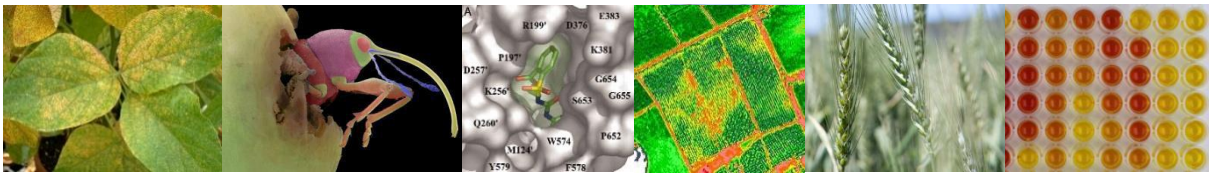
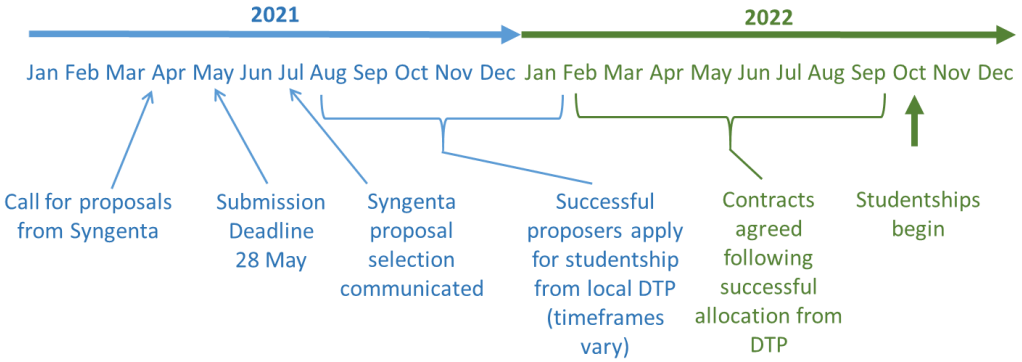


Syngenta Call for PhD CASE Proposals

2022 Student Intake.

The Syngenta Bioscience, Research Biology, Product Safety & Research Chemistry departments invite PhD CASE proposals in any of the science areas below. The deadline for submission is 28 May 2021, we will aim to communicate those we intend to support by end July. Successful proposers should then seek approval for a studentship from their local BBSRC DTP (or equivalent) allocation, if approved the studentship will proceed as a CASE studentship. Note that Syngenta does not have BBSRC studentships of its own, rather we will convert DTP studentships to CASE studentships (Non-BBSRC studentships which can also be converted to CASE under the same terms are suitable too). Students benefit from £10,000 p.a. uplift in funding (preferably divided between stipend (40%) and project costs (60%)), they are invited to our annual research collaborations conference at our Jealott's Hill Research Centre in Berkshire and benefit from a placement here. Students also receive additional supervision and, on a case-by-case basis, access to equipment and other Syngenta resources appropriate to their project. Proposals should be submitted using the online form linked below by **28 May 2021**

The process is summarised below:



We have identified 53 studentship topics which fall into 7 categories: 1) Agricultural Pests, Weeds and Pathogens; 2) Chemistry-Biology Interface; 3) Crop Biology; 4) Environmental Safety and Impact; 5) Human Safety and Toxicology; 6) Methods; 7) Modelling . Take care to correctly identify the category and topic your proposal addresses in the drop-down menus on the proposal form linked below and in subsequent footers. We look forward to seeing your proposals.

PROPOSAL FORM

The form is self-explanatory, any questions to anthony.flemming@syngenta.com

syngenta

Research Categories and Topics

Agricultural pests, weeds and pathogens	Chemistry-Biology Interface	Crop Biology	Environmental Safety and Impact	Human safety and toxicology	Methods	Modelling

1	Understanding the mechanisms of herbicide synergy
2	Understanding seedbank dynamics using simulated seedbanks
3	Alternative control options for soil pest insects
4	Invertebrate nervous and neuromuscular systems
5	Insecticide Resistance
6	Toxicokinetics in invertebrate pests
7	Fundamental understanding of thiamine pyrophosphate-dependent enzymes from plants
8	Understanding herbicide selectivity in Soybean
9	Xenobiotic detoxification in fungi and oomycetes
10	Fungal and oomycete plant pathogens: essential processes for life, infection, in planta growth, and plant-pathogen interactions.
11	Development of tools for fungal and oomycete plant pathogens
12	Fungicide resistance risk prediction and monitoring
13	The Structural Biology of Pathogen Resistance
14	Chemistry-led projects on Biology
15	Plant health: Nutrient Use Efficiency
16	Relevance of laboratory E Fate study conditions to "real world" conditions.
17	Improving prediction of wildlife exposure through the use of new technologies
18	Quantifying the impacts of farming practices on soil health indicators and their societal and economic benefits
19	How do we determine realistic worst case environmental persistence values globally under actual use conditions
20	Integrating (bio)availability into the European Plant Protection Products (PPP) risk assessment framework
21	Applying meta-analysis techniques to published environmental monitoring studies and data.
22	Non-first order degradation of pesticides in soil in laboratory and field studies.
23	Stereoisomer-specific fate of pesticides in environmental compartments and EU risk assessment
24	Structure-activity-relationship development for atmospheric photooxidation of volatile and semi-volatile compounds relevant to pesticide chemical space
25	Measuring and modelling biodegradability of small molecules* in soil
26	Understanding physiological modes of action across species and chemicals
27	Differential biotransformation (metabolism) in invertebrates
28	Evaluation of adaptive vs adverse responses
29	Stereoisomerism in relation to human exposure to pesticides
30	Fish metabolism and feeding studies
31	Allergic reactions to pesticides
32	Precision agriculture, disruptive technologies and exposure to pesticides
33	Dermal absorption of pesticides
34	Dietary metabolism and ADME in relation to human health
35	Modification of in vitro endocrine activity screens to include simulated metabolism
36	Exploring The Utility Of Transcriptomics Data In Toxicology
37	Toxicity screenings using Organ-On-A-Chip in vitro models
38	Exploring Methods For Predicting Future Regulatory Topics of Concern For Crop Protection Active Ingredients Registration and Reregistration
39	Bioaccessibility and bioavailability of pesticide residues
40	Methodologies to reduce animal testing
41	In planta detection of disease
42	Image analysis in biology
43	Protein structure-function relationships
44	Synthetic biology
45	Developing microfluidic platforms to enable high-throughput screening of enzymes and cells from fungi, insects, plants and algae
46	Mass spectrometry imaging of Xenobiotics
47	Chemical Proteomics
48	In vitro metabolomics
49	Analytical Methods for complex biological matrices
50	Automated measurement of growth and reproduction
51	Development of ecological models for chemical risk assessment
52	Development of toxicokinetic-toxicodynamic models for chemical risk assessment
53	Applicability of parameter free models for toxicokinetics

Each area is described in more detail in the following pages, with example papers for background or inspiration, and Syngenta contacts.

PROPOSAL FORM

Agricultural pests, weeds and pathogens

1. Understanding the mechanisms of herbicide synergy

Combinations of herbicides with diverse modes of action are often utilized in crop protection as a means to complete the spectrum of weeds controlled, or to manage populations of weeds which may exhibit resistance to one or more herbicidal mode of action. Only a subset of combinations exhibit synergy and only a smaller subset of those confer a synergistic effect that is of practical utility for weed control. Even for modes of action well known to exhibit synergy in combination, such as HPPD and PSII herbicides, the mode of action itself is insufficient to predict synergistic performance as different chemical sub-classes within the same mode of action can respond differently in combinations. A more detailed understanding of the fundamental mechanisms of herbicide synergy could allow prediction of synergistic combinations and guide structure-based design of new herbicidal molecules.

Contact: Melanie Watkins melanie.watkins@syngenta.com

2. Understanding seedbank dynamics using simulated seedbanks

Weed infestations pose a serious threat to the sustainable intensification of agriculture. Weeds compete with crops and have a massive impact on crop yields and quality. When weeds escape control, they produce large numbers of seeds that create persistent seedbanks increasing weed pressure in future years. In addition, persistent weed seedbanks act as a reservoir of genetically diverse biotypes, leading to herbicide resistance and complicating efforts to manage them. Climate change is predicted to increase the density of agricultural weed seedbanks. Weed populations are regulated by the dynamics of the seedbank, yet our understanding of weed seedbanks is limited and often simply anecdotal. We seek proposals to develop a 'model seedbank' using Alopecurus myosuroides (blackgrass, a key herbicide resistant grassweed in Europe) that can be used understand below-ground interactions within the soil seed bank. The key questions we seek to address are:

1. What is the interaction between factors such as soil health, microbial diversity, soil moisture and temperature and seed persistence?

2. How can we make future predictions about seedbank dynamics (eg. emergence timing, infestation level...) based on past data?

3. What factors can be manipulated to reduce seedbanks (number and persistence of seeds)?

Contact: Thomas Holloway Thomas.Holloway@syngenta.com & Gael Le Goupil gael.le_goupil@syngenta.com

3. Alternative control options for soil insects (entomopathogenic fungi, semiochemicals)

Syngenta is looking for alternative control concepts for the control of soil insects (e.g. wireworms) targeting specifically Europe. Currently chemical options are challenged in Europe and it is very questionable when and if at all a new soil insecticide could be registered.

A few alternative products are available (entomopathogenic fungi) but do not work sufficiently well and leave room for the development of a new concept.

We are working currently on the development of an alternative concept for the control of wireworms by using semiochemcials (push & pull) and would greatly benefit from external expertise and collaboration.

Contact: Benedikt Kurz benedikt.kurtz@syngenta.com

4. Invertebrate nervous and neuromuscular systems

These systems are the targets of many successful pesticides. Protein targets therein include: acetylcholine esterase, nicotinic acetylcholine receptor, GABA and glutamate gated chloride channel, voltage gated sodium channel, transient receptor potential channel (vaniloid), ryanodine receptor. We are interested in fundamental and applied research into these systems in invertebrates including pests, appropriate models or in vitro systems. Topics could include: pharmacological analysis of target proteins and associated methodologies; pharmacological characterisation of receptors, ion-channels and their associated proteins in the native state; understanding *in vivo* subunit composition and stoichiometry for multisubunit proteins; evolutionary differences in pharmacology among species, etc.

Example papers: Cash, F., S. W. Vernon, et al. (2016). "Central cholinergic synaptic vesicle loading obeys the set-point model in *Drosophila*." Journal of Neurophysiology 115(2): 843-850.

Contact: Jim Goodchild jim.goodchild@syngenta,com Fergus Earley fergus.earley@syngenta.com

5. Insecticide Resistance

Insecticide resistance is a major threat for sustainable crop production. In principle, resistance research covers evolutionary topics with two broad subjects: 1) elucidation of resistance mechanisms i.e. identifying the underlying cause of the phenotype and 2) studying the spatiotemporal nature of resistance i.e. how fast and how far does resistance spread throughout populations and landscapes. Topics may focus on one pillar or combine the two. Proposals may include studies aimed toward the discovery of resistance mechanisms through state of the art 'omics approaches, experimental evolution to improve resistance forecasting, pest migration, population genetics etc.

Example papers: Bass, C., et al. (2011). Mutation of a nicotinic acetylcholine receptor β subunit is associated with resistance to neonicotinoid insecticides in the aphid *Myzus persicae*. BMC Neuroscience, 12(1), 51. https://doi.org/10.1186/1471-2202-12-51

Contact: Christoph Zimmer christoph.zimmer@syngenta.com

6. Toxicokinetics in invertebrate pests

The success of a potent pesticide against its target organism(s) depends largely on its toxicokinetic profile. This can be seen as the capacity of the compound to penetrate into the individual, resist detoxification and excretion processes to a sufficient extent and arrive at its specific molecular target. In arthropods, the composition of the cuticle and the action of proteins related to detoxification and excretion are critical determinants of insecticide toxicokinetic, and therefore, its efficacy. We are interested in fundamental and applied research related to the absorption in agricultural pest invertebrates, particularly in the differential uptake between beneficiary (e.g., honeybees) and pest species. The penetration of a xenobiotic into an invertebrate conventionally takes two major routes, the cuticle and the gut. We would be particularly interested in developing high-throughput novel platforms to characterize the absorption of a range of different

xenobiotics (including insecticides). One example of such a method could be the CaCo2 system, used to study absorption in mammals. Other systems that may produce similar outputs addressing the absorption of xenobiotics would also be of interest.

Example papers: Balabanidou, V., Grigoraki, L. and Vontas, J., 2018. Insect cuticle: a critical determinant of insecticide resistance. Current opinion in insect science, 27, pp.68-74. Lea, T., 2015. Caco-2 cell line. The impact of food bioactives on health, pp.103-111.

Contact: Jacob Riveron (jacob.riveron_miranda@syngenta.com) & Joe Hawkins (joe.hawkins@syngenta.com)

7. Fundamental understanding of thiamine pyrophosphate-dependent enzymes from plants

Enzymes that use the cofactor thiamine pyrophosphate (TPP) have been exploited as successful herbicide targets, particularly acetolactate synthase (ALS), which is required for branched-chain amino acid biosynthesis. However its mechanism of inhibition is unusual and recent publications suggest that certain classes of these herbicides inactivate ALS by forming adducts or breaking the thiazolium ring of the TPP cofactor. Other TPP-dependent enzymes, such as transketolase, pyruvate dehydrogenase and 1-deoxy-D-xylulose-5-phosphate synthase, are less well characterised in plants and we would like to increase our fundamental understanding of their biochemical mechanisms and to characterise novel inhibitors.

Example papers: Lonhienne T., et al. (2018). Structural insights into the mechanism of inhibition of AHAS by herbicides. Proc Nat Acad Sci USA, 115, E1945-E1954.

Contact: Christian Noble christian.noble@syngenta.com

8. Understanding herbicide selectivity in Soybean

Selective herbicides are used to control weeds whilst leaving the crop uninjured. The basis of robust selectivity is most commonly conferred by differential metabolism, with higher rates of metabolism required in crops as compared to competing weeds. Cytochrome P450s and glutathione transferases (GSTs) are most frequently responsible for selectivity but both belong to large gene families which makes identification of individual herbicide-metabolising enzymes difficult. Of the major crops, soybean poses a particular challenge as unlike monocot crops such as wheat or maize, herbicide safeners are not used to enhance crop safety in dicot crops, although interestingly dicots appear to respond rapidly at the transcript level to safener application. We are interested in new approaches to identify and functional characterise soybean P450s and GSTs involved in herbicide metabolism, and to understand their expression profile with regard to growth stages, tissue types and response to external stimuli such as safeners or environmental conditions.

Example papers: Kato et al., (2020) Identification of a cytochrome P450 hydroxylase, CYP81E22, as a causative gene for the high sensitivity of soybean to herbicide bentazon. Theor Appl Genet 133: 2105-2115. Skipsey et al., (2011) Xenobiotic responsiveness of Arabidopsis thaliana to chemical series derived from a herbicide safener. J Biol Chem 286: 32268-32276.

Contact: Melissa Brazier-Hicks Melissa.Brazier-Hicks@syngenta.com

9. Xenobiotic detoxification in fungi and oomycetes

We are interested in projects that improve our understanding of the contribution of detoxifying mechanisms i.e. metabolic enzymes such as P450s or efflux transporters and their transcriptional regulation mechanisms, in limiting the activity of xenobiotics in plant pathogenic fungi and oomycetes. Also, novel tools or approaches for quantifying these effects efficiently or at scale would be of interest. The species of most interest are *Septoria tritici*, rust species and oomycetes such as *Phytophthor*a species, but capabilities in other species would be useful.

Example papers: Zwiers & De Waard, (2000) Fungal Genet Biol. 30 :115-25 Characterization of the ABC transporter genes MgAtr1 and MgAtr2 from the wheat pathogen *Mycosphaerella graminicola*; Shin et al. (2018) Toxins 2018, 10, 112; doi:10.3390/toxins10030112 Fungal Cytochrome P450s and the P450 Complement (CYPome) of *Fusarium graminearum*

Sang, H., Hulvey, J. P., Green, R., Xu, H., Im, J., Chang, T., & Jung, G. (2018). A Xenobiotic Detoxification Pathway through Transcriptional Regulation in Filamentous Fungi. mBio, 9(4), e00457-18. https://doi.org/10.1128/mBio.00457-18

Contact: Mike Csukai michael.csukai@syngenta.com, Andreas Mosbach andreas.mosbach@syngenta.com, George.Giannakopoulos@syngenta.com , ian.southworth@syngenta.com

10. Fungal and oomycete plant pathogens: essential processes for life, infection, in planta growth, and plant-pathogen interactions.

We are interested in gaining fundamental understanding and characterisation of essential pathways/proteins in plant pathogens. Of particular interest are *Septoria tritici*, rust species and oomycetes such as *Phytophthora* species. Topics would include characterisation of specific proteins involved in growth/infection, validation of their essentiality, potential to be "druggable" (i.e. inhibited by small molecules). Development of a method for studying the function/inhibition of the protein of interest would be highly desirable.

Example papers: Rancati, et al. (2018) Nature Reviews Genetics 19: 34–49

Contact: Mike Csukai michael.csukai@syngenta.com, Natalie Tomkins natalie.tomkins@syngenta.com

11. Development of tools for fungal and oomycete plant pathogens

There are many tools for studying genetic and chemical-genetic interactions in yeast, projects towards developing a similar tool set for plant pathogenic fungi and oomycetes would be highly desirable. Examples include the development of genetic tools enabling genome-wide explorations as well as the development of cell biology reporter systems covering main biological processes.

Example papers: Goranov & Madhani, Cold Spring Harb Perspect Med. (2015) 5: doi: 10.1101/cshperspect.a019596; Piotrowski et al., (2017) Nature Chem. Biol. 13: 982-993, Michel et al., (2017) eLife.doi 10.7554/elife.2370, Roy et al., (2018) Nature Biotech. doi: 10.1038/nbt.4137

Contact: Mike Csukai michael.csukai@syngenta.com, Gabriel Scalliet gabriel.scalliet@syngenta.com

12. Fungicide resistance risk prediction and monitoring

Resistance to fungicides is a global threat to food security. An early understanding of resistance risk towards novel fungicides is crucial for developing most sustainable solutions (comparing fungicides, doses, mixtures, spray programs). We are interested in projects aimed at developing experimental evolution systems towards the diagnosis of resistance risk in plant pathogens.

Fungicide resistance monitoring requires the detection of rare resistant genotypes among very large numbers of spores. We would be interested in collaborating on a project to develop and evaluate novel sampling methods (including both fixed spore traps and mobile devices, such as flying drones). The downstream automated analysis and reporting of epidemics of the pathogen and fungicide resistance evolution is another area of research we would be interested in proposals around.

Example papers: Agresti et al., (2010) PNAS doi: 10.1073/pnas.0910781107, Voordeckers and Verstrepen, (2015) Curr Opin Microbiol. doi: 10.1016/j.mib.2015.06.018, Gutiérrez-Alonso et al., (2017) Evolutionary Applications doi: 10.1111/eva.12511

Contact: Stefano Torriani stefano.torriani@syngenta.com, Gabriel Scalliet gabriel.scalliet@syngenta.com

13. The Structural Biology of Pathogen Resistance

Structural Biology unites the principles of molecular biology, biochemistry, and biophysics in the study of the molecular structure of biological macromolecules and how this relates to their function. We are interested in understanding how the central to mitochondrial bioenergetics bc1 membrane protein complex alters its structural dynamics upon binding to ligand molecules. Moreover, we wish to understand the impact of mutations on the protein structure and how they change the effects of ligand binding in order to understand potential target-based resistance mechanisms. We would welcome proposals relevant to modelling the structural aspects of membrane protein function and/or pesticide resistance; techniques for fermenting and isolating protein targets from plant pathogens for structure determination and new or improved approaches to biochemistry, X-ray crystallography and high-resolution cryo-electron microscopy (cryo-EM).

Contacts: Urvashi Thacker urvashi.thacker@syngenta.com Darren Baldock darren.baldock@syngenta.com Henryk Korza henryk.korza@syngenta.com Jenny Moore jenny.moore@syngenta.com

Chemical-Biology Interface

14. Chemistry-led projects on Biology

We are interested in chemistry-led proposals at the boundary of chemistry and biology that will help us to identify starting points for new approaches to the control of agrochemical pests, including diseases, insects and weeds. This includes the identification of novel biochemical modes of action and methods for the design of inhibitors and modulators of them, including new and improved biophysical methods, and chemical biology more generally. Proposals should ideally suit BBSRC remit rather than EPSRC (for which we will have a separate call later in the year). We are looking for ideas that, if successful, will represent a significant step forward; we are happy to support high risk proposals that have the potential to make a big impact. We are not interested in incremental improvements to methods that are already well-established.

Contact: Bill Whittingham william.whittingham@syngenta.com

Crop Biology

15. Plant health: Nutrient Use Efficiency

Fertiliser inputs to agricultural productions systems, although essential to maintain crop yields, are economically costly and have a negative impact on the environment. With increasing pressure to develop sustainable agricultural systems, there is an urgent need to develop solutions to reduce fertilisers inputs whilst increasing crop nutrient use efficiency. We are searching for proposals focusing in a chemical biology approach to identify small molecules, small RNAs, or peptides, that improve the uptake and utilisation of fertilisers by crops. The applicants, with previous knowledge in crop nutrition, may focus on high throughput phenotyping strategies, big data analysis and, the capacity to elucidate the mode of action of selected promising molecules.

Contact: Zaida María Andrés González Zaida_maria.andres_gonzalez@syngenta.com

Environmental safety and impact

16. Relevance of laboratory E Fate study conditions to "real world" conditions: a) Exclusion of processes/conditions relevant to actual use of pesticides; b) Understanding microbial community structure impact on study outcomes; c) Environmental relevance of non-extracted residues

OECD Environmental Fate test guidelines are designed to investigate environmental process in isolation under strictly controlled conditions, very different from the field. Laboratory studies are not able to capture the complex interactions between processes, or the potential contributions of processes excluded by the requirements of the experimental procedure. Furthermore, the processing of the soil may lead to disturbances in the microbial community structure, affecting the degradation rates measured, particularly of those compounds degraded by specific soil microbes that may be particularly sensitive if to such disturbances. In addition, all regulatory studies result in formation of non-extracted residues (NER). Remobilization of such residues after an extended time periods is perceived as a hidden risk, which is not well understood.

Previous research has investigated the impact of using non-UV light to allow algal populations to contribute (either by direct metabolism or by indirect effects on the heterotrophic community), the rhizosphere effect, the impact of bi-directional water movement in soil and the impact of soil storage on community structure.

We are interested in proposals to develop new laboratory study designs that more accurately reflect the extent of microbial degradation under actual use conditions by incorporating more agricultural realism and the potential for remobilization of non-extracted residues.

Example papers:

Thomas KA, Hand LH (2011). "Assessing the potential for algae and macrophytes to degrade crop protection products in aquatic ecosystems." Environmental Toxicology and Chemistry 30(3): 622-631. http://dx.doi.org/10.1002/etc.412

Hand LH, Gougoulias C, Bramke I, Thomas KA, Oliver RG (2020). "Evaluation of the Rhizosphere Contribution to the Environmental Fate of the Herbicide Prometryn." Environmental Toxicology and Chemistry 39(2): 450-457. https://setac.onlinelibrary.wiley.com/doi/abs/10.1002/etc.4604

Hand LH, N. C., Kuet SF, Oliver RG, Harbourt C, El-Naggar EM (2015). "Quantifying soil surface photolysis under conditions simulating water movement in the field: a new laboratory test design." Environmental Toxicology and Chemistry 34(10): 2236-2243. http://dx.doi.org/10.1002/etc.3074

Pesaro, M., Nicollier G., et al. (2004). "Impact of soil drying-rewetting stress on microbial communities and activities and on degradation of two crop protection products." APPLIED AND ENVIRONMENTAL MICROBIOLOGY 70(5): 2577-2587. https://dx.doi.org/10.1128%2FAEM.70.5.2577-2587.2004

Nielsen et. al.. 2011, 62, 105–116. Soil biodiversity and carbon cycling: a review and synthesis of studies examining diversity–function relationships. European Journal of Soil Science. https://doi.org/10.1111/j.1365-2389.2010.01314.x

Contacts: Laurence Hand laurence.hand@syngenta.com and Samantha Marshall samantha.marshall@syngenta.com

17. Improving prediction of wildlife exposure through the use of new technologies

One of the most challenging areas of risk assessment in the terrestrial environment is quantifying the likely actual exposure of wildlife to pesticides through food. Currently for birds and mammals this is based on energetics and literature data on diet composition and for honeybees is based on energetics resulting in assumptions of 3-8 times bodyweight in nectar per day being consumed. For other species the data is extremely sparse and there is increasing interest in oral exposure of non-target arthropods, e.g. how many aphids do ladybirds consume per day, and other pollinators. eDNA has proven a possible technology for

measuring consumption of crop seeds by small mammals, can this or other technologies be used to answer similar questions across a wider range of scenarios, i.e. measure real exposure directly under field conditions?

Example papers: Wang P. et al., (2019) Environmental DNA: An Emerging Tool in Ecological Assessment, Bulletin of Environmental Contamination and Toxicology, 103, 651-656.

Contact: Helen Thompson helen.thompson@syngenta.com

18. Quantifying the impacts of farming practices on soil health indicators and their societal and economic benefits

With the ongoing pressures of climate change and degradation of croplands worldwide has come an awareness of the importance of soil health and management practices to sustainable farming. A healthy soil retains structural integrity under varying environmental conditions, water holding capacity and biodiversity, in addition to providing a large reservoir for carbon storage. Benefits include efficient fertilizer utilization, drainage and erosion control, nutrient cycling and greenhouse gas reduction. These benefits are broadly recognized but poorly quantified as yet; there is a clear need to relate tangible on-farm and environmental benefits to sustainable farming practices such as reduced tillage and the use of cover crops, incorporate these into net-zero carbon models, and properly incentivize best management techniques. Research projects that expedite progress toward these goals are encouraged.

For more background information, please visit the Soil Health Institute YouTube channel: https://www.youtube.com/channel/UCeBuJZT0GiS-iVxaPNfqkww

Contact: Jeff Perine jeff.perine@syngenta.com

19. How do we determine realistic worst case environmental persistence values globally under actual use conditions

Concern over the persistence of compounds in soil is growing globally. Terrestrial Field Soil Dissipation studies (TFDs) have traditionally been used to refine laboratory derived endpoints to provide a more realistic assessment of persistence. These studies provide more realistic data because they provide an integrated degradation rate from many processes acting simultaneously. However, test systems for measuring the degradation of chemicals in field soils are, by their nature, a compromise between what is required to generate usable analytical data and agronomic realism. In the EU concerns have been raised around the use of field studies using bare plots to refine modelled exposure values. This is because the degradation rate determined in field studies includes contributions from processes that take place on the surface of the soil that will cease once the compound moves down the soil profile. To meet the needs of the FOCUS models for soil degradation data without the contribution of surface processes, these test systems have been altered further by covering the plots with sand. The resulting test system design is highly artificial. It lacks the presence of growing plants. It is maintained in darkness and has reduced air flow, temperature, and moisture fluctuations. In combination these factors are likely to reduce the degradation rates of many chemicals nevertheless these data are being used by authorities as an indication of “persistence”. The aim of this theme is to develop the evidence base to support the development of an integrated experimental and modelling approach to provide realistic worst case estimates of persistence across the global range of agro-climatic conditions.

Contact: Robin Oliver robin.oliver@syngenta.com

20. Integrating (bio)availability into the PPP risk assessment framework

European Plant Protection Products Regulations and related guidance documents do not currently take bioavailability into account in the risk assessment framework. Consequently, there is the risk of misalignment in the integration of exposure predictions and effects measurements. Furthermore the failure to consider availability leads to inconsistencies in the assessment of the potential risks presented by molecules that are persistent in soil. This is because there is currently no discrimination between molecules that are persistent because they are unavailable (hence unlikely to be taken up by non-target organisms or to leach) and those that are persistent due to chemical stability (which may be taken up or leach). The aim of this theme is to identify key issues in the PPP risk assessment paradigm where the utilisation of existing empirical or predictive assessments of (bio)availability would reduce uncertainty.

Contact: Robin Oliver robin.oliver@syngenta.com

21. Applying meta-analysis techniques to published environmental monitoring studies and data: Seeking insights for the sustainable safe use of current pesticides and the design of safer future alternatives

A comprehensive meta-analysis of published environmental measurement studies, at regional or global scales, could provide insight into the drivers of environmental exposure and potential impacts. For example, historical trends in the concentrations of legacy and current-use pesticides, considering the evolution of land usage, could help to understand areas of focus for optimising the sustainable use of current pesticides and, potentially, to design safer plant protection products, and their application techniques, in the future. Whilst a number of meta-analysis studies have been conducted for surface waters (see references below), in comparison there is a paucity of similar analysis and interpretation of pesticide-in-soil and pesticide-in-air measurement data.

Example papers:

S. Stehle and R. Schulz, PNAS (2015), Agricultural insecticides threaten surface waters at the global scale, Vol. 112, pp. 5750-5755

S. Stehle, S, Bub and R. Schulz (2018), Compilation and analysis of global surface water concentrations for individual insecticide compounds, Science of the Total Environment, Vol. 639, pp. 516-525

J.-Z. Wang H.-Z. Li and J. You (2012), Distribution and toxicity of current-use pesticides in sediment of a lake receiving waters from areas in transition to urbanization, Environmental Pollution, Vol. 161, pp. 128-133

J. Wolfram et al. (2019), Insecticide risk in US water: drivers and spatiotemporal modelling, Environmental Science and Technology, Vol. 53, pp. 12071-12080

Contact: Dave Johnson dave.johnson@syngenta.com

22. Non-first order degradation of pesticides in soil in laboratory and field studies: what are the principal causes and implications for environmental safety and the assessment of environmental safety in regulatory contexts?

Significant departure from non-simple-first-order chemical kinetic behaviour is frequently observed in standard laboratory studies of pesticide degradation in soil. Such behaviour is also often seen in field-scale chemical-dissipation studies. Reasons for, for example, biphasic degradation behaviour could be manifold and related to properties of the chemical, the soil environment, or both. Regulatory pesticide databases are a potentially a rich source of data to provide the basis for a holistic review cases where first order behaviour and non-first-order are observed. An analysis of such data may allow questions regarding degradation mechanisms, soil effects, molecule-specific effects to be looked at, in relation to the overall behaviour of soil-applied chemical over short, intermediate and longer timeframes.

Contact: Dave Johnson dave.johnson@syngenta.com

23. Stereoisomer-specific fate of pesticides in environmental compartments and EU risk assessment: putting flesh on the bones of the EFSA guidance, for 'reasonable worst-case' vs. 'unrealistic worst-case' environmental risk assessment

In principle, the environmental risk of a chemical plant protection product could be determined by the toxicological/ecotoxicological and environmental-fate behaviour of its constituent stereoisomeric forms. This is the basis of the 2019 EFSA guidance [1]. For dietary risk assessment it is clear that the consumer could be exposed to the pesticide residues (and their stereoisomer composition) at the time of harvest of the crop. For non-target organisms, however, potential exposure to residues does not in such discrete events or with such defined timing(s). Realistic/reasonable representations of the latter are required in order for environmental risk assessments to be conducted in a manner that allows risk assessments to be refined on the basis – i.e., appropriate interpretation – of environmental-fate data. Overly conservative approaches could needlessly lead to the conduct of additional invertebrate and vertebrate (eco)toxicity testing to characterise stereoisomer-specific toxicity. Approaches for the interpretation of fate data – and their use in defining environmental risk assessments – would greatly benefit from ideation, development and testing.

Example paper: Guidance of EFSA on risk assessments for active substances of plant protection products that have stereoisomers as components or impurities and for transformation products of active substances that may have stereoisomers, EFSA Journal 2019;17(8):5804.

Contact: Dave Johnson dave.johnson@syngenta.com

24. Structure-activity-relationship development for atmospheric photooxidation of volatile and semi-volatile compounds relevant to pesticide chemical space

Currently, the vast majority of atmospheric lifetimes – and, hence, transport potential – of active substances of plant protection products are based on structure-activity-relationship (SAR) estimates of reaction rate. The SAR developed by Roger Atkinson (considering gas-phase reactivity towards OH radicals, O3 molecules and NO3 radicals) is essentially based upon the principles of group additivity. Structural elements common within different 'families' of chemical pesticides are not necessarily well represented within the training data set that was used to define rules of the Atkinson SAR. Atmospheric reactivity, and lifetime, estimates would greatly benefit from alternative approaches or additional data generation to 'tune' traditional SAR approaches to the agrochemical 'molecular space'.

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25. Measuring and modelling biodegradability of small molecules* in soil

Soil, either as a habitat for microorganisms or a sorbent for small molecules* such as pesticides, is highly heterogeneous both in respect of the microscale physical structure and chemical composition. Macroscopically, when a pesticide is applied to soil, it is generally described by distribution between the solid, water and air phases, with the phase distribution parameterized as Kd and KH. However, on the microscopic scale, the 3-dimentional soil porous medium is structured in form of aggregates where a multitude of microenvironments is created within the intra- and inter-aggregate pore space and surfaces. Intra-aggregate pores can be many orders of magnitude smaller than inter-aggregate pores. Presence of water in the soil pore system is fragmented under unsaturated conditions, often in patches of thin film of moisture along the surfaces of soil particles, thus limiting microbial mobility. For a chemical coming into contact with soil, driven by chemical concentration gradients, some of the molecules diffuse into the micro- and nanopores, and become isolated and less accessible, leading to reduced chemical availability to microbial degradation.

Migration of the molecules from the isolated sites back to the soil porewater is rate limiting, as compared to the molecules sorbed at the soil-water interface. A clear understanding of the interactions among chemical, soil, and microorganisms and the influence of plant growth will enable rational chemical design to optimise availability for biological performance and reduce exposure to the environment. Given the general understanding of these interactions, we are interested in methodologies to measure and quantify:

1. Biodegradability in the soil bio-accessible zone (pore water and soil-water interfaces)
2. How plant uptake activates/promotes chemical (and microbial) migration to rhizosphere for enhanced degradation/metabolism
3. Relationship of microbial degradation with sorption – mechanisms that cause slower or faster metabolism by sorption for different compounds
4. Methods to measure and quantify bioavailability
5. Studies to elucidate soil surface catalytic role in biodegradation (e.g., clay colloids, humic/fulvic acids etc.).
6. Modelling tools based on mechanistic understanding of interactions among the compound(s) of interest, soil, plant and microorganisms
7. How can this understanding help in differentiating between chemicals of different structures and properties?

*Small molecules definition: A small molecule is a low molecular weight organic compound, typically involved in a biological process as a substrate or product. Metabolomics usually studies small molecules within a mass range of 50 – 1500 daltons (Da). It includes drugs, metabolites and agrochemicals (modified from European Bioinformatic Institute).

Example papers: Alexander, M. Aging, bioavailability, and overestimation of risk from environmental pollutants Environ. Sci. Technol. Vol. 34, No. 20, 2000. Chen, W., A Laabs, RS Kookana, and WC Koskinen. Coupled Sorption and Degradation Kinetics and Non-First Order Behavior. ACS Symposium Series; American Chemical Society: Washington, DC, 2014. Ortega-Calvo, J. J., Harmsen, J., Parsons, J. R., Semple, K. T., Aitken, M. D., Ajao, C., ... & Peijnenburg, W. J. (2015). From bioavailability science to regulation of organic chemicals. Environ. Sci. Technol. 2015, 49, 17, 10255. Schwarzenbach, René P., et al. Environmental Organic Chemistry, John Wiley & Sons, Incorporated, 2016.

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26. Understanding physiological modes of action across species and chemicals

Predictive ecotoxicology would enable risk assessors to project the impact of untested chemicals on environmental organisms, yet we are currently not very proficient at this. Poor knowledge on physiological modes of action (how a chemical affects the energy allocation in an organism), and how they vary across species and toxicants, is a major knowledge gap. The key to advancing predictive ecotoxicology is the systematic, rigorous characterization of physiological modes of action across biological species. The aim of this proposed research project is to characterise physiological modes of action across different biological species. The research involved will be a combination of laboratory experiments and bioenergetics modelling, i.e. Dynamic Energy Budget (DEB) modelling. This research aims to populate the matrix of species and toxicants with sufficient physiological mode of action data to enable identification of patterns, and from those patterns inference of general rules, theory and models. This would involve laboratory experiments with a choice of invertebrate species as well as ecological (DEBtox) modelling.

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27. Differential biotransformation (metabolism) in invertebrates

The ability to biotransform and detoxify man-made organic chemicals is a key ecotoxicological process because it can greatly affect the biologically effective dose. Very little is known about biotransformation pathways and rates and how they differ across biological species. The aim of this project is to measure and model the toxicokinetics of selected chemicals in different invertebrate species (e.g. aquatic or terrestrial

macroinvertebrates). The research would require access to high resolution mass spectrometry facilities and expertise as well as experimental facilities for toxicokinetic experiments.

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Human safety and toxicology

28. Evaluation of adaptive vs adverse responses

As we seek to evaluate human toxicity risks earlier when inventing new Crop Protection molecules, several new approaches use in vitro assays to determine a point of departure assays to for safety assessment. This "POD" can be described as the tipping point between adaptive and adverse responses where the cell is in its normal, safe state, if the amount of damage is less than background. Once damage exceeds the background level, stress pathway activation occurs to manage the insult, an adaptive response. In this new state of adaption, the cell may be reversibly vulnerable to an additional insult, which, while normally be innocuous, would be capable of producing an adverse effect on the cell. An adverse response results from overwhelming the functional reserve of the cell to protect itself with stress pathway activation, increasing amounts of damage, and spread of stress pathway activation as multiple subcellular systems incur increasing damage. The tipping point is identified as the point of irreversible change when a return to normal homeostasis is no longer possible. Prior to reaching the tipping point, the cell can return to normal homeostasis if the stress pathway activation has been sufficient to repair the damage.

One of the challenges of using this approach is to determine what these thresholds are especially

How do we determine what is a normal response? To aid the translation of in vitro data for in vivo relevance we need to compare the adaptive capacity/homeostatic range for the same biomarkers in vivo.

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29. Stereoisomerism in relation to human exposure to pesticides

In 2019, the European Food Safety Authority (EFSA) published a guidance document outlining requirements for the conduct of risk assessment for pesticidal active substances, metabolites or impurities that contain stereoisomers in their composition. In order to minimise animal testing, best use of available information should be made. However, in truth little information exists on the relative toxicity of the different isomers to mammals and other non-target organisms and also the potential exposure to different isomeric ratios. Therefore, the guidance relies largely on uncertainty factors to allow for a potential shift in isomeric ratios. For non-racemic mixtures and compounds with multiple chiral centres, the uncertainty factors could be considerable. This first-tier approach applies to both human (dietary and non-dietary) and environmental risk assessment. Where the first tier is not satisfactory, further information on actual isomeric ratios in residues, or specific toxicity data on the individual isomers may be required. We are interested in proposals for projects to deliver a better understanding of the biotic and abiotic factors which influence interconversion, metabolism and degradation of stereoisomers and/or how stereoisomerism impacts human and environmental exposure. This includes exposure via different environmental compartments including soil, water and other media, for instance exposure to surface residues after foliar application of a pesticide. Improved understanding could allow a more informed approach to risk assessment in relation to stereochemistry.

EFSA guidance on stereoisomers: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5804

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30. Fish metabolism and feeding studies

The European regulation for plant protection products (Regulation (EU) No 283/2013) states that metabolism studies on fish may be required where the plant protection product is used in crops whose parts or products, also after processing, are fed to fish and where residues in feed may occur from the intended applications. Emerging guidance indicates that an assessment of metabolism is required only for active substances with a log PO/W, ≥ 3.0 and the potential to afford residues > 0.1 mg/kg in the fish total diet (dry weight) based on the intended applications and subsequent residues in fish feed items. Fish dietary burden tools are currently in development but the design and conduct of the metabolism and corresponding feeding studies is not well defined. It is acknowledged that a significant number of studies are conducted in the Ecotoxicology arena to assess the effect of chemicals (e.g. veterinary medicines, agrochemicals) on fish. We are interested in proposals to understand more about the conduct of these studies and whether they could be used to inform the conduct and design of the fish metabolism/feeding studies. These could identify an opportunity to use studies which are currently conducted to support Ecotoxicological assessments, as surrogates for fish dietary burden assessments.

Example paper: Schlechtriem C, Bischof I, Atorf C, Bergendahl E, Seymour P, Whalley P. Development of a regulatory testing procedure to study the metabolism of pesticides in farmed fish. Pest Manag Sci. 2016;72(2):362-370. doi:10.1002/ps.4007

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31. Allergic reactions to pesticides

One of the key considerations for pesticides is whether they may cause allergic reactions in exposed populations, and how to assess the level of risk. Skin sensitisation studies for plant protection products have been carried out by murine local lymph node assay (LLNA), Guinea pig maximisation tests or Buehler tests. Where a plant protection product gives a positive result, typically the label will communicate this and adequate protective equipment should be specified for the operator handling the undiluted product. However, more recently, concerns have been raised regarding unprotected populations which may be exposed to dilutions of sensitising formulations, and there have been requirements for quantitative assessments of the risk involved. The determination of a threshold concentration for risk assessment can also be challenging in the absence of preferred study data from the LLNA. Another consideration is the reduction of animal testing, for which there has been increasing interest in developing in vitro and in silico tools for predicting skin sensitisation. Could these tools help identify a suitable threshold for quantitative risk assessment?

Research in this area could help to address this situation and allow more robust assessment of the risk of sensitisation for all exposed populations.

Example paper: D. A. Basketter. Skin sensitization: strategies for the assessment and management of risk

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32. Precision agriculture, disruptive technologies and exposure to pesticides

Interest in spatial and temporal precision application has been growing in recent times as we strive more and more to minimise pesticide inputs into agriculture. This has the potential benefits of reducing environmental impact and reducing financial outlay on agrochemicals for the farmer, making for a more sustainable future. However, there are also potential benefits for human health. Most human risk assessments are dependent on the amount of active substance used and technologies which reduce inputs should reduce exposure. Testing this hypothesis, developing the concept and looking to quantify the reduction in exposure would make for some potentially impactful research. Disruptive technologies like drone application and other unmanned systems may also influence human exposure, but comparatively little research seems to have been carried out

in this area. Research into exposure in relation to precision agriculture delivery systems which may be in academic development could be of particular interest.

Proposals related to this area could also offer opportunities for inter-disciplinary collaboration with different Syngenta functions.

Example papers: Precision agriculture and the future of farming in Europe (Scientific Foresight Study) European Parliamentary Research Service, Scientific Foresight Unit (STOA) PE 581.892

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33. Dermal absorption of pesticides

Assessment of the dermal absorption potential for pesticidal products is routinely conducted to support human risk assessments., typically following the fate of either the formulation concentrate or “end use” field dilutions when applied to human skin in vitro for an exposure period of 6-8hrs which mimics normal agronomic practice. The overall distribution of the applied dose is measured across a number of experimental compartments with the aim to account for 100% +/- 10% of the applied dose by the end of the study (24hrs in total). The compartments are:

- Donor chamber
- Skin wash
- Stratum corneum (tape strips)
- Epidermis/dermis
- Receptor fluid

Several aspects of dermal absorption remain relatively poorly understood. One such area isthe ultimate fate of material measured in in vitro beyond the 24h study duration. Clearly, dose material present in the receptor fluid during/at the end of the study can be considered absorbed. Conversely, it is also generally accepted that dose material present in the first two tape strips of the stratum corneum is unlikely to become bioavailable. The potential for dose material in the remaining stratum corneum and/or epidermis/dermis to become bioavailable beyond the 24 hour monitoring period remains a point of much discussion. The EFSA 2017 guidance document on dermal absorption deals with this uncertainty by the conservative addition of any skin bound residue to dose material found in receptor fluid to give an overall dermal absorption value. Question : In order to address this area of uncertainty, what additional experimental data could be generated to address the fate of skin bound residue and provide a realistic assessment of the dermal absorption potential of pesticidal products.

We would welcome proposals focusing on this and other issues relating to dermal absorption of pesticides.

EFSA guidance on dermal absorption: https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2017.4873

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34. Dietary metabolism and ADME in relation to human health

A number of areas are of interest to our Product Metabolism and Analytical Sciences platform which relate to dietary metabolism and ADME of pesticides. Broadly, these include:

In vitro methodologies to reduce animal testing. The US EPA has issued a directive to reduce animal studies by 30 percent by 2025 and eliminate them entirely by 2035. In the metabolism area, this would involve alternative approaches to livestock metabolism and ADME studies

Predictive exposure/effects models in mammals. Particular interests are in "Multi-layered" exposure models (target species versus environmental behaviour versus mammalian exposure) and the reduction of exposure-related uncertainty factors in risk assessments.

Dietary bioavailability. Examples of collaborative projects Syngenta has been involved with in this area are 'Understanding the Behaviour of Conjugated and Bound Residues : Impact on Human Risk Assessments' and 'In Vitro Bioaccessibility of Plant Associated Pesticide Residues.' Other research could work towards understanding the actual bioavailability aspect of pesticide residues, with the ultimate aim being the conduct of more realistic assessments for consumers. These would be based on what they are actually exposed to, which may be different (hypothesis is lower) than the inputs currently used based on our metabolism/residues database.

We would welcome any proposals based on these areas.

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35. Modification of in vitro endocrine activity screens to include simulated metabolism

Whilst in vitro screens represent valuable tools for the investigation of the endocrine activity of chemicals, all internationally recognized test guidelines for the conduct of these assays do not include provisions for the introduction of simulated metabolism (e.g. through incubation with the microsomal S9 fraction). As such, regulatory agencies often do not accept a negative response in such assays to have adequately assessed the potential for endocrine activity as the possibility of a metabolically activated toxicophore cannot be excluded. In such situations it is commonly expected that companies like Syngenta will "follow up" negative in vitro assays with higher tier vertebrate toxicity studies (e.g. the Hershberger assay or the uterotrophic assay) to confirm the absence of endocrine activity in a metabolically capable system.

To address this issue Syngenta is seeking proposals to understand the feasibility of modifications to the below OECD test guidelines to include simulated metabolism:

OECD Test Guideline 455 (Performance-Based Test Guideline for Stably Transfected Transactivation In Vitro Assays to Detect Estrogen Receptor Agonists and Antagonists)

OECD Test Guideline 458 (Stably Transfected Human Androgen Receptor Transcriptional Activation Assay for Detection of Androgenic Agonist and Antagonist Activity of Chemicals)

OECD Test Guideline 456 (H295R Steroidogenesis Assay)

Ideally proposed solutions will attempt to remain as closely aligned to the established OECD test guideline as possible to maximize regulatory acceptability

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36. Exploring The Utility Of Transcriptomics Data In Toxicology

The assessment of new crop protection chemicals for human safety is currently achieved using toxicity studies performed on vertebrate models as surrogates for humans. These studies are resource intensive, slow and are not fully representative of the human safety situation. Several proposed frameworks for next generation of toxicity assessments typically include, in an initial tier of analysis, some form of broad coverage assay that aims to identify any potential for off-target effects. This is usually suggested to use many cell lines and transcriptomics or other high content measurements [1]. We, and others, are curating lists of genes as compendia of "toxomes" that is the set of genes that if perturbed could act as molecular initiating events (MIEs) for a toxicity or serve as biomarkers of MIEs or their subsequent key events. These toxome compendia

are derived from bioinformatic analyses and public and Syngenta generated transcriptomic data. Before we can use these methods with confidence there are some critical questions to address:

i. How best to identify the cell lines to include in the panel? That is for a particular risk assessment problem (e.g. the toxome for DART, Cancer, General Repeat Dose Chronic toxicity) and available budget, how can we rationally select the best set of cell lines to provide the necessary degree of confidence that we haven't missed a potential target?

ii. How can we efficiently demonstrate that any specific individual or multiple protein-target perturbation from any given arbitrary gene set (i.e. a toxome compendium) will result in a detectable signal using in vitro transcriptomics using a genetic perturbation (e.g. CRISPR/Cas9)? And if we cannot, how can we identify the minimal affordable set of measurement types we need to include to be confident we haven't missed a critical perturbation?

iii. How can we efficiently identify small molecule model chemicals to test that any specific individual or multiple protein-target perturbation from any given arbitrary gene set (i.e. a toxome compendium or an in vivo toxicogenomic signature) will result in a detectable signal using transcriptomics using a chemical perturbation? And further can we identify that a small molecule perturbation is the result of a specific (set of) protein target perturbations?

Example paper: [1] Thomas et al. (2019) Toxicol Sci 169(2):317-332

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37. Toxicity screenings using Organ-On-A-Chip in vitro models

Pesticides have been extensively used throughout history to control pests and increase crop yield. Their main subclasses are generally divided based on their target pests, including insecticides, fungicides and herbicides. Although pesticides are beneficial to agricultural productivity, they often share the same molecular targets with non-target species. In order to reduce animal testing, we are interested in developing Organ-On-A-Chip in vitro models with focus on pesticides that impact:

i. The central nervous system (CNS) - directly either directly by targeting voltage-gated sodium, calcium and chloride channels or indirectly by causing oxidative stress or inhibiting enzymes, such as acetylcholinesterase. There is an increasing need to develop validated in vitro brain models that recapitulate the complex physiological microenvironment.

ii. The blood brain barrier(BBB) – although this is a highly selective barrier responsible for regulating the passage of nutrients as well as protecting the brain from toxins and xenobiotics, many chemicals can surpass the BBB reaching their targets within the mammalian brain.

iii. The immune system – can be compromised by many chemicals and current immunotoxicity guidance requires the use of labour-intensive animal models.

Developing Organ-On-A-Chip screening assays would be invaluable for prioritization of safe active ingredients, proposals in this area would be welcome.

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38. Exploring Methods For Predicting Future Regulatory Topics of Concern For Crop Protection Active Ingredients Registration and Reregistration

The regulatory approval process for the use of a new active ingredient for crop protection (CP) varies considerably by country and region due to the different crops grown, application methods for CP products, societal concerns and legal frameworks extant in each country. Nevertheless, it involves the integration of a

wide variety of data on the potential fate and effects of a chemical and the exposures that may result due to the proposed uses. This integration always occurs in a risk assessment to determine whether the proposed uses of an active ingredient (AI) are safe. In addition, some countries and regions also apply cut-off criteria to eliminate molecules with societally undesirable properties, regardless of whether the uses have been established as safe. Finally, as the science of toxicology and the societal acceptability of environmental chemicals evolves, the concerns evaluated by regulatory agencies also evolves. When coupled with the fact that the R&D process for the creation of a new CP active ingredient typically takes over 10 years, the regulatory evaluation criteria for a new AI is potentially different to the criteria used in the design and selection of that chemical.

Consequently, the ideal approach to "de-risk" projects during research and development would allow our teams to rapidly decide on whether and why a chemical had the potential to fail in this complex and uncertain process, including a prediction of the development of likely regulatory concerns to be addressed in that future assessment. This would allow us to focus resource on dealing with those critical issues through chemical design, or to refocus our limited resources to more promising projects. Therefore, we need to understand how we can better infer the potential and anticipated failure modes for our new active ingredient projects using all the available relevant and emerging data as it evolves through time.

Recently, Whaley et al [1] have highlighted the importance of systematic evidence mapping over a domain of knowledge as a tool to enable rapid chemical safety assessments. Tripodi et al [2] have shown how vector embeddings over a biological knowledge graph to provide mechanistic explanations of toxicogenomics data. And Myklebust et al [3] have produced the Toxicological Effect and Risk Assessment Knowledge Graph (TERA) for chemical effect prediction. Furthermore, Duan and Chiang [4] illustrate how a knowledge graph could be used to help predict the maturity of emerging technologies by location and time. Together these highlight the theoretical possibility that node or property embeddings derived from a knowledge graph of the holistic CP human and environmental safety risk assessment domain and their associated science, policy and societal discourse map may be useful to predict future and emerging regulatory issues and so provide more systematic and timely foresight of the evolution of regulatory practice. The feasibility of the creation of such a knowledge graph and the identification of appropriate methods of analysis needs further evaluation.

References:

[1] Whaley et al (2020) https://ehp.niehs.nih.gov/doi/10.1289/EHP6994

[2] Tripodi et al (2020) https://doi.org/10.1016/j.tiv.2020.104877

[3] Myklebust et al (2019) https://arxiv.org/pdf/1908.10128.pdf

[4] Duan and Chiang http://dx.doi.org/10.1145/3006386.3006388

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39. Bioaccessibility and bioavailability of pesticide residues

For pesticide registration an assessment is made on the safety of any residue remaining in the edible portion of the treated crop. This assessment does not typically consider the bioaccessibility and/or bioavailability of pesticide residues. It has been demonstrated that the proposed bioaccessible concentration can often be higher using the standard solvent extraction methods in metabolism and residue studies, than if synthetic gastrointestinal extractions are used.

Additionally, only a proportion of that bioaccessible residue may subsequently be bioavailable. Insufficient knowledge on bioaccessibility and bioavailability could therefore hamper an accurate risk assessment.

We are interested in proposals to develop new laboratory study designs that more accurately reflect bioaccessibility and/or bioavailability of pesticide residues in consumer relevant commodities.

Example Papers: Craggs M, Gibson GR, Whalley P, Collins CD (2020) "Bioaccessibility of Difenoconazole in Rice Following Industry Standard Processing and Preparation Procedures." J. Agric. Food Chem. 68 (37): 10167-10173. https://pubs.acs.org/doi/10.1021/acs.jafc.0c02648Benner J, Gledhill A, Chung Chun Lam C, Roberts K, Booth J, Crook S, Skidmore M (2007) "Conjugated Residue Behaviour: Impact on Human Health Assessment." DEFRA (Department for Environment Food and Rural Affairs), 2007, Final report, PS2510. http://randd.defra.gov.uk/Document.aspx?Document=PS2510_6773_FRP.docSkidmore MW, Benner JP, Chung Chun Lam C, Booth JD, Clark T, Gledhill AJ, Robert KJ, (2007) "Bioavailability of Common Conjugates and Bound Residues. Pesticide Chemistry: Crop Protection, Public Health, Environmental Safety, Ed. Hideo Ohkawa, Hisashi Miyagawa, Philip W. Lee, ISBN: 978-3-527-31663-2. https://onlinelibrary.wiley.com/doi/pdf/10.1002/9783527611249

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40. Methodologies to reduce animal testing

The EPA has made a commitment to move away from animal testing by; reducing its requests for, and funding of, mammal studies by 30 percent by 2025 and eliminating all mammal study requests and funding by 2035.

The potential impact of this in the metabolism area is the need to find new approach methods (NAMs) for the provision of data relating to absorption, distribution, metabolism and excretion in mammalian systems and also an understanding of the qualitative and quantitative metabolism in livestock.

We are interested in proposals to review existing methodologies and identify new methodologies that could enable the move to alternatives to animal testing.

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Methods

41. In planta detection of disease

Precision agriculture is becoming increasingly important, and because of this early and efficient non-destructive detection of fungal diseases in whole plant systems will be crucial. Zymoseptoria tritici is a long-sought target for in planta detection due to its extended latent, asymptomatic colonization of leaf material. Early in planta detection of Z. tritici would allow for effective, early stage disease management.

Tools such as Stimulated Raman spectroscopy (SRS) imaging offer an opportunity to enable the early detection and quantification of Z. tritici by detecting metabolic differences and diseased plant cells. These will allow for the discrimination between disease significant signatures and healthy or abiotically stressed leaf material.

We would welcome projects that look to further build upon tools such as SRS imaging, or other novel tools for the early detection of plant disease.

Example Paper: Farber, C., Mahnke, M., Sanchez, L. and Kurouski, D., 2019. Advanced spectroscopic techniques for plant disease diagnostics. A review. TrAC Trends in Analytical Chemistry, 118, pp.43-49.

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42. Image analysis in biology

We are interested in both image processing techniques and hardware to deliver new approaches in plant, insect, and cell phenotyping. This is driven by a need for rapid, accurate assessment of symptomology and mode of action. This could include deep learning or other machine learning approaches and collection & interpretation of hyperspectral/multispectral images. We would also be interested in novel assays or methodologies that would effectively enable image analysis. As the technology develops, we would like to explore potential applications of virtual and augmented reality to illustrate weed, pest and disease control.

Example Papers: Pound, M et al (2017). “Deep machine learning provides state-of-the-art performance in image-based plant phenotyping”. GigaScience, 6, 2017, 1–10

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43. Protein structure-function relationships

We are interested in research to develop novel assay methods or tools, or to integrate existing technologies in novel ways, that would enable structure-function analysis of proteins relevant to insecticide research. Such approaches would enable the functional or pharmacological consequences of protein sequence editing to be visualised. Of particular interest would be known or potential insecticide target proteins that are membrane-bound proteins and difficult to resolve structurally using x-ray crystallography or cryo-EM. Topics could include membrane protein expression, purification and reconstitution in artificial membranes, model lipid bilayers, high content microscopy, biosensor systems, amperometry etc.

Example papers: Omote H, Moriyama Y. Vesicular neurotransmitter transporters: an approach for studying transporters with purified proteins. Physiology (Bethesda). 2013 Jan;28(1):39-50. doi: 10.1152/physiol.00033.2012. PMID: 23280356.

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44. Synthetic biology

The identification, characterisation and engineering of biological systems for discovery, optimisation and production of molecules for crop protection. For many years, bacterial, fungal and plant systems have been shown to be prolific producers of natural products with desirable agrochemical properties. We are interested project to develop tools to facilitate research into the discovery and scaled-production of such compounds from a variety of biological systems, including cyanobacteria. Recent studies into cyanobacteria have unveiled their ability to produce a variety of natural products with promising herbicidal activity. We are interested in projects to explore the biochemical potential of cyanobacteria with the aim of identifying molecules with herbicidal activity and gaining an understanding of both the mechanisms of action and biosynthesis.

We are also looking for opportunities in the Biocatalysis space. Our primary interest is the derivatisation of natural product scaffolds using either single enzymes or enzymes in cascade. We are interested in projects that look to explore the range of in vitro transformations on natural product scaffolds, using innovative solutions for further development.

Example papers: Hodgson et al. (2019). “Identification of key enzymes responsible for protolimonoid biosynthesis in plants: Opening the door to azadirachtin production”. PNAS. 116 (34) 17096-17104 ; Williams, Szwalbe, et al. (2016). “Heterologous production of fungal maleidrides reveals the cryptic cyclization involved in their biosynthesis”. Angewandte Chemie (International ed.). 55. 10.1002

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45. Developing microfluidic platforms to enable high-throughput screening of enzymes and cells from fungi, insects, plants and algae

Microfluidics holds significant potential as an enabling technology for the implementation of ultra-high throughput, sustainable and cost-effective screening platforms. The ability to investigate questions of key interest to agrochemical development is often constrained by practical limitations on the number of cells or enzyme variants that can be analysed under different conditions. We are interested in collaborating with research groups experienced in the design of bespoke microfluidic systems in order to investigate how this technology can be applied to organisms and enzymes of interest to Syngenta. Examples of microfluidics applications we would like to explore include sorting of different cell populations, high throughput

phenotyping of mutagenized/wild type cells of different species, combinatorial drug studies and the screening of enzyme variant libraries in search of novel or optimized catalytic properties.

Example papers: Yu, Ziyi, C. R. Boehm, J. Hibberd, C. Abell, Jim Haseloff, S. J. Burgess and Ivan Reyna-Llorens. Droplet-based microfluidic analysis and screening of single plant cells. PLoS ONE 13 (2018); Beneyton, T., Wijaya, I., Postros, P. et al. High-throughput screening of filamentous fungi using nanoliter-range droplet-based microfluidics. Sci Rep 6, 27223 (2016); Haidas, D., Bachler, S., Köhler, M., Blank, L. M., Zenobi, R., & Dittrich, P. S. Microfluidic Platform for Multimodal Analysis of Enzyme Secretion in Nanoliter Droplet Arrays. Anal. Chem. 91(3), 2066–2073 (2019)

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46. Mass spectrometry imaging of Xenobiotics

We are interested in unlabelled techniques capable of imaging xenobiotic uptake, distribution and metabolism in both insects and foliar systems. We are particularly interested in mass spectrometry imaging techniques such as MALDI, DESI, SIMS and LAESI for the monitoring on crop protection chemicals in target systems. This can be a focus on improving sample preparation, data acquisition or data interpretation techniques for samples of insects (including bees) or plants (crops or weeds). We are interested in exploring the limitations and scope of these techniques with a view to better understanding and improving techniques to map the distribution of crop protection chemicals in insect and plant systems, as well as the possibility to detect in situ metabolism.

Example Papers: Bhandari et al “Metabolite localization by atmospheric pressure high-resolution scanning microprobe matrix-assisted laser desorption/ionization mass spectrometry imaging in whole-body sections and individual organs of the rove beetle Paederus riparius”. Anal Bioanal Chem (2015) 407:2189–2201. Link. Ohtsu et al “Development of a visualisation method for imidacloprid in Drosophila melanogaster via imaging mass spectrometry” Analytical Sciences (2018), 34, 992. Link.

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47. Chemical Proteomics

Knowledge of the molecular targets of commercialised agrochemical pesticides as well as those in the R&D pipeline is fundamental to understand a wide range of issues such as intrinsic potency, selectivity between one pest species and another, risk of resistance development as well as selectivity between target and non-target organisms. Chemical proteomic approaches have developed rapidly over recent years and we are interested in novel methodologies that could be applied to understand how our chemistries interact with biological systems, particularly key crop pest species. This fundamental knowledge on the mechanism of action will help drive the development of the next generation of effective and safe pesticides.

Example papers: Medina-Cleghorn, D. et al. (2015). “Mapping Proteome-Wide Targets of Environmental Chemicals Using Reactivity-Based Chemoproteomic Platforms”. Chemistry & Biology 22: 1394–1405. Ziegler, S. et al. (2013). “Target Identification for Small Bioactive Molecules: Finding the Needle in the Haystack”. Angew. Chem. Int. Ed. 52: 2744 – 2792

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48. In vitro metabolomics

In vitro metabolomics could provide useful insights into predicting the toxicological effects of pesticide candidate compounds on both target and off-target organisms and guide screening activities. We seek proposals aimed at identifying suitable in vitro models and the characterisation of their metabolic responses would be of interest as well as the exploration of in vivo to in vitro translation of known in vivo metabolic biomarkers.

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49. Analytical Methods for complex biological matrices

An ongoing analytical challenge is the ability to quantitatively and qualitatively analyse small molecules from complex biological matrices such as plant, livestock, soil and sediment extracts. Methodologies have evolved over the years utilising sample clean-up techniques and sophisticated instrumentation but the drive to achieve lower quantitation and detection limits and the need to identify increasingly lower levels of small polar metabolites means that this area continues to be problematic. Areas of interest include:

- Rapid, selective, transferable, trace level analytical methods in complex matrices.
- Quantification and clean-up of small, polar analytes which show poor selectivity by conventional techniques.
- Analysis of chiral molecules and mixtures of isomers in complex matrices.
- Accurate metabolite identification by mass spectroscopy e.g. strategies to identify positions of hydroxylation/substitution or confirm isomer conformation.

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50. Automated measurement of growth and reproduction

Organism growth curves and reproductive output are important biological characteristics. Current methods to measure growth and reproduction of the life cycle are often resource intensive because they involve many manual steps. This limits our understanding of species vulnerability to stress, including chemicals in the environment because measuring the impact of toxicants on growth and reproduction is key to assess environmental risks of chemicals. A step change in our ability to study the ecotoxicology of man-made substances can be achieved by improved, and partially automated, experimental methods to measure responses of invertebrates to chemical stress. The aim of this project is to develop high throughput, automated laboratory assays to measure growth curves and reproductive output over the life cycle of invertebrate species. This includes optimisation of experimental protocols and demonstration in case studies with toxicants.

Example paper: Duckworth, J., Jager, T., Ashauer, R., 2019. Automated, high-throughput measurement of size and growth curves of small organisms in well plates. Scientific Reports 9, 10.

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Modelling

51. Development of ecological models for chemical risk assessment

The risk that chemical pose to organisms in the environment depends on the species' life history, environmental boundary conditions and ecological interactions. The aim of this research is to develop ecological models that increase the environmental relevance and realism of chemical risk assessment compared to current methods. The research should include a strong component of model testing with field or laboratory data.

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52. Development of toxicokinetic-toxicodynamic models for chemical risk assessment

The risk that chemical pose to organisms in the environment depends strongly on environmental conditions and stressors in addition to chemicals. Current environmental risk assessment is based on standardised laboratory bioassays with constant exposure concentrations and at optimal food and temperature conditions. However, exposure to chemicals in the environment is time-variable, food availability varies and so does temperature. In theory, toxicokinetic-toxicodynamic (TKTD) models, such as Dynamic Energy Budget (DEB) models can account for these factors and extrapolate the results of laboratory assays to realistic environmental conditions. In practice, very few studies have tested the predictions of such models against real data (lab or field) and we know very little about how accurate and reliable these model predictions are. This research aims at developing DEB-TKTD models and testing their predictions against novel, bespoke experimental data. A wide range of terrestrial or aquatic invertebrate species would be of interest.

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53. Applicability of parameter free models for toxicokinetics

Network based models (e.g. petri nets) are increasingly being used in systems biology where kinetic parameters are unknown. Such approaches are particularly useful in such situations because they allow for statements about the biological network's dynamic behaviour, without the need to know the kinetic parameters, which are often unavailable or difficult to determine experimentally. A key issue with these approached is whether, in their semi-quantitative nature, it is possible to accurately simulate the dynamics of chemical absorption, distribution, metabolism, and elimination (ADME) from different routes of exposures and could they be used to evaluate quantitative associations between exposures and biomarker measurements. The aim of this project is to study the applicability and potential for such parameter-free approaches for predictive toxicity and whether and under what conditions they can be used for quantitative risk assessment.

Example papers: Koch, I (2014) Petri nets in systems biology, Software & Systems Modeling, 14:703-710; Loizou, G, Soendiff, M, Barton, HA et al. Development of good modelling practice for physiologically based pharmacokinetic models for use in risk assessment: The first steps. Reg Tox & Pharma 50:400-411.

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Appendix – useful information.

Commercial crop protection chemicals and target proteins:

The resistance action committees (for herbicides, fungicides & insecticides) each produce posters grouping current commercial agrochemicals by target protein – they offer a useful overview of our industry. Commercial agrochemicals are typically available from the chemical vendors, we can often provide small samples from our dispensary for Syngenta supported projects.

http://www.irac-online.org/documents/moa-structures-poster-english/

http://www.frac.info/docs/default-source/publications/frac-mode-of-action-poster/frac-moa-poster-2018.pdf?sfvrsn=e5694b9a_3

http://hracglobal.com/files/moaposter.pdf

Globally important pest species for Syngenta:

Invertebrates	
Lepidoptera	*Chilo suppressalis, Chrysodeixis includes, Cnaphalocrocis medinalis, Cydia spp, Elasmopalpus lignosellus, Helicoverpa armigera, Heliothis virescens*, Plutella xylostella*, Sesamia inferens, Spodoptera spp., Tuta absoluta*
Hemiptera	*Aonidiella aurantii, Aphis craccivora, Aphis gossypii*, Bemisia tabacci*, Cacopsylla pyri, Diaphorina citri, Dichelops melacanthus, Euschistus heros*, Lygus spp., Myzus persicae*, Nilaparvata lugens, Rhopalosiphum padi, Thrips tabaci, Trialeurodes vaporariorum*
Coleoptera	*Diabrotica spp.*, Leptinotarsa decemlineata, Agriotes spp., Phyllophaga spp., Meligethes aeneus, Anthonomus grandis, Psylliodes chrysocephala, Phyllotreta spp., Cerotoma trifurcata.*
Diptera	*Bactrocera spp, Delia radicum, Drosophila suzukii*
Nematoda	*Heterodera glycines, Heterodera schachtii, Meloidogyne incognita, Pratylenchus zeae*
Arach-nida	*Panonychus ulmi/citri, Tetranychus urticae**

Species in each taxonomic grouping are listed alphabetically. * Indicates species of particular importance in agrochemical research.

Fungi & Oomycetes	
Ascomycetes	*Alternaria solani*, Botrytis cinerea*, Cercospora spp, Colletotrichum spp*, Fusarium graminearum*, Magnaporthe oryzae, Zymoseptoria tritici**
Basidiomycetes	*Phakopsora pachyrhizi*, Puccinia graminis f. sp. tritici, Puccinia recondita, Puccinia striiformis var. tritici, Puccinia triticina,*
Oomycetes	*Phytophthora spp. (capsici/infestans*), Plasmopara viticola, Pythium spp.**

Species in each taxonomic grouping are listed alphabetically. * Indicates species of particular importance in agrochemical research.

Weeds	
Monocots	*Alopecurus myosuroides, Avena fatua, Digitaria spp, Echinochloa crus-galli, Echinochloa colonium , Lolium spp, Setaria faberi, Setaria viridis.*
Dicots	*Amaranthus retroflexus, Amaranthus palmerii, Conyza canadensis, Ipomoea spp, Papaver rhoeas*

Species in each taxonomic grouping are listed alphabetically. Only species of particular importance are listed.

Pest impact on agriculture:

Oerke, E. C. (2005). "Crop losses to pests." The Journal of Agricultural Science **144**(1): 31-43.

Savary, S. *et al*. (2019). "The global burden of pathogens and pests on major food crops." Nature Ecology & Evolution **3**: 430–439.