FEED FOR FOOD: FEED COMPONENTS AT THE FOOD SECURITY-FOOD SAFETY INTERFACE

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Introduction

The ‘farm-to-fork’ approach promoted by the European Union (1) requires the assessment and control of major components of the food production chain, with emphasis on primary production. Foods of animal origin are produced by living organisms: based on this simple truth, the availability, quality and wholesomeness of foods of animal origin are closely related to the living environment of food-producing animals, and primarily on their feedingstuffs. Accordingly, feed additives and contaminants feature prominently among the opinions delivered by the European Food Safety Authority (EFSA) (2). Feed quality obviously supports food security, by satisfying the nutritional requirements and ensuring the welfare of farm animals. Indeed, the food security issue goes beyond meeting the basic community needs for proteins, fat and energy. First, animal feedingstuffs should not subtract useful ingredients to the human diet, thus feed materials should not have any possible significant use as main human foods. Then, feeds should support nutritional security, *i.e.* foods of animal origin should provide an adequate and balanced intake of such nutrients as vitamins and trace elements. As a consequence, the role of feed ingredients, including additives and contaminants, in shaping the safety of human food has stimulated an update of the concept of zoonoses, to include health risks related to the undesirable carry-over of natural substances or xenobiotics (3).

In order to discuss the diverse implications of feedingstuffs at the food security-food safety interface, this chapter presents a few examples related to three main issues: i) safety of feed materials not employed in human diet; ii) feed components to reduce the exposure to toxic contaminants; iii) safety and efficacy of feeds enriched with nutrients.

Safety of feed materials not employed in human diet

Feed materials that meet animal requirements and do not subtract resources to human diet deserve a lot of interest, but this should not lead to forget about safety issues, that might be related either to the intrinsic presence of undesirable substances and/or to the production process being liable to contamination.

A telling example is hemp, assessed by EFSA in 2011 (4). Hemp (*Cannabis genus*) is still an important textile worldwide: as by-products, several types of feed materials are derived, including seed, seed-derve meal/cake and oil and whole plant. Due to the high content in lipids and protein hemp materials can be useful complement of farm animal nutrition, at inclusion rates < 5%; the whole hemp plant has a high fibre content, making it suitable for ruminants at daily amounts of up to 1.5 kg (dry matter) for dairy cows. Alongside with advantages, hemp contains the potent psychotropic substance tetrahydrocannabinol (THC), which is mostly associated to the leaves. The hemp varieties allowed for cultivation in Europe need not to exceed 0.2% THC in dry matter; the average THC content detected in an European survey

(2006-2008) was 0.075%, 2.6% of the samples exceeding the maximum content. Hemp seeds are practically free of THC (maximum 0.012%). THC carry-over does occur: the parent compound and active metabolites may be distributed to the fat fraction of different tissues and edible products. The limited data available allowed to assess consumer exposure through bovine milk only; the transfer rate of oral THC to milk from dairy cows is likely 0.15%. Compared to the abundance of studies on the pharmacological effects of THC, few could be used to derive a dose-response for unwanted psychotropic effects: based on human data, a Provisional Maximum Tolerated Dose (PMTDI) of 0.0004 mg/kg_{bw} was derived, taking into account remaining uncertainties (possible enhanced susceptibility of children and neuroendocrine effects upon exposure *in utero*). Since the PMTDI is based on acute pharmacological effects, the consumer exposure assessment considered a single high consumption of milk and/or dairy products, according to conservative values derived from the EFSA Comprehensive European Food Consumption Database (2 L milk equivalents for adults, 1.5 L for children). Exposure scenarios were built on varying intake of hemp plant derived feed material s, milk yields and maximum allowed or average THC content: in all instances, consumer exposure to THC was considerably (2- to 90-fold) above the PMTDI for adults and for small children (1-3 years). On the other hand, the same exposure calculations applied to hemp seed-derived feed materials were always below the PMTDI. Upon this assessment, that could not take into account the THC carry-over in other foods due to the lack of data, the EFSA has recommended that whole hemp plant-derived feed materials would not be used for animal nutritional purposes and to introduce a maximum THC content of 10 mg/kg to hemp seed-derived feed materials. The issue of THC exposure through milk should be viewed as a real one in many developing countries, where a large production of hemp exist and no official limits for THC are enforced: in the northern part of Pakistan 50% of buffaloes fed hemp-containg fodder showed the marker metabolite THC-COOH in their milk, and 29% of small children consuming that milk had detectable levels of THC-COOH in their urine (5).

In recent years, increasing demand for ethanol as a fuel additive and decreasing dependency on fossil fuels have resulted in a dramatic increase in the amount of grains used for ethanol production, and in a major output of distillers Dried Grains With Solubles (DDGS) as main by-product, as well as a global commodity (6). Thus, the quest for energy of developed and emerging countries has changed the use of a large fraction of cereals, such as corn and sorghum. On the other hand, cereals as biofuel may re-enter the food production chain as DDGS are envisaged to become major feed materials that might displace other energy protein sources in animal diets. Several recent studies show that various kinds of corn and sorghum DDGS can be suitable feed materials for pigs (7) and cattle (8) from the standpoint of growth and performance. However, DDGS present potential safety issues that should not be overlooked. High compositional variation is a main problem, especially in the inorganic fraction (e.g. phosphorus), mainly due to processing steps, such as the amount of condensed solubles added to distiller wet grains and the effect of fermentation yeast. Such changes may affect animal welfare and the environmental output of animal excreta (6). Mycotoxins are the main contamination problem of DDGS, also because contaminated grain not suited for animal or human consumption might be used for biofuel production; if present, mycotoxins may concentrate in DDGS about 3-fold over the original material (6). DDGS may contribute significantly to chronic, low level exposure of pigs to fumonisin B(1) (9), On the other hand, a survey on representative DDGS samples from the U.S. ethanol industry showed no significant concerns: contamination by aflatoxins, deoxynivalenol, T-2 toxin, and zearalenone was low, 10% of samples contained fumonisin levels higher than those recommended for the most sensitive species (equids and rabbits), and the containers used for export shipping of DDGS did not seem to contribute to mycotoxin production (10). Thus, DDGS may be suitable and safe fee materials, provided that proper risk management strategies are in place.

Feed components to reduce the exposure to toxic contaminants

Feed contaminants are a broad issue for veterinary public health: they range from undesirable feed components (4) through to contaminants related to specific steps of food production, such as storage or cross-contamination and to environmental pollutants. Management of feed contaminants relies primarily on the implementation of good practice in feed production; specific developments may include safe and effective aditives supporting detoxification as well as feed sources less prone to contamination (11).

The increasing interest in mycotoxins through climate change and, especially, global marketing of feed and food ingredients has prompted attention towards methods to combat the unavoidable presence of mycotoxins in feeds. One of the strategies for reducing the exposure to mycotoxins is to decrease their bioavailability by including various mycotoxin-adsorbing agents in the compound feed, such as aluminosilicates; another strategy is the degradation of mycotoxins into non-toxic metabolites by using biotransforming agents such as bacteria/fungi or enzymes (12). The EFSA has recently evaluated the modified aluminosilicate bentonite (dioctahedral montmorillonite) as feed additive for the reduction of feed contamination by mycotoxins (13). The recommended use levels of up to 0.3% in complete feed were not considered to pose safety concerns to farm animals; at 0.5% and higher no toxicity is observed, but bentonite may interfere with the bioavailability of the essential trace element manganese and interact with coccidiostats. No hazards to consumers are foreseen; indeed bentonite has a very low roxicity and is authorised for use in human food without restriction in Europe. However, bentonite exposure of workers involved in feed mixing or handling should be kept under control, as the additive has a high dusting potential and inhalation exposure increases susceptibility to pulmonary infections in rodents. Much attention was given to the assessment of efficacy, as in such case effectiveness has a direct bearing on feed safety. *In vitro* studies showed the ability of bentonite to adsorb aflatoxins in aqueous media at different pH values and, to a lower degree, in gastric juice; *in vitro* systems are an effective screen, however they cannot completely mimic the complex situations during digestion. Two *in vivo* studies in dairy cows exposed to feed containing <5 μg/kg of Aflatoxin B1 (maximum tolerated concentration in Europe) demonstrated a significant reduction in the milk excretion of the relevant metabolite, aflatoxin M1, at recommended use levels. Thus, effective aflatoxin binding in feed was shown for dairy cows, and the conclusion was extended to all ruminants. However, no conclusion could be taken for any other animal species due to the absence of *in vivo* data. The European approach envisages that mycotoxin binding agents may be used only when mycotoxins in feeds are within the maximum tolerate levels, so to check any residual low-level, long-term pressure on animal production; otherwise, the agents must not be employed to “recover” feeds or feed materials that are unsuitable for use, taking also into account that efficacy is nor always demonstrated (14). In conclusion, mycotoxin-binding agents, or other feed additives, have to be used within good animal husbandry practice and cannot replace it.

Fish farming is characterized by the primary role of feed materials of animal origins, i.e., oil an protein sources derived by aquaric organisms. This renders the prouction of fish liable to bioaccumulation and carry-over to human diet of persistent, lipophyllic endocrine disrupters (polychlorinated biphenyls, dioxins, brominated flame retardants) and methylmercury (15). As a consequence high levels of contaminants may somewhat reduce the recognized beneficial action of nutrients (e.g. omega-3) for which fish is a substantial source (15); contaminants might also impinge on metabolic pathways regulated by nutrients (16). The hazards from aquaculture feed contaminants are especially related to the developing lifestages: methylmercury specifically affects brain development (17), endocrine disrupters impair the hormone network regulating the programming of the organism (18). As for methylmercury, a European survey showed that in complete feedingstuffs for fish 8% of samples exceeded the maximum tolerated level of 1 mg/kg total feed. The resulting contamination levels in farmed salmonids indicate that the weekly consumption of two fish meals, as recommended by nutritionists, would not pose any appreciable health risk to consumers; however, limited data exist for other farmed fish species, that can be, nonetheless, important for consumer's intake (17). EFSA has pointed out feeds as a critical point to reduce consumers' exposure to bioaccumulating contaminants whilst maintaining the nutritional benefits of fish farming (15).

The integrated project AQUAMAX (European 6th framework programme) has been implemented to support fish farming, as a sustainable and safe source of nutrients, through an interdisciplinary effort. The primary AQUAMAX objective has been to develop feeds based on sustainable alternatives to fish meal and fish oil, producing healthy and minimally contaminated fish that are highly nutritious and acceptable to consumers; to this purpose, vegetable ingredients have been exploited in order to set novel diets with minimal contamination levels suitable for major aquaculture species (Atlantic salmon, rainbow trout, gilthead sea bream, common carp and Indian major carp). Life Cycle Assessment showed that the development of new feeds led to improvements in terms of net primary production, whilst the increased use of vegetable sources can induce an increase in land competition as well as other impacts such as eutrophication and terrestrial ecotoxicity. Morever, AQUAMAX focussed on risk-benefit assessment for consumers' health. Health benefits of fish farmed on the new diets are assessed in an intervention trial on pregnant women at high risk for atopic disease, and their offspring, based on the possible preventive action by a good intake of long chain omega-3 fatty acids. In addition, the direct toxic effects of relevant contaminants (including brominated flame retardants, highly present in fatty fish and still insufficiently considered by feed and food monitoring programmes) are assessed together with the modulating effects of beneficial nutrients in fish farmed with traditional and novel diets; toxicology studies are performed on prepubertal rodents, as models of children considered as a vulnerable group of direct consumers, and using realistic intake levels. Finally, project's actions included also the assessment of consumer's perception of both farmed fish and fish fed with new diets. AQUAMAX has concluded in 2010, the output of publications being still on course: objectives and achievements are presented in the project's website (www.aquamaxip.eu). Ultimately, AQUAMAX shows that feed quality and wholesomeness can be fully relevant to the new conceptual framework of "sustainable food safety", covering actions to promote the health of generation(s) to come through intervetions on the food chain (19).

Safety and efficacy of feeds enriched with nutrients

Nutrients are often supplemented to feedingstuffs to prevent possible primary deficiencies and/or secondary deficiencies due to, for example, increased requirements by high-producing animals. Extensive research is carried out since years to enhance nutrient's bioavailability, such as the development of a number of organic compounds of essential trace elements; however, enhanced bioavailability might entrain a higher carry-over to edible tissues and products, with potential safety problems (20). Nutrients are not safe by definition: as regards nutritional feed additives, the general approach adopted by EFSA seeks that the estimated intake from foods of animal origin plus the background intake from other dietary sources needs not to exceed the Upper tolerable intake Level (UL), as the highest level of daily intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population (e.g. the seminal opinion of the Panel on Additives and Products or Substances used in Animal Feed, FEEDAP, on iodine use in feedingstuffs) (21). Thus, the real consumers' advantage from nutritional fee additives stems from guaranteeing animal welfare and production without posing risks of any excessive exposure. In some cases, the safety assessment requires a special consideration to potentially vulnerable consumers subgroups. In assessing the safety of vitamin A in animal nutrition, the FEEDAP considered that the UL (3000 µg retinol ester -RE- from preformed vitamin A) was appropriate for the general population; however, data on adverse impact bone health risk suggested a lower UL to protect elderly people, as a vulnerable population subgroup. Insufficient dose-response data did not allow to establish a new UL, but only a provisional guidance level of 1500 µg RE/day for persons at a greater risk of osteoporosis and bone fracture, particularly postmenopausal women. About half of the intake of total vitamin A in European consumers comes from carotenoids in vegetable foodstuffs of plant origin, the other half from preformed vitamin A in foods of animal origin. Only preformed vitamin A is of safety concern: liver, and to a lesser extent, milk fat and egg yolk are the significant sources. The countries of Mediterranean Europe show proportions of population exceeding the UL and the guidance value in the range of 5% and 10% respectively, while the proportion in Northern Europe are much lower ($\leq$3%); consumption of liver, milk, including dairy products, and supplements containing vitamin A.are the main determinants of high intake in the different countries. Most important, the FEEDAP Panel noted that maximum allowed concentrations of vitamin A in feeds in Europe largely exceeded the animal requirements. Thus, in order to avoid extreme values in foods of animal origin and protect vulnerable consumers while maintaining adequate levels in animal nutrition, the FEEDAP Panel recommended to reduce maximum vitamin A contents for complete feed and complementary feedingstuffs, as well as to monitor preformed vitamin A in foods of concern after introduction of revised maximum contents (22). EFSA assessments are based on exposure data relevant to Europe; thus, it might not be ruled out alltogether that in a different context (age group distribution, vitamin A intake, etc.), the assessment outcome could have also been different.

Therefore, nutitional aitives in fees should meet animal requirements. However, using feeds to enrich foods animal origin is considered a worthwhile evelopment by several industries and research groups. In 2011 the FEEDAP Panel has assessed a selenised yeast intended to improve the quality of animal product by increasing their Selenium content, hence their nutritional value; the proposed usage level was up to maxim allowed content of total selenium in feedingstuffs, 0.5 mg/kg. A certain increase of the selenium content of edible tissues and products is a characteristic consequence of Se supplementation to the diet; under this respect, the selenized yeast was markedly more effective than inorganic sources, eliciting an evident, dose-related rise in deposition. Higher bioavailability is related to composition of selenium from selenized yeast, which is 70% selenomethionine: this is incorporated into proteins, where it is interchangeable with sulfur containing methionine, as well as acting as Selenium reservoir. In its turn, higher bioavailability has a significant bearing on consumer exposure, too. A conservative exposure assessment for adults and small children (age 1-3 years), was based on food consumption values from the Comprehensive European Food Consumption Database, as in (4), and adding background intake. Estimated exposure of adults was below the UL (300 µg/day). For small children the likely total exposure after consuming milk, meat and eggs from animals treated with 0.2-0.26 and 0.3-0.35 mg/kg feed of selenium from selenized yeast, plus background intake from food of non-animal origin of 10 µg/day, was 66 and 75 µg/day, respectively: by comparison, the age-adjusted UL for children 1-3 years old is 60 µg/day. Taking into account that i) selenium excess may cause actual health risks in humans, and ii) the inherent conservativeness of exposure assessment (based on 95th percentile consumption values of consumers only, thus excluding non-consumers from calculations), The FEEDAP Panel concluded that safety of vulnerable consumers, in this case children of 1-3 years of age, is given only at a maximum supplementation level of 0.2 mg/kg feed of Selenium fron selenized yeast. The FEEDAP Panel also identified a need for specific analytical methods to detect organic compounds of essential trace elements in feed, independent from the inorganic element background (23). Based on the recent EFSA assessment, enrichment of foodstuffs with Selenium through animal feed supplementation can only be considered on a case-by-case basis, in areas with a recognized Selenium deficiency and should be integrated with a plan to monitor Selenium intake, with a special attention to vulnerable groups.

Concluding remarks

It is worthwhile promoting research on novel feed materials and additives that can improve animal production, increase nutrient content of foods of animal origin and reduce the carbon footprint of farm animal rearing; consumer safety assessment should be considered a necessary component of such research, as safe feedingstuffs are one essential basis of food safety (1-3).

Whereas development of safer feedingstuffs requires the toxicological expertise, toxicology could also upgrade its approaches; when neeed, risk assessment could adress, in a comparative ways, different scenarios in order to indicate the solution presenting the lowest risk. Examples are provided by EFSA opinions on hemp (4), distinguishing the safety implication of different hemp-derived feed materials, as well as on vitamin A and selenized yeast (22, 23), indicating options to safeguard both animal nutrition requirements and prevention of risks for vulnerable consumers groups. In the meanwhile, feed science and technology can provide a remarkable contribution to improved safety, by developing new ingredients less liable to contamination (AQUAMAX) or through the characterization of production processes of novel feed materials in order to set risk management strategies (6). The synergy between toxicological risk assessment and feed science and technology might even be viewed as a small-scale model of the integration between food security and food safety.

Finally, the EFSA assessments have to consider primarily European feed and food practices as well as exposure scenarios; based on analogous data, conclusions might be different in settings other than Europe. Nevertheless, EFSA assessments point out frameworking criteria that hold valid beyond Europe. Two examples are quoted as final remarks. First, safety assessment should always identify and consider possible population subgroups that may have increased exposure and/or susceptibility: as well evidenced by the endocrine disrupting contaminants, the developing organism can be a critical target of both risks and actions aimed at risk reduction, according to the "sustainable food safety" approach (19). Second, novel feed additives and technology should always be intended to support good farming practices, not to replace them; indeed, the health and welfare of food-producing living organisms is a primary element to ensure food security as well as food safety.

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