Exceptions to the NDIN Requirement – Articles Used for Food / Chemical Alteration

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DSHEA Amendments

FDCA 413(a) [21 U.S.C. 350b]

- A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) [21 U.S.C. 342(f)] unless it meets one of the following requirements:
  - (1) The dietary supplement contains only dietary ingredients which have been present in the food supply as *an article used for food in a form in which the food has not been chemically altered*.
  - [(2) = submission of NDIN]

Implementing regulation

21 C.F.R. 190.6 Requirement for premarket notification.

- (a) At least 75 days before introducing or delivering for introduction into interstate commerce a dietary supplement that contains a new dietary ingredient *that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered*, the manufacturer or distributor of that supplement, or of the new dietary ingredient, shall submit [the required NDIN].

What's an article used for food?

- 21 U.S.C. 321(f). The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.
- 21 CFR 1.276(b)(5)(ii). What definitions apply to this subpart [Prior Notice of Imported Food]: Examples of food include fruits, vegetables, fish, including seafood, dairy products, eggs, raw agricultural commodities for use as food or as components of food, animal feed (including pet food), food and feed ingredients, food and feed additives, dietary supplements and dietary ingredients, infant formula, beverages (including alcoholic beverages and bottled water), live food animals, bakery goods, snack foods, candy, and canned foods.

…many such articles…

- 21 CFR Parts 130-169. Numerous foods w/ standards of identity
- 172.510. Natural flavoring substance and natural substances used in conjunction with flavors = ~120 botanicals
- 182.10. Spices and other natural seasonings and flavorings = 80+ botanicals.
- 182.20. Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) = 150+ botanicals.
- 182.40. Natural extractives (solvent-free) used in conjunction with spices, seasonings, and flavorings = 5 botanicals.
- 182.50. Certain other spices, seasonings, essential oils, oleoresins, and natural extracts = 4 animal-derived (civet, musk)

…many such articles…

- 21 CFR Part 172. Food additives permitted for direct addition to food for human consumption.
  - Subpart D. Special dietary and nutritional additives
  - Subpart F. Flavoring agents and related substances
  - Subpart G. Gums, chewing gum bases and related substances
- 21 CFR § 182.60. Synthetic flavoring substances and adjuvants
- 21 CFR Part 184. Direct food substances affirmed as GRAS

FDA's Draft NDI Guidance (2016)

Is an NDI notification required for a dietary supplement containing an NDI if the supplement contains only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered?

- No, an NDI notification would not be required in this situation because of the exception to the notification requirement for dietary supplements that contain only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered.
- Example: Ingredient X is a food additive that was approved for use to sweeten baked goods in 1993 and was marketed for that use before October 15, 1994, but was not marketed for use as a dietary ingredient in dietary supplements before that date. ABC Company wants to market a supplement that contains Ingredient X, and it plans to use the same form of Ingredient X used as a sweetener in baked goods. … Although Ingredient X is an NDI because it was not marketed as a dietary ingredient before October 15, 1994, ABC Company is not required to submit an NDI notification … because Ingredient X has been present in the food supply as an article used for food in a form in which the food has not been chemically altered….

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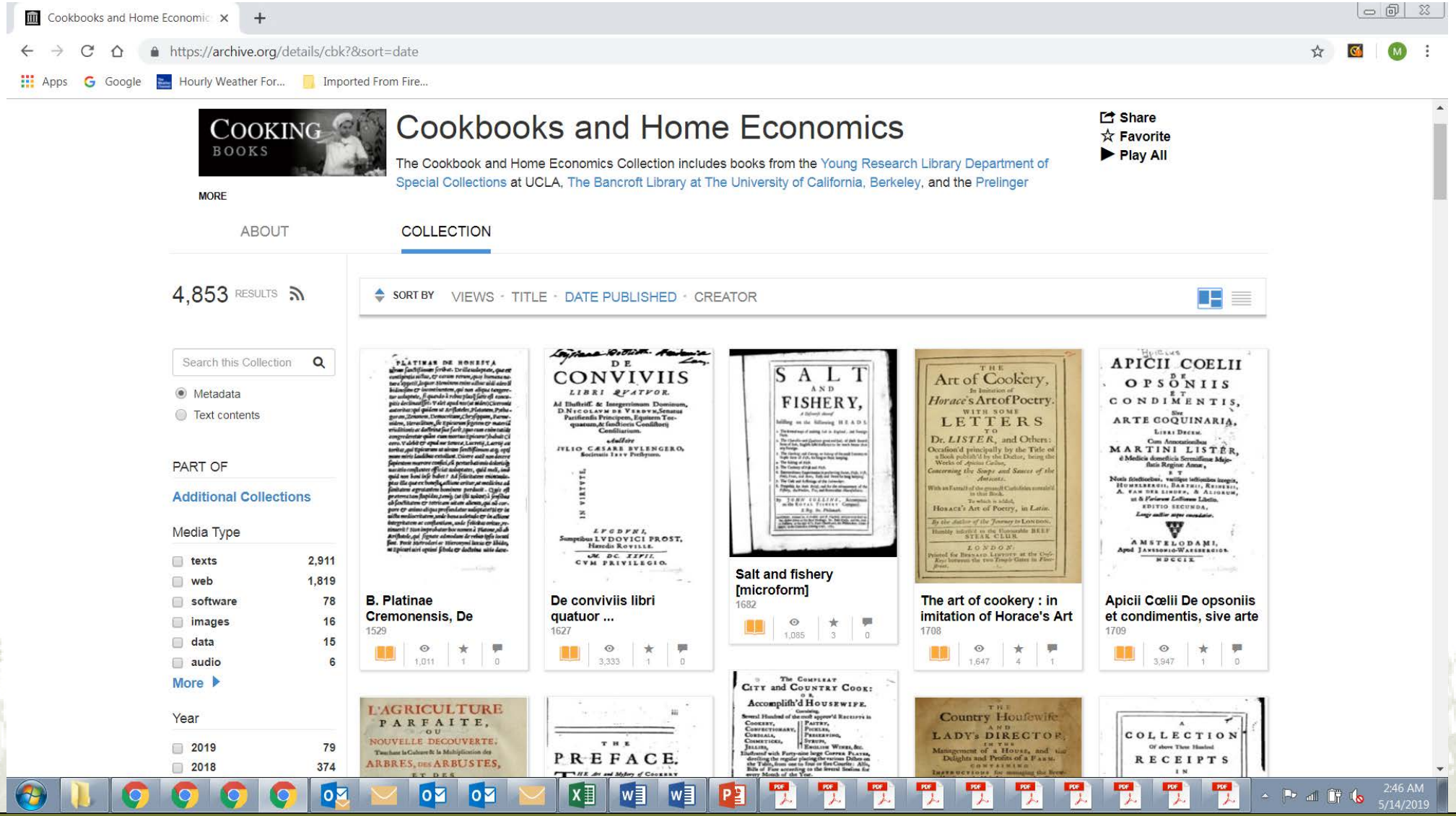

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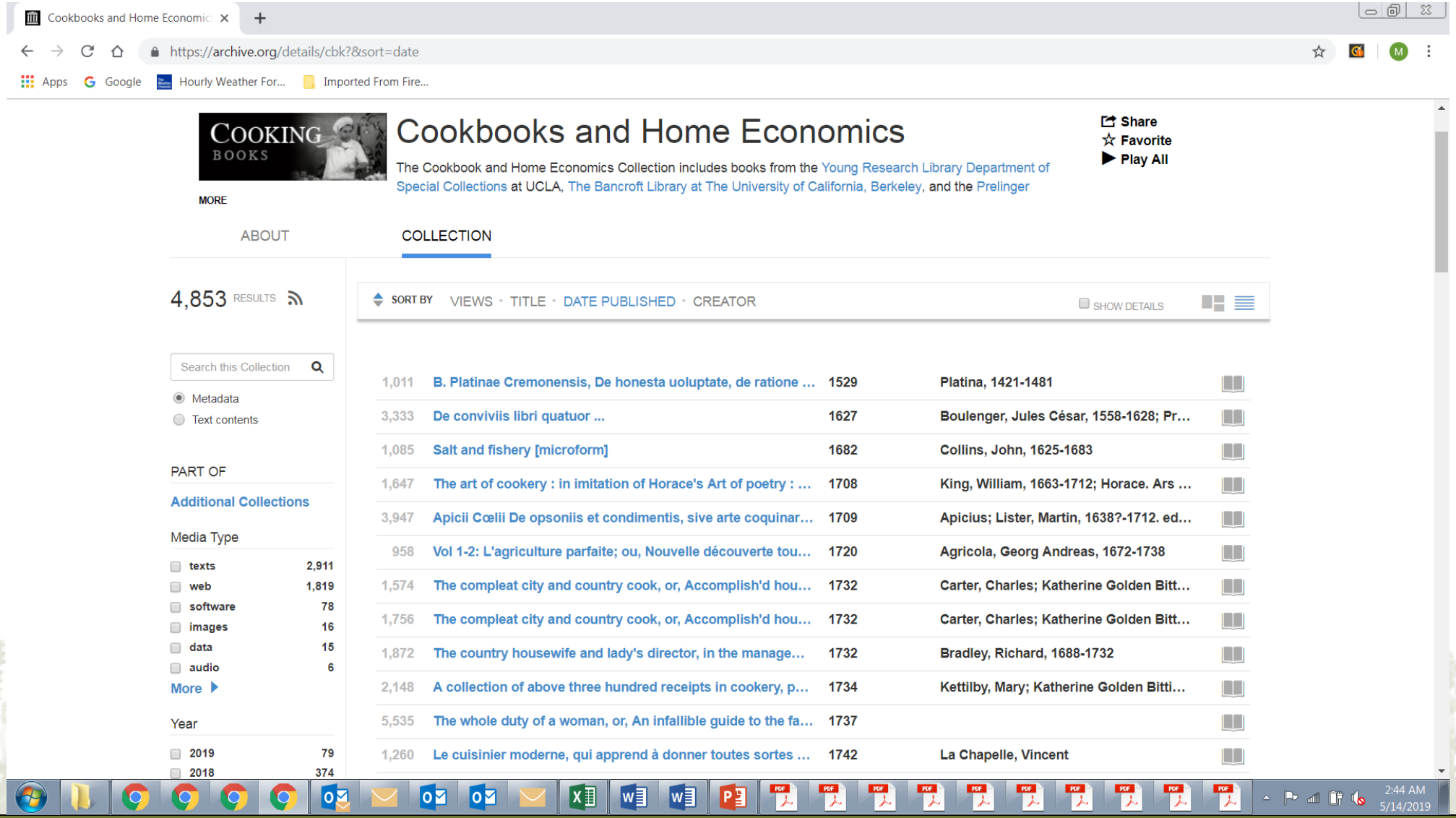

What is chemical alteration?

Congressional Statement of Agreement (Oct. 1994)

- In section 413(a)(1), added by section 8, the term ‘chemically altered’ does not include the following physical modifications: minor loss of volatile components, dehydration, lyophlization [sic], milling, tincture or solution in water, slurry, powder, or solid in suspension.

FDA's Draft NDI Guidance (2016)

What are examples of processes that chemically alter an article of food present in the food supply?

- A process that makes or breaks chemical bonds, unless the bonds created by the process are reversed when the ingredient is dissolved in water (e.g., creation of a soluble salt) or during ingestion. Example: hydrolysis.
- Removal of some components of a tincture or solution in water, which changes the chemical or molecular composition or structure of the mixture. Examples: chromatography, distillation, and filtration.
- Use of solvents other than water or aqueous ethanol to make an extract or tincture. The official legislative history of DSHEA specifies that "solution in water" and "tincture" (solution in aqueous ethanol) are not processes that chemically alter a food. However, other solvents typically alter the composition of the extract in significantly different ways, usually by extracting different types of constituents than are extracted using water and aqueous ethanol.

FDA's Draft NDI Guidance (2016)

What are examples of processes that chemically alter an article of food present in the food supply?

- High temperature baking or cooking of an ingredient that has not previously been baked or cooked, unless the process causes only minor loss of volatile components with no other changes to the chemical or molecular composition or structure of the ingredient.
- Changing the manufacturing method for an ingredient such that the chemical or molecular composition or structure is significantly different. Examples: changes that alter the composition of materials used to make the ingredient, use of a different solvent, or use of a chromatographic matrix instead of a passive filter.
- Application of nanotechnology that results in new or altered chemical properties of the ingredient.

FDA's Draft NDI Guidance (2016)

What are examples of processes that chemically alter an article of food present in the food supply?

- Changing agricultural or fermentation conditions to alter the chemical or molecular composition or structure of the ingredient. Examples: sprouting garlic or fermenting yeast using a medium containing large amounts of sodium selenite to create large amounts of organic selenium compounds.
- Fermentation using a fermentation medium different from the one used to make conventional foods in the food supply. Example: use of a defined commercial growth medium to produce a microorganism previously made by fermenting milk into dairy products like yogurt or cheese.
- Use of a botanical ingredient that is at a different life stage than the life stage of the botanical ingredient used as a conventional food. Examples: making an extract from unripe instead of ripe apples or using the mycelium instead of the fruiting body of a fungus.

FDA's Draft NDI Guidance (2016)

What processes for manufacturing a dietary ingredient from an article of food present in the food supply do not result in chemical alteration?

- FDA considers this list [in the Congressional Statement of Agreement] to represent examples of manufacturing processes that do not involve chemical alteration, but not necessarily a complete list of such processes.
- In general, FDA considers a process that does not result in chemical alteration to mean a process that: (1) involves an ingredient composed of one single raw material, or derived from a single raw material using a manufacturing process that involves only physical steps (e.g., water extraction and condensation); and (2) does not involve attempts to selectively increase the concentration of particular active ingredients or cause a chemical reaction (other than esterification) that would modify the covalent bonds of any substance in the original material.
- Some of the processes characterized as "physical modifications" in the Congressional Statement of Agreement (milling, slurry, powder, or solid in suspension) do not alter the chemical or molecular composition or structure of the ingredient.

FDA's Draft NDI Guidance (2016)

What processes for manufacturing a dietary ingredient from an article of food present in the food supply do not result in chemical alteration?

- Dehydration, lyophilization, or making a tincture, solution in water, or slurry can be said to change the composition of the ingredient, but only by changing the amount of water (or ethanol, in the case of a tincture). FDA regards such a minor change in composition as extremely unlikely to change the safety profile of an ingredient used in conventional food. Similarly, a minor loss of volatile components during processing is unlikely to change the safety profile of an ingredient used in conventional food.
- In a typical extraction, however, the first step is solution in water or another solvent, followed by filtration to remove undissolved material. This is a much larger change in the composition of the ingredient. FDA generally regards extraction that includes a filtration step or that involves the use of a solvent other than water or alcohol (aqueous ethanol) as a process that chemically alters the source ingredient and therefore triggers the NDI notification requirement for the resulting dietary ingredient.

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THANK YOU!

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