Regulation (EU) 503/2013

Assessment of 90-day studies on the whole genetically modified food/feed

24-25 October 2018

efsa
European Food Safety Authority

Outline

- Legal requirements & technicalities
- Risk assessment by EFSA
- Procedural considerations

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Legal requirements

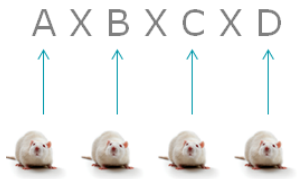
According to Reg. (EU) No. 503/2013

- Single events

The applicant shall include a 90-day feeding study with whole food and feed in rodents for the assessment of food and feed containing, consisting of or produced from genetically modified plants with a single transformation event

- Stacked transformation events

In the case of stacked transformation events obtained by conventional crossing of genetically modified plants containing one or several transformation event(s), a 90-day feeding study with whole food and feed in rodents shall be included for each of the genetically modified plant with a single transformation event which was used.



An additional 90-day feeding study with whole food and feed in rodents with the genetically modified plant with the stacked transformation events shall be included where indications of potential adverse effects are identified during the assessment of: (i) the stability of the inserts; (ii) the expression of the inserts; and (iii) the potential synergistic or antagonistic effects resulting from the combination of the transformation events.

Technicalities

According to Reg. (EU) No. 503/2013

- GLP
- OECD TG 408
- Tailored requirements (e.g. IHT)
- EFSA SC 2011→ hypothesis-driven 90-day studies (e.g. power analysis)

According to EFSA Explanatory statement (2014)

- Two scenarios:
  - Hypothesis-driven
  - Non hypothesis-driven
- Details on study design, conduct and analysis

EFSA (European Food Safety Authority), 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. EFSA Journal 2014;12(10):3871, 25 pp., doi:10.2903/j.efsa.2014.3871

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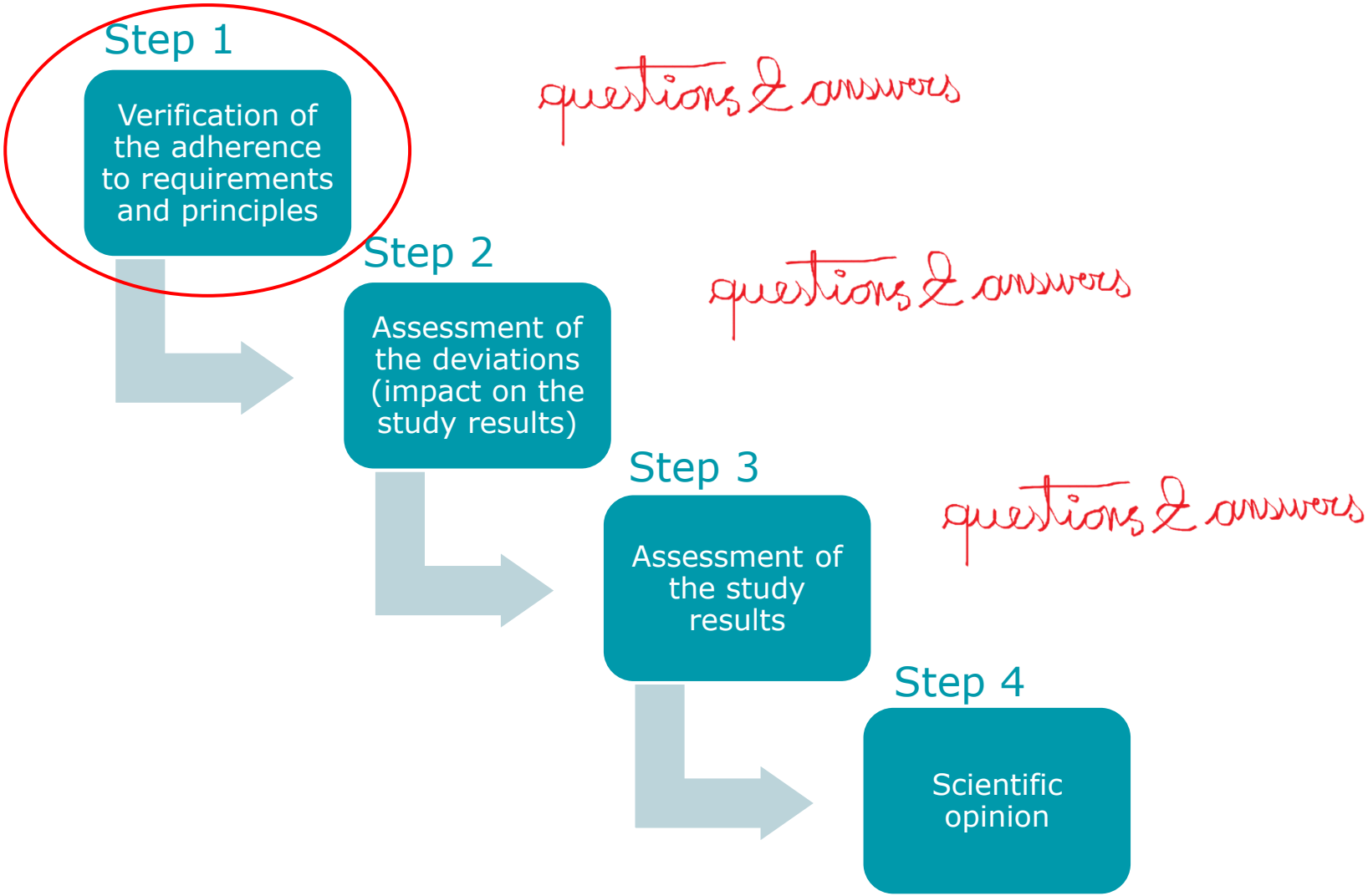
Risk assessment by EFSA– the flow



Risk assessment by EFSA

- Detailed scrutiny to check for the adherence to the requested frame

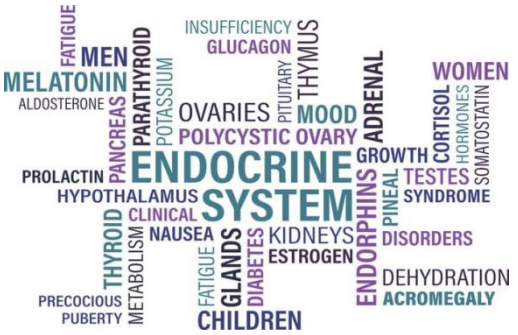
  - ✓ Reg.(EU) 503/2013
  - ✓ OECD TG408
  - ✓ GLP
  - ✓ EFSA SC 2011
  - ✓ EFSA 2014

- Framework contract in place

Example of EFSA checklist

1	**Guidelines - OECD TG 408**
2	**GLP statement**
3	**Test item**
	Identity
	Treatment with the intended herbicide (if applicable)
	Type
	Production, processing, storage conditions
	Compositional analyses, biological and chemical contaminants
	Stability
4	**Control material (reference material)**
	Pedigree
	Type
	Production, processing, storage conditions
	Compositional analyses, biological and chemical contaminants
5	**Test/control/reference diets**
	Preparation
	Compositional analyses, biological and chemical contaminants (incl. GM)
	Concentration of the test item
	Homogeneity
	Stability of the test substance in the formulation
6	**Test system**
7	**Dose groups and dose levels selection**

New! June 2018 **ED**



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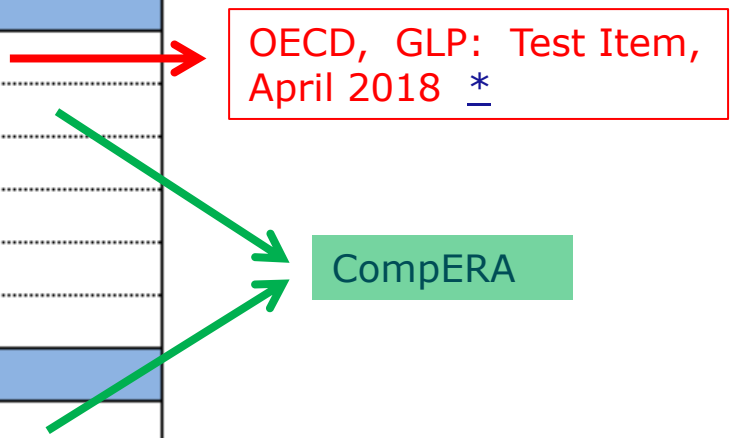

Example of EFSA checklist

8	**Measurements and observations**
	In-life observations, body weight, feed consumption and water consumption
	General clinical observations, detailed clinical observations
	Inspection for signs of morbidity and mortality
	Ophthalmological examination (optional)
	Functional observations and locomotor activity
	Body weight at least once a week
	Food consumption at least weekly
	Clinical pathology
	Haematology
	Coagulation
	Clinical chemistry
	Urinalysis
	Terminal procedures and pathology
	Gross necropsy
	Organ weight
	Histopathology
11	**Experimental settings**
	Experimental unit
	Allocation of animals to cages and cages to treatments
	Blinding and concealment
	Sample size
12	**Raw data**

Frequent questions

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Test, control material& diets

- Identity
- Pedigree (similarity CC vs GM)
- Treatment with the intended herbicide (HT)
- Source and chain of custody
- Stability
- Homogeneity and concentration

Dose levels

Frequent questions

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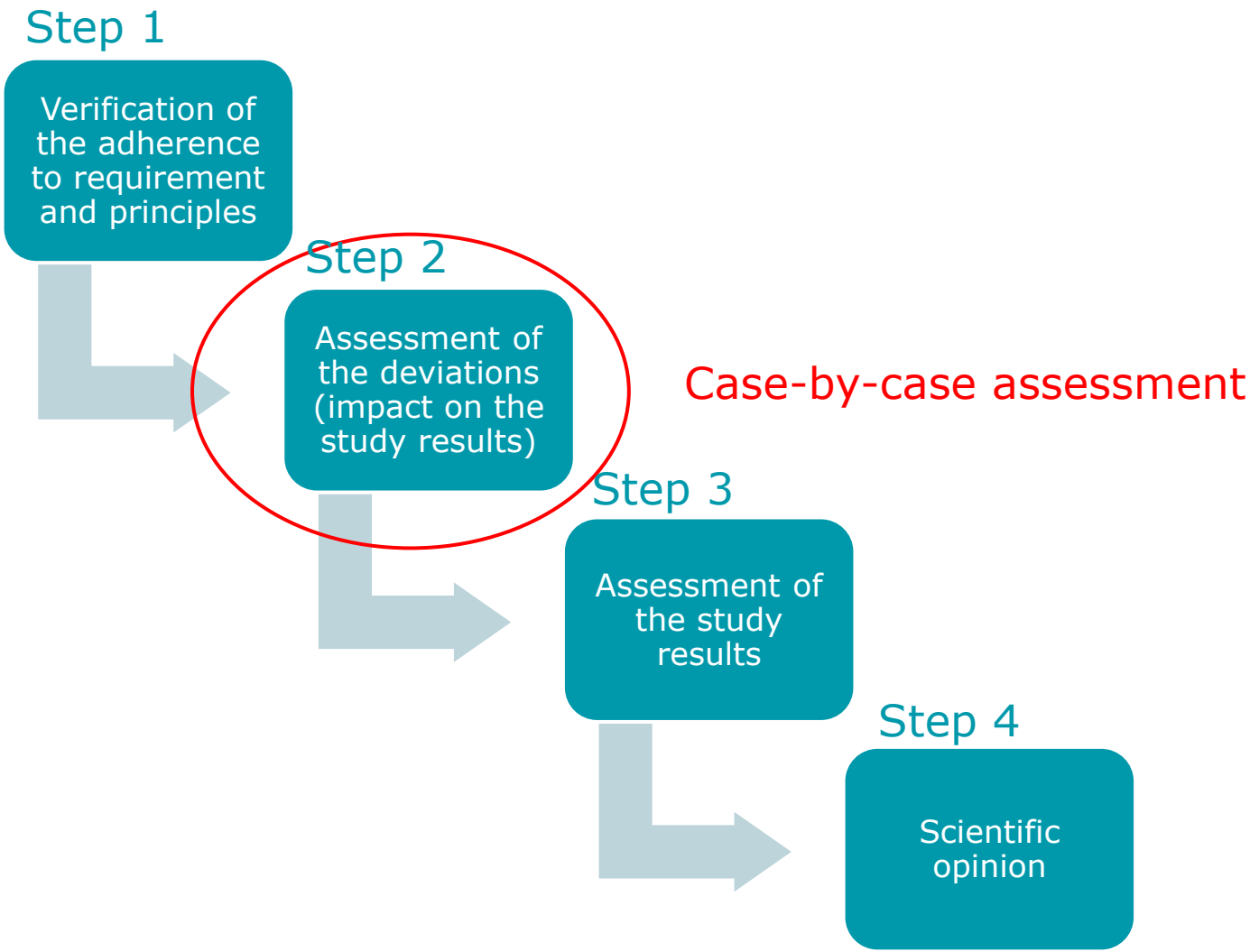
Missing histopathology

Experimental design, Stats

- Randomisation procedure
- Cage disposition
- Missing data
- Cage effects (social housing)
- Flowchart (statistical analyses and the outputs obtained)
- Outlier checks, data transformation and choice of model.
- Goodness-of-fit
- Full output of the models

Risk assessment by EFSA– the flow



90-day studies on single events in stacks

Case A: new studies

Case B: studies previously submitted in the context of singles

- studies spontaneously submitted
- none impacted the RA conclusion of the single event
- many completed before EFSA SC, 2011
- some flagged in the scientific opinions of singles as containing some weaknesses with regard to OECD TG 408 and/or EFSA guidance documents.

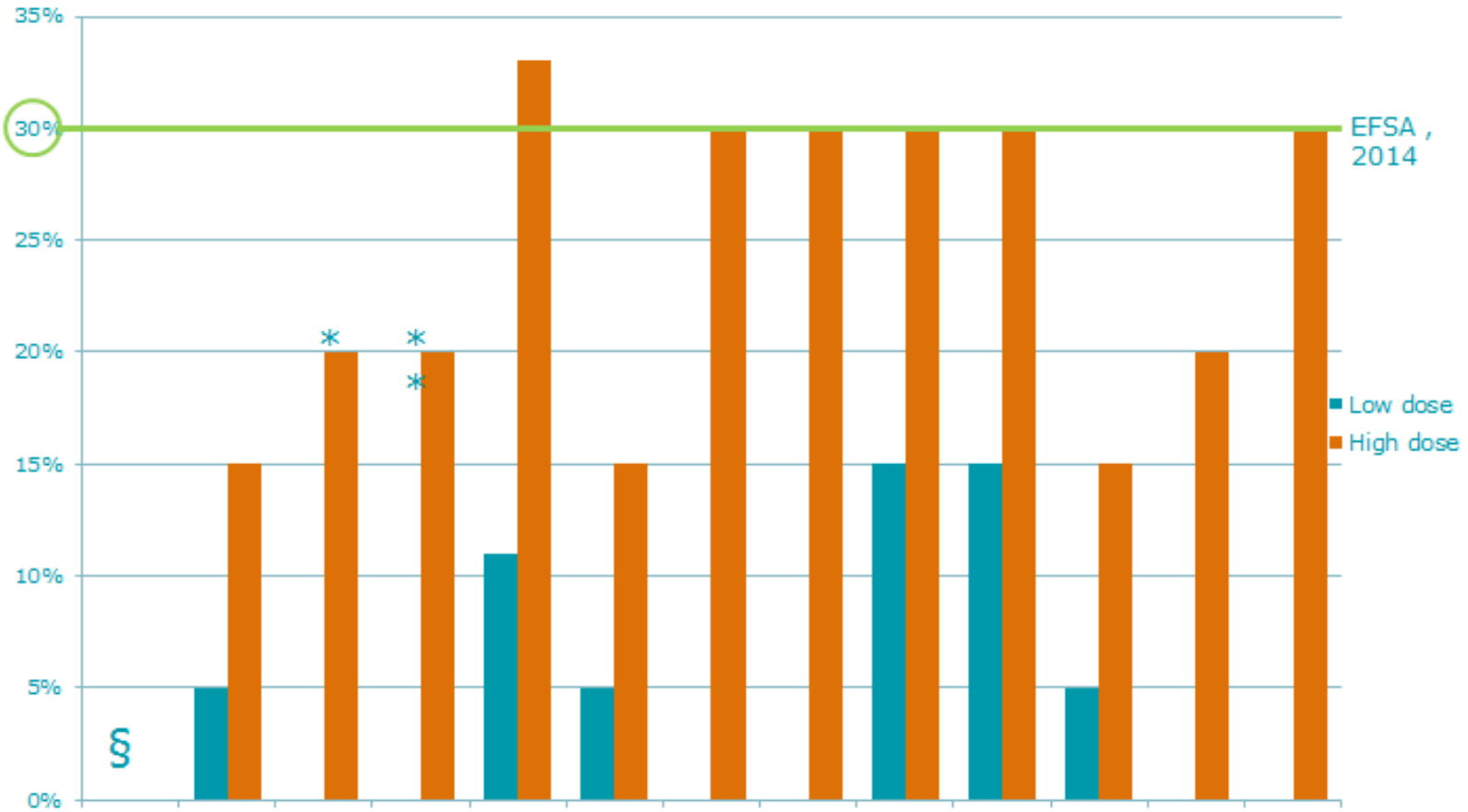
In the context of stacks EFSA checks for ADHERENCE to relevant documents/guidance

Critical weaknesses

- Study design
  - Low number of experimental units
  - GM plant material not treated with the intended herbicide(s)
  - Low dose tested
- Data analysis
  - Missing histopathology

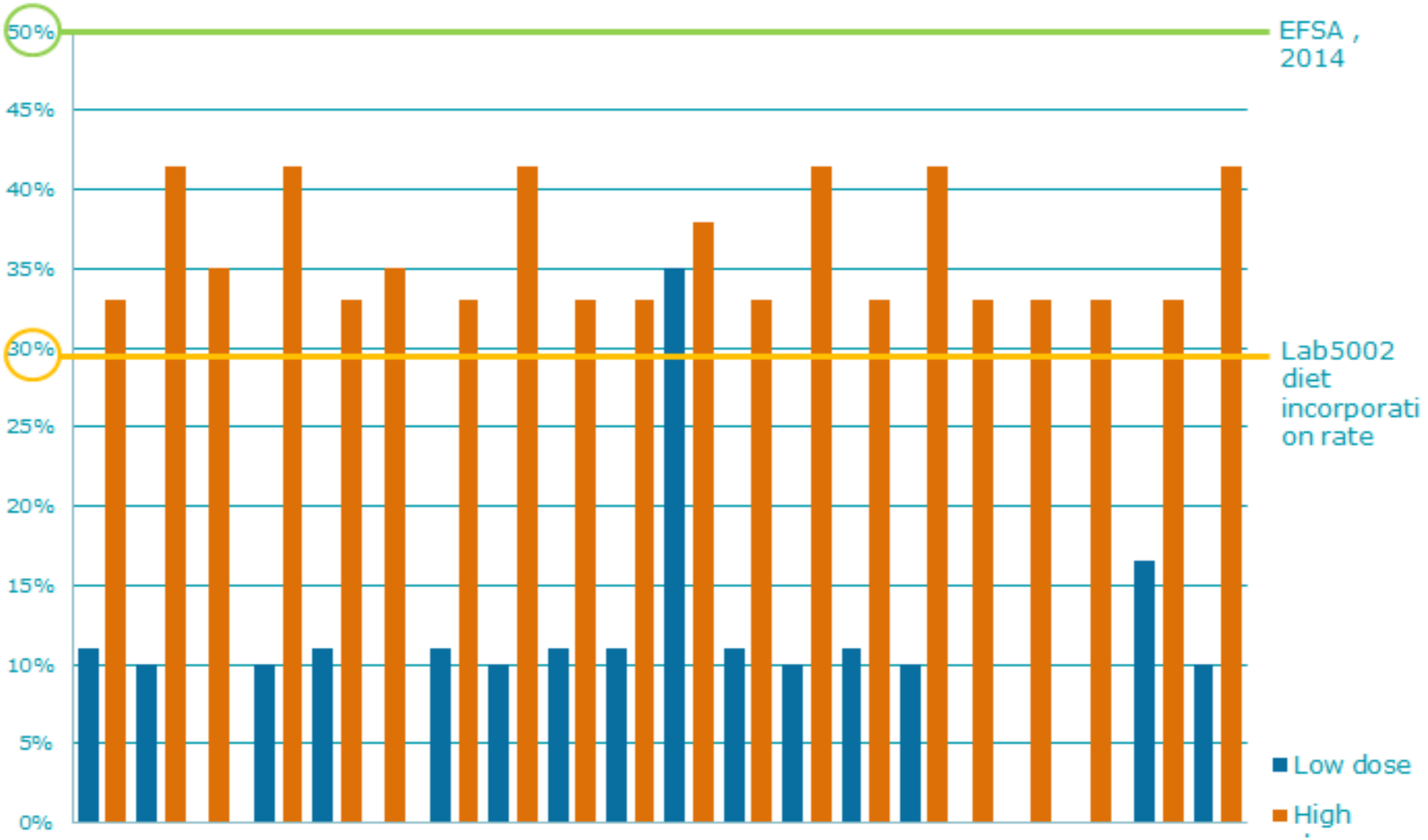
Dose groups and levels (incorporation rate)

soybean



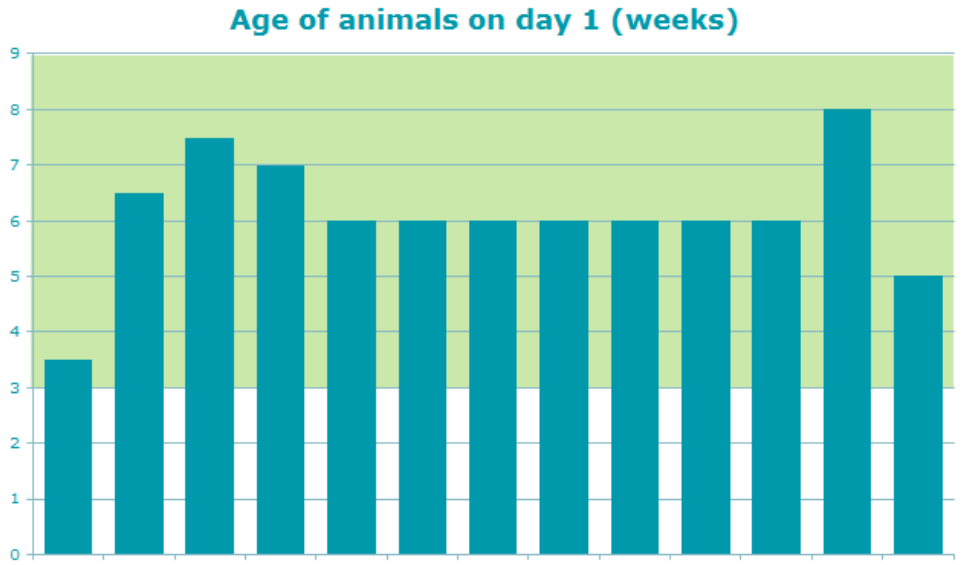
Dose groups and levels (incorporation rate)

maize

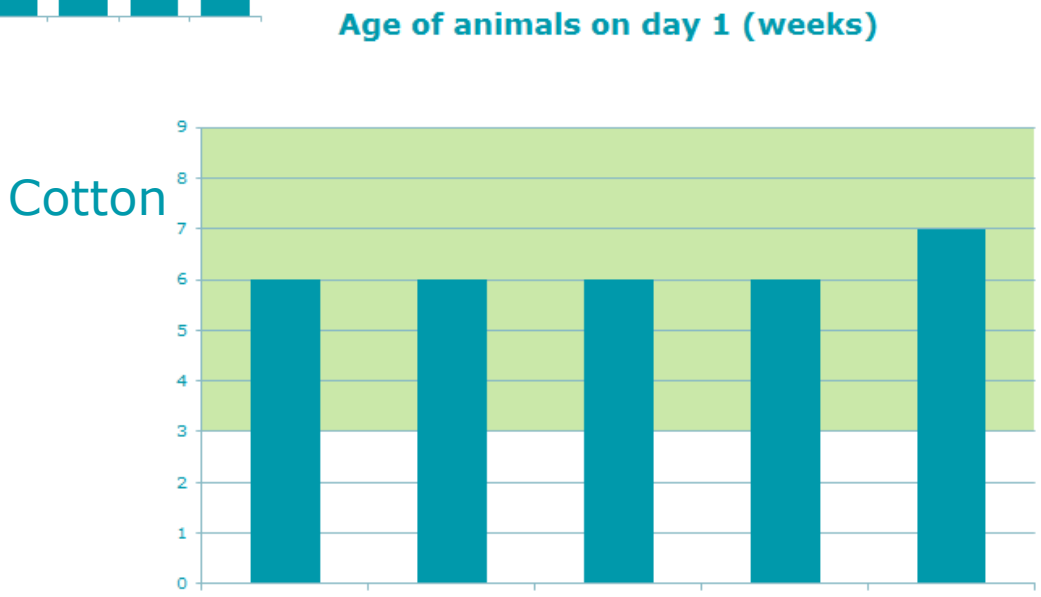


Number of experimental units

Test system - Age of the animals



Soybean



Cotton

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Procedural considerations

Pertaining to stacks applications

- Stand-alone dossiers
  - Redundant questions under different applications
  - Stepwise submission of studies accepted
  - Additional info is 'processed' as soon as received, irrespective of the dossier
- Submission of additional info
  - Thanks to inform us of delayed and anticipated submission
  - By the requestor only
- If new study is required, clear identification (study report number) and where to find it

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