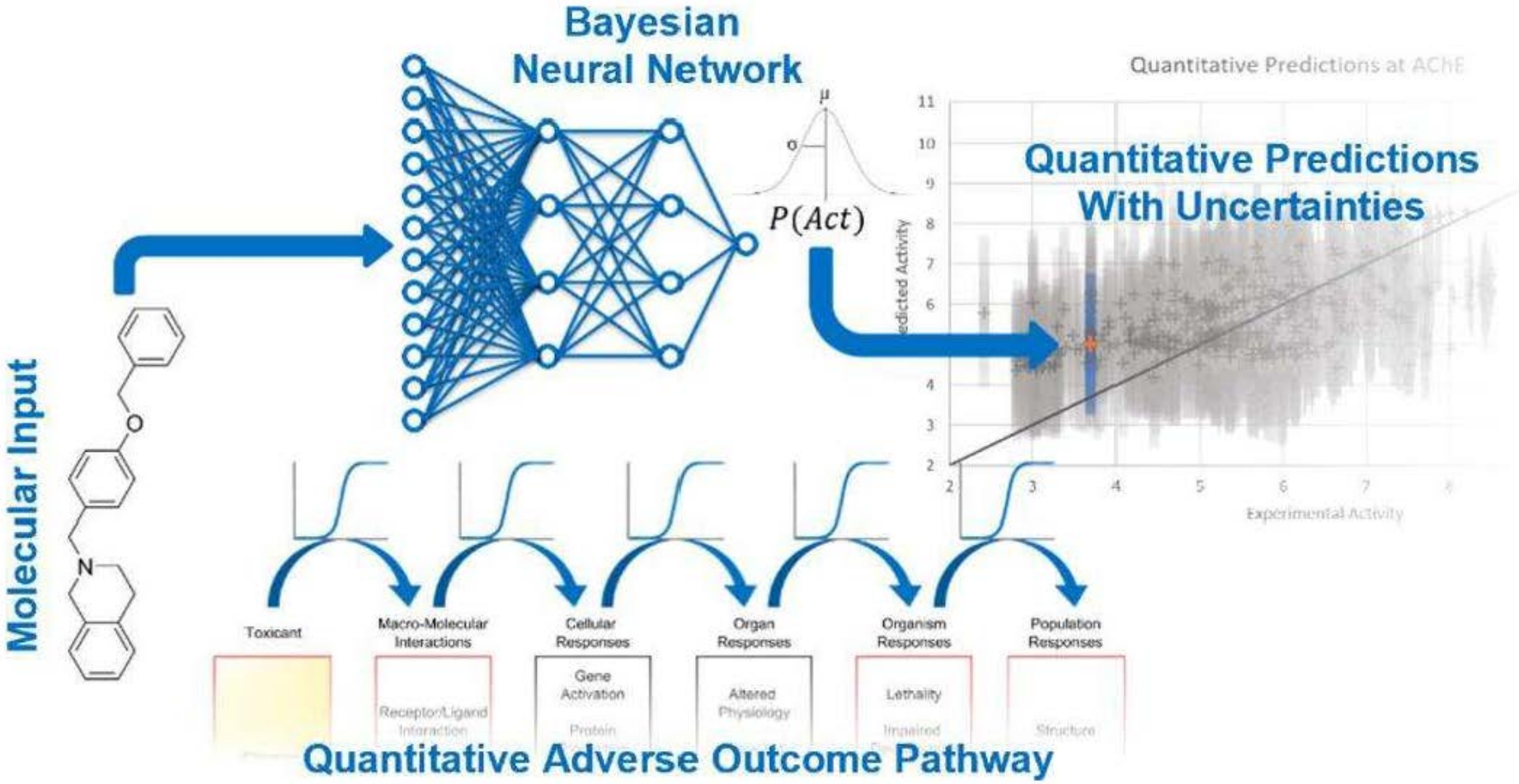
Defining and achieving critical goals for chemical assessment using new (and old?) methods

ICCVAM Annual Forum
May 2023

Amy D Kyle, PhD MPH (retired)
University of California
School of Public Health
<adkyle@berkeley.edu>

Key points

- Work of "NAMs" community is impressive, important, inspiring (3 I's)
- Need for confidence is key -- but goes beyond the "scientifics"
  - Communication -- major needs for even basic intelligibility
  - Common vocabulary and consistent metrics (NIST)
- Identify and engage full range of stakeholders:
  - Beyond agencies/researchers/industry "experts"
  - Affected communities, populations; policy relevant actors; judiciary
  - Reach acceptability for the full environmental health community
  - Address integrity
- Encompass needs of the future – don't remodel the past
  - Reality-based "mixtures," combinations of agents as part of the design
  - Earlier predictors of impact
  - Address human and non-human populations beyond the lab
  - How to move into regulatory processes largely built in the 1980s


Bayesian
Neural Network
μ
σ
P(Act)
Quantitative Predictions at AChE
Quantitative Predictions
With Uncertainties
Experimental Activity
Molecular Input
O
N
Toxicant
Macro-Molecular
Interactions
Cellular
Responses
Organ
Responses
Organism
Responses
Population
Responses
Gene
Activation
Altered
Physiology
Lethality
Quantitative Adverse Outcome Pathway

From UC Davis

Increasing Level of Community Involvement, Impact, Trust, and Communication Flow

Outreach	*Consult*	*Involve*	*Collaborate*	*Shared Leadership*
Some Community Involvement *Communication flows from one to the other, to inform* Provides community with information. Entities coexist. Outcomes: Optimally, establishes communication channels and channels for outreach.	*More Community Involvement* *Communication flows to the community and then back, answer seeking* Gets information or feedback from the community. Entities share information. Outcomes: Develops connections.	*Better Community Involvement* *Communication flows both ways, participatory form of communication* Involves more participation with community on issues. Entities cooperate with each other. Outcomes: Visibility of partnership established with increased cooperation.	*Community Involvement* *Communication flow is bidirectional* Forms partnerships with community on each aspect of project from development to solution. Entities form bidirectional communication channels. Outcomes: Partnership building, trust building.	*Strong Bidirectional Relationship* Final decision making is at community level. Entities have formed strong partnership structures. Outcomes: Broader health outcomes affecting broader community. Strong bidirectional trust built.

Reference: Modified by the authors from the International Association for Public Participation.

MAKING INTENTIONAL CONNECTIONS AMONG PARTNERS, PURPOSE, ACTIVITY, AND APPROACH

WHO?	WHY?	WHAT?	HOW?
Who are the **partners** and what are their expectations for participation?	What is the **purpose** of the partner's participation?	What **activity** are the partners participating in?	What **approach** fosters the appropriate level of partner participation?

ALERT INFORM INVOLVE COLLABORATE CO-CREATE

OUTREACH « *Continuum of partner participation* » **ENGAGEMENT**

OUTREACH	CONSULT	INVOLVE	COLLABORATE	EMPOWER
One-way provision of information	Information and feedback	Two-way information flow	Partnership and trust-building	Shared leadership
"We will keep you informed."	"We will acknowledge your concerns, and provide feedback on how public input influenced the	"We will ensure that your concerns and aspirations are directly reflected in the alternatives developed."	"We will ask you to be a key, active, and present player to help us build the right solutions."	"We will implement what you decide."

A Strategic Framework for Community Engagement in Oceans and Human Health. MA Carson, DM Doberneck, et al. 2022 https://doi.org/10.1029/2022CSJ000001

Policy, Science Converge - real life conditions

President Biden and Vice President Harris campaigned on confronting longstanding environmental injustices and inequities, and they have delivered with actions that make a positive difference in people's lives.

Since coming into office, they have worked tirelessly to ensure that, the voices, perspectives, and lived experiences of environmental justice communities are heard in the White House and **reflected in the priorities, policies, investments, and decision-making of the Federal Government.**

- White House Environmental Justice Advisory Committee
- New tools to identify areas of impact
- New priorities for funding in areas of disproportionate impact
- Policy work toward cumulative risks and impacts

PUBLIC COMMENT DRAFT – DO NOT CITE OR QUOTE

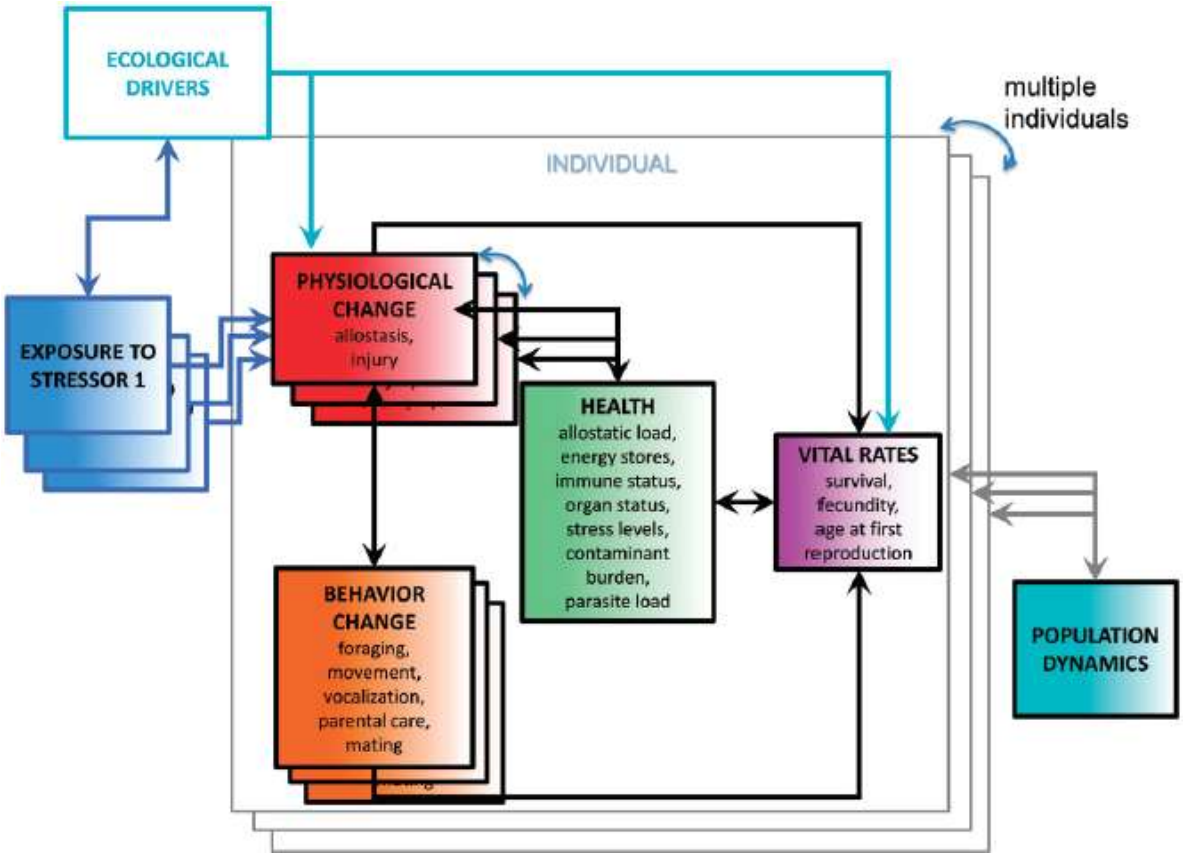
EPA Document# EPA-740-P-23-001
February 2023
Office of Chemical Safety and
Pollution Prevention

United States
Environmental Protection Agency

Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act

1 INTRODUCTION

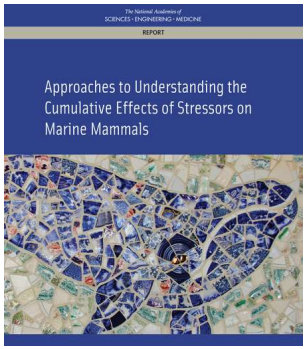
The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the Toxic Substances Control Act (TSCA), the Nation's primary chemicals management law, in June 2016. Through the amended statute, the U.S. Environmental Protection Agency (EPA or the Agency) is required, under TSCA section 6(b), to conduct risk evaluations to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to potentially exposed or susceptible subpopulation(s) (PESS) identified by EPA as relevant to the risk evaluation, under the conditions of use (COU). TSCA section 6(b)(4)(A) requires EPA to consider PESS, which are subpopulations "who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly" [15 U.S.C. § 2602(12)]. Several reports from the National Research Council (NRC)—including the 1994 report *Science and Judgment in Risk Assessment*, the 2008 report *Phthalates and Cumulative Risk Assessment: The Tasks Ahead*, and the 2009 report *Science and Decisions: Advancing Risk Assessment*—have highlighted the importance of understanding the combined risk from multiple environmental stressors (NRC, 2009, 2008, 1994). These reports, as well as legislation such as the Food Quality Protection Act of 1996 (FQPA), have driven, in part, EPA's evolving work on cumulative risk assessment (CRA).



Building on a model of multiple effects on individual animals, this diagram incorporates population effects

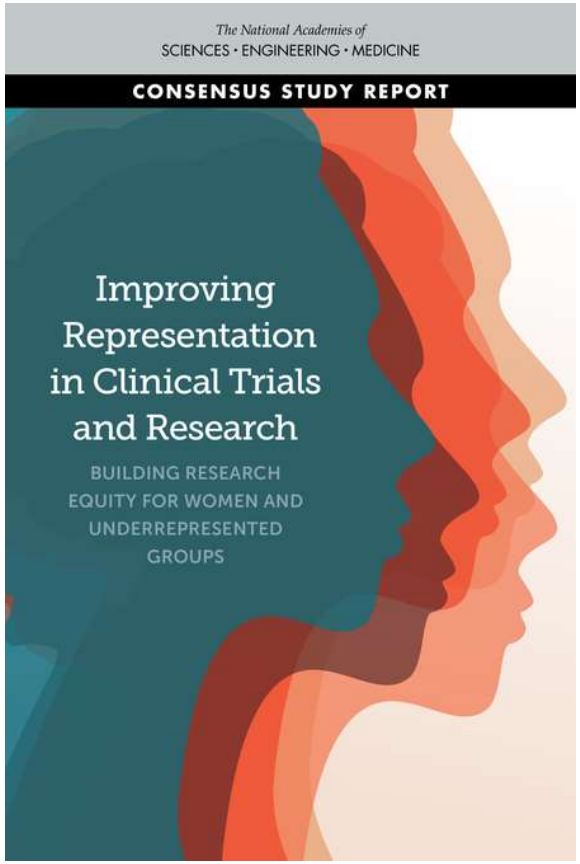
Cumulative impacts of multiple stressors (including chemicals) for marine mammal populations

. . . examination of common adverse outcome pathways underscores the importance of **understanding and detecting changes at lower levels of biological organization, such as at the cellular or organ response level, before they exert potentially irreversible effects at individual or population levels**. However, it is also imperative to collect information to understand the linkages and processes by which such lower-level responses eventually translate into individual or population-level impacts.



NASEM. 2017. Approaches to Understanding the Cumulative Effects of Stressors on Marine Mammals. https://doi.org/10.17226/23479.

Focus and process can change for better



Ongoing redesign of clinical research protocols to represent the population including women and people of color

The United States has long made substantial investments in clinical research with the goal of improving the health and well-being of our nation. There is no doubt that these investments have contributed significantly to treating and preventing disease and extending human life. Nevertheless, clinical research faces a critical shortcoming. Currently, large swaths of the U.S. population, and those that often face the greatest health challenges, are less able to benefit from these discoveries because they are not adequately represented in clinical research studies. While progress has been made with representation of white women in clinical trials and clinical research, there has been little progress in the last three decades to increase participation of racial and ethnic minority population groups. This underrepresentation is compounding health disparities, with serious consequences for underrepresented groups and for the nation.

NASEM. 2022.

Thank you