EFSA guidance on allergenicity assessment of GM plants

Antonio Fernandez-Dumont

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Allergenicity guidelines

SCIENTIFIC OPINION

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Guidance on allergenicity assessment of genetically modified plants

EFSA Panel on Genetically Modified Organisms (GMO),
Hanspeter Naegeli, Andrew Nicholas Birch, Josep Casacuberta, Adinda De Schrijver, Mikolaj Antoni Gralak, Philippe Guerche, Huw Jones, Barbara Manachini, Antoine Messéan, Elsa Ebbesen Nielsen, Fabien Nogué, Christophe Robaglia, Nils Rostoks, Jeremy Sweet, Christoph Tebbe, Francesco Visioli, Jean-Michel Wal, Philippe Eigenmann, Michelle Epstein, Karin Hoffmann-Sommergruber, Frits Koning, Martinus Lovik, Clare Mills, Francisco Javier Moreno, Henk van Loveren, Regina Selb and Antonio Fernandez Dumont

Abstract

- **Non-IgE-mediated adverse immune reactions**
- ***In vitro* protein digestibility**
- **Endogenous allergenicity**

Keywords: guidance, allergenicity assessment, newly expressed proteins, endogenous allergenicity, GMO

EFSA mandate: allergenicity guidelines

- **Why?**
  - To consider new developments in the area
  - To address MS/NGOs/EP/applicants comments
  - To assist on practical implementation of regulatory requirements
- **Stakeholder/public engagement**
  - "Focus group" consultative body
  - Workshop
  - Public consultation
  - InfoSession

Immune-mediated adverse reactions

IgE-mediated	Immediate hypersensitivity reactions
Combined IgE- and non-IgE-mediated	Eosinophilic oesophagitis Eosinophilic gastroenteritis Eosinophilic gastroenterocolitis
Non-IgE-mediated	Food enteropathy Celiac disease Food protein induced enterocolitis Heiner syndrome

Adapted from: The University of Manchester, 2013. Literature review: EFSA supporting publication 2013:EN-527, 40 pp

Immune-mediated adverse reactions

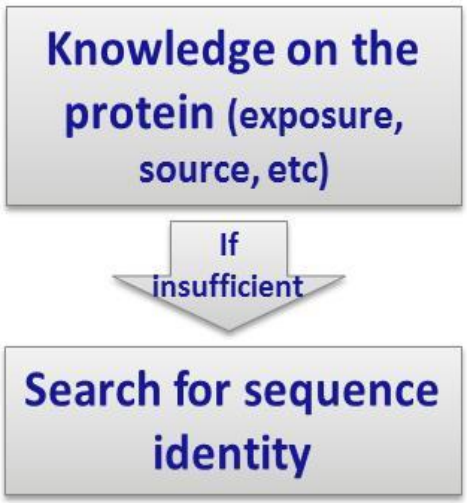
Celiac disease
Clear cause-effect relationship

Non-IgE-mediated

- Food enteropathy
- Celiac disease
- Food protein induced enterocolitis
- Heiner syndrome

RA of (novel) proteins: celiac disease

Fig 1. Stepwise approach for risk assessment



RA of (novel) proteins: celiac disease

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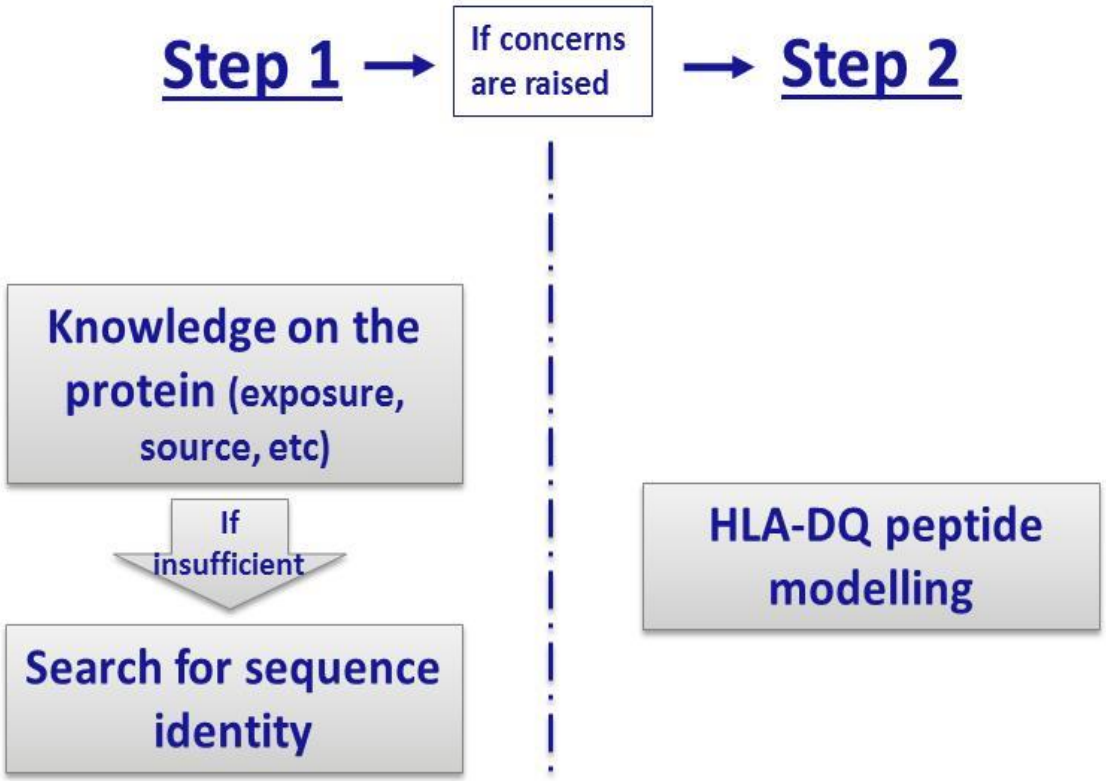

RA of (novel) proteins: celiac disease

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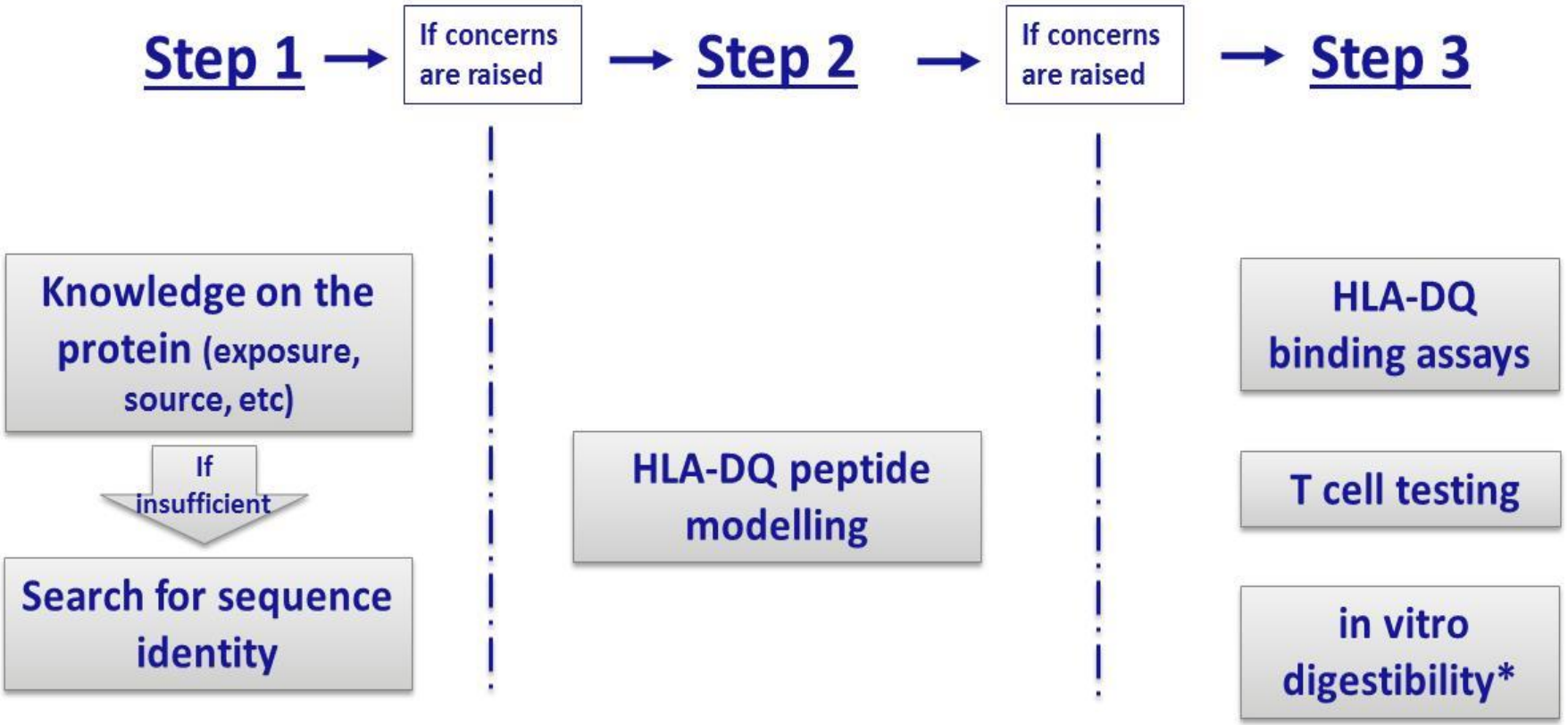


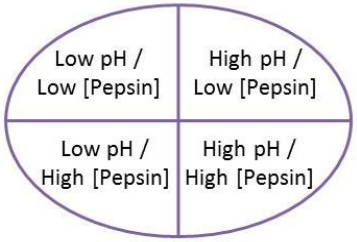
* for details, please see chapter on *in vitro* digestibility

RA of (novel) proteins: *in vitro* digestion

- **Risk assessment considerations**
  - No recommendation in the form of guidance
  - A refined *in vitro* digestion test proposed
    An interim phase needed –> EFSA procurement
- **Annex B**
  - Additional considerations for the interim phase
  -

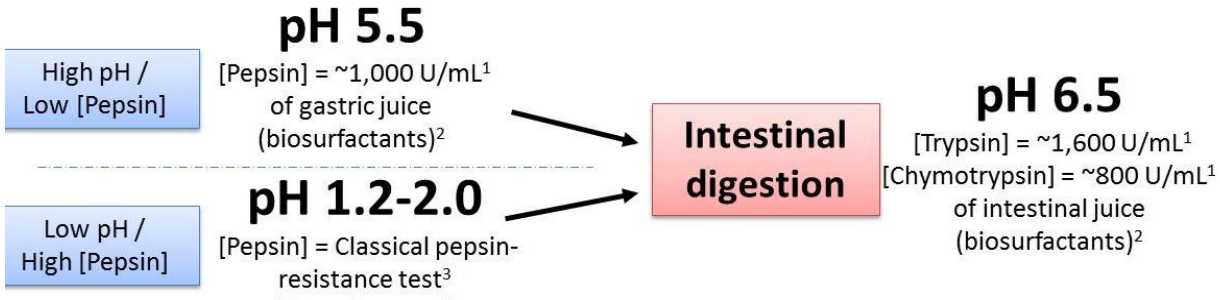
Examples for test conditions – digestion conditions

Possible gastric conditions:



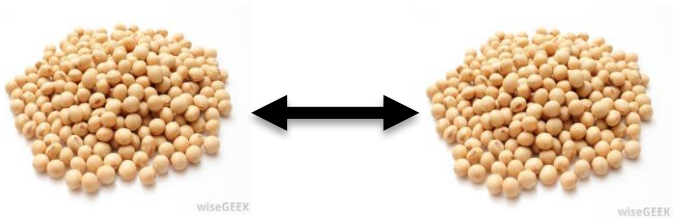
Elderly/adults in fasted state
Elderly/adults in fed state
People with impaired gastric function
People taking antacids
Infants

Proposed gastrointestinal conditions:

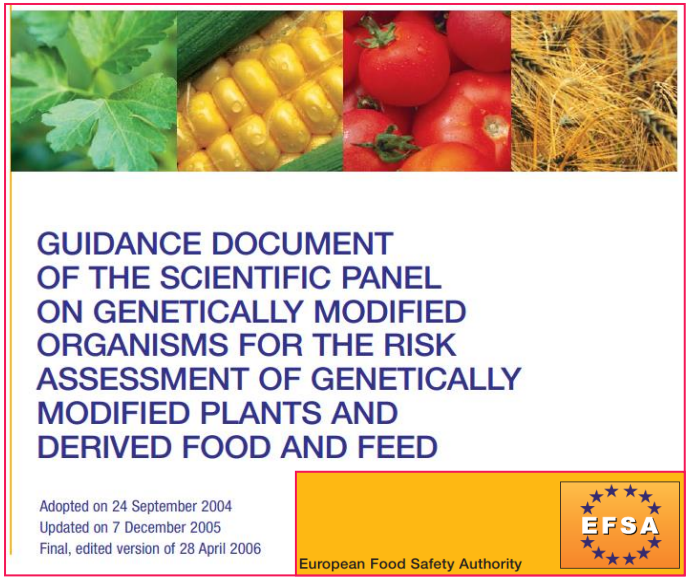


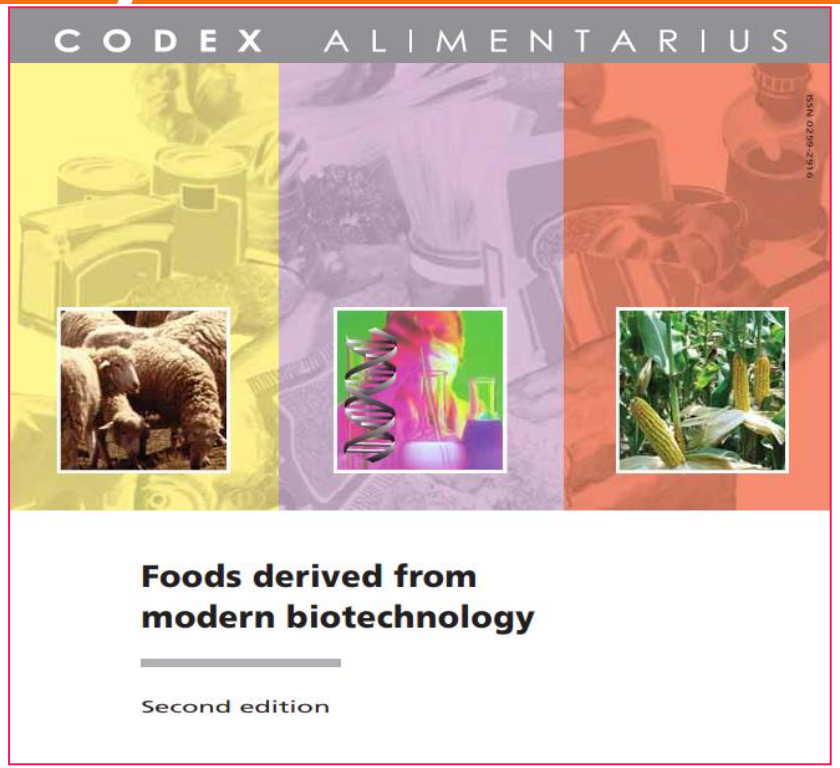
Endogenous allergenicity

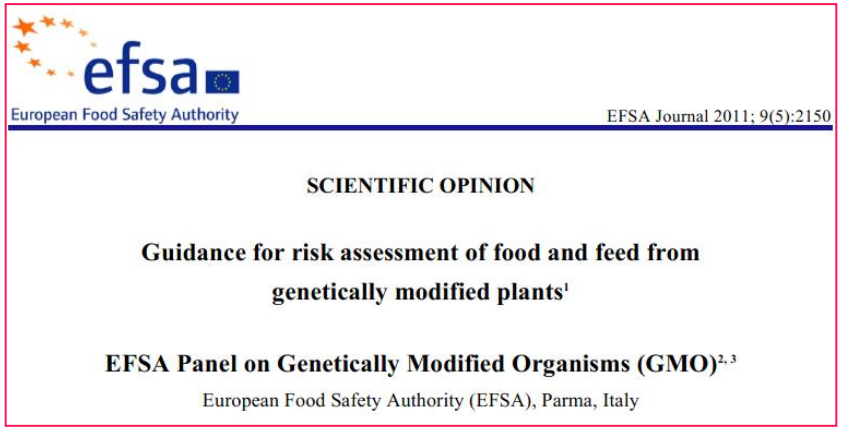
Comparative approach



"non-GM" "GM"







Relevant plants for analysis

- Analysis performed on a case-by-case basis
- For «common allergenic foods»
- To date: soybean is the main crop analysed
- Other GM plants than soybean: whenever considered necessary

Relevant allergens for quantification

EU Regulation 503/2013

OECD consensus soy 2012
Soy allergen list:
'potential soybean allergens'

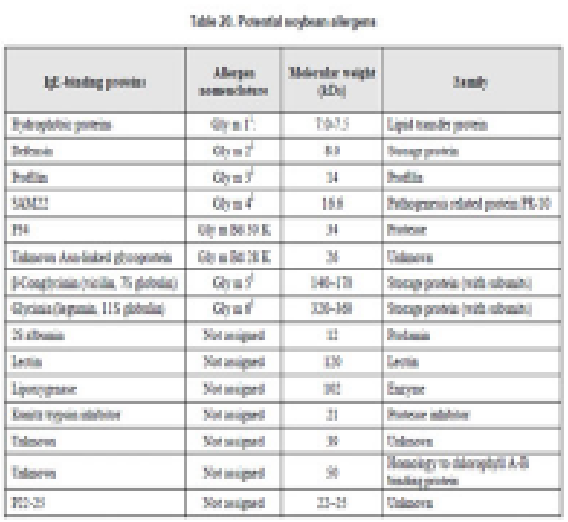


Table 20. Potential soybean allergens

IgE-binding proteins	Allergen nomenclature	Molecular weight (kDa)	Family
Hydrophobic proteins	Gly m 1[1]	7.0-7.5	Lipid transfer proteins
Beta-conglycinin	Gly m 2[1]	8.9	Storage proteins
Profilin	Gly m 3[1]	14	Profilin
SAM22	Gly m 4[1]	18.0	Pathogenesis related proteins PR-10
P34	Gly m Bd 30 K	34	Protease
Unknown Asn-linked glycoprotein	Gly m Bd 28 K	28	Unknown
β-Conglycinin (vicilin, 7S globulin)	Gly m 5[1]	140–170	Storage proteins (with subunits)
Glycinin (legumin, 11S globulin)	Gly m 6[1]	320–360	Storage proteins (with subunits)
2S albumin	Not assigned	12	Profilin
Lectin	Not assigned	120	Lectin
Lipoxygenase	Not assigned	102	Enzyme
Kunitz trypsin inhibitor	Not assigned	21	Protease inhibitor
Unknown	Not assigned	39	Unknown
Unknown	Not assigned	50	Homology to chlorophyll A-B binding proteins
P52-55	Not assigned	52–55	Unknown

Source: adapted from L'Hocine and Boye, (2007); updated with information from WHO/IUIS (2012)

[1] WHO/IUIS (2012) Allergen nomenclature recognised by WHO and IUIS

Evidence check

Evaluation of literature for all single allergens

and

Comparison and complementation with databases (EFSA, 2010)

and/or

Systematic Reviews

Clinical relevance shown

Relevance for GMO risk assessment

Example in Annex C

WHO/IUIS

Considerable peer-reviewed literature

Table 20. Potential soybean allergens

IgE-binding proteins	Allergen nomenclature	Molecular weight (kDa)	Family
Hydrophobic proteins	Gly m 1[1]:	7.0-7.5	Lipid transfer protein
Defensin	Gly m 2[1]	8.0	Storage protein
Profilin	Gly m 3[1]	14	Profilin
SAM22	Gly m 4[1]	16.6	Pathogenesis related protein PR-10
P34	Gly m Bd 30 K	34	Protease
Unknown Asn-linked glycoprotein	Gly m Bd 28 K	26	Unknown
β-Conglycinin (vicilin, 7S globulin)	Gly m 5[1]	140–170	Storage protein (with subunits)
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2S albumin	Not assigned	12	Prolamin
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Lipoxygenase	Not assigned	102	Enzyme
Kunitz trypsin inhibitor	Not assigned	21	Protease inhibitor
Unknown	Not assigned	39	Unknown
Unknown	Not assigned	50	Homology to chlorophyll A-B binding protein
P22-25	Not assigned	22–25	Unknown

SBP proteins Gly m 7

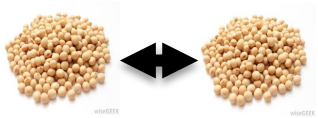
Others: Gly m CPI, Gly m EAP,…

Limited/non-existent peer-reviewed literature

Methodology

- **Quantitative ELISA**
- **Quantitative mass spectrometry**

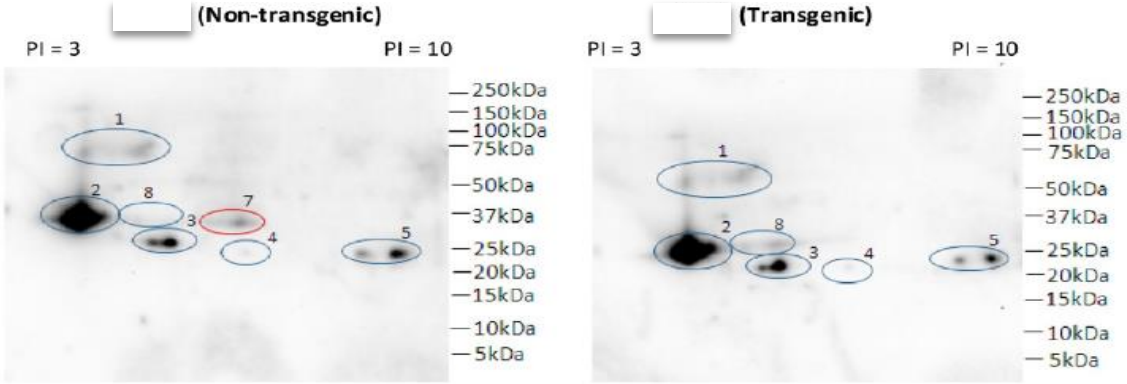
comparative approach



"non-GM" "GM"

Future development of an allergen compositional database (natural variability)

Historically: **human sera (IgE-binding)**

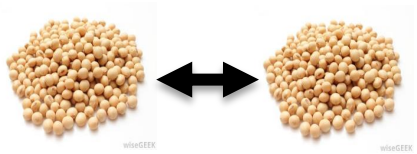


Goodman et al. 2013, J. Agric. Food Chem. 2013, 61, 8317-8332

Data interpretation

- **Natural variability of allergens**

comparative approach



"non-GM" "GM"

- **On case-by-case basis**
  - Magnitude and number of changes
  - Clinical relevance of the allergen(s) involved
  - Exposure considerations
  - Clinical evaluation (if needed):
    - DBPCFC comparison GM vs non-GM
    - Dose-distribution curves to single allergens

Allergenicity guidelines

Thank you for your attention

Main contributors:

JM Wal, P Eigenmann, M Epstein, K Hoffmann-Sommergruber, F Koning, M Lovik, C Mills, FJ Moreno, H van Loveren, R Selb and A Fernandez-Dumont