Incorporating Computational Approaches into Safety Assessment

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Presentation Outline

- Introduction to the Food Additives Program at FDA
- Safety Assessment and Toxicology Guidance
- Where computational approaches fit in
- Case study example
- Conclusion

The Federal Food, Drug, and Cosmetic Act of 1938 (FD&C Act)

- 1958 Food Additives Amendment to the FD&C Act defined “food additive”.
- Required pre-market approval of new uses of food additives.
- Established the standard of safety, the standard of review, and formal rulemaking procedures for food additives.
- GRAS substances are excluded from the definition of a food additive.

- In 1960, Color Additive Amendments required pre-market review for color additives.
- FD&C Act was further amended in 1997 with the passing of the FDA Modernization Act (FDAMA) to establish a mandatory premarket notification process for food contact substances.

The Food "Ingredient" Universe

Direct Food Additives:
Sweeteners; preservatives; nutrients; fat substitutes; texturizers (e.g., thickeners, emulsifiers); flavors

Secondary Direct: Antimicrobials (meat and poultry processing); defoamers; ion exchange resins

Food Irradiation Equipment:
To process food or to inspect food

GRAS Substances: Enzymes; fibers; proteins; lipids; sugars; MSG; antimicrobials; phytosterols/stanols; flavors; infant formula ingredients

Food Contact Substances:
Coatings (paper, metal, etc.); new/recycled plastics including polymers and monomers; paper; adhesives; colorants, antimicrobials, and antioxidants in packaging; packaging

Color Additives: In food, animal feed, drugs, cosmetics, and medical devices (e.g., sutures, contact lenses)

Foods/Ingredients Produced Via Biotechnology: Plants w/ herbicide resistance or insect resistance; delayed ripening, etc.

General Safety Standard

- The term “SAFE” is defined in 21 CFR 170.3(i) as a “reasonable certainty in the minds of competent scientists that a substance is not harmful under the intended conditions of use.”
- Safety assessment is based on a reasonable certainty of no harm on a case by case basis.
- Safety evaluation is required for food additives AND impurities

Delaney Anti-Cancer Clause

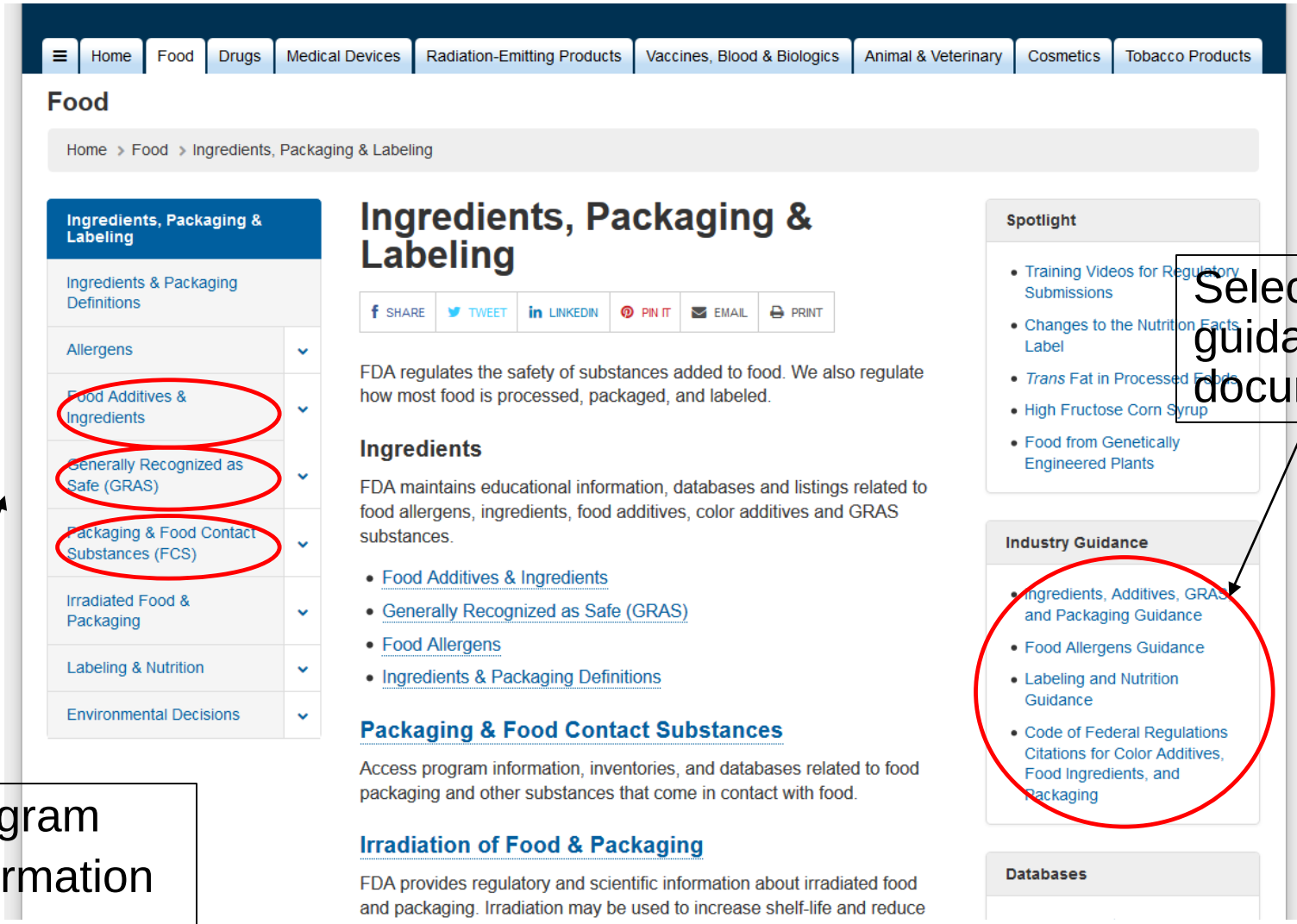
- General safety standards inapplicable to carcinogenic food additives
- Use of a food additive that *has been shown to induce cancer in humans or animals upon oral ingestion can not be approved*
- No level of exposure to a carcinogenic food additive can be considered safe under the FDC Act.
- Constituents and impurities are evaluated by quantitative risk assessment

Regulation vs. Guidance

- **Regulatory Information:** FDA issues regulations to implement its statutory authority. The regulations can create ***binding*** obligations and have the ***force of law***.

- **Guidance Documents:** Guidance documents represent FDA's ***current thinking*** on a topic. They do not create or confer any rights for or on any person and ***do not operate to bind FDA or the public***. Guidance documents are prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue. An alternative approach may be used if the approach satisfies the requirements of the applicable statutes and regulations.

fda.gov/Food/IngredientsPackagingLabeling/



Select guidance documents

Program Information Pages

FDA Guidance Documents

1. **Administrative**

   http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081807.htm

2. **Chemistry**

   http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081818.htm

3. **Toxicology**

   http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081825.htm

4. **Environmental**

   http://www.fda.gov/Food/GuidanceRegulation/ucm081049.htm

Information Needed to Support Evaluations

- **Identity** of the food additive and all impurities
- **Manufacturing** process, technical **effect**, and intended **conditions of use**
- The submitter's **determination** of safety
- Data and information that form the **basis** of the **safety determination**, and
- **Environmental** considerations

"Reasonable Certainty of No Harm"

Exposure Assessment

Driven by the intended use
- NHANES Data
- Migration Data
- Food types

Hazard Identification

- Analysis of Structure (structural Alerts)
- Genetic Toxicity Assessment
- QSAR Assessment

Risk Assessment

- Point of Departure and NOAEL determination
- Unit Cancer Risk Characterization
- Margin of Exposure and ADI Calculation

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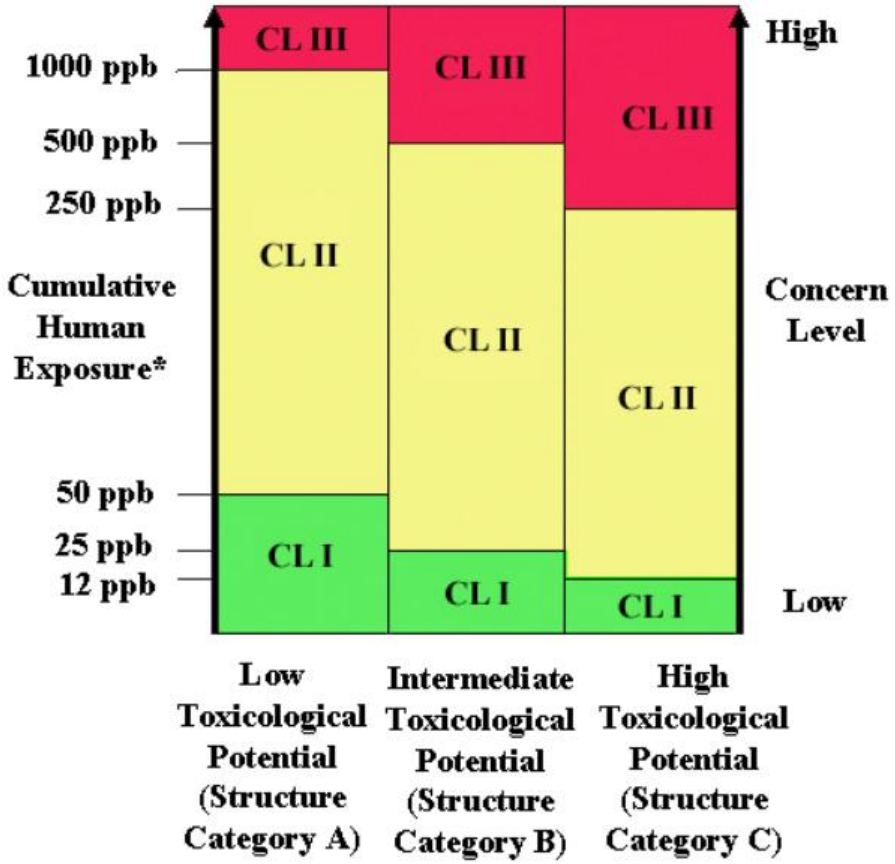
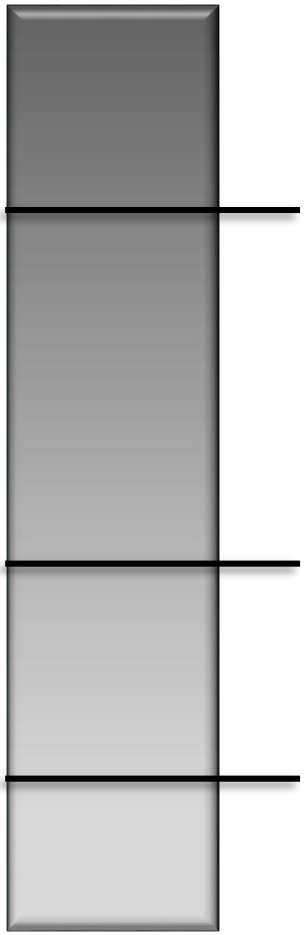
Pre-market Structure and Exposure Based Testing Tiers – FDA 1993 Redbook

IV. Concern Levels (CL) as Related to Human Exposure and Chemical Structure



Pre-market Exposure Based Tiered Testing Recommendations - FCNs



> 50 µg/kg bw/day
Additional tox studies (ie long term, carc, R/D, ADME, etc.)
May require a FAP

2.5 - 25 µg/kg bw/day
In vivo genotoxicity testing
In vivo animal data (2 species)

0.025 → 2.5 µg/ kg bw/day
In vitro genotoxicity testing
(carcinogenesis hazard ID)

< 0.025 µg/kg bw/day
Literature review, structure analysis,
no specific testing recommended

Uses of Computational Info in OFAS

- Hazard identification tool
  - Identify highly concerning structures.
  - Identify recommended endpoints for testing.
    - Provide specific toxicity testing recommendations
- Risk Assessment
  - Identify structural analogs with bioassay data or cancer risk values
  - Extrapolate a unit cancer risk (UCR) from the bioassay data
  - Use the UCR and exposure estimate to predict the lifetime cancer risk for the compound
- Decision support tool
  - Multiple (Q)SAR and database tools used
  - Fill gaps in toxicity data (ie read-across)
  - Used in weight of evidence evaluations.

Computational data to support very low levels of exposure

- No specific testing is generally recommended unless alerting information is identified
- Safety assessment focus on potential carcinogenicity.
- Review relevant existing toxicity data:
  - Literature search, Carcinogenicity bioassays, Genotoxicity assays
- Conduct structure activity relationship (SAR) analysis;
  - SAR analysis helps answering questions:
    - (1) Does the chemical contain structural alerts?
    - (2) Do we have experience with the chemical?
  - Analyzing FCS and constituents using “expert” systems (e.g. CASEultra, DEREK, Leadscope) and FDA’s internal databases
  - Qualitative in nature: low, moderate, high level of concern

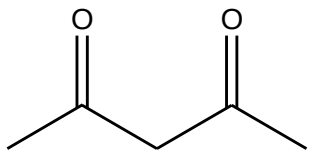
SAR in Pre-market Safety Assessment

- Estimating risk using SAR or (Q)SAR
  - Qualitative SAR –ID structural alerts (hazard ID)
  - Quantitative SAR– read across for safety at low levels of exposure
    - Identify analogs
      - Structure
      - Physical/chemical properties
      - Predicted metabolites
      - Toxicological profile
      - Quality of analog data
    - Extrapolation of data
      - Consideration of exposure
      - Application of safety factors

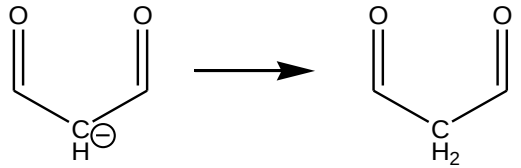
Read-across in Safety Assessment - case study.

- Exposure on FCS and impurities were low – testing generally not recommended.
- Genetic toxicity studies on analog – positive.
  - in vitro chromosomal aberration test and
  - in vivo micronucleus test (mice).
- Hazard ID tests indicate concern potential carcinogenicity.
- No carcinogenicity data were available through literature searches.

Analog Search – acetylacetone



- Several potential analogs were identified, including acetaldehyde, acetone, acetic acid, cyclohexanone, prohexadione and sodium malonaldehyde.
- **Sodium malonaldehyde** was considered the **closest structural analog** with relevant available genotoxicity and **carcinogenicity data**
- Sodium malonaldehyde is expected to be protonated at stomach pH, **giving malonaldehyde (MA), a compound structurally similar to AA**



Na+

Structure IV Structure IV-2

Cancer Risk Assessment of AA

- FDA considered sodium MA a suitable analog for AA and used its Unit Cancer Risk**,** to calculate the upper-bound worst-case cancer risk for AA
- Risk level was 100 fold lower than the historically acceptable 1/1,000,000 cancer risk level.
- No safety concern.

SAR Analysis: Tools to Consider*

- Structure alert schemes or decision tree approaches
- Analog searching – various programs allow substructure and similarity searching:

- Increasing number of tools available! - ensure your tool is fit for purpose.
  - ChemID plus
  - OECD QSAR Toolbox
  - ToxTree and TTC
  - EPA DSSTox
  - Danish (Q)SAR Database
  - MDL QSAR
  - Lhasa Limited (Derek)
  - MultiCASE
  - Leadscope,
  - OFAS internal structure-searchable databases (CERES)
  - etc.

**Reference herein to any specific commercial products, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government .*

Computational approaches in Safety Assessment -Conclusions

- Provide safety assessment including SAR analysis and supporting documentation
- Ensure tools used are fit for purpose
- Bridging argument – if proposing, support with documentation
- A pre-notification consultation may be helpful

Thanks
For
Your
Attention!