Antimicrobials in Food Contact Applications and Masterbatches

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Topics for Today's Presentation

- Overview of EPA/FDA Food Contact Relationship
- EPA Statutory Framework
- Division of Jurisdiction between EPA and FDA
- Under what circumstances will EPA perform a dietary risk assessment?
- Masterbatches
- Antimicrobial Food Contact Regulation in the EU
- Appendix – EPA Dietary Risk Assessment

EPA And FDA Food Contact Regulation: Parallel Worlds?

EPA World: FIFRA

- Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) is the statute under which EPA regulates pesticides. FIFRA is in the Agriculture Code: 7 U.S.C. § 136a, et seq.
- The FIFRA definition of a pesticide is “any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest.” FIFRA § 2(u)(1).
- Sale or distribution of an unregistered pesticide is unlawful.

EPA World: FIFRA

- Pests
  - Defined by EPA to include, "[a]ny fungus, bacterium, virus, prion, or other microorganism, **except for those on or in living man or other living animals and those on or in processed food or processed animal feed, beverages, drugs** (as defined in FFDCA § 201(g)(1)) **and cosmetics** (as defined in FFDCA § 201(i)). 40 CFR § 152.5(d).
- FIFRA – Risk benefit standard for registration, *except* for uses that may result in food residues.

EPA World: FFDCA 408

- FFDCA Section 408 authorizes EPA to set standards governing pesticide chemical residues in/on food.
  - Tolerances (maximum legally permissible levels for pesticide residues in food).
  - Exemptions from tolerance (no numeric limit but use conditions).
  - A tolerance or exemption must cover all pesticide residues on food in commerce or the food is adulterated under FFDCA.
- FFDCA 408 standards also apply to FIFRA food uses (food not in commerce, e.g. in homes) through FIFRA section 2(bb).

Standard Applied by EPA under FFDCA 408

- Current safety standard established through the Food Quality Protection Act of 1996, which amended both FIFRA and FFDCA
  - Key driver was “Delaney Clause” in section 408 prohibiting carcinogens in pesticide residues.
  - FQPA amended FFDCA Section 408 to eliminate “Delaney Clause” and include stricter safety standards (“a reasonable certainty of no harm”).
  - Required consideration of sensitive subpopulations.
  - Shortly after passage of FQPA, EPA reassessed over 9,000 pesticide tolerances, revoking or modifying almost 4,000.
- EPA process for risk assessment of preservatives in a food contact treated article is outlined in Appendix

Division of Jurisdiction between EPA and FDA

- EPA jurisdiction over food contact antimicrobials is governed by the definitions of “pesticide chemical” and “pesticide chemical residue” in FFDCA § 201(q).
- The definition is quite complex. FDA Guidance on Antimicrobial Food Additives (1999): https://www.fda.gov/food/guidanceregulation/ucm077256.htm
- Food in commerce that contains a “Pesticide Chemical Residue” is deemed adulterated unless EPA has issued a tolerance or exemption from tolerance under FFDCA § 408.

FDA World: FFDCA 409

- FFDCA Section 409, administered by FDA, provides mechanisms to authorize food additives (substances which result or may reasonably be expected to result in becoming a component of food).
- Applies to residues that fall outside the “Pesticide Chemical Residue” definition.
- 409 contains Delaney Clause and doesn’t contain the additional conservatism in 408.

Example: Antimicrobial Impregnated into Residential Counter Top

- EPA:
  - Regulated by EPA under FIFRA, incorporating Section 408 standard if the antimicrobial is intended to "have an ongoing effect on the food contact surface."
- FDA:
  - Not regulated, as any residues will be on food not in commerce.

Example: Antimicrobial Impregnated into Commercial Counter Top

- EPA Regulation under 408: Preservative to prevent degradation of surface.
- FDA Regulation under 409: Preservative used for in-can preservation of pigment used in counter surface.
- Key consideration: "ongoing effect on the food contact surface"?

Example: Antimicrobial Impregnated into Food Packaging

- EPA:
  - Antimicrobials applied to food packaging not included in the definition of “pesticide chemical” so excluded from EPA FIFRA regulation.
- FDA:
  - Regulated as a “food contact substance” under Section 409.

Compound-specific example: 1,2-Benzisothiazolin-3-one (BIT)

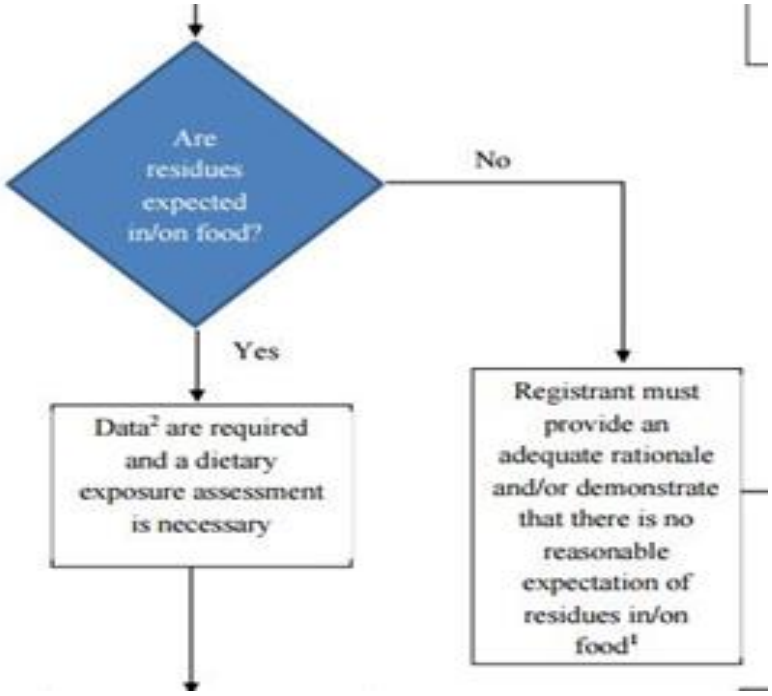
- EPA Registration Review Final Work Plan reads:

  Since the 2005 RED, new uses as cleaning products and dishwashing detergents were granted and FCNs became effective for wet state preservatives, biocides in uncured liquid rubber latex used to manufacture repeat-use rubber gloves, and for can-end cements. Since these can contribute to dietary (food) exposure, the agency will need to conduct both acute and chronic dietary exposure assessments for all population subgroups to support registration review (page 21 of 52).

Under what Circumstances will EPA perform a Dietary Risk Assessment?

- Liquids used on food contact hard surfaces, regardless of whether or not there is a potable rinse.
- Treated materials that may result in pesticide residue on food, except food packaging.
- Uses in and around food preparation or service areas.
- EPA Use Site Index indicates the way in which EPA determines whether a dietary assessment is needed: https://www.epa.gov/pesticide-registration/antimicrobial-pesticide-use-site-index

EPA Guidance Decision in Antimicrobial Use Site Index



No current, practical approach to demonstrate "that there is no reasonable expectation of residues in/on food."

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EPA Increasing Label Specificity for Food Contact Approvals

- "Old" style label:

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

Polymer compounds:
For use as a mildewcide in PVC, polyurethane, and other polymer compounds. Use 0.4 to 2.1 pounds of [redacted] per 100 pounds of compounded polymer system. To insure uniform distribution throughout the formulation it is recommended that [redacted] be pre-blended with plasticizer or other liquid ingredient before the final compounding step.

- Label provides general information
  - Does not specify food contact or non-food contact.

EPA Increasing Label Specificity for Food Contact Approvals

- "New" style label:

Do not incorporate this product into any food contact polymer unless the subject food contact polymer is approved and listed in 21 CFR, Parts 174 through 186 (inclusive), or in the United States Food and Drug Administration's "Food Contact Substance Notification System." Any incorporation of this product into an approved and listed food contact polymer must comply with the specific use conditions listed in 21 CFR, Parts 174 through 186 (inclusive), or in the United States Food and Drug Administration's "Food Contact Substance Notification System," for such food contact polymer. Any incorporation of this product into any food contact substance (including but not limited to non-polymer substances) other than an approved and listed food contact polymer is prohibited.

Plastics - including films, sheets, slabs, and molded plastic parts
The additive may be incorporated into the finished product at up to 20.0% by weight or at least 0.3% for bulk plastics. Contac [redacted]. to determine the appropriate amount [redacted] for individual finished products.

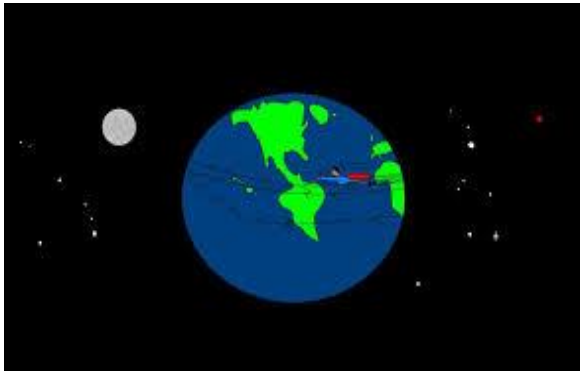
Food contact* and non-food contact uses:

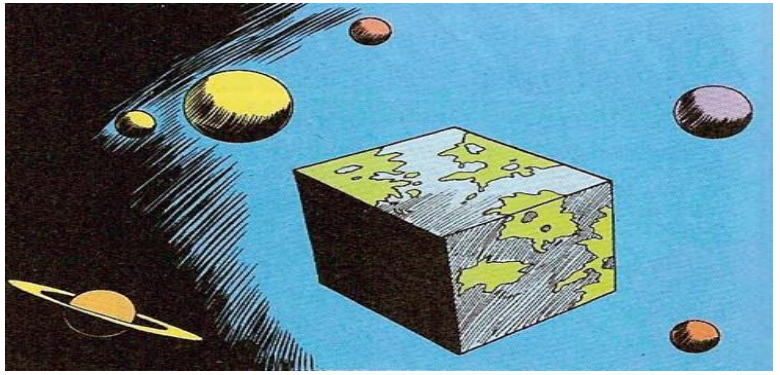
Appliances and equipment
Beverage processing equipment (including mixers, transfer equipment, pumps, bottlers, canners, bottles, dispensers and fermenters)
Brush bristles
Conveyor belts
Countertops
Cups
Cutting boards
Dishes
Food and drink containers
Food wrap (including coated deli paper, coated meat interleavers and plastic wrap)
Gaskets
General purpose containers
Kitchen and food processing utensils and supplies
Liners
Non-woven fabrics
Packaging
Plastic film
Shelving, cookers, grinders, choppers, peelers and countertops

Observations

- EPA and FDA maintain parallel regulatory schemes for antimicrobials that may result in residues on food under sections 408 and 409 of FFDCA respectively.
- Agencies generally operate independently and take different approaches to exposure and risk assessments, but recent coordination growing.
- EPA has begun referring to FDA approvals on pesticide labels, expanding need for FDA approvals for biocides.

Observations on EPA And FDA Food Contact Regulation





408 → **?** ← **409**

Treated Article Intermediates or Masterbatches

Treated Article Intermediates / Masterbatches

- Key Provision: 40 CFR 152.25(a) – The Treated Article Exemption.
- Sale or distribution of a pesticide is unlawful unless it is registered.
- Food contact uses must not be "inconsistent" with FIFRA label.
- 152.25(a) states that treated articles are pesticides ***but*** establishes an exemption from the registration requirement for such articles provided they:
  - Have been treated with a pesticide registered for that purpose
  - Make claims limited to protecting the article itself

Treated Article Intermediates / Masterbatches

- Literal reading of 152.25(a) precludes sale of unregistered masterbatches intended to provide protection to downstream articles.
  - Masterbatches are unregistered pesticides
  - No way for EPA to control concentration in final article and thereby ensure safety.
  - EPA has sought to bring enforcement actions against masterbatches including antimicrobials being sold to downstream users.
- However, EPA has been inconsistent in its interpretation.
  - Issued some registrations that specifically identify concentrates.
  - Letters to registrants from early 2000's imply masterbatches may be acceptable.

Treated Article Intermediates / Masterbatches

- EPA Intermediates presentation at March 2015 Antimicrobial Workshop included the following:

Example:

- A material preservative is labeled to protect plastic at rates up to 5% active ingredient (AI). An "intermediate" plastic pellet is produced containing 20% AI. If distributed/sold, the pellets require registration. Not "registered for such use" (exceeds allowed rate).
- Production continues on-site (i.e., no sale/distribution of pellets) and results in plastic sheet "intermediates" that contain 5% or less AI. As long as the sheets are in compliance with the label of the registered pesticide and only allowable claims are made, the sheets qualify under the TAE [treated article exemption]. If the plastic sheets are sold and used to make shower curtains containing 2.5% AI and the shower curtain is in compliance with the label of the registered product and only allowable claims are made, the shower curtains qualify under the TAE."

Treated Article Intermediates / Masterbatches

- Some techniques may be helpful in continuing to work with masterbatches:
  - Custom Blending (40 CFR § 167.3)
  - Contract Application
- Contract language and compliance with the contract and regulations are critical in these arrangements.

Treated Article Intermediates / Masterbatches: Current State of Play

- EPA continues to maintain that any product that is sold or distributed and is intended to impart protection to another article, is a pesticide under FIRFA and must be registered.
- Registrants have informed EPA of importance of masterbatches and that they are offered for sale.
- EPA prefers compliance to enforcement and has committed to issue guidance.
- Until then, companies must gauge enforcement risk, seek legal advice.
- Compliance with food contact approvals/limitations on label (as well as FDA clearances) is critical.

Observations

- Masterbatches present particular issues of FIFRA compliance in addition to food contact issues in many situations.
- It is important to understand risks associated with particular approaches.

Antimicrobial Food Contact Regulation in the EU: A High Level Summary

Treated articles under the BPR

- BPR devotes the entire Article 58 to treated articles which are not biocidal products (no primary biocidal function)
- Article 58(2) – as amended: A treated article shall not be placed on the EEA market unless all active substances contained in the biocidal product that **it** was treated with or incorporates are EU approved for the relevant PT and use; and the restrictions are met (exception: fumigation and disinfection of premises)
  - placed on the market means: first making available as the treated article **itself**
  - active substance contained in the biocidal product means: its presence in the treated article is not the requirement
  - it was treated with or incorporates means: the treated article **itself** and not of its component parts (i.e. complex articles require complex analysis)
  - EU approved for the relevant PT and use means: 0% threshold on all active substances which are not permitted pursuant to Article 58(2).

Treated Articles: Commission's approach

Final Note for Guidance on Treated articles - December 2014

- *Article 3(1) (l) of the BPR defines a treated article as '…any substance, mixture or article which has been treated with, or intentionally incorporates one or more biocidal products'. As indicated in Article 58 (2) to (4), the provisions of Article 58 apply to treated articles in the form in which they are placed on the EU market)*, i.e. it does not concern directly components of complex articles or intermediate forms which are not themselves placed on the EU market. CA Nov. 14-Doc.6.1

Food Contact Materials and the Biocidal Products Regulation

- Products within the scope of Regulation 1935/2004 on Materials and articles intended to come into contact with food (the **Framework Regulation**) are no longer excluded from the scope of the BPR
- Scope of the Framework Regulation:
  - Materials and articles, including active and intelligent food contact materials and articles, which in their finished state:
    - are intended to be brought into contact with food; or
    - are already in contact with food and were intended for that purpose; or
    - can reasonably be expected to be brought into contact with food or to transfer their constituents to food under normal or foreseeable conditions of use.
- Annex I of Regulation 1935/2004 lists 17 groups of materials covered by its scope; including Plastics, Paper, Rubber, Glass, Ceramics, Silicones, Textiles, Wood; but also Printing inks, Adhesives, and Coatings

Food contact materials and articles and the BPR

- Potential Biocidal Product Types (PT) in food contact applications:
  - **Surface biocides** (PT4) – intended technical effect in the food contact article**;**
  - **Process biocides** (PT 6, 7, 9, 11, 12) – not intended to have an effect and to be present in the final food contact material or article;
- All these were previously exempt from the scope of the BPD; now they are covered by the BPR; either as Biocidal Products or Treated Articles.
- It is important to understand whether a food contact material is a “treated article” under the BPR

Use of biocides in food contact plastic materials and articles

- Plastics Regulation 10/2011 has a **positive list for all authorised additives** (with some important derogations) – the Union list
  - ’additives’ means a substance which is intentionally added to plastics to achieve a physical or chemical effect during processing of the plastic or in the final material or article; it is intended to be present in the final material or article;
  - ‘polymer production aid’ means any substance used to provide a suitable medium for polymer or plastic manufacturing; it may be present but is neither intended to be present in the final materials or articles nor has a physical or chemical effect in the final material or article;
- **Surface biocides are considered additives**, so for plastics applications they should be listed on the Union list
- **Process biocides** may still be used as **Polymer Production Aids** (PPAs) are under derogation from the Union list
- **Food preservatives** are **excluded from the scope of the BPR**, as covered by Regulation (EC) No 1333/2008 on food additives

Use of biocides in food contact plastics materials and articles (cont.)

- **Dual regulation**:
  - Under the **Food contact legislation**:
    - Some surface biocides as additives are under derogation from the Union list: listed in the so called Provisional list, permitted in food contact plastics, their use is subject to national law and FR
    - Process biocides as PPAs are also under derogation from Union list, only subject to national law and FR
  - Under the **BPR** most of these applications are considered **treated articles**, subject to Article 58 requirements under the BPR, harmonised at EU level. Active substances must be listed under Article 95 for the relevant product type.
- Dual authorization proposed in Discussion Document from the Commission from July 2013:
  - **ECHA** for authorising the active substance
  - **EFSA** for establishing use restrictions

Masterbatches Under the BPR

- Note for Guidance CA-May15-Doc.6.2 recognizes that Masterbatches are an area of substantial uncertainty.
- Key Provisions:
  - (12) The principle must be that at least once in the supply chain in which a biocidal substance is being used, a biocidal product has to be defined.
  - (13) The person responsible for placing a good on the EU market is responsible for checking compliance with the rules applicable to such a good.
  - (17)(b) A masterbatch should be regarded as a biocidal product if it is has a biocidal function in the form in which it is supplied to the user,
  - (17)(g) Based on the same reasoning, intermediate masterbatches shall not be regarded as biocidal products, when they are not intended to exert a biocidal function in the form in which they are supplied to the user.

https://circabc.europa.eu/webdav/CircaBC/SANTE/BPR%20-%20Public/Library/documents_finalised/CA-Sept15-Doc.6.2%20-%20Final%20-%20Masterbatches.docx

Observations:

- Several complex aspects to EU regulation, in which compliance can be challenging.
- EU Developing Policy Approach to BPR/Framework Regulation interface
- Focus has been on establishment of Maximum Residue Levels (MRLs) for active substances contained in biocidal products
- Risk based approach focusing on active substances with potential for consumer exposure
- Proposal for no further actions when:
  - Consumer exposure is unlikely
  - No appreciable risk
  - No transfer to food is expected – No migration

APPENDIX:
EPA Dietary Risk Assessment Process

How Does EPA Conduct Dietary Risk Assessments?

Dietary Exposure Assessment for antimicrobials used in or on food contact surfaces

- EPA screening level modeling approach very conservative
- Higher Tier Analysis - Dislodgeable surface residue + default transfer coefficients
- Further Refinement – Measured residue data

How Does EPA Conduct Dietary Risk Assessments?

Selection of Toxicity Endpoints

- Determination by EPA's Antimicrobial Division Toxicity Endpoint Selection Committee (ADTC).
- Most sensitive endpoint from FIFRA testing.
  - Chronic endpoints are typically used.
  - Sensitization also of concern.

How Does EPA Conduct Dietary Risk Assessments?

Application of Uncertainty Factors

- Uncertainty factors are applied to the endpoint values to determine appropriate reference dose.
  - 10X for inter-species extrapolation;
  - 10x for intra-species variability;
  - 3x for lack of a chronic endpoint;
  - 3x for lack of a chronic endpoint;

  Values can range from 3 to 300 (10 x 10 x 3).

How Does EPA Conduct Dietary Risk Assessments?

Application of FQPA Safety Factor

- FQPA safety factor is then applied to the reference dose to meet “reasonable certainty of no harm standard” in FFDCA Section 408
- Special consideration of sensitive subpopulations;
- Default value is 10x;
- Values can be reduced to 1x if EPA determines the toxicity data set is complete.

How Does EPA Conduct Dietary Risk Assessments?

Example of EPA assigned Safety/Uncertainty Factors

Nuosept 95 (common name: Azadioxabicyclooctane) Revised Dietary Exposure Scoping Document dated April 20, 2017 (EPA-HQ-OPP-2013-0604-0005).

- Uncertainty factor: 300 (10 x 10 x 3).
  - 10x for inter-species extrapolation;
  - 10x for intra-species variability;
  - 3x for lack of a chronic endpoint.
- FQPA safety factor.
  - 10x – due to lack of a 2nd developmental toxicity study and a repro study.

https://www.regulations.gov/document?D=EPA-HQ-OPP-2013-0604-0005