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SPECIAL ISSUE

Ten years of EFSA's FEEDAP Panel and its main achievements

Andrew Chesson, Jürgen Gropp, Alberto Mantovani, Claudia Roncancio[1]

European Food Safety Authority (EFSA), Parma, Italy

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ABSTRACT

The inauguration of the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) early in 2003 coincided with the introduction of new and extensively revised legislation in the form of Regulation (EC) No 1831/2003 controlling the use of feed additives in the European Union (EU). Inevitably this legislation has had a defining effect on the range and extent of the work undertaken by the Panel. For the first time this Regulation included groups of feed additives not previously assessed, such as those designed to improve ensiling or to reduce the uptake of mycotoxins. Many hundreds of flavouring substances never assessed before are also foreseen for "re-evaluation". The scope of the work undertaken by the FEEDAP Panel is extremely broad and derives both from the range of materials used as additives and the scope of the assessment required by the legislation. Thus additives may range from mineral clays to micro-organisms and from colourants to coccidiostats. For each, the legislation requires an assessment of safety for the target animal, for consumers of products derived from treated animals, for the environment and for those handling the additive during feed processing or on-farm and is also required the assessment of efficacy . During these nine years, the Panel has made considerable efforts to provide applicants with guidance documents to help them in the preparation of the dossier and with the aim of increasing transparency to set the basis for the assessment to be made by the Panel.

KEY WORDS

Feed additives, efficacy, safety, guidance

[1] Correspondence: feedap@efsa.europa.eu

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INTRODUCTION

The inauguration of the FEEDAP Panel early in 2003 coincided with the introduction of new and extensively revised legislation in the form of Regulation (EC) No 1831/2003[2] controlling the use of feed additives in the European Union. Inevitably this legislation has had a defining effect on the range and extent of the work undertaken by the Panel. For the first time this Regulation included groups of feed additives not previously assessed, such as those designed to improve ensiling or to reduce the uptake of mycotoxins. It also required that the many hundreds of "flavours" previously authorised as a single entity should be individually assessed and separately authorised and listed in a new EU Register of Feed Additives.[3] Finally, in recognition that many of the generic authorisations under the old legislation derived from Member State lists of permitted feed additives and that documented evidence relating to their safety did not exist or was limited in scope, Regulation (EC) No 1831/2003 also foresaw a "re-evaluation" of many existing additives. To enable this to be done with minimum disruption to trade, a period of seven years was allowed from the introduction of the legislation to allow producers/distributors time in which to prepare for the re-evaluation process. The time allotted for notification and application ended in November 2010 and at that time applications covering more than 1 000 individual feed additives had been received by the European Commission.

The scope of the work undertaken by the FEEDAP Panel in response to Regulation (EC) No 1831/2003 is extremely broad and derives both from the range of materials used as additives and the scope of the assessment required by the legislation. Thus additives may range from mineral clays to micro-organisms and from colourants to coccidiostats. For each, the legislation requires an assessment of safety for the target animal, for consumers of products derived from treated animals, for the environment and for those handling the additive during feed processing or on-farm. In addition, to the provisions of the General Food Law[4], an assessment of efficacy is also required. Only when an additive is intended for use solely with pet animals, a more restricted assessment is made. As a consequence the data requirements to fulfil the various elements of an assessment can be demanding and may vary considerably depending on the nature of the additive and its purpose. The Panel has made considerable efforts to provide applicants with guidance to ensure that the appropriate data are made available. To this end the Panel made a substantial contribution to the Implementing Rules documented in Regulation (EC) No 429/2008[5] and augmented this with 19 separate detailed EFSA guidance documents[6]. Some cover the broad categories of additives recognised in Regulation (EC) No 1831/2003, while others deal with more specific topics such as the design of animal experiments or assessing consumer and user safety. The members of the Panel have regularly contributed to meetings with stakeholders organised by EFSA and by other bodies, to help ensure that the assessment of feed additive can be completed in an efficient and timely manner.

1. DEFINITION OF A FEED ADDITIVE

Feed additives in the EU are defined as substances, micro-organisms or preparations, other than feed material and premixtures, which are intentionally added to feed or water in order to perform, in particular, one or more of the following functions: favourably affect the characteristics of feed (technological) or animal products, favourably affect the colour of ornamental fish and birds (sensory); satisfy the nutritional needs of animals (nutritional); favourably affect the environmental consequences of animal production, favourably affect animal production, performance or welfare (zootechnical); or have a coccidiostatic or histomonostatic effect (coccidiostats).

[2] Regulation (EC) 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29

[3] http://ec.europa.eu/food/food/animalnutrition/feedadditives/comm_register_feed_additives_1831-03.pdf

[4] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety

[5] Regulation (EC) 429/2008 of the European Parliament and of the Council of 25 April 2008 on the preparation and the presentation of applications and the assessment and the authorisations of feed additives.

[6] http://www.efsa.europa.eu/en/feedap/feedapguidance.htm

2. WORKLOAD OF THE FEED UNIT AND FEEDAP PANEL

The risk assessment is carried out by the FEEDAP Panel, which consists of 21 experts in the areas of animal nutrition, physiology, toxicology, microbiology, veterinary medicine, and ecotoxicology. The assessment finishes with the adoption of a scientific opinion which is the basis for the European Commission to grant or deny the authorisation of the product for its use in the EU market. Any person seeking the authorisation of a given additive should submit an application to the European Commission and a technical dossier to EFSA. The dossier should be compiled following Commission Regulation (EC) No 429/2008 and the guidance documents that EFSA has prepared in order to help the applicants.

Since its inauguration, the FEEDAP Panel has adopted over 400 opinions dealing with authorisations of feed additives, 160 of these since 2009 (Figure 1). Approximately 47 % of the opinions were for zootechnical additives, 20 % for technological additives, 16 % for nutritional additives, 9 % for sensory additives and 8 % for coccidiostats.

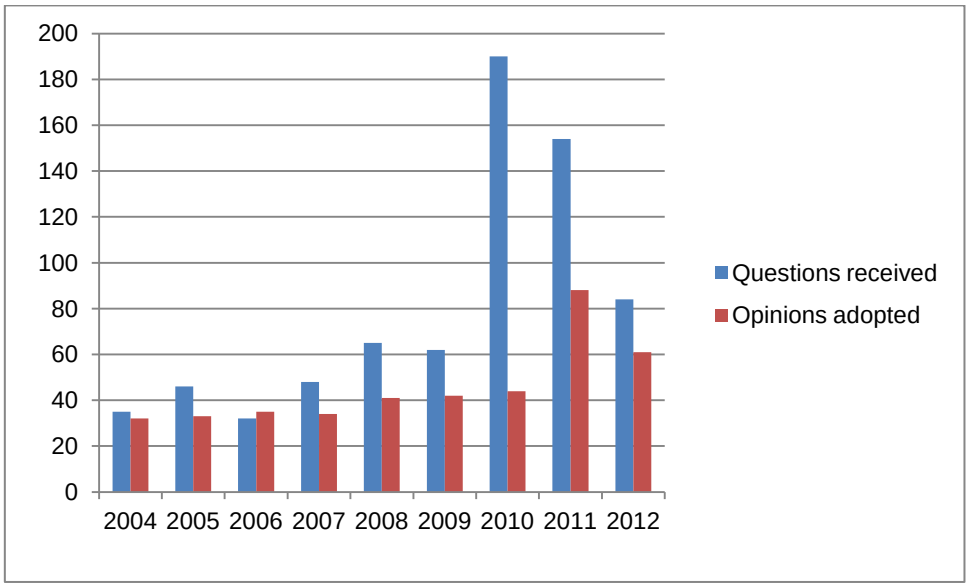

Figure 1: Number of questions received and opinions adopted by the FEEDAP Panel from 2004 to June 2012.

3. AREAS OF WORK OF THE FEEDAP PANEL

3.1. Microbiological safety

Microorganisms feature in many FEEDAP Panel assessments, either as feed additives in their own right (probiotics) or as a source of enzymes, vitamins, amino acids, colourants and other compounds. Those directly fed to animals usually derive from the digestive tract of animals and belong to the group of organisms referred to as commensals, which are assumed to be, at worst, harmless residents of a healthy gut. The FEEDAP Panel was instrumental in the development and subsequent adoption by the Scientific Committee of a reduced assessment process for a selection of such organisms referred to as the Qualified Presumption of Safety (QPS)[7]. This has allowed a rapid assessment of the safety of such organisms for the target animal, consumers of animal products and the environment focusing only on the potentially hazardous aspects of the organisms (the "qualification" in QPS). For bacteria of any origin this includes the presence of determinants of resistance to antibiotics of clinical and

[7] Available from http://www.efsa.europa.eu/en/efsajournal/pub/2497.htm

veterinary importance. The digestive tract of animals is a known reservoir of resistance to antibiotics with a small but real risk of carry-over into foods for human consumption. The Panel took the view that, in the light of the developing problems of antibiotic resistance, it would be irresponsible to deliberately introduce into feed bacteria known to carry resistance determinants. Consequently, its scientific advice to the Commission has been to exclude such organisms from the food chain. However, establishing what constitutes resistance in commensal organisms has proved a challenge. The FEEDAP Panel was among the first to tackle this problem. It published the very first proposal on this subject in the form of one of its guidance documents and has regularly reviewed its position in the light of new scientific developments with the result that this guidance document (EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), 2012a) has achieved international recognition. Although QPS has greatest value when applied to probiotics, it also contributes to the safety assessment of additives derived from microorganisms, removing concerns that the additive may be contaminated by other undesirable products of the fermentation.

Another advantage of the QPS approach to safety assessment is that it allows some groups of organisms known to contain hazardous strains still to be assessed by this method. A prime example is the genus *Bacillus* (and related genera) known to contain strains capable of elaborating a range of toxins harmful to humans. In another specific guidance document, the assessment methods needed to distinguish between toxigenic and non-toxigenic strains of *Bacillus* have been elaborated (EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), 2011a). Increasingly this now relies on a bioinformatic analysis of the entire genome, something which was not practical when the first version of this guidance was developed. However, not all assessments of organisms require a full genomic analysis. In one of its most recent guidance documents (EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), 2012b) the Panel has provided a method of distinguishing those strain of *Enterococcus faecium* which may, under certain clinical settings, carry a risk. This is based on phenotypic evidence of resistance to a single antibiotic and the presence of any one of three genetic markers of virulence.

3.2. Ensuring safety for the target animals

The purpose of the tolerance studies in Directive 87/153/EEC[8] was an approximate identification of the margin of safety of the highest additive concentration proposed in feed and information on the expected risks from accidental overdosing. In contrast, Regulation (EC) No 429/2008 defines the aim of the tolerance test as to provide a limited evaluation of short-term toxicity of the additive to the target animals. Consequently, the establishment of a margin of safety, when the additive is consumed at higher doses than recommended, was turned to a second position.

The new purpose of tolerance studies required a detailed description of the experimental design, including endpoints and duration of studies. A graded system of endpoints was introduced depending on tolerance to overdoses. If a hundredfold overdose is tolerated, only zootechnical parameters are required. If tolerance amounts to the tenfold of the used level, haematological and routine clinical biochemical parameters have to be added. If the margin of safety is less than ten, necropsy and case-by-case histological examinations should be performed. The conclusions are strictly limited to the safety of the highest use level, if a higher concentration was tolerated. If safety for three major species has been demonstrated by tolerance studies showing approximately the same margin of safety, the safety of the use level can be extrapolated to other major and all minor species. No tolerance studies are required for amino acids, for vitamins which do not accumulate and for trace elements with a long history of use, if maximum contents in feed are set by legislation.

However, for the several hundreds of flavouring substances, where no tolerance studies are available and their conduct could hardly be required, a new system for assessing target animal safety had to be established for those flavourings which are assessed as safe for food use. The first tier consists in a comparison of human exposure to the intended animal exposure at the level of the metabolic body

[8] Council Directive 87/153/EEC of 16 February 1987 fixing guidelines for the assessment of additives in animal nutrition. OJ L 64, 7.3.1987, p. 19

weight. In the large majority of cases assessed so far, animal exposure exceeds that of humans by a multiple. Tier 2 is based on No Observed Effect Levels (NOELs) from laboratory animals, a safety factor of 100 is applied to derive safe concentrations for the target animals from 90-day studies. This factor may be reduced in cases where there are chronic studies available and increased for shorter study durations. Tier 2 requires setting default values for body weight and feed consumption of target animals. If no reliable NOEL values can be found, the Threshold of Toxicological Concern (TTC) approach is applied (JECFA, 1996). This system can (theoretically) also be applied in case of other approved food additives.

3.3. Ensuring consumer's safety

The many compounds covered by the remit of the FEEDAP Panel pose different consumer safety issues. In all instances consumer exposure is restricted to specific foods of animal origin, i.e. edible tissues and products derived from target species. Moreover, consumer exposure is mediated by the metabolism of the target species; critical scientific evidence does encompass pharmacokinetics, including the identification of major metabolites, and deposition studies in field conditions, for time length compatible with animal production and at the maximum levels intended for use. However, situations may be very different between the three major groups of xenobiotics, biological feed additives (enzymes, probiotics) and nutritional additives (trace elements, vitamins). For xenobiotics, like coccidiostats, a full toxicological package (including genotoxicity, carcinogenicity if appropriate, and reproductive/developmental toxicity) is normally required; this may lead to the definition of an Acceptable Daily Intake (ADI) and of maximum residue limits. However, to derive an ADI from studies with laboratory animals, it presupposes the similarity of metabolism between target and laboratory animals to ensure that laboratory animals have been exposed to the same metabolites as the consumer will be exposed by consuming food from treated animals. For the many enzymes and probiotics, no consumer exposure to residues is normally expected; although in some cases a limited toxicological package (*in vitro/in vivo* genotoxicity and repeated-dose toxicity in rodents) may be required, to identify any unexpected effects.

Nutrients are tricky issues that elicited substantial elaboration by the FEEDAP Panel. Whereas some nutrients (e.g. the majority of water-soluble vitamins or amino acids) do not raise safety concerns, for several other nutrients, tolerable upper intake levels (ULs) or at least guidance values have been established by human nutritionists (EFSA, 2006), generally based on adverse effects of excess intakes in humans. As for consumer exposure to nutritional additives, the FEEDAP Panel had to consider both deposition elicited by the additive and the background intake from other dietary sources. The FEEDAP Panel has made large use of ULs and deposition estimates, and in some cases this has lead to identify potential concerns.

In such cases, accurate assessment of consumer exposure is important. Regulation (EC) No 429/2008 provides the food basket, equal to that used by the European Medicines Agency (EMA) for veterinary drug and by the Joint Expert Committee on Food Additives (JECFA) of the WHO/FAO, to be applied for feed additives of xenobiotic nature. For other feed additives (e.g. vitamins, trace elements) more realistic data should be applied. The FEEDAP Panel has been among the first panels to make use of the EFSA Comprehensive European Food Consumption Database to derive a new food basket for adults and toddlers based on consumers only (liver consumption data may be questionable if derived from a population where the majority does not consume liver) providing consolidated values for consumption of meat, liver, kidney, fat, milk, eggs and honey at the 95th percentage level. The food basket contains consumption default values for chronic and acute high consumption. Since it is very unlikely that the same individual would be a high consumer of more than two food items at the same time, for the risk assessment it is only considered the two food items that provide the highest intake values are only.

3.4. Ensuring safety for the users

For the classical criteria to assess user (persons handling the additive) safety like irritancy to skin and eyes and skin sensitisation, well-established animal models and increasingly validated *in vitro* models are available. This is not the case for the risk assessment by inhalation. Regulation (EC) No 429/2008 requires an inhalation toxicity study when the amount of particles below 50 µm exceeds 1 %. Irrespective of the fact that inhalation studies are mostly not provided in the application, this requirement is not satisfactory. Toxicity studies may describe the potential hazard, but exposure, the second element needed for risk assessment, is not covered. Also particle size distribution does not allow a quantifiable conclusion on the dusting potential. Furthermore, dusting potential does not indicate the amount of active substance potentially reaching the alveoli. In case of the fraction of particles below 50 µm exceeds 1 %, and in addition to a measurement of the dusting potential in mg/m³, the guidance (EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), 2012c) on how to assess user safety requires the determination of particle size distribution in the dust by laser diffraction and, if formulated additives are tested, an analysis of the active substance in the dust. The concentration of the active substance in the dust is not necessarily the same as in the additive.

The stimulus to develop a scenario under which the exposure of the user in a premix factory could be estimated was found in an application in which quantitative estimations on the inhalation exposure of users to 26-hydroxy-cholecalciferol in a premix factory were made. Certain default values are necessary, as the number of premixtures produced per working day, the time for a contact of the additive with air could create dust and the volume of air inhaled by the user during this time. The scenario was further refined for additives which are applied only for certain animal species or categories, by adjusting the number of premixtures to the percentage of feed produced for that animal species on a European or national basis. The model as described in the guidance document (EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), 2012c) contains also data from the Deutsches Institut für Normung e.V. (DIN EN 481, 1993) on the alveolar availability of dust particle sizes. By these figures the alveolar uptake of a certain substance by inhalation of the user can be precisely estimated and quantified.

For substances with a high toxic potential which undergo a rapid metabolism in the liver after oral intake, additional inhalation toxicity studies still appear indispensable.

3.5. Environmental risk assessment

Consideration of the environmental impact of feed additives is important since administration of feed additives typically occurs over long periods, often involves large groups of animals and the constitutive active substance(s) may be excreted to a considerable extent either as the parent compound or its metabolites. The approach taken by the FEEDAP Panel reflects in particular: (i) the common practice in which manure is stored and spread in Europe and the way feed additives leach to groundwater and drain or runoff from grassland and arable land to surface water; (ii) the different European fish production systems including ponds, tanks and sea cages.

To determine the environmental impact of feed additives, a stepwise approach shall be followed (EFSA, 2008a). All additives have to be assessed through Phase I to determine if a significant environmental effect of the additive is likely and whether a Phase II assessment is necessary. Exemption from Phase II assessment may be made on one of two criteria (negligible impact due to the chemical or biological nature of the additive or the predicted environmental concentration being too low to be of concern), unless there is scientifically-based evidence for concern.

3.6. Assessing efficacy of the feed additives

The FEEDAP Panel has as a simple principal position concerning efficacy studies (EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), 2011b). Additives which exert their effect(s) in the animal should be studied under *in-vivo* conditions independent from the

sometimes erroneous description of a functional group. Consequently, the efficacy of mycotoxin binders can only be assessed by *in vivo* trials. All other additives which have an effect on the feed (or water for drinking) should be studied *in vitro*.

The next principle covers the number of studies. True efficacy can never be derived from some few studies, partially conducted under the well controlled conditions of a research institute. On the basis of these studies, only a rough estimate of the probability of efficacy can be made. If only one or two studies are provided, even this is completely impossible. The FEEDAP Panel therefore requires a minimum of three studies with significant positive effects for an efficacy assessment. It is recognised that it is difficult to mimic field conditions in a controlled experiment and that, depending on the nature of the additive, significant effects may not be consistently revealed. Consequently, the possibility of using meta-analysis could be considered when the number of trials available is greater than three.

Studies should be designed to demonstrate the efficacy of the additive – normally of the lowest recommended dose – by targeting sensitive parameters in comparison to a negative and, optionally, a positive control group. A dose-titration study is recommended to provide the rationale for the selection of the recommended dose or dose range. Where a maximum recommended dose is proposed, relevant data should be provided. For statistics, the experimental unit is the smallest unit to which a given treatment is applied. If animals are penned in groups and all the animals in the pen share the same feed source, then the experimental unit for all zootechnical parameters is the pen, not the individual animal.

To demonstrate *in vivo* efficacy different types of studies can be performed. Generally, unspecific parameters (e.g. growth, feed conversion, milk yield, laying performance, carcass composition, reproduction performance) can only be reliably measured in long-term efficacy studies, whereas effects on more specific parameters (e.g. digestibility, reduced nitrogen or phosphorus excretion, palatability) can be demonstrated in short-term efficacy studies. As the mode of action becomes better known, more studies could be performed as short-term studies.

Also additives for which an *in vitro* testing is considered satisfactory for demonstration of efficacy need certain rules (EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), 2012d) on how the tests should be performed (e.g. silage additives which have never been assessed before as feed additives).

For additives intended for the preparation of silage from all (or unspecified) forages, separate tests should be made with one example of each of the categories: 'easy to ensile forage (>3 % soluble carbohydrates in the fresh material)', 'moderately difficult to ensile forage (1.5-3.0 % soluble carbohydrates in the fresh material)' and 'difficult to ensile forage (<1.5 % soluble carbohydrates in the fresh material)'. Where claims are restricted to sub-categories of forage described in terms of dry matter, the dry matter range should be explicitly stated. Within each test, a minimum of three replicates is required. This requires in turn the use of non-parametric methods for statistical evaluation.

3.7. Assessing feed materials

Feed materials are not usually assessed by the FEEDAP Panel, but they might be if there are specific issues relevant to safety. In 2011, the FEEDAP Panel faced such a challenge, as it was requested to deliver a scientific opinion on the safety of hemp (*Cannabis sativa*) as animal feed. In this case, the safety issue was the presence of tetrahydrocannabinol (THC) in hemp-derived feed materials and the possible carry-over by milk to consumers (EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), 2011c).

3.8. Scientific assistance in international negotiations

The FEEDAP Panel has been involved in providing risk assessment of substances discussed at international fora e.g. discussion at the Codex Alimentarius Commission. In the context of discussions within Codex Alimentarius, EFSA was asked by the European Commission to provide an opinion on

the JECFA evaluation for ractopamine (WHO 2004, 2006). Ractopamine (a β-adrenoreceptor agonist) is authorised in different countries outside the EU as a feed additive for growth promotion of fattening pigs and cattle. In the EU, the use of ß-agonists for that purpose is generally forbidden. The FEEDAP Panel concluded that the human study used by JECFA, to derive the ADI could not be taken as a basis due to a series of inadequacies identified and consequently no proposal for MRLs could be made (EFSA, 2009). The Committee for Veterinary Medicinal Products (CVMP) of EMA fully supported the conclusions of the FEEDAP Panel.

4. PRESENT AND FUTURE CHALLENGES

Nine years after adoption of Regulation (EC) No 1831/2003 and based on the experience of the FEEDAP Panel with applications and discussions with stakeholders it seems appropriate to consider a modification of the feed additive categories. There is an obvious inconsistency between the defined functions of feed additives (see 1.) and the derived categories (technological, sensory, nutritional and zootechnical additives and the coccidiostats) and their functional groups including its definitions. Two examples may be mentioned. In the first, functional groups which exert their mode of action in the animal are listed under the technologicals, which are primarily defined by *in vitro* functions in the feed. The second are microorganisms, a functional group of zootechnicals characterised as affecting favourably the performance of animals in good health, and defined as gut flora stabilisers, however those microbial products affect the gut microbiota of target animals beneficially mostly only when the natural flora is in some way disturbed. As a matter of fact, efficacy of most "gut flora stabilisers" has been demonstrated by better growth or feed efficiency.

The introduction of new categories/functional groups would help to provide a closer link between Article 5 and Article 6 of Regulation (EC) No 1831/2003 as an aid to applicants and subsequent users of the feed additives. Additional categories/functional groups would facilitate the attribution of new additives by the applicant. This added clarity will help applicants in their development of dossiers and aid the work of the risk assessors/managers by providing more accurate and relevant information. The proximity of mode of action to the definitions of functional group offer greater opportunities to demonstrate efficacy by selecting the most scientifically relevant criteria. This may present significant opportunities to avoid or at least minimise the need for animal experimentation. The re-evaluation process would be facilitated by offering new potential entries where efficacy cannot be demonstrated in the category/functional group to which the additive is currently allocated. It would also help to avoid the loss of valuable additives. The Panel made proposals for new grouping, introduction and definition of categories and functional groups (EFSA 2008b).

One of the most challenging future tasks of the Panel (and of EFSA) would be a better harmonisation of risk assessment between the different EFSA Panels and other authorities like EMA and European Chemical Agency (ECHA). This might trigger the development of guidance documents on how to perform the risk assessment for substances which are used for different purposes (i.e. food and feed additives, pesticides and feed additives, chemicals and feed additives, veterinary drugs and feed additives).

About the authors

Andrew Chesson, Chair of the FEEDAP Panel from 2003 to 2012; **Jürgen Gropp**, Vice-Chair of the FEEDAP Panel from 2003 to 2012; **Alberto Mantovani**, Vice-Chair of the FEEDAP Panel from 2009 to 2012; **Claudia Roncancio**, Head of the FEED Unit.

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