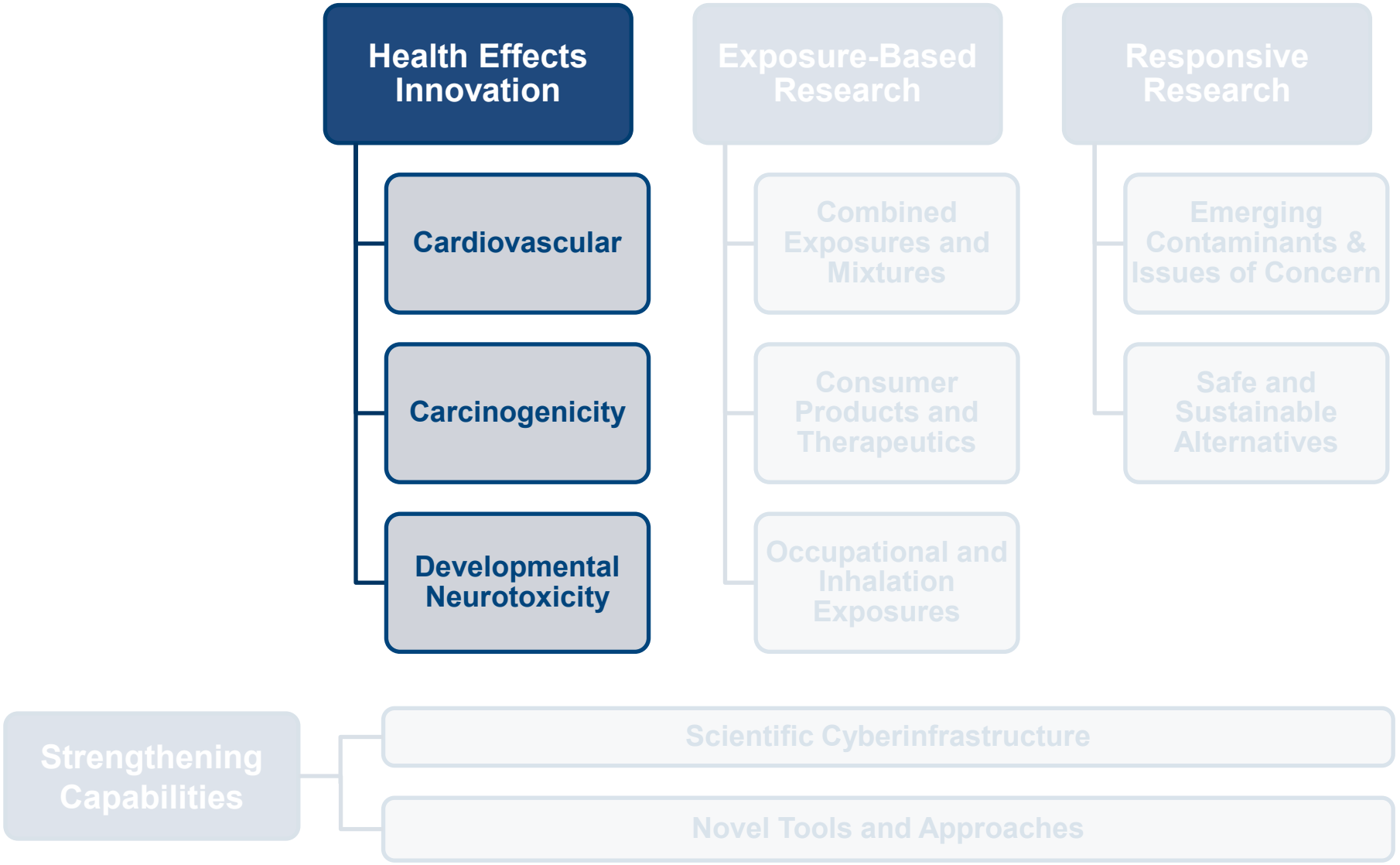
Cardiovascular Health Effects Innovation Program Update

Brandy Beverly, Ph.D.

ICCVAM Public Forum
May 26-27, 2022

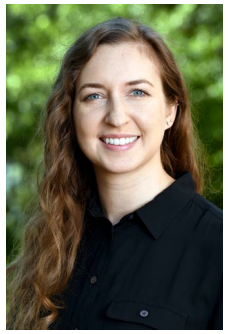
Strategic areas of focus



Cardiovascular HEI Program Management Team

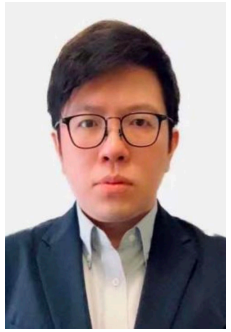

Scott Auerbach


Brandy Beverly


Rachel Dee


Nicole Kleinstreuer


Shagun Krishna


Pan Li


Sreenivasa Ramaiahgari


Kelly Shipkowski


Xian Wu


Kevin Dreher


David Gerhold


Brian Berridge

Problem Statement

- Chronic progressive cardiovascular (CV) disease is a primary cause of morbidity and mortality in the United States and globally.
- Current approaches to environmental hazard assessment do not include specific assessments of CV bioactivity and hazards
- There is no defined approach to identify agents that might be contributing to contemporary and common CV diseases.

Cardiovascular Health Effects Innovation Program

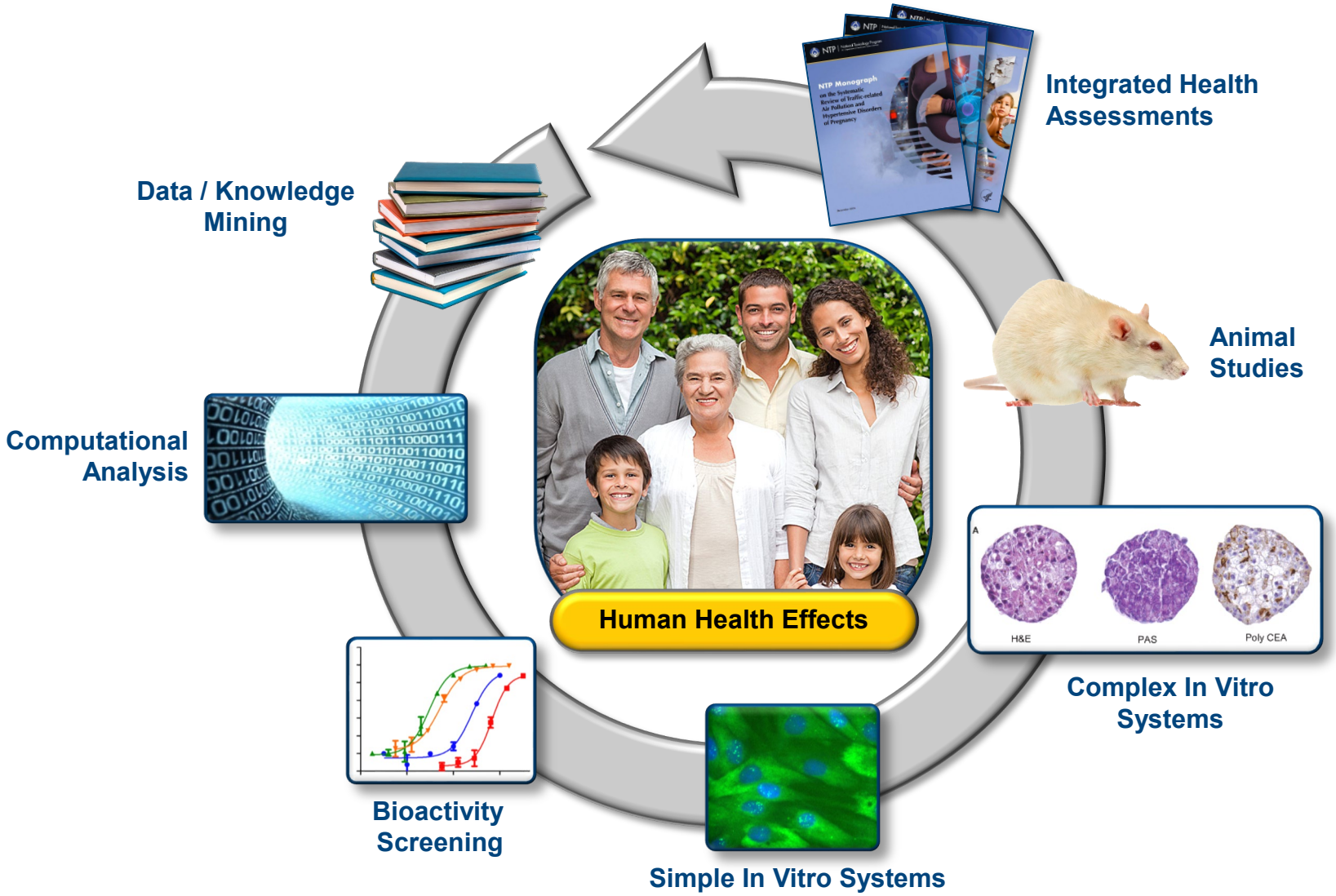
Objectives

- Leverage existing knowledge to define key 'failures modes' as a biological framework for modeling, link those modes to mediators of mechanistic bioactivity and screen existing databases to identify putative CV hazards.

- Develop a suite of assay/testing/modeling/knowledge management capabilities that aligns to the current Division of the National Toxicology Program (DNTP) Translational Toxicology Pipeline and apply it, in an integrated fashion, to provide an evidence-based approach to assessing CV bioactivity of environmental substances.

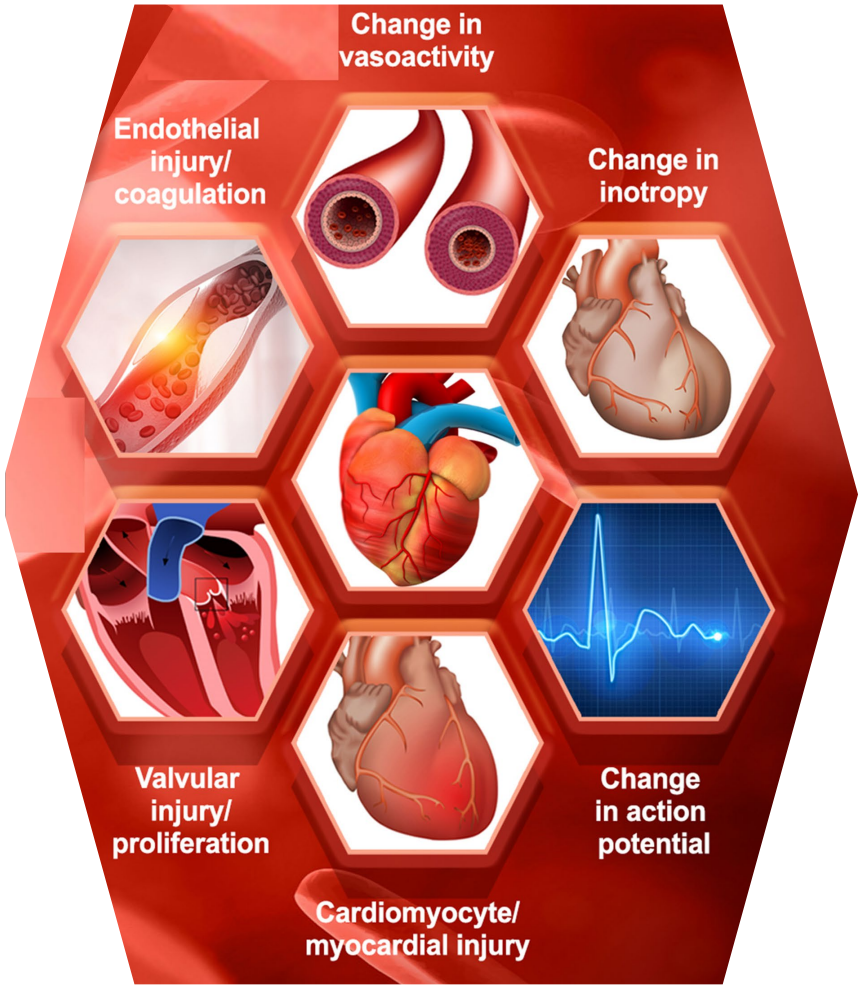
- Develop and implement an innovative capability for identifying potential environmental contributors to specific and contemporary clinical CV diseases.

Translational Toxicology Pipeline



Organizational framework – failure modes

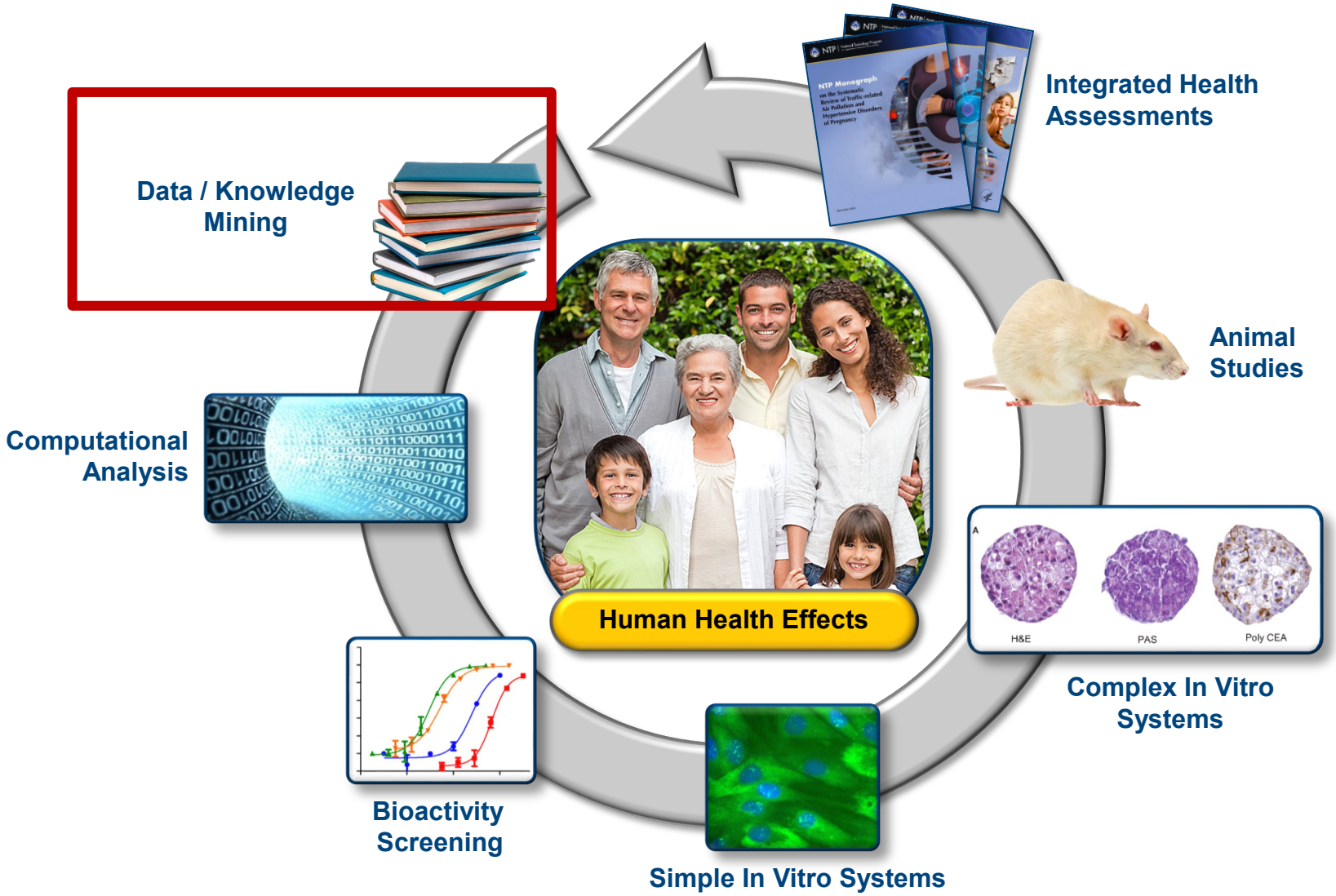
- **CV Failure Modes**: The finite number of primary responses to CV toxicity leading to adverse outcomes or disease *[HESI].*



Chem. Res. Toxicol. 2021, 34, 2, 566–583.

Leveraging existing data

Translational Toxicology Pipeline



Leveraging existing data

Systematic evidence mapping to characterize environmental contributors to CV toxicity

Human Outcomes
Hover over the table headings to select + or - to expand or collapse the table contents.

Health Outcome Category	
Subcellular/Molecular	15
Cellular/Tissue	10
Organ	108
Disease and Clinical Events	328
Grand Total	408

Human Outcomes
Hover over the table headings to select + or - to expand or collapse the table contents.

Health Outcome Category	Final proposed Outcome Category Term	
Subcellular/Molecular	IL-8	2
	Other	11
	Null	8
Cellular/Tissue	Other	7
	Null	3
Organ	Angina pectoris	1
	Aorta pulse weave velocity	1
	Blood pressure	6
	Carotid plaques	8
	Diastolic blood pressure	54
	Echocardiograms	4
	Gray scale median	2
	Heart rate	19
	Hypertension	2
	Intima-media thickness	4

Reference Search

To search, type into text box and press Enter. Click the small 'x' at the right side of the box to clear the search.

References

112227
409815
650308
731342
955768
959790
1283158
1460672
1519619
1519620
1521980

Filter by Race/Ethnicity

(All)

Asian	11
Black (Non-Hispanic)	60
Hispanic or Latina/o	25
Indigenous American /Alaska N..	5

Filter by Study Location

(All)

*Multiple locations	8
Australia	1
Austria	1
Belgium	3

Filter by Sex

(All)

Female only	53
Male only	168
Male and Female	216
Not Specified	21

Filter by Exposure

(All)

Mixture	1-hydroxynaphthalene	1
	1-hydroxyphenanthre..	1
	1-hydroxypyrene	1
	1,1,1-Trichloroethane	1

Filter by Co-morbidities

(All)

Autoimmune disease	1
Cancer	4
Cardiovascular disease	33
Diabetes	60

Filter by Timing of Exposure Measurement

(All)

Perinatal – puberty (gestation–..	35
Puberty/teen – young adult (13..	64
Adult (19–55 years old)	360
Aging adult (55+ years old)	302

Filter by Age Range

(All)

Perinatal – puberty (gestation–..	34
Puberty/teen – young adult (13..	68
Adult (19–55 years old)	375
Aging adult (55+ years old)	325

Filter by Study Design

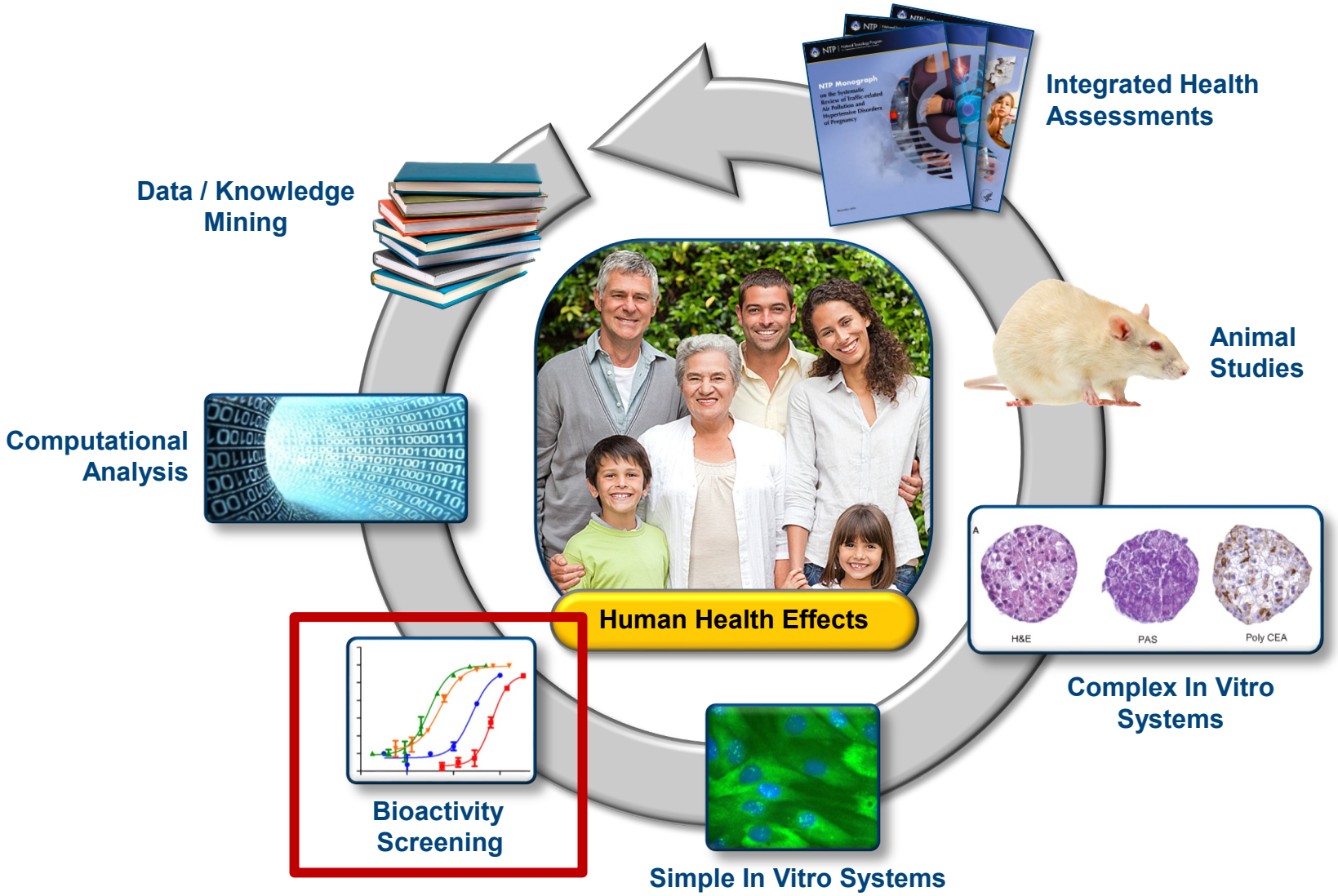
(All)

Case-control	18
Cohort	250
Controlled exposure study	3
Cross-sectional	120

Number of Studies

0 — 408

Translational Toxicology Pipeline



Mechanistic targets and CV system effects

Mechanistic Targets Compiled:

- Secondary pharmacological screening for predicting drug candidate toxicity.
- Cellular processes collected from literature
- NCATS BioPlanet database (https://tripod.nih.gov/bioplanet/#)
- Clinical biomarkers

GPCRs
Ion channels
Signal protein
Vascular tissue
Cellular events
Cofactors
Enzymes
Nuclear receptors
Transcription factors
Biomarkers
Transporters

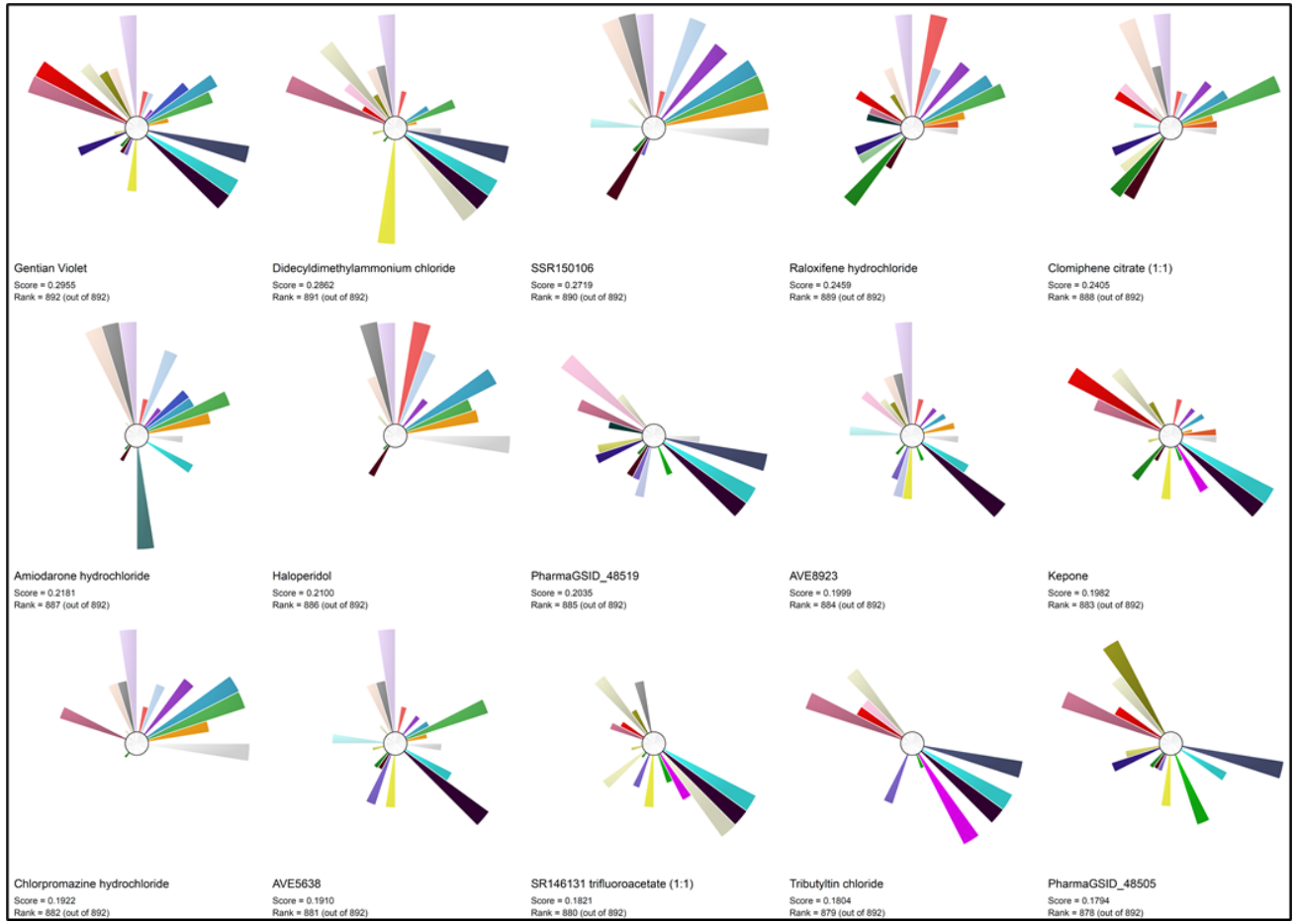
Slice	Target name		Effect	Reference	Slice Color
ADORA	Adenosine Receptor	GPCR	Vasodialation, alterations in BP	Bowes et al., 2012	
ADRB	Adrenergic Receptor	GPCR	Arrhythmia, Alterations in BP	Bowes et al., 2012	
CHRM	Muscarinic Acetylcholine Receptor	GPCR	Alterations in BP and HR, tachycardia	Bowes et al., 2012	
DRD	Dopamine Receptor	GPCR	Alterations in BP and HR, Vascular relaxation	Bowes et al., 2012	
EDNR	Endothelin Receptor	GPCR	Alterations in BP, Can exert adverse effects during	Bowes et al., 2012	
HTR	Serotonine Receptor	GPCR	Alterations in BP, Potential cardiac valvulopathy	Bowes et al., 2012	
AVPR	Vasopressin Receptor	GPCR	Alterations in BP and HR, Cardiac hypertrophy	Bowes et al., 2012	
HRH	Histamine Receptor	GPCR	Positive inotropy	Bowes et al., 2012	
OPR	Opioid Receptor	GPCR	Alterations in BP and Cardiac contritility	Bowes et al., 2013	
CHRNA	Cholinergic receptor	ion channel	Alterations in BP and HR	Bowes et al., 2012	
SCN1A	Voltage-gated Sodium Channel	ion channel	Slowed cardiac conduction; prolonged QRS interval	Bowes et al., 2012	
CACNA	Voltage-Gated Calcium Channel	ion channel	Alterations in BP, QT prolongation, Arrhythmia	Bowes et al., 2012	
KCNH2	Potassium Voltage Gated Channel	ion channel	QT prolongation	Bowes et al., 2012	
VEGF	Vascular Endothelial Growth Factor	signal protein	Alterations in BP , Cardiac Ischemia	Touyz & Herrmann, 2018	
VascularTissue	Vascular Tissue	vascular tissue	Myocardial ischemia, cardiac Arrhythmias		
OxidativeStress	Oxidative Stress	cellular events	Cellular Hypertrophy; Cardiac Cell Death	Takimoto & Kass, 2007	
MtDysfunction	Mitochondrial Dysfunction	cellular events	Cardiac dysfunction; Cardiomyopathy	Marin-Garcia, 2003	
TissueFactor	Tissue Factor	cofactors	Alterations in BP and ventricular hypertrophy, Atherosclerosis	Bode & Mackman, 2015	
PDE	Phosphodiesterase	enzymes	Alterations in cardiac contractility, HR and BP	Bowes et al., 2012	
MAO	Monoamine Oxidase	enzymes	Alterations in BP	Bowes et al., 2012	
JNK	c-Jun N-terminal kinase	enzymes	Vascular injury, cardiac hypertrophy	Muslin, 2008	
TyrKinase	Tyrosine Kinase	enzymes	Alterations in BP, LV dysfunction, conduction abnormalities, QT prolongation	Lamore, Kohnken, Peters, & Kolaja, 2020	
AroPro	Aromatase Protein	enzymes	Ischemic heart disease	Khosrow-Khavar et al., 2017	
ACHE	Acetylcholinesterase	enzymes	Alterations in BP and HR	Bowes et al., 2012	
COX	Cyclooxygenase	enzymes	Myocardial infarction; Alteration in BP; Ischaemic stroke; Atherothrombosis	Bowes et al., 2012	
ERAlpha	Estrogen receptor Alpha	nuclear receptor	Abnormal cardiac contractility, cardiac hypertrophy	Pugach, Blenck, Dragavon, Langer, & Leinwand, 2016	
NR3C1	Glucocorticoid receptor	nuclear receptor	Alterations in BP; Arrhythmia	Bowes et al., 2012	
PPARG	Peroxisome Proliferator Activated Receptor γ	nuclear receptor	Cardiac hypertrophy , Atherosclerosis	Das & Chakrabarti, 2006	
AHR	Aryl Hydrocarbon Receptor	transcription factors	Vascular Inflammation , Atherosclerosis	Wu et al., 2011	
AP-1	Activating Protein-1	transcription factors	Atherosclerosis	Meijer et al., 2012	
HIF	Hypoxia Inducible Factor 1	transcription factors	Ischaemia disease	Semenza, 2014	
NFKB	NF Kappa B	transcription factors	Atherosclerosis	Fiordelisi et al, 2019	
TP53	Tumor Protein p53	transcription factors	Alteration in cardiac function	Mercer & Bennett, 2006	
ICAM1	Intercellular adhesion molecule 1	biomarkers	Markers of endothelial dysfunction	Boyd et al., 2008	
IL6	Interleukin 6	biomarkers	Markers of inflammation and oxidative stress	Chu et al., 2020	
t-PA	Tissue Type plasminogen activator	biomarkers	Markers of atherosclerosis and endothelial dysfunction	Mason, 2017	
PAI -1	Plasminogen activator inhibitor	biomarkers	Markers of atherosclerosis and endothelial dysfunction	Mason, 2017	
NPA	Natriuretic peptide A	biomarkers	Release in response to elevation in LV filling pressure and	Mason, 2017	
SAA1	Serum amyloid A1	biomarkers	Direct promotion of vascular dysfunction through SAA within vascular tissues	Berg, Polokoff, O'Mahony, Nguyen, & Li, 2015	
SLC6A	Serotonin transporter	transporters	Pulmonary Hypertension,Cardiac Arrhythmiasand Cardiac V	Bowes et al., 2012	

Chem. Res. Toxicol. 2021, 34, 2, 566–583.

Mechanistic targets and CV system effects

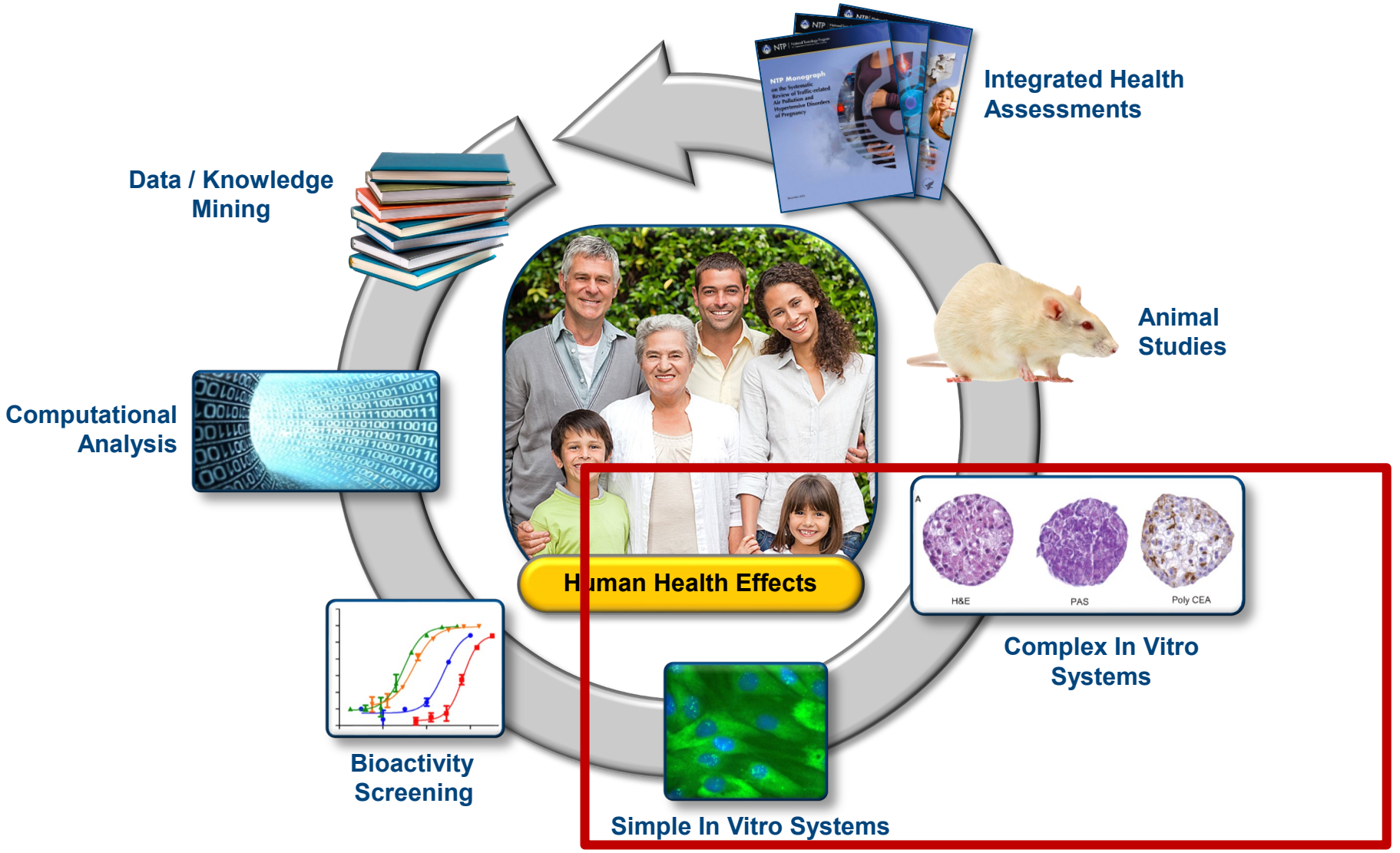
- The CardioToxPi profiles of the fifteen highest ranked ToxCast chemicals are shown in this figure.

- Examples include several QACs, organotins and other pesticides, and several drugs (some with known CV effects).

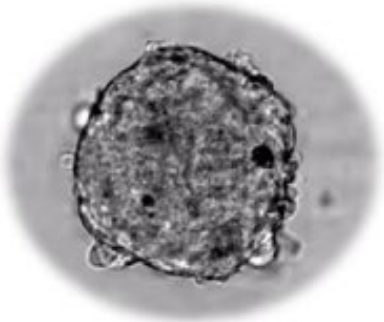


Chem. Res. Toxicol. 2021, 34, 2, 566–583

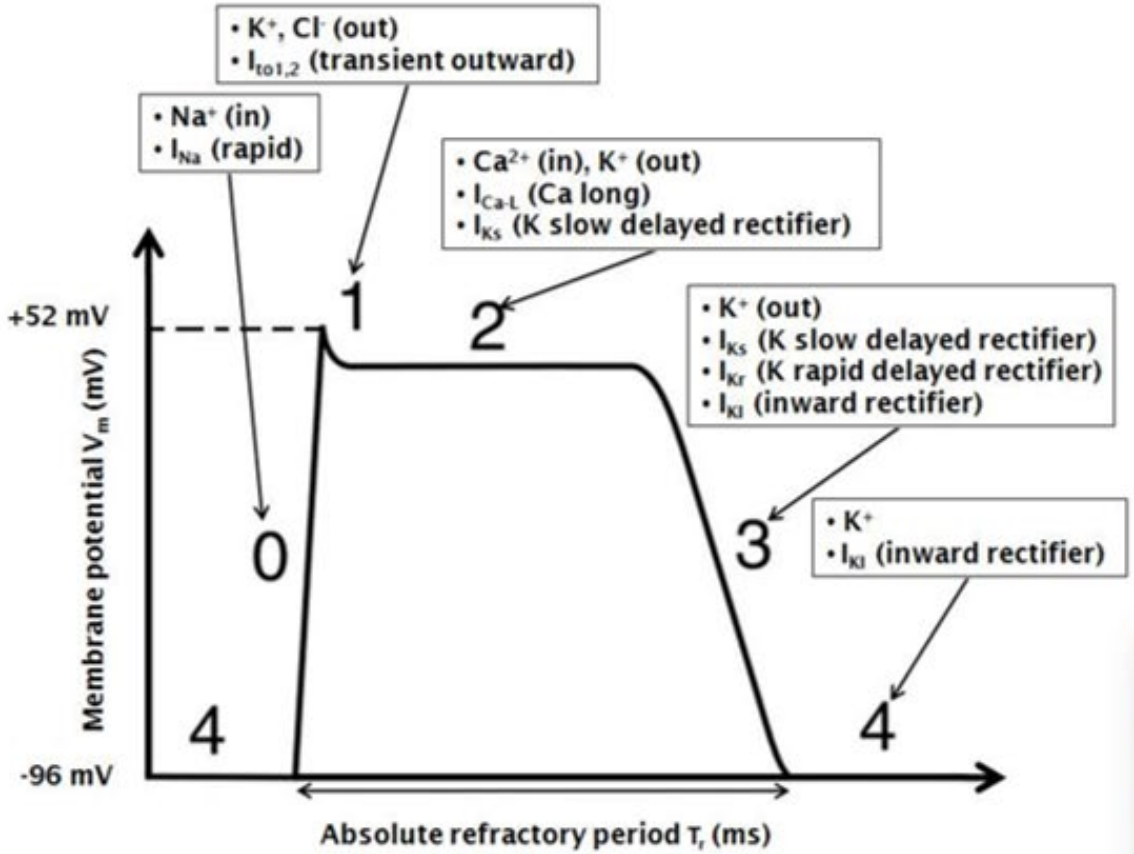
Translational Toxicology Pipeline



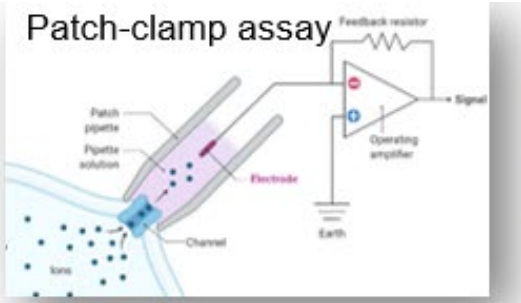
In vitro systems



Human iPSC derived cardiomyocyte spheroids

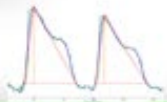


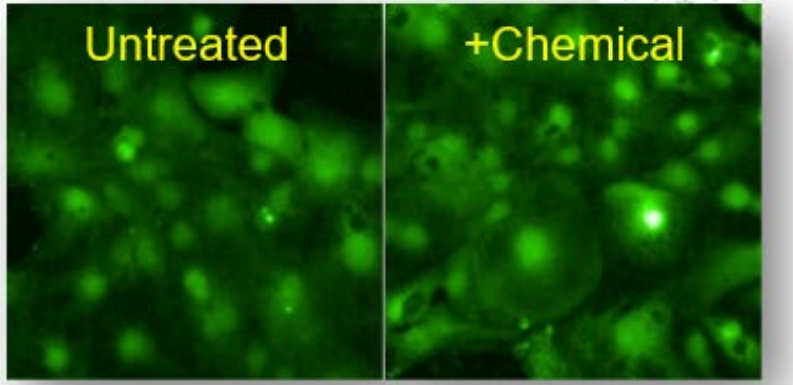
Patch-clamp assay



Multielectrode Array

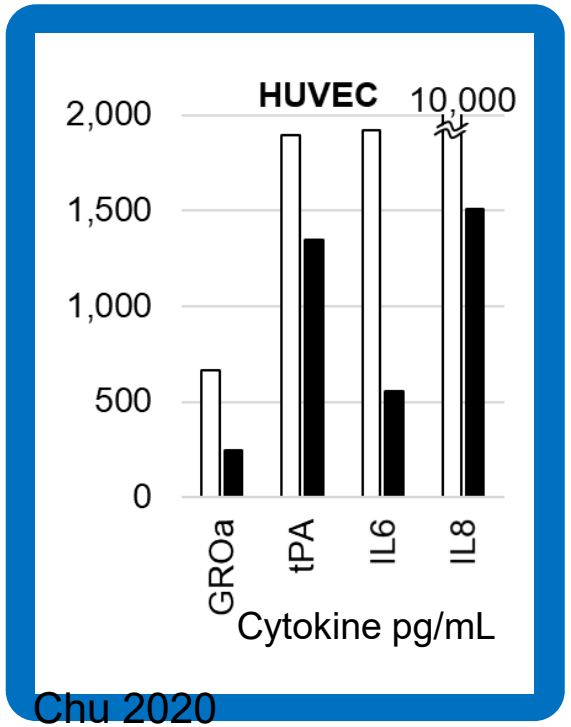
Calcium Transients



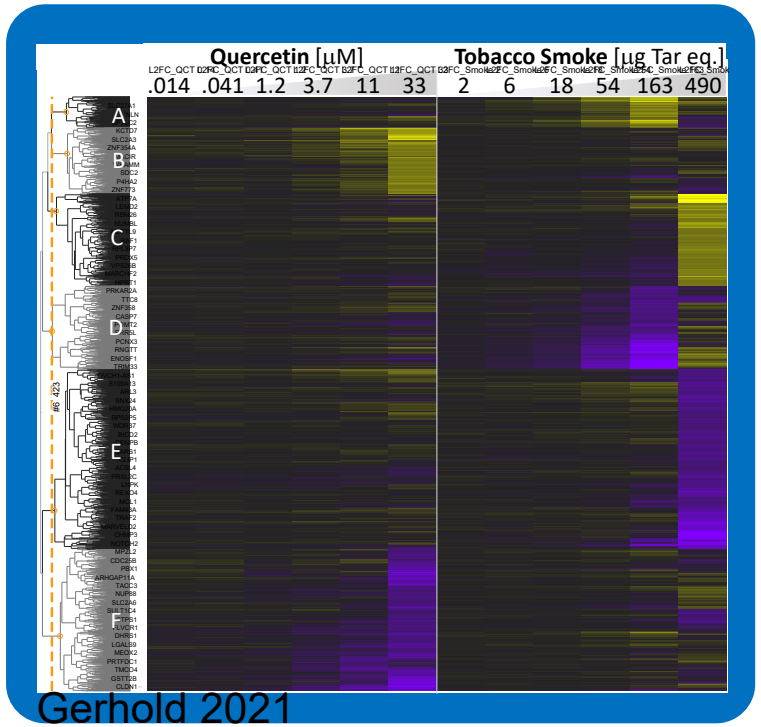


In vitro systems

- HUVEC endothelial cells
  - Cytotoxicity
  - Cytokine profiles
  - RNA sequencing
  - Vasoactivity
  - Coagulation

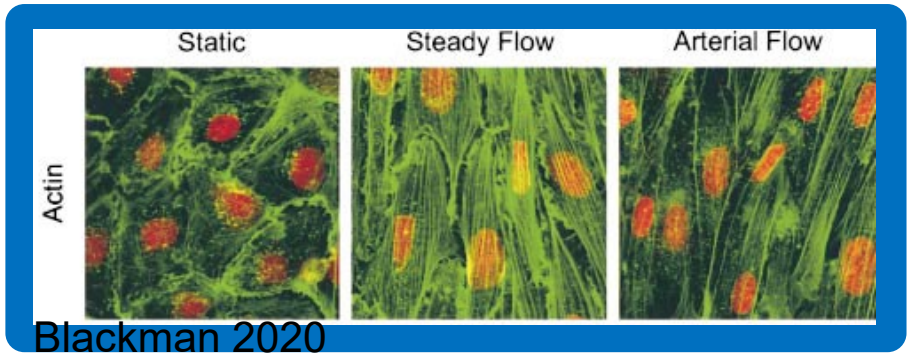


Chu 2020



Gerhold 2021

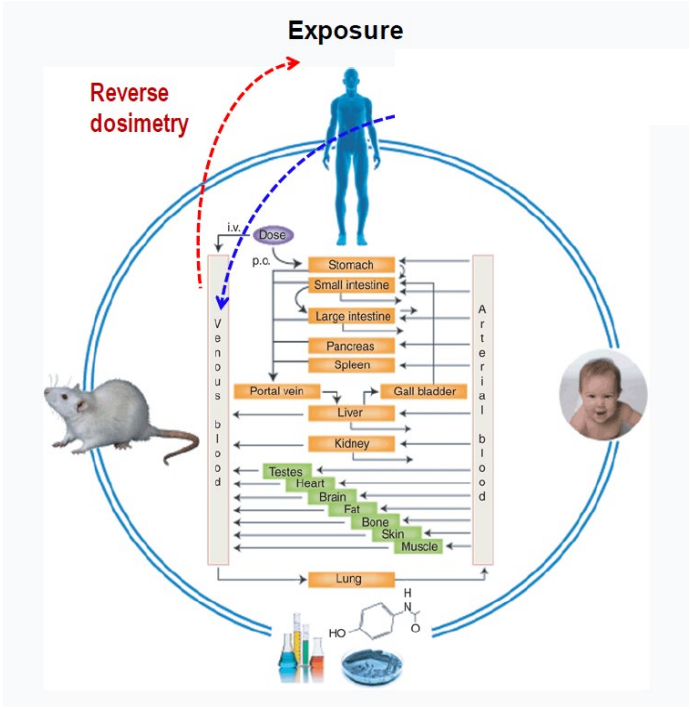
- Coculture and flow models, other endothelial beds

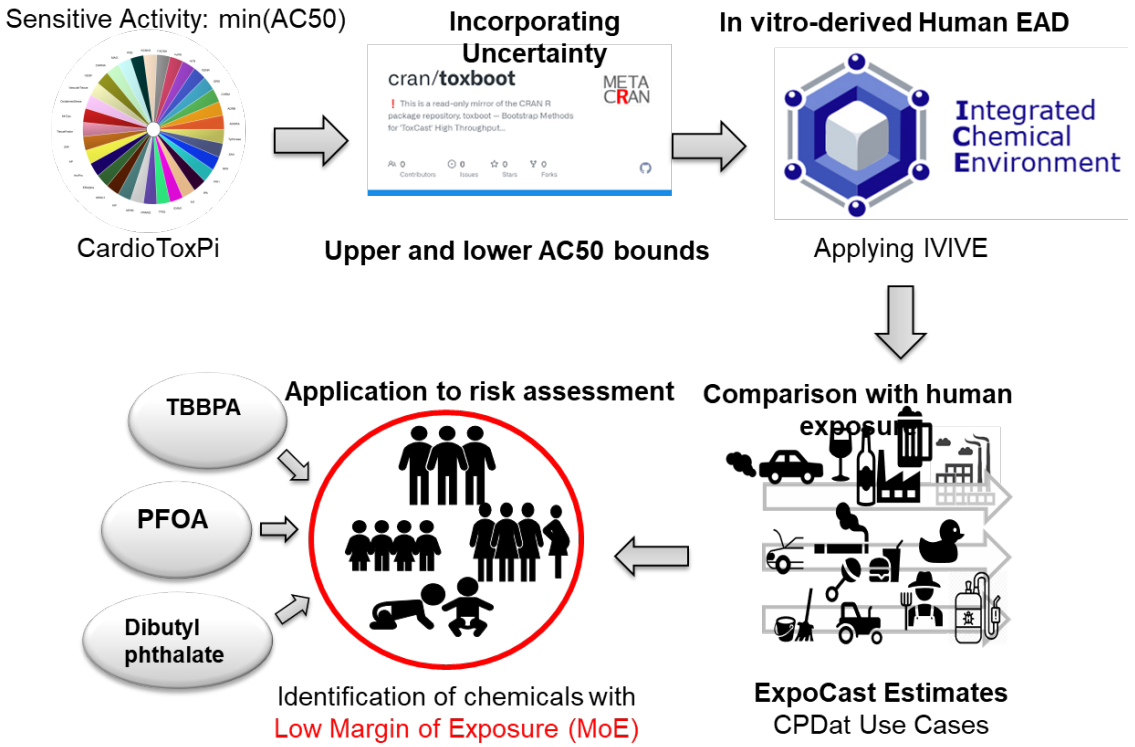


Blackman 2020

Contextualizing in vitro data

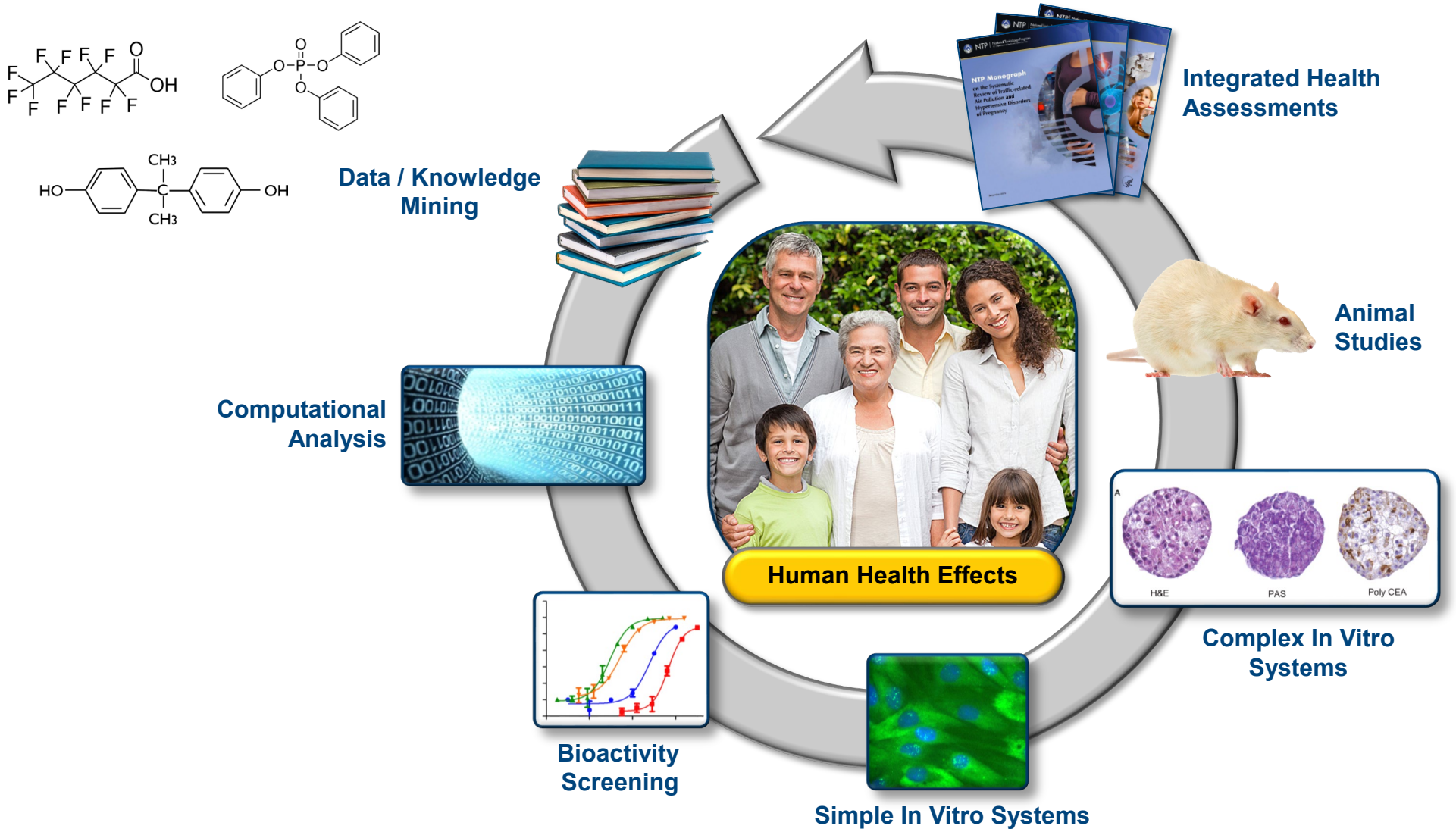
In vitro to in vivo extrapolation (IVIVE) uses physiologically based pharmacokinetic models to predict the in vivo equivalent administered doses (EADs) that would lead to internal concentrations at which in vitro bioactivity was observed.





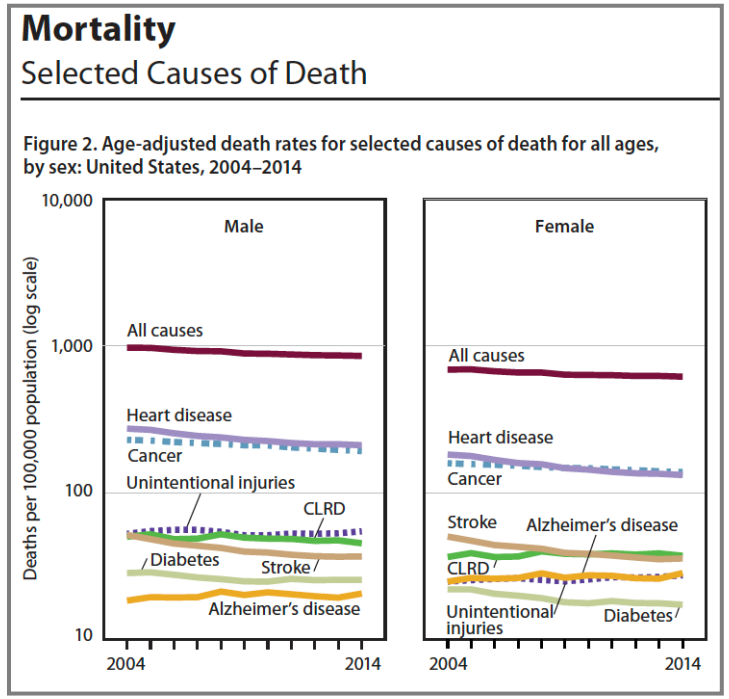
IVIVE was applied to identify the margins of exposure (MoE) based on the in vitro bioactivity profiles, mapped to the six CV failure modes, for previously identified chemical assay pairs.

Translational Toxicology Pipeline



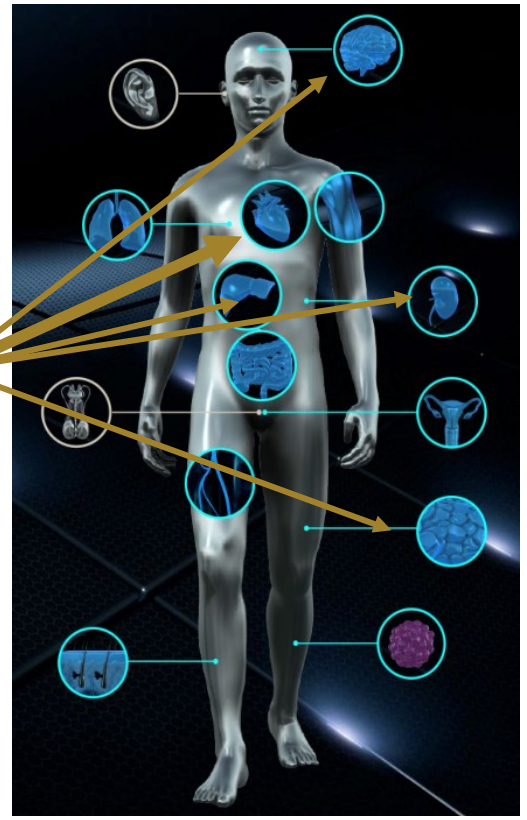
Developing approaches to understand CV diseases

Shifting from agent-based to disease-focused health effect assessments

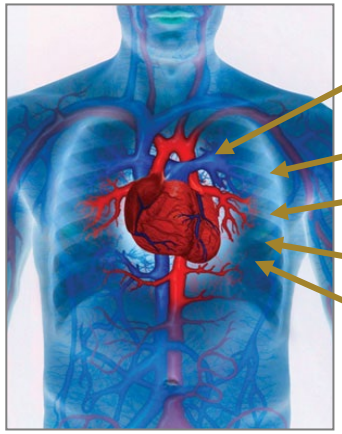


X lbs./yr. commercial production

Agent Y



Incidence of common diseases

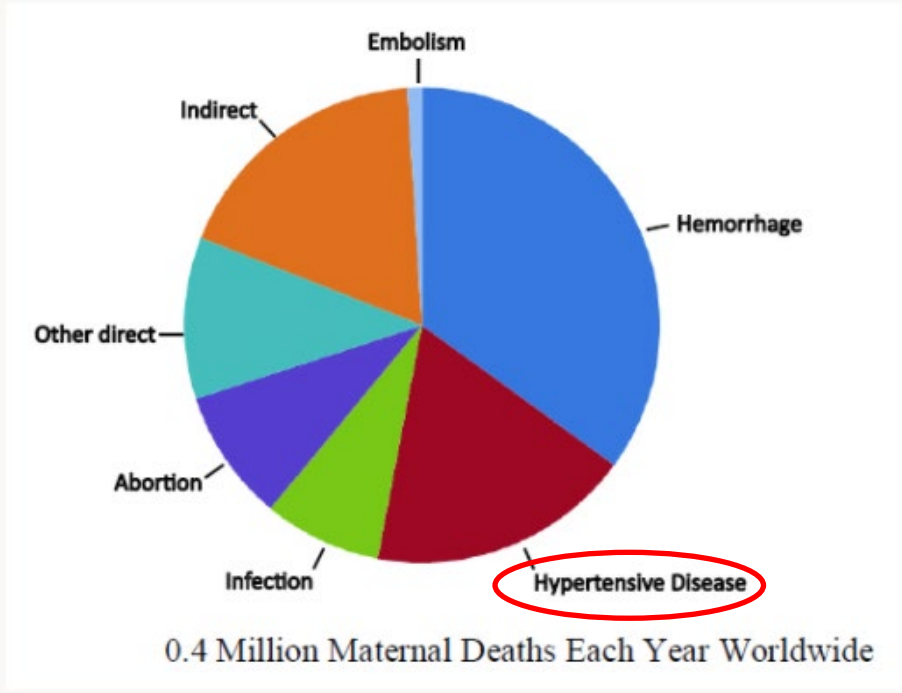


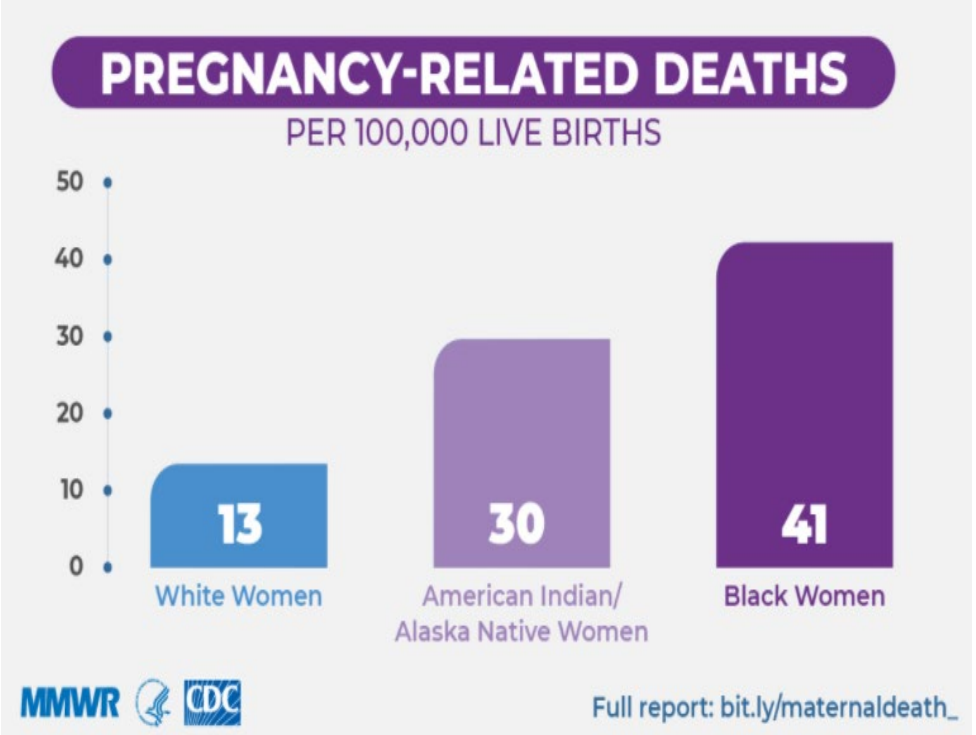
Agent A
Agent B
Agent C
Agent Y
Agent Z

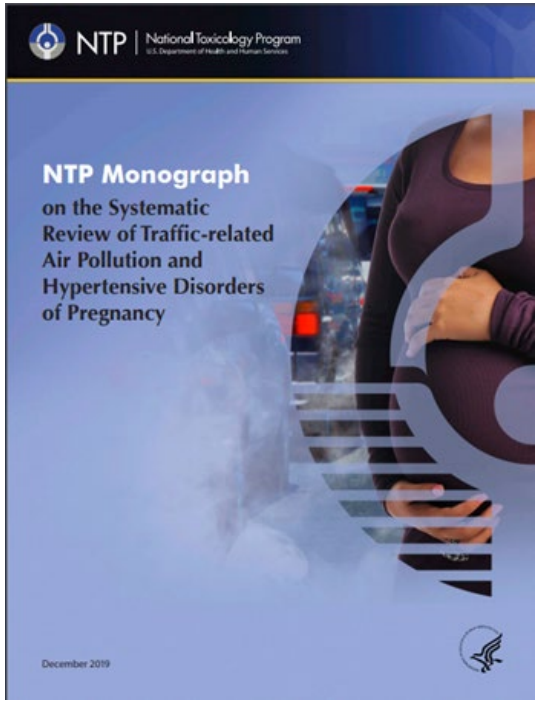
https://ncats.nih.gov/tissuechip/chip

Environmental contributors to hypertensive disorders of pregnancy

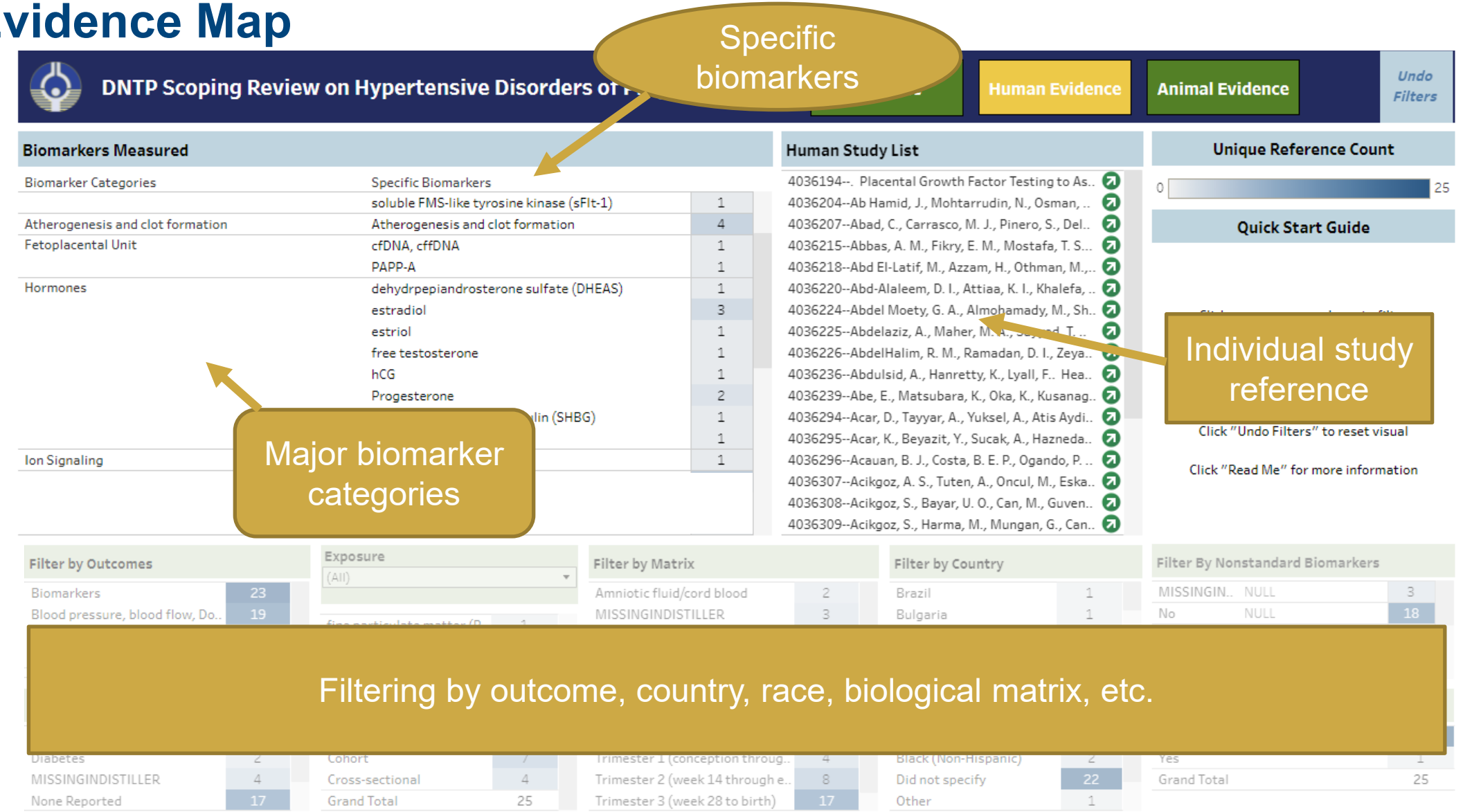
Causes of maternal deaths each year







Evidence Map



Thank You!