

EPA Dietary Risk Assessments: Why are they relevant? How are they performed?

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Topics of Discussion

- Overview of EPA/FDA responsibilities for dietary risk assessments
- Examples of the division of jurisdiction
- EPA dietary risk assessments – when and how

EPA And FDA Food Contact Regulation: Two Regimes in Almost the Same Space



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.

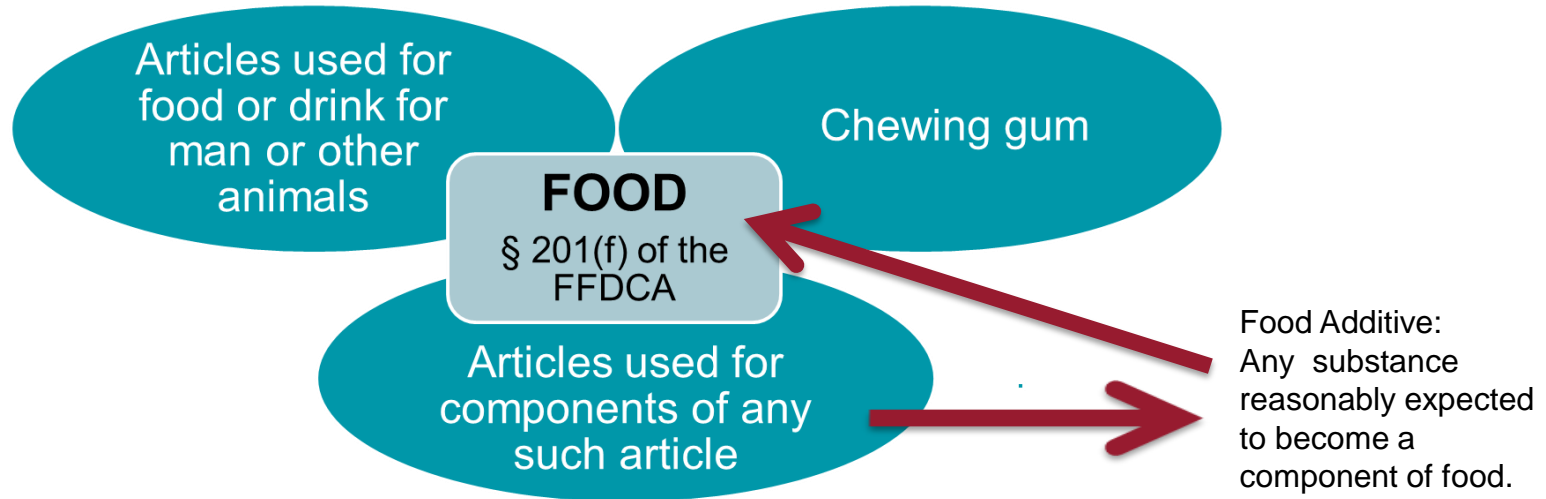
- The FIFRA definition of a pesticide is “any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest.” FIFRA § 2(u)(1).
- Under FIFRA, EPA approves specific pesticide labels which include allowable uses and directions.
- Sale or use of pesticide in a manner inconsistent with the label is unlawful.

■ 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).

What Is Food?

- 1906: “Food” shall include all articles used for food, drink, confectionery, or condiment by man or other animals, whether simple, mixed, or compound
- From 1938 on:



What is Processed Food?

- The term “processed food” means any food other than a raw agricultural commodity and includes any raw agricultural commodity that has been subject to processing, such as canning, cooking, freezing, dehydration, or milling.
21 U.S.C. § 321(gg).



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 § 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 § 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.

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.
- Section 409 contains Delaney Clause.

FFDCA Section 409(c)(3)(A) – “Delaney Clause”

(3) No such regulation shall issue if a **fair evaluation of the data** before the Secretary -

(A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe: *Provided*, that no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal...

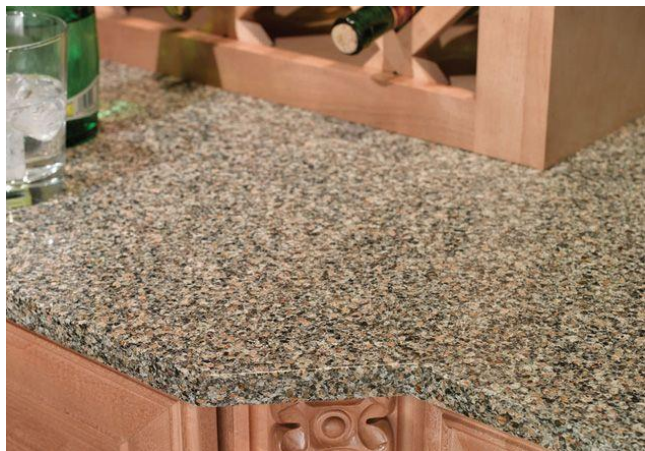
Division of Jurisdiction between EPA and FDA

- Example: Egg Washes

- EPA:
 - Regulated under Section 408 if product is intended to control microbial growth in the rinse water.
- FDA:
 - Regulated under Section 409 if product is intended to limit contamination on the egg because microorganisms on processed foods are not pests.
- Joint regulation:
 - If the product makes both claims.



Example: Antimicrobial Impregnated into Commercial Counter Top



- EPA:
 - Regulated if the antimicrobial is intended to “have an ongoing effect on the food contact surface.”
- FDA:
 - Regulated as a “food contact substance” under Section 409 if the antimicrobial is “not intended to have an 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.

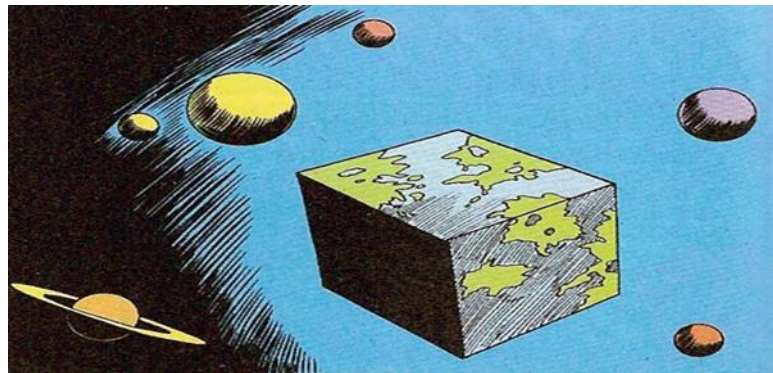
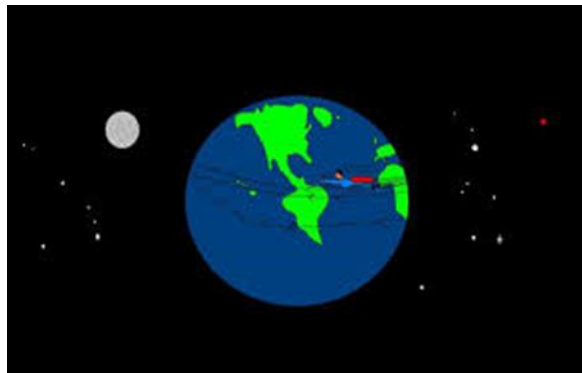


Example: Residential Dishwashing Product

- EPA:
 - Antimicrobial claim for dishes subject to analysis under Section 408 of FFDCA.
- FDA:
 - Other ingredients considered as not leaving significant residue, so not regulated as a “food contact substance” under Section 409.



Observations on EPA And FDA Food Contact Regulation

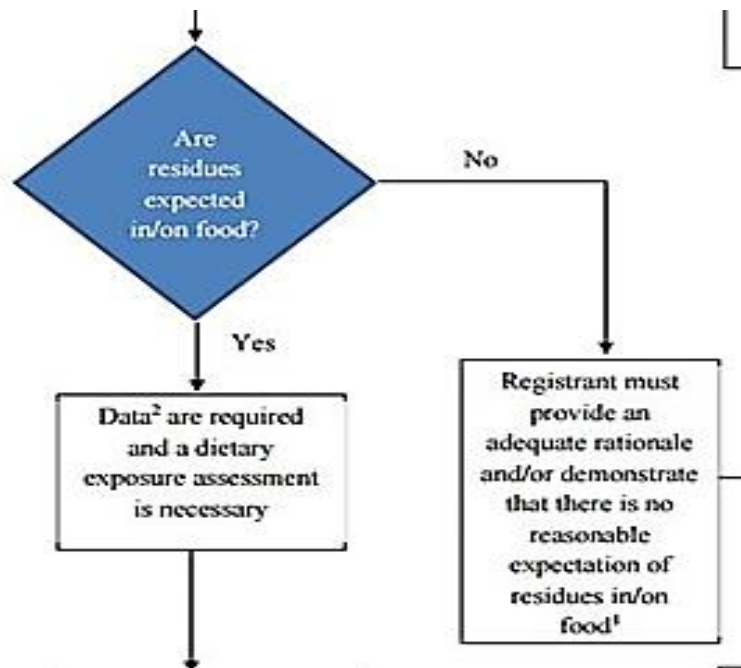


408 → ? ← 409

Under what Circumstances will EPA Perform a Dietary Risk Assessment?

- Liquid antimicrobials 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.
- Antimicrobial 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>

Antimicrobial Use Site Index



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

How Does EPA Conduct Dietary Risk Assessments?

- Key Aspects of Risk Assessment:
 - Exposure (*What is the surface residue concentration?*)
 - Endpoint (*What is the hazard? What is the toxicity reference value for that hazard?*)
 - Safety Factors:
 - Hazard endpoint uncertainty factors
 - FQPA: Additional safety factors depending upon data base completeness (Section 408(b)(2)(C)(i)(III))
 - <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/determination-appropriate-fqpa-safety-factors>

How Does EPA Conduct Dietary Risk Assessments?

- No overall EPA guidance.
- EPA has proceeded on a case-by-case basis.
- EPA's tools, plus individual decisions provide insights into EPA risk assessment approach.

Determining Dietary Exposure for a Risk Assessment

- Indirect Food Use: e.g., liquid antimicrobials used on non-porous, hard surfaces in ***Residential Settings***:
 - Indirect Dietary Residential Exposure Assessment Model (iDREAM).
 - Developed to estimate acute and chronic indirect ingestion exposure that can result from use of disinfectants and sanitizers on kitchen surfaces.

<https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/indirect-dietary-residential-exposure-assessment>

Determining Dietary Exposure for a Risk Assessment

- Indirect Food Use: e.g., liquid antimicrobials used on non-porous, hard surfaces in **Commercial Settings**:
 - Food Contact Sanitizing Solutions Model (FCSSM) released May 2017.
 - Developed to estimate indirect dietary exposure to components of sanitizing solutions used in commercial settings.

<https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/food-contact-sanitizing-solutions-model-fcssm>

FCSSM: Available from the EPA Web Site

fcssm-spreadsheet-version-1.xlsm - Microsoft Excel

Input Required:	Units:	Comments:	Alternative Input:
AI-use Active Ingredient Concentration (%)	5 %	1% = 10000 ppm	ppm a.i.
Concentration of A.I. at use (ppm)	50000 ppm	Final product concentration in ppm	
Concentration in (µg/cm ²)	50 µg/cm ²	*assuming 1 mg/cm ² of product on surface	
aPAD (or aRID)	75 mg/kg BW/day (ppm)		
cPAD (or cRID)	20 mg/kg BW/day (ppm)		

SUMMARY				
If changes are made, click to update Click to display Summary Values	Use Scenario 2		Use Scenario 3	
	With Dairy- Acute	With Dairy- Chronic	Without Dairy- Acute	Without Dairy- Chronic
	%aPAD	%cPAD	%aPAD	%cPAD
General US population	0.004	0.005	0.003	0.004
Infants <1 year old	0.005	0.012	0.002	0.006
Children 1-2 years old	0.005	0.010	0.003	0.007
Children 3-5 years old	0.004	0.009	0.003	0.006
Children 6-12 years old	0.003	0.006	0.002	0.004
Teens 13-19 years old	0.002	0.004	0.002	0.003
Adults 20-49 years old	0.002	0.003	0.002	0.003
Adults 50+ years old	0.003	0.004	0.002	0.003
Females 13-49 years old	0.002	0.003	0.002	0.003

- Calculates **acute** and **chronic** exposure and risk for US general population & 8 subpopulations.
- User inputs at-use concentration (from label) and acute PAD/chronic PAD.
- Intended for dairy processing equipment and/or food processing equipment and utensils only.

Determining Dietary Exposure for a Risk Assessment

- Indirect Food Use: e.g., antimicrobials used as ***material preservatives*** in food contact surfaces.
- EPA screening-level modeling approach very conservative.
- Higher Tier Analysis: Dislodgeable surface residue + default transfer coefficients.
- Further Refinement: Empirical residue data.

Determining Toxicity Endpoints for a Risk Assessment

- Determination by EPA's Antimicrobial Division Toxicity Endpoint Selection Committee (ADTC).
- Most sensitive endpoint from FIFRA Part 158W testing.
 - Acute and Chronic endpoints are determined.
 - “Population Adjusted Doses” (PADs) derived and compared to estimated exposures (“margin of exposure”).
 - Sensitization also of concern.
 - Published in EPA's “Dietary Exposure Scoping Document.”

PAD = Reference Dose ÷ FQPA Safety Factor

Table 6. Toxicity Endpoints and Points of Departure for Dietary Exposure Assessment of Chlorinated Isocyanurates			
Exposure Scenario	Dose Used in Risk Assessment, UF	Point of Departure (POD)	Study and Toxicological Effects
Acute Dietary (females 13+)	NOAEL= 200 mg/kg/day ^A UF = 100	Increased incidence of hydrocephaly at 500 mg/kg/day.	Developmental Toxicity – Rabbit (MRID 42054101)
	Acute RfD = 2.0 mg/kg/day		
Acute Dietary (General Population)	N/A	No appropriate endpoint was identified for the general population	
Chronic Dietary	NOAEL = 154 mg/kg/day ^A UF = 100	Decreased survival in male rats and lesions of the urinary tract and heart at the next highest dose of 502 mg/kg/day.	Chronic Toxicity / Carcinogenicity- Rat (MRID 00126362)
	Chronic RfD = 1.5 mg/kg/day		

Adjustments to the Exposure / Hazard: EPA's Conservative Approach

- Uncertainty factors are applied to the hazard endpoint values to determine appropriate reference dose.
 - Values can range from 3 to 300.
- FQPA safety factor is applied 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.
- Uncertainty/safety factors can total 3000.

Evaluation of Risk Assessment Estimates



Population Group	Including Dairy		Without Dairy	
	Chronic Exposure (Dose) (µg/kg/day)	% cPAD (Food Only)	Chronic Exposure (Dose) (µg/kg/day)	% cPAD (Food Only)
General U.S. Population	11.0410	0.007	8.8354	0.006
All Infants (<1 year old)	27.5054	0.018	13.3325	0.009
Children 1-2 years old	23.7913	0.016	16.8003	0.011
Children 3-5 years old	20.5731	0.014	15.4542	0.010
Children 6-12 years old	13.5428	0.009	10.5543	0.007
Youth 13-19 years old	9.7511	0.007	7.8449	0.005
Adults 20-49 years old	8.2950	0.006	6.7797	0.005
Adults 50-99 years old	8.8907	0.006	7.3947	0.005

Highest exposed population subgroups are bolded
Percentage aPAD are rounded to 1 or 2 significant figures

- Exposure must be less than the PAD.
- If exposure is greater than PAD, EPA will demand uses must be dropped / modified until exposures fall to acceptable levels.

Output of the EPA Dietary Risk Assessment

Table 7. Summary of Use Patterns and Models used for Dietary Assessments of chlorinated isocyanurates		
Use Sites Covered by the Model	Model Used in the Assessment	Application Rate of Active Ingredient (ai) Inputted ²
Residential food contact surfaces (countertops, sinks etc.)	Residential Tier 1A	5953 ppm ¹
Agriculture/Farm Structure and Equipment, food greenhouses, mushroom houses	Commercial Tier 1A	
Animal Housing (poultry, swine, zoos and farms)		
Commercial, Institutional, Industrial Premises		
Food Processing Equipment (includes dairy/cheese, poultry, meat and seafood) and utensils	Food Contact Sanitizing Solutions Model (FCSSM)	5953 ppm ¹
Egg Wash/ Sanitizing	Dietary Exposure Evaluation Model - Food Commodity Intake Database (DEEM-FCID)	105 ppm ¹
Animal drinking water ³	Not assessed	89 ppm ³

¹Rate exceeds the existing tolerance exemption of 100 ppm for 180.940(a), (b) and (c)

² In terms of available chlorine

³ This use is categorized as indirect food. There are no models available to calculate exposure from this use. Therefore, exposure from animal drinking water will not be assessed.

General Label Directions For Use (chlorinated cyanurates)

SANITIZER [PERFORMANCE]

This product {or marketed product name} is an effective Sanitizer against [*Staphylococcus aureus*] [and] [*Salmonella enterica*] at 100 ppm with a 1 minute contact time.

[SANITIZER FOR FOOD AND BEVERAGE PROCESSING AND FOOD HANDLING OPERATIONS]

[Prepare a 100 ppm solution; refer to Dilution Chart for the number of tablets to use]

This product is recommended for sanitizing all types of hard, non-porous equipment and utensils used in [food processing and canning plants,] [bottling plants,] [breweries,] [fish processing plants], [meat and poultry processing plants,] [milk handling and processing plants,] [stores,] [restaurants,] [and] [institutional dining establishments.] Use a 100 ppm available chlorine solution [(refer to Dilution Chart)] to sanitize previously cleaned processing and packaging equipment. [Add 1 tablet to 1 quart of water {optional statement to be used only for 334 mg tablet.}] Allow at least a 1 minute contact time before draining. Allow adequate draining before contact with beverages.]

Specific Label Directions for Use (chlorinated cyanurates)

[EGG PROCESSING PLANTS

[Prepare a 100 ppm solution; refer to Dilution Chart for the number of tablets to use] Clean and destain egg shells prior to sanitizing. To clean egg shells, spray with a 90°F to 120°F solution containing 100 ppm available chlorine solution [(refer to Dilution Chart). [Add 1 tablet to 1 quart of water {optional statement to be used only for 334 mg tablet.}] Spray-rinse the cleaned eggs with warm (not hot) potable water. Only clean, whole eggs may be sanitized. Dirty, cracked or punctured eggs may not be sanitized.

To destain egg shells, immerse the eggs in a 90°F to 120°F solution containing 100 ppm available chlorine [(refer to Dilution Chart)]. After destaining, the eggs must be cleaned by spraying with an acceptable cleaner. Follow with a potable water rinse.

To sanitize clean shell eggs intended for food or food products, spray with a solution containing 100 ppm available chlorine [(refer to Dilution Chart)]. The solution must be equal to or warmer than the eggs, but not to exceed 130°F. Wet eggs thoroughly and allow to drain. Eggs that have been sanitized with this chlorine compound may be broken for use in the manufacture of egg products without a prior potable water rinse. Eggs must be reasonably dry before casing or breaking. The solution must not be reused for sanitizing eggs.

Thoroughly clean and sanitize all egg cups, breaking knives, trays and other equipment that come into contact with "off" eggs. First, clean all equipment. Before placing back in use, spray with a solution containing 100 ppm available chlorine [(refer to Dilution Chart)]. Allow surfaces to completely drain before contact with egg product. To sanitize egg freezers and dryers (tanks, pipelines and pumps), use the spray method of treatment (see Sanitizing Application Methods section). This procedure is generally used to sanitize large, non-porous surfaces that have already been cleaned of physical soil.

Prepare a solution containing 100 ppm available chlorine [(refer to Dilution Chart)]. [Add 1 tablet to 1 quart of water {optional statement to be used only for 334 mg tablet.}]. Heavily apply spray to all surfaces the eggs will touch.

Thoroughly spray all treated surfaces, comers and turns. Allow at least a 1 minute contact time before draining. Allow equipment to drain adequately before contact with eggs.]

Reference Notes

- Chlorinated Isocyanurates Registration Review Docket
<https://www.regulations.gov/docket?D=EPA-HQ-OPP-2012-0794>
- Chlorinated Isocyanurates: Dietary Exposure Scoping Document
<https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0794-0013>
- ADBAC Registration Review Docket
<https://www.regulations.gov/docket?D=EPA-HQ-OPP-2015-0737>
- DDAC Registration Review Docket
<https://www.regulations.gov/docket?D=EPA-HQ-OPP-2015-0740>

Closing Observations



- Division of jurisdiction between EPA and FDA can be complex.
- EPA views the potential for residues on food broadly and applies the more restrictive dietary exposure standard to pesticides with those uses.
- EPA tools plus risk assessments provide insights industry can follow.

Closing Observations



Questions?