

Overview of Temporal Considerations for Risk Assessment of Acute Scenarios

Stan Barone Jr., MS., PhD.,
Risk Assessment Division
Office of Pollution Prevention and Toxics



OUTLINE OF OVERVIEW

- Context for health/risk assessment
 - Scenario development
 - Problem formulation
- Extrinsic & Intrinsic Factors
 - Exposure factors/behavior
 - Critical windows of vulnerability
- Summary of hazard principles
- Summary of exposure calculations
- Summary of risk calculations
- More Information

EXPOSURE CONTEXT IN RISK ASSESSMENT

Uses and Scenarios Determined By Social And Economic Factors

- Occupational
- General population
- Consumer exposures

Exposure

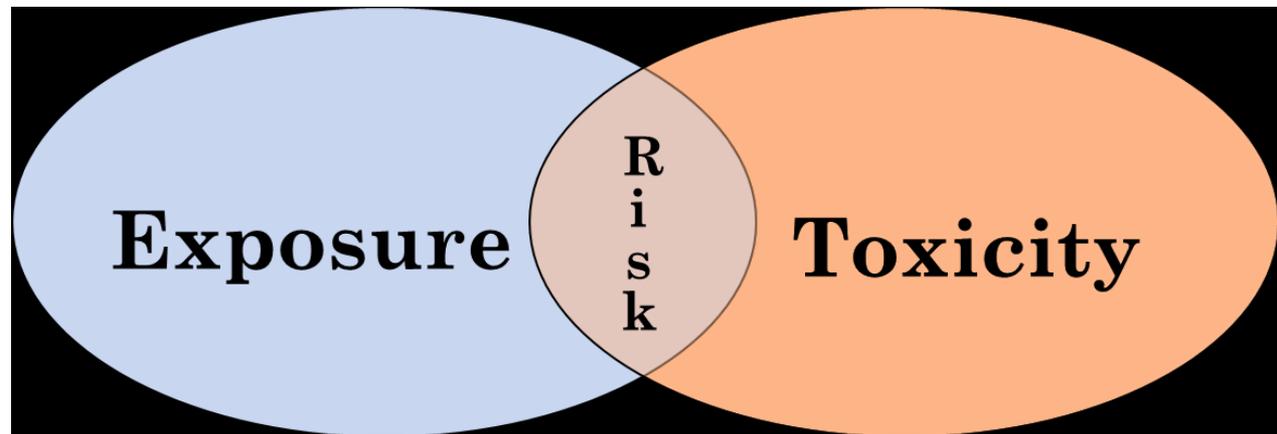
- Duration
- Pattern
- Route of exposure

CHEMICAL SPECIFIC FACTORS

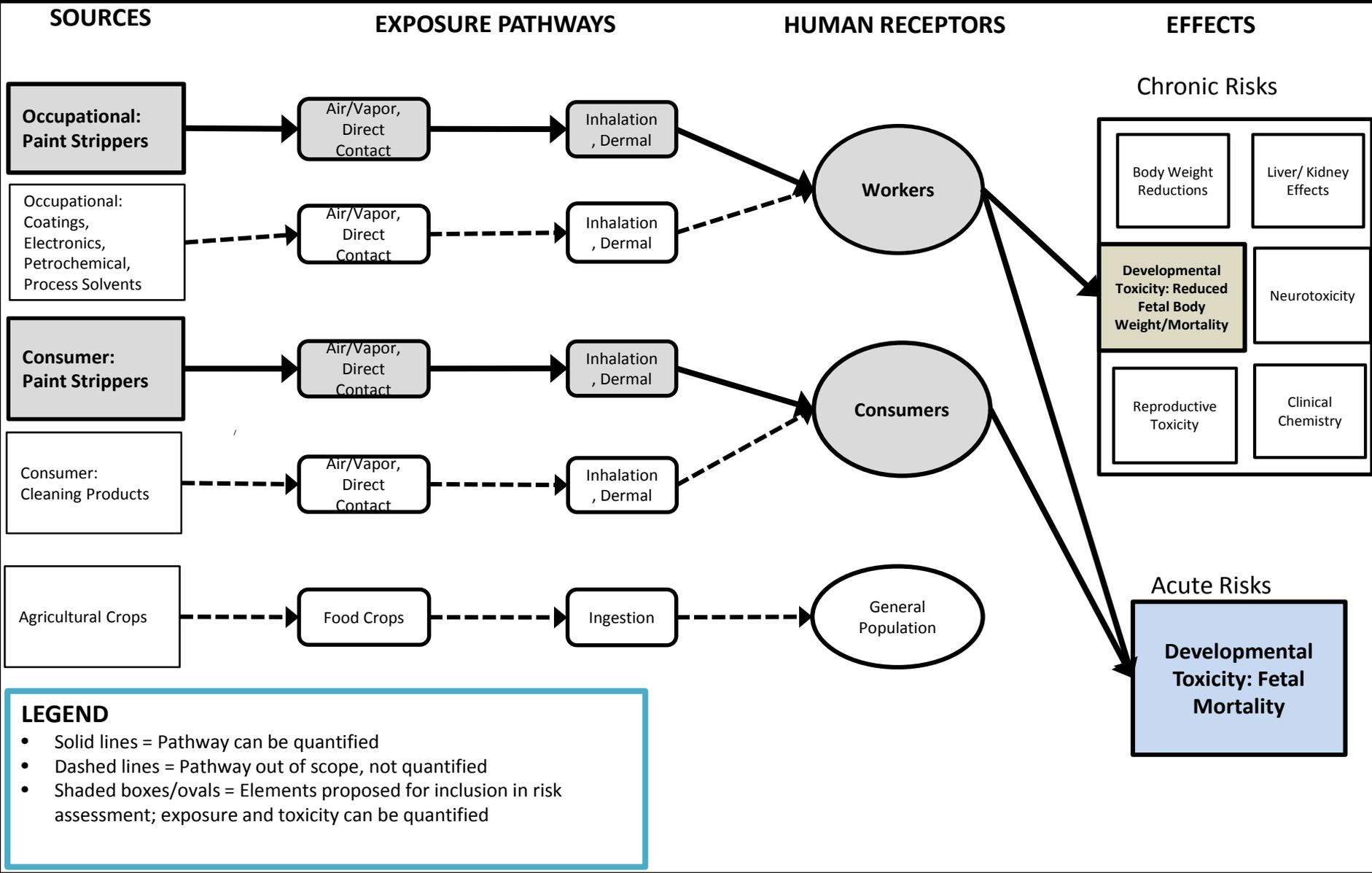
- Physical chemical properties
 - Solubility in water (log k_{ow})
 - Volatility/vapor pressure @ 20°C
 - Melting point
- Environmental Fate
 - $\frac{1}{2}$ life in environmental media
- Persistence
 - Abiotic and Biotic breakdown
- Bioconcentration and Bioaccumulation

REVIEW TOXICITY AND EXPOSURE ASSESSMENT OUTPUTS

- The first component in risk characterization is to gather, review, compare, and organize the outputs of the exposure and hazard-toxicity assessments, exposure duration, frequency, and magnitude
- Pathways and receptors
- Toxicity values



Conceptual Model from Problem Formulation



DURATION ADJUSTMENT

Fit for purpose hazard or risk?

emergency response guidance e.g., PALs and AEGLs

Acute typically time weighted average (TWA)

- Occupational 8 hr TWA
- Consumer 24 hr TWA
- General population 1-24 hr TWA (e.g., fence line)?

Chronic scenarios typically

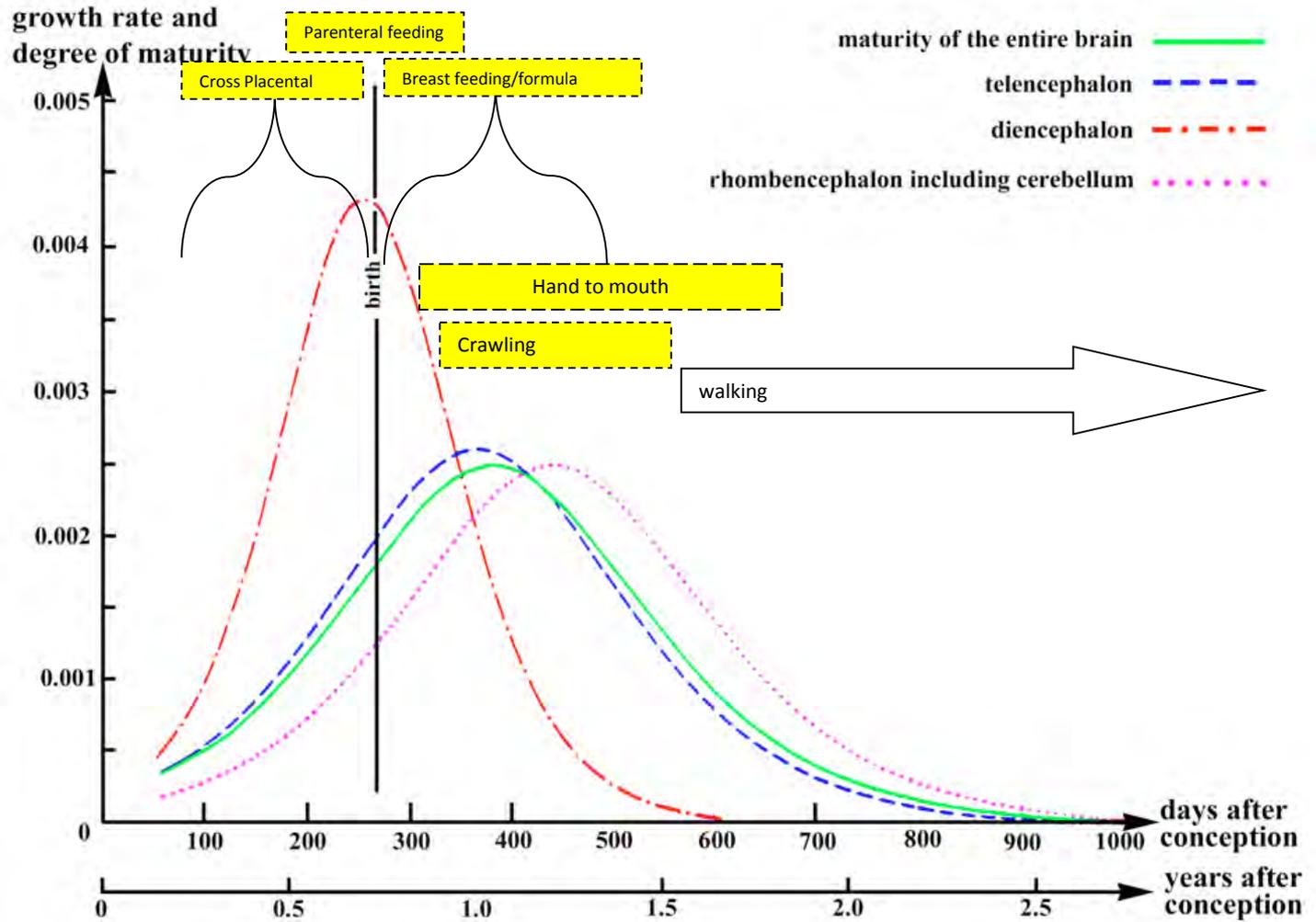
- Average daily dose
- Life-time average daily dose

INTRINSIC & EXTRINSIC FACTORS

- Exposure Factors: Sex and Life-Stage Dependent
- Biological Factors: Life-Stage Dependent
 - Pharmacokinetic
 - Pharmacodynamics
- Considerations and Types of outcomes for acute risk estimation:
 - Reversible (e.g., hypoxia, narcosis)
 - Irreversible (e.g., lethality, terata)
 - Latent expression

EXAMPLE OF OVERLAP OF EXPOSURE FACTORS WITH CRITICAL DEVELOPMENTAL PERIODS

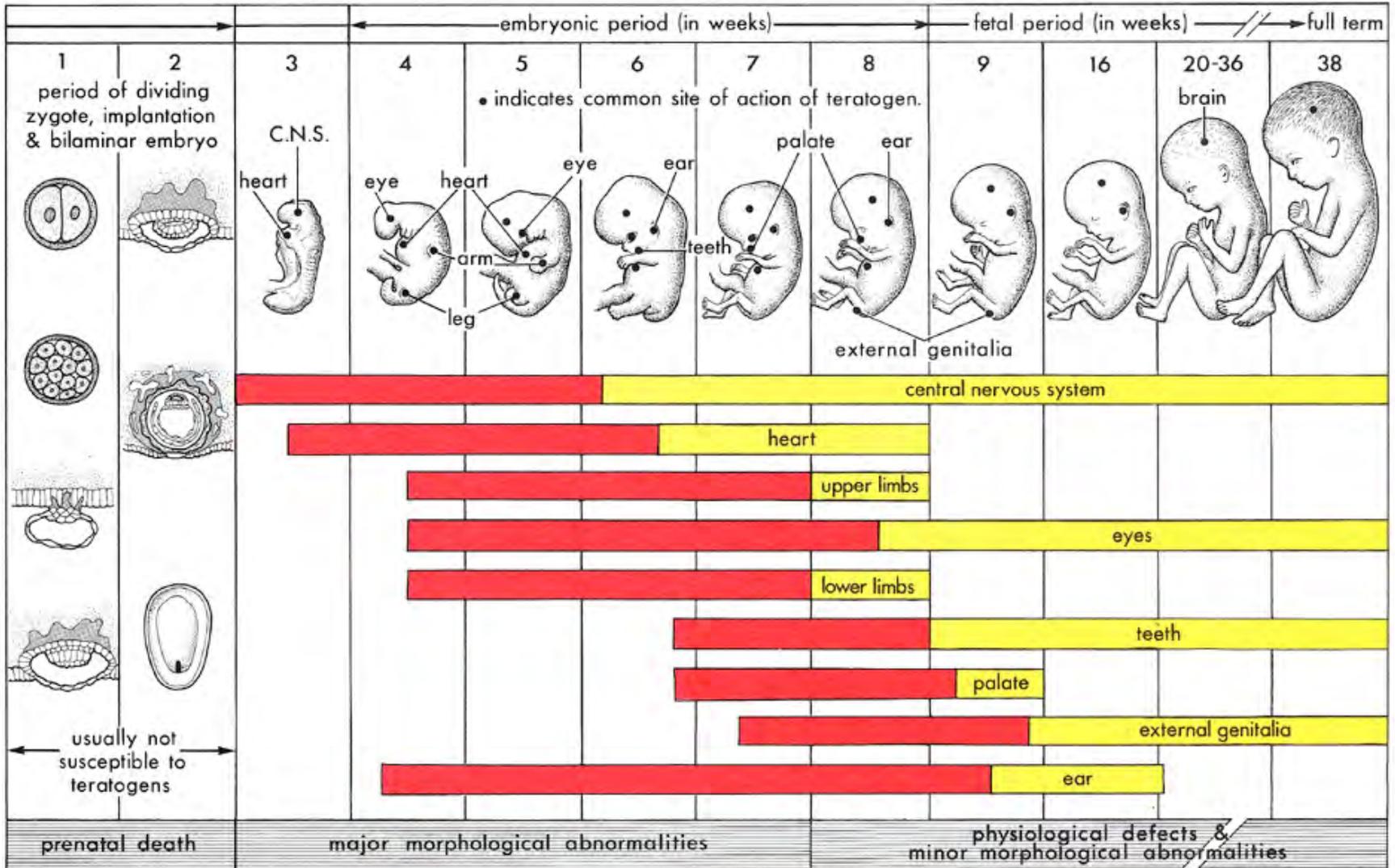
HUMAN BRAIN GROWTH RATE AND OVERLAP WITH EXPOSURE CONSIDERATIONS



ACUTE EXPOSURES RESULT IN?

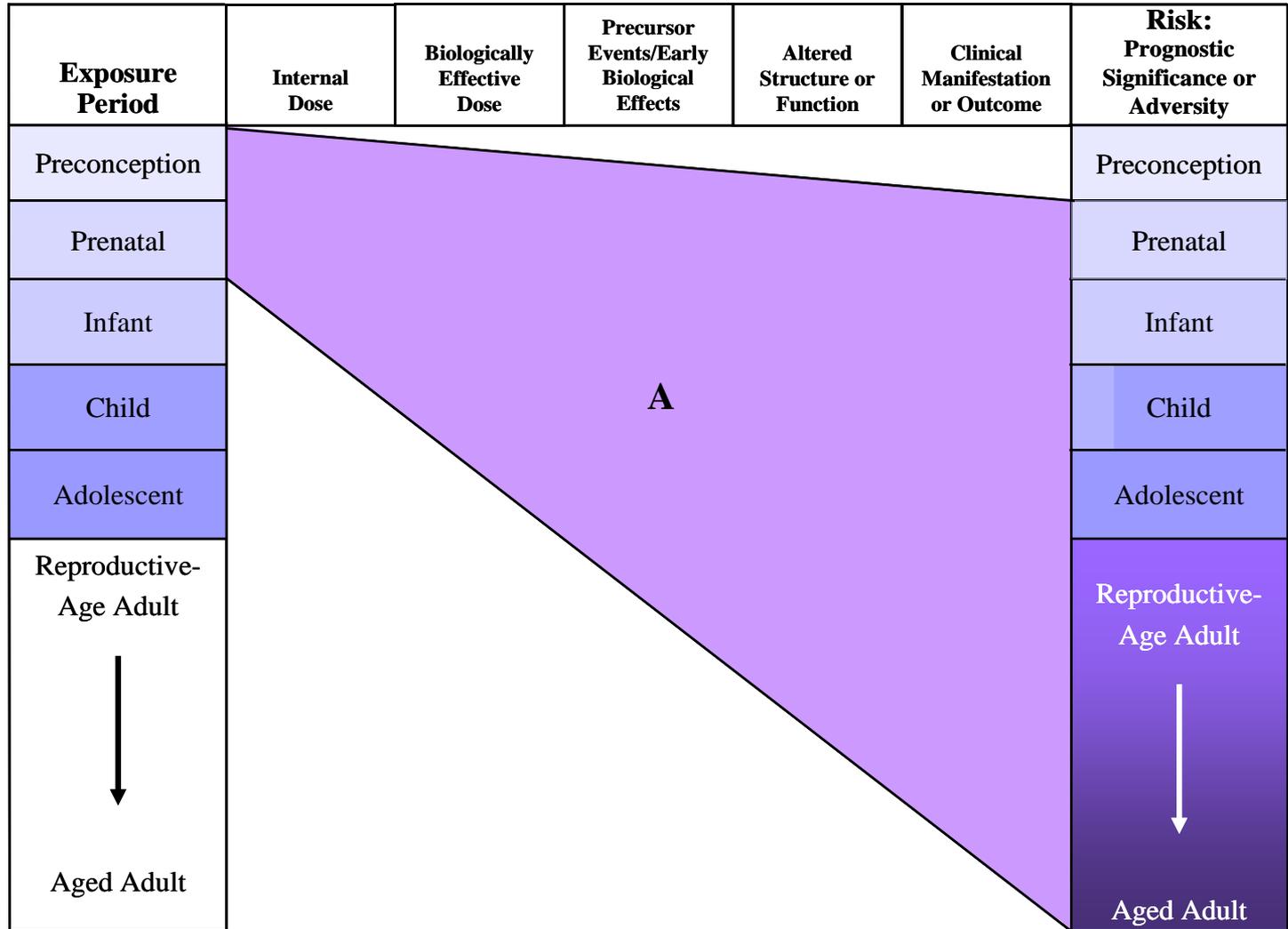
- Acute exposures- acute effects
 - Adult
 - Developmental
- Acute exposures – chronic effects/irreversible
 - Death
 - Terata
 - Latent effects not manifested until unmasked by aging or pharmacological challenge?

Critical Periods Of Development



Moore, 1982; *The Developing Human*

LIFE-STAGES OF OUTCOMES AFTER DEVELOPMENTAL EXPOSURE



LIFE-STAGES OF OUTCOMES AFTER DEVELOPMENTAL EXPOSURE

Exposure Period	Internal Dose	Biologically Effective Dose	Precursor Events/Early Biological Effects	Altered Structure or Function	Clinical Manifestation or Outcome	Risk: Prognostic Significance or Adversity
Preconception						Preconception
Prenatal						Prenatal
Infant						Infant
Child						Child
Adolescent	B					Adolescent
Reproductive-Age Adult						Reproductive-Age Adult
↓						↓
Aged Adult						Aged Adult



HAZARD AND DOSE RESPONSE

Choice of less than lifetime exposure studies ($< 1/10$ the of lifespan) for chronic health effects **Point of Departure (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

Outlined in EPA RfC/RfD document and

EPA Children's Risk Assessment Framework

EXPOSURE CALCULATION

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)

CHRONIC OCCUPATIONAL EXPOSURE CALCULATIONS

The average daily concentration (ADC) and lifetime average daily concentration (LADC) are used to estimate workplace exposures for non-cancer and cancer risks, respectively. These exposures are estimated as follows:

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

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

SCREENING LEVEL RISK ESTIMATION

QUANTIFYING NON-CARCINOGENIC HAZARD

- The hazard quotient (HQ) is the ratio of the exposure level at a site to the reference dose

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

- Hazard quotient values are variable, with values less than and equal to 1 generally considered indicative of acceptable hazard

RISK CALCULATION

Cancer

$$\text{Risk} = \text{Human Exposure} \times \text{IUR}$$

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

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

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

- Where:
- MOE = Margin of exposure (unitless)
- Hazard value (POD) = HEC or HED (ppm)

GUIDANCE WITH RELEVANCE TO ACUTE EXPOSURES

- [Guidelines for Developmental Toxicity Risk Assessment](#)
- [Guidelines for Carcinogen Risk Assessment-](#)
- [Guidelines for Carcinogen Risk Assessment-](#)
- [A Review of the Reference Dose and Reference Concentration Processes](#)
- [A Framework for Assessing Health Risk of Environmental Exposures to Children](#)
- [Exposure Factors Handbook](#)
- [Summary Report of the Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy When Assessing Exposure to Children](#)
- Acute Exposure Guideline Levels for Airborne Chemicals- <http://www.epa.gov/aegl>
- Hazardous waste- <http://www3.epa.gov/epawaste/hazard/tsd/td/combust/finalmact/ssra/05hhrap7.pdf>
- Acute, 8-hour and Chronic Reference Exposure Levels (chRELs)- <http://oehha.ca.gov/air/allrels.html>
- Health effects glossary- <http://www3.epa.gov/airtoxics/hlthef/hapglossaryrev.html>

RESOURCES



To learn more about TSCA Work Plan
Chemicals & Assessments:

<http://www2.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-chemicals>