REGULATORY RISK ASSESSMENT AND FOOD INNOVATION IN EUROPE

Nutrition and Food Innovation Unit (NIF)
GMO Team

efsa
EUROPEAN FOOD SAFETY AUTHORITY

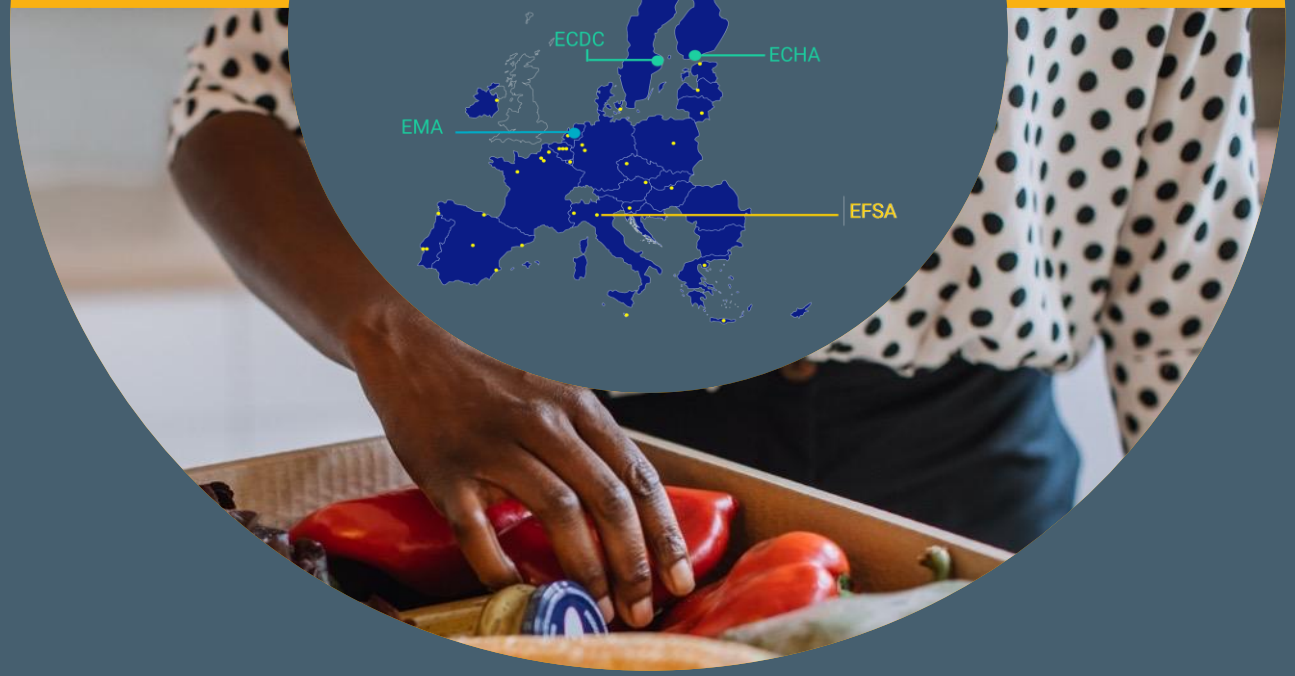
OUTLINE

- Scientific Panels and Committee
- Guidance for GMOs
- Pillars of GMO Risk Assessment

- Scope and Traits of GMOs
- Future opportunities for Protein Safety
- Stacked events

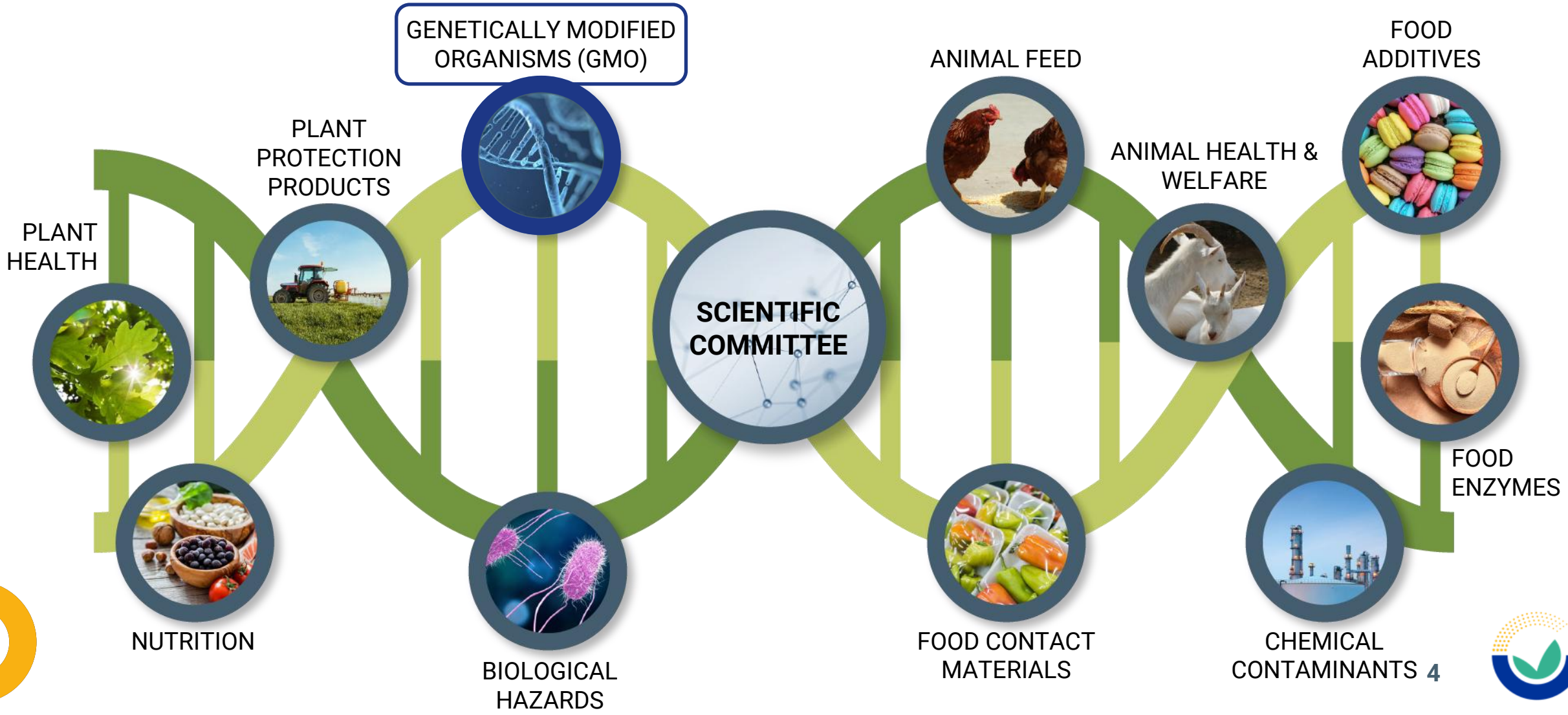
- Horizon scanning and opinions
- Plants, Microorganisms and Animals

What is EFSA?

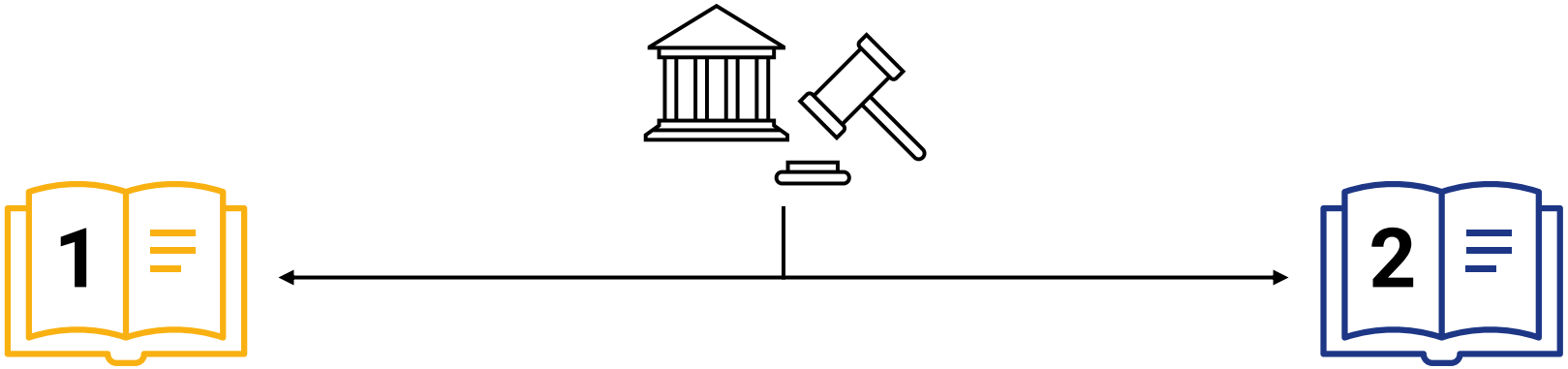


- Reference body for risk assessment of food and feed in the EU
- 2002
- Restore confidence in the EU food supply
- Clearly separate risk assessment from risk management

THE SCIENTIFIC PANELS AND COMMITTEE



EU LEGAL FRAMEWORK FOR GMO RISK ASSESSMENT



Directive 2001/18/EC

On the deliberate release into the **environment** of GMOs

AMENDMENTS FOR ERA

Directive (EU) 2018/350

Regulation (EC) No 1829/2003

On GM **food** and **feed** including derived products

IMPLEMENTATION for PLANTS

Regulation (EU) 503/2013

THE 4 PILLARS OF THE GMO RA

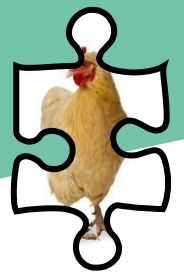
1
Molecular characterisation (**MC**)

- Description of methods
- Info on vectors, inserted/deleted sequence(s), new traits
- Info on the protein expression levels
- Bioinformatics data
- Genetic/phenotypic stability

2
Comparative analysis (**CA**)

- Agronomic and phenotypic characteristics
- Compositional data

3
Food/Feed risk assessment (**FF**)



- Toxicological assessment
- Allergenicity assessment
- Dietary exposure
- Nutritional assessment
- PMM

4
Environmental risk assessment (**ERA**)

- Persistence/ invasiveness
- Gene flow
- (non-)target organisms
- Biogeochemical cycles
- PMEM

GUIDANCE DOCUMENTS

- ✓ legal completeness of incoming dossiers
- ✓ avoid Additional Data Requests
- ✓ make assessments consistent & transparent

+ need for

- *Stakeholders meetings (Twice per year)*
- *Digital Tools for interaction*
- *General Pre-Submission Advice*
- *Technical hearings with experts*
- *Clarifying Teleconferences*

Scientific guidance

Applicable to all applications (submitted before o

GM Plants – Molecular characteris

Main guidance

- **2011:** Guidance on risk assessment of **food a**

Molecular characterisation

- **2018** Explanatory note on the determination o the context of genetically modified plant applic
- **2024** Technical Note on the **quality of DNA se** characterisation of genetically modified plants
- **2025** Risk assessment considerations for **RNAi-based genetically modified plants**

Food/feed safety

- **2014** Explanatory statement for the applicability of the Guidance of the EFSA Scientific Committee on conducting repeated-dose **90-day oral toxicity study** in rodents on whole food/feed for GMO risk assessment
- **2017** Guidance on **allergenicity** assessment of genetically modified plants
- **2019 Human dietary exposure** assessment to newly expressed proteins in GM foods

Comparative assessment

- **2011** Guidance on the selection of **comparators**
- **2015** Guidance on the **agronomic and phenotypic** characterisation of genetically modified plants
- **2018** Explanatory note on the **selection of forage material suitable** for the risk assessment of GM feed of plant origin

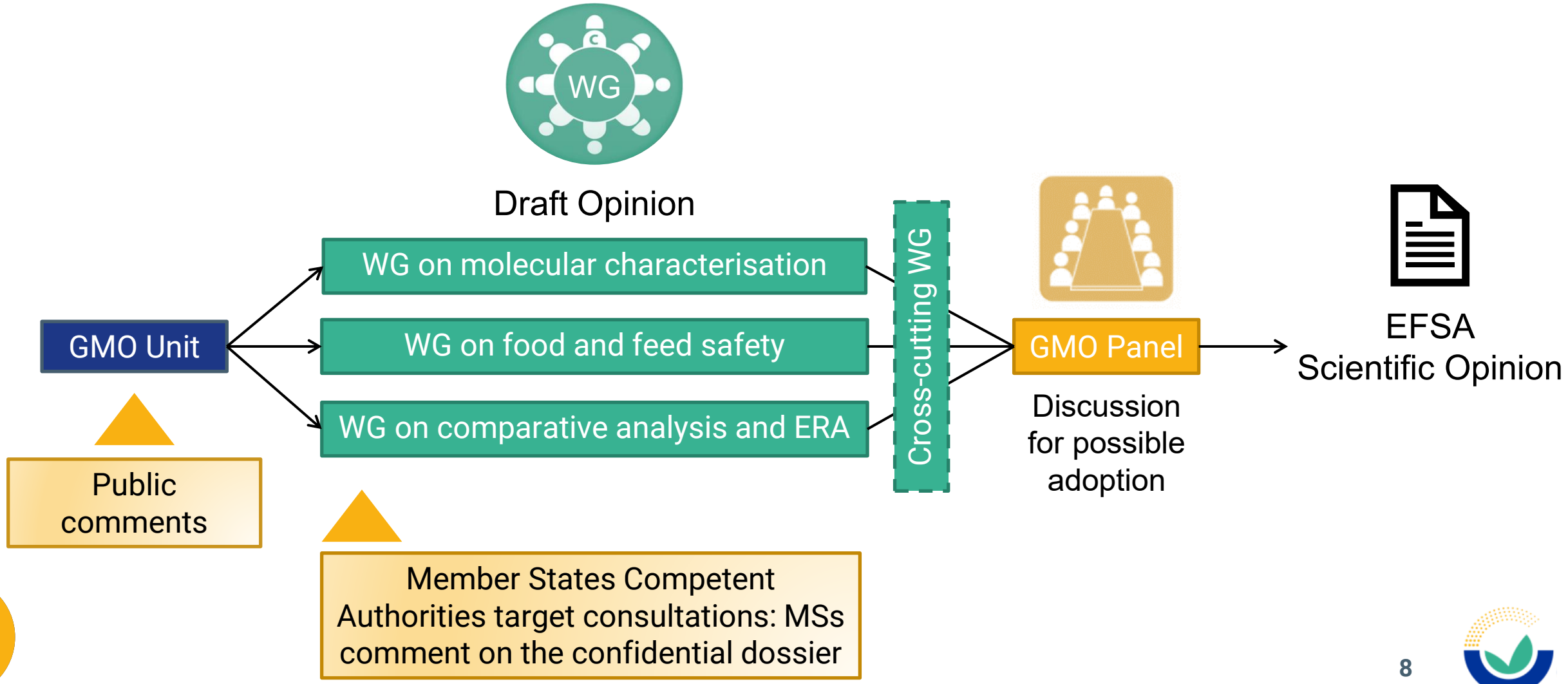
GM Plants - Environmental *Risk Assessment*

- **2010 Environmental risk assessment** of GM plants
- **2017** Explanatory note on **DNA sequence similarity** searches in the context of the assessment of horizontal" gene transfer from plants to microorganisms

GM Plants - Post Market Monitoring

- **2011** Guidance on **Post-market environmental monitoring (PMEM)** of GM plants

WORKING GROUP (WG)



Risk Assessment experiences

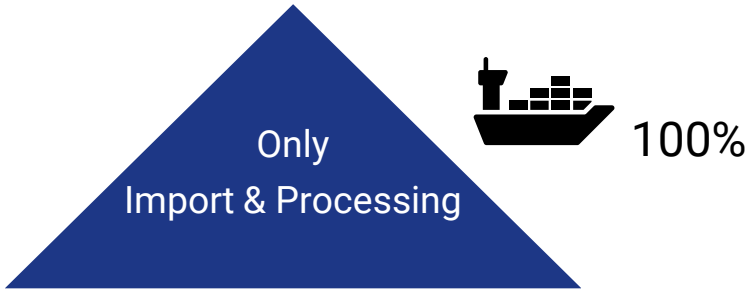
Scope and Traits of GMOs

Future opportunities

- ❑ Protein safety
- ❑ Stacked events

TRAITS OF GMO APPLICATIONS

BEFORE 2013



TODAY





Maize	Soybean	Cotton	OSR	Sugar Beat

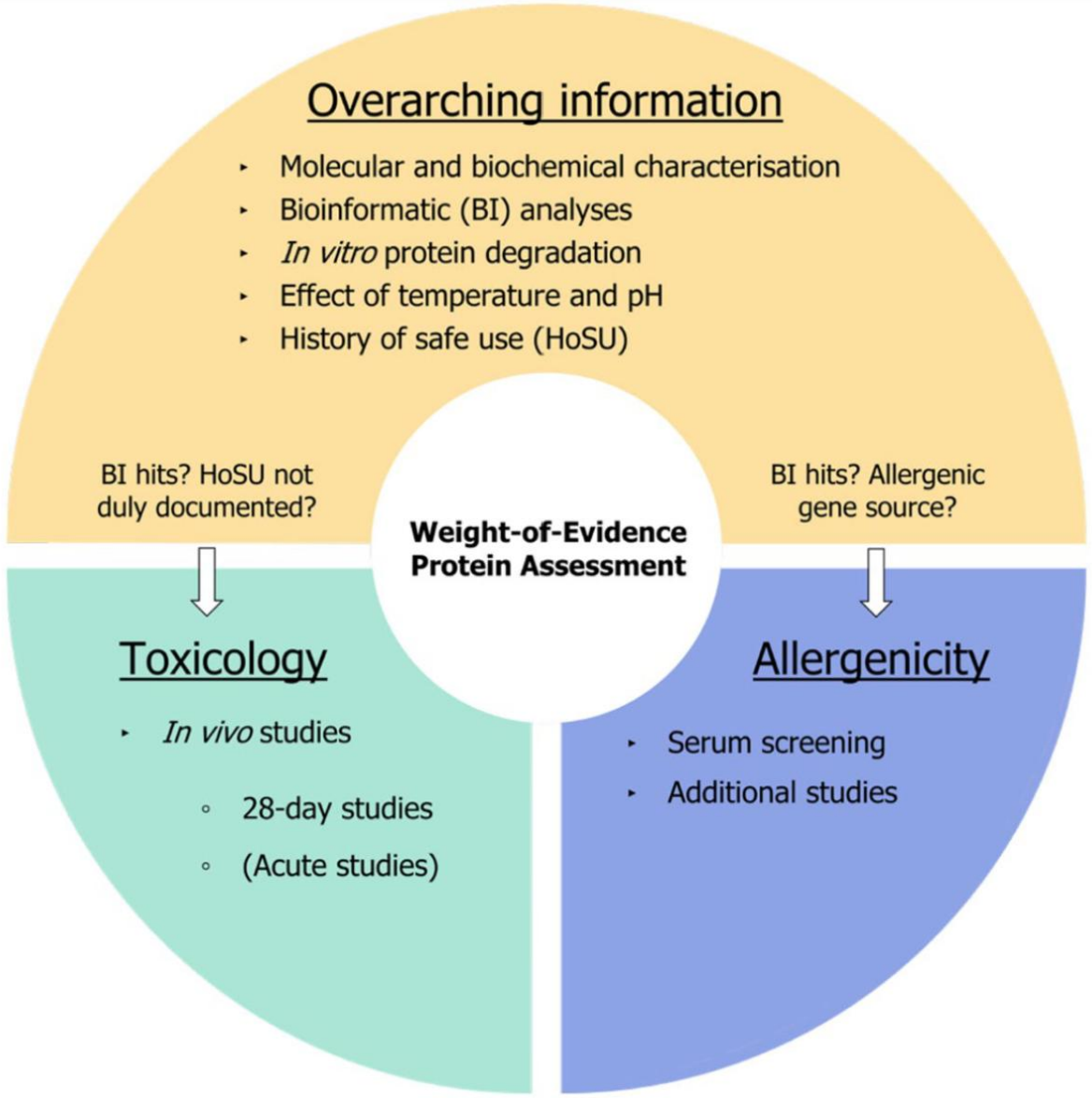
Single and stacks events

TRAITS

Insect resistance
Herbicide tolerant
Drought tolerance
Metabolic
Yield enhanced
Male sterility

REGULATION 503 – PRESENT REQUIREMENTS FOR NEPS

>Food and Feed assessment
>> PROTEIN SAFETY of NEPs



EFSA SELF-MANDATE: FUTURE OPPORTUNITIES OF PROTEIN SAFETY

Present Requirements (Current Situation)

- Codex Alimentarius and in EU, Regulation No 503/2013

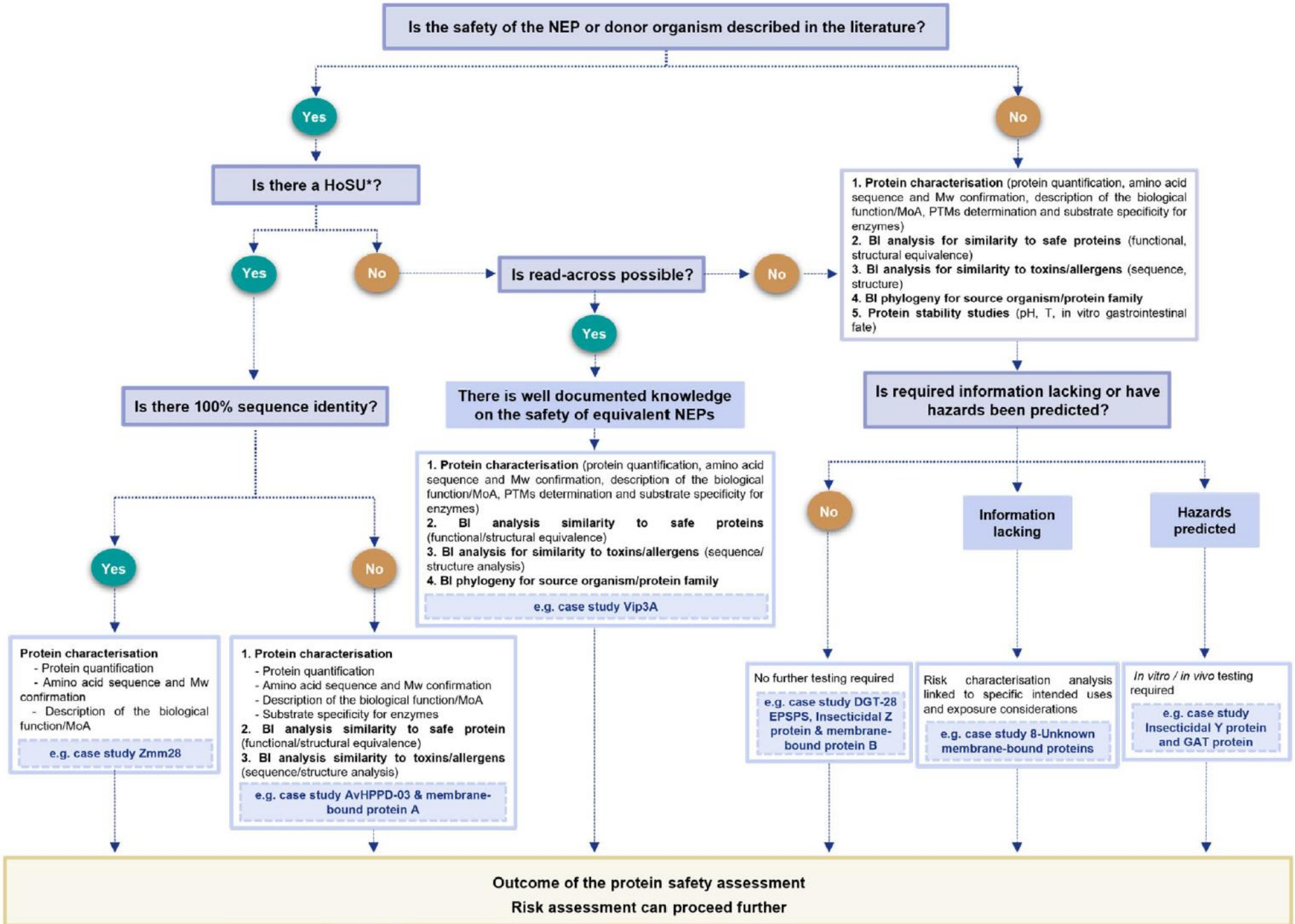
Experience Gained (Challenging from complex cases)

- High number of new proteins
- New proteins difficult to characterise/test
  - Membrane-bound
  - Transcription factors
- New proteins displaying potential hits with known allergens or toxins

Future opportunities

provide complementary/alternative methods

ADOPTED 30 June 2025

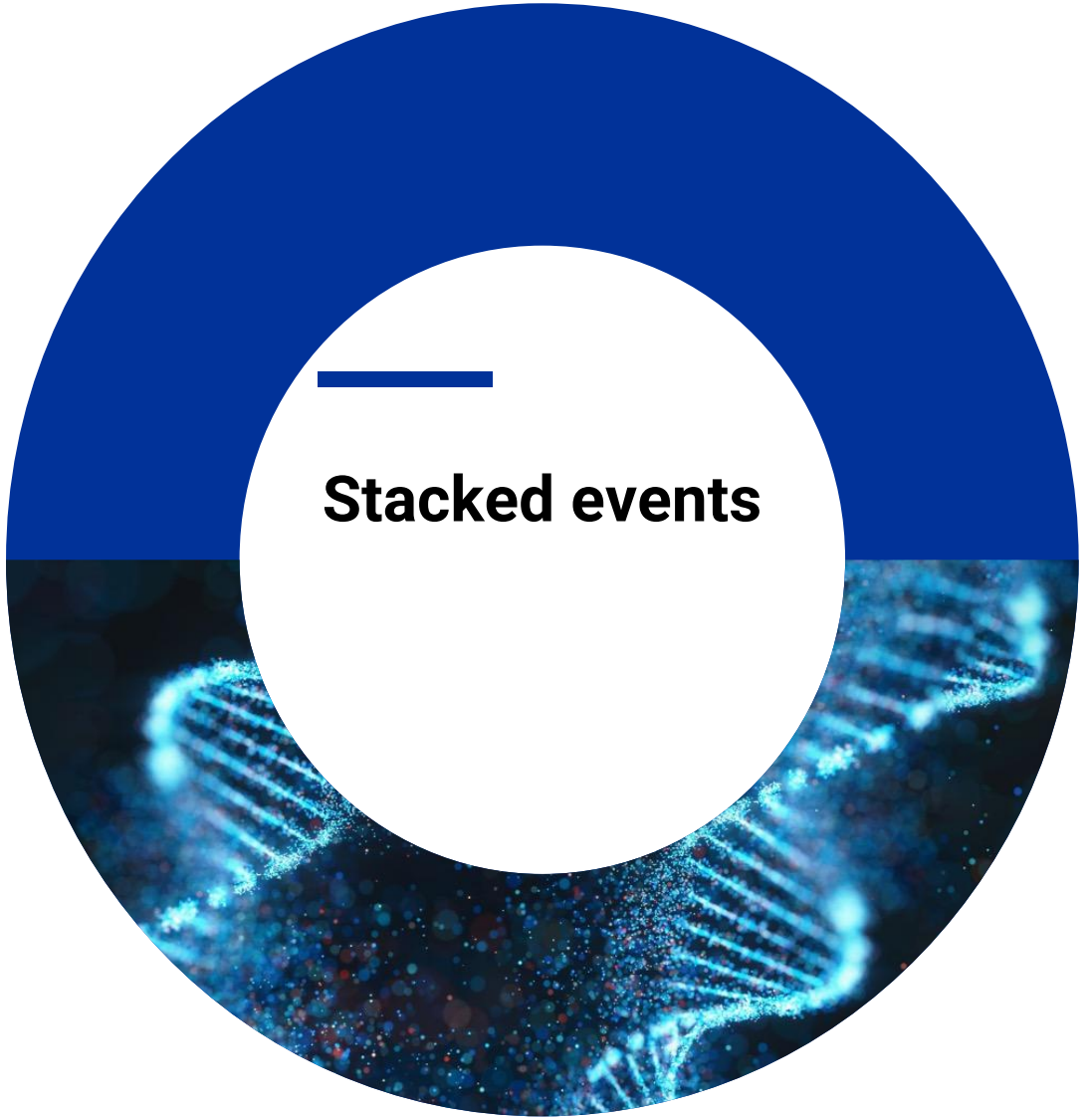

Is the safety of the NEP or donor organism described in the literature?
Yes
No
Is there a HoSU*?
Yes
No
Is read-across possible?
No
Yes
1. Protein characterisation (protein quantification, amino acid sequence and Mw confirmation, description of the biological function/MoA, PTMs determination and substrate specificity for enzymes)
2. BI analysis for similarity to safe proteins (functional, structural equivalence)
3. BI analysis for similarity to toxins/allergens (sequence, structure)
4. BI phylogeny for source organism/protein family
5. Protein stability studies (pH, T, in vitro gastrointestinal fate)
Is required information lacking or have hazards been predicted?
Is there 100% sequence identity?
There is well documented knowledge on the safety of equivalent NEPs
1. Protein characterisation (protein quantification, amino acid sequence and Mw confirmation, description of the biological function/MoA, PTMs determination and substrate specificity for enzymes)
2. BI analysis similarity to safe proteins (functional/structural equivalence)
3. BI analysis for similarity to toxins/allergens (sequence/structure analysis)
4. BI phylogeny for source organism/protein family
e.g. case study Vip3A
No
Information lacking
Hazards predicted
Yes
No
Protein characterisation
- Protein quantification
- Amino acid sequence and Mw confirmation
- Description of the biological function/MoA
e.g. case study Zmm28
1. Protein characterisation
- Protein quantification
- Amino acid sequence and Mw confirmation
- Description of the biological function/MoA
- Substrate specificity for enzymes
2. BI analysis similarity to safe protein (functional/structural equivalence)
3. BI analysis similarity to toxins/allergens (sequence/structure analysis)
e.g. case study AvHPPD-03 & membrane-bound protein A
No further testing required
e.g. case study DGT-28 EPSPS, Insecticidal Z protein & membrane-bound protein B
Risk characterisation analysis linked to specific intended uses and exposure considerations
e.g. case study 8-Unknown membrane-bound proteins
In vitro / in vivo testing required
e.g. case study Insecticidal Y protein and GAT protein
Outcome of the protein safety assessment
Risk assessment can proceed further

DEVELOPMENT NEEDS - 3 PRIORITIES

- **HoSU:** define with measurable criteria (e.g., generations of exposure, consumer-group size, intake metrics) and minimum consumption thresholds
- ***In silico* tools:** Tox/Allergen databases: connect, populate with “safe proteins” + Red Flags for interpretation
- ***In vitro* tools: in vitro digestion and other key pathways**
  - Test whether harmonised in vitro digestion protocols are suitable for determining the gastrointestinal fate of proteins
  - Identify and qualify NAMs for key pathways to harm, such as gut barrier integrity and immune sensitization
  - Read-outs, biological relevance etc….

EFSA welcomes research activities and seeks collaboration: workshop 12-13 November ONLINE

EVENT 1 X EVENT 2 X .....

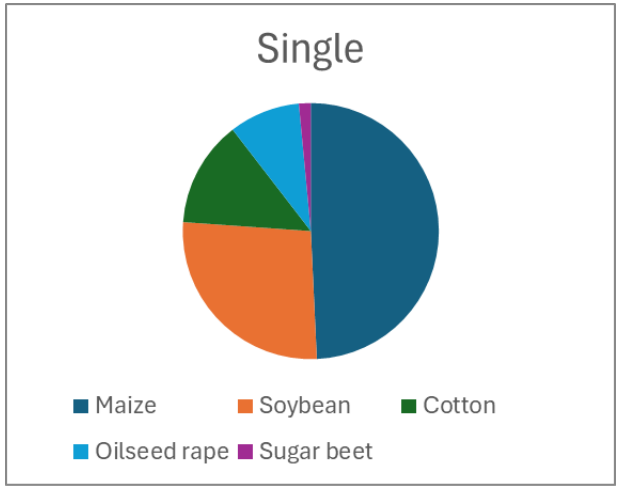


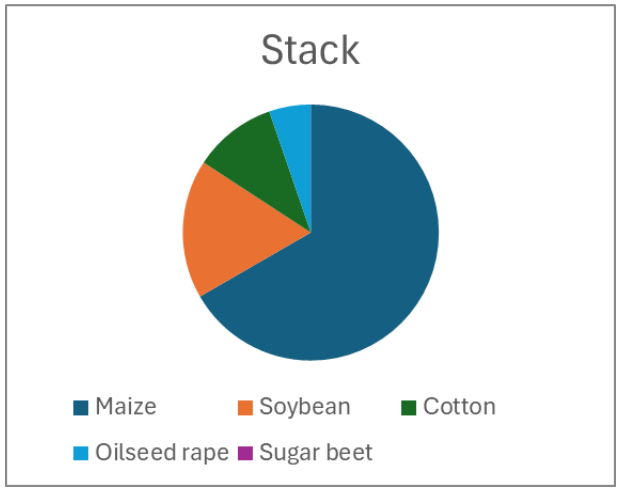
EXPERIENCE GAINED BY THE GMO PANEL

In the last 20 years, the EFSA GMO Panel assessed almost 130 applications, of which about 60 were for stacks*.

Crop	Single adopted #	Stack adopted #
Maize	33	38
Soybean	18	10
Cotton	9	6
Oilseed rape	6	3
Sugar beet	1	0
TOTAL	67	57

Single and stack applications adopted per species



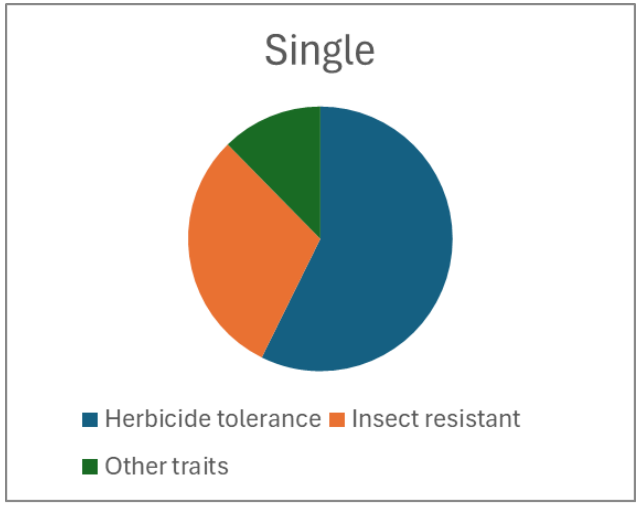


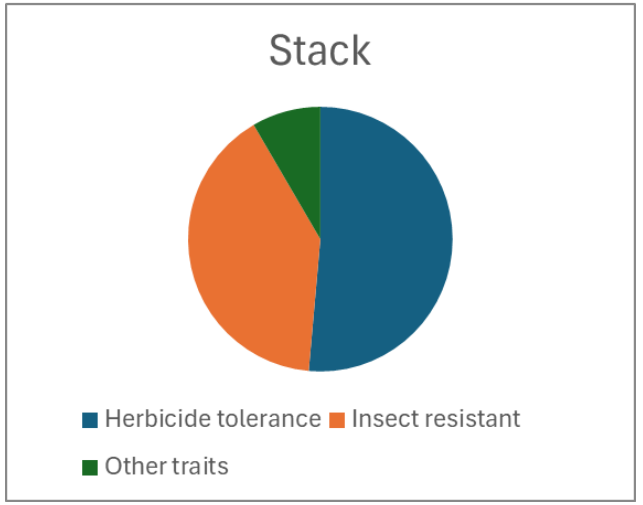
*updated up to January 2025

EXPERIENCE GAINED BY THE GMO PANEL

Trait	Single adopted #	Stack adopted #
Herbicide tolerance	51	55
Insect resistant	27	43
Other traits	11	9

Single and stacked applications adopted per trait





DISCUSSION WITH EXPERTS

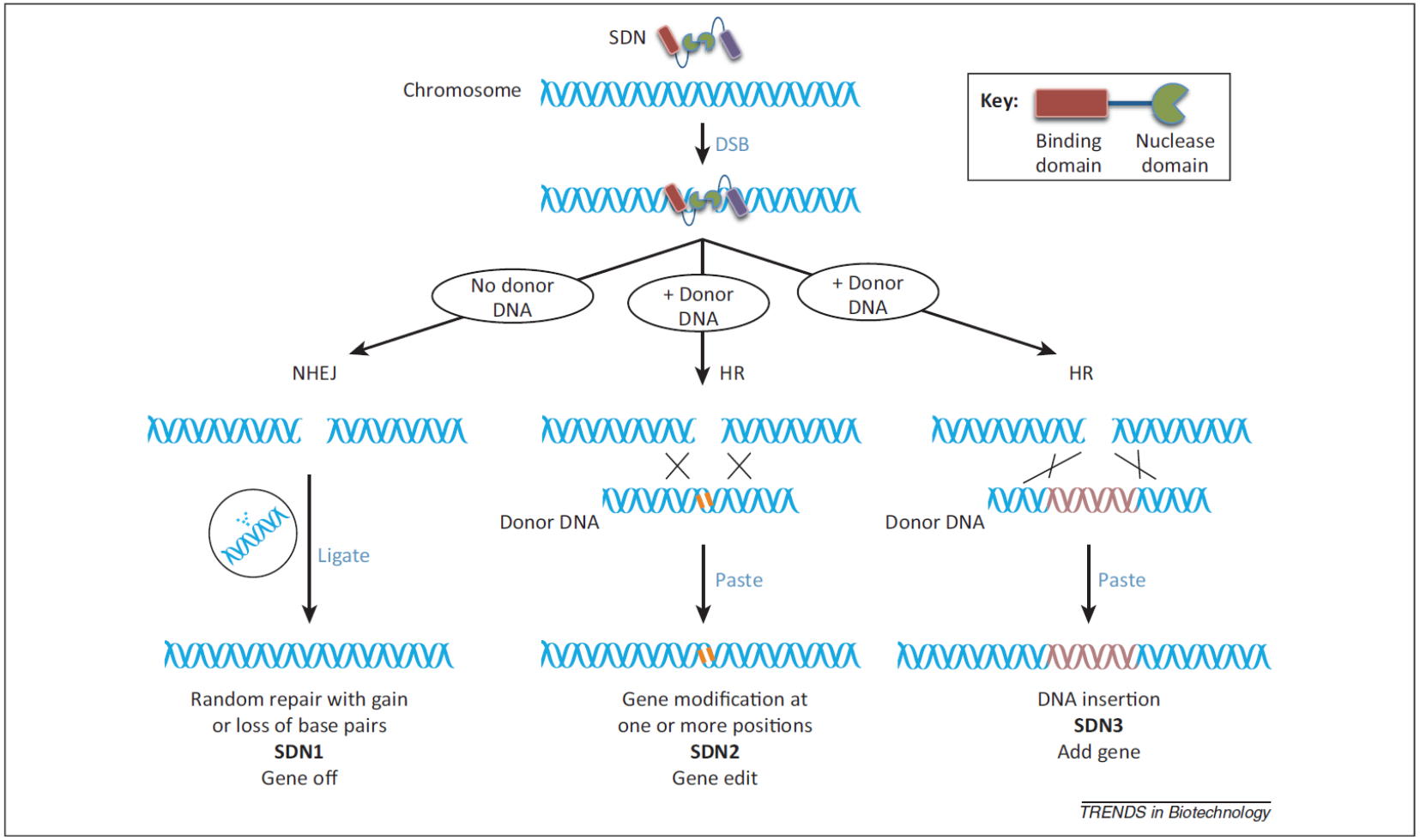
- Based on the experience accumulated during more than 20 years assessing single and stacked events, the GMO Panel is discussing whether in **justified cases**, some specific sets of data may not be necessary for the assessment of the stacks.

- The cross-cutting WG of the GMO Panel is leading the discussion. The focus is on the scientific evidence used to assess interactions between single events, and whether the weight of such evidence may change for specific stacks.

Inputs for risk management on new developments in Biotechnology

- Horizon scanning and opinions
- NGTs, SynBio, Gene drives
- Plants
- Microorganisms
- Animals

SDN1, SDN2, SDN3



Podevin N. et al., 2013, after EFSA Journal 2012;10(10):2943

SERIES OF MANDATES FROM EU COMMISSION TO EFSA

Scientific Opinions including RA considerations

Overall request Term of Reference (ToR)

Horizon Scan

BIOTECHNOLOGY MANDATES

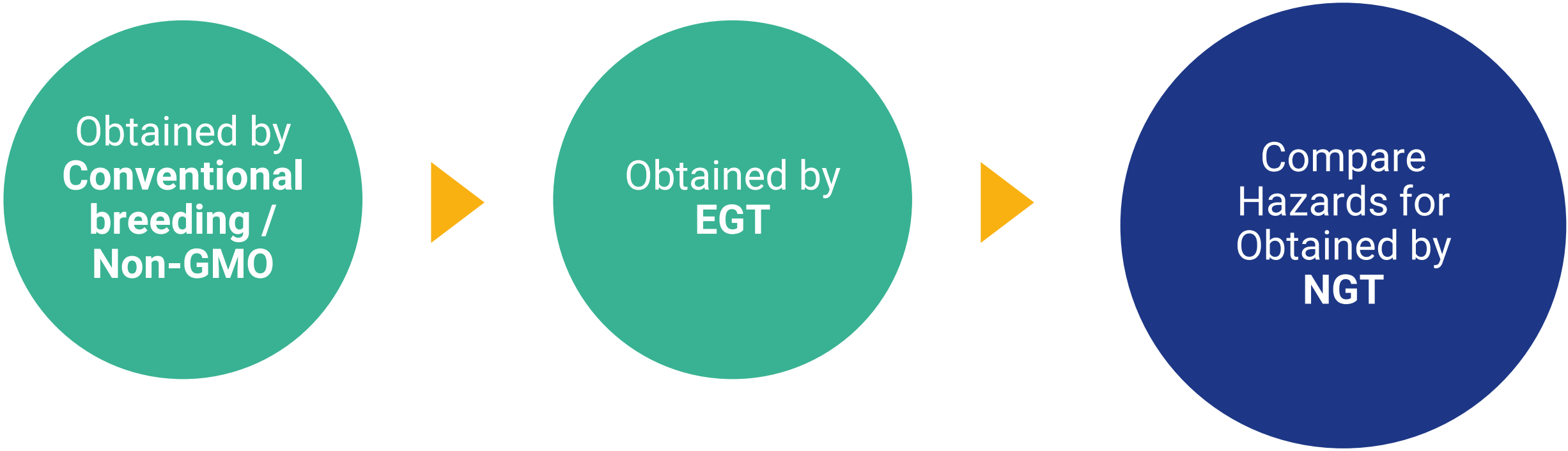
Synthetic biology

In **microorganisms** (FF) / in **plants** * (FF) In **microorganisms** (MC + ERA) / in **plants** (MC + ERA)	4 Published **link / link** **link / link**	**2020-2022**

Gene Drives

Evaluation of existing EFSA guidelines for assessment of **genetically modified insects containing engineered gene drive**	Published, **link**	**Nov 2020**

GENERAL APPROACH TO ADDRESS EC REQUESTS



BIOTECHNOLOGY MANDATES - NGT

Plants

*developed through **cisgenesis and intragenesis**	Published, **link**	**Feb 2012**
*developed using **Zinc Finger Nuclease 3 and other Site-Directed Nucleases**	Published, **link**	**Oct 2012**
*developed using type 1 and type 2 **Site-Directed Nucleases and Oligonucleotide Directed Mutagenesis**	Published, **link**	**Nov 2020**
*Update - developed through **cisgenesis and intragenesis**	Published, **link**	**Oct 2022**
*Criteria for risk assessment of plants developed through **targeted mutagenesis and cisgenesis**	Published, **link**	**Oct 2022**

Microorganisms

new developments in biotechnology applied to **microorganisms** (new genomic techniques)	Published, **link**	**July 2024**

Animals

*new developments in biotechnology applied to **animals** (including synthetic biology & new genomic techniques)	Published, **link**	**July 2025**

OVERALL CONCLUSIONS FROM EFSA

- Horizon scanning reports showing cases that are close to market
- No new hazards associated NGTs were identified compared to EGTs and conventional breeding
- There is a need for flexibility in the data requirements for the risk assessment, as on a case-by-case lesser amounts of data might be needed

*Opinions are subject to literature scans to capture relevant publications in the remit of the mandates

GM MICROORGANISMS RA GUIDANCE

Microbial characterisation and ERA

Applies to:

- Biomasses
- Active agents

primary and secondary routes of exposure

Environments considered: All exposed to the product (except human and animal gut)

AREAS OF ENVIRONMENTAL RISK

- As defined in Commission Directive (EU) 2018/350 on the ERA of GMOs (Annex II Section D.1)

Persistence and invasiveness	Horizontal gene transfer	Effects on target organisms	Effects on non-target organisms	Effects on humans or animals	Effects on biogeochemical processes	Effects of management techniques
						

BIOMASSES

ACTIVE AGENTS

EXCEPTIONS

- General (e.g.):
  - Biomasses not containing genes of concern
- Specific per area of risk (e.g.):
  - Persistence and invasiveness- GM active agents which modification results in traits already present in microorganisms of the same taxonomic in the receiving environmental microbiome(s).
  - Effects on non-target organisms- GM active agent interacts solely with the target organism.

NGT ANIMALS

No new hazards
AHAW –NGT specific
Guidance updates

Adopted: 30 June 2025

DOI: 10.2903/j.efsa.2025.9566

efsa JOURNAL

SCIENTIFIC OPINION

New developments in biotechnology applied to animals: An assessment of the adequacy and sufficiency of current EFSA guidance for animal risk assessment

EFSA Panel on Genetically Modified Organisms (GMO) | Josep Casacuberta | Francisco Barro | Albert Braeuning | Ruud de Maagd | Michelle M. Epstein | Thomas Frenzel | Jean-Luc Gallois | Frits Koning | Antoine Messéan | F. Javier Moreno | Fabien Nogué | Alan H. Schulman | Christoph Tebbe | Eve Veromann | Leslie Firbank | Debora Glandorf | Mette S. Herskin | Simon Geoffrey Lillico | Robin Ornsrud | Anna Troedsson-Wargelius | Michele Ardizzone | Paolo Lenzi | Ana M. Camargo | Nikoletta Papadopoulou | Reinhilde Schoonjans | Marika Vitali | Giovanni Savoini

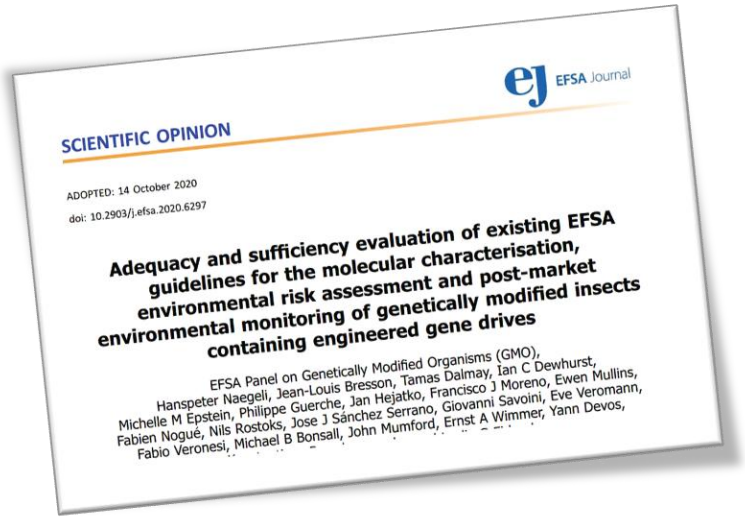
Correspondence: nif@efsa.europa.eu

The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts

Abstract

EFSA was requested by the European Commission to provide a scientific opinion on new developments in biotechnology, including new genomic techniques, as applied to animals for food, feed and other agricultural uses. A horizon-scanning exercise identified a variety of animals obtained with new genomic techniques, with the potential to reach the EU market in the short, medium and long term. No novel hazards have been identified that are linked to either the modification process or the newly introduced trait, when SDN-1, SDN-2 and comparable techniques (e.g. base editing or prime editing) were compared to established genomic techniques (EGTs) or conventional breeding. Hazards posed by SDN-3 are of the same nature as those posed by EGTs and the targeted insertion may reduce the potential hazards associated with the disruption of endogenous genes and/or regulatory elements in the recipient genome. Hazards posed by the new trait resulting from the introduced transgenic or intragenic DNA sequence are of the same nature as those posed by EGTs. Hazards posed by the new trait resulting from the intro-

GENE DRIVES – 2020 – 2023 - 2025 YANN DEVOS



EFSA Journal

SCIENTIFIC OPINION

ADOPTED: 14 October 2020

doi: 10.2903/j.efsa.2020.6297

Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives

EFSA Panel on Genetically Modified Organisms (GMO), Hanspeter Naegeli, Jean-Louis Bresson, Tamas Dalmay, Ian C Dewhurst, Michelle M Epstein, Philippe Guerche, Jan Hejatko, Francisco J Moreno, Ewen Mullins, Fabien Nogué, Nils Rostoks, Jose J Sánchez Serrano, Giovanni Savoini, Eve Veromann, Fabio Veronesi, Michael B Bonsall, John Mumford, Ernst A Wimmer, Yann Devos,

2 yrs

€ 400 K

Andrew Roberts (Agriculture & Food Systems Institute, US)

Michael Bonsall (University of Oxford, UK)

Boet Glandorf (NL)

David O'Brochta (Foundation for the National Institutes of Health, US)

Geoff Ridley (Landcare Research New Zealand Limited, NZ)

Jörg Romeis (Agroscope, CH)

Patrick Rudelsheim (Perseus, BE)

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- **Ad hoc WG experts**
- **GMO Team EFSA (18):** ARDIZZONE Michele, BONATTI Martina, DE SANCTIS Giacomo, FERNANDEZ DUMONT, FERRARI Arianna, GENNARO Andrea, GOUMPERIS Tilemachos, JACCHIA Sara, KAGKLI Dafni Maria, LENZI Paolo, LEWANDOWSKA Aleksandra, MARTIN CAMARGO Ana, MEZZADRI Martina, NERI Franco Maria, OLSHEVSKA-GRIGOROV Yustina, PAPADOPOULOU Nikoletta (TL), RAFFAELLO Tommaso
- **Contractors (protein safety)**
- **ISA experts, MS Competent Authorities**
- **HoU – Ana Afonso**

CONTACT US

- For submitting a dossier for market approval or **catalogue of services to applicants, SME support, General pre-submission advice**: https://www.efsa.europa.eu/en/applications/gmo

- For any questions about EFSA: https://connect.efsa.europa.eu/RM/s/help

THANKS!

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