WHO Principles and Methods for the Risk Assessment of Chemicals in Food (EHC 240) – A brief overview

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AMERICAN BEVERAGE ASSOCIATION

Agenda

- *Codex Alimentarius* and JECFA
- International Programme on Chemical Safety (IPCS) Principles and Methods for the Risk Assessment of Chemicals in Food (Focus: Food Additives)
  - Risk Assessment (Chapters: 2, 4 -7)
  - Special considerations for substances consumed in small amounts (Chapter: 9)
  - Specifications – Chemical Characterization and Testing Methodologies (Chapter: 3)
- Key Takeaways

Codex Alimentarius and The Joint (FAO/WHO) Expert Committee on Food Additives and Contaminants (JECFA)

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

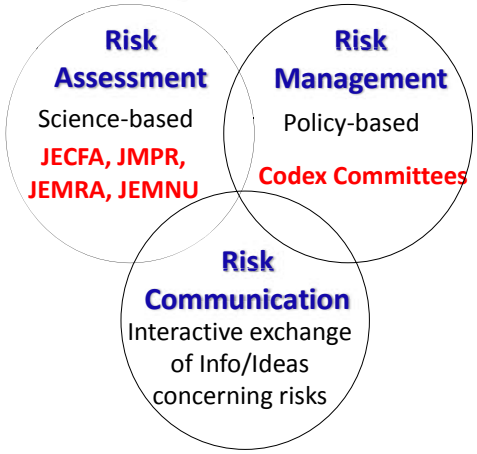
- Harmonization of global standards and guidelines
- WTO Sanitary and Phytosanitary Standards (SPS) agreement

Issue

Non-science based standards and guidelines → MARKET ACCESS →

Here is what Codex standards attempt to do…

WHO Risk Analysis Framework (1987)



Scientific Assessment

- Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA)
- Joint FAO/WHO Meetings on Pesticide Residues (JMPR)
- Joint FAO/WHO Expert Meeting on Risk Assessment (JEMRA)
- Joint FAO/WHO Expert Meetings on Nutrition (JEMNU)

IPCS Principles and Methods for the Risk Assessment of Chemicals in Food (Environmental Health Criteria EHC 240)

EHC 240

- Background
- Risk Assessment (Chapters: 2, 4 -7)
- Special considerations for substances consumed in small amounts (Chapter: 9)
- Specifications – Chemical Characterization and Testing Methodologies (Chapter: 3)

Background

- 1973 WHO EHC Programme objectives (in part):
  - "To promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results."
- EHC monographs…
  - '[R]epresent a thorough evaluation of risks and are **not**, in any sense, **recommendations for regulation or standard-setting**.'
  - 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.
- EHC 240 'Principles and Methods for the Risk Assessment of Chemicals in Food' provides guidance and builds on the following EHC monographs:
  - EHC 70 (1987) – Principles for the Safety Assessment of Food Additives and Contaminants in Food
  - EHC 104 (1990) – Principles for the Toxicological Assessment of Pesticide Residues in Food

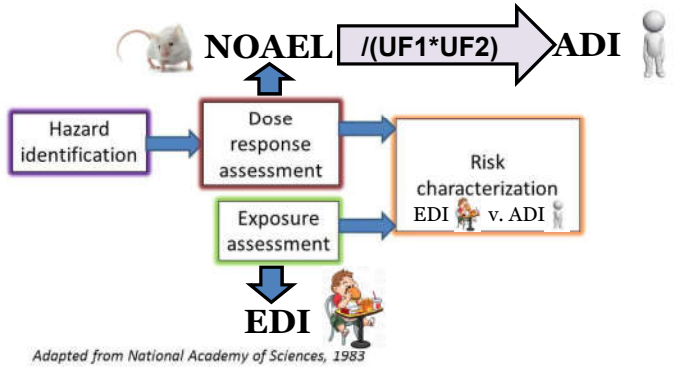
Risk assessment

Fundamentals of Food Additive Safety

Dose makes the poison (Paracelsus - 16th century)

Significant Electrolyte Imbalance = Death

Risk assessment



Risk assessment - Hazard Identification

- Objective (Identification of hazard)
- Scope - Toxicological studies
  - *In vivo* (predominantly rodents - as surrogate for humans - and humans)
  - *In vitro* (cell cultures, tissue preparations)
    - 3Rs: Reduce/refine/replace animal testing (NOTE: *in silico*/*in vitro* approaches are not yet capable of replacing animal testing for most end-points of concern)
- Principles
  - Tiered testing approaches (based on nature/use of substance)
  - Scientifically sound methods and approaches
    - Assess adequacy of **study design**
    - Absorption, distribution, metabolism and excretion (**ADME**) allows selection of appropriate test species/doses
  - Appropriate **statistical analyses** and critical **data interpretation**

Risk assessment - Hazard Identification

- Human studies (e.g., surveillance, adverse event reports, individual case studies epidemiological – i.e., RCTs, observational cohort, cross-sectional, case-control)
- 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

Risk assessment - Hazard Identification

"**Critical evaluation of study designs** and their **findings** and **interpretation of the results** are the **most important steps** in **risk assessment**." - EHC 240 *Summary* (p.l)

Key considerations:

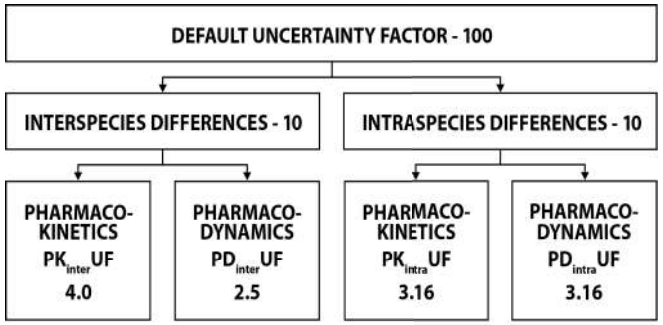
- Human relevance – Mode of action in rodents relevant to humans?
- Study design – controls including historical, interspecies differences, etc. (OECD guidelines) according to GLPs
- Statistical analyses
- Interpretation of findings – direct/indirect effects
- Weight-of-evidence

Risk assessment - Hazard Characterization

- Dose-Response Assessment (most relevant endpoint/most relevant species)
  - EHC 239 (2009) – Principles for Modelling Dose-Response for the Risk Assessment of Chemicals
  - Responses – Must distinguish between adaptive or adverse responses.
  - Risk estimation – Threshold versus non-threshold effects
- Point of departure (POD)
  - Low Observed Adverse Effect Level (LOAEL)
  - No Observed Adverse Effect Level (NOAEL)
  - Benchmark Dose Level (BMDL) – lower one-sided confidence limit
  - Similar food additives metabolized to common metabolite have a 'group' POD
- Extrapolation - Uncertainty factors (UF) and chemical-specific adjustment factors (CSAF)
  - Interspecies – UF default 10x can be reduced based on refined toxicokinetic (TK) and toxicodynamic (TD) differences between rodent model and humans
  - Intraspecies – UF default 10x can be reduced based on refined toxicokinetic (TK) and toxicodynamic (TD) variability between adult and children
- POD-Derived Thresholds
  - Threshold: Health-based guidance values (e.g., acceptable daily intake (ADI)) – w/o appreciable health risk
  - Risk estimates: Margin of exposure (MOE) calculation
  - Risk estimates: Negligible increased incidence of carcinogenicity (1 in 1,000,000)
  - Risk estimates: Linear low-dose extrapolation from a POD

Risk assessment - Hazard Characterization

UF & CSAF – IPCS 2005



Risk assessment – Exposure Assessment

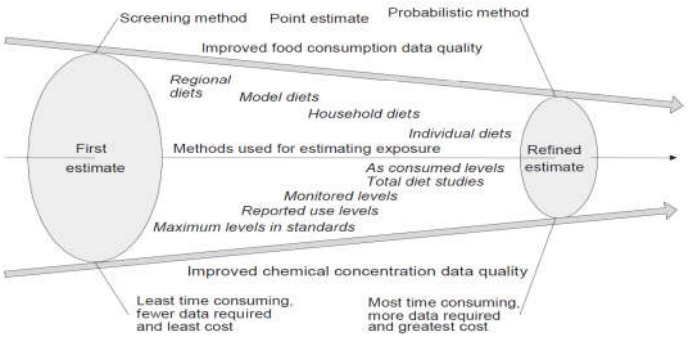
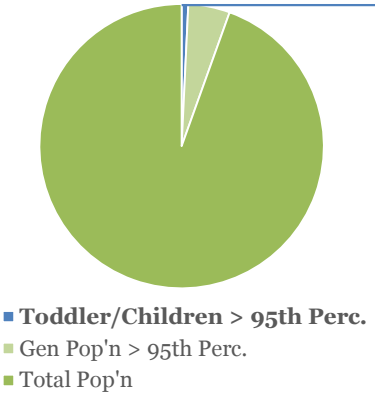


Fig. 6.1. Stepwise approach to obtaining realistic dietary exposure assessments

Risk assessment – Exposure Assessment

- 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

Risk assessment - Exposure Assessment
Estimated Daily Intake (EDI)

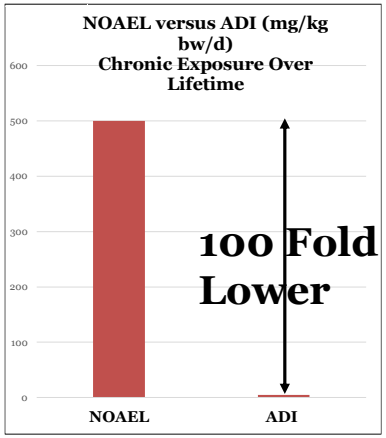


The 95th percentile among toddler/young children (within the general population) may represent extreme outliers.

Should really focus on 90th percentile!

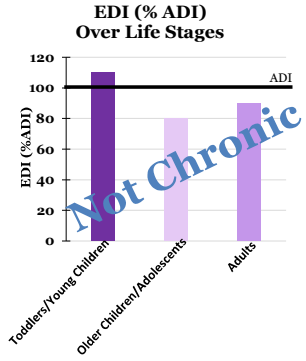
Risk assessment - Risk Characterization
Comparing NOAEL, ADI & EDI

- 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)



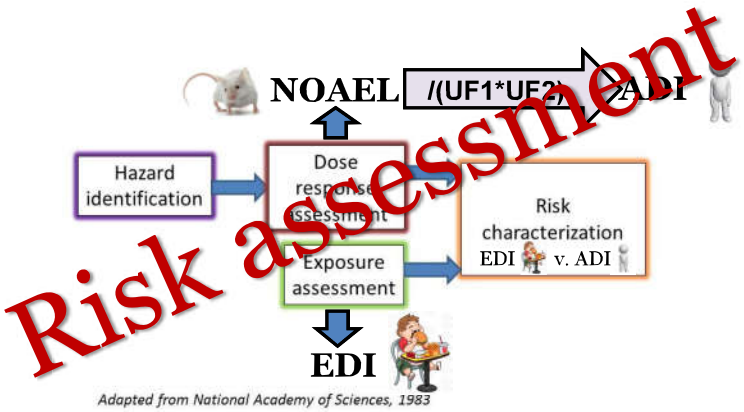
Risk assessment - Risk Characterization
How to interpret EDI against ADI?

- 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.



JECFA Periodic Reviews and Re-evaluations

- New manufacturing process
- New specification
- New data on the biological properties of the compound
- New data concerning nature and/or biological properties of impurities present
- Advances in scientific knowledge relevant to nature or mode of action
- Changes in consumption patterns, levels of use or dietary exposure estimates
- Improved requirements for safety evaluation.

Additional Chapters in EHC 240

- Special considerations for substances consumed in small amounts (Chapter: 9)
  - Threshold of Toxicological Concern –
    - Cramer classes (Procedure for the Safety Evaluation of Flavouring Agents)
    - Conservative estimates of dietary exposure + toxicity of structurally-related substances
  - Principles and procedures for the safety assessment of enzyme preparations
  - Processing aids
- Specifications of Identity and Purity – Chemical Characterization and Testing Methodologies (Chapter: 3)
  - Of sufficient quality to ensure safe use in food (methods of manufacture, food additive fraction, impurities)
  - Stability (in storage) and fate of food additives in food
  - Analytical methods

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Key Takeaways

Key Takeaways

- Regulatory frameworks must be science-based
- Risk assessment paradigm precautionary by nature
  - Hazard identification of most sensitive point-of-departure (POD) that has no adverse effect (or minimal response)
  - Opportunities exist to refine hazard characterization based on toxicokinetic/toxicodynamic similarities between test species and humans (i.e., CSAFs)
  - Probabilistic modeling of chronic dietary 'usual' exposure to drive towards realistic consumer practices - 90th percentile "consumers only" often represents high consumers (not 95th percentile)
  - Low exposure substances could use alternative approach to toxicity assessment (e.g., TTC)
- Food additives must be food-grade quality

Thank You

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