Safety for the Target Species: WHAT'S NEW?

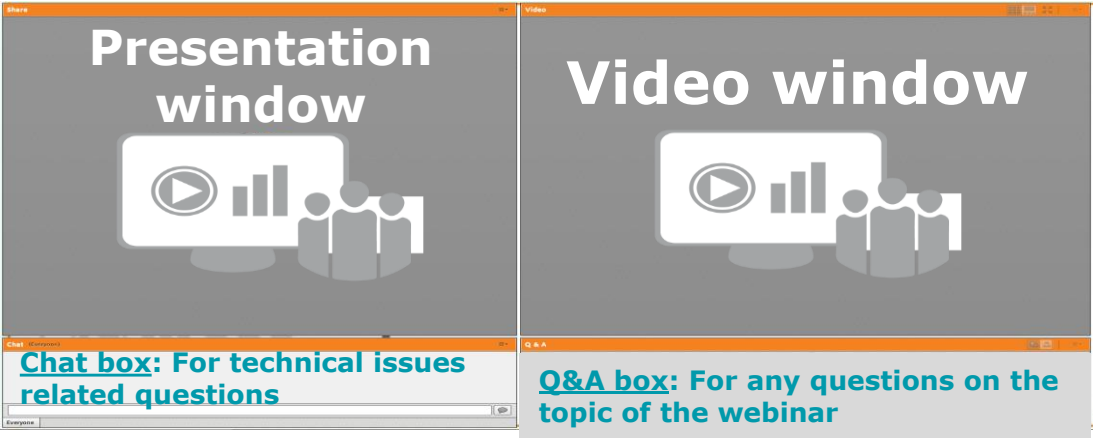
15 June 2018

FEED Unit

efsa
European Food Safety Authority

INTRODUCTION - GUIDE TO ATTENDEES

- The webinar **is being recorded!**
- The webinar **is in English** and questions should be submitted in English.
- You will be automatically connected to the audio broadcast. **One-way audio** (listen only mode)



Sending questions - Q&A box

- Questions should be **concise** and submitted **once**. Follow-up questions should be **self-explanatory**
- You can ask questions **until 11:00**
- You will see the **answer** right below the question row once replied by EFSA
- We will address all questions as soon as possible and until **11:15**
- If you do not receive an answer to your question, feel free to re-submit it through the **EFSA APDESK** web form later on:

http://www.efsa.europa.eu/en/applicationshelpdesk/askaquestion

Outline

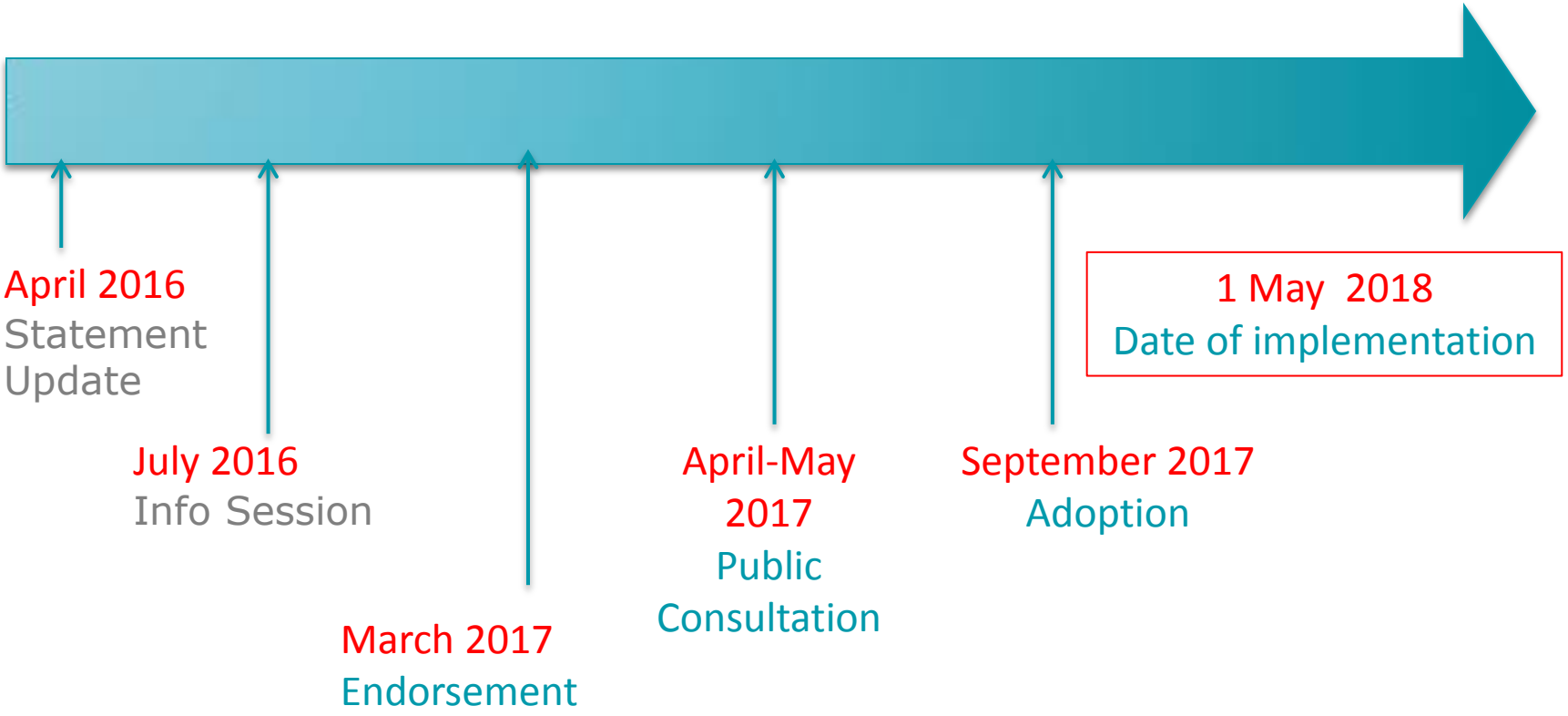
- Introduction
- Requirements of the guidance
  - Literature search
  - Toxicological studies
  - Tolerance trial
- Questions and answers
- Take home messages

Scope and programme of the webinar

Bring you through the **main features** of the new guidance focusing on the **novelties** through a few **examples**

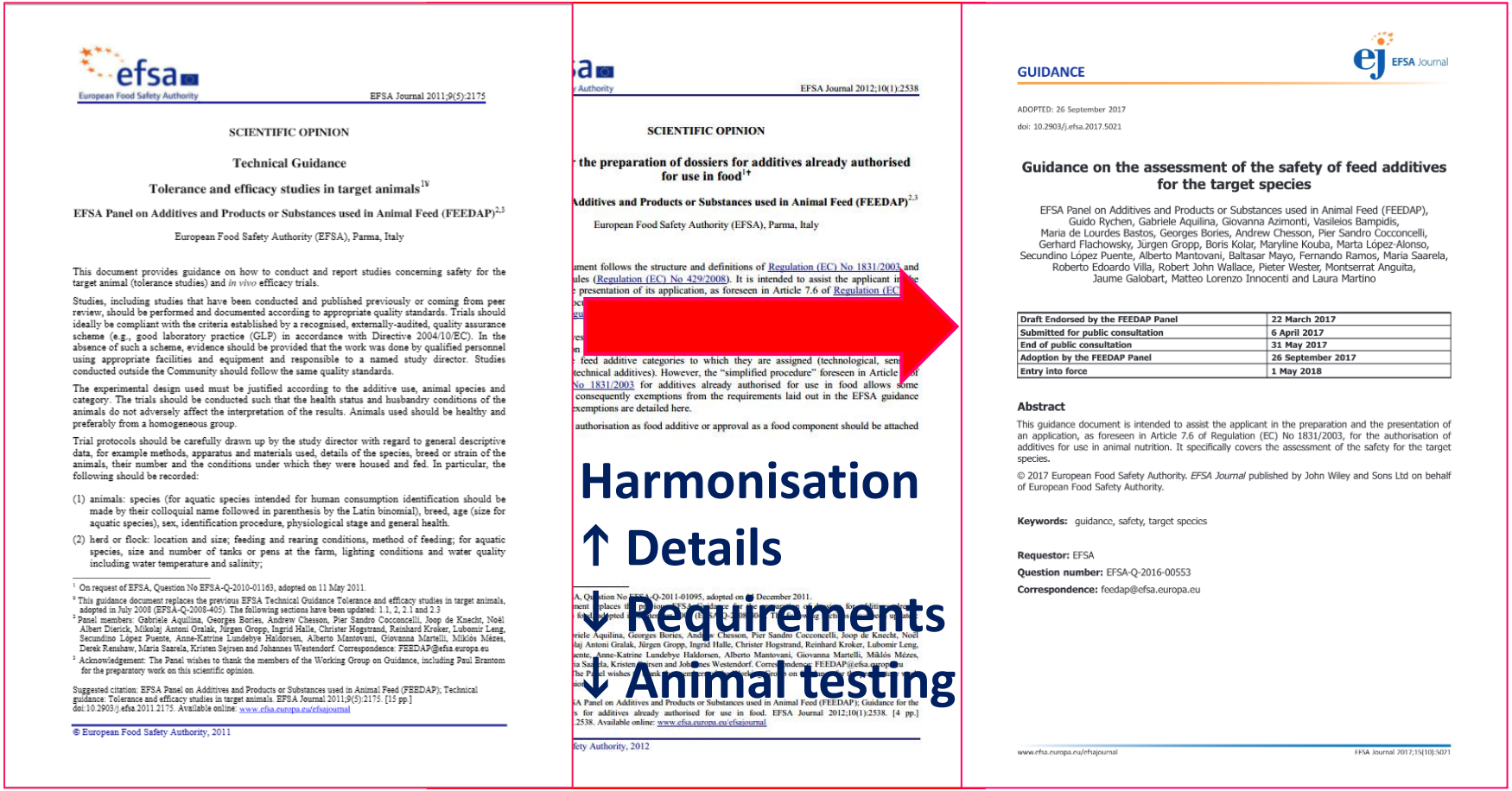
We will try to reply to some questions orally

History


April 2016
Statement
Update
July 2016
Info Session
March 2017
Endorsement
April-May
2017
Public
Consultation
September 2017
Adoption
1 May 2018
Date of implementation

Safety for the Target species

One single guidance



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EFSA Journal 2011;9(5):2175

SCIENTIFIC OPINION

Technical Guidance

Tolerance and efficacy studies in target animals[1,¥]

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

This document provides guidance on how to conduct and report studies concerning safety for the target animal (tolerance studies) and *in vivo* efficacy trials.

Studies, including studies that have been conducted and published previously or coming from peer review, should be performed and documented according to appropriate quality standards. Trials should ideally be compliant with the criteria established by a recognised, externally-audited, quality assurance scheme (e.g., good laboratory practice (GLP) in accordance with Directive 2004/10/EC). In the absence of such a scheme, evidence should be provided that the work was done by qualified personnel using appropriate facilities and equipment and responsible to a named study director. Studies conducted outside the Community should follow the same quality standards.

The experimental design used must be justified according to the additive use, animal species and category. The trials should be conducted such that the health status and husbandry conditions of the animals do not adversely affect the interpretation of the results. Animals used should be healthy and preferably from a homogeneous group.

Trial protocols should be carefully drawn up by the study director with regard to general descriptive data, for example methods, apparatus and materials used, details of the species, breed or strain of the animals, their number and the conditions under which they were housed and fed. In particular, the following should be recorded:

(1) animals: species (for aquatic species intended for human consumption identification should be made by their colloquial name followed in parenthesis by the Latin binomial), breed, age (size for aquatic species), sex, identification procedure, physiological stage and general health.

(2) herd or flock: location and size; feeding and rearing conditions, method of feeding; for aquatic species, size and number of tanks or pens at the farm, lighting conditions and water quality including water temperature and salinity;

[1] On request of EFSA, Question No EFSA-Q-2010-01163, adopted on 11 May 2011.

[¥] This guidance document replaces the previous EFSA Technical Guidance Tolerance and efficacy studies in target animals, adopted in July 2008 (EFSA-Q-2008-405). The following sections have been updated: 1.1, 2, 2.1 and 2.3

[2] Panel members: Gabriele Aquilina, Georges Bories, Andrew Chesson, Pier Sandro Cocconcelli, Joop de Knecht, Noël Albert Dierick, Mikolaj Antoni Gralak, Jürgen Gropp, Ingrid Halle, Christer Hogstrand, Reinhard Kroker, Lubomir Leng, Secundino López Puente, Anne-Katrine Lundebye Haldorsen, Alberto Mantovani, Giovanna Martelli, Miklós Mézes, Derek Renshaw, Maria Saarela, Kristen Sejrsen and Johannes Westendorf. Correspondence: FEEDAP@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Guidance, including Paul Brantom for the preparatory work on this scientific opinion.

Suggested citation: EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP); Technical guidance: Tolerance and efficacy studies in target animals. EFSA Journal 2011;9(5):2175. [15 pp.] doi:10.2903/j.efsa.2011.2175. Available online: www.efsa.europa.eu/efsajournal

EFSA Journal 2012;10(1):2538

SCIENTIFIC OPINION

…the preparation of dossiers for additives already authorised for use in food[1,†]

…Additives and Products or Substances used in Animal Feed (FEEDAP)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

…ument follows the structure and definitions of Regulation (EC) No 1831/2003 and …ules (Regulation (EC) No 429/2008). It is intended to assist the applicant in … presentation of its application, as foreseen in Article 7.6 of Regulation (EC …

… feed additive categories to which they are assigned (technological, sen… technical additives). However, the "simplified procedure" foreseen in Article … No 1831/2003 for additives already authorised for use in food allows some … consequently exemptions from the requirements laid out in the EFSA guidance … exemptions are detailed here.

… authorisation as food additive or approval as a food component should be attached …

Harmonisation

↑ Details

↓ Requirements

↓ Animal testing

…A, Question No EFSA-Q-2011-01095, adopted on … December 2011.

…riele Aquilina, Georges Bories, Andrew Chesson, Pier Sandro Cocconcelli, Joop de Knecht, Noël …laj Antoni Gralak, Jürgen Gropp, Ingrid Halle, Christer Hogstrand, Reinhard Kroker, Lubomir Leng, …ente, Anne-Katrine Lundebye Haldorsen, Alberto Mantovani, Giovanna Martelli, Miklós Mézes, …a Saarela, Kristen Sejrsen and Johannes Westendorf. Correspondence: FEEDAP@efsa.europa.eu …The Panel wishes to thank the members of the Working Group on Guidance, including Paul Brantom for the preparatory work on this scientific opinion.

…SA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP); Guidance for the …s for additives already authorised for use in food. EFSA Journal 2012;10(1):2538. [4 pp.] …:2538. Available online: www.efsa.europa.eu/efsajournal

…fety Authority, 2012

GUIDANCE

EFSA Journal

ADOPTED: 26 September 2017

doi: 10.2903/j.efsa.2017.5021

Guidance on the assessment of the safety of feed additives for the target species

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Guido Rychen, Gabriele Aquilina, Giovanna Azimonti, Vasileios Bampidis, Maria de Lourdes Bastos, Georges Bories, Andrew Chesson, Pier Sandro Cocconcelli, Gerhard Flachowsky, Jürgen Gropp, Boris Kolar, Maryline Kouba, Marta López-Alonso, Secundino López Puente, Alberto Mantovani, Baltasar Mayo, Fernando Ramos, Maria Saarela, Roberto Edoardo Villa, Robert John Wallace, Pieter Wester, Montserrat Anguita, Jaume Galobart, Matteo Lorenzo Innocenti and Laura Martino

Draft Endorsed by the FEEDAP Panel	22 March 2017
Submitted for public consultation	6 April 2017
End of public consultation	31 May 2017
Adoption by the FEEDAP Panel	26 September 2017
Entry into force	1 May 2018

Abstract

This guidance document is intended to assist the applicant in the preparation and the presentation of an application, as foreseen in Article 7.6 of Regulation (EC) No 1831/2003, for the authorisation of additives for use in animal nutrition. It specifically covers the assessment of the safety for the target species.

Keywords: guidance, safety, target species

Requestor: EFSA

Question number: EFSA-Q-2016-00553

Correspondence: feedap@efsa.europa.eu

Presumed safe – no need of studies

- No exposure
- Silage additives normal constituents of silage and no increase exposure
- QPS microorganisms
- Nutritional additives already authorised
- Other nutritional additives
  - Highly purified
  - QPS-GMM

Safety demonstration needed

2008

- Tolerance studies
  - *Toxicological studies*
  - *Literature*

2017

- Extensive literature search
- Toxicological studies in lab animals
- Tolerance studies

Extensive literature searches

Extensive literature search

- Identity of the active substance(s)/ agent(s)
- Levels in feed/target species
- Duration, replicates
- Parameters measured
- All toxicological end-points
- Conclusion on the absence of adverse effects

Extensive literature search

Databases

- Medline
- CAB Abstracts
- Scopus
- Science direct

Search strategy

(Chicken* or turkey* or poult* or broiler* or fowl*) **AND**

(*Bacillus subtilis* (XXXX) or TRADE NAME)

Dates

199X-201X

Inclusion/exclusion criteria

Include non-English papers

Toxicity data from repeated dose studies

Toxicity data from repeated dose studies

NOAEL/$BMDL_{10}$

Safe Concentration Feed (SCF)

SCF=((NOAEL/100)/FI) x 1000 x 0.88

Toxicity data from repeated dose studies

SCF=((NOAEL/100)/FI) x 1000 x 0.88

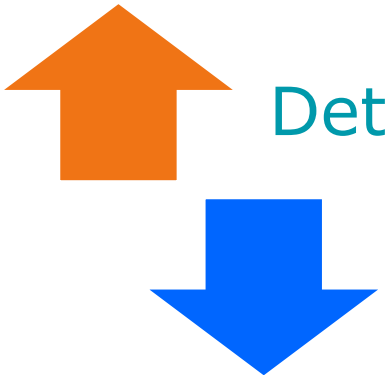
Animal category	Default values daily feed intake (g DM/kg body weight)	Values derived from	
		Body weight (kg)	Feed intake (kg DM/day)
Chicken for fattening	79	2	0.158
Laying hen	53	2	0.106
Turkey for fattening	59	3	0.176
Piglet	44	20	0.88
Pig for fattening	37	60	2.20
Sow lactating	30	175	5.28
Veal calf (milk replacer)	19	100	1.89
Cattle for fattening	20	400	8.0
Dairy cow	31	650	20.0
Sheep/goat	20	60	1.2
Horse	20	400	8.0
Rabbit	50	2	0.1
Salmon	18	0.12	0.0021
Dog	17	15	0.250
Cat	20	3	0.060
Ornamental fish	5	0.012	0.000054

Tolerance studies in target animals

Tolerance studies

AIM

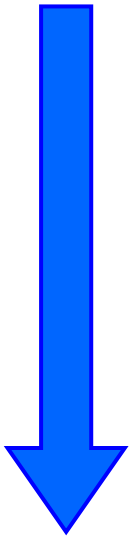
Limited evaluation of **short-term toxicity and margin of safety** of the additive to the target animals.



Details design and reporting

Animal testing

Design



Performance

Haematology
Blood chemistry

Gross pathology
Histopathology

Most sensitive animals

⇧ performance : + sensitive end-points


Male birds


First third of the laying period


Weaned piglets of both sexes


High-yielding in first 1/3 lactation


Male bovines at the beginning of the fattening


Juvenile phase

End-points

Performance

Feed intake, initial and final body weight, body weight gain, feed to gain ratio, *water intake*. Clinical observations including general health status, behaviour, morbidity and mortality (including culling).

laying rate, egg weight, shell quality, feed to egg mass ratio, egg mass/hen per day

milk production (also fat corrected milk), milk composition (total solids, protein, fat, lactose and urea), somatic cell counts, protein, fat and lactose yield

number of piglets born, piglets born alive, litter weight at birth and at weaning, number of piglets weaned, weaning to oestrus interval

End-points

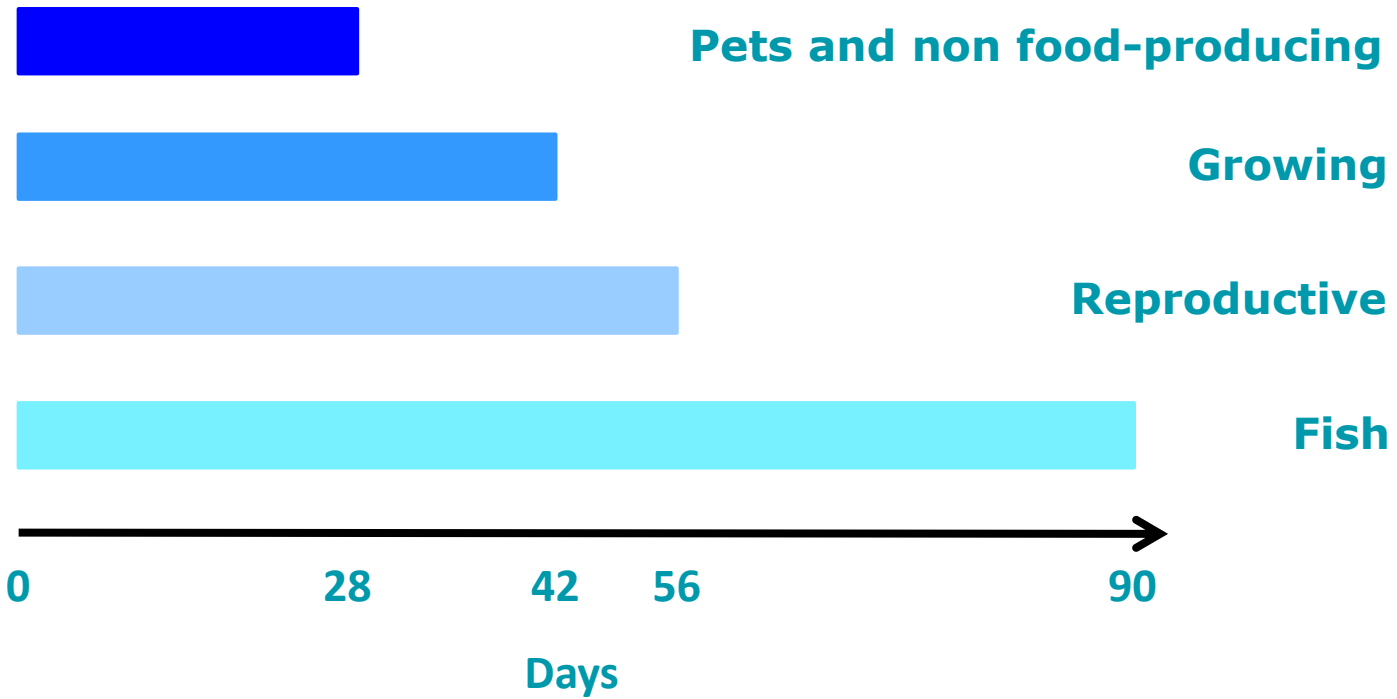
Haematology

Total count for red blood cells, packed cell volume, haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, total and differential counts for leukocytes, platelet counts, prothrombin time and fibrinogen

Clinical chemistry

Sodium, potassium, chloride, calcium, phosphate, magnesium, total protein, albumin, globulin, glucose, urea/uric acid (non-protein nitrogen for fish), cholesterol, creatinine, bilirubin, acute phase proteins, amylase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, gamma-glutamyltransferase, alkaline phosphatase and creatine kinase.

Duration


Pets and non food-producing
Growing
Reproductive
Fish
0
28
42
56
90
Days

Requirement for tolerance studies

One animal category → One study

Table 3: Extrapolation of tolerance data from certain species to other physiologically related species

From	To physiologically related species
Chickens for fattening	Other poultry for fattening (e.g. turkeys, ducks, goose, pheasants, quail, guinea fowl, ostrich) and ornamental birds
Laying hens	Other birds kept for egg production* (e.g. ducks, goose, pheasants, quail, guinea fowl, ostrich)
Pigs	Other Suidae
Calves or cattle	Other growing ruminants (e.g. sheep, goat, buffalo) at the corresponding developmental stage
Dairy cows	Other dairy ruminants (e.g. goat, sheep, buffalo)
Salmon or trout	Ornamental fish

*: Extrapolation to breeders (including turkeys) is only possible if additional data on breeding endpoints are available.

Reducing animal testing

One animal category → One study

Physiologically related species → Two studies

All Poultry

All Pigs

All ruminants

All fish

Reducing animal testing

One animal category	One study
Physiologically related species	Two studies
Multiple animal species	Three/four studies

Reducing animal testing

All Pigs and Poultry





All animal species




Statistical considerations

Experimental Unit

Randomisation /Blinding

Sample size determination

- Key end-points
- Magnitude of the effect and variability
- Statistical power
- Confidence level

Reporting

- Objectives, materials and methods, results, conclusions
- Trial protocol data sheet
- Individual data
- Certificates of analysis, veterinary reports,…
- Codes, log and statistical outputs

Questions Discussion & Concluding remarks

Take home messages

- Detailed information, more clarity, harmonisation and simplification
- Reduction of animal testing

Food ingredients
GMO
Nutrition
Pesticides
About Applications helpdesk

Scientific guidance(-)

- Guidance on the identity, characterisation and conditions of use of feed additives (implementation date 1 May 2018)
- Guidance on the characterisation of microorganisms used as feed additives or as production organisms (implementation date 1 September 2018)
- Guidance on the assessment of the safety of feed additives for the target species (implementation date 1 May 2018)
  - Trial Protocol Data Sheet – Terrestrial Animals
  - Trial Protocol Data Sheet – Aquatic Animals
- Guidance on the assessment of the safety of feed additives for the consumer (implementation date 1 May 2018)
  - Feed Additive Consumer Exposure (FACE) calculator
- Guidance on the assessment of the efficacy of feed additives (implementation date 1 September 2018)
  - Trial Protocol Data Sheet – Terrestrial Animals
  - Trial Protocol Data Sheet – Aquatic Animals
- Guidance on user safety
- Guidance on environmental risk assessment (under revision)

- Guidance on the renewal of authorisation of feed additives
- Guidance for the preparation of dossiers for the re-evaluation of certain additives already authorised under Directive 70/524/EEC

Reference Laboratory

Application toolbox

Track your application
Event calendar
Ask a question

Thank you for attending our webinar!

In case we did not manage to answer your question, feel free to re-submit it through the **EFSA APDESK** web form:

http://www.efsa.europa.eu/en/applicationshelpdesk/askaquestion

Please take 5 more minutes to fill out the evaluation form that you will shortly receive in your inbox.
Your feedback will help us improve our service.

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