Codex and IPCS Risk Assessment Framework: A Case Study on Benzoates

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Jun 9, 2017 IFIC's Monthly Member Update "When is Too Much Not Enough?"

"… [W]e are gorging ourselves on food information, but **we're starving for nutritional literacy**."

"In a media environment where **sound science takes a back seat to slick headlines**, … without reliable information about food, **public health challenges** such as obesity, food safety, and chronic diseases will be **much more difficult to overcome**."

- Joseph Clayton, CEO

Agenda

- Importance of Science in Regulatory Decision-Making
- CCFA Benzoate Background
- ICBA 2016 Benzoates Investigation
  - Exposure
  - ADI Considerations
- Key Takeaways
- Appendix
  - How is safety of food additives established?
    - Risk characterization
    - Comparing NOAEL, ADI & EDI
  - ICBA Refined Benzoate EDI Assumptions
  - Suggested Revisions to ADI – Interspecies Pharmacokinetics Differences

Importance of Science in Regulatory Decision-Making

Codex Alimentarius

1963 Joint UN FAO/WHO Food Standards Programme Dual Mandate

Science-based policies

Protect health of consumers

- International science-based standard setting

Fair Trade Practices

- Harmonization of global standards and guidelines
- WTO Sanitary and Phytosanitary Standards (SPS) agreement

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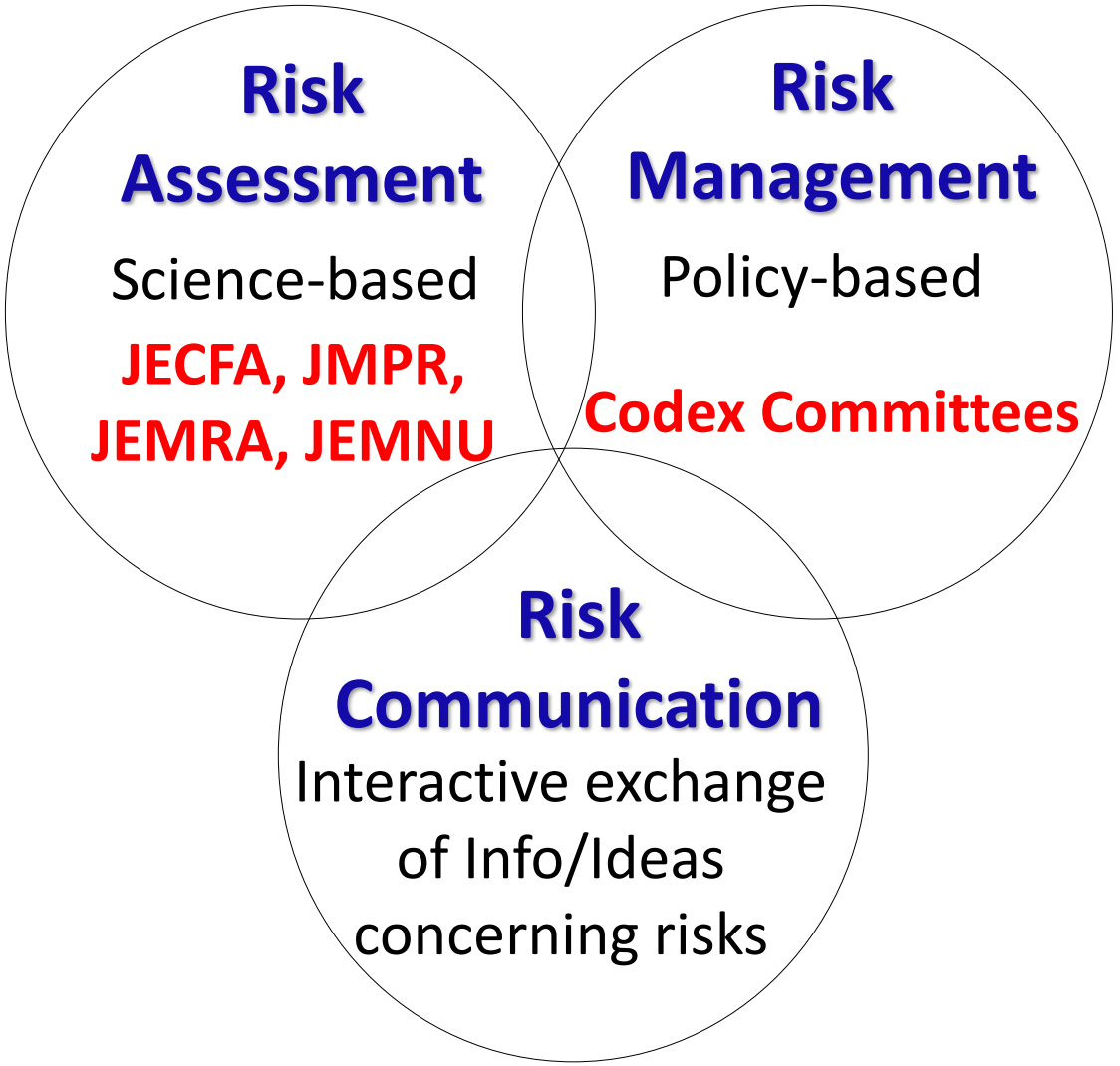
Here is what Codex standards attempt to do…

WHO Risk Analysis Framework (1987)



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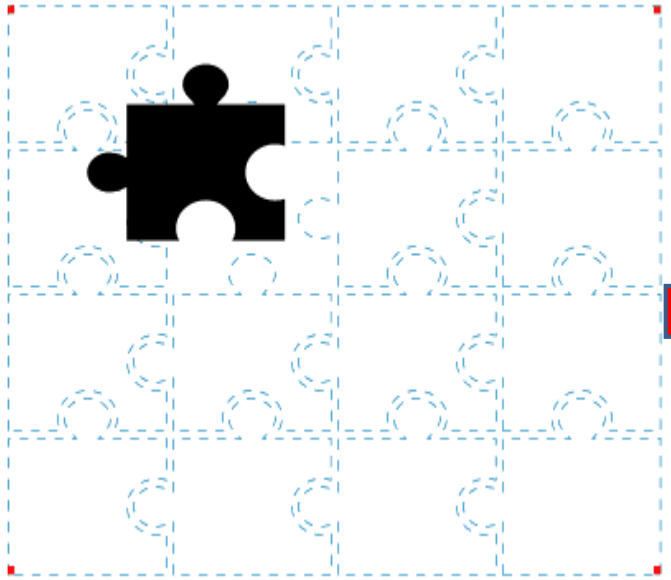
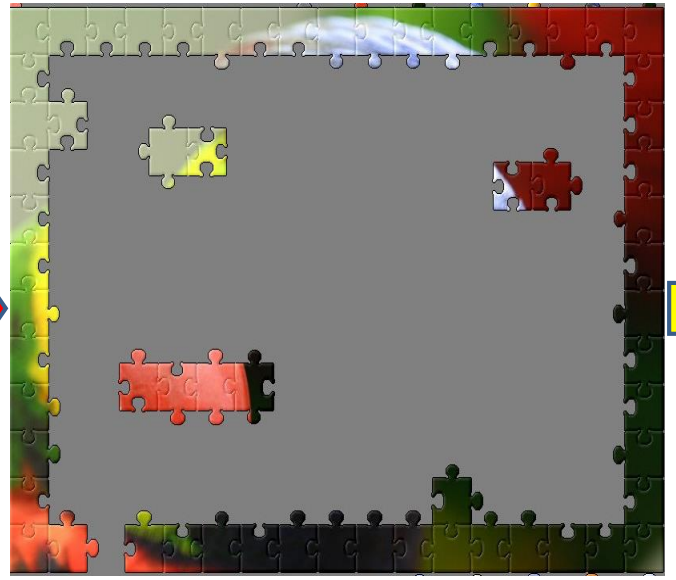
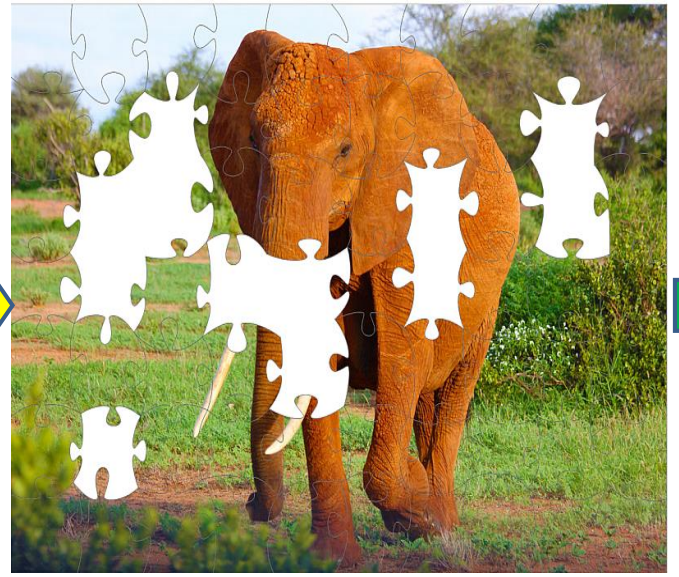
Science jigsaw – Piecing it together

One study **Limited evidence** **Clear evidence**







Building the evidence - Timeless

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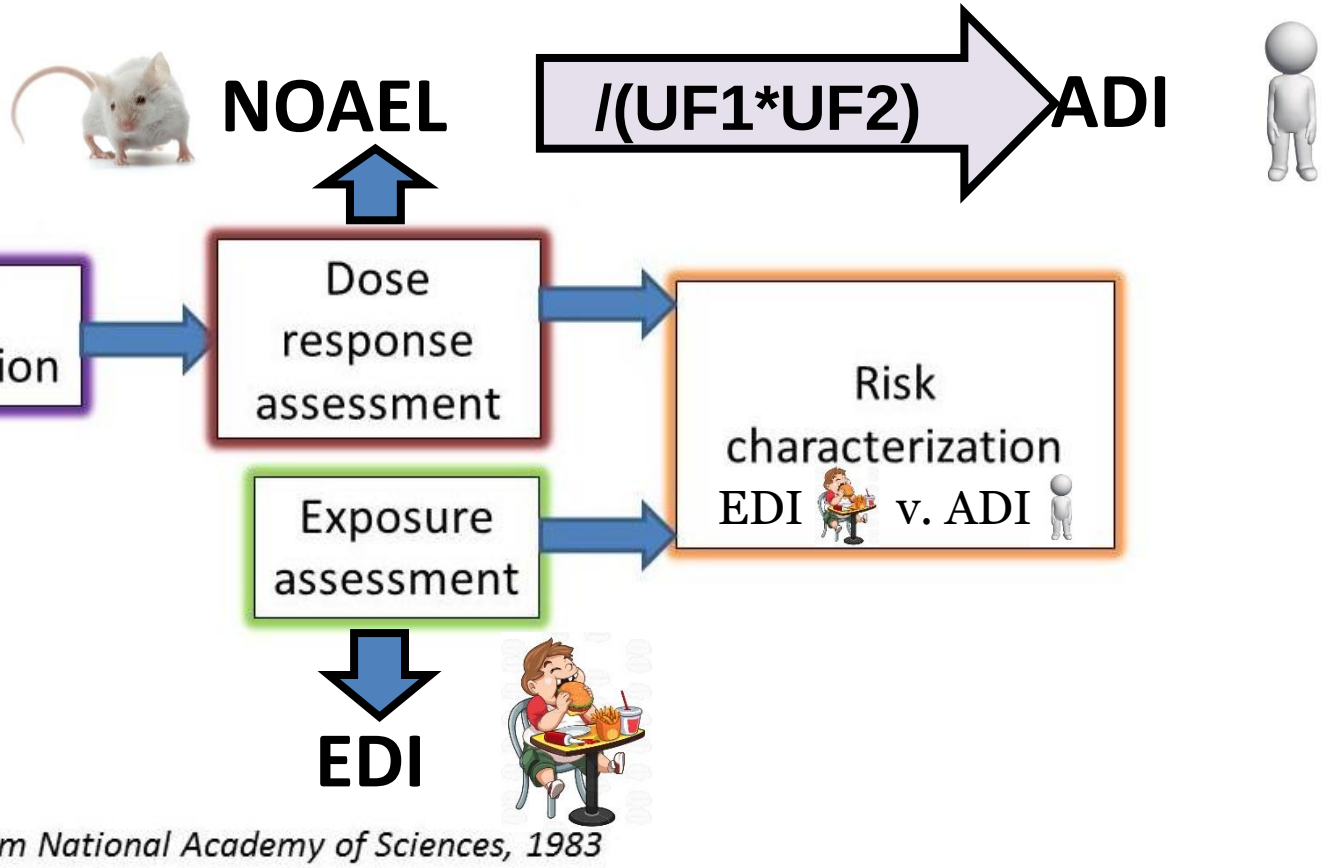
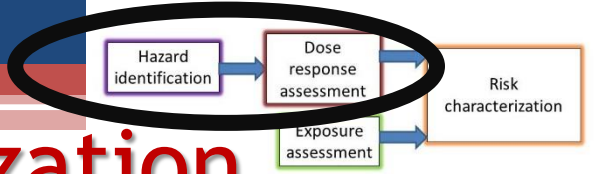
Risk assessment



Adapted from National Academy of Sciences, 1983

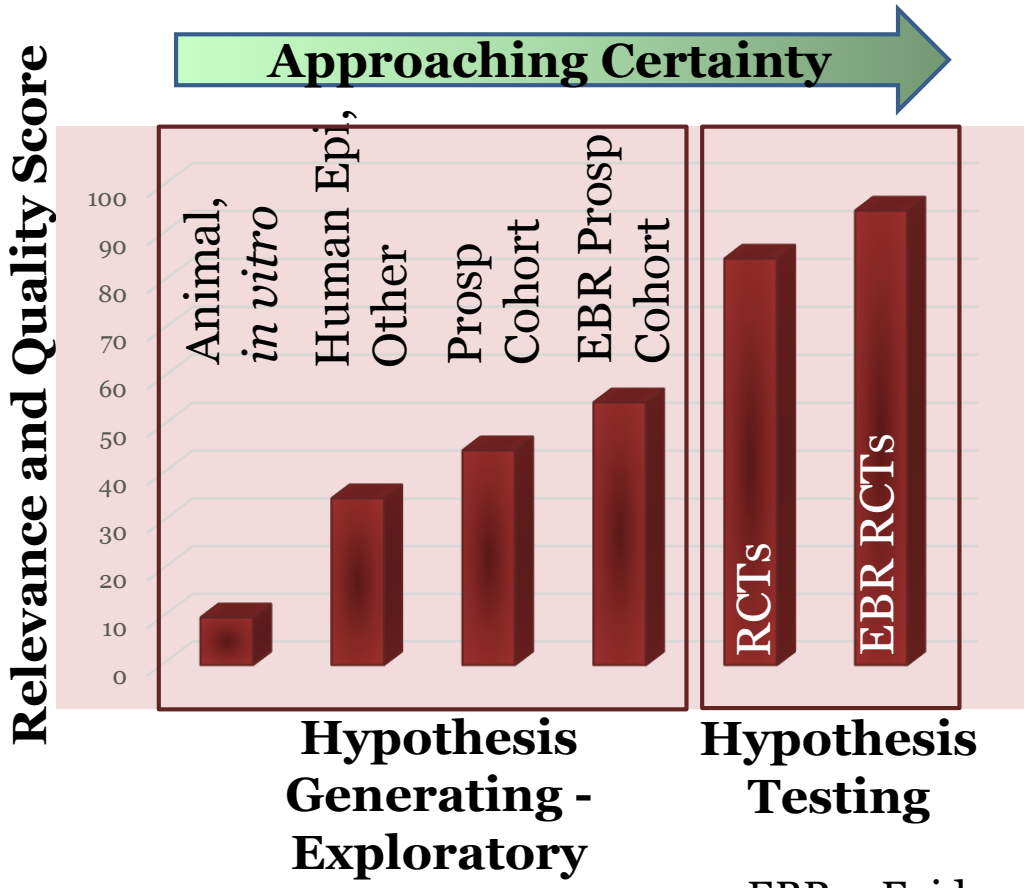


Risk assessment - Hazard ID and Characterization

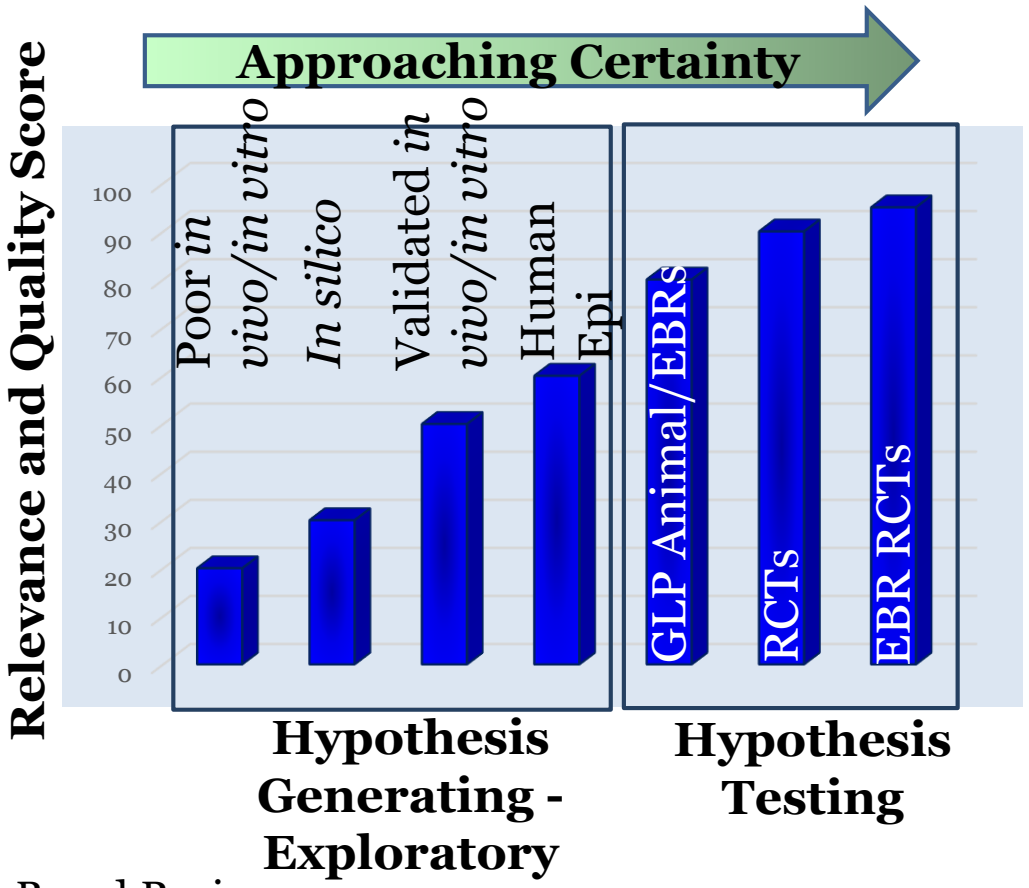
- Human studies (e.g., epidemiological – i.e., RCTs, observational cohort, cross-sectional, case-control; surveillance; etc.)
- Animal toxicological studies (human surrogate)
  - Wide range of endpoints (observational, functional, biochemical and pathological)
  - Two species (e.g., mice and rats) and both sexes (F/M)
  - Testing relevance to human exposure – model, route, frequency, duration, vehicle (e.g., diet, gavage, water)
  - Toxicity Testing
    - General Systemic Toxicity
    - Short-term (acute toxicity, subchronic toxicity)
    - Genotoxicity (DNA-reactive)
    - Carcinogenicity (long-term)
    - Reproductive/developmental toxicity – prenatal/postnatal in parents/offsprings and subsequent offspring development (equivalencies across species; maternal toxicity considerations)
    - Target Organ Toxicity
    - Additional testing if necessary (e.g., neurotoxicity, immunotoxicity, allergenicity via decision-tree approaches gastrointestinal considerations, etc.)
    - Mode of Action

How does science stack up?

Nutrition Science



Ingredient/Product Toxicology



EBR = Evidence-Based Reviews
(Systematic Reviews and Meta-Analyses)

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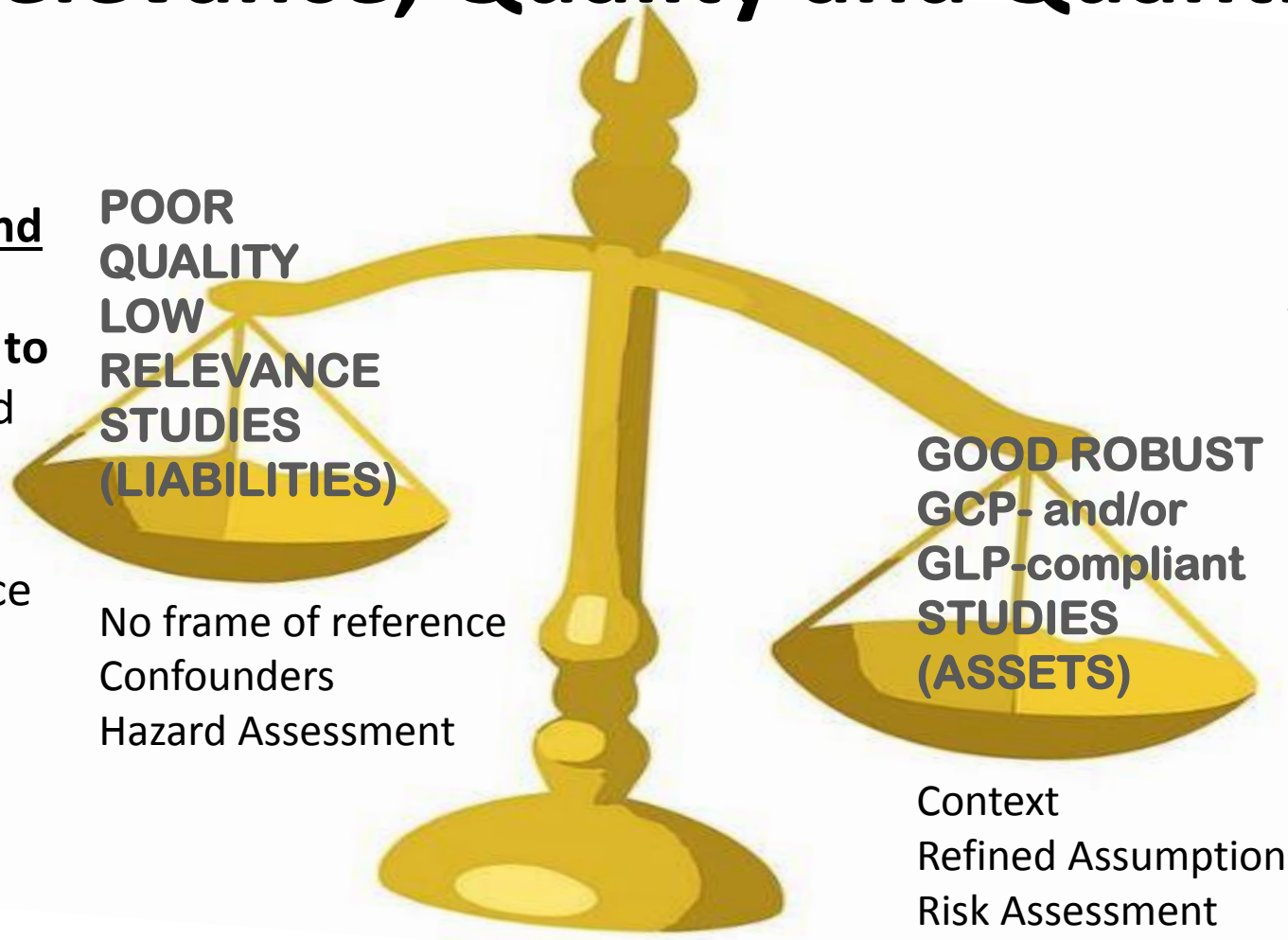
Scientific Weight of Evidence
Relevance, Quality and Quantity

World Health Organization

"In the evaluation of human health risks, **sound human data, whenever available, are preferred to animal data**. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies."

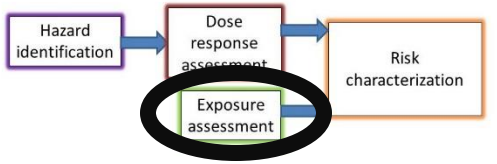


World Health Organization

"**Critical evaluation of study designs** and their **findings** and **interpretation of the results** are the **most important steps** in **risk assessment**."

Informed policy and regulatory decision-making

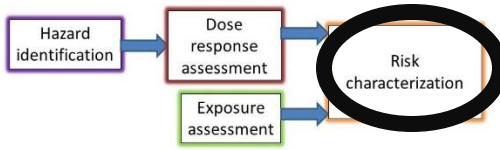
IPCS Risk assessment – Exposure Assessment



Adapted from National Academy of Sciences, 1983

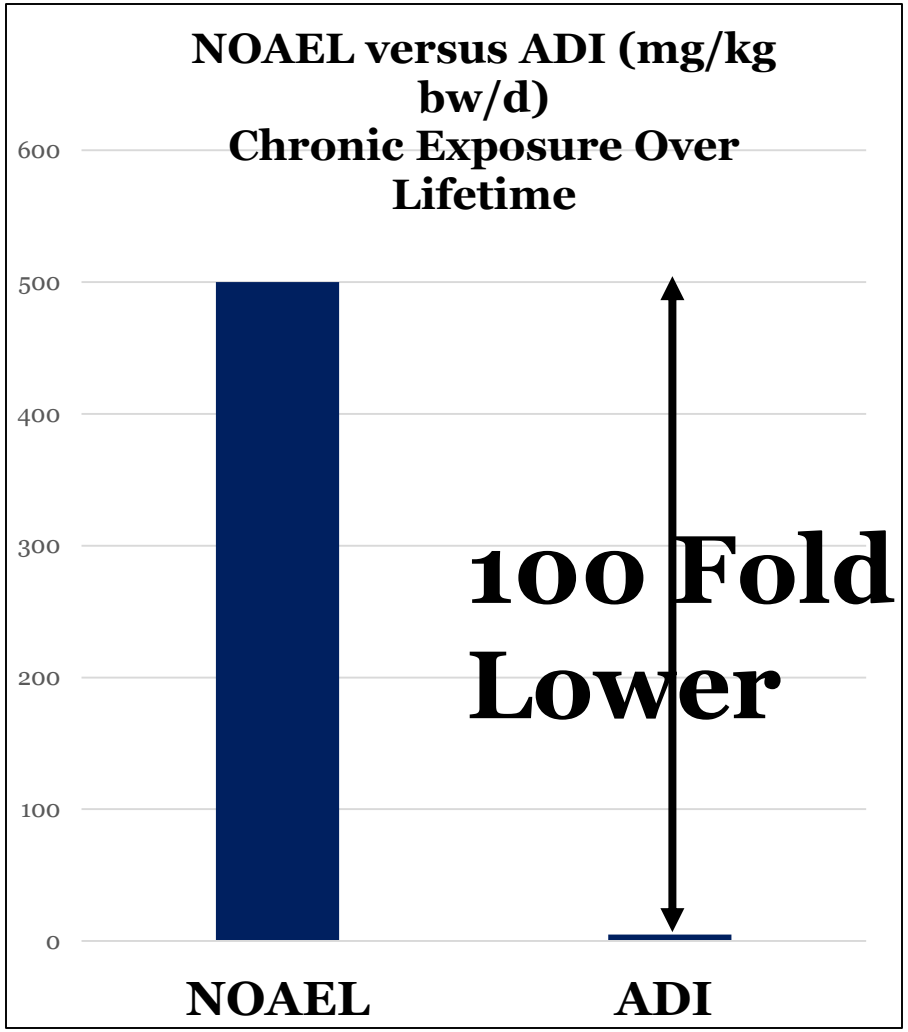
- Individual dietary survey data (most precise)
- Additive concentration only for proportion of market used in (not whole food category)
- Brand loyalty
- Chronic dietary 'usual' exposure - **90th percentile**
  "consumers only" often represents high consumers
- Dietary exposure to additive predominantly influenced by one food, use selected individual foods approach
- Model accuracy – food consumption data and food chemical concentration data applied to same specified food;
- Representative national populations to understand international situation
- Chronic exceedance over lifetime

IPCS Risk assessment – Risk Characterization Comparing NOAEL, ADI & EDI



Adapted from National Academy of Sciences, 1983

- NOAEL (*over lifetime)*
- Traditional ADI = NOAEL/100 (UFs)
- Opportunity exists to lower UF based on CSAF to derive evidence-based ADI
- EDI = Daily food consumption pattern x Additive Use Levels in Foods (per person)



Acronyms:
NOAEL=No Observed Adverse Effect Level
UF=Uncertainty Factors
ADI=Acceptable Daily Intake
EDI=Estimated Daily Intake

Is EDI <, = or > ADI?

CCFA Benzoate Background

Benzoate Technological Justification

- Propensity for microbial spoilage in beverages not well understood or appreciated
  - GHP, HACCP and GMP - ALWAYS
  - Ubiquitous microflora - 100% sterile environment impossible
  - ALL tools needed to minimize risk of spoilage in beverages
- Product-to-product differences determine *whether*, *which* and *at what levels* preservatives are necessary
  - Beverage formulations, packaging, processing, storage and distribution conditions and inherent microflora
- Micro-challenge tests to assure functionality
  - Levels < Minimum Inhibitory Concentrations (MIC) can cause adaptation, acquired resistance and tolerance
- Example: strawberry flavor concentrate (not poor hygiene) origin of *Asaia Lannensis* acetic acid bacteria in spoiled strawberry-flavored beverage in spite of presence of 200 mg/kg benzoate
  - Kregiel, D., A. Rygala, Z. Libudzisz, P. Walczak, E. Oltuszak-Walczak. *Asaia lannensis – the spoilage acetic acid bacteria isolated from strawberry-flavored bottled water in **Poland***. Food Control 26 (2012): 147-150.
- No good substitutes for benzoates
  - Sorbates less effective, generate off-notes and present operational impediments (fountain systems)

2015 JECFA Assessment Triggered Safety Concern at Codex

- Estimated daily intake (EDI) among toddlers and young children at presumed 95th percentile consumer-only population exceeded Acceptable Daily Intake (ADI)
  - In fact, the 97.5th percentile exposure from South African toddlers/young children 'consumers only' was actually used, NOT the 95th percentile (let alone the 90th percentile).

- As a result, 2016 CCFA lowered benzoate levels in beverages by as much as 75% in some cases to 250 ppm as benzoic acid which has created significant challenges

- Opportunities exist to refine assumptions both on exposure and hazard

International Council of Beverages Associations (ICBA) 2016 Benzoates Investigation Exposure (EDI) & Hazard (ADI)

Exposure Assessment - Refined Benzoate Estimated Daily Intake (EDI)

2016 ICBA exposure assessment approach meets and exceeds WHO Principles (EHC 240)

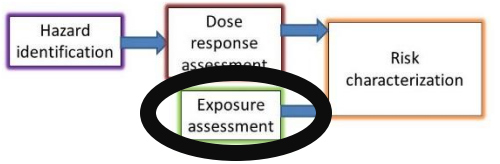
- Individual dietary survey data (most precise)
- Representative use levels based on market presence
- **Brand loyal 95th percentile consumer** 'worst-case' scenario considered
  (**standard is typically 90th percentile**)
- Individual foods approach – beverages (primary contributor to dietary benzoates)
- Accurate model – specific uses for specific beverage types
- Selected representative national markets to ensure adequate global protection
- No chronic exceedance of ADI, even for worst-case scenario

Refined Benzoate Estimated Daily Intake (EDI)

- Study Design
  - Countries included with ML > 250 mg/kg
    - Brazil, Canada, Mexico and U.S.A.
  - Designed to capture high intake populations

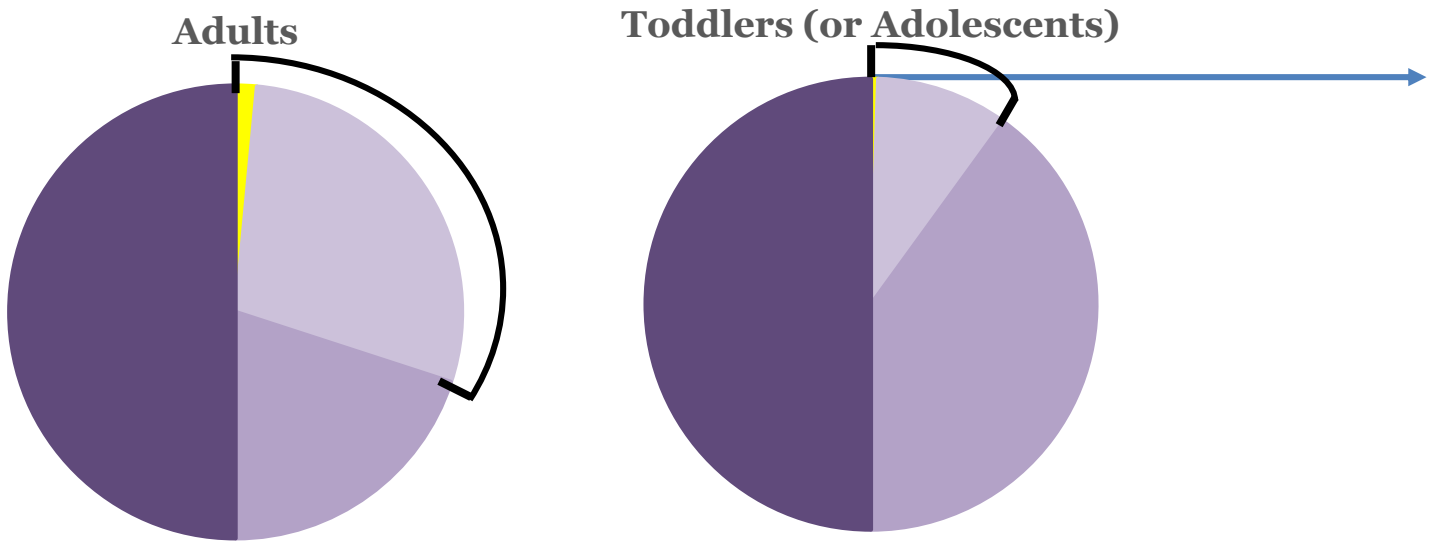
- Modelling Approaches
  - Individual-based data reflective of individual consumption patterns
    - Allows population breakdown by 'general population (per capita)'; 'consumers-only'; mean & 95th percentile; 'age breakouts;
    - Probabilistic modelling (based on market volume share)
    - Brand-loyal consumer modelling (worst-case scenario – max. level to main contributing category (i.e., regular CSD), market-weighted average to all others)
  - Probabilistic models and non-brand loyal categories – data based on market volume share.

Martyn, D., A. Lau and A. Roberts. 2017. Benzoates intakes from non-alcoholic beverages in Brazil, Canada, Mexico and the United States. Food Additives and Contaminants. Part A, 34:9, 1485-1499. https://doi.org/10.1080/19440049.2017.1338836



Adapted from National Academy of Sciences, 1983

Refined Benzoate ADI



Sliver of population (i.e., 95th percentile toddler) is being compared to ADI.

- **>95th Adults consumers**
- ≤95th Adults consumers
- All other consumers
- Non-consumers

- **>95th Toddlers (or Adolescents) consumers**
- ≤95th Toddlers (or Adolescents) consumers
- All other consumers
- Non-consumers

KEEP IN MIND –

EHC 240 suggests high consumers are represented by the 90th percentile.

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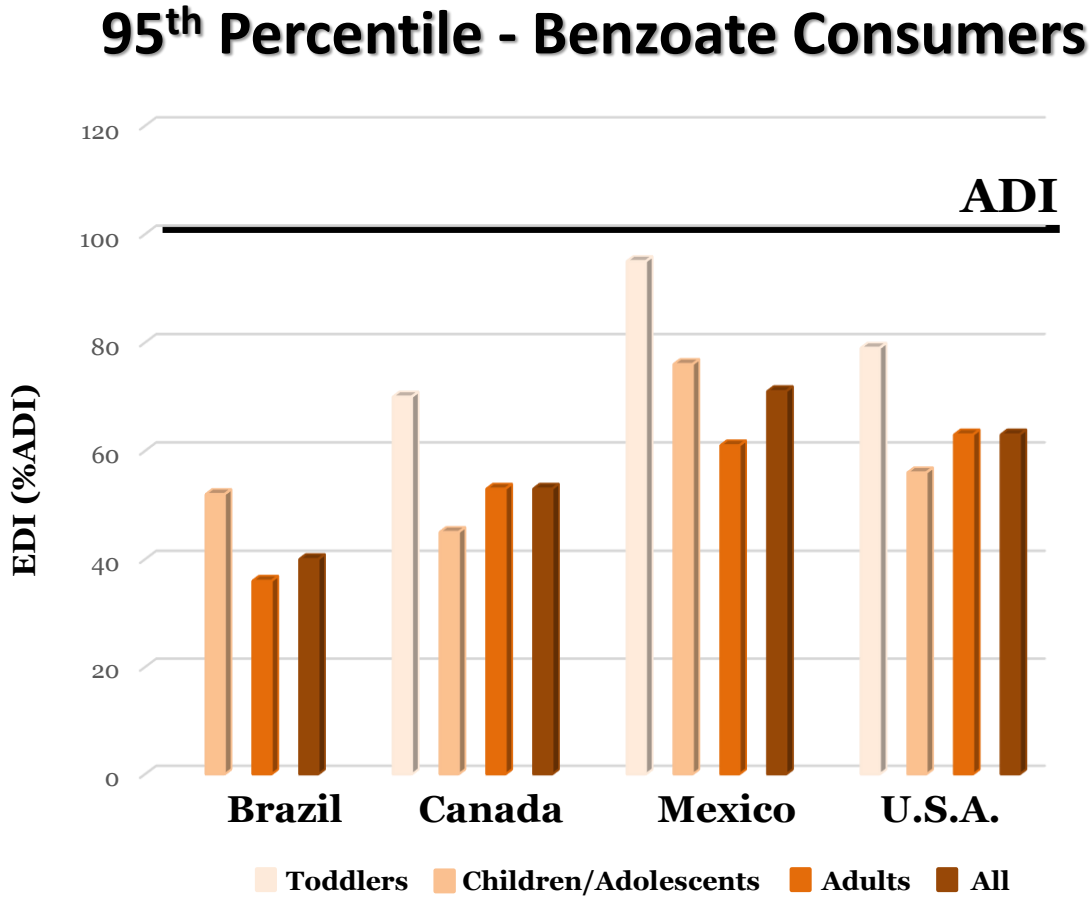
Refined Benzoate EDI

EDI (%ADI) Over Life Stages - Probabilistic



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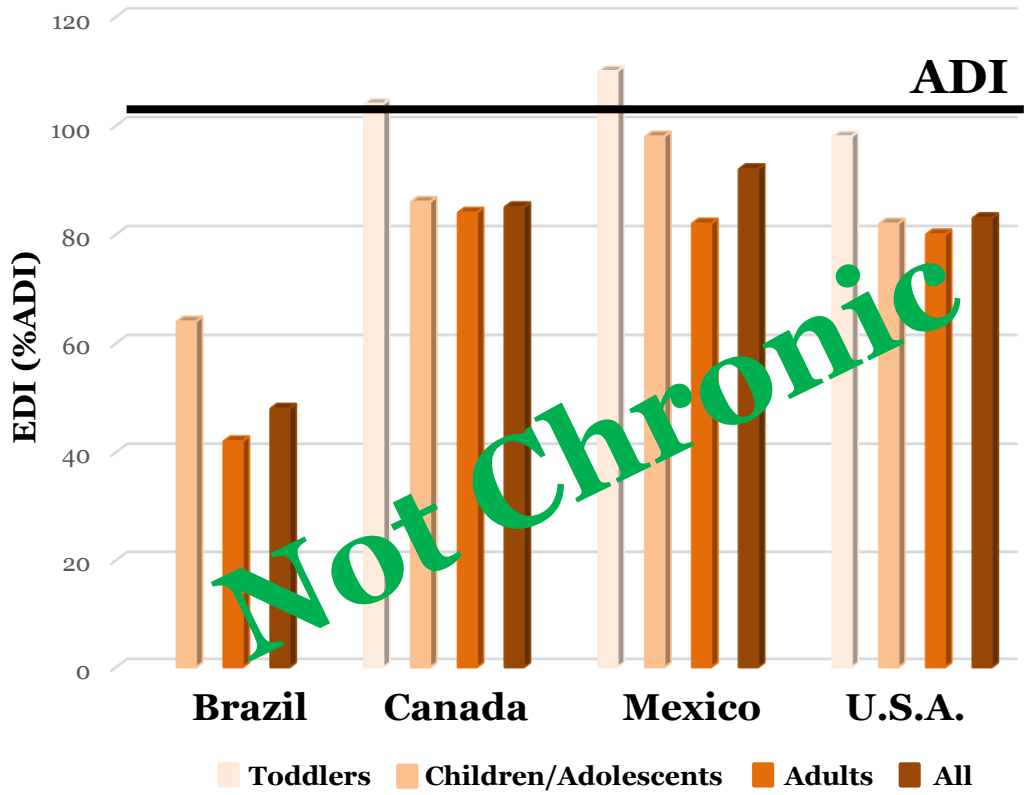
Refined Benzoate EDI

EDI (%ADI) Over Life Stages - Brand Loyal



KEEP IN MIND –

Represented here is:

- **The 95th percentile consumer, NOT the 90th percentile**
- **100% presence at Codex ML is assumed for regCSD to capture 'brand-loyalty', NOT market-distribution**

ADI incorporates default 100x uncertainty factor from 'default' no observed adverse effect level in rodents across a lifetime.

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Refined Benzoate Estimated Daily Intake (EDI)

- EDI from beverages - "No Safety Concern"
  - Based on 'high intake' markets
  - Refined complex exposure assessment model, using primarily individual dietary survey data
    - Market volume weighted use level information – representative of realistic consumer practices
  - Findings:
    - Toddlers/Young Children regular CSD brand loyal 95th percentile scenario results at ADI
    - Over a lifetime, EDI is below ADI – supports benzoate's long-term safe use
- Please see Appendix

Hazard Characterization - ADI Considerations

- Current JECFA ADI for Benzoates as Benzoic Acid - Conservative
  - "Default" **N**o **O**bserved **A**dverse **E**ffect **L**evel (NOAEL) – the highest dose tested – in pivotal study to derive ADI (Conservative)
  - ADI not based on a "true" NOAEL – could have been higher!
  - Utilized 100X uncertainty factor (UF) from the *default* NOAEL
  - 100X Uncertainty Factor (Conservative)
    - Benzoic Acid metabolized and excreted similarly in rodents and humans – little interspecies pharmacokinetic variation suggests opportunity to reduce uncertainty factor by at least 2x
    - Opportunity to increase ADI two-fold, by reducing 100X UF to 50X UF
  - Current: 0-5 mg/kg bw/day
  - Possibly higher?

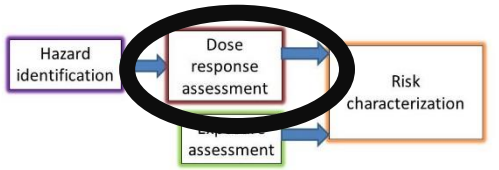
Hoffman, T.E., and W.H. Hanneman. 2017. Physiologically-Based Pharmacokinetic Analysis of Benzoates in Rats, Guinea Pigs and Humans: Implications for Estimating Interspecies Uncertainty Factors in Risk Assessments. *Computational Toxicology* 3:19-32 (https://doi.org/10.1016/j.comtox.2017.06.002)

Zu, K., D.M. Pizzurro, T.A. Lewandowski and J.E. Goodman. Pharmacokinetic Data Reduce Uncertainty Regarding the Acceptable Daily Intake for Benzoic Acid and Its Salts. *Regulatory Toxicology and Pharmacology*.89: 83-94. (https://doi.org/10.1016/j.yrtph.2017.07.012)

Endpoint	Human	Rat
Rate/Extent of Absorption	• Approximately 100% absorption after oral ingestion (e.g., Informatics, Inc., 1972 216-5980; IOMC, 2000 216-4218)	• Approximately 100% absorption after oral ingestion (e.g., Informatics, Inc., 1972 216-5980; IOMC, 2000 216-4218)
Rate/Extent of Metabolism	• Rapidly and completely metabolized (Informatics, Inc., 1972 216-5980; IOMC, 2000 216-4218; Tremblay and Qureshi, 1993 216-5939) • Peak plasma benzoic acid levels at 1-2 hours after oral administration (Kubota et al., 1988 216-5932; Kubota and Ishizaki, 1991 216-5930)	• Rapidly and completely metabolized (IOMC, 2000 216-4218; Bridges et al., 1970 216-5986; Thabrew et al., 1980 216-5984) • Peak plasma benzoic acid levels 3 hours after oral gavage administration (Adams et al., 2005 216-5922; JECFA, 1996 216-4405)[a]
Metabolites and Metabolic Enzymes	• Hippuric acid is the primary metabolite (Informatics, Inc., 1972 216-5980; IOMC, 2000 216-4218; Tremblay and Qureshi, 1993 216-5939) • At high doses (>500 mg/kg), benzoyl glucuronide is a secondary metabolite (Kubota and Ishizaki, 1991 216-5930; JECFA, 1996 216-4405) • Metabolism driven by conjugation with glycine; saturable process at high doses (i.e., ≥160 mg/kg) (Kubota et al., 1988 216-5932; Kubota and Ishizaki, 1991 216-5930; MacArthur et al., 2004 216-4214)	• Hippuric acid is the primary metabolite (Bridges et al., 1970 216-5986; Thabrew et al., 1980 216-5984) • At high doses (>500 mg/kg),[b] benzoyl glucuronide is a secondary metabolite (Adams et al., 2005 216-5922; JECFA, 1996 216-4405) • Metabolism driven by conjugation with glycine; saturable process at high doses (i.e., >120 mg/kg) (Schwab et al., 2001 216-5938; Gregus et al., 1992 216-7049; Simkin and White, 1957 216-6010; JECFA, 1996 216-4405)
Rate/Extent of Elimination/ Clearance	• 75-100% excreted as hippuric acid within 6-24 hours (Kubota et al., 1988 216-5932; Kubota and Ishizaki, 1991 216-5930)	• 75-100% excreted as hippuric acid within 24 hours (Bridges et al., 1970 216-5986; Thabrew et al., 1980 216-5984)

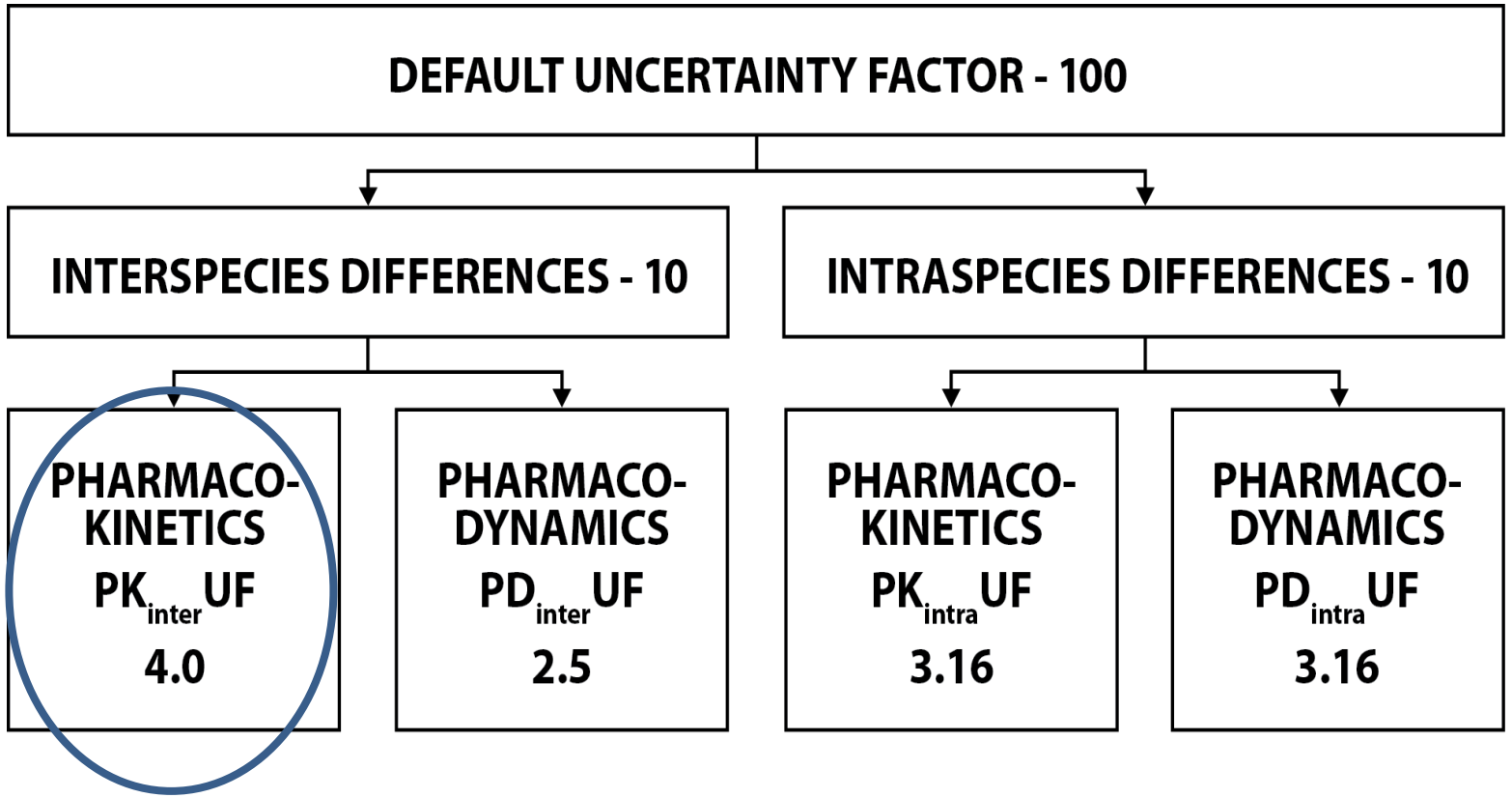
Zu, K., D.M. Pizzurro, T.A. Lewandowski and J.E. Goodman. Pharmacokinetic Data Reduce Uncertainty Regarding the Acceptable Daily Intake for Benzoic Acid and Its Salts. *Regulatory Toxicology and Pharmacology*. 89:83-94. (https://doi.org/10.1016/j.yrtph.2017.07.012)

Risk assessment - Hazard Characterization

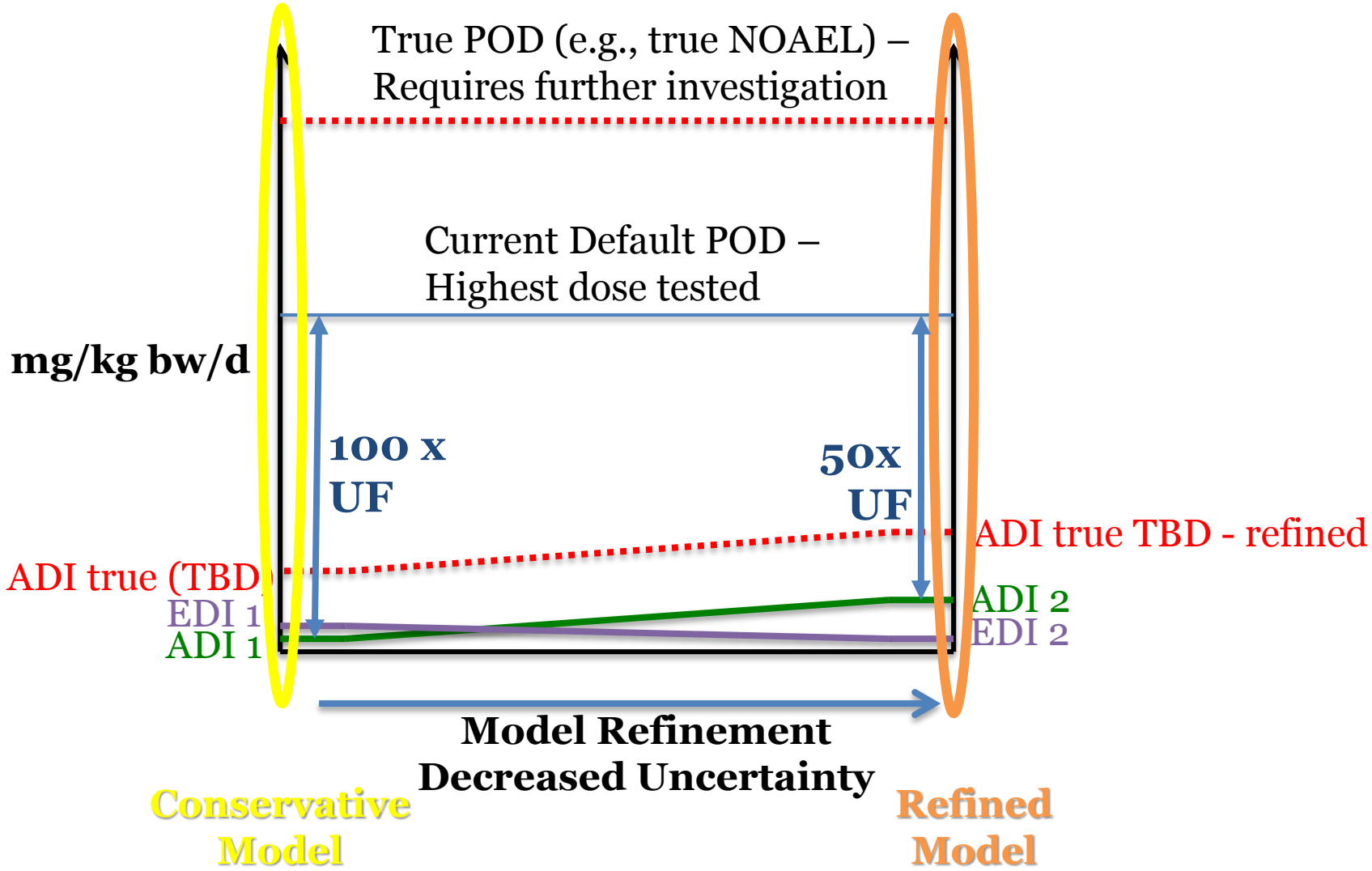


Adapted from National Academy of Sciences, 1983

UF & CSAF – IPCS 2005



Benzoate Risk Characterization – Model Refinement



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Next Steps

- ABA 2020 Goal - Update benzoate safety point of departure (PoD) to derive an appropriate ADI
  - Benzoate tox research plan developed
  - Research initiated, early 2018

Key Takeaways

Key Takeaways

- Regional differences should not preclude support for science-based positions in Codex
- ICBA updated and refined benzoate exposure assessment for beverages shows **benzoates in beverages pose no safety concern** based on:
  - 'High intake' markets setting ceiling for exposures
  - Application of WHO EHC 240 criteria (including representativeness)
  - Chronically, EDI is below current 'default' ADI – supports long-term safe use;
  - Toddlers/Children reg CSD brand loyal 95th percentile scenario at ADI;
  - ADI based on default NOAEL (**not true NOAEL**) – i.e., true ADI could be higher.
- Additionally, uncertainty factor for interspecies pharmacokinetic variability can be reduced by at least 2-fold (**possibly increase ADI** by at least 2x, from 5 to 10 mg/kg bw/d)
- Reductions to (or below) 250 mg/kg (as benzoic acid) are not scientifically warranted – examples of unintended consequences may include:
  - Increased spoilage/food waste;
  - Reduction in product shelf-life;
  - Disproportionate impact on smaller manufacturers.

Key Takeaways

Consumers deserve accurate ingredient safety information.

- We must *provide clear context around ingredient safety* in view of propensity for media sensationalism
  - **Communicate and contextualize ingredient safety properly** to reassure consumers
- We must *manage uncertainty* appropriately:
  - With generally accepted toxicological principles
  - And using **reasonable** assumptions

Thank You

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Appendix

How is safety of food additives established?

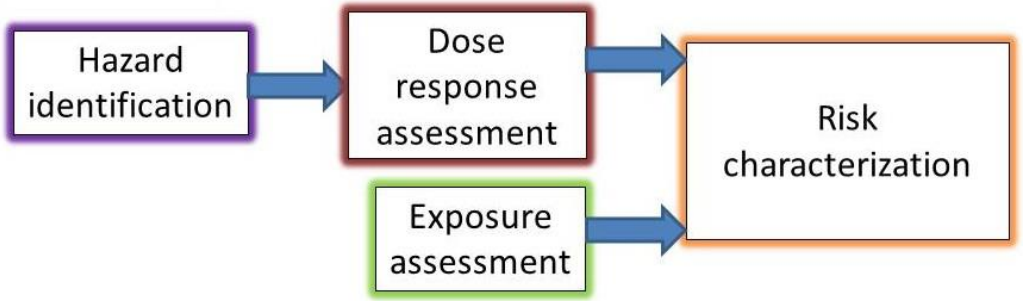
Risk characterization

Fundamentals of Food Additive Safety

- Dose makes the poison (Paracelsus)

Significant Electrolyte Imbalance = Death

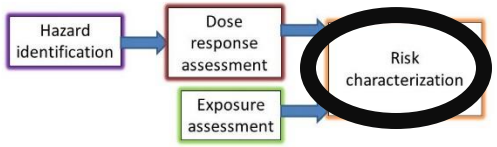
- How to establish additive safety?



Adapted from National Academy of Sciences, 1983

Risk characterization

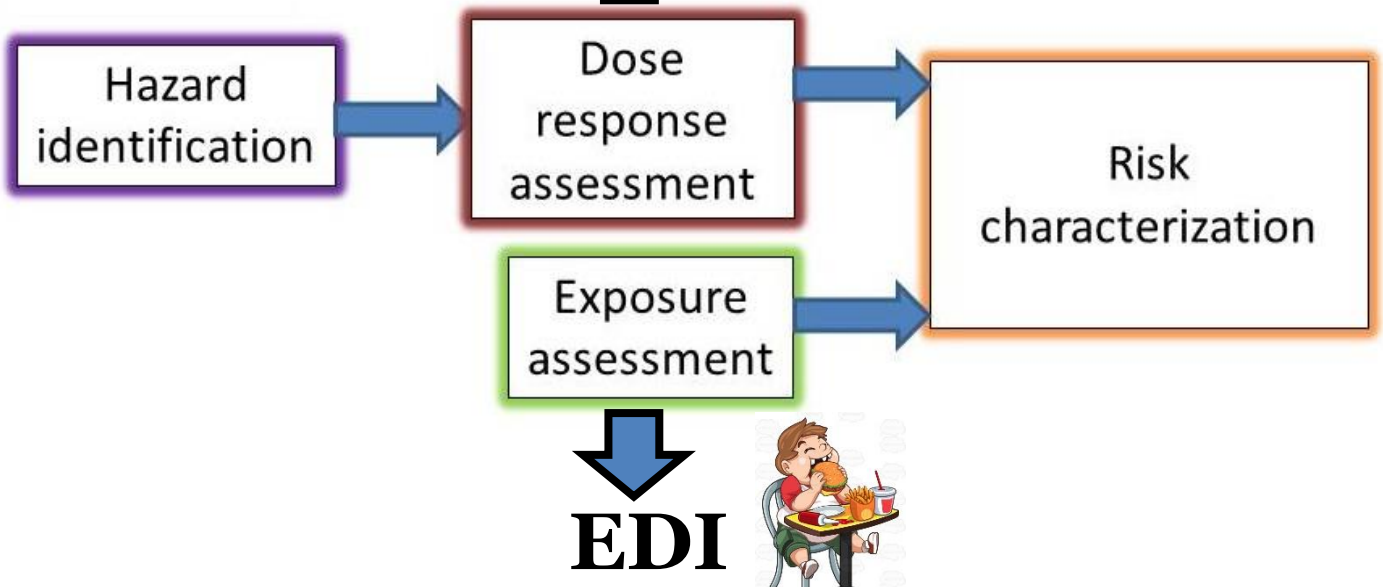
- How to establish additive safety (con't)?
  - Toxicology in rodents as surrogate for humans
  - Point of Departure (POD) may be No Observed Adverse Effect Level (NOAEL)
    - Incorporate precaution to extrapolate findings from rodents to humans - uncertainty factor UF1, traditionally 10x, lowered based on evidence
    - Incorporate precaution to account for human variability - uncertainty factor UF2, traditionally 10x, lowered based on evidence
  - Health-based guidance value is Acceptable Daily Intake (ADI) = NOAEL/(UF1xUF2)
  - Estimate risk by comparing the estimated daily intake (EDI) to ADI



Risk characterization

- How to establish additive safety (con't)?

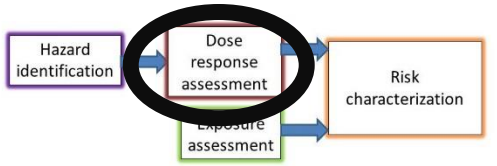
NOAEL /(UF1*UF2) ADI



Adapted from National Academy of Sciences, 1983

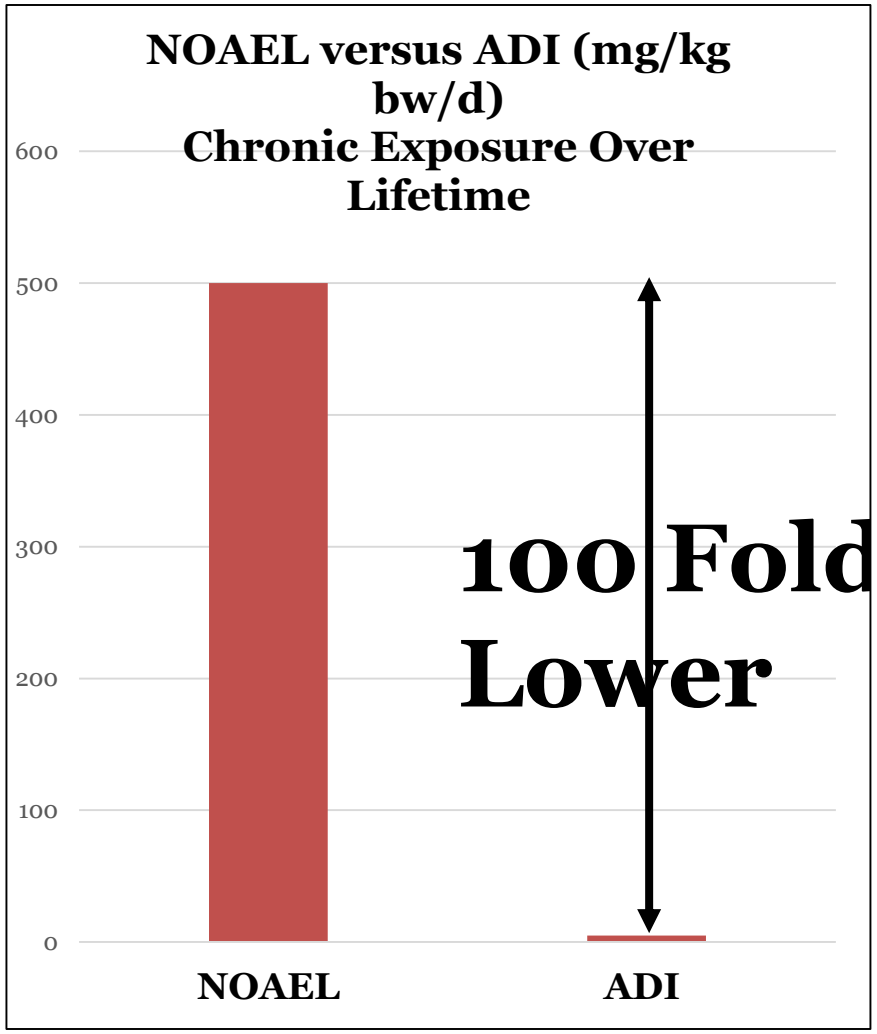
- Risk characterization: EDI  v. ADI 

Risk Assessment - Hazard Characterization Comparing NOAEL and ADI

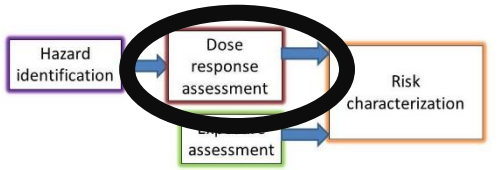


Adapted from National Academy of Sciences, 1983

- NOAEL (*over lifetime)*
- Traditional ADI = NOAEL/100 (UFs)
- Opportunity exists to lower UF to derive ADI based on evidence
- EDI = Daily food consumption pattern x Additive Use Levels in Foods (per person)



Risk assessment - Hazard Characterization



Adapted from National Academy of Sciences, 1983

UF & CSAF – IPCS 2005

DEFAULT UNCERTAINTY FACTOR - 100

INTERSPECIES DIFFERENCES - 10

INTRASPECIES DIFFERENCES - 10

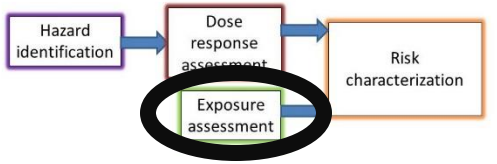
PHARMACO-KINETICS
$PK_{inter}UF$
4.0

PHARMACO-DYNAMICS
$PD_{inter}UF$
2.5

PHARMACO-KINETICS
$PK_{intra}UF$
3.16

PHARMACO-DYNAMICS
$PD_{intra}UF$
3.16

Risk assessment – Exposure Assessment



Adapted from National Academy of Sciences, 1983

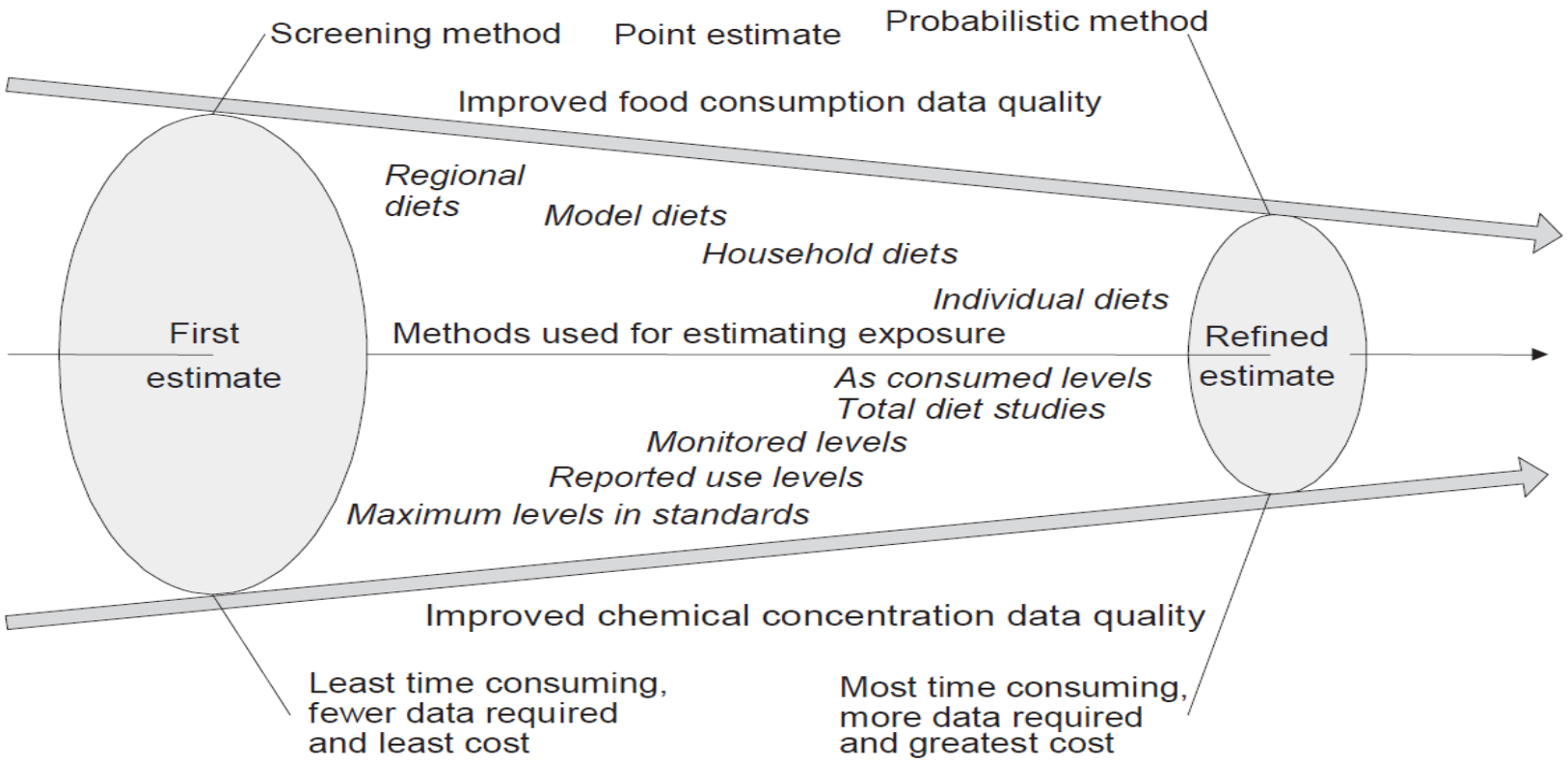
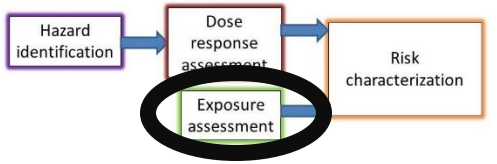
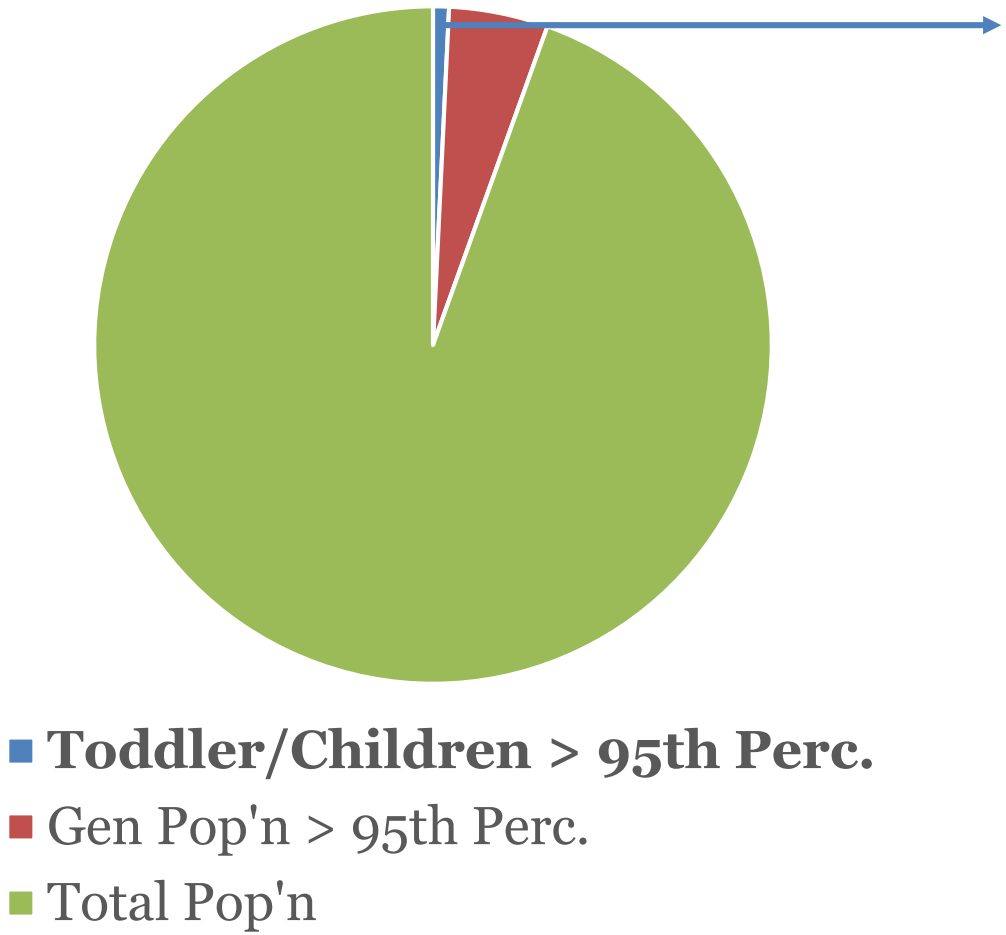


Fig. 6.1. Stepwise approach to obtaining realistic dietary exposure assessments

Risk assessment – Exposure Assessment Estimated Daily Intake (EDI)



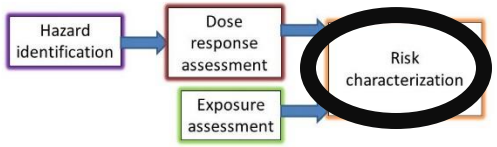
Adapted from National Academy of Sciences, 1983



This sliver of the population (extreme outliers) - 95th percentile toddler/young children consumers - is being compared to ADI.

KEEP IN MIND –

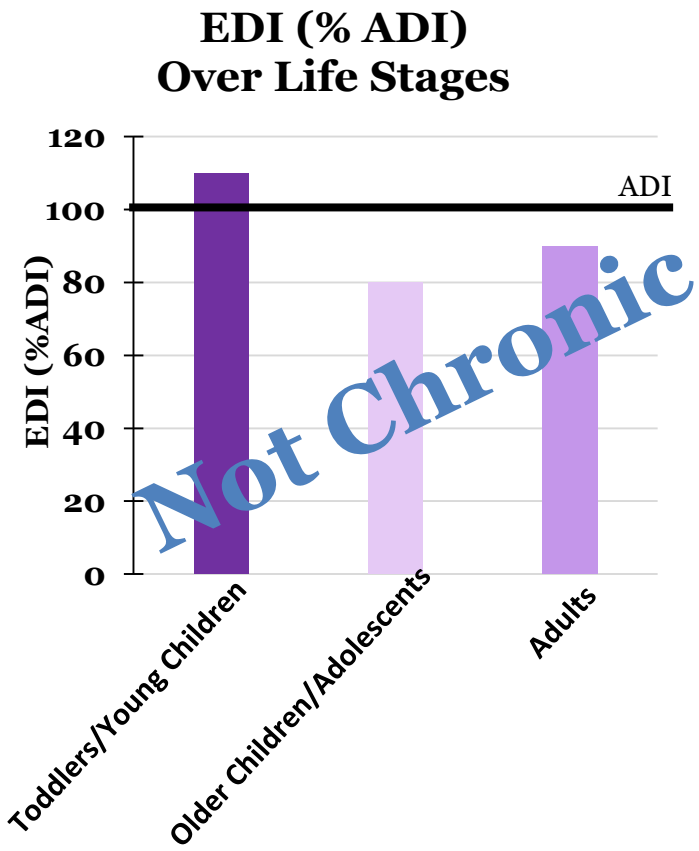
EHC 240 suggests high consumers are represented by the 90th percentile.



Risk Assessment – Risk Characterization
Compare NOAEL/ADI/EDI-Interpreting EDI against ADI?

Adapted from National Academy of Sciences, 1983

- EDI ≤ ADI
  - No further exposure refinement necessary
- EDI > ADI
  - Specific subpop?
  - Further refinement needed to seek more realistic scenarios
  - Verify exceedance across ALL life-stages
  - *Is ADI exceedance chronic across ALL life-stages?* No! Stop. No safety concern.



KEEP IN MIND –

ADI incorporates default 100x uncertainty factor from no observed adverse effect level in test species.

ICBA Refined Benzoate EDI Assumptions

WHO EHC 240	ICBA 2016 Approach	80th JECFA	EFSA 2016
Individual dietary survey data - most precise	Individual dietary records	Primarily population-based Summary Statistics - CIFOCOOss	Population-Based Summary statistics
Additive concentration only for proportion of market used in, not whole food category	• "Representativeness" • Market volume weighted use level information • Applied to specific beverage types within 14.1.4.	Maximum of typical range (i.e., 209 mg/L) applied to entire 14.1.4 beverage category (no market representativeness)	No market representativeness Maximum levels from very specific foods applied to broader category (Examples for children/adolescents: • Crangon 3,800 ppm to 9.2. processed fish/fish products category; • Level of 150 ppm applied to entire 14.1.4. flavoured drinks category; Example for infants/toddlers: • Non-heat treated dairy-based desserts 117 ppm to entire 1.4. flavoured fermented milk products category when mean only 5 ppm!)
Brand loyalty	Brand-loyal 95th percentile consumer to regCSD at all pHs	-	Brand-loyal consumers to multiple food categories – overly conservative
Chronic dietary exposure, 90th percentile "consumers only" often represents high consumers	• Per capita/"consumers only" • Age subgroups • 95th percentile • All beverages • Major contributing beverage (i.e., Reg CSD)	• Per capita/ "consumers only" • Age subgroups • 95th percentile • All beverages (NOTE: 10.9 mg/kg bw/d upper bound in young children 1-7 yrs was established for "consumers only" based on 97.5th percentile of South Africa consumption data)	• Per capita/ "consumers only" • Age subgroups • 95th percentile • All foods, multiple major contributors
Dietary exposure to additive predominantly influenced by one food, use selected individual foods approach	Focus on water-based flavored drink category	Focus on: • beverages (reported use levels), • or, all foods (analytical)	All foods
Model accuracy - food consumption data and food chemical concentration data applied to same specific food;	NHANES coupled with market-weighted levels for same specific beverage type in 14.1.4. Accurate model	Not specific Broadly applied benzoate maximum typical use level (i.e., 209 mg/L) to entire 14.1.4. beverage category (NOTE: Unclear whether water was included under 14.1 relative to consumption amounts)	Not specific Broadly applied benzoate regulatory maximum limit (i.e., 150 mg/L) to entire 14.1.4. beverage category (See examples above) Outdated analytical data
Representative national populations to understand international situation	Representative national markets Brazil, Canada, Mexico, U.S.A. "worst-case" scenario markets – adequate global protection	CIFOCOOss primarily EUMS and China, Japan and Philippines (for relevant age breakouts)	EUMS
Chronic exceedance over life	No	No	No