

The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

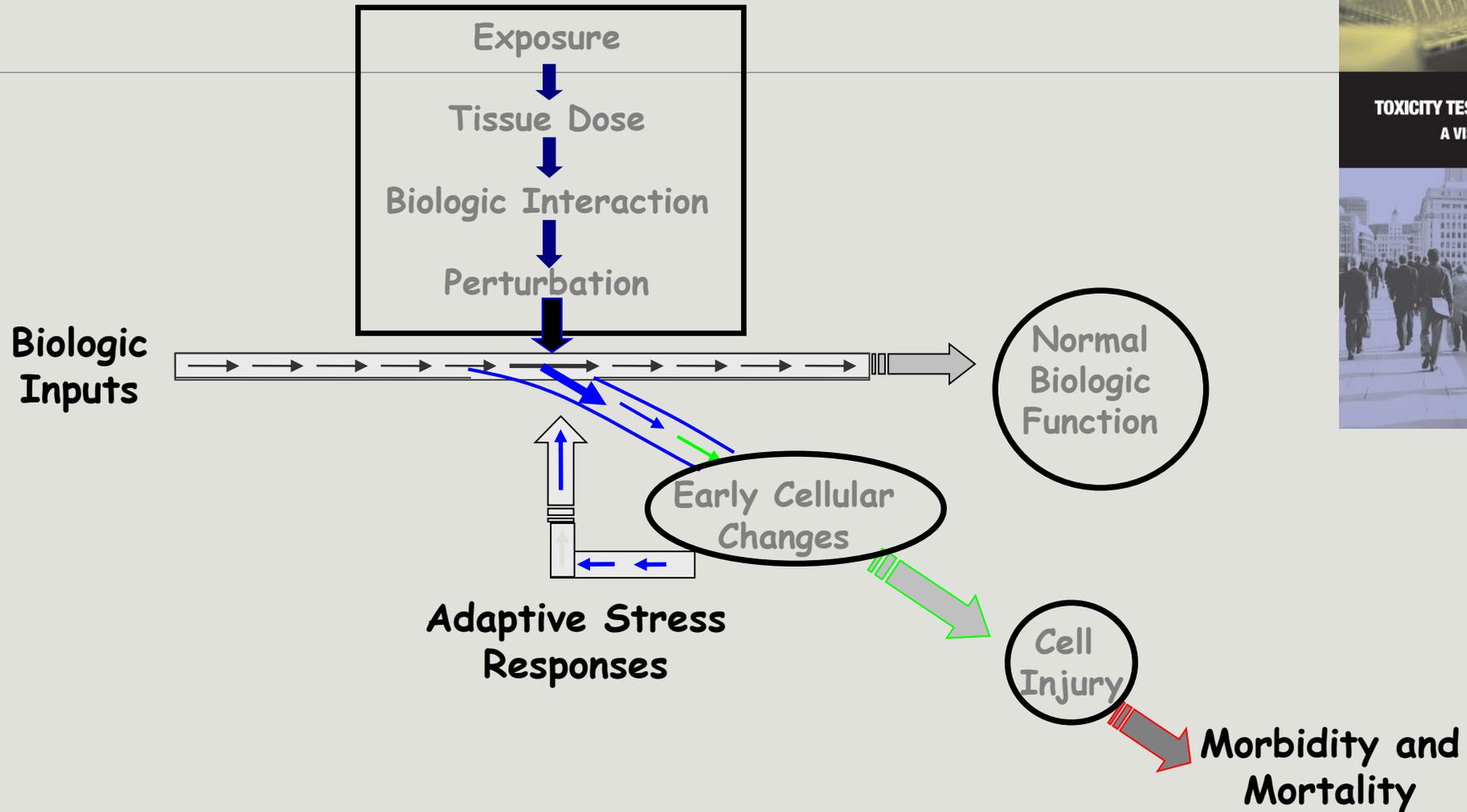
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Pathway-Based Toxicity Testing



TOXICITY TESTING IN THE 21ST CENTURY
A VISION AND A STRATEGY



NATIONAL RESEARCH COUNCIL

Key Characteristics of Carcinogens

1. Electrophilic or ability to undergo metabolic activation
2. Genotoxic
3. Alter DNA repair or cause genomic instability
4. Epigenetic alterations
5. Oxidative stressor
6. Induce chronic inflammation
7. Immunosuppressant
8. Modulate receptor-mediated effects
9. Immortalization
10. Alter cell proliferation, cell death, and nutrient supply

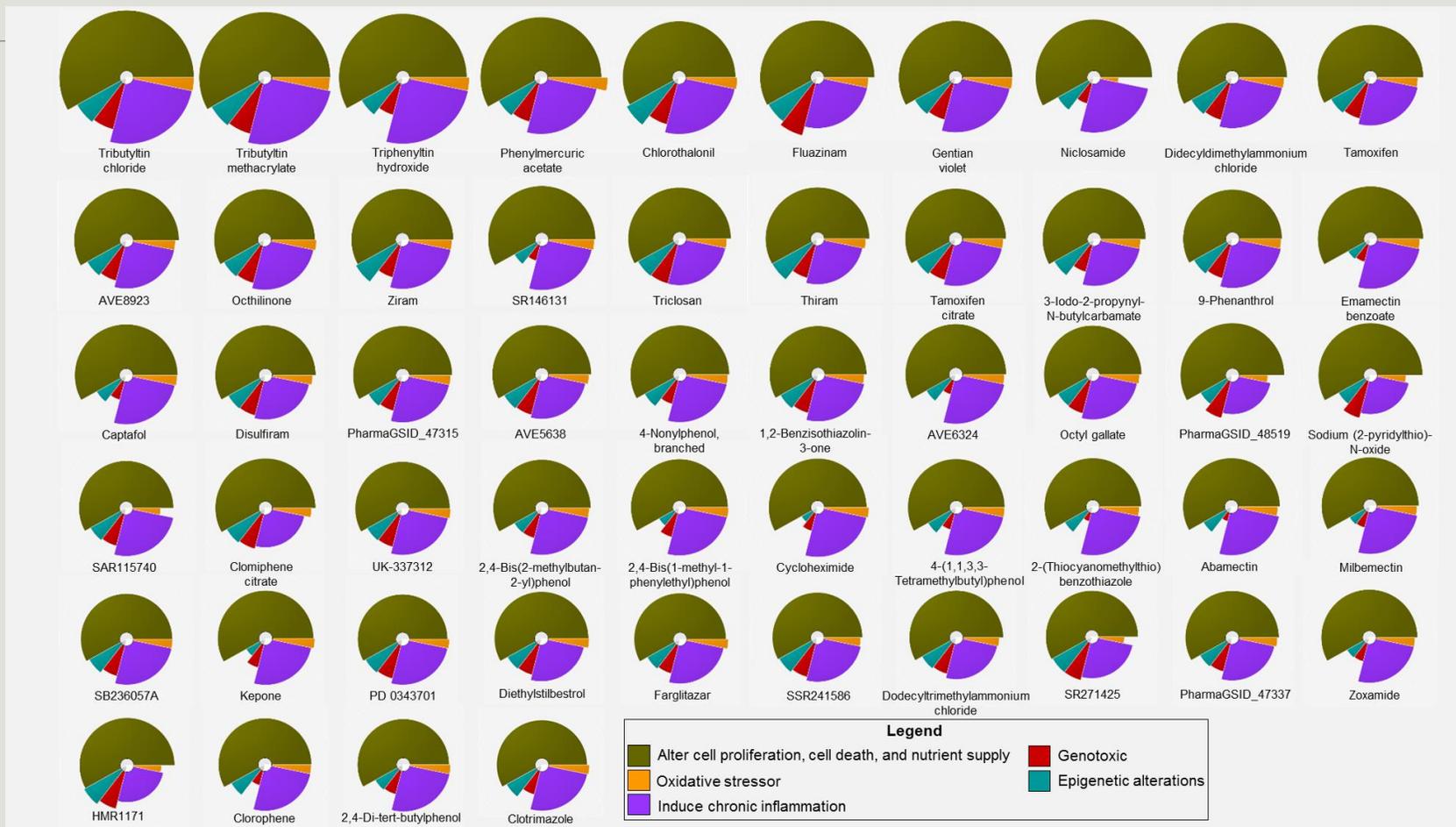
Gaps in Toxicity Pathway Assays

Key characteristic of carcinogens	Percentage of cancer pathway-related assays in a subset of ToxCast platforms linked to characteristic (OEHHA)	Percentage of cancer pathway-related assays in subset of ToxCast platforms linked to characteristic (IARC)
1. Electrophilic or ability to undergo metabolic activation	0% (0/137)	12% (31/265)
2. Genotoxic	4% (6/137)	0% (0/265)
3. Alter DNA repair or cause genomic instability	0% (0/137)	0% (0/265)
4. Epigenetic alterations	4% (6/137)	4% (11/265)
5. Oxidative stressor	4% (6/137)	7% (18/265)
6. Induce chronic inflammation	34% (46/137)	17% (45/265)
7. Immunosuppressant	0% (0/137)	0% (0/265)
8. Modulate receptor-mediated effects	0% (0/137)	35% (92/265)
9. Immortalization	0% (0/137)	0% (0/265)
10. Alter cell proliferation, cell death, and nutrient supply	67% (92/137)	26% (68/265)

SYSTEMATICALLY ADDRESS IDENTIFIED GAPS IN
TOXICITY PATHWAYS BY DEVELOPING AND
INCORPORATING NEW ASSAYS.

Recommendation #1

Key Characteristics Rarely Occur Singly



Top 50 Most Active on Key Characteristics

Tributyltin chloride	Octyl gallate
Tributyltin methacrylate	PharmaGSID_48519
Triphenyltin hydroxide ¹	Sodium (2-pyridylthio)-N-oxide
Phenylmercuric acetate	SAR115740
Chlorothalonil	Clomiphene citrate
Fluazinam	UK-337312
Gentian violet	2,4-Bis(2-methylbutan-2-yl)phenol
Niclosamide	2,4-Bis(1-methyl-1-phenylethyl)phenol
Didecyldimethylammonium chloride	Cycloheximide
Tamoxifen	4-(1,1,3,3-Tetramethylbutyl)phenol
AVE8923	2-(Thiocyanomethylthio)benzothiazole
Octhilinone	Abamectin
Ziram	Milbemectin (mixture of 70% Milbemycin A4, 30%
SR146131	Milbemycin A3)
Triclosan	SB236057A
Thiram	Kepone
Tamoxifen citrate	PD 0343701
3-Iodo-2-propynyl-N-butylcarbamate	Diethylstilbestrol
9-Phenanthrol	Farglitazar
Emamectin benzoate	SSR241586
Captafol	Dodecyltrimethylammonium chloride
Disulfiram	SR271425
PharmaGSID_47315	PharmaGSID_47337
AVE5638	Zoxamide
4-Nonylphenol, branched	HMR1171
1,2-Benzisothiazolin-3-one	Clorophene
AVE6324	2,4-Di-tert-butylphenol
	Clotrimazole

TEST HYPOTHESES BY FOLLOWING UP WITH TESTING OF CHEMICALS THAT SHOW MARKEDLY POSITIVE RESULTS ON IMPORTANT PATHWAYS.

Recommendation #2

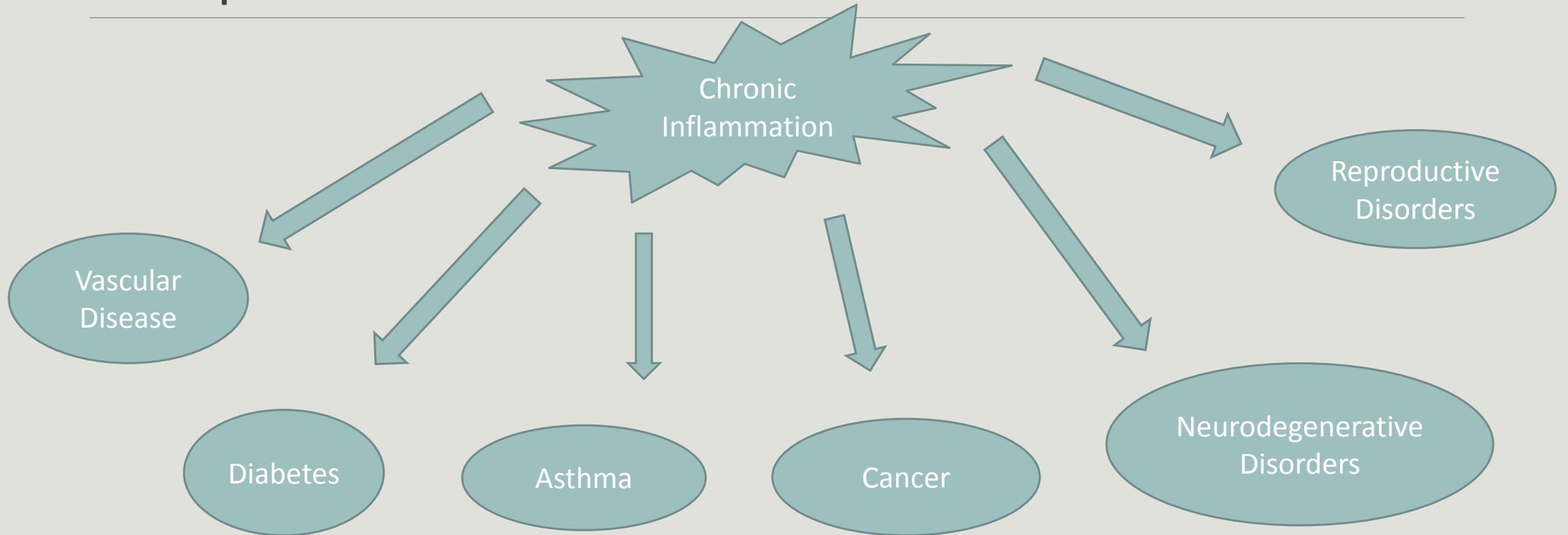
Key Characteristics of Carcinogens	Pathway Perturbations in Breast Cancer	Hallmarks of Cancer
Electrophilic or ability to undergo metabolic activation	-	-
Genotoxic	Genotoxicity	-
Alter DNA repair or cause genomic instability	-	Genome instability
Epigenetic alterations	Changes in transcription, translation, and epigenetic programming of genes associated with breast cancer	-
Oxidative stressor	Oxidative stress	-
Induce chronic inflammation	Inflammation	Inflammation
Immunosuppressant	Immune modulation	Evading immune destruction
Modulate receptor-mediated effects	Alterations in hormone levels, metabolism, or receptors; Altered activity or expression of peptide growth hormones	-
Immortalization	Limitless replication potential	Evading growth suppressors; Enabling replicative immortality
Alter cell proliferation, cell death, and nutrient supply	Cell cycle changes; Evasion of apoptosis	Sustaining proliferative signaling; Resisting cell death
-	-	Inducing angiogenesis
-	-	Activating invasion and metastasis
-	Autocrine growth	Reprogramming of energy metabolism
<i>Smith, 2016</i>	<i>Schwarzman, 2015</i>	<i>Hanahan, 2011</i>

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 144(5):646-74, 2011.

Schwarzman MR, Ackerman JM, Dairkee SH, et al. Screening for Chemical Contributions to Breast Cancer Risk: A Case Study for Chemical Safety Evaluation. Environ Health Perspect 123(12):1255-64, 2015.

Smith MT, Guyton KZ, Gibbons CF, et al. Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. Environ Health Perspect 124(6):713-21, 2016.

Toxicity Pathways Don't Lead to One Endpoint



Multiple “Characteristics of Badness”

Endpoints for Trichloroethylene (TCE)

- Kidney cancer
- Non-Hodgkin lymphoma
- Cardiac defects
- Leukemia
- Liver cancer
- Multiple myeloma
- End-stage renal disease
- Parkinson disease
- Scleroderma
- Chonal atresia
- Eye defects
- Low birth weight
- Fetal death
- Major malformations
- Miscarriage
- Neural tube defects
- Oral cleft defects (including cleft lip)
- Small for gestational age
- Breast cancer
- Cervical cancer
- Esophageal cancer
- Lung cancer
- Hodgkins disease
- Ovarian cancer
- Prostate cancer
- Rectal cancer
- Impaired immune system function
- Neurological effects (delayed reaction times problems with short-term memory, visual perception, attention, and color vision)
- Neurobehavioral performance deficits (i.e., delayed recall and deficits in visual perception), decreased blink reflex, and mood effects (i.e., confusion, depression and tension)
- Severe, generalized hypersensitivity skin disorder

Specific effect may depend on:

- Metabolic pathway (e.g., GST vs CYP for TCE)
- Timing of exposure
- Concentration and duration
- Other chemical and non-chemical stressors

HOW DO WE MOVE TOWARD MAKING DECISIONS
BASED ON THE PATHWAY DISRUPTION, NOT ON
EACH ENDPOINT?

Recommendation #3

Chemical Classes

Organohalogen flame retardants (~148 chemicals?)

Perfluoroalkyl/polyfluoroalkyl substances (PFAS) (~4730 chemicals?)

Ortho-phthalates (~20 parent phthalates?)

p, p'-bisphenols (Dozens?)

Non-halogenated aromatic phosphates (Dozens?)

Cyclosiloxanes

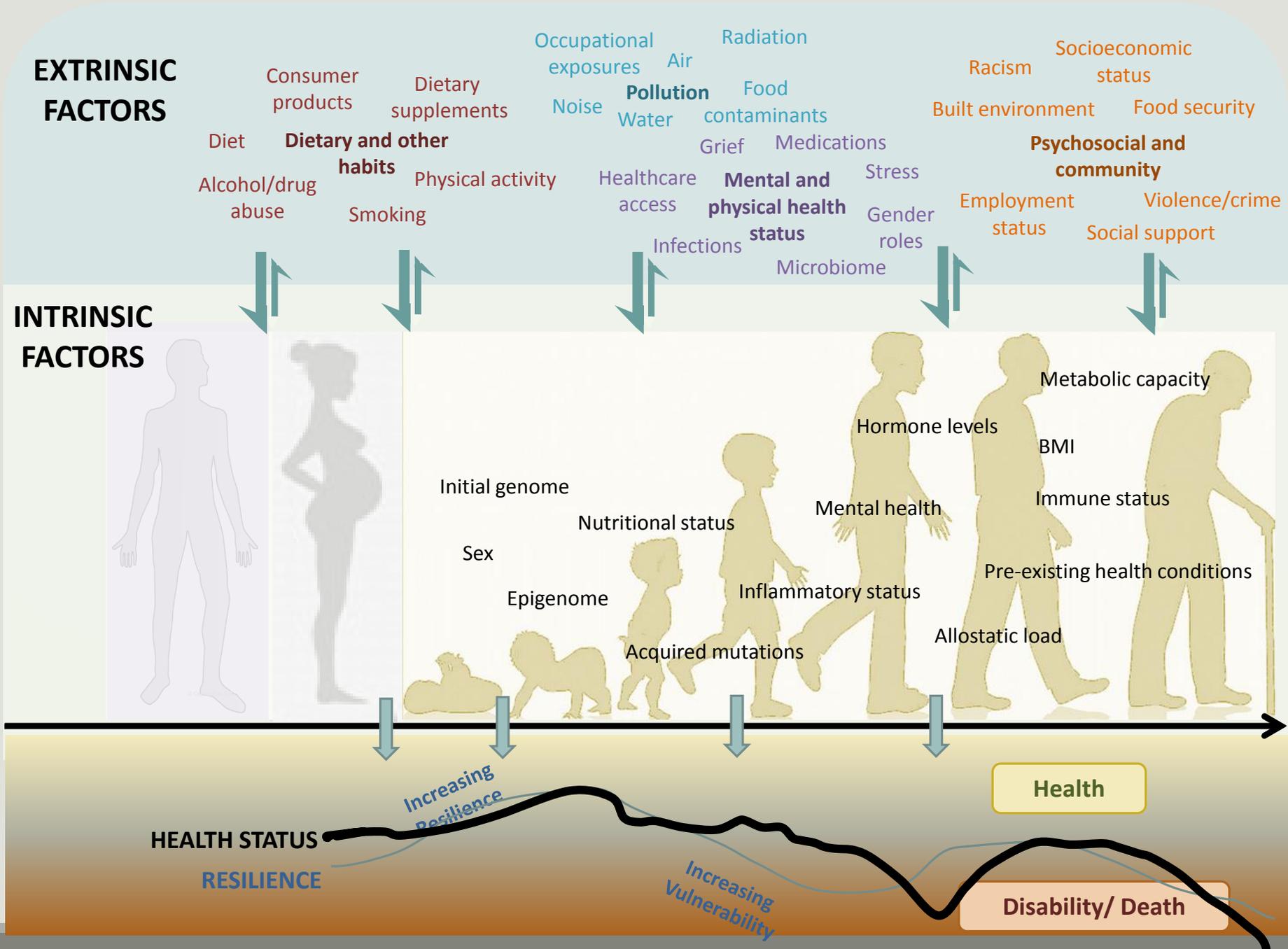
Polycyclic synthetic musks (~8 chemicals?)

Tetramethyl acetyloctahydronaphthalenes (~6 chemicals?)

- Krowech G, Plummer L, Hoover S, Sandy M, Zeise L, Solomon G. Identifying Chemical Groups for Biomonitoring. *Environ Health Perspect* 124(12): A219-226, 2016. DOI:10.1289/EHP537.
- NAS/BEST. Scoping Plan to Assess the Hazards of Organohalogen Flame Retardants. Expected publication April, 2019.
- <http://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/>

DEVELOP AND IMPLEMENT STRATEGIES TO
GROUP CHEMICALS INTO CLASSES AND IMPUTE
HAZARDS ACROSS THE CLASS.

Recommendation #4



EVALUATE HOW MULTIPLE STRESSORS,
INCLUDING NON-CHEMICAL STRESSORS,
PERTURB BIOLOGICAL PATHWAYS.

Recommendation #5

Summary of Recommendations

1. Systematically address identified testing gaps in toxicity pathways by developing and incorporating new assays.
2. Follow-up by testing of chemicals that show markedly positive results on important pathways.
3. Move toward making decisions based on the pathway disruption, not on each endpoint.
4. Develop and implement strategies to group chemicals into classes and impute hazards across the class.
5. Evaluate how multiple stressors, including non-chemical stressors, perturb biological pathways.



Thank You!