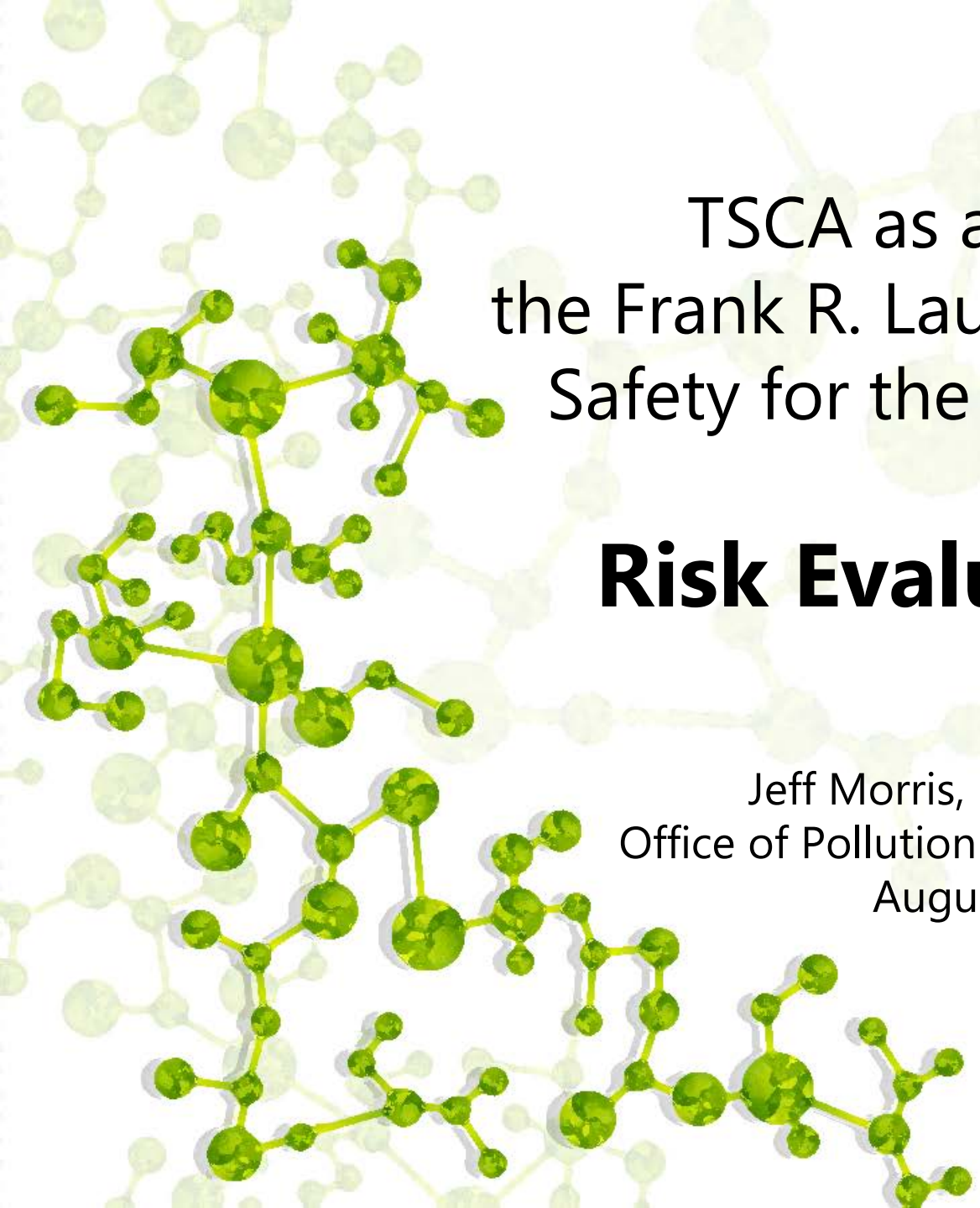


TSCA as amended by
the Frank R. Lautenberg Chemical Safety for the 21st Century Act

Risk Evaluation Rule

Jeff Morris, Deputy Director
Office of Pollution Prevention and Toxics
August 9, 2016

Purpose of the Meeting

- Overview of the law and meeting objectives
- Background on how EPA conducts risk evaluation
- Early input on procedural rulemaking for risk evaluation under new TSCA
  - All comments will be considered; docket opened.

The New Law

The "Frank R. Lautenberg Chemical Safety for the 21st Century Act" was signed by the President and went into effect on June 22, 2016

Amends and updates the Toxic Substances Control Act of 1976

Major Improvements Related to Existing Chemicals

- Mandatory duty on EPA to evaluate existing chemicals – clear and enforceable deadlines
- Chemicals assessed against a risk-based safety standard
- Must consider risks to susceptible and highly exposed populations
- Unreasonable risks identified in the risk evaluation must be eliminated
- Expanded authority to more quickly require development of chemical information when needed

Key Milestones

	New Chemicals	Existing Chemicals	Inventory / Nomenclature	CBI	Other	Fees
Day 1	Implement for all	- §6 rules under development will address new standards - Risk Assessments – will address new standards		- Review CBI claims for chem ID w/in 90 days		
6 Months		-Publish List of 10 Risk Assessments underway for WP Chemicals -January 1st of each year – updated plan for Risk Evaluations ** **Proposed rules – prioritization and evaluation**	Proposed rule – Active/Inactive		-Determine whether review small business definition warranted -Report to Congress on Capacity to Implement	**Proposed Rule
1 Year		-Final Rule: Prioritization Process **-Final Rule: Risk Evaluation Process (including guidance for manufacturer requests)** - Publish scope of first 10 risk evaluations	-Final Rule: Active/Inactive		--Establish SACC	**Final Rule
2 Year		-Negotiated Proposed Rule – Byproduct Reporting	-2½ years: Get active/inactive reports	-Rules re: CBI substantiation – 2.5 years -Guidance re: generic names	-Strategic Plan: Promote Alternative Test Methods -All policies, procedures, guidance needed	
3 Year		-3½ years -- 20 Risk Assessments underway (1/2 from WP, min) -20 Low Priorities identified -Proposed Rule – WorkPlan PBTs -Final Rule: Byproducts		-3½ years: Rule to establish plan for reviewing all CBI claims for active chemical IDs		
5 Year		-4 ½ years – Final Rule: PBTs		-Complete review of CBI claims for all active	-Report to Congress re: implementation of plan	**Not a statutory

Risk Evaluation Requirements

- Integrate and assess available information on **hazards and exposures for the "conditions of use" of the chemical substance**, including information that relevant to specific risks of injury to health or the environment and information on **potentially exposed or susceptible subpopulations**
  - *"Conditions of use"* – circumstances under which a chemical is *intended, known or reasonably foreseen* to be manufactured, processed, distributed in commerce, used or disposed of.
- Describe whether **aggregate or sentinel exposures** to a chemical substance under the conditions of use were considered, and the basis for that consideration

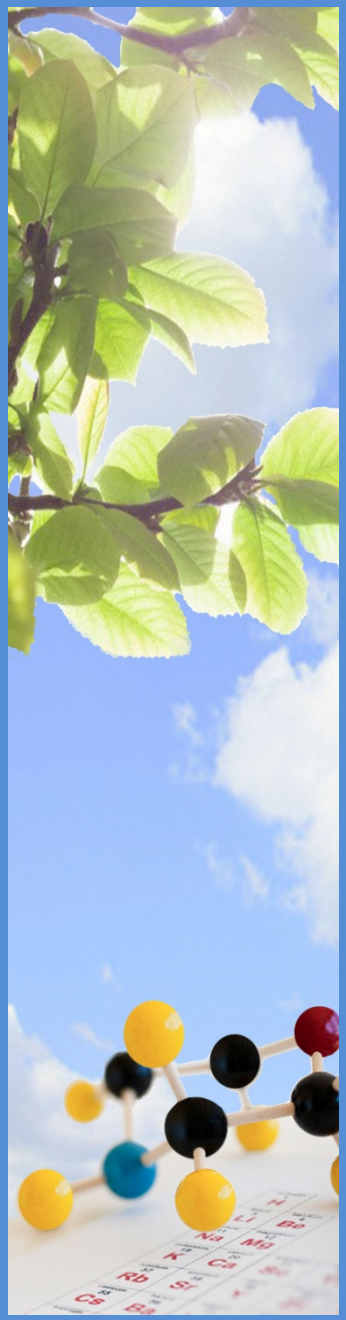
Risk Evaluation Process

- *High Priority* designation triggers mandatory risk evaluation to be completed in 3 years, with possible 6-month extension
- For each risk evaluation completed, EPA must designate a new high-priority chemical
- Within 3.5 years, EPA must have 20 ongoing chemical risk evaluations

EPA's Next Steps

Consider input received today, and written comments in the docket, to develop the proposed rule.

- Will be a procedural rule to establish **"a process to conduct risk evaluations"** of high priority chemicals.



United States Environmental Protection Agency

Overview of Risk Assessment Under TSCA -

Tala Henry Ph.D.

Director

Risk Assessment Division

Office of Pollution Prevention & Toxics

Risk Assessment Paradigm under TSCA

Under TSCA, OPPT evaluates and regulates, as appropriate, the full life cycle, i.e., manufacture (import), distribution in commerce, use and disposal, of industrial chemicals

- Safety Evaluation for a Wide Array of Industrial Chemicals:
- Existing and New Industrial Chemicals
- Data Availability/Quality Varies, but generally limited/incomplete
- New Risk Assessment/Management Challenges Continually Arise as New Chemistries and New Uses Emerge

Assessment Paradigm: How is TSCA Different?

Industrial Chemicals

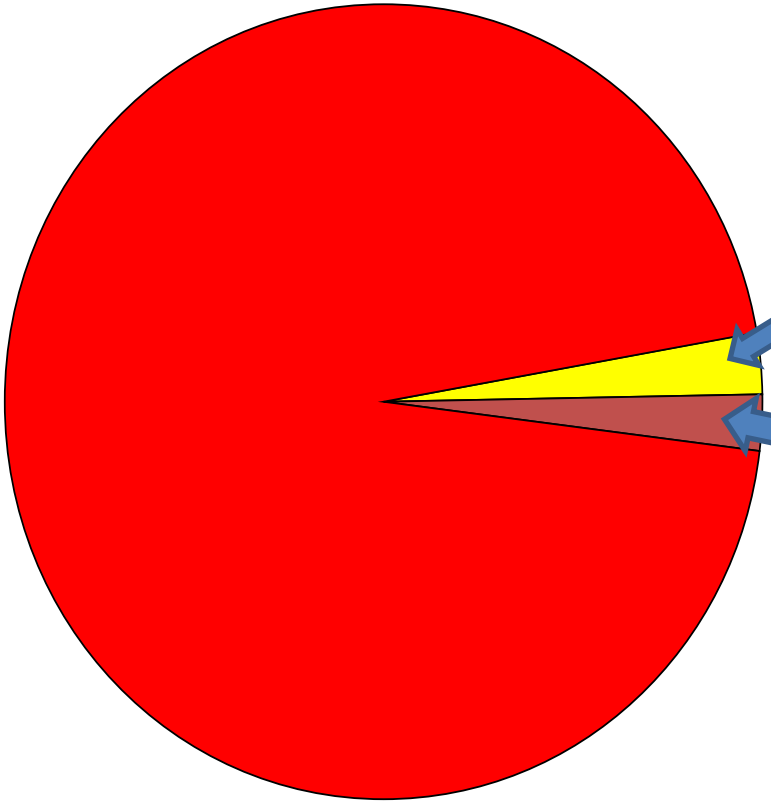
~84,000 Chemicals

Reviewed & Regulated under Toxic Substances Control Act (TSCA)

By Office of Pollution, Prevention, and Toxics (OPPT)

- **New Chemical Submissions do not require "new" data**
- **NEW mandate to assess existing chemicals**

U.S. Chemical Universe



Pesticides

~2000 Chemicals (Active Ingredients)

Reviewed and Regulated under FIFRA

By Office of Pesticides (OPP)

FIFRA requires experimental data

Food Additives, Drugs & Cosmetics

~2,000 AI

Federal Food, Drug, and Cosmetic Act

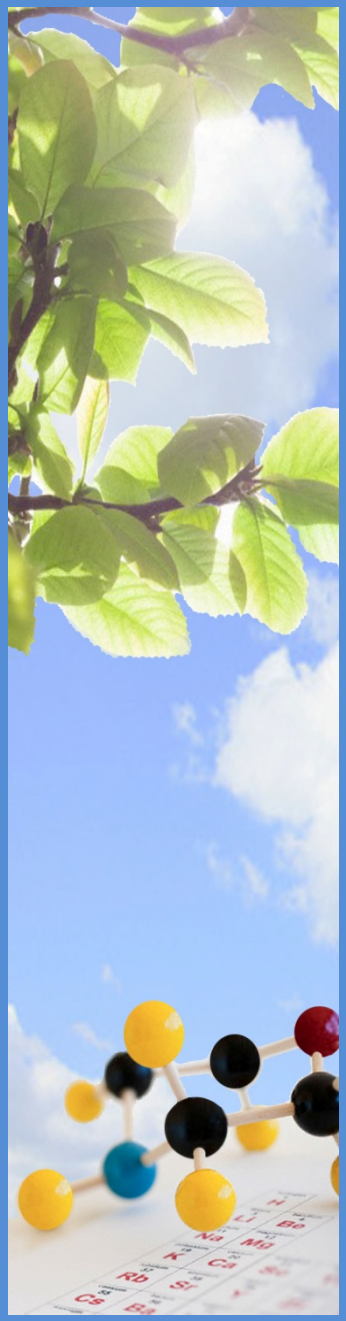
By OPP & FDA

FFDCA requires experimental data

DATA FOR ASSESSMENT UNDER TSCA

- New Chemicals
  - Computational approaches used extensively
    - QSAR and Expert Systems
    - Read-Across from Analogs/Categories
  - Tiered-Testing Approach: requests for higher tiered testing contingent on screening results

- Existing Chemicals
  - Established Test Guidelines; most testing for toxicity is *in vivo*
  - Read-Across from Analogs/Categories used extensively in screening programs (e.g., HPV)
  - Categories/Clusters used some in TSCA Work Plan Assessments



United States Environmental Protection Agency

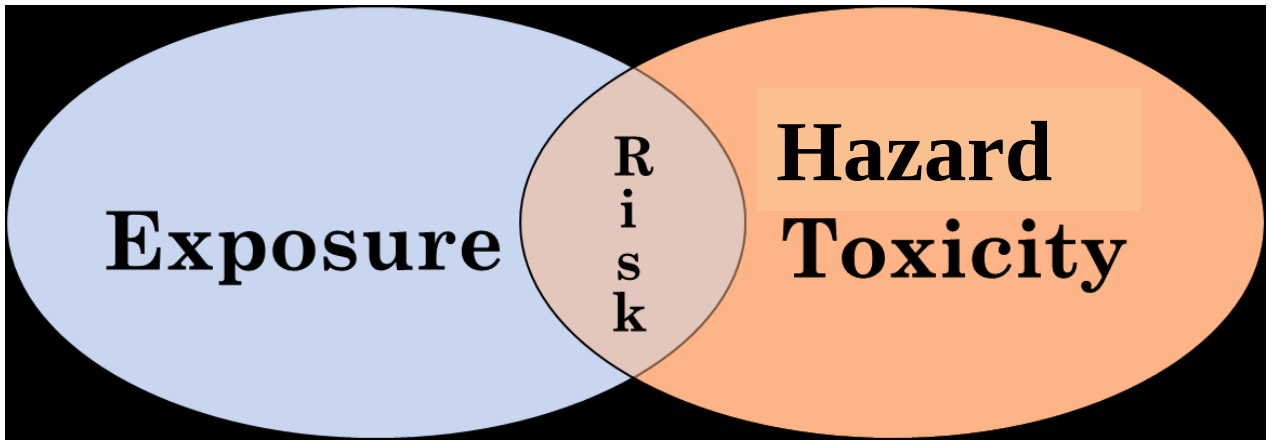
OPPT's Risk Assessment Process

Established EPA Risk Assessment Guidance

- 2014: Framework for Human Health Risk Assessment to Inform Decision-Making
- 1998: Guidelines for Ecological Risk Assessment

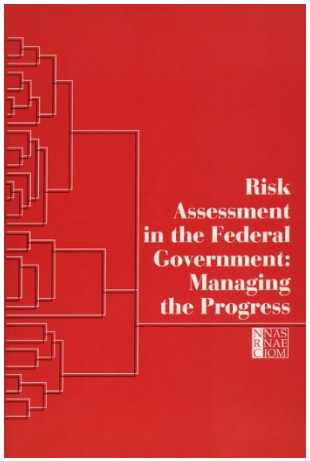
Scoping of Data & Information for Risk Assessment

- Gather, review and organize data and information on chemical uses, exposure: frequency, duration, & magnitude, ecological and health hazard data to be used
  - Sources: Manufacture/Import and Uses
  - Exposure Pathways, Routes and Receptors/Populations
  - Hazard Data: Hazard Values, Dose-Response



Not All Assessments Are Created Equal

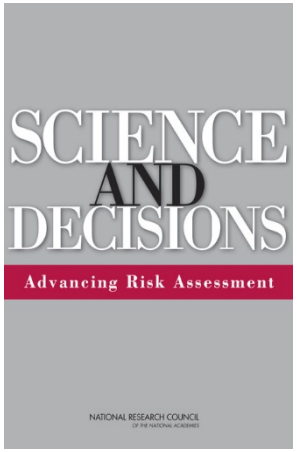
- "Fit for Purpose"
- Manufacture, Process & Uses Assessed
- Chemical-Specific Uses Define:
  - Exposure Pathways: Air, Water, Sediment, Soil, Fish
  - Exposure Routes: Inhalation, Oral, Dermal
  - Receptors/Populations
    - Occupational : Workers & Bystanders
    - General Population
    - Consumers: Users & Bystanders
    - Environment/Ecological
- Problem Formulation is critical first step



PROBLEM FORMULATION

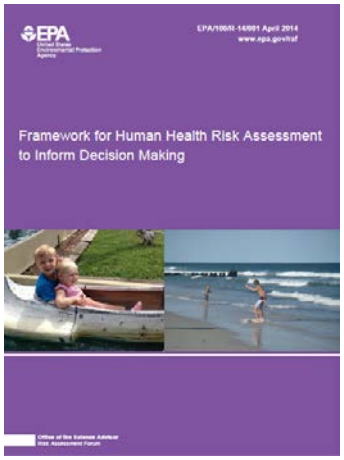
- 1983: NAS "Red Book*" frame the Risk Assessment Paradigm:
  - Risk Assessment = Haz ID + Dose-Response and Exposure Assessment

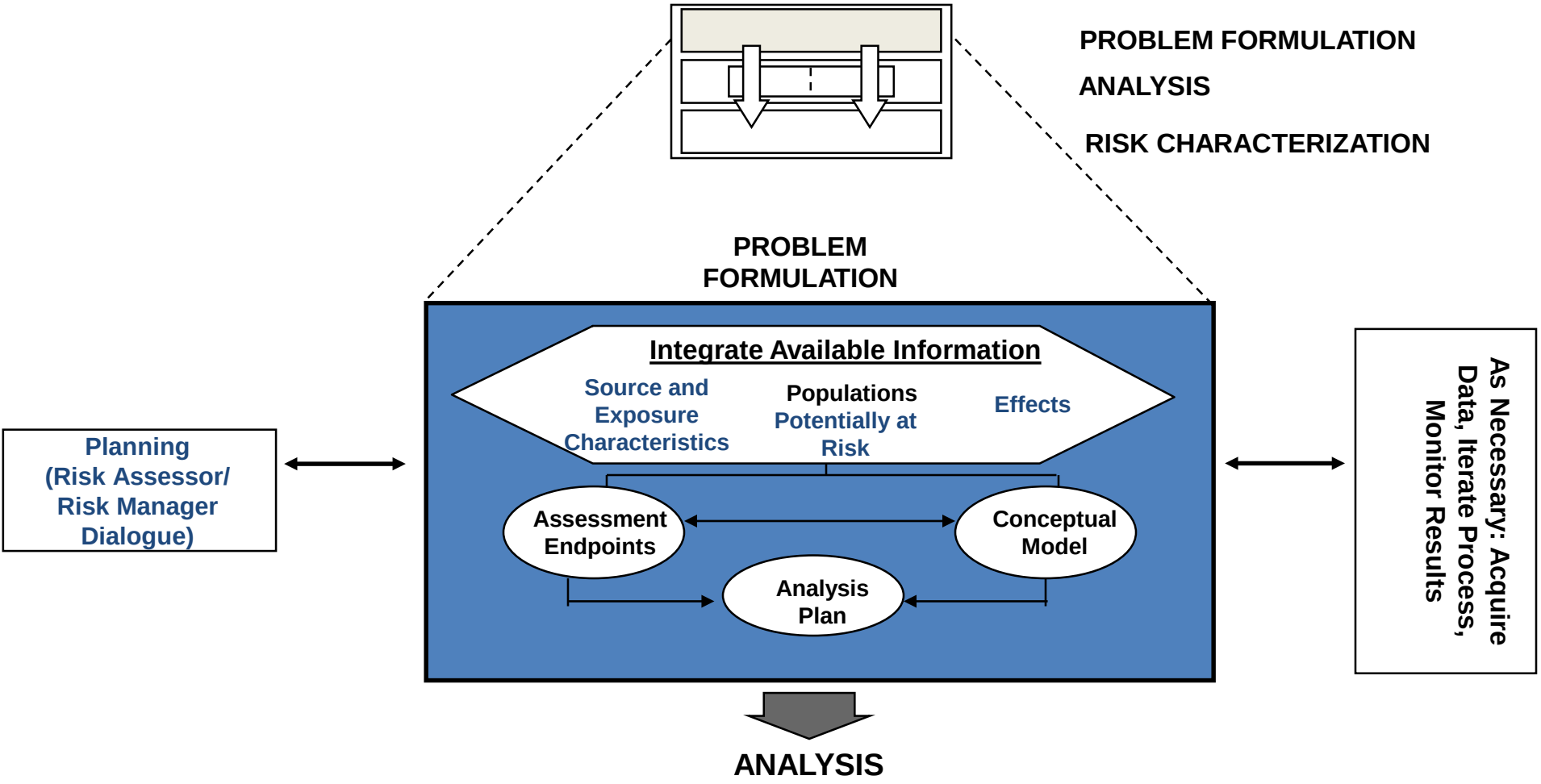
- 1992/1998: EPA's Guidelines for Ecological Risk Assessment explicitly incorporated Problem Formulation into the Risk Assessment Paradigm
  - 1992: Framework
  - 1998: Final Publication

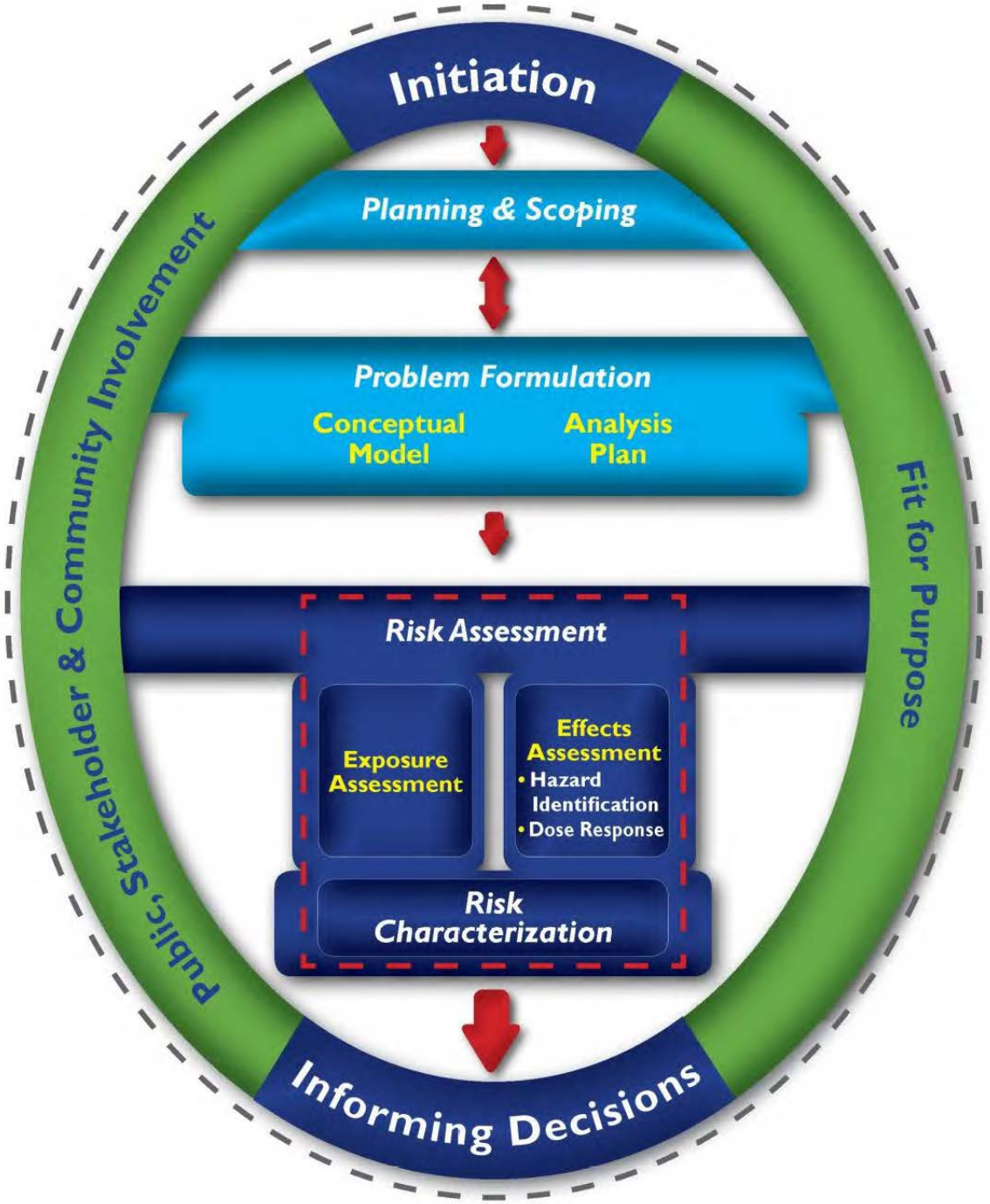


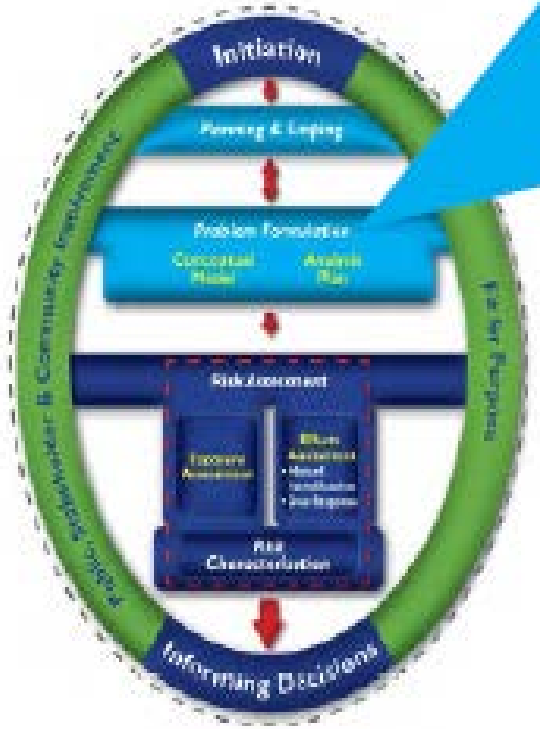
- 2011: NRC "Silver Book" recognized/affirmed the Importance of Problem Formulation and recommended to be integrated into Human Health risk Assessment paradigm in 2011

- 2014: EPA Incorporated into Framework for Human Health Risk Assessment




PROBLEM FORMULATION
ANALYSIS
RISK CHARACTERIZATION
PROBLEM FORMULATION
Integrate Available Information
Source and Exposure Characteristics
Populations Potentially at Risk
Effects
Assessment Endpoints
Conceptual Model
Analysis Plan
Planning (Risk Assessor/ Risk Manager Dialogue)
As Necessary: Acquire Data, Iterate Process, Monitor Results
ANALYSIS


Initiation
Planning & Scoping
Problem Formulation
Conceptual Model
Analysis Plan
Risk Assessment
Exposure Assessment
Effects Assessment
• Hazard Identification
• Dose Response
Risk Characterization
Informing Decisions
Public, Stakeholder & Community Involvement
Fit for Purpose



Key Considerations for Problem Formulation

Conceptual Model

- What are the human health risk pathways for this problem, including the elements for each dimension (e.g., populations and/or life stages at risk)?
- What factors and endpoints need to be analyzed?

Analysis Plan

- What approaches, methods and metrics will be used to assess exposures, effects and risk, including the associated uncertainty and variability?
- What is the strategy for developing new or using existing data? Are existing approaches adequate or are new approaches needed?

Problem Formulation

Problem Formulation

- EPA uses problem formulation to determine the extent to which data and tools are available to support the analysis

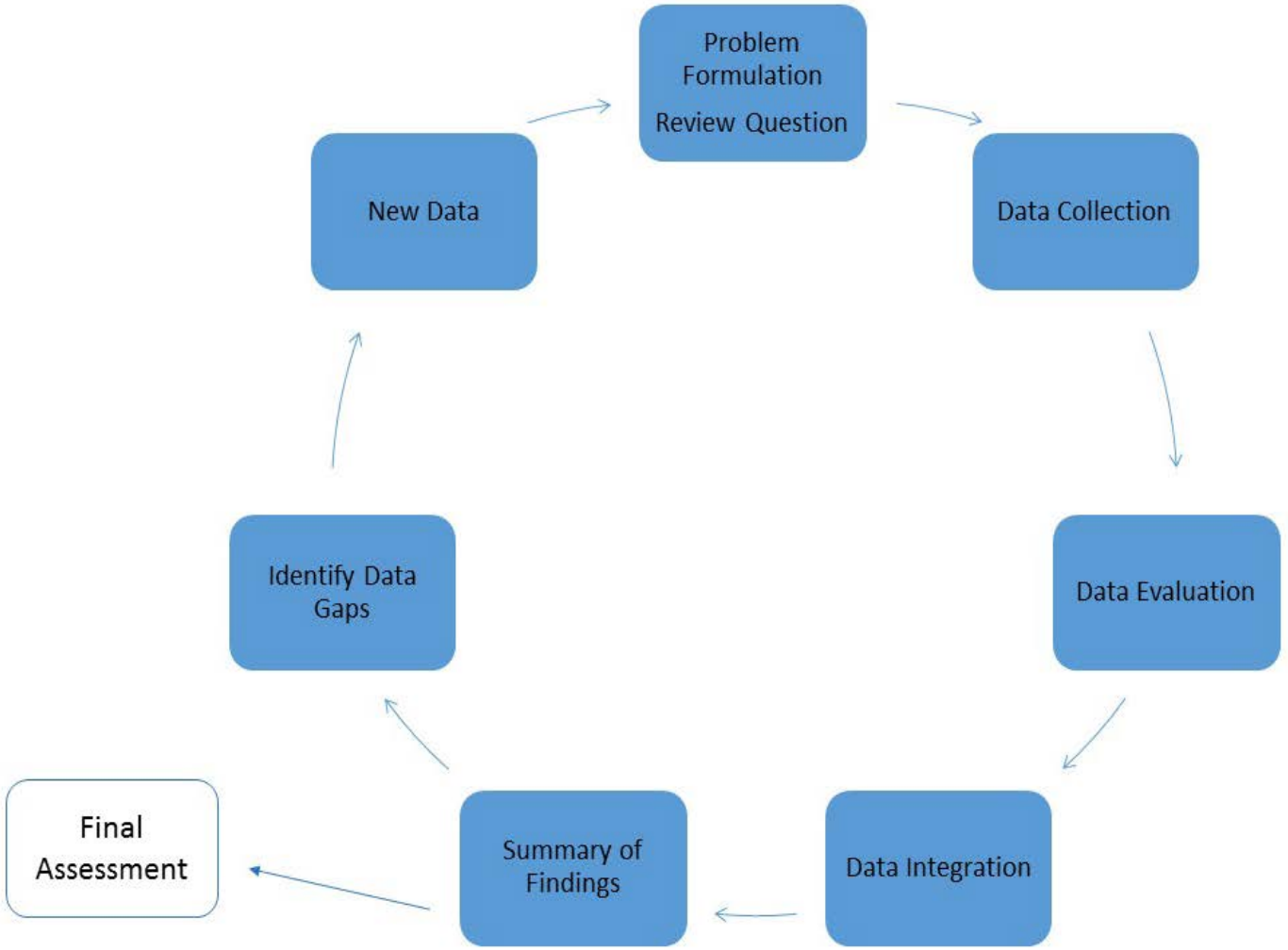
- Outcomes of Problem Formulation:
  - **Conceptual Model** – including a visual representation and written description of actual or predicted relationships between chemicals and human or wildlife, and
  - **Analysis Plan** – describing the intentions regarding the technical aspects of the risk assessment

Problem Formulation

Assessing & Integrating Available Information

- Data/Information Sources
- Data/Information Identification & Retrieval
- Systematic Review/Transparency
- Uncertainty

SYSTEMATIC REVIEW FRAMEWORK - OVERVIEW



Data Evaluation

When determining or evaluating the strengths and limitations of toxicity, clinical and epidemiological studies, numerous criteria are considered, including but not limited to the following:

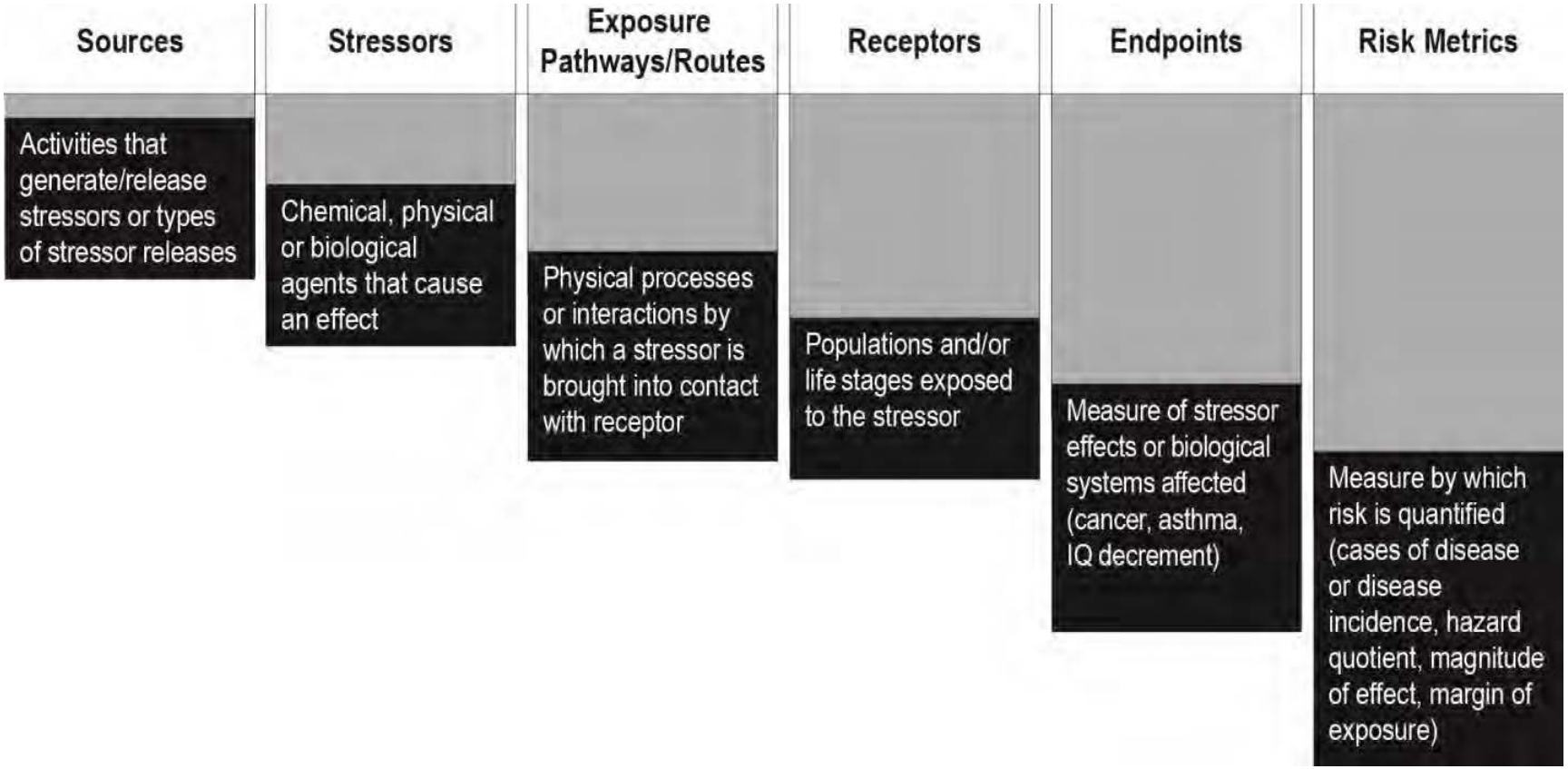
- adequacy of study design (Fit-for-Purpose)
- test substance identification (e.g., purity, analytical confirmation of stability and concentration),
- information about test animals (e.g., species, source, sex, age/lifestage/embryonic stage) and relevance to the endpoint(s) of interest,
- number of subjects in each dose/concentration group,
- dosing regimen (e.g., dose/concentration levels and controls including solvent controls),
- timing and duration of exposure, and relevance to the endpoint(s) of interest,
- route/type of exposure,
- test conditions (e.g., husbandry, culture medium),
- endpoints evaluated (e.g., schedule of observations, randomization and blinding procedures, assessment methods),
- reporting (quality and completeness)

Data Evaluation: Epidemiological data

Study Population	**-Recruitment Strategy, inclusion/exclusion criteria** **-Number, time period, age/sex/other distribution, geographic area** **-Participation rates (at each stage), eligibility, comparison group selection, attrition rate** **-Follow up** **-Comparability (exposed and non-exposed)**
Exposure	-Specific substance measured, analytical methods -Types of samples collected (matrix) -Exposure groups defined, methods to assign -Limit of detection or level of quantitation, number of samples above/below -Exposure distribution (central tendency, range, etc) -Potential for exposure misclassification -Use of TWAs for occupational studies -Empirical, estimated, or modeled exposures -Timing of collection -Validation of biomarkers
Statistical Analysis	-Power -Appropriateness of methods used -Reliable, consistent -Treatment of non-detects or < LOQ -Adjustment of variables -Explicit presentation of results -Significance levels clearly defined
Outcome	-Novel or validated assessment tools, appropriateness for study population -Blinding -Explicit, complete presentation of results -Timing -Confounding -Concordance of text with data results in tables -Potential bias

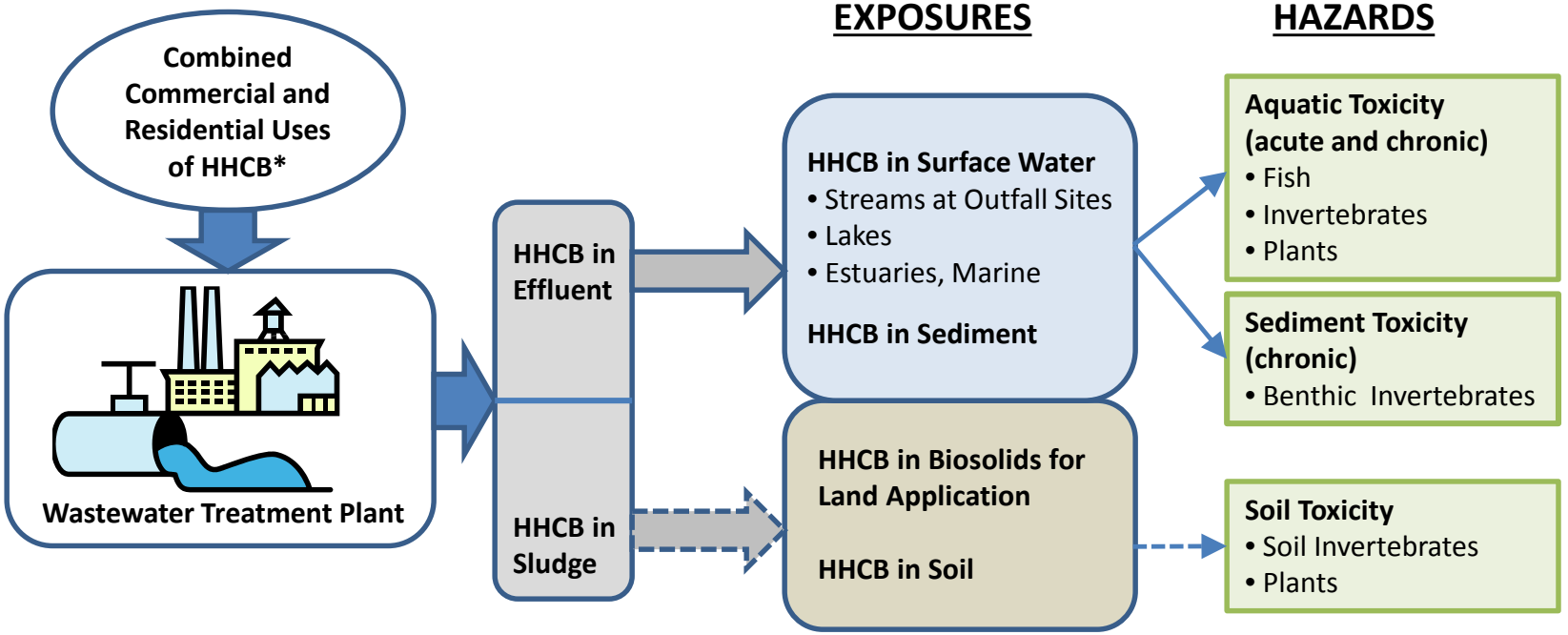
Conceptual Models

Example of a Generalized Conceptual Model With Examples of Possible Dimensions and Linkages



Conceptual Model from Problem Formulation

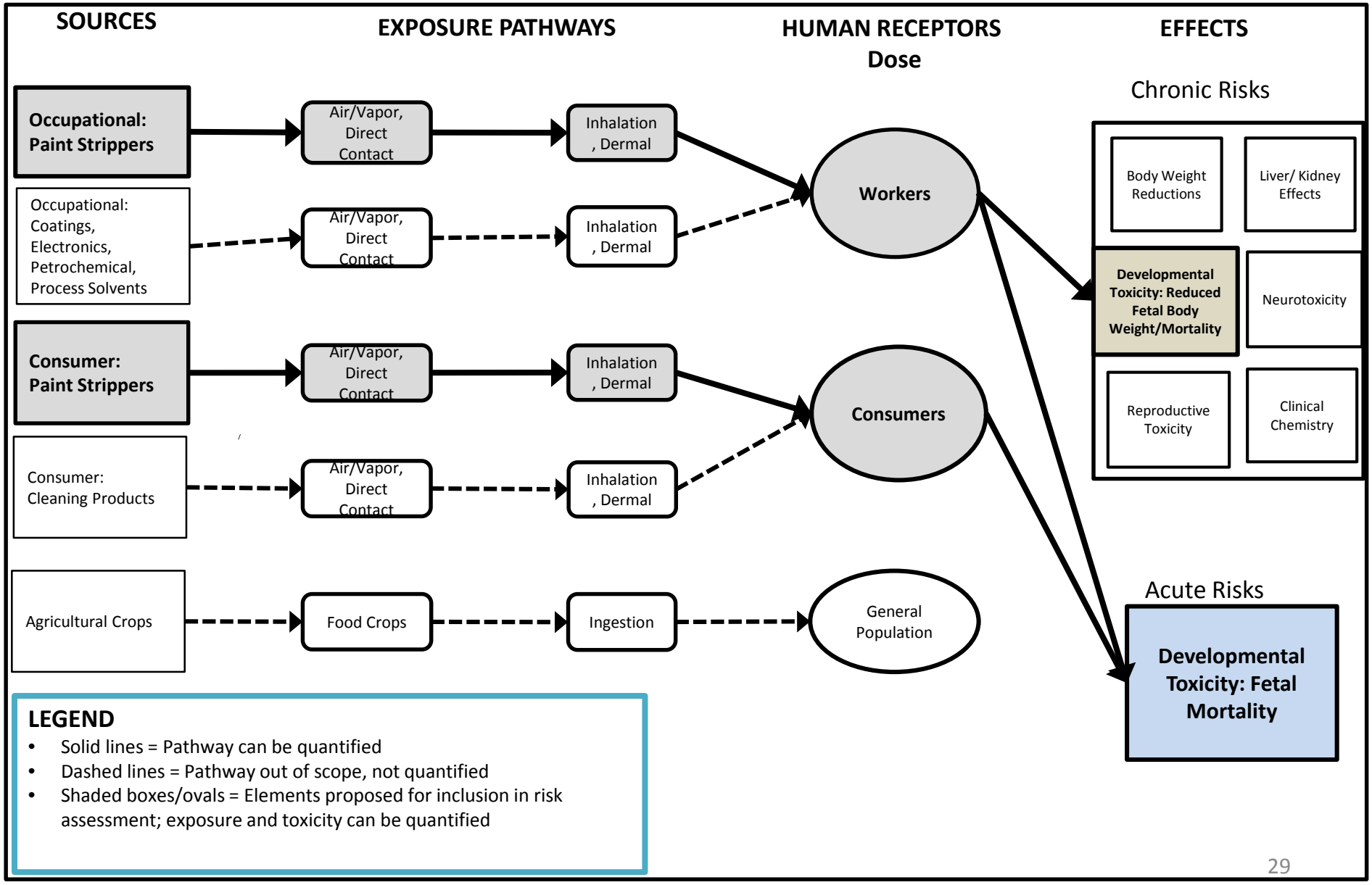
Example from HHCB Assessment – Ecological Only



*Includes all fragranced products such as soaps, detergents, fabric softeners, shampoos, cosmetics, and cleaners.

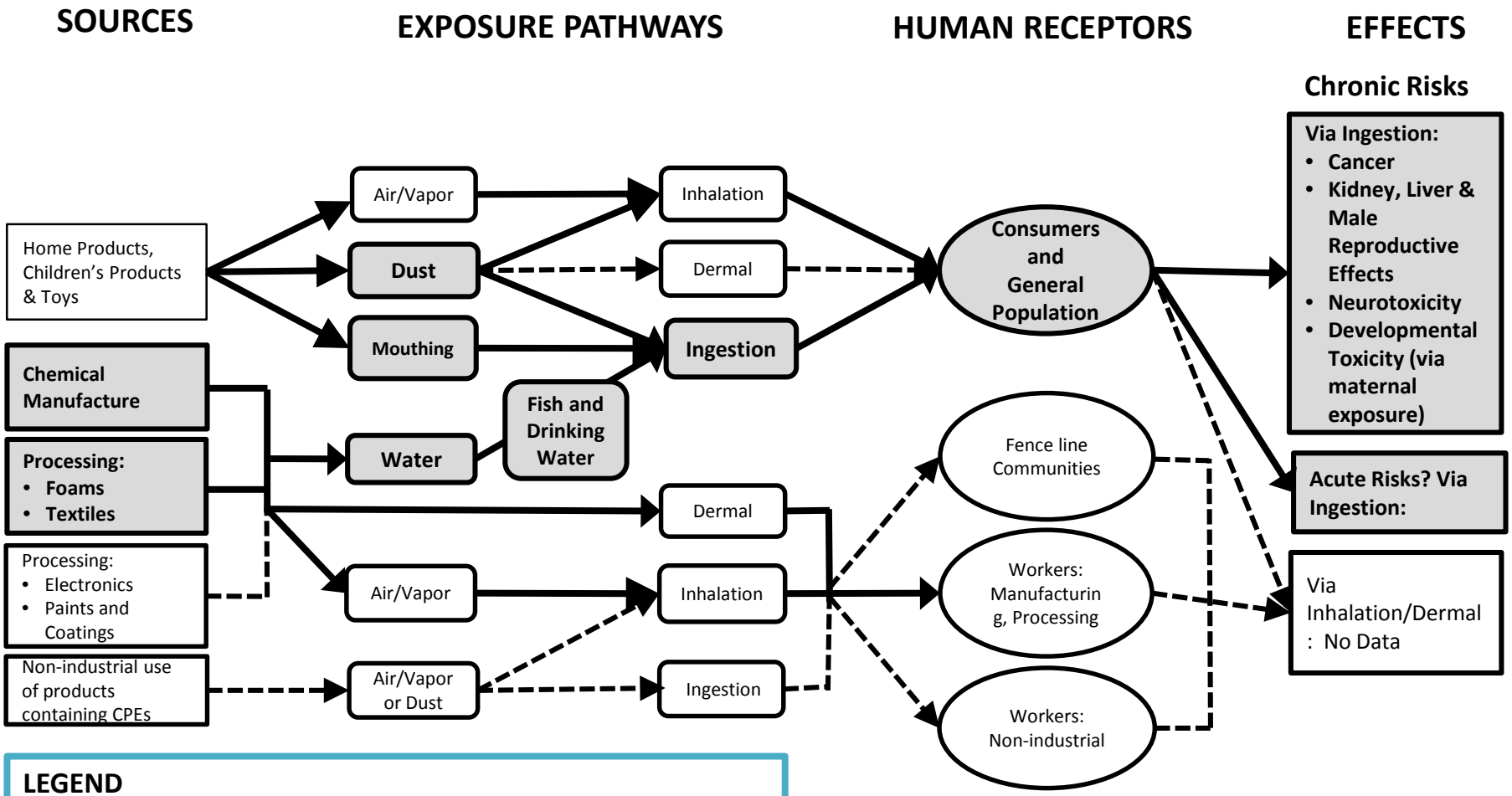
Conceptual Model from Problem Formulation

Example from N-methylpyrrolidone Assessment



Conceptual Model from Problem Formulation

Example from Chlorinated Phosphate Esters Problem Formulation & Initial Assessment



LEGEND

- Solid lines = Pathway can be quantified
- Dashed lines = Pathway uncertain, or not quantifiable
- Shaded boxes/ovals = Elements proposed for inclusion in risk assessment; exposure and toxicity can be quantified
- Unshaded boxes/ovals = Elements excluded from this risk assessment

EXPOSURE ASSESSMENT

Chemical Specific Factors

- Physical chemical properties
  - Solubility in water (log kow)
  - Volatility/vapor pressure @ 20^{o}C
  - Melting point
- Environmental Fate
  - ½ life in environmental media
- Persistence
  - Abiotic and Biotic breakdown
- Bioconcentration and Bioaccumulation

Exposure Assessment

Exposure Scenarios and Potentially Exposed or Susceptible Sub-Populations Assessed

- Occupational: manufacturing and processing; chemical-specific
- General population
- Consumer exposures: Chemical-Use specific
- Aggregate or Sentinel exposures considered

Exposure Characterization

- Duration
- Pattern
- Route of Exposure

Exposure Assessment: Fit for Purpose

Fit for purpose hazard or risk?

- Emergency response guidance e.g., AEGLs
- National assessment
- Site specific assessment

Acute typically time weighted average (TWA)

- Occupational 8 hr TWA
- Consumer 24 hr TWA
- General population 1-24 hr TWA (e.g., fence line, drinking water, fish consumption)

Chronic scenarios typically for occupational but may include general population and consumers

- Average daily dose
- Life-time average daily dose

Exposure Calculation: Acute

Acute exposures are estimated as follows:

$$AC = \frac{C \times ED}{AT}$$

where:

- AC = acute concentration (8-hr TWA)
- C = contaminant concentration in air (8-hr TWA)
- ED = exposure duration (8-hr/day)
- AT = averaging time (8-hr/day)

EXPOSURE CALCULATIONS: CHRONIC

Average Daily Concentration (ADC) and Lifetime Average Daily Concentration (LADC) are used to estimate ***workplace exposures*** for non-cancer and cancer risks, respectively, as follows:

$$\text{ADC or LADC} = \frac{\text{C} \times \text{ED} \times \text{EF} \times \text{WY}}{\text{AT}}$$

where:

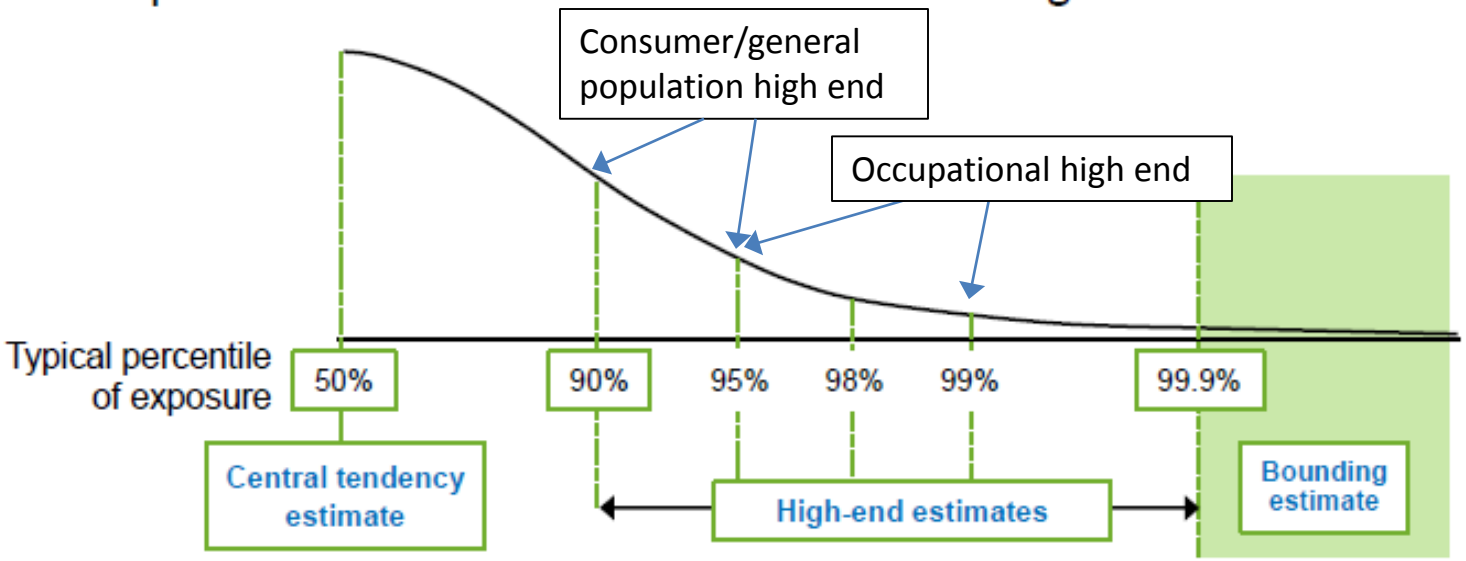
- ADC = average daily concentration (8-hr TWA) used for chronic non-cancer risk calculations
- LADC = lifetime average daily concentration (8-hr TWA) used for chronic cancer risk calculations
- C = contaminant concentration in air (8-hr TWA)
- ED = exposure duration (8 hr/day)
- EF = exposure frequency (260 days/yr)
- WY = working years per lifetime (40 yr)
- AT = averaging time (LT × 260 days/yr × 8 hrs/day;
  where LT = lifetime; LT = 40 yr for non-cancer risks; LT=70 yr for cancer risks)

- Parameters adjusted for ***consumers and general population exposures***

Exposure: Descriptive Measures

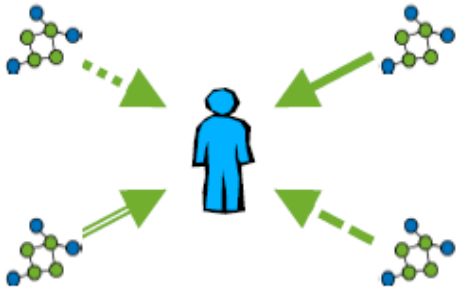
Exposure descriptors are estimates of specific points on the exposure distribution

- Based on selected parameter values
- May be for individual or population exposures
- Help assessors communicate with risk managers



AGGREGATING EXPOSURES

- Aggregate exposure assessments evaluate continued exposures to single chemical entity across multiple pathways and routes



- Data permitting, OPPT strives to aggregate exposures:
  - Multiple Sources/Uses:
    - multiple occupational use scenarios (e.g., 1-BP)
    - multiple consumer products (e.g., flame retardants)
  - Multiple pathways: dust is aggregate of uses; plus water ingestion and fish consumption (e.g., HBCD, TBBPA);
  - Multiple routes: dermal and inhalation (e.g., NMP)

Effects Assessment: Exposure Relevance

- Exposure Factors: e.g., Sex and Life-Stage Dependent
- Biological Factors: Life-Stage Dependent
  - Pharmacokinetic
  - Pharmacodynamics
- Acute Effects – Exposure Considerations
  - Developmental
    - Reversible (e.g., hypoxia, narcosis)
    - Irreversible (e.g., lethality, terata)
    - Latent expression
  - Adult
    - Reversible (e.g., hypoxia, narcosis)
    - Irreversible (e.g., lethality)
    - Latent expression
- Chronic Exposures – Exposure Considerations
  - Cancer and non-cancer

Hazard and Dose Response

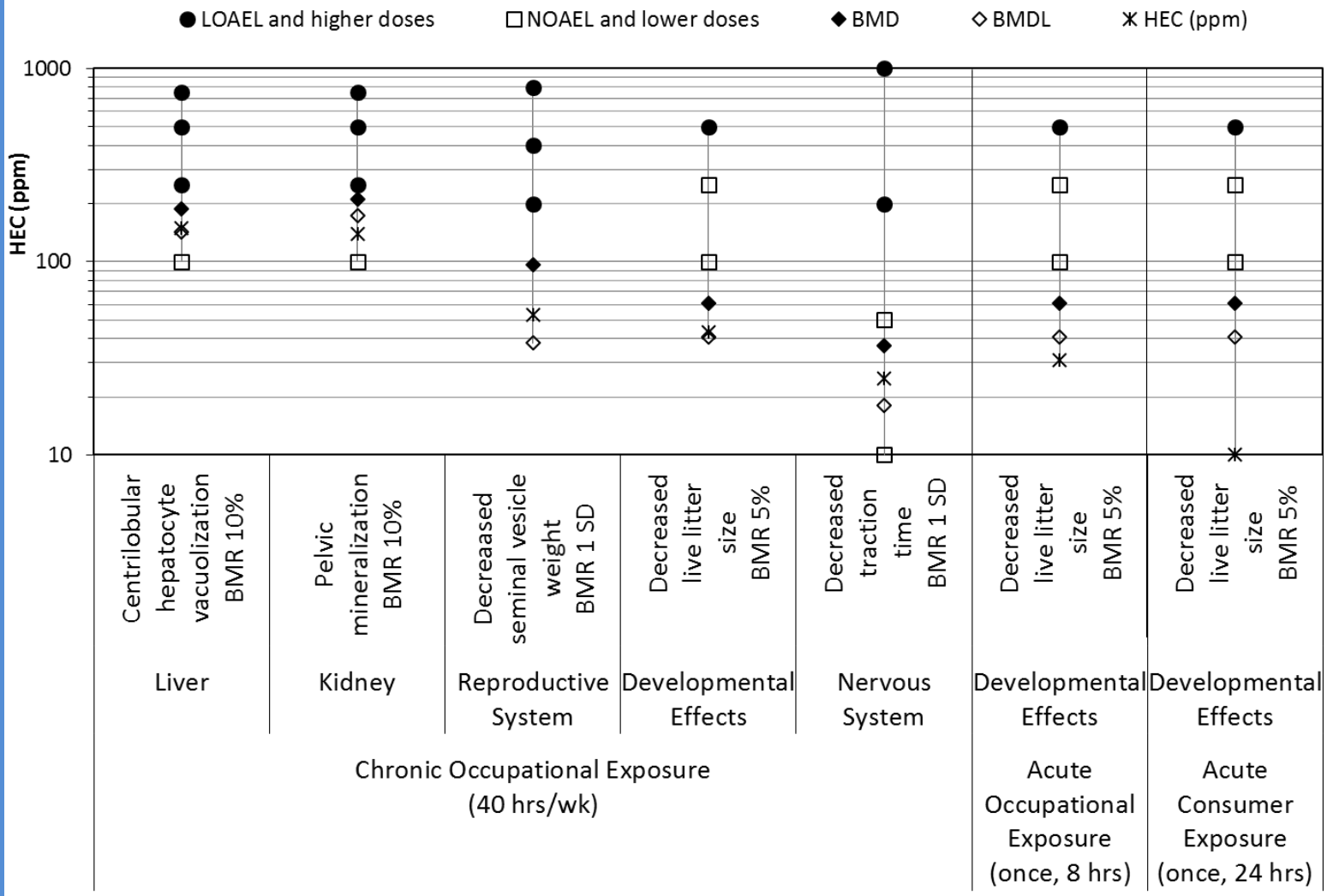
- Choice of less than lifetime exposure studies (< 1/10 the of lifespan) for chronic health effects **P**oint **o**f **D**eparture (**POD**)/Uncertainty Factors (UFs) = RfV
  - Typical of IRIS and PPRTV assessments
  - Use developmental endpoints –resulting from short durations of exposure for chronic POD.

- Development of RfV's or PODs for different durations
  - EPA RfC/RfD Guidance Document
  - EPA Children's Risk Assessment Framework

Hazard Value Relevant For Exposure Scenario

- A range of MOEs for acute and chronic risk estimates for respective exposure scenarios.
- For chronic exposure scenarios: a relatively low dose and short term/sub-chronic exposure can result in long-term adverse consequences.
- For acute exposure scenarios: most sensitive endpoints are often development and/or reproductive endpoints (e.g., TCE and NMP developmental toxicity).
  - Supported by EPA policy.
  - Science-based policy based on the presumption that a single exposure of a chemical at a critical window of development can be adverse (EPA's 1991 *Guidelines for Developmental Toxicity Risk Assessment* (pg. 38) *and 1996 Guidelines for Reproductive Toxicity Risk Assessment* (pg. 83)).

NON-CANCER DOSE-RESPONSE SUMMARY



SCREENING LEVEL RISK ESTIMATION

QUANTIFYING NON-CARCINOGENIC HAZARD for HEALTH AND ECOLOGICAL RECEPTORS

The hazard or risk quotient (HQ/RQ) is the ratio of the exposure level at a site to the reference dose

$$\text{HEALTH HQ/RQ} = \frac{\text{Acute or Chronic Exposure (i.e., ADD/C)}}{\text{Reference Value (POD/UFs)}}$$

$$\text{ECO HQ/RQ} = \frac{\text{Acute or Chronic Exposure}}{\text{Concentration of Concern (NOAEL or LOAEL (POD/UFs))}}$$

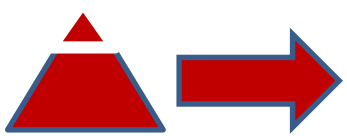
- HQ/RQ values are variable, with values **less** than and equal to 1 generally considered indicative of acceptable hazard

Risk Calculation

Non-Cancer MOE compared to benchmark MOE (UF)s

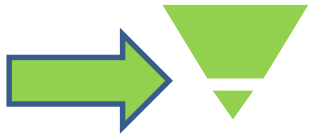
$$MOE_{acute\ or\ chronic} = \frac{Non-Cancer\ Hazard\ value\ (POD)}{Human\ Exposure}$$

- Where:
- MOE = Margin of exposure (unitless)
- Hazard value (POD) = HEC or HED (ppm)
- ***Risk estimate compared to Benchmark MOE (UFs) which is unacceptable risk level***



Risk

No Risk



Cancer

$$Risk = Human\ Exposure \times IUR$$

- Where:
- Risk = Cancer risk (unitless)
- Human exposure = Exposure estimate (LADC in ppm) from occupational exposure assessment
- IUR = Inhalation unit risk (a x 10^{-x} per ppm)

Peer Review as per EPA Policy

Peer Review Handbook 4th Edition, 2015

- A guidance manual, not a rule or regulation
- For scientific or technical (including economic and social science) work products.
- Conducted by qualified individuals (or organizations) who are independent of those who performed the work and who are collectively equivalent in technical expertise to those who performed the original work (i.e., peers).
- Emphasizes early categorization of the work product—preferably at the conceptual stage—into one of three categories: Influential Scientific Information (ISI); Highly Influential Scientific Assessment (HISA), which is a subset of ISI; or other as defined by the Office of Management and Budget (OMB) in its *Final Information Quality Bulletin for Peer Review* (OMB Peer Review Bulletin) (Appendix B).
- Management approval and documentation of key decisions throughout the peer review process are emphasized.
- Commitment to transparency in the peer review process by providing opportunities for public participation.

EPA Risk Assessment Guidance Exposure Assessment

- 1992: Guidelines for Exposure Assessment.
- 2011: Exposure Factors Handbook
- 2009: Guidance Document on the Development, Evaluation and Application of Environmental Models
- 2006: A Framework for Assessing Health Risk of Environmental Exposures to Children
- 2006: Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants

EPA Risk Assessment Guidance: Human Health Assessment

- 2014: Framework for Human Health Risk Assessment to Inform Decision Making
- 2005: Guidelines for Carcinogen Risk Assessment-
  - Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens
- 1998 Guidelines for Neurotoxicity Risk Assessment
- 1996 Guidelines for Reproductive Toxicity Risk Assessment
- 1991 Guidelines for Developmental Toxicity Risk Assessment
- 1986 Guidelines for Mutagenicity Risk Assessment

EPA Risk Assessment Guidance: Ecological Assessment

- 1998: Guidelines for Ecological Risk Assessment
- 2004: Generic Ecological Assessment Endpoints (GEAE) for Ecological Risk Assessment
- 1992: Framework for Ecological Risk Assessment

EPA Risk Assessment Guidance: Select Specific Topics

MODELING & APPROACHES

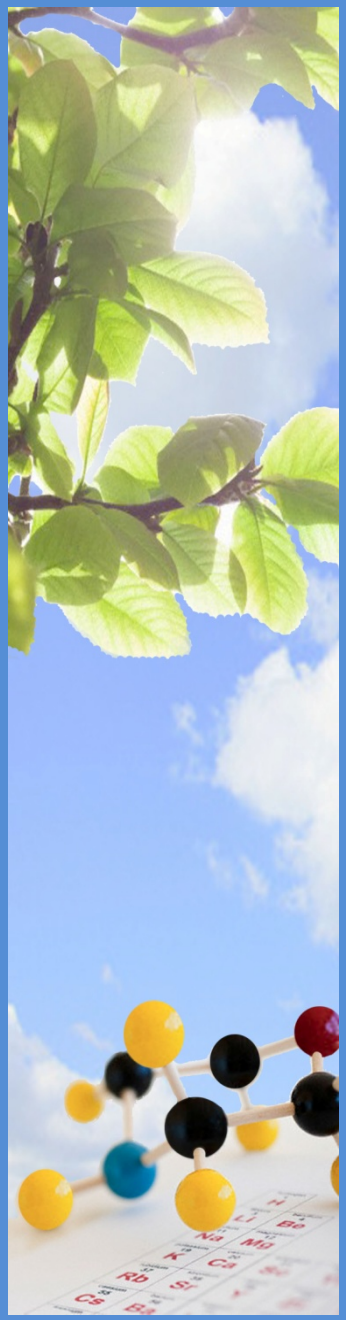
- 2014: Probabilistic Risk Assessment White Paper
- 2014: Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation
- 2012: Benchmark Dose Technical Guidance Document
- 2009: Guidance Document on the Development, Evaluation and Application of Environmental Models

METALS

- 2007: Framework for Metals Risk Assessment

CUMULATIVE & MIXTURES

- 2009: Considerations for Developing a Dosimetry-Based Cumulative Risk Assessment Approach for Mixtures of Environmental Contaminants
- 2008: Cumulative Health Risk Assessment of Multiple Chemicals, Exposures, and Effects: A Resource Document
- 2003: Framework for Cumulative Risk Assessment
- 1986: Guidelines for the Health Risk Assessment of Chemical Mixtures



United States Environmental Protection Agency

Meeting to Obtain Input on the New TSCA Proposed Rule for Chemical Risk Evaluation

EPA will consider comments submitted to docket

EPA-HQ-OPPT-2016-0400

Submit comments at www.regulations.gov by August 24, 2016.