EPA's New Approach To Cumulative Risk Assessment

Outline

- Concerns about cumulative exposures
  - Mixtures toxicology
  - Multiple stressor types
- EPA guidance for cumulative risk assessment
- Communicating about multiple hazards

Mixtures Toxicology

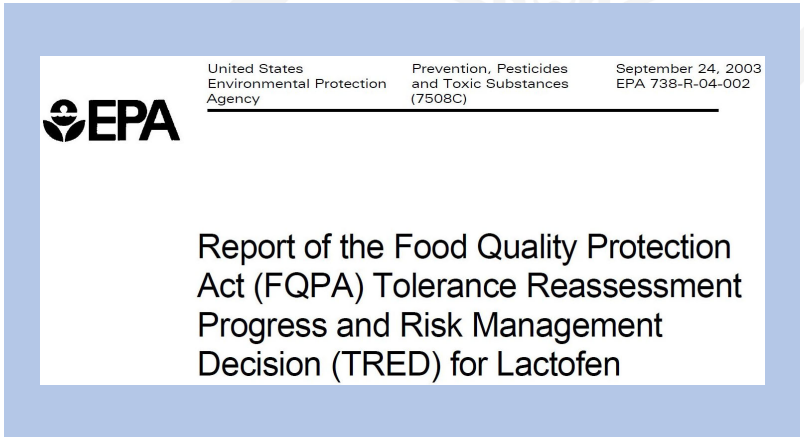
- Assumptions based on perception
  - Combining chemical exposures increases risks
  - Synthetic or processed chemicals are more toxic
- Chemicals with same mechanism of action and target tissues can enhance responses
- Chemical A can impair detoxification of Chemical B
- Antagonism also happens
- Limited direct testing of mixtures

Retrospective RA
Typically Adds Multiple Chemical Risks

- Common applications
  - Site investigation/cleanup
  - Community health investigations
- Assumption of Additivity
  - Hazard index – summation of non-cancer exposures vs. threshold levels
  - Excess cancer risk - cumulative
- Protective where different MoA
- Uncertain regarding missing stressors and super-additive interaction (synergism)

Prospective RA – Typically Single Chemical

- Common applications
  - Product registrations
  - Permitting
  - Facility hazard assessments
- Frequently basis for hazard characterization
- Limitation vs. “Out-of-Scope…”
  - Future risks not broadly characterized – public wants comprehensive RA
  - “Goal was to assess the ___, not all risks”



Stressors Beyond Point Sources/Products

- Background (non-point source) chemicals
  - Anthropogenic
  - Naturally occurring
- Nutritional/pharmacological inputs
- Physical
  - Noise
  - Particulate
- Psychosocial stressors

USEPA Efforts
Policy Goals Push Technical Advances

- Environmental Justice (1994 Exec. Order)
- Food Quality Protection Act directive (1996)
- Stakeholder engagement/litigation
- Scientific recognition
  - NAS/NRC panel recommendations
  - EU experts focus on receptor vs. chemical starting point (NoMiracle Project)
- Risk Assessment Forum (USEPA)

Cumulative Risk Assessment vs. Cumulative Impact Assessment

CRA

Quantitative/Semi-quantitative

Stressors or Receptor Oriented
Consider additional risk factors in risk characterization step:
- exposure-response modifier (10-fold for children/sensitive receptors)
- supplemental analysis

CIA

Descriptive/Qualitative

Community/Population Oriented
Characterization based on number, type of impacts
No common metric across stressors
Health, well being, quality of life
Community burdens and resiliency

Timeline of USEPA CRA Guidance

Guidance on Cumulative Risk Assessment, Part 1, Planning and Scoping

- 1997
- Starting point
- Not much beyond planning

Framework for Cumulative Risk Assessment

- 2003
- Added particularly to risk characterization

Pesticide Cumulative Risk Assessment: Framework for Screening Analysis

- 2016
- Registration, prospective RA oriented

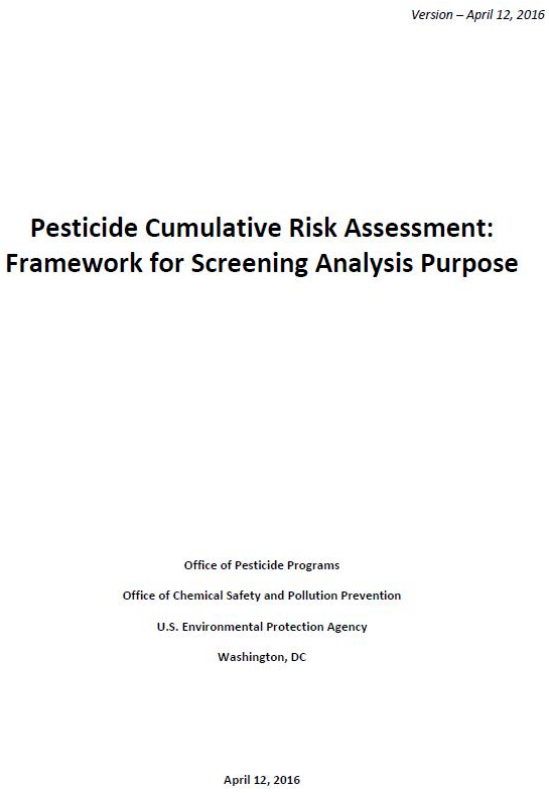
Guidelines for Cumulative Risk Assessment Planning and Problem Formulation

- 2023
- Formalizes WoE, DQO consideration

New USEPA Guidance Documents

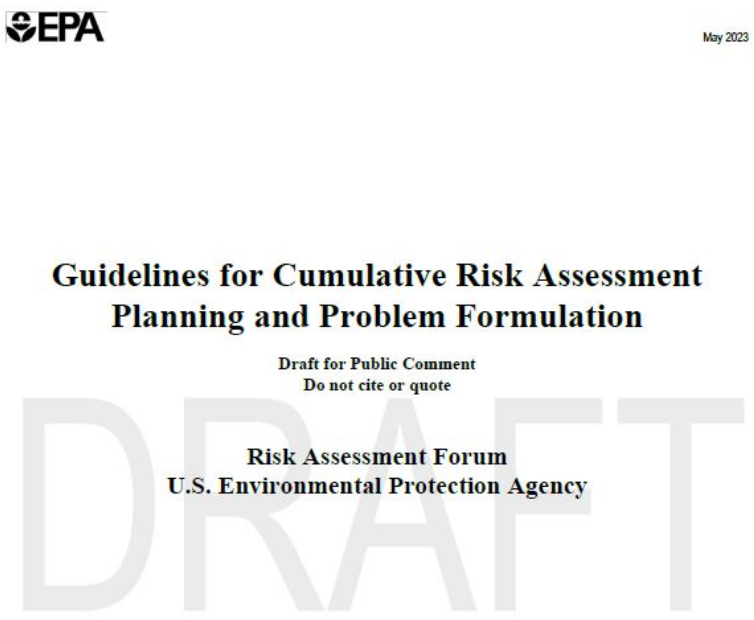
- Guidelines for Cumulative Risk Assessment Planning and Problem Formulation, Risk Assessment Forum, 2023
  https://www.epa.gov/risk/guidelines-cumulative-risk-assessment-planning-and-problem-formulation
- Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act, Office of Chemical Safety and Pollution Prevention
  https://www.epa.gov/system/files/documents/2023-02/Draft%20Phthalate%20CRA%20Approach.pdf
- Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act, Office of Chemical Safety and Pollution Prevention
  https://www.epa.gov/system/files/documents/2023-02/Draft%20Phthalate%20CRA%20Approach.pdf
- Pesticide Cumulative Risk Assessment: Framework for Screening Analysis Purpose, Office of Pesticide Programs
  https://www.regulations.gov/document/EPA-HQ-OPP-2015-0422-0019

CRA Framework for Pesticides



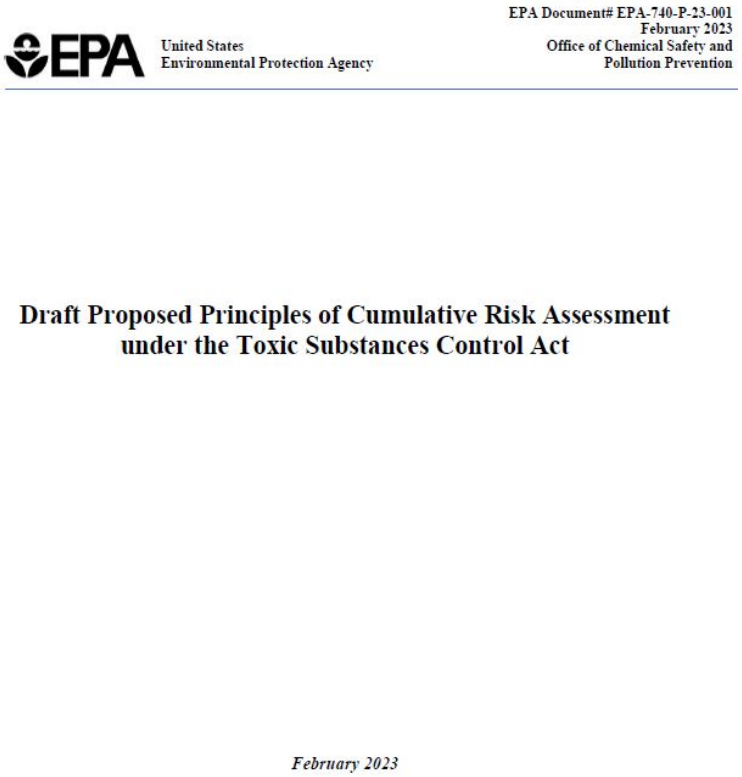
- Statutory mandate to “account for” cumulative
  - Federal Food Drug & Cosmetic Act
  - Screening level simplifications where relevant
- Tiered approaches (1-3) for exposures via
  - Dietary
  - Residential
- Common Mechanism Group (CMG)
  - Sensitive endpoints via common mechanism
  - Key biochemical elements, not all
  - Relative potency factors based on most toxic
  - Organophosphates (OPs), N-methyl carbamates (NMCs), chloracetanilides, triazines, pyrethrins and pyrethroids

Guidelines for CRA



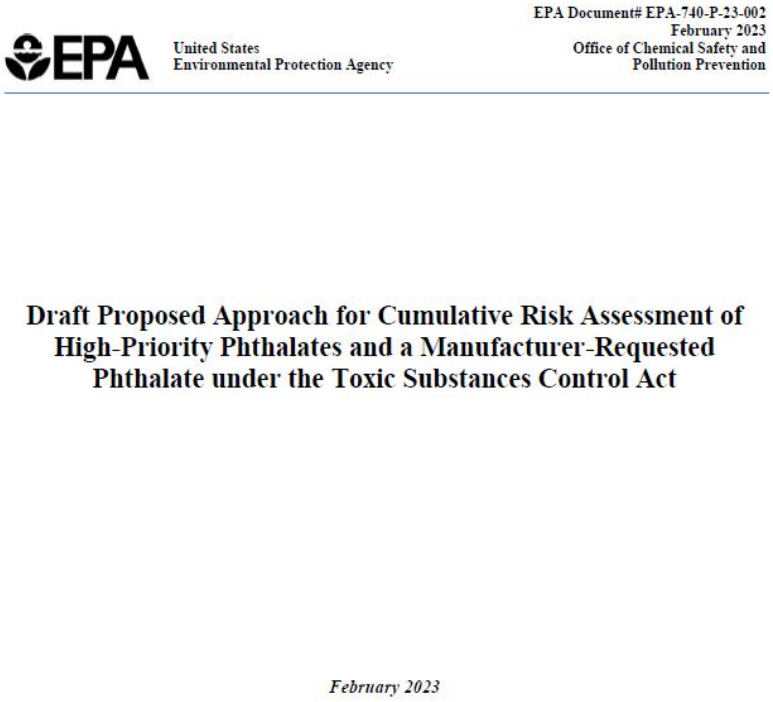
- Weight of evidence
  - Identify studies/information suitable, comparable for inclusion in analysis
  - Match to initiators, goal of RA
- Exposure-response modifiers
  - Biological – genetics, lifestages, diseases, atypical physiological function, psychosocial stress
  - Behavioral – occupational choices, hand-to-mouth
- Tiers (0-4) – assumptions sufficient that further information not warranted
- Phases – Identify most important stressors first, then proceed as relevant

CRA Principles Under TSCA



- TSCA/Lautenberg:
  - Does not mandate CRA
  - Requires use of best information, which suggests multiple stressor groupings – use of CRA – sometimes
- General population and PESS
  - Potentially exposed or susceptible subpopulations
  - Occupational, consumer, bystander, fenceline, tribal
- Tiered approaches for
  - Toxicological similarity
  - Evidence of co-exposure over relevant timeframe
- Chemical stressors only & additivity as default

CRA Approach for Phthalates


EPA Document# EPA-740-P-23-002
February 2023
Office of Chemical Safety and Pollution Prevention

EPA United States Environmental Protection Agency

Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act

February 2023

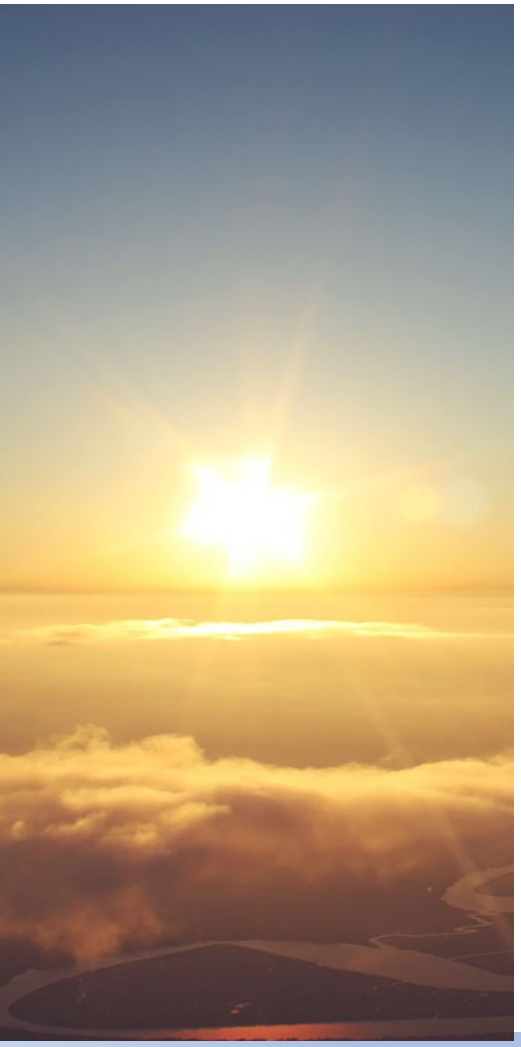
- Risk Evaluations required under TSCA
  - Agency required to make determinations for individual chemicals – conditions of use
  - Stakeholders and science drove decision for CRA
- 5 priority chemicals, 2 requested Risk Evaluations
  - di-ethylhexyl phthalate (DEHP), butyl benzyl phthalate (BBP), dibutyl phthalate (DBP), di-isobutyl phthalate (DIBP), and dicyclohexyl phthalate (DCHP), di-isononyl phthalate (DINP) and di-isodecyl phthalate (DIDP)
- Presenting Approach, not Outcome
  - Includes comprehensive toxicology summary by agency
  - CRA to inform individual Risk Determinations

CRA Approaches for Hazard Definition

- Group all but DIDP for CRA, treat additively
- Relative potency factors
  - For several gestational and post-natal endpoints
  - Select during CRA – may not be the same reference phthalate
- Select (during CRA) sensitive endpoint for “phthalate syndrome”– grouping of male reproductive/developmental effects
  - Considering - decreased fetal testosterone and expression of cholesterol transport and steroidogenesis genes
  - Dropping – reduced anogenital distance, retained nipples, seminiferous tubule atrophy, multinucleated germ cells

CRA Approaches for Receptors/Stressors

- PESS
  - Male infants, toddlers, children
  - Pregnant women, women of reproductive age – i.e., *in utero* exposures
- Include exposures from various products/sources
- Cumulative exposure estimated for PESS who are also:
  - Workers
  - Fenceline community
  - Consumers



Phthalate CRA Takeaways

- Good resource for agency thinking on phthalate effects
- DIDP distinctions being accepted by agency
- Use measured, sensitive endpoint, not “syndrome”
- Additivity for the grouping
- Account for background/other source exposures
- TSCA following through to use CRA

Communicating Management of Multiple Stressors

- Manageable, not inevitable weakness
- Prioritize – stressors and receptors
- Emphasize hazards that group (common biological mechanisms) – those that do not

Explaining CRA Internally

- Without effective communication about hazards, perceptions amplify risks and combinations
- Agency guidance serves a point of reference for your own considerations - “following EPA guidance…”
- Agency not relying on one tool – incorporating specifically:
  - Multiple sources (same substance)
  - Multiple substances (grouping)
  - Other stresses affecting receptor vulnerability

Summary

- Cumulative risk assessment advancing based on agency adoption
- Potential to increase trust/credibility with community-oriented stakeholders
- New guidance is incremental, not revolutionary
- Monitor the phthalate CRA – will serve as precedent