Assessment of feed additives and contaminants: an essential component of food safety

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Summary. Feed additives make the bulk of chemicals used in animal production, thus representing a major issue for safety of foods of animal origin. This paper summarizes the approaches adopted by the European Food Safety Authority to perform risk analysis of feed additives as regards the whole food production chain, including target species, consumers, occupational exposure and the environment. Feed safety must consider also environmental contaminants; in particular feeds can be a major vehicle for human dietary intake of persistent pollutants such as polychlorinated biphenyls. Critical issues include toxicological characterization, pathways of feed contamination as well as transfer to animal products. The possible effects of feed additives and contaminants on the overall safety and nutritional quality of human diet are discussed.

Key words: toxicology, risk, food, environment, nutrition.

INTRODUCTION

Foods are produced by living organisms, either plants or animals; thus, the environment where the food-producing organisms grow, including the feeds that are eaten by food-producing animals are essential determinants of the wholesomeness and quality of our diet. Feeds must satisfy the nutritional requirements of the relevant animal species. Moreover, feed composition in the industrialised world, as well as in a growing fraction of developing Countries, should support cost-effective and timely production of meat, eggs milk by selected, specialised breeds [1]; in the meanwhile, the requests of consumers for foods with a given taste, texture or colour have to be taken into account.

Last but not least, feeds are a essential component of the food production chain from the safety standpoint. Feed contamination has been the cause of major European alarms, such as the dioxin-polychlorinated biphenyls (PCB) contamination of poultry products in Belgium [2]. Such episodes did have consequences, from both the regulatory and the research point of view, such as the production of scientific data for a more refined risk analysis of dioxins and dioxin-like PCB, including the pathways of feed-to-food transfer [3].

Besides ingredients (and their possible contaminants), feeds utilized in intensive farming require the use of a diverse range of additives, alike human foods throughout the industrialized world. In fact, feed additives make the bulk of chemicals used in animal production, thus representing a major issue for safety of foods of animal origin. As laid down by the EC regulation [4] they are a large and heterogeneous group of compounds added to feeds due to their nutritional (vitamins, trace elements), zootechnical (such as growth promoters, coccidiostats and anti-blackhead compounds), sensory (colourants and flavours) or technological (antioxidants, preservatives, emulsifiers, etc.) role; moreover, the increasing importance of enzymes and microorganisms as probiotics should be taken into account. Such a diverse range of compounds entrain a number of specific issues besides the general objective of ensuring that possible residues in animal products would not pose any appreciable risk to consumers.
RISK ASSESSMENT OF FEED ADDITIVES

The “farm-to-fork” approach promoted by the European Union [5] requires the assessment and control of major components of the feed production chain, with emphasis on primary production. Accordingly Europe has given a significant attention to the assessment of feed additives, that shall be based on three main principles [6]: a) pre-market authorisation, b) positive list principle, and c) thorough assessment of possible effects on human and animal health as well as on the environment.

Since 2003, risk analysis of feed additives is task of the Panel on additives and products or substances used in animal feed (FEEDAP) within the European Food Safety Authority (EFSA) (http://www.efsa.eu.int/science/feepad/catindex_en.html).

Assessing a feed additive is a complex process that requires a comprehensive, multidisciplinary approach to assess all aspects relevant to use of a given substance. Compounds intended for deliberate addition/use in animal feed should have a proven efficacy, should be safe for animals and consumers at the intended dose levels. The safety for the user/worker should be assessed, as well as ecotoxicity; in fact, mass use of feed additives in intensively farmed animals may lead to a significant environmental exposure through animal excreta [7].

In the meanwhile, different outstanding issues can be identified for groups of additives.

As regards microorganisms and enzymes [8], concerns about residues are unlikely; safety evaluation is focussed on such issues as production of toxins, residual pathogenicity and induction of cross-resistance; sensitization of workers to microbial protein products might also deserve attention.

For chemicals employed in feeds, e.g., coccidiostats, acceptable daily intake (ADI), maximum residue limits (MRL) and withdrawal period are determined through the overall assessment of pharmacokinetics and toxicological studies, along the same line as for veterinary drugs [9]; alike other compounds (pesticides, contaminants) special attention is given to hazards (e.g., endocrine disruption) that may be of particular concern for vulnerable phases of the life cycle, such as pregnancy and childhood [10].

For nutrients such as mineral salts and vitamins, the conventional toxicological approach used for xenobiotics is not relevant. Instead, a careful evaluation of the balance between requirements and possible excess has to be performed in both target species and consumers [11].

It is therefore useful to compare two different instances of FEEDAP assessments: one based on the ADI-MRL approach, the other based on the interaction between nutritional and safety evaluation.

Monteban, a coccidiostat product based on narasin

Within a general evaluation at European level of coccidiostats for compliance with regulatory requirements, FEEDAP was requested to evaluate the efficacy and safety of Monteban, a product containing not less than 10% of narasin activity as the active substance [9]. Although previous data indicate that narasin is effective as coccidiostat for broiler chickens at a dose range of 60-80 mg/kg of complete feed, no recent field studies are available to prove the compound being still efficacious at the dose range. The development of resistance against coccidiostats, including narasin, is well recognized; however, it may effectively counteracted in practice by rotation or by shuttle programs, and no unusual resistance to narasin is expected to appear.

Monteban at the use level for chickens is dangerous to horses, turkeys and rabbits. Tolerance test showed a small margin of safety (about 1.4) in target animals; moreover, the interaction with some medicinal substances (i.e. tiamulin) justify a warning label against the simultaneous use of these substances.

Narasin, at the levels used for treatment of coccidiosis, is also effective in the prevention of necrotic enteritis in chickens. The compound is active against Gram-positive bacteria, while Enterobacteriaceae are resistant. There is no cross-resistance to other antimicrobials except to salinomycin. Increased shedding of Salmonella is unlikely to occur under practical conditions.

Narasin is absorbed to an unknown extent and excreted rapidly by the chicken. The excretion routes are not established in the chicken whereas faecal excretion prevails in the rat. The main metabolic pathway is similar in the chicken and rat and it involves oxidative processes; narasin metabolites in tissues and excreta are qualitatively similar. The liver is the target tissue for total residues. However, unchanged narasin disappear quickly from tissues, while it is somewhat more persistent in the skin/fat where it represents the major fraction. Each of the many narasin metabolites represent less than 10% of the total tissue residues; therefore, for food control purposes narasin could be retained as a practical marker residue and skin/fat as marker tissue. Narasin may concentrate in the egg yolk [12]; however, the compound is not intended for use in laying hens.

Alike other coccidiostats, many toxicological studies on narasin were of unsatisfactory quality. The critical effects were focal degeneration of skeletal muscles, including the diaphragm, and peripheral neuropathy in dogs: accordingly, the no-observed-effect-level of 0.5 mg kg bw day seen in the one-year dog study was used to set the ADI of 5 µg kg^{-1} bw (equal to 300 µg day for a person of 60 kg body weight).

A uniform MRL (maximum residue limit) for all tissues is proposed as 0.05 mg narasin kg wet tissue. The withdrawal time of 1 day would be considered sufficient. Validated methods are available which allow monitoring of narasin in premixes and complete feedstuffs and the determination of the marker residue, narasin, in the liver, kidney, muscle and skin/fat of the chicken.

As regards occupational safety, monteban can cause irritation to the eyes but not to the skin. Inhalation studies in dogs showed that narasin is potentially highly toxic by the inhalation route, compared with the oral route. Moreover, it has sensitization potential by skin contact and by inhalation. However, the product is for-
mulated as granules with a low dusting potential. For this reason, it is expected that workers will not be exposed by inhalation to toxic levels of narasin dust as a result of its handling. Nevertheless, FEEDAP recommended the use of appropriate personnel protective equipment for the workers.

Data were insufficient for an adequate environmental risk assessment. Based on the available information on the toxicity, fate and behaviour of narasin, it cannot be excluded that the use at the recommended dose range poses a risk for soil organisms. Insufficient data was provided to assess the risk for the aquatic environment and secondary poisoning of birds and mammals.

Therefore, although a ADI and MRL could be defined, FEEDAP noted a deficiency of data on both efficacy and environmental impact of narasin.

A trace element: iodine

Iodine [11] is a well-known essential trace element for humans and animals, due to its incorporation into the thyroid hormones and the dramatic effects on growth and development of low iodine intake, leading to hypothyroidism. The European Commission asked EFSA to evaluate the physiological requirements for iodine of the different animal species and to advise on the possible detrimental effect of the current levels authorised under Directive 70/524/EC (4, 20 and 10 mg/kg feed for horses, fish and all other species, respectively).

The iodine requirements for farm animals vary between 0.1 and 1.1 mg/kg feed. Within species the requirements are influenced by physiological demands for growth, reproduction or lactation and also by dietary factors (goitrogens). In most cases iodine supplementation of daily ration is necessary due to the low iodine content of plant feedingstuffs. Although, large European areas are iodine-deficient, nowadays clinically evident iodine deficiency in animals is rather scarce due to feed supplementation.

Based on the limited available data, maximum tolerable dietary iodine levels can be defined for some species, 5 mg/kg feed for laying hens and higher than 60 mg/kg feed for farmed fish. The iodine tolerance of pigs and fish is far above the EU regulations; moreover, the tolerances are 3 to 10-fold higher than the requirement, allowing sufficient compensation for potential goitrogenic substances in feed. However, at present the upper safe level for dairy cow, calf, chicken for fattening, turkey, sheep, goat and rabbit can not be determined.

Higher dietary iodine supply results in increasing iodine excretion mainly by urine, but also via milk and eggs, and to a considerably smaller extent in body deposition (except seafood). Among food from terrestrial animals milk and eggs show the highest iodine concentrations. All available data on iodine concentrations in foods of animal origin as well as estimates of dietary intake in Europe do not support an association between current levels of iodine feed supplementation and risks of excessive iodine intake in humans. It must be noted, however, that the actual, current levels of use in mammals and birds are lower than the maximum levels authorised under Directive 70/524/EC. On the other hand, the worst case scenario model calculations with milk and eggs based on the authorized maximum iodine level in feed, show that the upper tolerated limit of iodine intake in humans could be exceeded for adults and adolescents (i.e., 600 or 450 µg/day, respectively) [13]. Reducing iodine to a maximum of 4 mg/kg complete feed for dairy cows and laying hens would result in a satisfactory margin of safety for the consumption of milk and eggs, still fulfilling the iodine requirements in farm animals. As for farmed fish supplementation of the diet with the maximum recommended levels (20 mg iodine/kg) will still result in lower tissue concentrations than those found in wild marine fish.

FEEDAP stressed that iodine supplemented feeds are not the single nor possibly the major source of iodine in human diet. Iodine-enriched salt, supplemented food items, tablets, and beverages may all contribute to the overall iodine intake. Moreover milk iodine may originate from feeding as well as several other sources (notably disinfectants).

Iodine in feed enters the environment via direct excretion of faeces and urine on pasture or spreading of sludge and slurry. This resulting environmental concentration is well below the background concentration and it is therefore not expected to pose an environmental risk.

Overall, FEEDAP stressed the need for more and updated information on iodine requirement and tolerance in animals as well as on the actual impact of iodine supplements in feeds on total iodine dietary intake of humans.

RISK ASSESSMENT OF FEED CONTAMINANTS IN EUROPE

Within the EFSA, feed contaminants are primarily task of the Panel on contaminants in the food chain, that deals also with undesirable substances not covered by any other panel such as mycotoxins (EFSA Panel on contaminants in the food chain http://www.efsa.eu.int/science/contam/catindex_en.html).

Contamination of feeds by environmental xenobiotics is a major topic for veterinary public health. For instance, feeds can be a major vehicle for the presence in human diet of PCBs and other persistent organic pollutants that bioaccumulate in the fatty portion tissues; examples are the Belgian PCB/dioxin incident [2] and the recurrent alarms over the high concentration of such pollutants in fish meals used as feeds for farming of salmonids and other fish species [14]. Other examples are heavy metals [15] and brominated flame retardants [16]. The latter are widespread compounds, able to both bioaccumulate and act as endocrine disrupters in laboratory animals: however, few data are available concerning feed contamination and feed-to-food transfer.

The stepwise risk analysis of feed additives cannot be applied to contaminants. A case-by-case approach is adopted: critical issues include characterization of
toxicological hazards, the possible pathways of feed contamination as well as transfer of parent compound or metabolites to foods of animal origin. Thus, a major target for risk analysis would be to pinpoint potential situations of higher exposure that may require measures for risk management. Under this respect it is worthwhile to compare the assessments of naturally occurring undesirable elements (heavy metals) and of man-made contaminants (pesticides).

A heavy metal: arsenic

Arsenic [17] is a naturally occurring element, present in soil, ground water and plants. Regions with high geological occurrence of inorganic arsenic have been identified, in particular in Asia and other non-European countries. In Europe, environmental arsenic levels are rather low, with the exception of distinct geographical or industrial areas.

Arsenic is a metalloid, displaying different valences resulting in a broad variety of arsenic compounds with diverse chemical characteristics. Inorganic and organic forms of arsenic also differ significantly in their toxicity, the organic arsenic compounds exhibiting a very low toxic potential. Consequently, the potential adverse effects of arsenic to animal (and human) health are determined by the inorganic fraction in a given feed (or food) product, and data reporting only total arsenic in food materials are difficult to interpret in terms of the ability to induce adverse effects.

Drinking water many contain significant amounts of inorganic arsenic and upper limits have been set in most countries. Seafood and fish have been identified as major source of arsenic in the human diet and in animal feed materials that contain products derived from fish or other marine organisms. In seafood and fish, arsenic is present predominantly in the organic forms of arsenobetaine and arseneocholine, which are virtually non-toxic.

Analytical data from Europe on total arsenic in feed materials do not indicate arsenic levels of concern in materials others than fish-derived products, for which further data on chemical speciation are needed to identify the actual levels of inorganic arsenic. As the carry-over of arsenic in its inorganic form into edible tissue of mammals and poultry is low, food derived from terrestrial animals contributes only slightly to human exposure.

In conclusion, arsenic contamination of water may be of higher concern than foods, both vegetables and of animal origins, because of the bioavailability of the inorganic fraction. Conversely, failure to consider the contribution of different arsenic species on their bioavailability could introduce a substantial bias into the estimation of risks associated with exposure.

A pesticide: camphechlor

Camphechlor [18] (also called toxaphene) is a non-systemic insecticide that was used on crops and animals. It has been the most heavily applied pesticide in many areas and replaced DDT in the early 1970s. However, its use is now phased out in most of the world.

Technical camphechlor mixtures show a complex composition, with at least 202 different compounds identified. Due to its persistence it has found a widespread distribution. Environmental biotransformation and accumulation in the aquatic environment has led to relatively high levels of certain camphechlor congeners in fish, marine mammals and sea birds while other congeners rapidly degrade.

Camphechlor is readily absorbed from the gastrointestinal tract and distributed to the lipid portion of the organism. It crosses the placenta and transfers to milk as demonstrated in animals and humans. Alkene other chlorinated insecticides, toxic effects target the nervous system, liver and thyroid; immunotoxicity appears as the critical effect with a NOAEL of 100 µg/kg bw in the macaque.

Likewise other halogenated pollutants, fish oil and fish meal are the main sources of camphechlor exposure of farmed animals, particularly fish. Human dietary exposure is mainly from fatty fish, which is estimated to be between 1 and 25 ng/kg bw/day. High fish consumers may have intakes of about 60 ng/kg bw/day, which has still a good safety margin with the most sensitive NOAEL.

The congeners CHB 26, 50 and 62, which accumulate in the food chain, can serve as indicators of camphechlor contamination. Moreover, congeners CHB 40, 41, 42 and 44, should also be included in analytical studies as they are also found in fish samples and CHB 42 appears to be one of the most toxic congeners. Furthermore, the congener CHB 32 should be included as an indicator for a recent contamination, since it is a major component of technical camphechlor and it degrades rapidly in the environment.

There are substantial data gaps for camphechlor. Detailed occurrence data for camphechlor in feedstuffs and food of animal (other than fish) and plant origin are lacking. There is also a general lack of congener specific toxicity data as well as data on oral toxicity for farmed fish. Thus it is difficult to perform a proper risk assessment.

CONCLUSIONS

Feed additives require a careful evaluation with the support of up-to-date scientific information, in order to evaluate their efficacy and safety in the modern farm animal rearing. Feed contaminants are an unavoidable problem, but they can be reduced by good farming practices, including the development of nutritional sources less liable to contamination.

The examples of EFSA evaluation presented in this paper indicate the need for new research data, with particular regard for certain areas, such as:

- the nutritional requirements, efficacy and tolerance in the modern conditions of farm animal rearing. This would support the definition of optimum types and levels of feed ingredients and additives, thus helping to reduce the burden of farm animal diseases and the consequent use of veterinary drugs, with the ultimate result of increasing safety of the food chain;
the evaluation of actual exposure of the consumers through the feed-to-food transfer of residues and contaminants, in comparison with other sources of intake, considering also different dietary patterns and age- and sex-related susceptibilities within the population [3, 11, 17, 18];

last but not least, feed ingredients and additives which are factors involved in the nutritional quality of foods of animal origins. Iodine supplementation in British dairy herds led to iodine “contamination” of milk and dairy products; the resulting contribution to prevent endemic goitre has been defined “an accidental public health triumph” [19]. A more recent approach is the modulation of the content of cardioprotective effects of omega-3 polyunsaturated fatty acids in fish tissues by differential feeding [20]. Thus, in some instance feeds and feed ingredients might support preventive strategies to reduce the burden of human disease. Therefore, the assessment of feed additives and contaminants has to be viewed within the global goal of a healthier human diet. An example is the EFSA advice on safety and nutritional contribution of wild and farmed fish [21]. EFSA acknowledges that high-level consumers of highly contaminated areas (Baltic sea) might exceed the maximum tolerated levels for such compounds as methylmercury, PCBs or dioxins. Nevertheless, fish makes an important nutritional contribution to the diet, and it is considered beneficial to cardiovascular health. Thus, guidance on fish consumption should be made at national level, taking into account total dietary exposure of relevant contaminants and species/types and quantities of fish most suited to consumers’ diets. Concerning farmed fish, fish oil and fish meal are the most important sources of organic contaminants and possibilities for reducing contaminants levels in fish feed should be further explored. Therefore, it is envisaged the development of “comparative risk-to-benefit analysis” approaches.

Overall, this short excursus indicates that compounds present in feeds are an essential component of the quality and safety of foods of animal origins as outlined by the “farm-to-fork” conceptual framework of the European food safety.

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