U.S. FOOD & DRUG ADMINISTRATION

Session II: Requirements and Challenges in Various Legislations

U.S. FDA's View

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Risk Assessment of Genotoxic Compounds:
Challenges and Future Perspectives
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Definitions/Background

Food additives include additives that are directly added to food with the intent of having a particular technical effect on food, and therefore, are referred to as "direct food additives", as well as components of materials used in manufacturing, packing, packaging, transporting, or holding food such that their use is not intended to have a technical effect on food but may result in those components migrating to food, and therefore, are referred to as "indirect food additives" (also known as **"Food Contact Substances"** (FCSs)).

Impurities (also termed "constituents") of the FCS include the residual starting materials, catalysts, adjuvants, production aids, by-products, and breakdown products that are expected to result in dietary exposure from the intended use of the FCS.

Understanding How the FDA Regulates Food Additives and GRAS Ingredients | FDA. Online at: https://www.fda.gov/food/food-additives-and-gras-ingredients-information-consumers/understanding-how-fda-regulates-food-additives-and-gras-ingredients
Packaging & Food Contact Substances (FCS) | FDA. Online at: https://www.fda.gov/food/food-ingredients-packaging/packaging-food-contact-substances-fcs
Y. J. Zang, S. V. Kabadi, Food additives. Patty's Toxicology, Seventh Edition. 2024 John Wiley & Sons

The Delaney Clause

- The **Delaney Clause**, enacted in 1958, prohibits the FDA from approving any additives, direct or indirect, that induce cancer in humans or animals after ingestion.

- Although the Delany Clause results in a zero-risk standard for food and color additives that have been shown to be carcinogenic, FDA applies a de minimis cancer risk standard to the risk-based assessment of constituents.

- The **FDA's Constituents Policy** allows cancer risk assessments to be conducted under the general safety clause for a constituent that has carcinogenic potential without triggering the Delaney Clause.

Y. J. Zang, S. V. Kabadi, Food additives. Patty's Toxicology, Seventh Edition. 2024 John Wiley & Sons

Safety Assessment Framework

Pre-Assessment
Identify chemicals

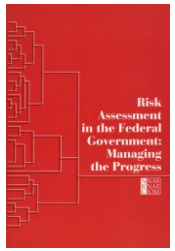
Hazard Identification
Screening of substances for toxicological concern

Exposure Assessment
Estimate exposure intake values

Dose Response Assessment
Determine toxicological endpoints of concern and derive a threshold value (if needed)

Risk Characterization
Assess margin of safety

- Expert judgment
- Totality of data/information
- Weight of evidence
- Sufficiently conservative



Based on: National Research Council, *Risk Assessment in the Federal Government: Managing the Process* **(Red Book 1983)**

Consideration of Chemical Structure and Toxicokinetic Profile

Chemical structure, class of the agent, and chemical features such as solubility and stability

Expected metabolism, reactivity, and biological activity*

*Nanoparticles have special considerations for their physiochemical properties and need for particle characterization.

Consideration of the bioavailability and target tissue of the substance after oral exposure

Tiered Exposure-Based Safety Assessment Approach

Testing Tier	Dietary Concentration (ppb)	Estimated Daily Intake (µg/kg bw/d)	Recommended Toxicological Testing	
			Toxicological Endpoint	Recommended assay
I	≤ 0.5	≤ 0.025	Carcinogenicity	No testing recommended Literature search
II	≤ 50	≤ 2.5	Carcinogenicity/ Genetic Toxicity	- Bacterial reverse mutation assay - In vitro mammalian chromosomal aberration assay or an in vitro mouse lymphoma tk± assay
III	≤ 1000	≤ 50	Carcinogenicity/ Genetic Toxicity and Systemic Toxicity	- Two in vitro genotoxicity assays (above) - In vivo test for chromosomal damage using rodent hematopoietic cells - Two subchronic oral toxicity tests, one in a rodent species and one in a non-rodent species
IV	> 1000	> 50	Additional testing required as determined on a case-by-case basis.	

Guidance for Industry: Preparation of Food Contact Notifications for Food Contact Substances (Toxicology Recommendations). Online at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-preparation-food-contact-notifications-food-contact-substances-toxicology

Cut-off Level of Concern for Genotoxicity/Carcinogenicity

The FDA's Genetic Toxicity Assessment Committee (GTAC) concluded that, in general, a substance whose use results in an estimated dietary exposure of less than **0.05 ppb (50 pptr, 0.0025 µg/kg bw/d)** would generally be expected to not pose a safety concern even if the substance is found to be genetically active.

- The scientific reasoning is that 85% of all carcinogens with alerting structures have a median toxic dose (TD_{50}) corresponding to less that an 10^{-6} risk at 0.05 ppb in the diet.

- This 0.05 ppb cut-off is not considered as an absolute cutoff and is applied on a case-by-case basis upon evaluating the totality of data.

Meeting of the Genetic Toxicology Assessment Committee (GTAC), Re: the cutoff level of concern for genetically toxic substances and the Redbook Genetic Toxicology Chapter (01/14/1999).

Cancer Risk Assessment

- For constituents, if a carcinogenicity study is either positive or equivocal, then a lifetime cancer risk (LCR) should be derived for the chemical.
  - An LCR is an upper-bound, lifetime cancer risk to humans from exposure to a constituent.

- When calculating the LCR:
  1. Use tumor data from the most sensitive species, strain, sex, and study;
  2. Assume tumors arising at multiple sites are independent of each other;
  3. Calculate a unit cancer risk (UCR) (i.e., the slope of a straight line drawn from the lowest apparent effect dose to zero); and
  4. Calculate LCR based on the estimated exposure:

$$LCR = EDI \text{ (or } CEDI) \times UCR$$

- A LCR below or within the 10^{-8} level or 10^{-6} is considered a historically acceptable cancer risk level for a carcinogenic impurity with an incremental or cumulative exposure, respectively.

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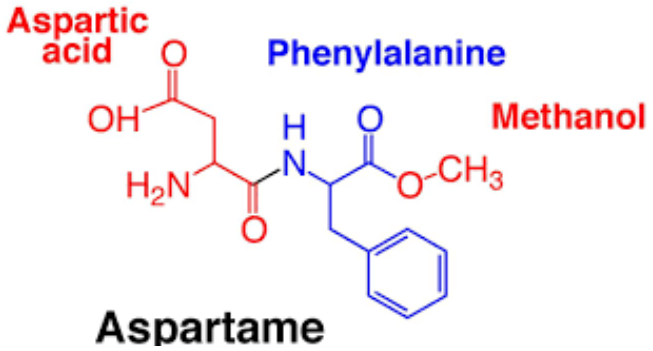
Case Example: Aspartame

A sweetener authorized as a food additive in the U.S. under certain conditions of use.

- Following oral exposure, aspartame is fully hydrolyzed in the gastrointestinal tract of humans and animals into three metabolites: phenylalanine, aspartic acid and methanol.
  - **These metabolites form at levels much lower than those derived from common foods.**
- Mixed results for genotoxicity; however, there are major limitations with study design and no systemic exposure to aspartame is expected upon oral exposure → no concern for genotoxicity after oral exposure
- No concern for carcinogenicity in animals
- Unconvincing evidence of association of aspartame exposure and cancer and non-cancer endpoints in humans
- FDA ADI of up to 50 mg/kg bw/d and JECFA ADI of 0-40 mg/kg bw/d

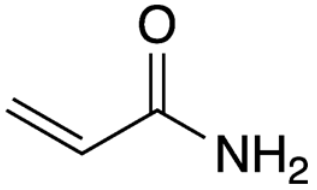


Aspartame and Other Sweeteners in Food | FDA. Online at: https://www.fda.gov/food/food-additives-petitions/aspartame-and-other-sweeteners-food
Ninety-sixth meeting - Joint FAO/WHO Expert Committee on Food Additives (JECFA). Online at: https://www.who.int/publications/m/item/ninety-sixth-meeting-joint-fao-who-expert-committee-on-food-additives-(jecfa)

Case Example: Acrylamide

A monomer/constituent of polymeric food contact substances intended for certain uses.

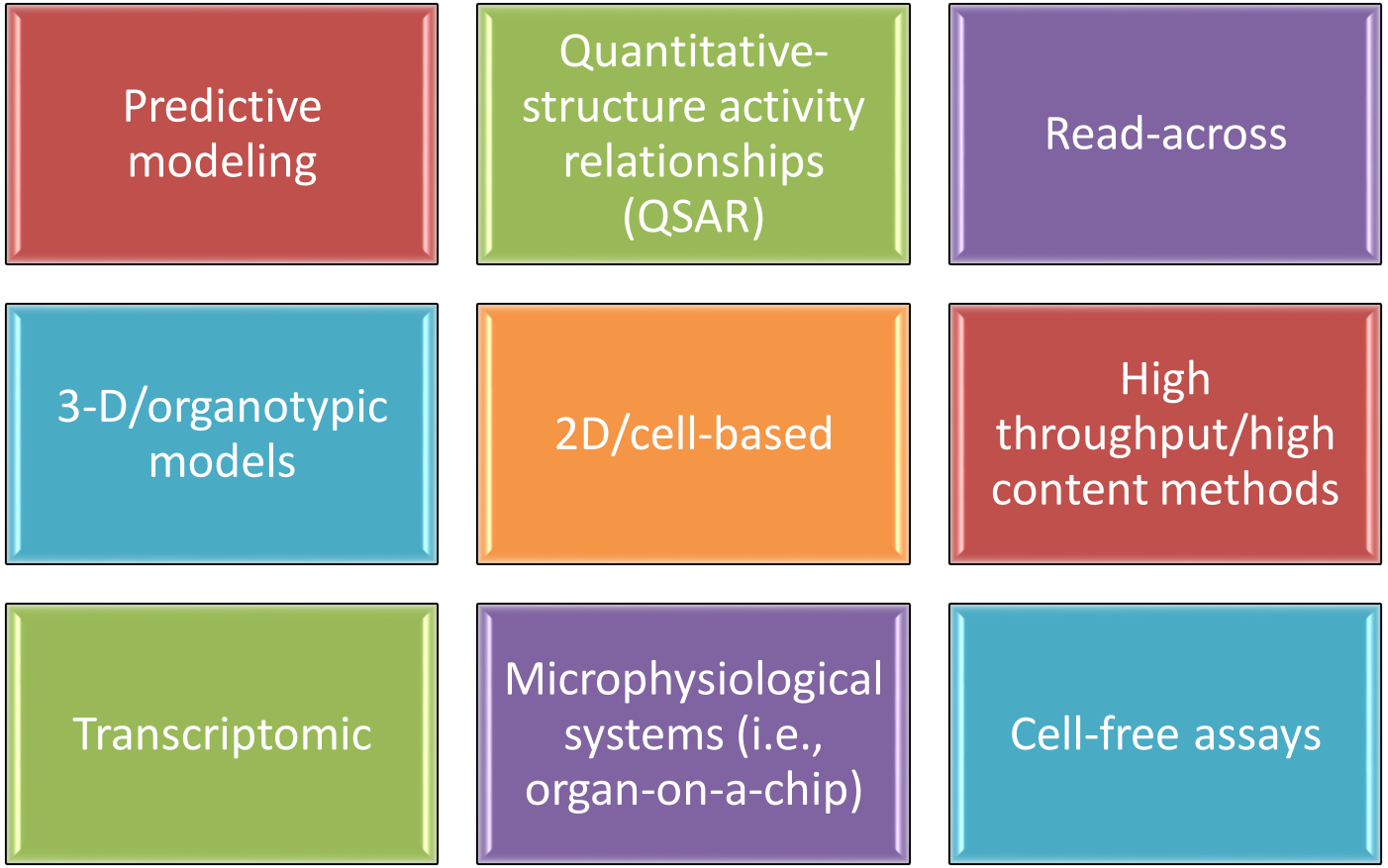
- Estimated mean dietary intake from foods is 0.36 µg/kg bw/d
  - Generated in a wide variety of foods (breakfast foods, potato chips, coffee, etc.)
- Positive genotoxicity data
- Reported carcinogenic incidences in a 2-year rat drinking water bioassay
- FDA's UCR value of 0.72 $(mg/kg\ bw/d)^{-1}$
- Basis of no safety concern for exposure to acrylamide from food contact use include:
  - EDI of acrylamide from food contact use is much less than its mean dietary intake from foods of 0.36 µg/kg bw/d.
  - LCR for EDI of acrylamide is less than the Agency's historically acceptable risk level of 10^{-8} for incremental exposure to a potentially carcinogenic impurity.



Acrylamide | FDA. Online at: https://www.fda.gov/food/process-contaminants-food/acrylamide

Exploring New Approach Methodologies (NAMs) for Evaluating Genotoxic Potential

- NAMs are in vitro, in chemico or in silico methods and/or integrated approaches.
- QSAR and read across are useful to support safety assessments in a weight-of-evidence approach.
- FDA promotes the development of alternative test methods to support the replacement, reduction and/or refinement of animal testing.



Examples of NAMs

FDA's Predictive Toxicology Roadmap (2017)
Advancing New Alternative Methods at FDA (2021)

I thank you for your kind attention.

Further questions?
Contact me at:

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