

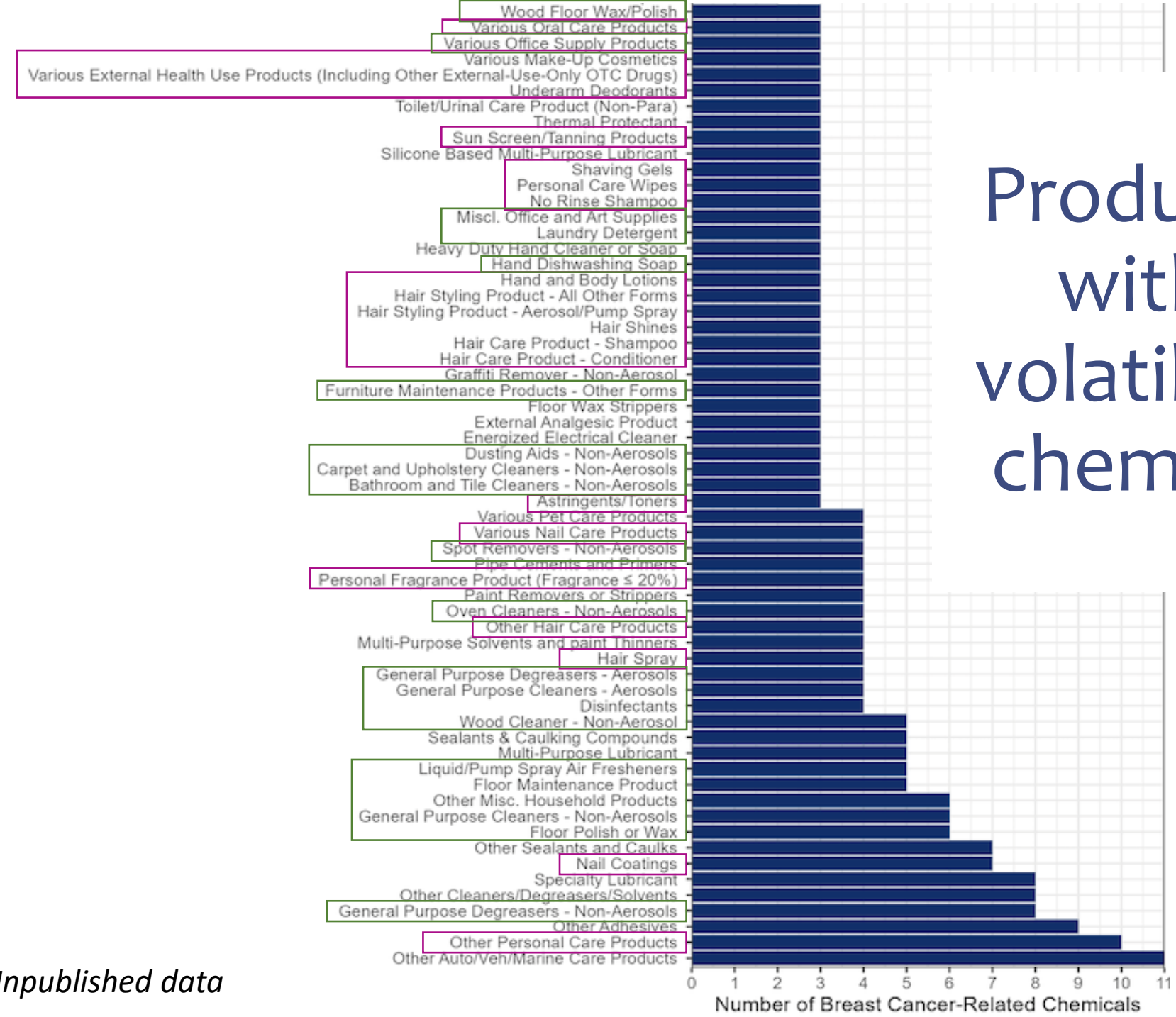
23 volatile BCRCs

in

145 product categories

Unpublished data

Product categories with 3 or more volatile BC-relevant chemicals (BCRCs)

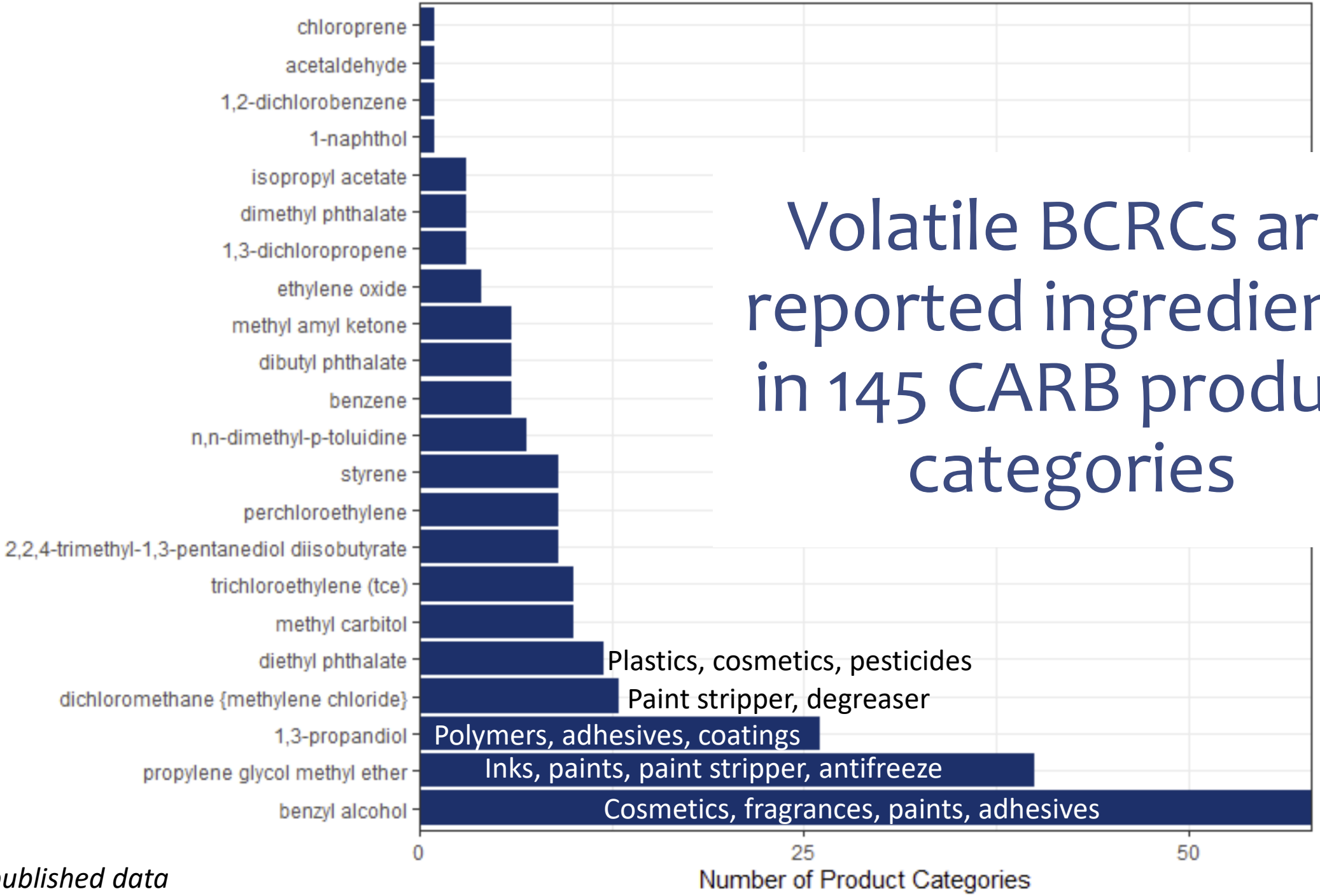


Personal care products

Household products

Unpublished data

Volatile BCRCs are reported ingredients in 145 CARB product categories



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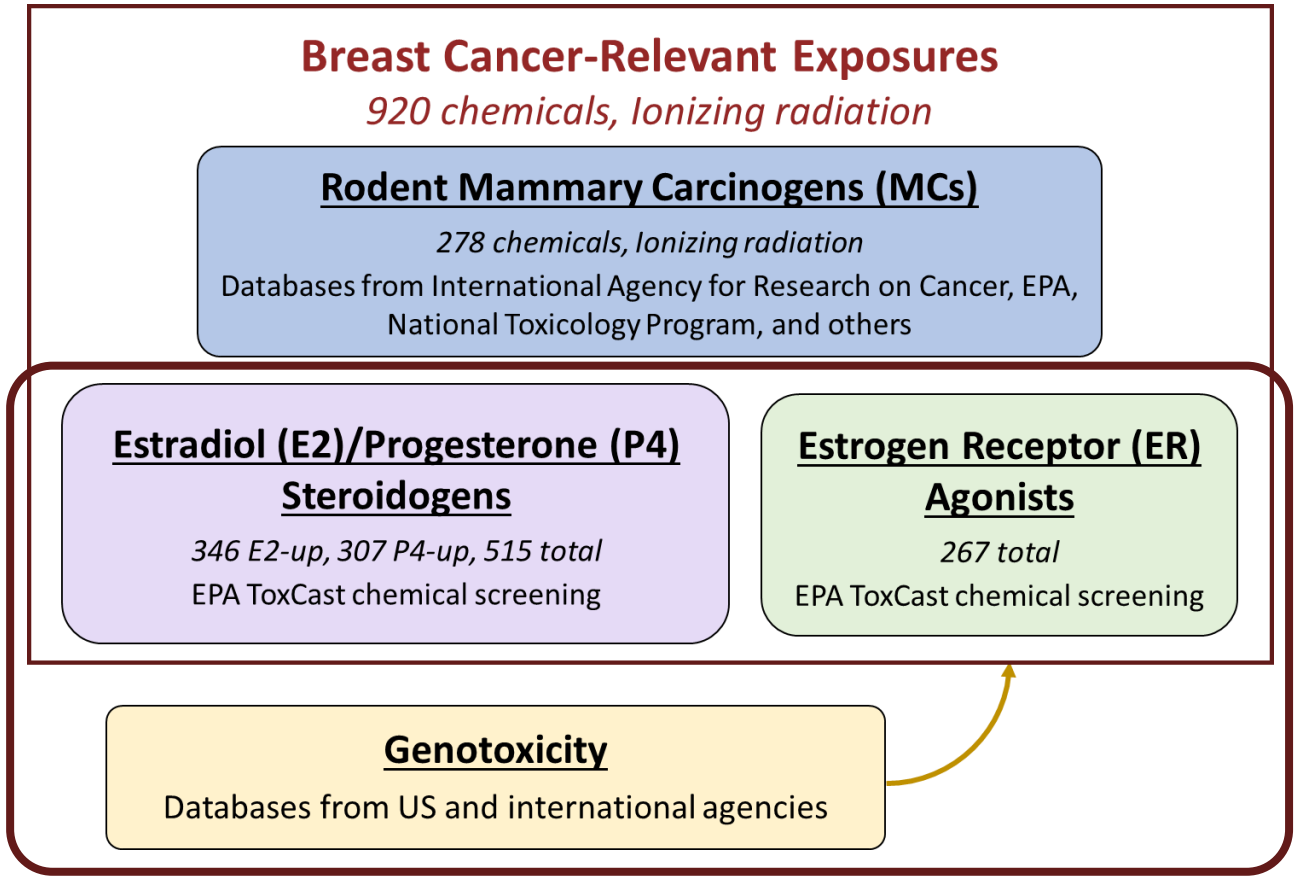
Summary: Setting priorities through hazard identification and exposure characterization

Key Characteristics of Breast Carcinogens

- Mechanistic flags for concern, even in absence of *in vivo* data
- Measurable in high throughput assays



Prioritize for reduction based on

- Biology
  - Animal tumors
  - Magnitude of effect
  - Combination of EDC + Gentox
- Exposures
  - Common sources
  - Heavy usage
  - Intake levels
  - Emissions

Acknowledgments

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Contributors

Silent Spring Institute

- Ruthann Rudel, MS
- Rashmi Shakti
- Julia Brody, PhD
- Kristin Knox, PhD
- Robin Dodson, ScD
- Elissia Franklin, PhD
- Jennifer Liss Ohayon, PhD
- Mary Beth Terry, PhD

UC Berkeley

- Megan Schwarzman, MD
- Claudia Polsky, JD

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CALIFORNIA BREAST CANCER RESEARCH PROGRAM

Kay et al, *EHP* 2024
Key Characteristics to ID BCRCs

Shakti et al, *ES&T Letters* 2024
BCRCs in plastics

Knox et al, *ES&T* 2023
Air emissions of Prop 65 VOCs