EDITORIAL

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EFSA is working to advance the environmental risk assessment of genetically modified crops to better protect butterflies and moths

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The cultivation of genetically modified (GM) crops is subject to a prospective risk assessment and regulatory approval in most jurisdictions worldwide. In the risk analysis process, the role of risk assessors such as the European Food Safety Authority (EFSA) and its Panel on Genetically Modified Organisms (GMO Panel) is to assess any risk that the cultivation of a GM crop may pose to human and animal health and the environment, and recommend options for risk mitigation, if necessary. Decisions to approve the cultivation of a GM crop are taken by risk managers, i.e. the European Commission and Member States of the European Union (EU).

Risk to butterflies and moths

The EFSA GMO Panel has performed pan-European environmental risk assessments (ERAs) for the cultivation of several GM maize events that express an insecticidal protein from the biocontrol agent

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Bacillus thuringiensis (*Bt*) (i.e. Cry1Ab for MON810 and Bt11, and Cry1F for 1507).[1,2,3] The *Bt*-protein expressed in maize MON810/Bt11 and 1507 confers protection against lepidopteran maize insect pests (i.e. target organisms) such as the European corn borer (*Ostrinia nubilalis*) and the Mediterranean corn borer (*Sesamia nonagrioides*). However, the potential exposure of non-target (NT) butterflies and moths (Lepidoptera) through the ingestion of harmful amounts of *Bt*-maize pollen deposited on their host plants in or near *Bt*-maize fields has been identified as a concern associated with the cultivation of lepidopteran-active *Bt*-maize.

Modelling

Quantifying the risk to NT Lepidoptera arising from the ingestion of *Bt*-maize pollen at pan-European level can be challenging. This is primarily due to the heterogeneity and complexity of receiving environments, which may cover different scenarios in terms of pedo-climatic zones, agricultural systems, landscape structures, exposure to *Bt*-maize pollen and NT lepidopteran species (including their habitat use, body size and larval susceptibility to the *Bt*-protein) (Lang et al., 2020; Arpaia, 2021).[4,5] Therefore, modelling approaches are followed to predict outcomes (i.e. risks to NT Lepidoptera) from data and understand how complex systems work (Topping et al., 2020).[6] Models can provide a valuable contribution to the weight of scientific evidence considered in prospective ERAs and complement the need to gather additional data in relevant receiving environments.

Risk characterisation

Since 2009, the risk to NT Lepidoptera due to ingestion of *Bt*-maize pollen has been quantified by the EFSA GMO Panel through estimates of larval mortality generated by the models developed by Perry et al. (2010, 2012;[7,8] see also Perry et al. (2011, 2013).[9,10] These models integrate a mortality–dose relationship based on laboratory bioassays, with a dose–distance relationship from a maize crop based on field measurements. Mortality is estimated within a *Bt*-maize field and at various distances from it. Perry et al. (2012) extended the initial model to: (1) differentiate between small-scale, local mortality and global mortality allowing for exposure effects at larger scales; (2) account for the between-species variability in lepidopteran susceptibility to *Bt*-proteins; (3) assess the efficacy of various risk mitigation measures; and (4) study different host plant densities in crops and field margins.

In its 2009 Scientific Opinion,[11] the EFSA GMO Panel used the Perry et al. (2010) model to estimate the risk to NT Lepidoptera following ingestion of maize MON810 pollen. The model generated estimates for three widespread European species (*Vanessa atalanta*, *Inachis io* and *Plutella xylostella*) in 11 representative maize ecosystems in four European countries. Based on the model predictions, the GMO Panel recommended risk managers to mitigate the possible exposure of NT Lepidoptera to maize MON810 pollen. Subsequently, the GMO Panel recalibrated the aforementioned model to simulate and assess potential adverse effects resulting from the exposure of NT Lepidoptera to maize 1507 pollen under representative EU cultivation conditions.[12] A similar exercise was carried out for maize MON810/Bt11.[13] In the 2015 Scientific Opinion of the GMO Panel,[14] calculations were further refined to provide updated quantitative estimates of exposure levels, accounting for new information on maize pollen deposition over long distances.

EFSA procurement

The EFSA GMO Panel acknowledged several types of uncertainties including: (1) uncertainties pertaining to the structure of the Perry et al. (2010, 2012) models, mostly caused by the lack of data

1 https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1149
2 https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2005.213
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13 http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2478/epdf
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from bioassays estimating the susceptibility of a wider range of 'real' NT Lepidoptera for most assessed *Bt*-maize events; and (2) uncertainties contributing to the variability in exposure of NT Lepidoptera to *Bt*-maize pollen.[14] Moreover, none of the models that have been developed for assessing risks associated with the cultivation of lepidopteran-active *Bt*-maize on NT Lepidoptera at that time (e.g. Holst et al., 2013; Lang et al., 2015; Fahse et al., 2018)[15,16,17] did explicitly take the landscape structure and crop management into account. Consequently, uncertainty remained about the actual risk to NT Lepidoptera at the landscape scale and risk mitigation measures to recommend. To address these uncertainties, EFSA outsourced the development of a spatially and temporally explicit model that would account for landscape structure, crop management, sublethal effects and weather.

The first spatially explicit model (*briskaR*) that estimated NT Lepidoptera mortality more realistically at both local/individual level and landscape scale and assessed the effectiveness of risk mitigation measures, was developed by Leclerc et al. (2018)[18] (see also the EU-FP7-research project AMIGA; Walker et al., 2019; Baudrot et al., 2021a).[19,20,21] As part of the EFSA procurement, Baudrot et al. (2021b)[22] extended the *briskaR* model to integrate: (1) a wider range of possible maize pollen dispersal curves; (2) the variability of exposure to *Bt*-maize pollen over time through toxicokinetic–toxicodynamic models; (3) sublethal effects of *Bt*-proteins on the reproduction and development of NT Lepidoptera; and (4) multiannual and cumulative effects of chronic exposure.

In addition, Baudrot et al. (2021b) conducted a sensitivity analysis and expert knowledge elicitations (EKE) on identified sources of uncertainty, ran the model using real-world case studies, and developed a user-friendly model interface, which are briefly described below.

- ***EKE:*** Renowned experts in the field[23] estimated distributions and uncertainties of the most sensitive parameters (for which few data are available) of the model at an EKE workshop, covering pollen deposition, the slope of dose–response mortality, sublethal effects and the interaction with environmental stressors (such as the microsporidian parasite *Nosema*).
- ***Global sensitivity analysis:*** Key factors that may affect mortality of NT lepidopteran larvae were addressed in a global sensitivity analysis. This analysis revealed that the variability of landscape-related parameters (such as spatial crop aggregation, distance from *Bt*-maize fields, pollen dispersal and deposition, exposure patterns) affected larval mortality more than the variability in larval susceptibility to the *Bt*-protein between individuals (as typically tested and determined in laboratory bioassays).
- ***Model implementation:*** Two real-world case studies (i.e. Catalonia (North-West Spain) and Baden-Wurttemberg (South-West Germany)) were used to run the model under contrasting environmental conditions, and identify key factors that adversely affect larvae of *Papilio machaon*. This assessment confirmed the effect of landscape patterns and crop management practices at a local level.
- ***User-friendly interface:*** A user-friendly model interface (allowing users to perform case-specific assessments) was created to facilitate model uptake and use by risk assessors and risk managers, and thus inform regulatory decision-making.

In the light of the 2018 EFSA Scientific Committee guidance on uncertainty analysis in scientific assessments,[24] an uncertainty analysis of the *briskaR* model and some of its parameters has been conducted and will be published in the first half of 2021.

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[15] https://www.sciencedirect.com/science/article/abs/pii/S0304380012005315
[16] http://www.sciencedirect.com/science/article/pii/S0006320715301300
[17] https://www.sciencedirect.com/science/article/pii/S0304380018300152
[18] https://www.sciencedirect.com/science/article/pii/S0048969717333879
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[21] https://www.sciencedirect.com/science/article/pii/S014765132031054X
[22] https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/sp.efsa.2021.EN-6443
[23] Salvatore Arpaia, Ludovit Cagan, Abigail Colson (EKE facilitator), Gema P Farinós, Andy Hart (EKE facilitator), Helen Hesketh, Niels Holst, Andreas Lang, Marina S Lee, Antoine Messéan, Mylène Ogliastro, Mathias Otto, Aislinn Pearson, Joe N Perry, Jörg Römbke and Constanti Stefanescu.
[24] https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5123

Outlook

Baudrot et al. (2021b) illustrated how modelling approaches such as *briskaR* can inform prospective ERAs for NT Lepidoptera by providing estimates of mortality at both local/individual level and landscape scale for a wide range of different receiving environments across the EU. Such estimates would enable risk managers to implement possible risk mitigation measures that are adapted to the relevant receiving environments and specific protection goals (including for regionally protected NT lepidopteran species) under their jurisdiction.

However, additional efforts are required to deliver more robust and realistic risk estimates, reduce uncertainties, and transition to more holistic ERAs for butterflies and moths. Such efforts would need to focus on optimising the integration of modelling, empirical data and monitoring (e.g. Streissl et al., 2018; Lee et al., 2021; More et al., 2021),[25,26,27] enabling a more dynamic, iterative interplay between risk assessment and risk management (Topping et al., 2020).

- ***Modelling:*** The extended *briskaR* model does not consider the various ecological factors (including environmental stressors) that may affect the population dynamics of NT Lepidoptera. Since such factors may influence potential adverse effects caused by *Bt*-maize pollen, their integration may contribute to the further improvement of current modelling capabilities. This integration will be facilitated by the modularity and the open-source feature of the extended *briskaR* model.
- ***Empirical data:*** Current and new empirical data will inform the revision of model components and development of supplementary ones. To fine tune model predictions, more data are needed on: (1) the species-specific susceptibility of NT lepidopteran larvae to *Bt*-proteins for a broader range of potentially exposed NT lepidopteran species; (2) the occurrence and distribution of host plants in and around maize fields; (3) the deposition and fate of maize pollen on the leaves of specific host plants; and (4) the additive or synergistic effects caused by exposure to additional environmental stressors.
- ***Monitoring:*** The integration of monitoring approaches (such as post-market environmental monitoring which is mandatory for the cultivation of lepidopteran-active *Bt*-maize in the EU) is required to cross-validate the outcomes of prospective ERAs for NT Lepidoptera and assess the effectiveness of risk mitigation measures. Thereby, monitoring would serve as an early warning check of divergency from expected results and hence provide feedback on the effectiveness of the model. While monitoring would provide new input data to the model, such data would also be required to support model validation and its calibration for regulatory purposes.

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Abbreviations

Bt *Bacillus thuringiensis*
EKE expert knowledge elicitation
ERA environmental risk assessment
GM genetically modified
GMO genetically modified organism
NT non-target