



Environmental Exposure and Cancer

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Nothing to Disclose

Agenda



Overview and Definitions



Environmental Exposures and Cancer

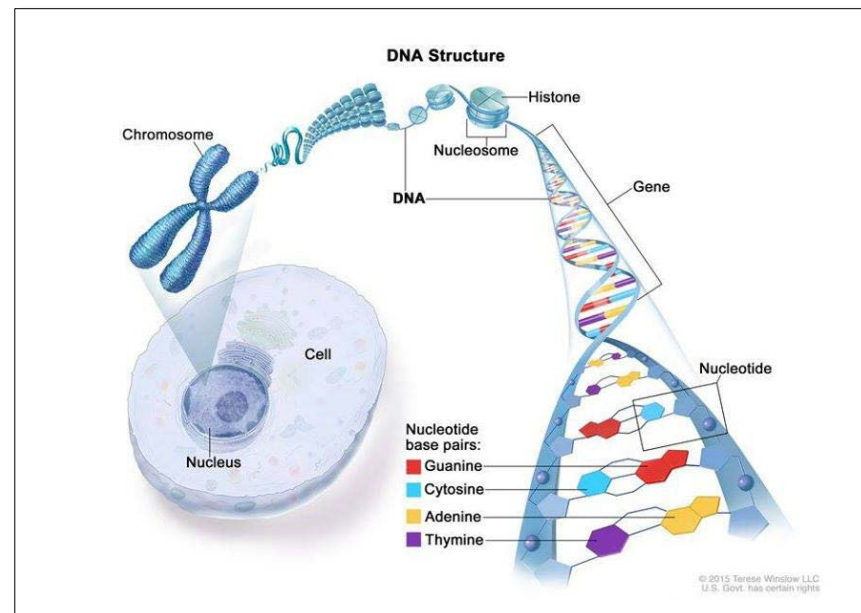
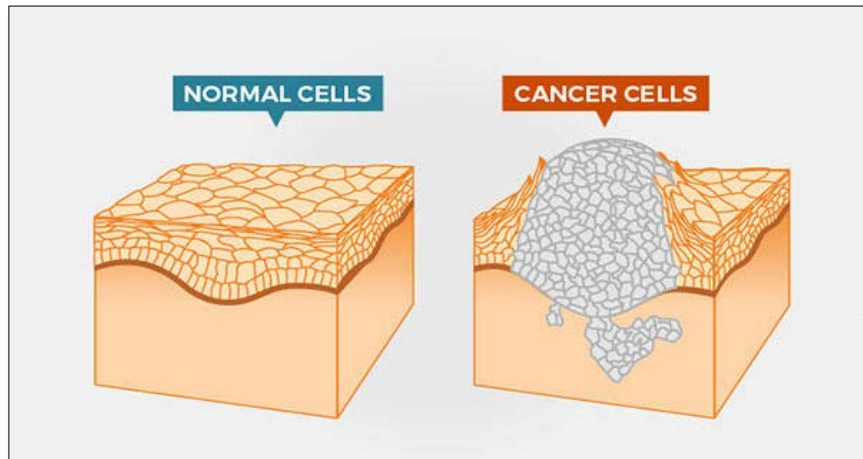


Challenges and Opportunities for Studying
the Environment and Cancer



Summary

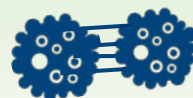
The Complexity of Cancer



>100
Types
of Cancer



Abnormal cell growth which spreads through the body



Errors as cells divide

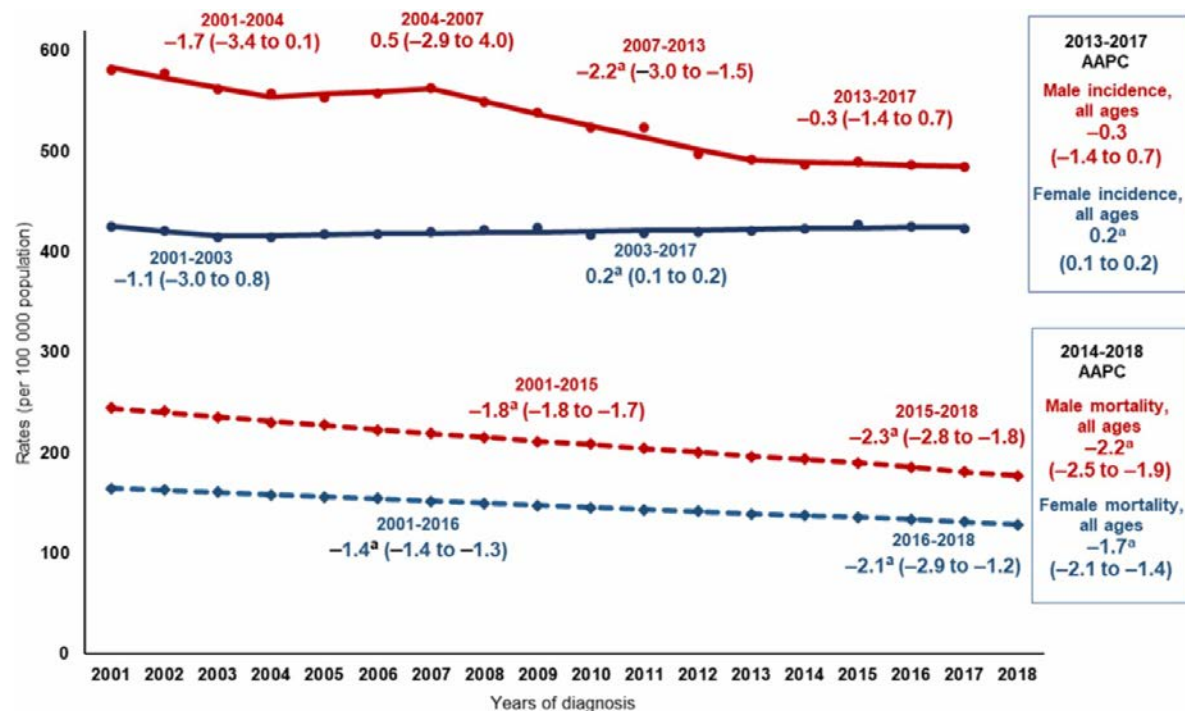


Damage to DNA from the environment

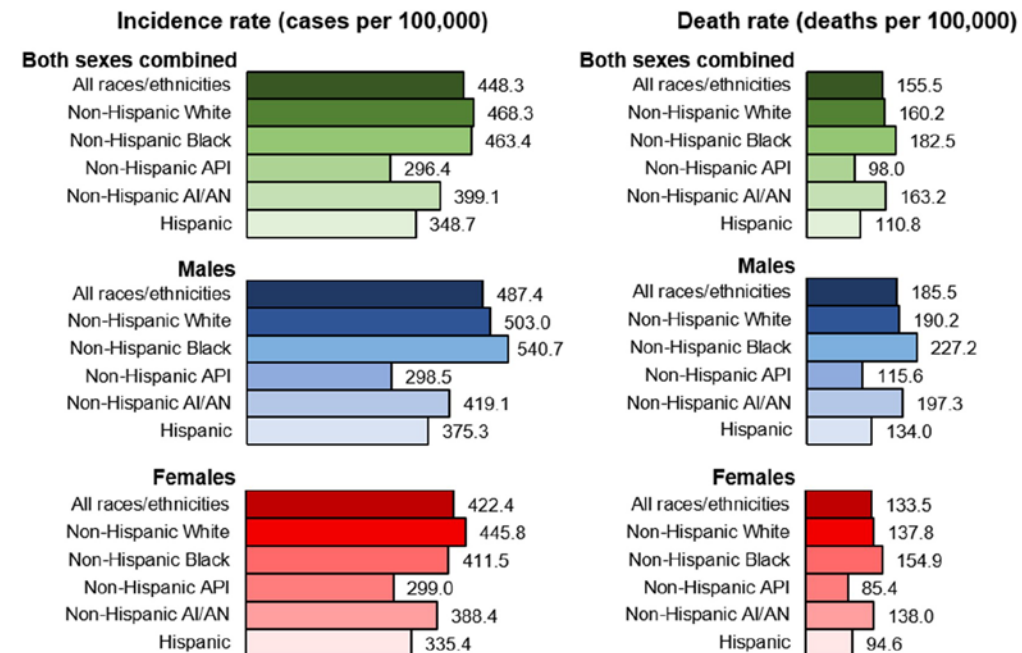


Inherited genetics

Cancer Trends



Trends in age-standardized incidence (2001-2017) and mortality (2001-2018) rates, all cancer sites combined, all ages, all races and ethnicities combined, by sex.



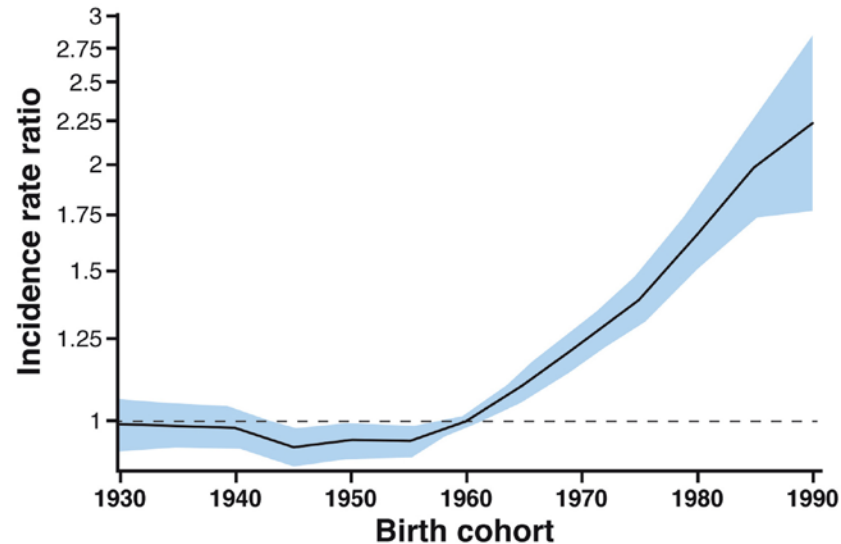
Age-standardized, delay-adjusted overall cancer incidence rates (2013-2017) and age-standardized overall cancer death rates (2014-2018), all cancer sites combined, all ages, by sex and racial and ethnic group.

Increasing Incidence of Cancer: Environmental Etiology?



Increased incidence for melanoma, colorectal cancer among young adults, liver cancer, and kidney and renal pelvis cancer

Incidence rate ratios for colorectal cancer by birth cohort.

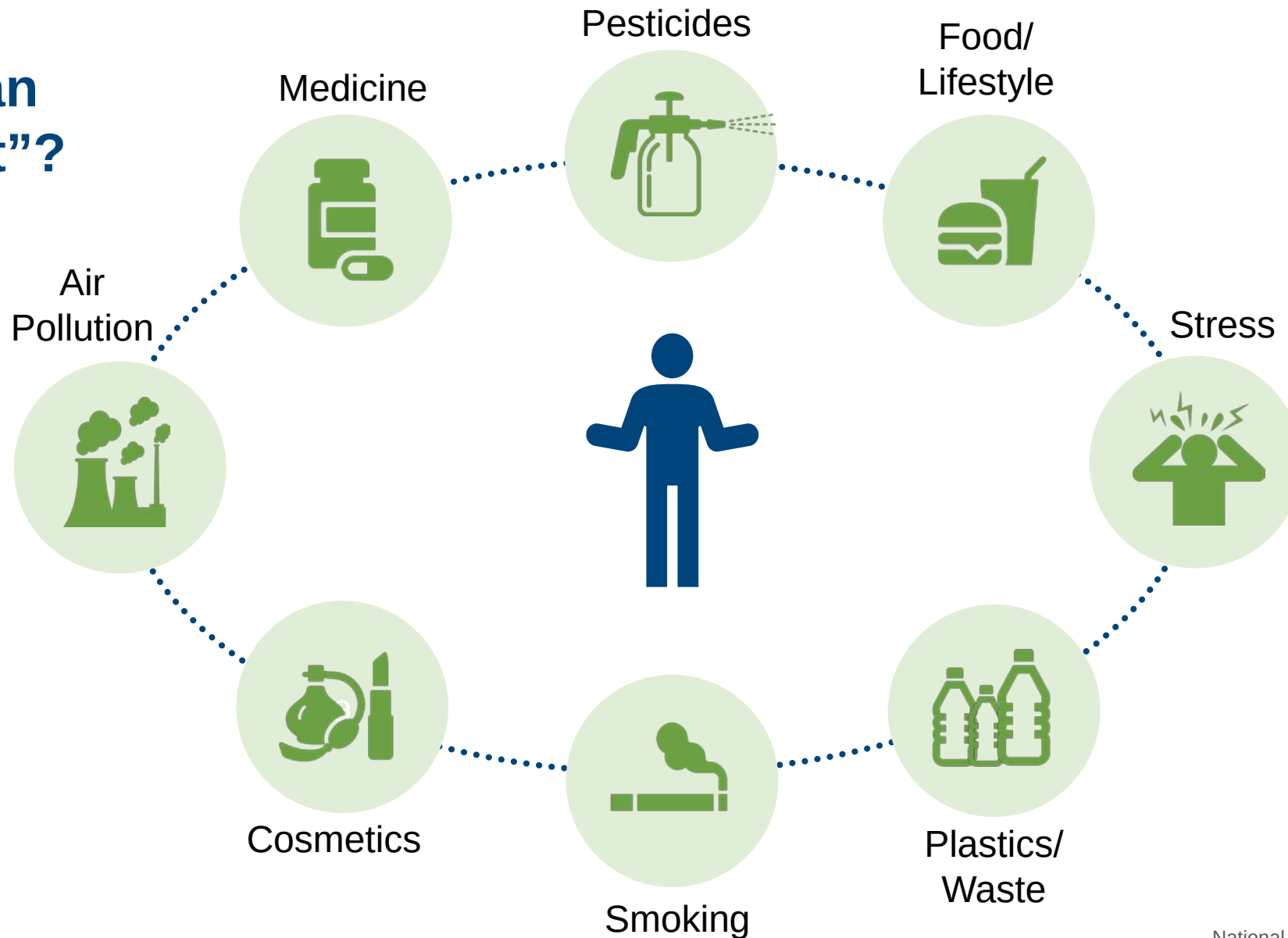


Source: Stoffel, E.M., et al. *Gastroenterology*, Vol 158(2): 341-353. 2020.
<https://doi.org/10.1053/j.gastro.2019.07.055>

Average annual percent change (AAPC) in delay-adjusted incidence rates (2013-2017) for all sites and the 18 most common cancers in men and women

Islami, F., et al. *J Natl Cancer Inst*, djab131. 2021. <https://doi.org/10.1093/jnci/djab131>

What Do We Mean by “Environment”?



Review of evidence

National Toxicology Program

Evaluates agents of public health concern through toxicology and molecular biology

NTP Report on Carcinogens:

- Currently lists 248 agents, substances, mixtures, and exposure circumstances
- Categorizes exposures as (1) **known to be human carcinogen**, or (2) **reasonably anticipated to cause cancer in humans**



NTP, 2016. Report on Carcinogens, Fourteenth Edition.
<https://ntp.niehs.nih.gov/go/roc14>

Review of Evidence

WHO International Agency for Research on Cancer (IARC) Monographs

Expert working groups assess evidence that an agent is carcinogenic

Has evaluated >1,000 agents and identified >500 as carcinogenic, probably carcinogenic, or possibly carcinogenic to humans

International Agency for Research on Cancer



Table 4. Integration of streams of evidence in reaching overall classifications (the evidence in *bold italic* represents the basis of the overall evaluation)

Stream of evidence			Classification based on strength of evidence
Evidence of cancer in humans ^a	Evidence of cancer in experimental animals	Mechanistic evidence	
<i>Sufficient</i>	Not necessary	Not necessary	Carcinogenic to humans (Group 1)
Limited or Inadequate	<i>Sufficient</i>	<i>Strong (b)(1) (exposed humans)</i>	
<i>Limited</i>	<i>Sufficient</i>	Strong (b)(2–3), Limited, or Inadequate	Probably carcinogenic to humans (Group 2A)
Inadequate	<i>Sufficient</i>	<i>Strong (b)(2) (human cells or tissues)</i>	
<i>Limited</i>	Less than Sufficient	<i>Strong (b)(1–3)</i>	
Limited or Inadequate	Not necessary	<i>Strong (a) (mechanistic class)</i>	
<i>Limited</i>	Less than Sufficient	Limited or Inadequate	Possibly carcinogenic to humans (Group 2B)
Inadequate	<i>Sufficient</i>	Strong (b)(3), Limited, or Inadequate	
Inadequate	Less than Sufficient	<i>Strong b(1–3)</i>	
<i>Limited</i>	<i>Sufficient</i>	<i>Strong (c) (does not operate in humans)^b</i>	Not classifiable as to its carcinogenicity to humans (Group 3)
Inadequate	<i>Sufficient</i>	<i>Strong (c) (does not operate in humans)^b</i>	
All other situations not listed above			

^a Human cancer(s) with highest evaluation

^b The strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans must specifically be for the tumour sites supporting the classification of *sufficient* evidence in experimental animals.

IARC Monographs Preamble (2019)

How do we characterize carcinogens?

Abilities of an agent to:

- 1 Act as an electrophile either directly or after metabolic activation
- 2 Be genotoxic
- 3 Alter DNA repair or cause genomic instability
- 4 Induce epigenetic alterations
- 5 Induce oxidative stress
- 6 Induce chronic inflammation
- 7 Be immunosuppressive
- 8 Modulate receptor-mediated effects
- 9 Cause immortalization
- 10 Alter cell proliferation, cell death, or nutrient supply

Environment and Cancer

Types of Exposures



Physical exposures

- Climate, radiation, sunlight/UV



Lifestyle factors

- Tobacco, diet and nutrition



Chemical exposures

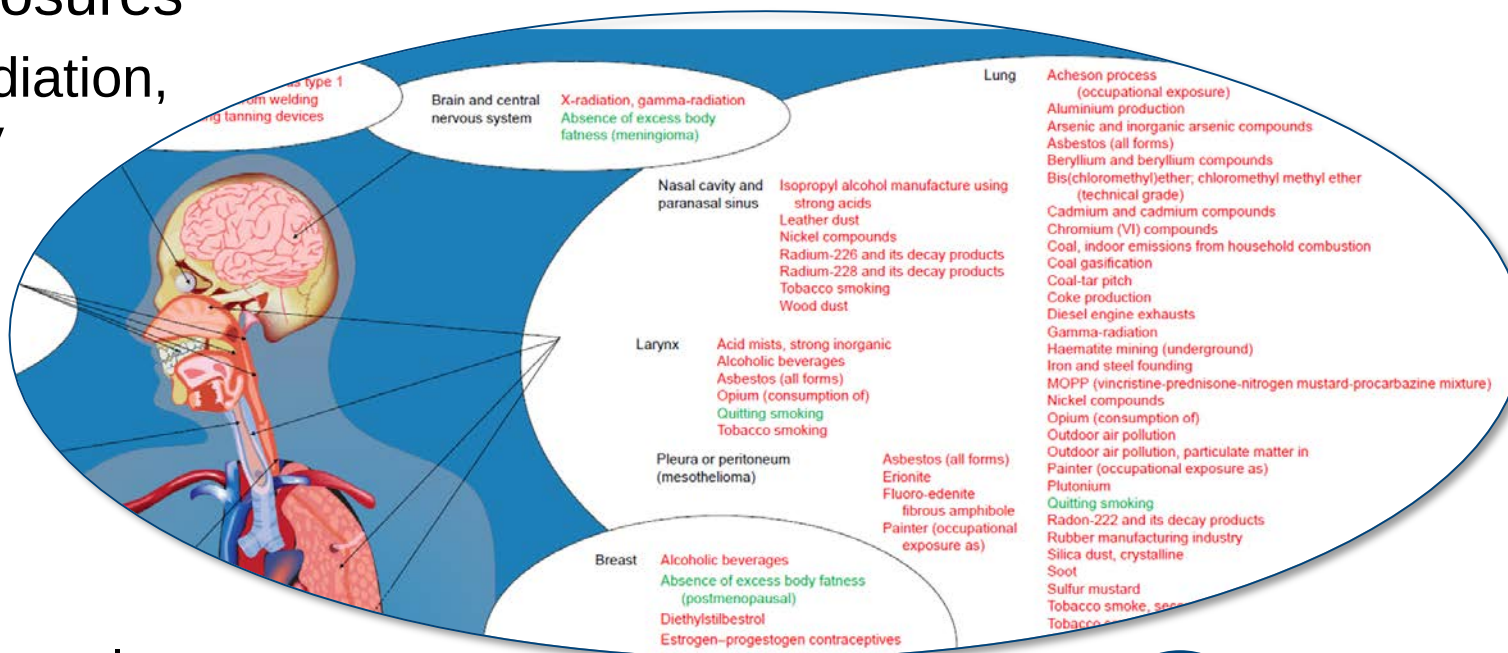
- Pesticides, solvents, gases



Infectious agents



Hormones



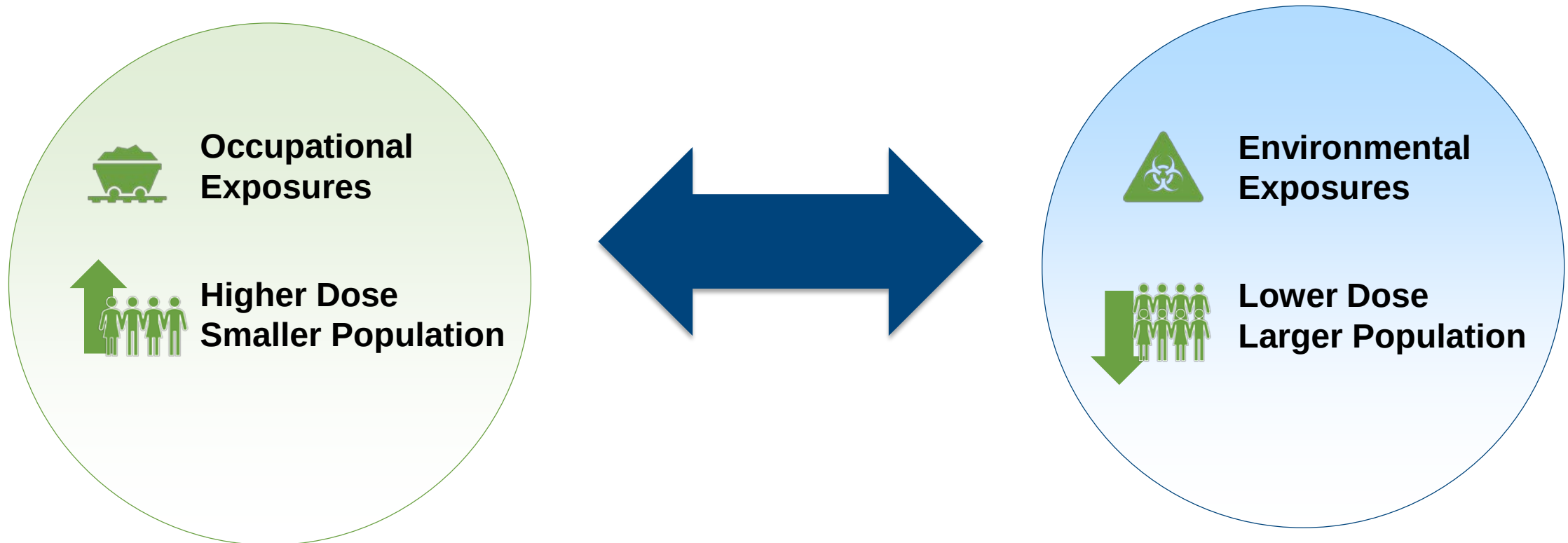
Carcinogenic Exposures in the Occupational Setting

- Much of what we know is through exposures in the occupational setting
 - ↑ High dose
 - ↑ High frequency
 - ➡ Long duration
- Occupational setting provides opportunities for studying exposures:
 - Targeted populations, documentation of exposure

Material/cancer	Reference	Location	Study population	Study type	Evidence of effect
Asbestos/lung	Lynch and Smith [37] 1935	South Carolina	Asbestos textile workers	Single case	Weak
	Doll [21] 1955	England	Asbestos workers	Cohort	Weak
	Selikoff et al. [38] 1964	USA	Insulation workers	Cohort	Moderate
	McDonald et al. [39] 1980	Canada	Chrysotile miners	Cohort	Strong
	Dement et al. [40] 1983	USA	Asbestos textile workers	Cohort	Strong
	Seidman et al. [41] 1986	USA	Amosite workers	Cohort	Strong
Benzene/leukemia	Mallory et al. [42] 1939	UK	Various occupations	Case series	Weak
	Vigliani and Saita [43] 1964	Italy	Various occupations	Case series	Weak
	Ishimaru et al. [44] 1971	Japan	Various occupations	Case series	Moderate
	Aksoy et al. [45] 1974	Turkey	Shoemakers	Case series	Moderate
	Infante et al. [46] 1977	Ohio	Pliofilm makers	Cohort	Moderate
	Rinsky et al. [47] 1987	Ohio	Pliofilm makers	Cohort	Strong
	Yin et al. [48] 1987	China	Benzene producers	Cohort	Strong

Occupational exposure studies contribute to exposure knowledge in the general population

Many Occupational Exposures Occur in Non-Occupational Settings



Population Studies

Exposure assessment:

? What are the characteristics of exposure?

↓ How can exposure be reduced?

🕒 Has exposure changed over time?

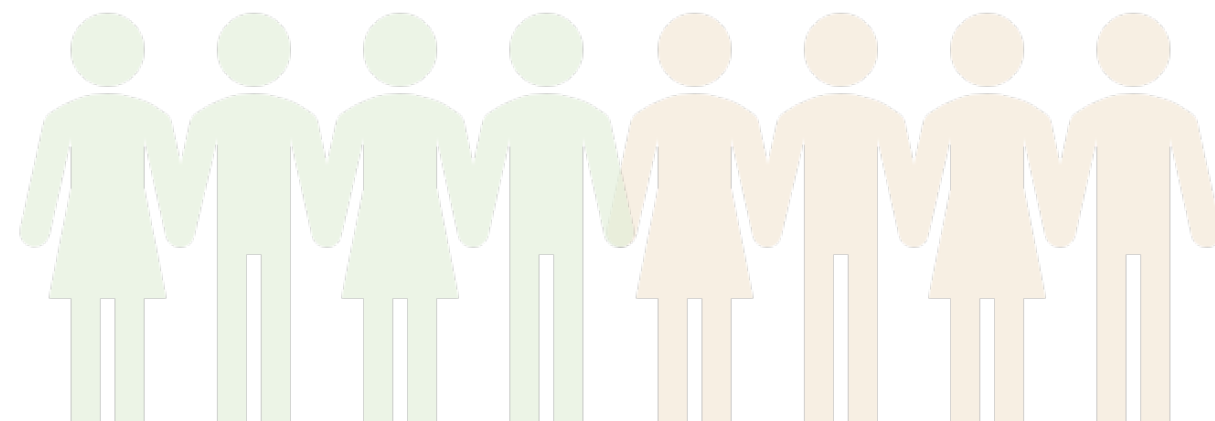


Challenges:

🕒 Latency, estimating exposure, exposure-outcome association

Measurement methods:

📊 Cohorts, longitudinal studies, mechanistic studies, animal studies, biomonitoring



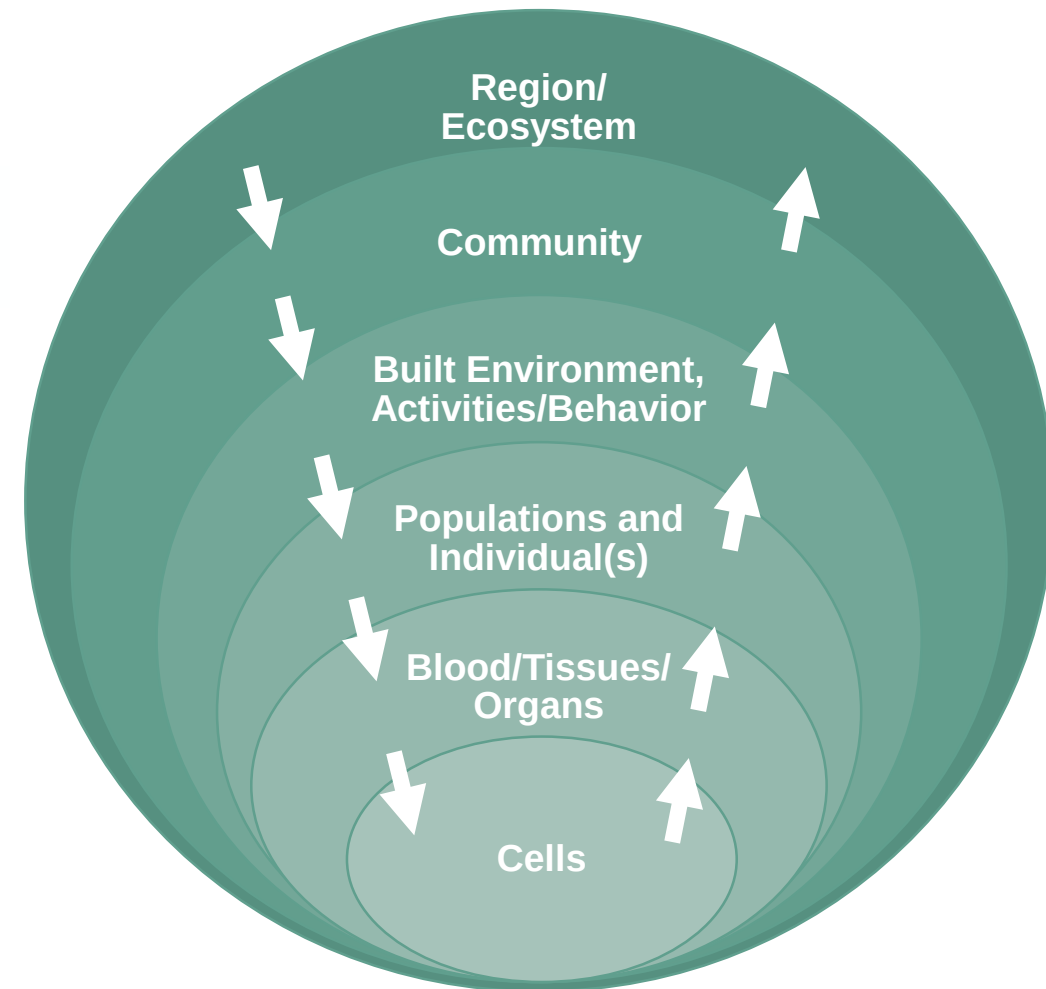


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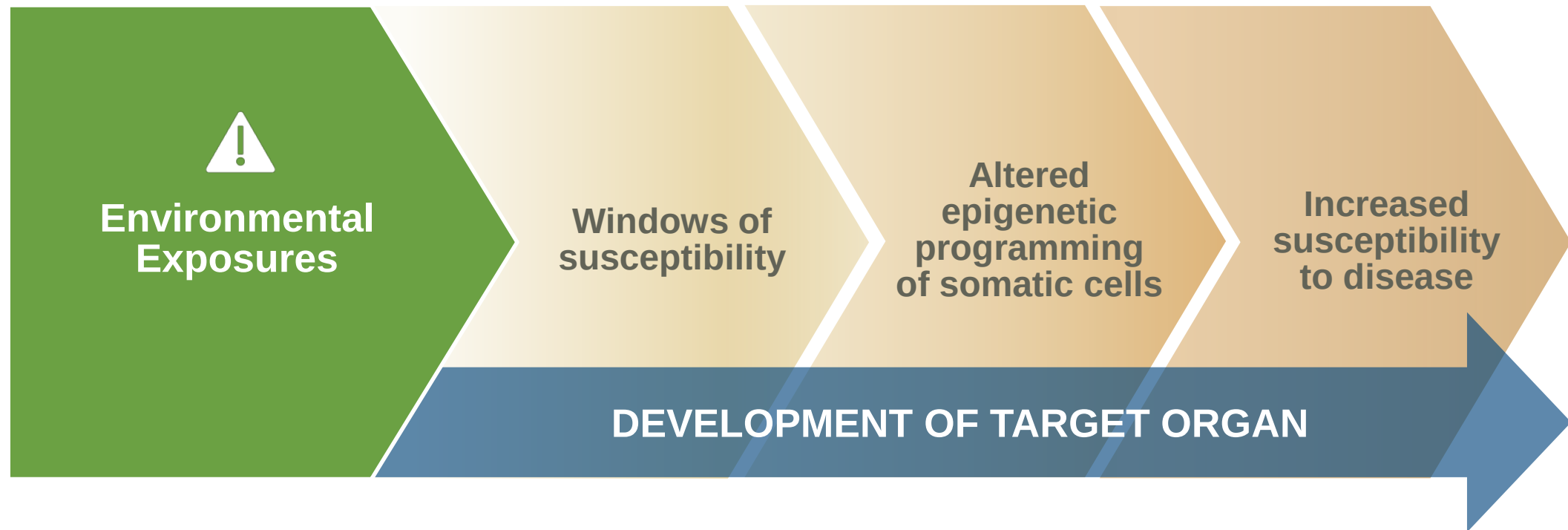
Challenges and Opportunities for Studying Exposures and Cancer Risk

The Complexities of Documenting Exposures

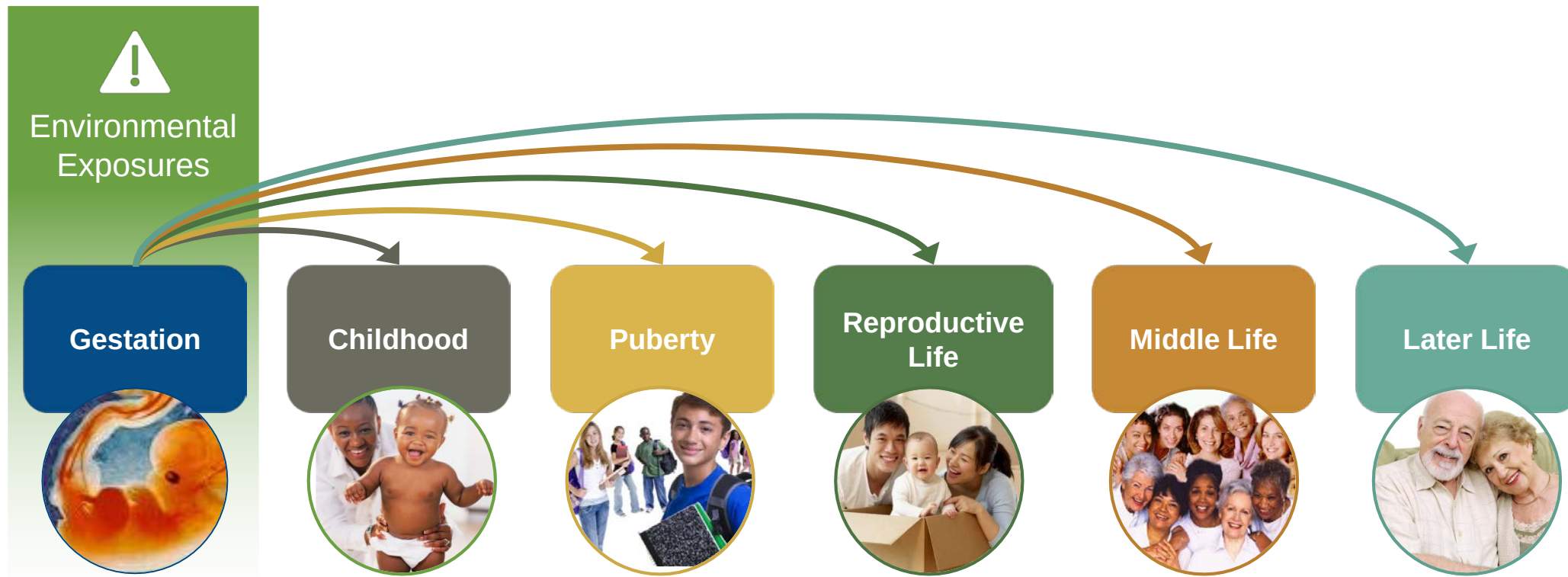
	Classes: Physical, Chemical, Biological, Psycho-social
	Sources: Air, Water, Soil, Food, Consumer Products, Medicines
	Places: Home, School, Work, Neighborhood, Community, City, State, Region
	Time: Fetal, Child, Adolescent, Young Adult, Adult, Elderly
	Contact: Skin, Lungs, Diet
	Where: Lungs, Neuro, Skin, GI, other organs
	Targets: Biological pathways



Disease Outcome is Related to Site and Mechanism of Action of Environmental Exposures



The Complexities of Time: Lifelong Effects of Early-Life Exposures



Research Challenges - Measuring Environmental Exposures

In the Environment



Mixtures



Interactions



Amount of dose



Retrospective
assessment is faulty

In the Body



Genetic susceptibility



Single or multiple windows

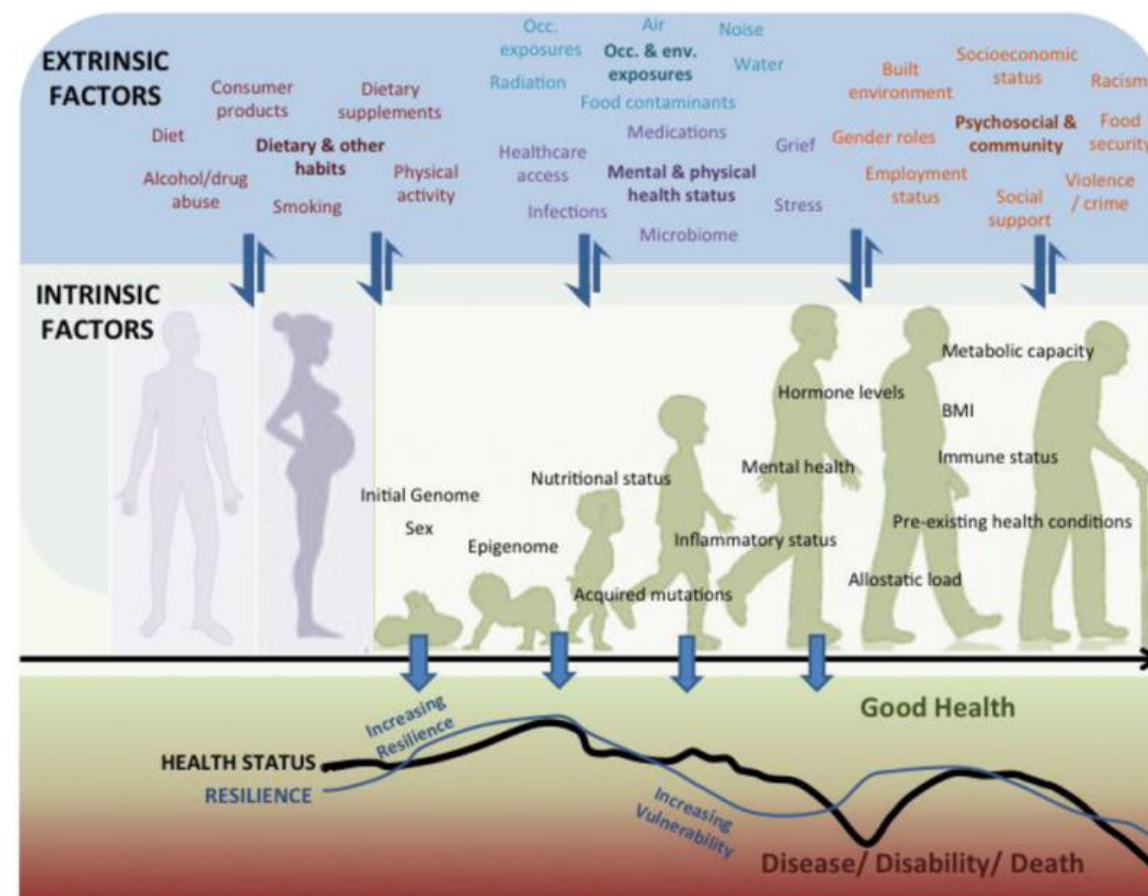
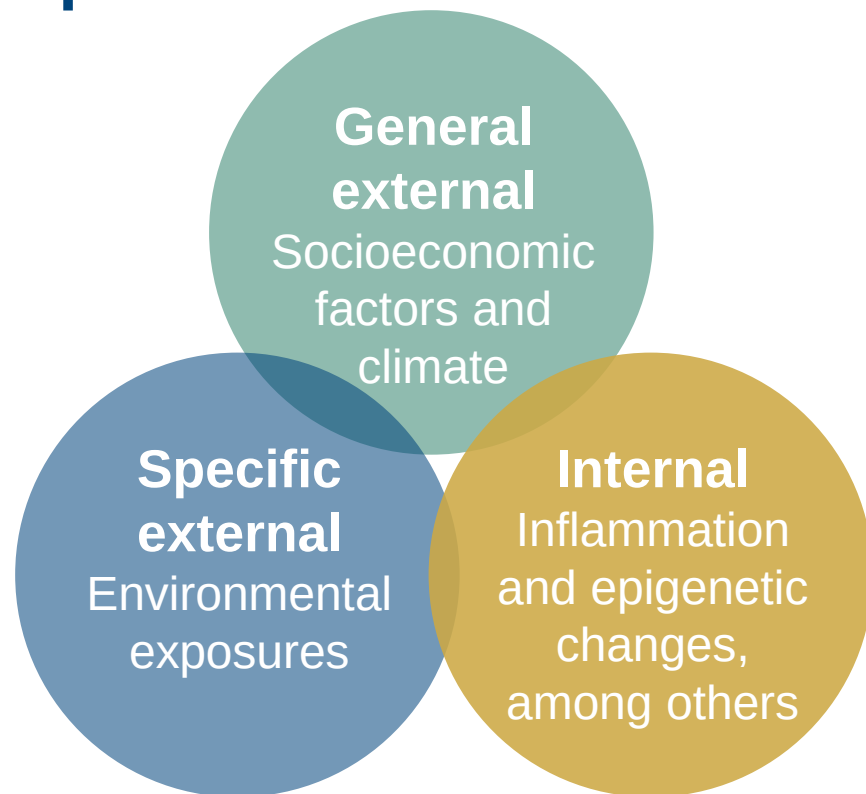


Tissue specific effects

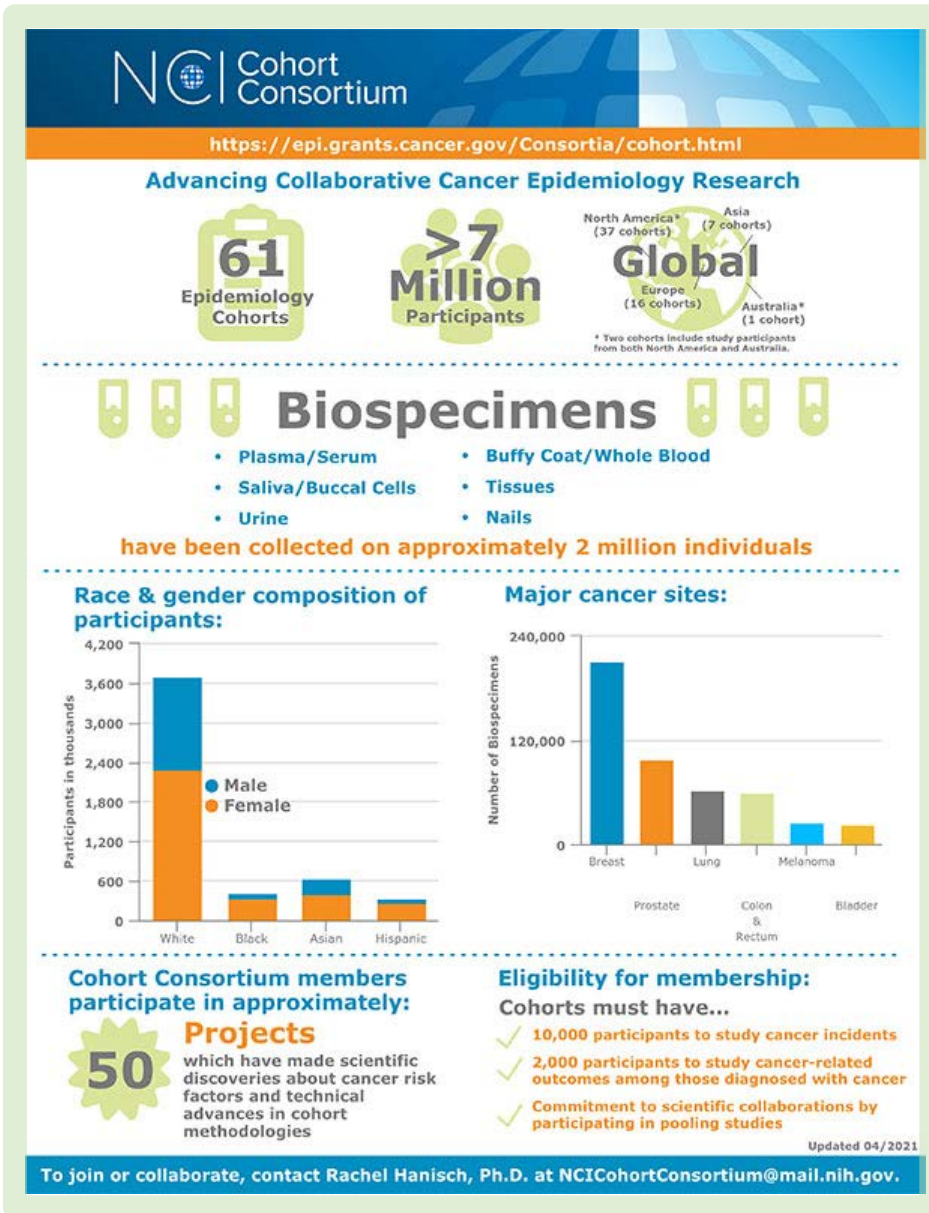


Trans-generational effects

The Exposome

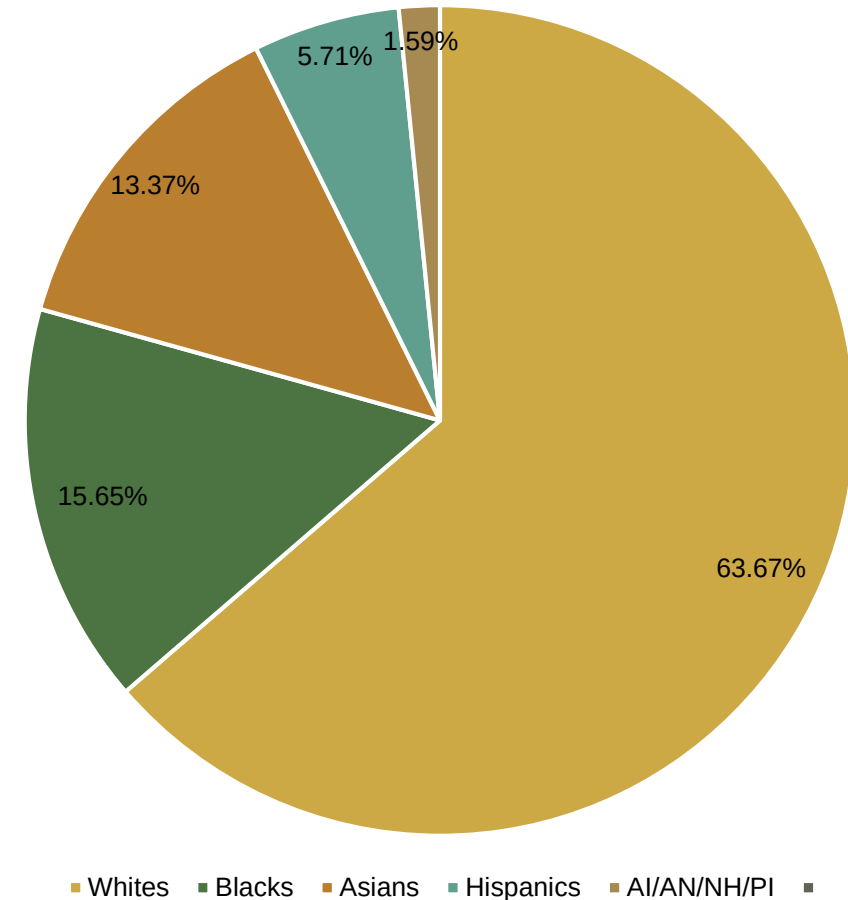


Implications for examining environmental health disparities

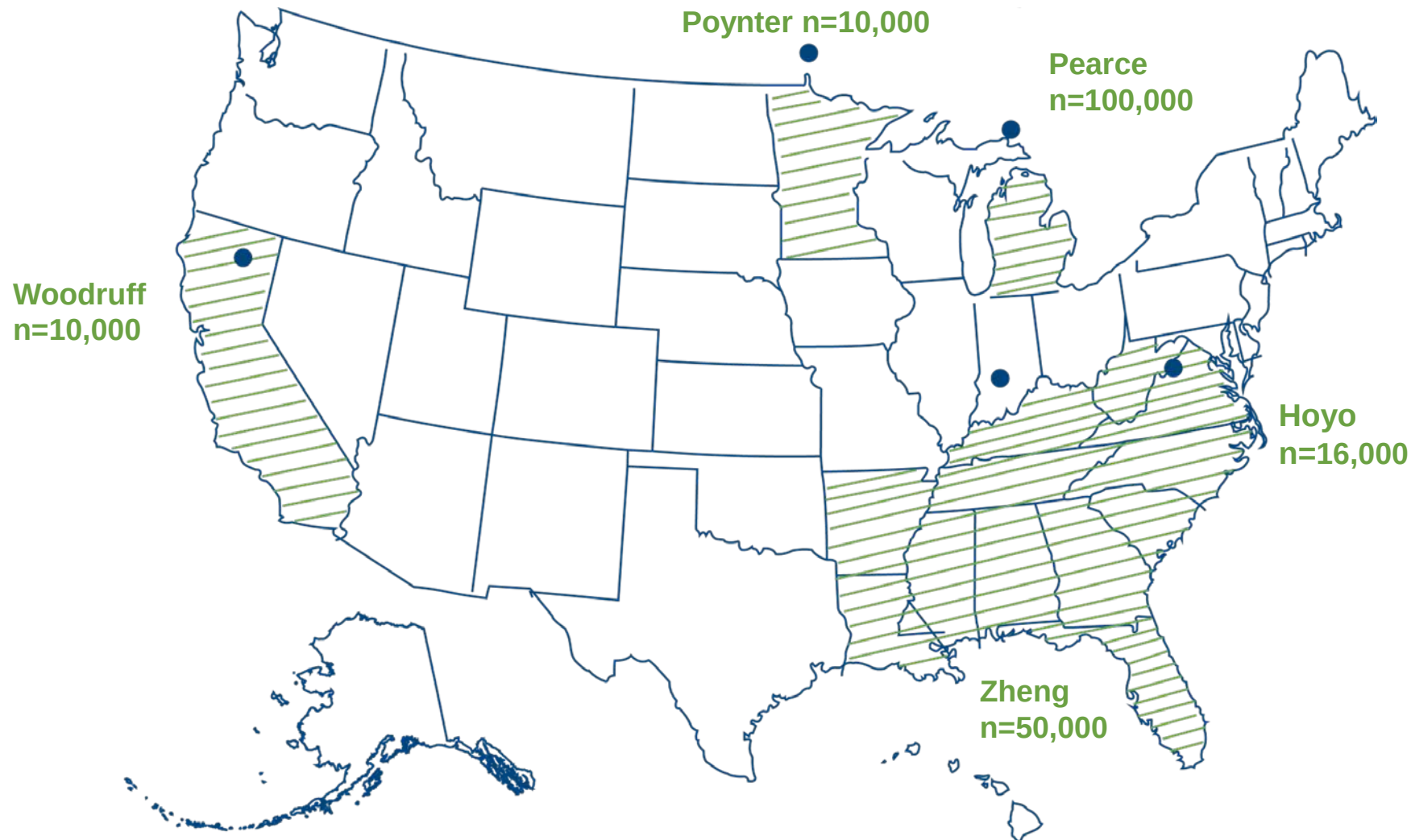


Total enrollment ~1.1 million

Racial/Ethnic Distribution



Cohorts for Environmental Exposures and Cancer Risk



- Five new cohorts
- Diversity of Populations
- Wide set of exposures
- Population-based studies in communities at risk from environmental exposures
- Scientific collaboration with NIEHS
- Potential for major public health advancement

The Human Health Exposure Analysis Resource: 2019 - 2024



Goal

Provide infrastructure for adding or expanding exposure analysis to advance understanding of the impact of environmental exposures on human health throughout the life course



Looking Ahead



Further evaluation of probable and possible carcinogens that affect large populations is warranted



Agents linked to cancer in animals



Incorporate biologic and mechanistic components in prospective designs



Evaluation of cancer risk associated with low levels of environmental contaminants and complex mixtures



Investigations of environmental exposures in different populations





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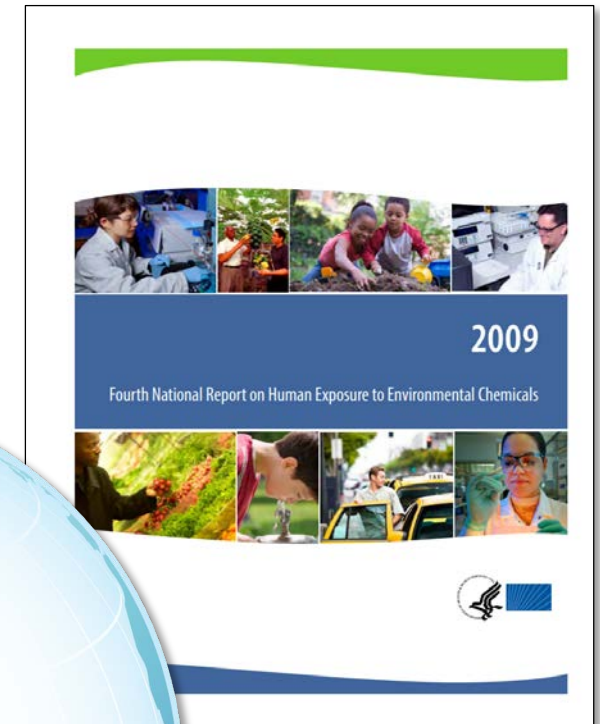
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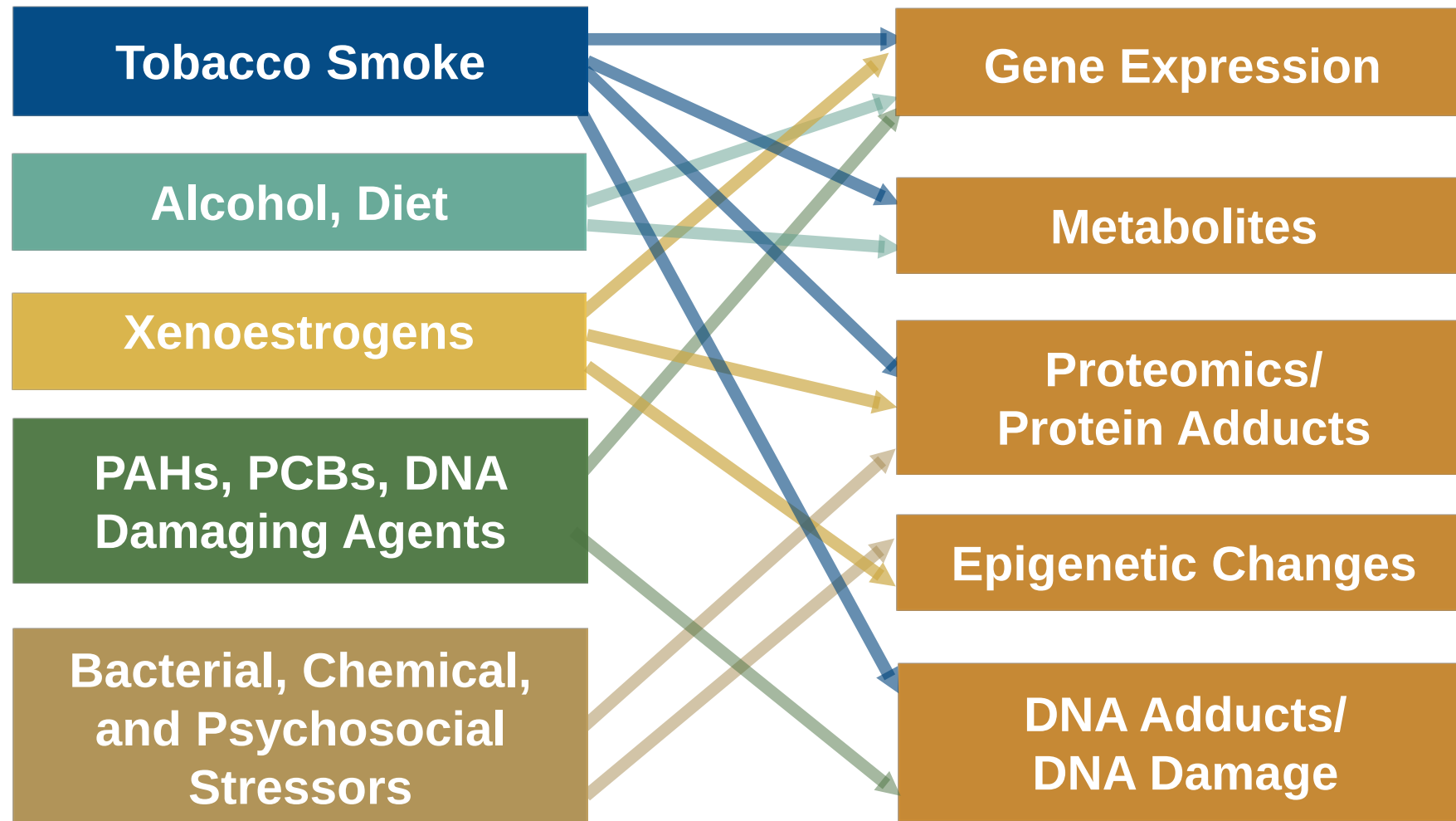
Backup Slides

Tools and Resources

- **National Biomonitoring Program**
- **Human Health Exposure Analysis Resource (HHEAR)**
- **Cohorts:**
 - National Cancer Institute's Cohort Consortium
 - New Cohorts to Assess Environmental Exposures and Cancer Risk (CEECCR)
- **Biobanks**



Linking Exposure with Biological Responses



Individual Variation in Cancer Outcomes and Environmental Exposures

- A vast majority of diseases result from complex interactions between genes and the environment
- Different people respond to the same environmental exposure differently due to:



Timing



Genetic susceptibility



Comorbidity



Lifestyle

