by contractures forming in joints contributes to the development of DA, likely because movement is required for normal joint development (*1*). In addition, mechanical forces regulate bone development, and the generation of tension by muscles is critical for normal tendon development.

Finding that expression of the gain-of-function allele of *Piezo2* in young adult mice does not cause DA symptoms is reassuring. It narrows down a time window for potential therapeutic intervention that could lead to lifelong improvement for the affected patients. One surprisingly simple treatment option is explored by Ma *et al.* The omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA), a membrane lipid that is commonly found in fish and food supplements, affects PIEZO2 function and negates the gain-of-function effect of the DA5-causing *PIEZO2* mutation. Feeding the *Piezo2* mutant mice with a diet rich in EPA prevented joint malformations and the associated behavioral defects. Perhaps a similar treatment might help human patients, although this needs further clinical investigation.

The study by Ma *et al.* provides exciting new insights into the mechanisms that cause DA. Notably, both gain-of-function and loss-of function mutations in PIEZO2 have been linked to DA, but the different mutations lead to distinct pathologies. Moreover, there is patient-to-patient variability in the pathologies caused by the same mutation, with variability in the degree to which different joints, fine motor function, and touch sensation are affected; the manifestation of ophthalmoplegia and restrictive lung disease; or even the presence of cerebellar malformations (*1, 5, 6*). Further studies will be necessary to define the mechanisms by which dominant and recessive alleles of *PIEZO2* act in distinct cell types to cause various DA symptoms. The study of Ma *et al.* is an important step in this direction and sets the tone for further investigations into the clinical implications of PIEZO2-mediated pathogenesis. ■

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FOOD PRODUCTION

Insects as feed for livestock production

Insect farming for livestock feed has the potential to replace conventional feed

By **Arnold van Huis**[1] *and* **Laura Gasco**[2]

Livestock production makes up 70 to 80% of the world's agricultural land use and yet only produces ~18% of all calories and 25% of all proteins consumed by humans. To grow food for livestock uses 33% of the world's cropland. Although lifestyle changes, such as vegetarianism and veganism, may help to achieve sustainability in food production, the global demand for meat consumption is still increasing, so it is also crucial to consider more efficient ways to rear livestock. Insects as animal feed can supplement the current sources of livestock feed, which mostly comprise fishmeal and soybean meal. The use of insects as livestock feed can improve sustainability because insects can transform low-value organic wastes (e.g., fruits, vegetables, and even manure) into high-quality feed. Insect ingredients are also a valuable source of nutrition for animals with many possible health benefits.

Globally, domesticated animals receive more than 1.1 billion tons of feed every year, with 44% going to meat chickens and egg-laying hens, 28% to pigs, 4% to fishes and other seafood, and 3% to pets. The enormous demand for animal feed production creates sustainability concerns—for example, farming soy can involve deforestation, biodiversity loss, and the use of pesticides (*1*). Insect production emits few greenhouse gases and ammonia, and requirements for water and land are low. The largest environmental impact of their production is the feed when using mixed grain (*2*), but this could be overcome by using organic waste as feed instead. Insects have a high feed-conversion efficiency (animal weight gain divided by feed consumed), probably because insects are cold blooded (poikilotermic), which means that they do not expend energy maintaining a constant body temperature—it varies with that of the environment. The disadvantage of this dependence on ambient temperatures is that energy requirements for rearing insects are higher compared with growing crops for feed.

Insects are a valuable source of high-quality protein as well as other essential nutrients for animal feed. Beyond the nutrient supply, insects also provide active compounds that can exert a positive effect on animal health and act as potential antibiotic replacements (*3*). Chitin, a component of insects' exoskeletons, is a biopolymer that mammals lack and is therefore targeted by their immune system. In vivo trials performed on fish, poultry, and pigs showed that consumption of chitin boosted the immune system; halted pathogen proliferation; favorably modulated the host's intestinal bacterial communities; and had antioxidant, hypolipidemic, and hypocholesterolemic properties (*3*). Insects naturally produce a high diversity of antimicrobial peptides (*4*) to protect themselves from the microorganism-laden environment in which they live. Moreover, fatty acids, such as lauric acid (which is particularly abundant in black soldier fly larvae), also show strong antimicrobial properties when given as feed to animals (*3*).

Among the many insect species that can be reared as animal feed, those currently being used include flies—e.g., the black soldier fly (*Hermetia illucens*) and the common house fly (*Musca domestica*)—and mealworms, such as the yellow mealworm (*Tenebrio molitor*). Usually, the larval stages or prepupae of these species are used as feed. Black soldier flies are the preferred species because the larvae can be reared on a wide range of organic matter (including waste, such as agricultural and food waste) and can thrive in environments that are considered unhygienic (such as in manure) for other animals.

What is the effect of including insect products in the feed of fish, poultry, pigs, and pets? For aquaculture (fish) species, the inclusion of up to 30% full-fat or defatted insect meals had little observable difference compared with fishmeal, which remains the optimal protein source for aqua feeds (*5*). For marine species, attention should be paid to long-chain polyunsaturated fatty acids, which are absent in insect products unless added to the food source (the rearing substrate) for the insects. In poultry feeds, the

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Organic waste can be used to feed black soldier flies (*Hermetia illucens*), whose larvae are a rich source of animal protein.

inclusion of insect feed up to ~30% has been reported to fully substitute soybean meal or other conventional plant protein sources. However, for black soldier fly meal, optimal inclusion seems to be ~10% because small histological issues in the intestines have been observed in poultry above this level (*6*). Live black soldier fly larvae also promote the natural foraging behavior of birds and decrease feather picking, which positively affects their welfare and health (*7*). Compared with aquaculture or poultry sectors, relatively little research has been performed on pigs where partial or full substitution of soybean meal or fishmeal was obtained using moderate (10 to 20%) amounts of yellow mealworm or black soldier fly (*8*). However, higher amounts of substitution of insect-based feed may lead to decreased digestibility for pigs (and possibly other animals). Although only 3% of all feed produced is for pets, currently ~50% of the insect industry is engaged in producing for this sector. During the past 2 years, large companies have advertised pet food containing insects, highlighting, among other things, the hypoallergenicity of insect-containing feed. Research on insect meal in pet food should focus on nutritional adequacy, food safety, and whether it is hypoallergenic (*9*).

The insect species, its development stage, rearing substrate, and processing method (such as whether it undergoes drying and defatting) all affect the overall nutritional value and therefore determine its inclusion level in feed formulation. There are large variations in nutrient composition within the same insect species because of different production methodologies (*10*). This makes it difficult to compare the results of trials using insects as livestock feed. Only when the nutrient composition and amino acid profile are properly balanced can total replacement of fishmeal and soybean meal be possible without compromising animal performance, product quality, or animal health.

Currently, the quantities of insects produced are not enough to sustain the demand for agricultural feed, and the prices of insect feed are not competitive. Studies from a highly productive pilot plan demonstrated that feeding livestock with black soldier fly could become more beneficial (than soymeal or fishmeal) if insects are fed with unused organic matter (*11*). As has been done for other livestock species, the determination of the nutritional requirements of insects is a further fundamental step. This will allow maximum production by combining waste of different origins. Indeed, several waste types have been combined to match a feed formulation covering the nutritional needs of diverse insects (*12*, *13*). Because the farming of insects as "minilivestock" is very different from livestock farming, there are additional challenges and issues to overcome, including automation of production techniques, optimization of bioconversion by an efficient interaction between microbes in the insect gut and feed substrate, disease management, making use of the short life cycle of insects to select efficient strains of insects and microbes for certain diets, food safety issues, and processing. Standardization of research methodologies is desirable to allow the comparison of the efficiency of insects in bioconverting waste into high-quality nutrients (*14*).

Regulatory frameworks for insect-derived products are slowly being implemented. For example, in 2017, the European Union (EU) permitted the use of insects as aquafeed and authorized insect-derived processed animal proteins in poultry and pig feed in 2021. The use of live larvae is only permitted under national legislation in some countries. Because pets (dogs and cats) do not enter the food chain, no restrictions apply to the use of insect-derived proteins in pet foods. Owing to safety concerns, in some countries (including EU countries), the use of catering waste, manure, slurry, or other products of animal origin as substrates to feed insects is forbidden. Insect producers' associations are working with legislators to change this restriction, but further research is required to assess the safety of using waste to avoid any pathogen transmission.

Functional benefits of insect protein in animals are promising but need further confirmation. A major challenge for the insect sector is to deliver reliable quantities of insect meal of high quality and consistency. The scaling up of production depends on whether cheap organic wastes can be safely used and easily biotransformed into high-quality insect products and whether legislative frameworks are conducive to this approach. ■

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