NTP
National Toxicology Program

NTP Research Problem Formulation

Scott Masten, Ph.D.
Office of Nomination and Selection
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 15 – 16, 2016

Outline

- Inputs
- Formulating questions
- Project development
- Introduction to new projects
  - Thallium compounds
  - Synthetic turf and crumb rubber
  - Glyphosate
- Environmental exposures and viral infection-related health outcomes

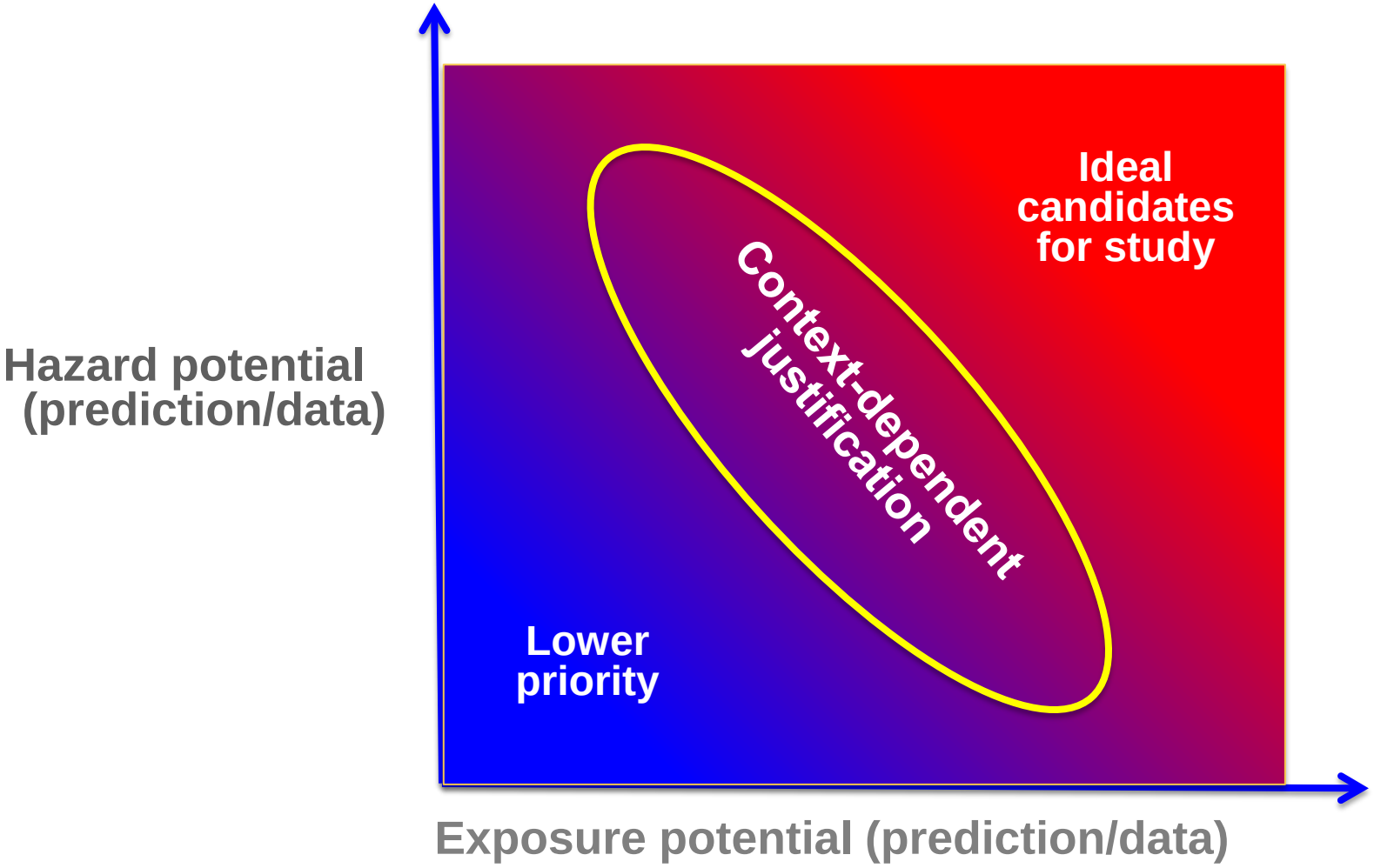
Nominations to NTP for research and testing

- Many different sources
  - Open and transparent
  - Anyone can nominate a substance or issue for study at any time
- Widely varying level of specificity
  - Well defined substance-specific data needs
  - Broad ‘exposure’ topics
  - Vague health concerns
- Projects designed to be responsive to formally identified research needs or recommendations

What Does the NTP Study?

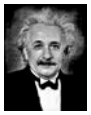
- Individual or classes of chemical, biological, or physical substances nominated due to:
  - Elevated public health concern based on the extent of human exposure and/or suspicion of toxicity
  - Substantial knowledge gaps regarding human health outcomes of interest
- Thematic research aimed at:
  - Improving predictive ability of current tools
  - Addressing mechanisms and pathways of toxicity
  - Informing risk assessment approaches

Exposure and hazard considerations



Formulating Research Questions

“The mere formulation of a problem is far more essential than its solution, which may be merely a matter of mathematical or experimental skill. To raise new questions, new possibilities, to regard old problems from a new angle requires creative imagination and marks real advances in science.”

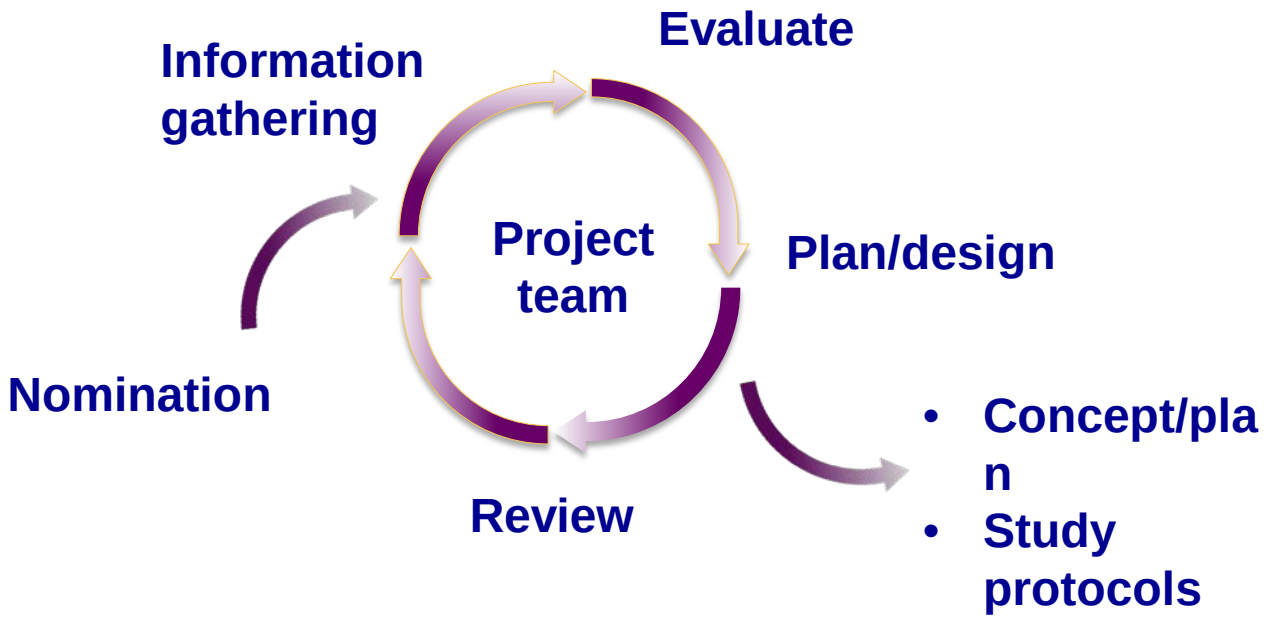


Einstein and Infeld, *Evolution of Physics* (1938)

Problem Formulation

Iterative and interactive

- Scoping activities
  - Literature review and analysis
  - Formation of cross-disciplinary teams
  - Internal review forums
  - Engage agency partners



NTP Research Project Development

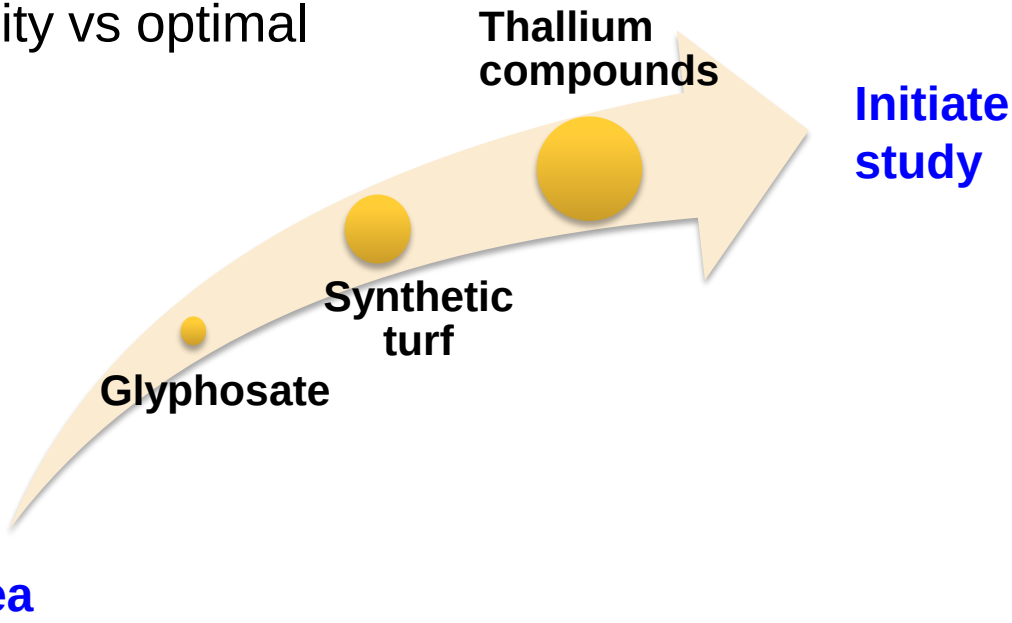
Strategy and Approach

- Each project is different
  - Primary end user(s)
  - Fit within NTP research portfolio
  - Leverage other ongoing efforts
- Use best tools available to address outstanding questions
  - Assemble a workable testing strategy
  - Maintain flexibility for periodic adjustments
- Tailor outputs to match anticipated users and decision-making timeframe

NTP Research Project Development

Life cycle considerations

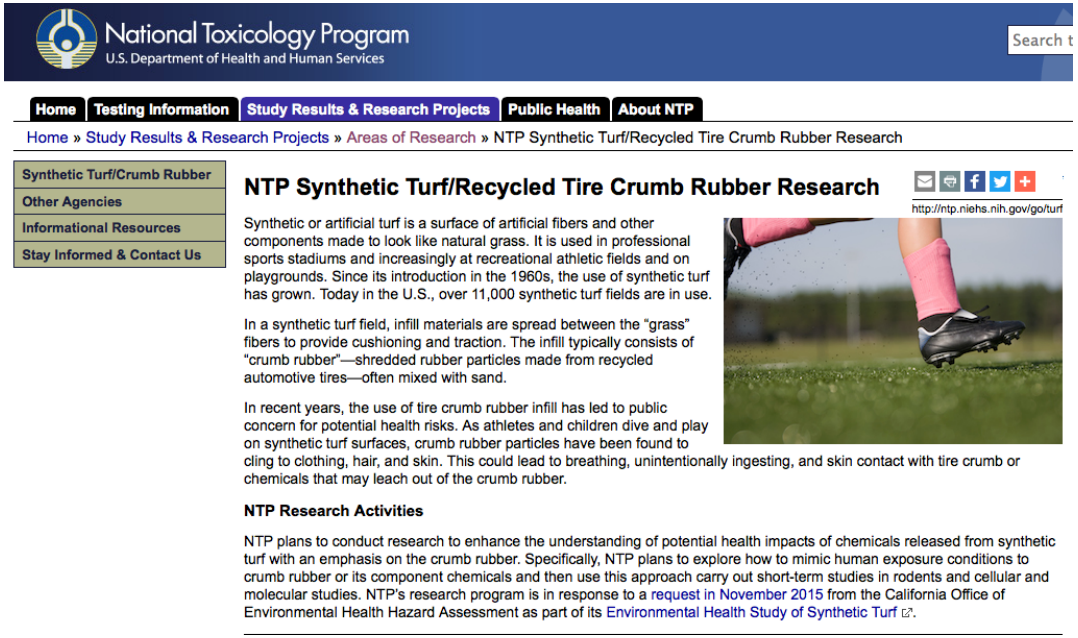
- How refined is the topic/need when it comes to us
- Anticipated effort required to formulate questions and develop viable approaches
- Value of input at different stages
  - Timing trade-off, opportunity vs optimal



Stakeholder Engagement

Opportunities throughout project development

- Consult with agency partners
- Public input
  - Published requests for information
  - Public meetings
- Planning and review documents available through NTP web site
  - BSC meeting pages
  - Topic-specific pages



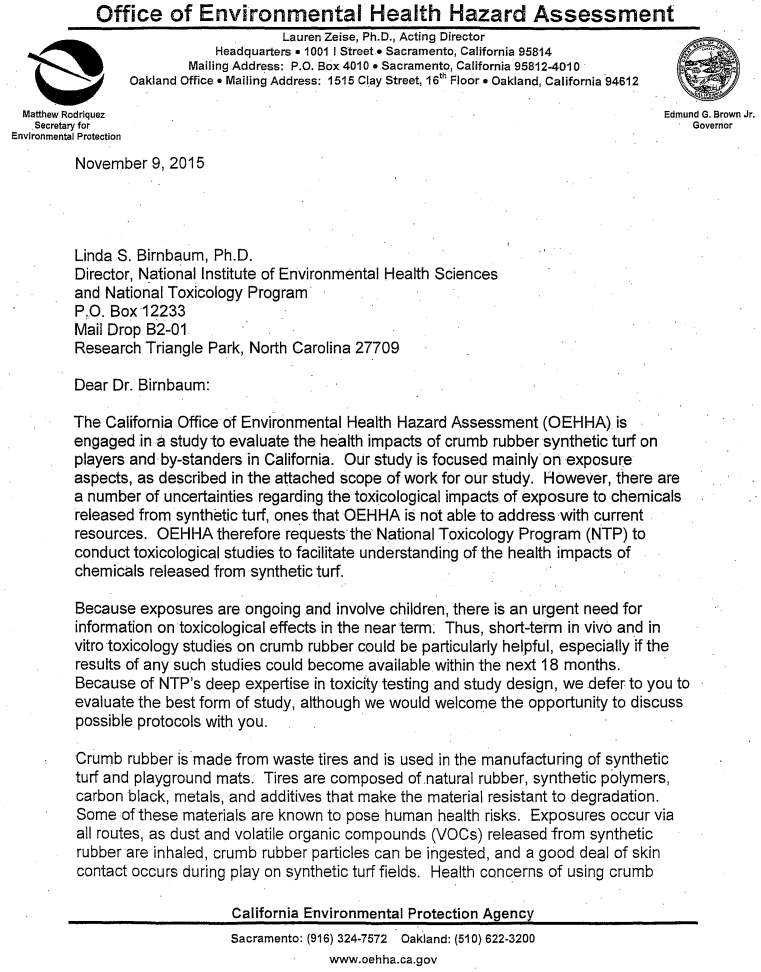
Thallium Compounds

Request and needs

- Specific data needs identified by EPA program office
  - Provide data to support development of risk values used in regulatory setting
- Known toxic compound with only a handful of toxicology studies, each with one or more limitations
- Guidance values exceeded in several exposure scenarios
- Scoping focused on recent literature and environmental occurrence
  - Little research activity on this topic
  - Lacking information to understand species and lifestage sensitivity, critical endpoints, thallium species in various media

Inputs and research questions

- Media and public inquiries as far back as 2008
- Recent nominations from private citizens and OEHHA
- Inherently variable material composition
- Very limited information available to evaluate potential exposure pathways and health effects
- Questions are many and open-ended



Office of Environmental Health Hazard Assessment

Lauren Zeise, Ph.D., Acting Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Matthew Rodriquez
Secretary for
Environmental Protection

Edmund G. Brown Jr.
Governor

November 9, 2015

Linda S. Birnbaum, Ph.D.
Director, National Institute of Environmental Health Sciences
and National Toxicology Program
P.O. Box 12233
Mail Drop B2-01
Research Triangle Park, North Carolina 27709

Dear Dr. Birnbaum:

The California Office of Environmental Health Hazard Assessment (OEHHA) is engaged in a study to evaluate the health impacts of crumb rubber synthetic turf on players and by-standers in California. Our study is focused mainly on exposure aspects, as described in the attached scope of work for our study. However, there are a number of uncertainties regarding the toxicological impacts of exposure to chemicals released from synthetic turf, ones that OEHHA is not able to address with current resources. OEHHA therefore requests the National Toxicology Program (NTP) to conduct toxicological studies to facilitate understanding of the health impacts of chemicals released from synthetic turf.

Because exposures are ongoing and involve children, there is an urgent need for information on toxicological effects in the near term. Thus, short-term in vivo and in vitro toxicology studies on crumb rubber could be particularly helpful, especially if the results of any such studies could become available within the next 18 months. Because of NTP's deep expertise in toxicity testing and study design, we defer to you to evaluate the best form of study, although we would welcome the opportunity to discuss possible protocols with you.

Crumb rubber is made from waste tires and is used in the manufacturing of synthetic turf and playground mats. Tires are composed of natural rubber, synthetic polymers, carbon black, metals, and additives that make the material resistant to degradation. Some of these materials are known to pose human health risks. Exposures occur via all routes, as dust and volatile organic compounds (VOCs) released from synthetic rubber are inhaled, crumb rubber particles can be ingested, and a good deal of skin contact occurs during play on synthetic turf fields. Health concerns of using crumb

California Environmental Protection Agency

Sacramento: (916) 324-7572 Oakland: (510) 622-3200
www.oehha.ca.gov

Glyphosate

Inputs

- Published commentary
- Discussions with agency partners
  - EPA
  - WHO
- Research needs identified in authoritative assessments
  - ANSES
  - EFSA
  - JMPR
- Additional rodent cancer studies not needed

GMOs, Herbicides, and Public Health

Philip J. Landrigan, M.D., and Charles Benbrook, Ph.D.

"the National Toxicology Program should urgently assess the toxicology of pure glyphosate, formulated glyphosate, and mixtures of glyphosate and other herbicides." *Landrigan and Benbrook Perspective in N Engl J Med Aug 20, 2015*


REVIEW Open Access

Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement

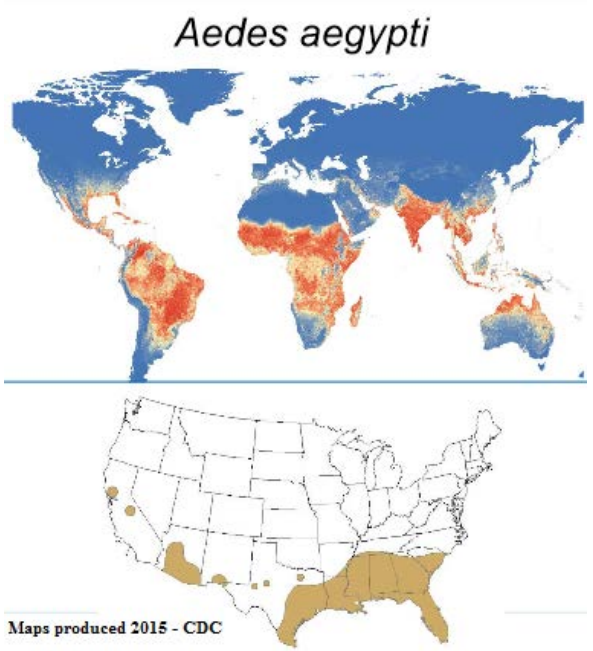
John Peterson Myers[1,13*], Michael N. Antoniou[2], Bruce Blumberg[3], Lynn Carroll[4], Theo Colborn[4], Lorne G. Everett[5], Michael Hansen[6], Philip J. Landrigan[7], Bruce P. Lanphear[8], Robin Mesnage[2], Laura N. Vandenberg[9], Frederick S. vom Saal[10], Wade V. Welshons[11] and Charles M. Benbrook[12*]

"..common commercial formulations of GBHs [glyphosate-based herbicides] should be prioritized for inclusion in government-led toxicology testing programs such as the U.S. National Toxicology Program…" *Myers et al. Environmental Health (2016) 15:19*

Environmental and Viral Exposures

Vector-borne diseases are a global public health problem

- Responsible for >17% of all infectious diseases and >1 million deaths annually
  - >2.5 billion people in 100+ countries at risk of contracting dengue
- Vectors include mosquitoes, ticks, sandflies, fleas
- Significant challenges in vector control, health surveillance and treatment
- Common vector and/or similar virus
  - *Aedes egypti:* Zika, dengue, chikungunya, yellow fever
  - Flavivirus: Zika, dengue, West Nile, various encephalitis viruses, yellow fever



Environmental and Viral Exposures

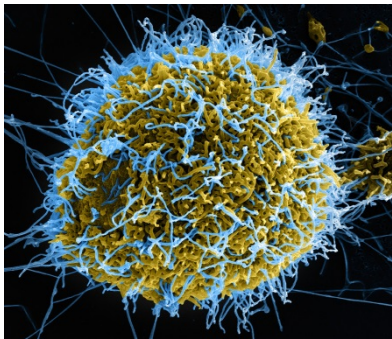
Basis for current interest

- Long-standing NTP focus on
  - Immunotoxic and developmental effects of environmental agents
  - Combined environmental exposures
- Public concern for
  - Safety of vector control programs
  - Delayed and/or subtle health outcomes
- Environmental chemical exposures can
  - Interact with viral infection to affect the same health outcome
  - Alter immune function and disease resistance
- Large prospective studies to study Zika infection and adverse pregnancy outcomes

Environmental and Viral Exposures

Primary research question and approach

- What environmental exposures might increase susceptibility to adverse health outcomes due to mosquito-borne viral infection?
  - Identify common environmental exposures of concern in areas where there re is significant exposure to *Aedes egyptii* or flaviviruses
  - Review literature for plausible relationships between stressor exposure, (neuro)developmental toxicity, and/or immunomodulation
  - Conduct studies in experimental animal models to address knowledge gaps and characterize potential to alter host resistance to [surrogate] viral infection



New NTP Research Projects

Today's session

- Presentations by project leaders
  - Thallium compounds- Dr. Kelly Shipkowski
  - Synthetic turf and crumb rubber - Dr. Abee Boyles
  - Glyphosate - Dr. Stephanie Smith-Roe
- Clarifying questions
- Public comments
- Comments from assigned Board discussants
- Board discussion

BSC input requested

- Relevance of the research activity considering the NTP mission and goals
- Appropriateness of steps outlined to formulate the research problem and for gathering input
- Other comments on rationale, scope, significance

Questions or comments?