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Preface to the special issue of Food and Chemical Toxicology on the outcomes of the MARLON project on veterinary epidemiology of potential health impacts of genetically modified feeds in livestock

This special issue is a collection of articles dedicated to the impact of genetically modified (GM) animal feeds on the health of livestock. It features the outcomes of the research project titled "Monitoring of Animals for Feed-related Risks in the Long Term (MARLON)". MARLON was a three-year research project funded by the European Union's (EU) Seventh Framework Program for research and technology development (MARLON, 2015). It focused on monitoring livestock in commercial production scenarios for potential health impacts associated with feeds containing GM ingredients. There has been a rapid rate of adoption of GM feed ingredients especially GM-soybean, maize, oilseed rape and cottonseed in non-EU countries, since their commercial large-scale introduction in the mid-90s (James, 2017). They are now common ingredients in livestock feed. In addition to addressing GM feeds, the methodology and insights gained from the project can be broadly applied to the surveillance of health effects of livestock feeds and hazards in general.

MARLON operated at the interface of science, legislation, and policy. It brought together scientists from 11 European institutions with complementary expertise including veterinary health and epidemiology, livestock production, biosafety of GM crops, and food and feed safety. MARLON's activities included stakeholder consultations, a training course, and a final conference. The main outcomes of MARLON were new knowledge, guidelines, and methodologies for monitoring GM feed ingredient-related health impacts for key stakeholders including European regulators. MARLON's progressive approach relates to the possibility that monitoring of GM feeds and foods may become necessary because they are regulated and can only be marketed after regulatory approval. In fact, EU legislation on GM foods and feeds has a provision that a post-market monitoring *may* be required based on the outcome of the pre-market risk assessment (EU, 2003). Thus, a key outcome of MARLON was providing European policy makers with pertinent new knowledge on several safety topics regarding GM crops which added to the outcomes from other EU projects including the GMSAFOOD, GRACE, and G-TwYST projects and the French government-funded GMO90 + project that focussed on *in vivo* and *in vitro* biomarkers, methods for safety testing of GM crops, and collation of the existing evidence on the potential health, environmental, and economic impacts of GM crops.

When the MARLON project began, there were a few challenges to address. For example, a requirement for *case-specific monitoring* to verify potential risks identified or assumptions made during the pre-market safety assessment was only necessary for foods derived from GM oilseed crops with a modified fatty acid composition, which might have potential to impact human nutrition and health. In addition, there was a requirement for general, passive surveillance of animal health impacts as part of the *general surveillance* carried out for all GM crops that had received approval for "environmental release" (*e.g.*, field cultivation, import and processing of seeds and other viable GM crop products) (EU, 2001). Therefore, MARLON activities had to be anticipatory because it was not possible to rely on past case-specific monitoring experience. This was especially challenging because negative health effects due to approved GM products were not known to exist. Another challenge was that the approach to developing monitoring methods should be universally applicable because it was not possible to foresee for which combination of GM feed, livestock species, and health parameters monitoring could be required. Additionally, it was necessary to use data from existing animal health surveillance activities, which were either generic or focused on the impact of non-feed-related animal health.

This special issue addresses the following questions:

- Are there known health impacts related to GM-crop-derived livestock feeds? (De Vos and Swanenburg, 2018)?
- Would it be possible to measure the exposure of animals to specific GM feed ingredients? (Nadal et al., 2018)?
- Can health indicators be specified by regulators for the monitoring of livestock for possible health effects of GM feeds? (De Santis et al., 2018)?
- How are different feed and livestock production chains organized and characterised (*e.g.*, husbandry practices, regulations, traceability, and health checks)? (Kleter et al., 2018)?
- Is it possible to design monitoring programs to exploit data from existing surveillance for the detection of unusual trends in animal health parameters such as those collated in IPAFEED, and relate this to the consumption of GM feeds? (Vince et al., 2018)?

De Vos and Swanenburg, in their review of the literature, addressed whether there are known health impacts related to GM-crop-derived livestock feeds (De Vos and Swanenburg, 2018). They focussed on controlled livestock feeding studies to collate state-of-the-art knowledge on health parameter (*e.g.*, serum chemistry, pathology, etc.) perturbations associated with the feeding of GM ingredients. From this, it was concluded that feeds formulated to include first-generation GM crops were at least as safe as feeds produced from non-GM feed ingredients. They state that it is too early to reach a conclusion regarding second-generation GM crops (with improved outputs traits) because these have only recently become available. A systematic annotation of the health parameters measured in livestock

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feeding studies is provided in the IPAFEED database (IPAFEED, 2015; Vince et al., 2018). Regulators can now use information from IPAFEED to assess the design of monitoring schemes based on previously reported health parameters.

The review by Nadal and co-workers (Nadal et al., 2018) focussed on whether it would be possible to measure the exposure of animals to specific GM feed ingredients with the notion that it might link exposure to ingredients with adverse health effects in an individual or cohort of animals. They also addressed whether ingredients could be traced and detected throughout the feed and livestock production chains, and whether there are markers for exposure in livestock animals (*e.g.*, via uptake of GM material from feed into tissues, fluids, and excreta). The review concludes that although it is possible to measure the presence of specific ingredients in feeds based on GM-crop-related proteins or DNA, there are no markers for animal exposure. Therefore, traceability measures have not yet traced and quantified an animal's exposure to a specific GM feed ingredient.

De Santis and co-workers addressed whether health indicators can be specified by regulators for the monitoring of livestock for possible health effects of GM feeds in their review (De Santis et al., 2018). They explored four scenarios: 1) potential allergic reactions induced by GM feeds as compared to non-GM feeds in livestock animals; 2) horizontal gene transfer from consumed GM crops to intestinal microorganisms and the host animal; 3) reduced incidence of mycotoxins in GM feeds; and 4) nutritionally altered GM crops. The authors concluded that there were no adverse effects to GM feeding in the literature for these scenarios. There is evidence, however, of beneficial effects related to a reduction of the mycotoxin fumonisin in insect-resistant GM crop varieties and through nutritional enhancement of crops.

The Kleter and co-workers' (Kleter et al., 2018) review approached the organization and characterization of different feed and livestock production chains (*e.g.*, husbandry practices, regulations, traceability, and health checks) with the aim to determine how the movement of feeds and animals through the production chain is recorded and how this could be used for monitoring of animal health effects. The authors concluded that for livestock, traceability at herd or individual levels are possible depending on the livestock species. Although the existing animal traceability systems are designed for infectious disease reporting or animal identification, it is not possible to trace GM ingredients (even if it is labelled correctly) back to the farms of origin or to verify the distribution and inclusion level in the feeds.

The last review by Vince and co-workers addresses designing monitoring programs to exploit data from existing surveillance for the detection of unusual trends in animal health parameters, such as those collated in IPAFEED, and relate this to the consumption of GM feeds. The review reveals a broad methodology to assist the monitoring of GM feed-related health effects (Vince et al., 2018). This was a key challenge for MARLON because there were no recorded GM feed-related health effects and no methods for quantifying prior exposure of the animals to GM feed. The authors reviewed various types of existing veterinary surveillance, which aim at providing evidence for freedom from specific diseases, early detection of outbreaks, and monitoring of endemic diseases including syndromic surveillance (*e.g.*, non-specific health parameters), risk-based surveillance, collection-point-based surveillance, checkpoint surveillance, sentinel herd surveillance and representative surveys. In addition, they reported on a probabilistic approach towards syndromic surveillance that estimates the likelihood that an effect will be detected above background variability through existing reporting systems. Importantly, this approach considers the production chain, from farmer via veterinarian and clinical laboratory, to post-mortem abattoir inspection. The authors concluded that observed effects or deviating trends would need follow-up with confirmatory research under controlled conditions and suggested that managers should consider cost-effectiveness compared with alternative options when setting up a surveillance scheme.

In summary, the reviews in this issue provide comprehensive overviews of published controlled feeding livestock studies with GM crops checking for health impacts beyond solely performance, the possibilities to detect GM feed ingredients and the animals' exposure to them, the possibility to employ health indicators for four hypothetical scenarios including allergenicity, horizontal gene transfer, changed mycotoxin levels, and nutritional improvement, the organization of feed and livestock production chains in Europe, and the possibilities for applying veterinary epidemiology to surveillance of possible GM feed-related health impacts. The generic, statistical approach developed within MARLON will assist in the design of monitoring programs based on syndromic surveillance for GM and non-GM feeds which would then rely on existing data of health syndromes commonly measured in livestock production. This also concurs with recent trends in syndromic surveillance, mining of big data, and domestic animal toxicology.

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