Non-IgE Mediated Food Allergy Risk Context for Novel Protein Safety

CropLife International and EuropaBio View

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Definitions for Risk Context – Non-IgE Mediated Factors and a Weight-of-Evidence

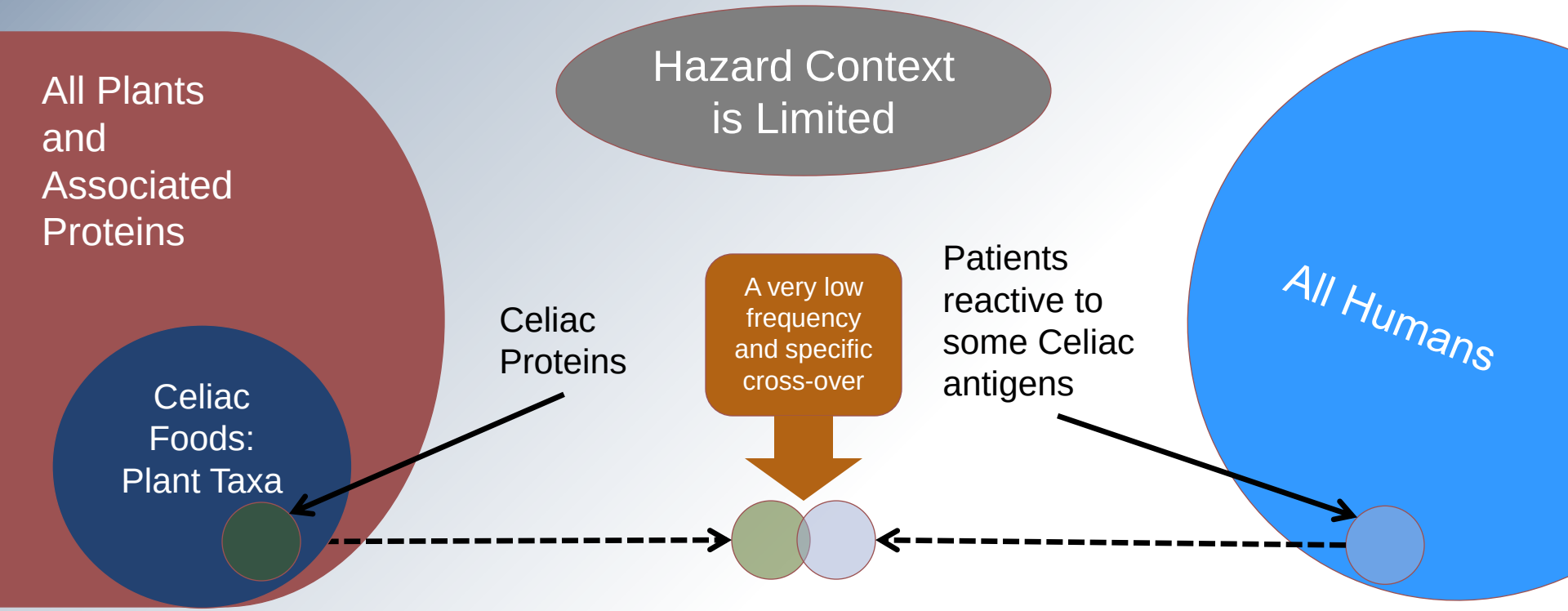
- **Hazard** – a few proteins (5 genus representation (2 oat genus') cause specific enteropathies.
  - The hazard only affects a small subset of people (patients).
  - Antigens are protein specific and not the same across the 4 (5) Celiac associated species.

- **Risk Factor** – a presumptive hazard-containing scenario. Not necessarily transferred by one protein to another GM product.
  - Example given by wheat – a known IgE and non-IgE mediating food.

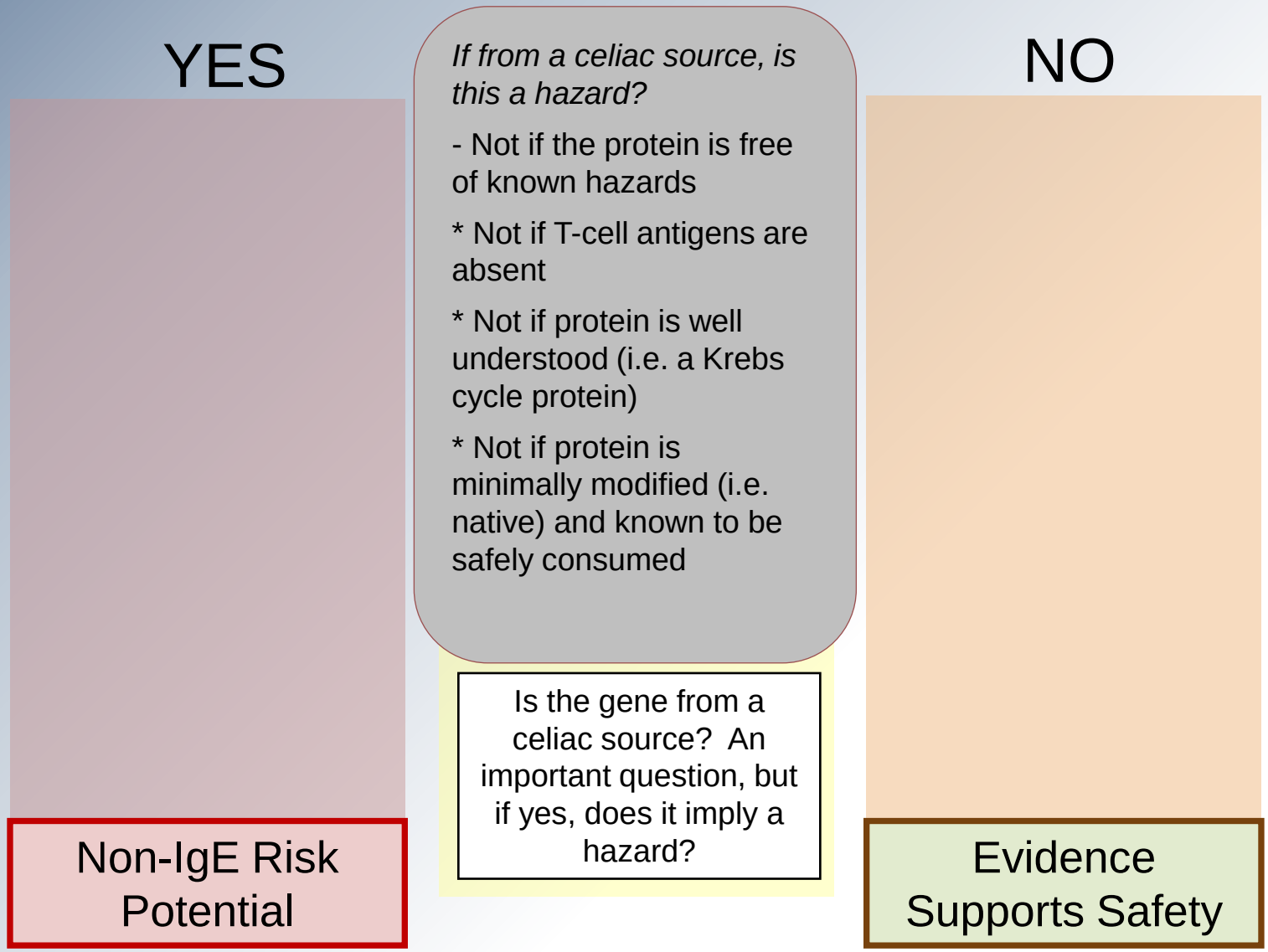
- **Risk** = a defined adverse effect (Hazard) X Exposure
  - Hazard ***alone*** does not implicate a novel protein as having risk
    - Native protein moved to new GM species is still native in its function/structure
  - Exposure ***alone*** does not implicate a novel protein as having risk

Hazard Concept for Sensitizing Proteins Associated with Non-IgE Mechanisms

- There are several enteropathies associated with T-cell mediated inflammatory conditions with Celiac Disease being best understood in relation to exposure to food proteins.



Identifying Potential Hazards for a Novel Protein



Characterizing Non-IgE Mediated Allergy Potential is In-line with Allergy Assessment Guidelines

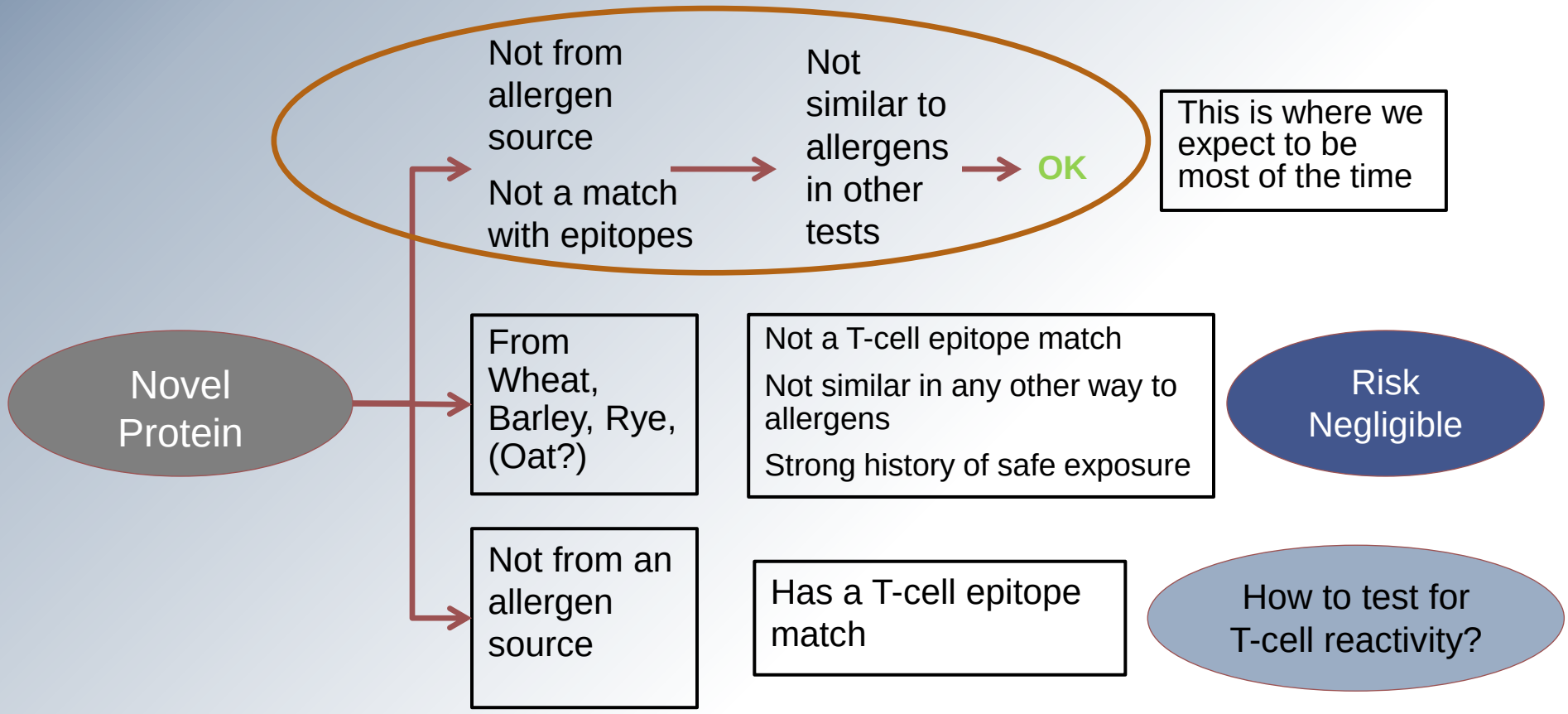
- Proteins are already assessed for their potential to be similar to known allergens through bioinformatic means;
  - This has traditionally included wheat, barley and rye proteins
- Small, known celiac T-cell epitopes can be searched to identify potential biological relevance

Exact epitope matches would indicate a potential need to follow-up with testing oriented to T-cell specific reactivity

A difference from existing Codex guidance, IgE serology testing would not be appropriate in response to a bioinformatic alignment

Non-IgE Mediated Allergy Mechanisms Require Further Research

If a protein shared a T-cell epitope with a wheat celiac protein, it is unclear which *in vitro* methods could clarify the potential for adverse exposure in sensitive patients



Questions to Help Define the Necessity for Special Non-IgE Mediated Food Risk Language – Are we Already Covering this?

- Source Organism Alone – Can it define a risk factor or hazard?
  - Organism cannot define hazard for a single protein the way it would for a whole food
  - Cannot define hazard in exclusion of weight-of-evidence.
- Bioinformatic comparison – is the novel sequence the same or different than known celiac epitopes?
  - We have the databases.
- Verification testing – this is required if a sequence has some plausible evidence for interacting adversely with the immune system.
  - Are technical tools available to do this? The main difference is that serology would not be appropriate.
- Are the considerations substantially different than those we have in place for existing novel protein allergy safety?

Discussion Points and Concluding Remarks

- Which non-IgE mediated immune reactions are considered?
  - Several are covered in Mills et al (2013), and their consideration from a novel protein safety perspective begins in a similar way as with IgE-mediated allergy – compare with known allergens.
    - An allergen protein is assessed for any of the many clinically relevant allergy conditions– i.e., it becomes listed in an allergen database – just as many wheat, barley and rye proteins have for years.

- Risk criteria and evaluation approaches for assessing non-IgE mediated concerns are identical to IgE-mediated concerns in terms of initial ***screening***…
  - Screening by understanding (full assessment includes all studies):
    1) Characterization of novel protein, including, but not limited to source organism
    2) Results of bioinformatic screening