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Agrochemical ADME and the Syngenta Digital Revolution

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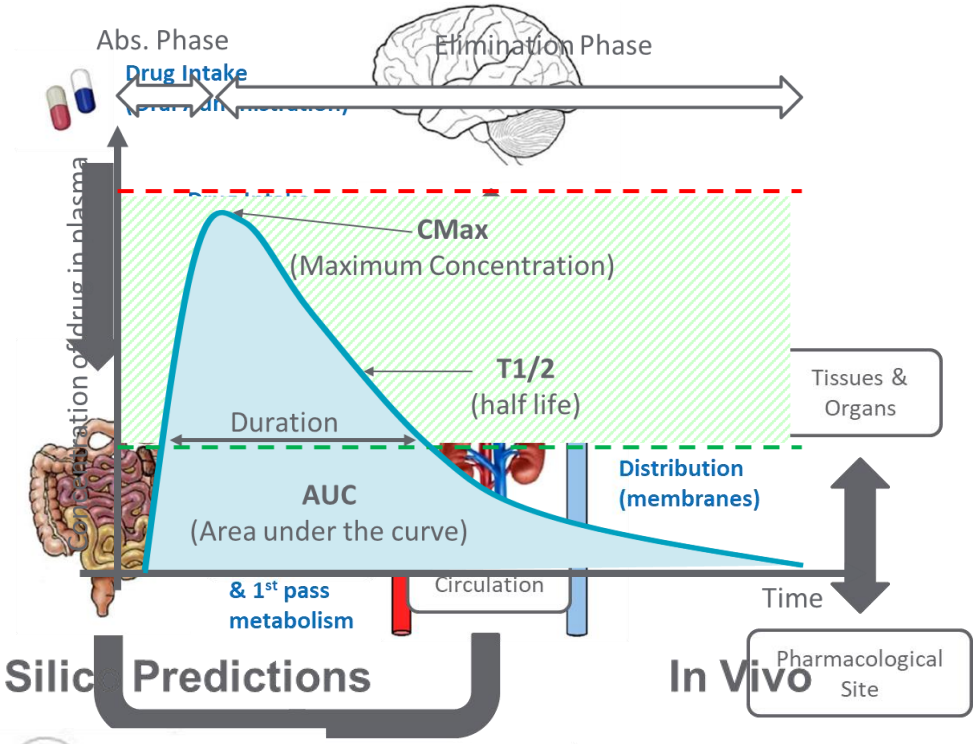
Introduction

- How does our understanding of ADME in AgChem compare to Pharma?
- What PhysChem properties are important in AgChem?
  - How are they measured and used?
- How can prediction models be used in projects to improve chemical design?
- What can we learn from each other?

ADME understanding in Pharma

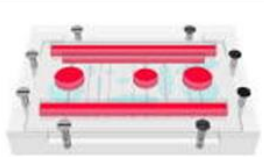
- Comprehensive understanding of ADME processes to have a pharmacological effect.
- Can generate blood concentration-time profiles that quantify bioavailability.
- Clear understanding of correlations between screens and the impact of different scales on bioavailability.
  - Driven by inability to test on target *in* vivo at an early stage.



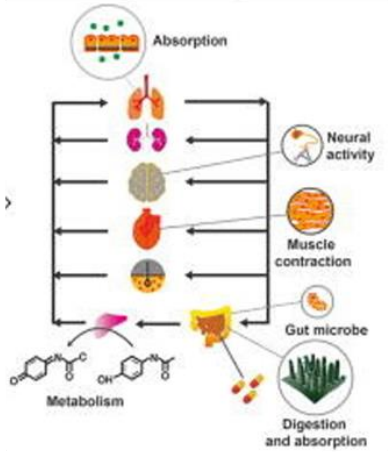
Rules of Thumb | **In Vitro ADME Assays** | **In Silico Predictions** | **In Vivo**

MW < 500 Da
CLogP < 5
H-bond donor < 5
H-bond acceptor < 10

Design
(Feedback to chemical design)



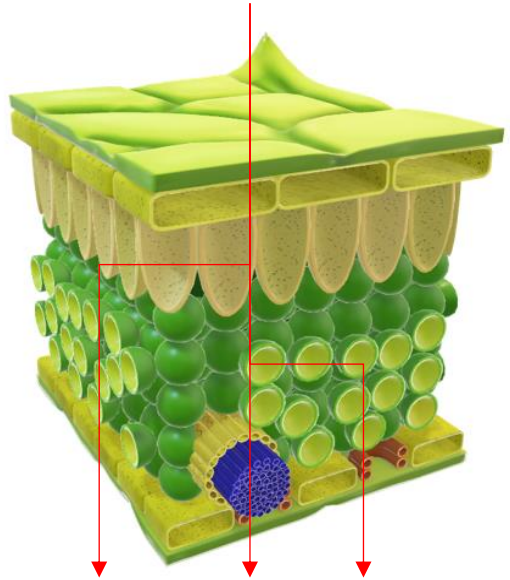
Translation
(scaling organ sizes and flow rates)



Interpretation
(*in vitro* to *in vivo* translation)

Pharma vs AgChem ADME Similarities

- The right physical chemical properties are required to reach the target site.
  - Requirement to cross membranes is universal.
- Both need to consider; **Bioavailability (including ADME) x Potency = Activity**
- **PhysChem properties are key to understanding ADME processes.**



Bioavailability including ADME ✕ **Potency** = **Activity**

Combination of mobility and loss processes – a compound must overcome a number of hurdles before it reaches the active site.

Highly dependant on:

- Application route
- Environmental factors
- Species of interest & host (insects, pathogen, plant)
- Location of active site

Effect at the target is reasonably well understood

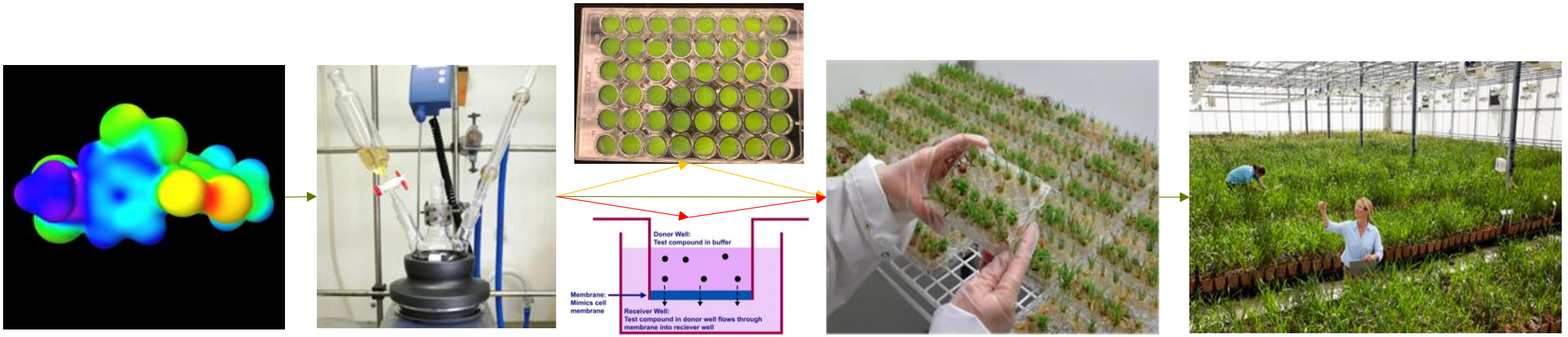
- *In vitro* assays
- Crystal structures
- Docking simulations

Measured & definitive

Bioavailability for AgChem… the proportion of an active ingredient which enters the desired target and is able to have an effect.

ADME in AgChem

- AgChem can test target organisms in early screens at high throughput.
  - There has been little need for the development of high throughput *in vitro* ADME assays.
  - Becoming increasingly difficult to translate high potency compounds *in vitro* into high activity *in vivo* without better ADME assays and understanding.
- Biokinetics (on cells, tissues and organisms) does exist within AgChem but still under development.
  - Multiple complex processes happening at once.
- Rely mainly on physical properties of compounds to understand and predict bioavailability.
  - Need to bridge the ADME gap with new *in vitro* assays.



Why is ADME understanding difficult in AgChem?

Multiple targets needed to be understood!

Weed control

Disease control

Insect control

Nematode control

Abiotic stress

Yield and quality

Multiple targets means multiple ADME processes to understand!

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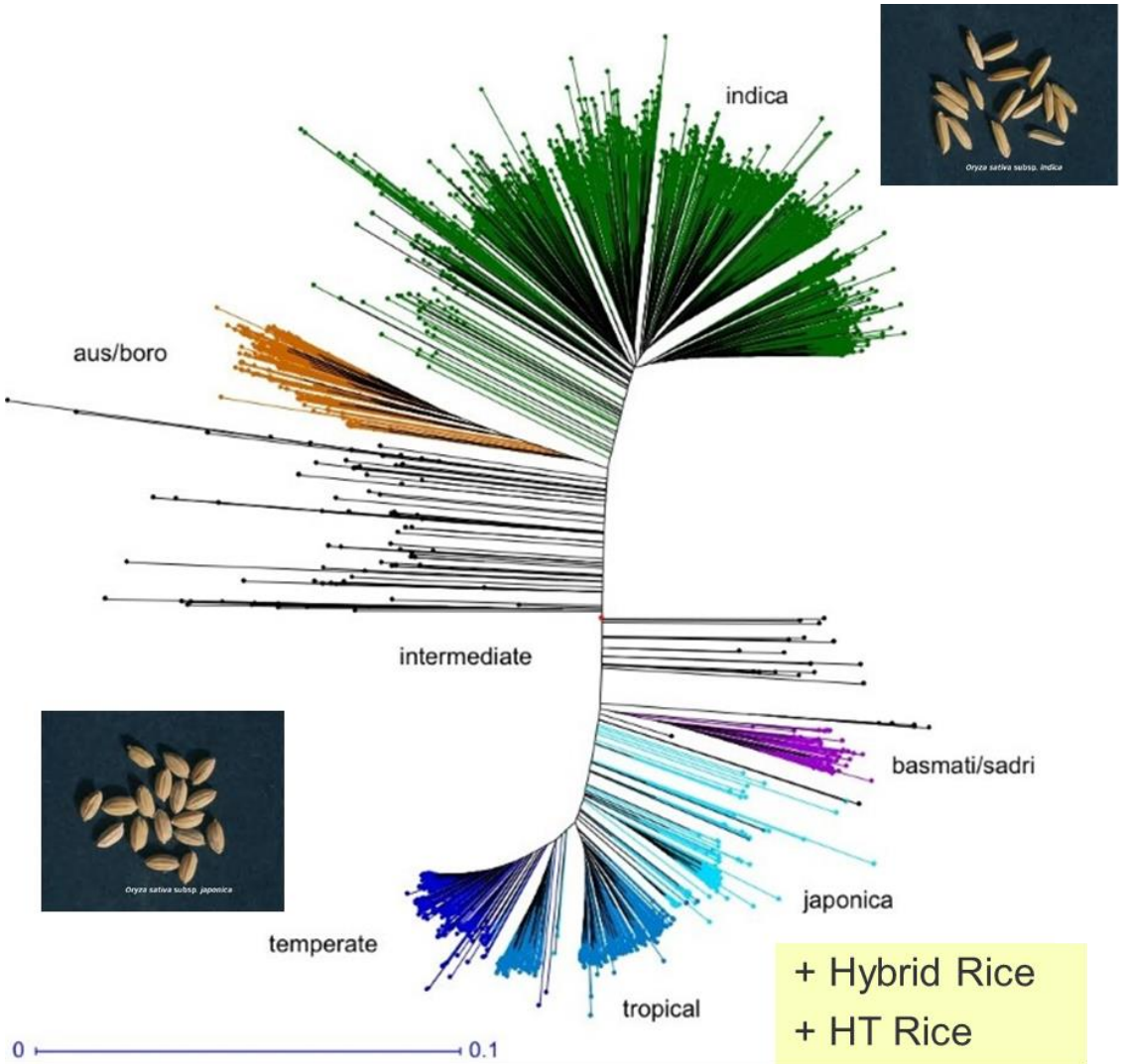
Multiple Considerations to Understand ADME – Disease Control

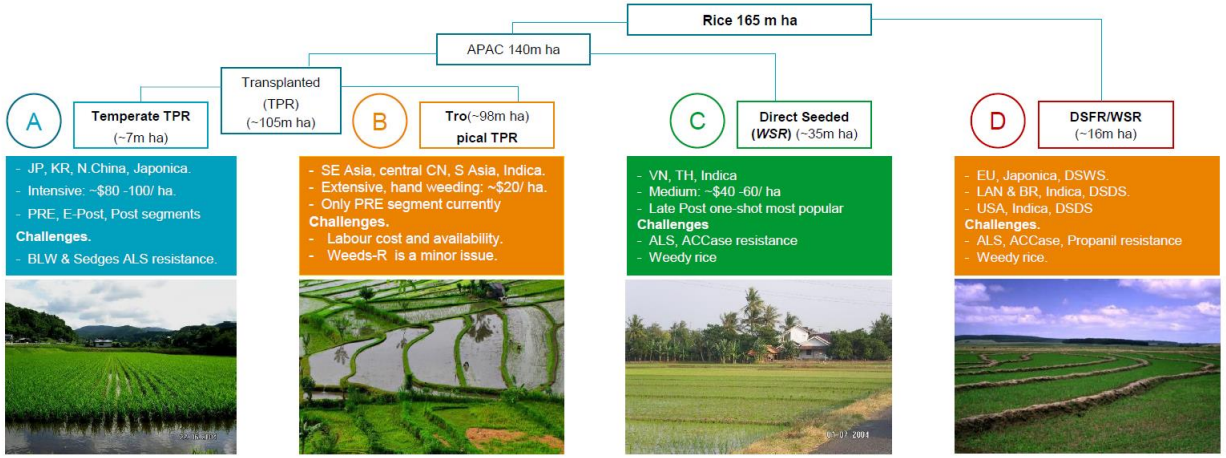
Disease control

Specialty & Vegetables			Cereals	Rice
Powdery mildew	Grey Mould	Leaf Spots	Rusts	Blast Fungus
				

- Within a fungicide project we are trying to understand the ADME of:
  - The AI into different pathogens.
  - The AI into different crops.
  - The interaction between the crop and the pathogen.
  - The AI into non-target organisms, such as; other plants, mammalian and aquatic.
    - Adapted a lot of the models developed in Pharma, but other areas have needed AgChem specific development.

Even One Target can be a Challenge - Rice





- Common in SE Asia

- Country dependant
- Common in China

- Mainly TPR
- Common in JP

Japan: "One-Shot"

To design a compound with the "perfect properties" to work across different environments, different applications and selective across a wide genetic spectrum is challenging.

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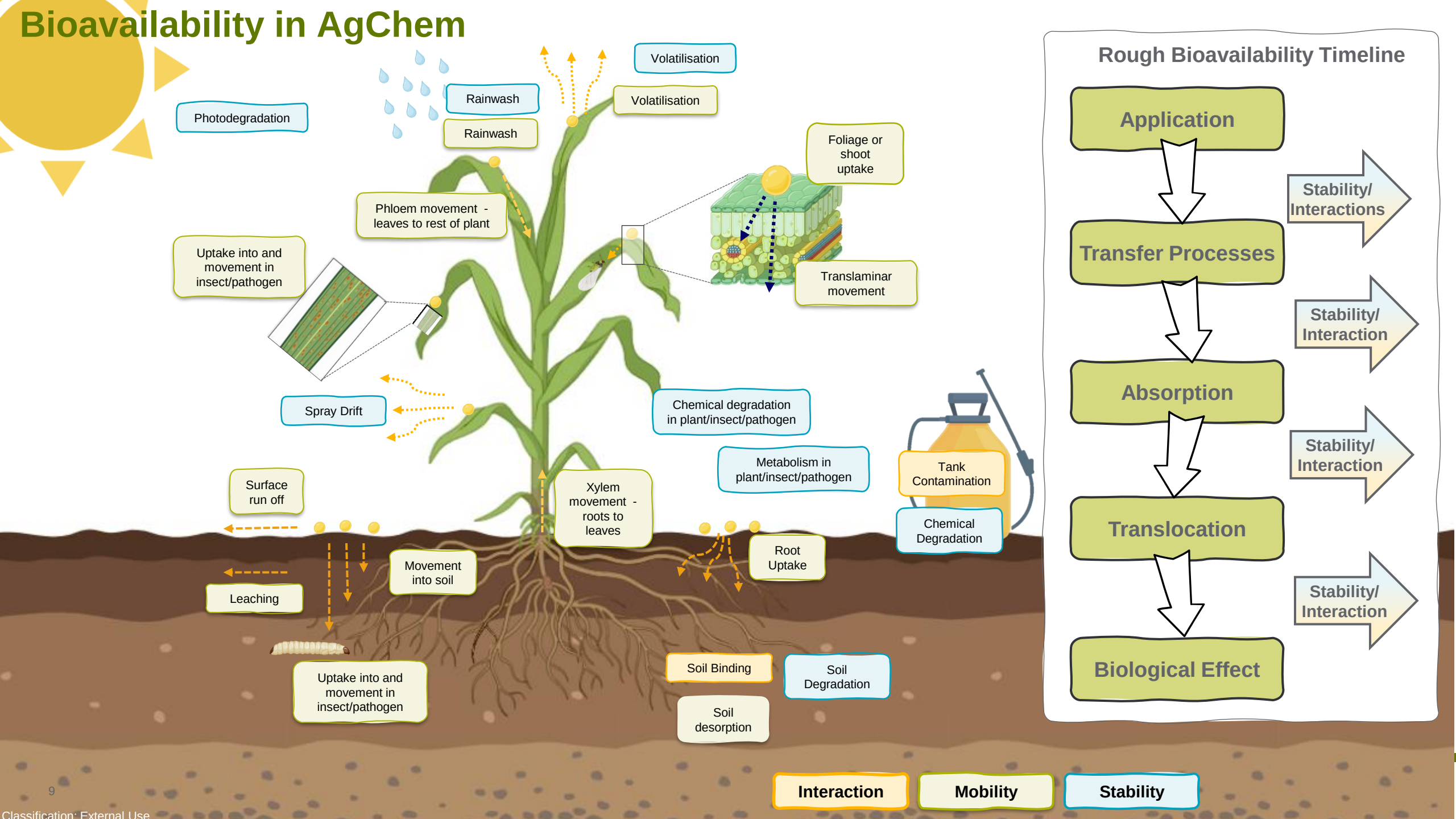
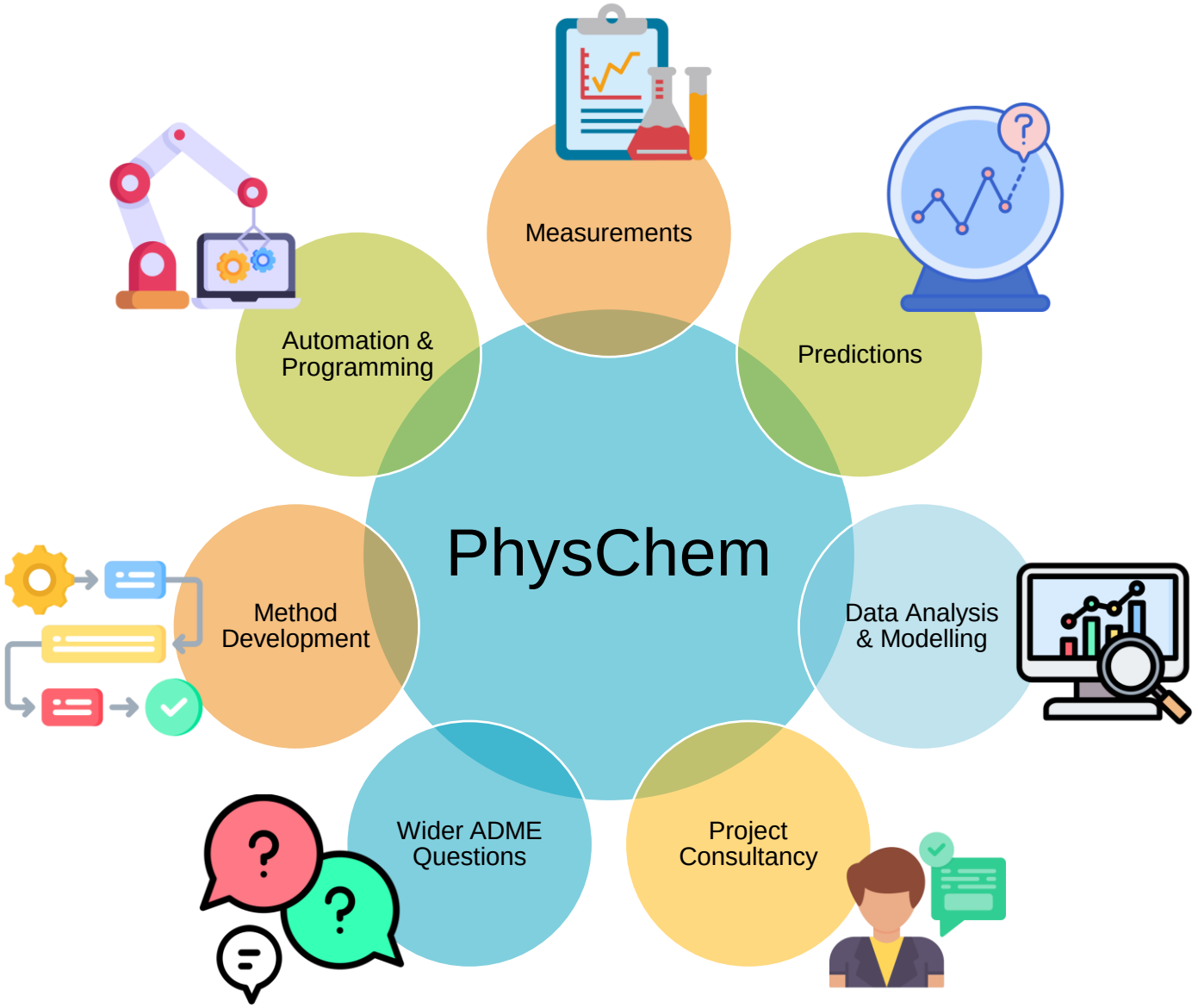
Bioavailability in AgChem



What does the PhysChem Group at Syngenta do?

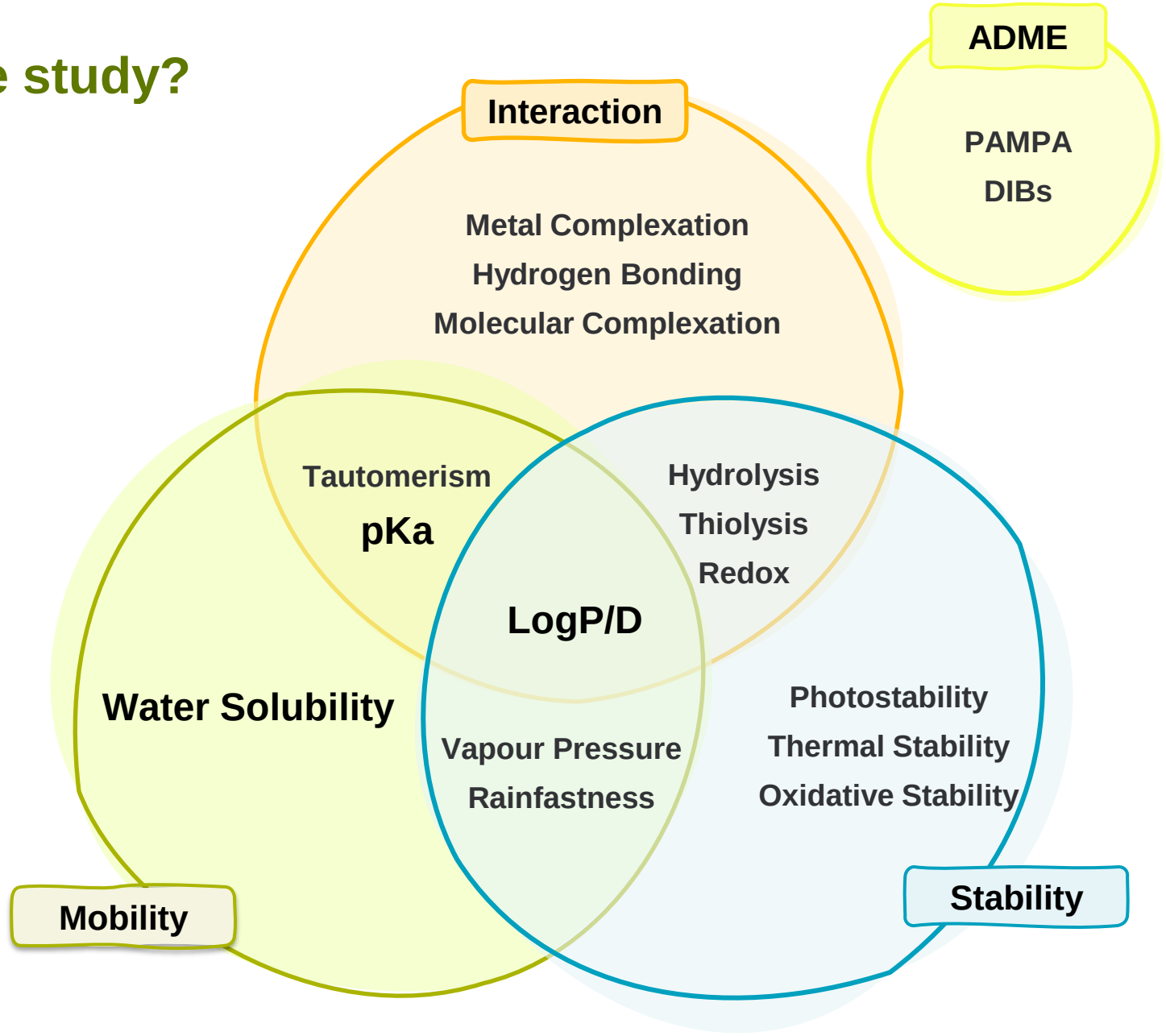


What Physical Properties do we study?

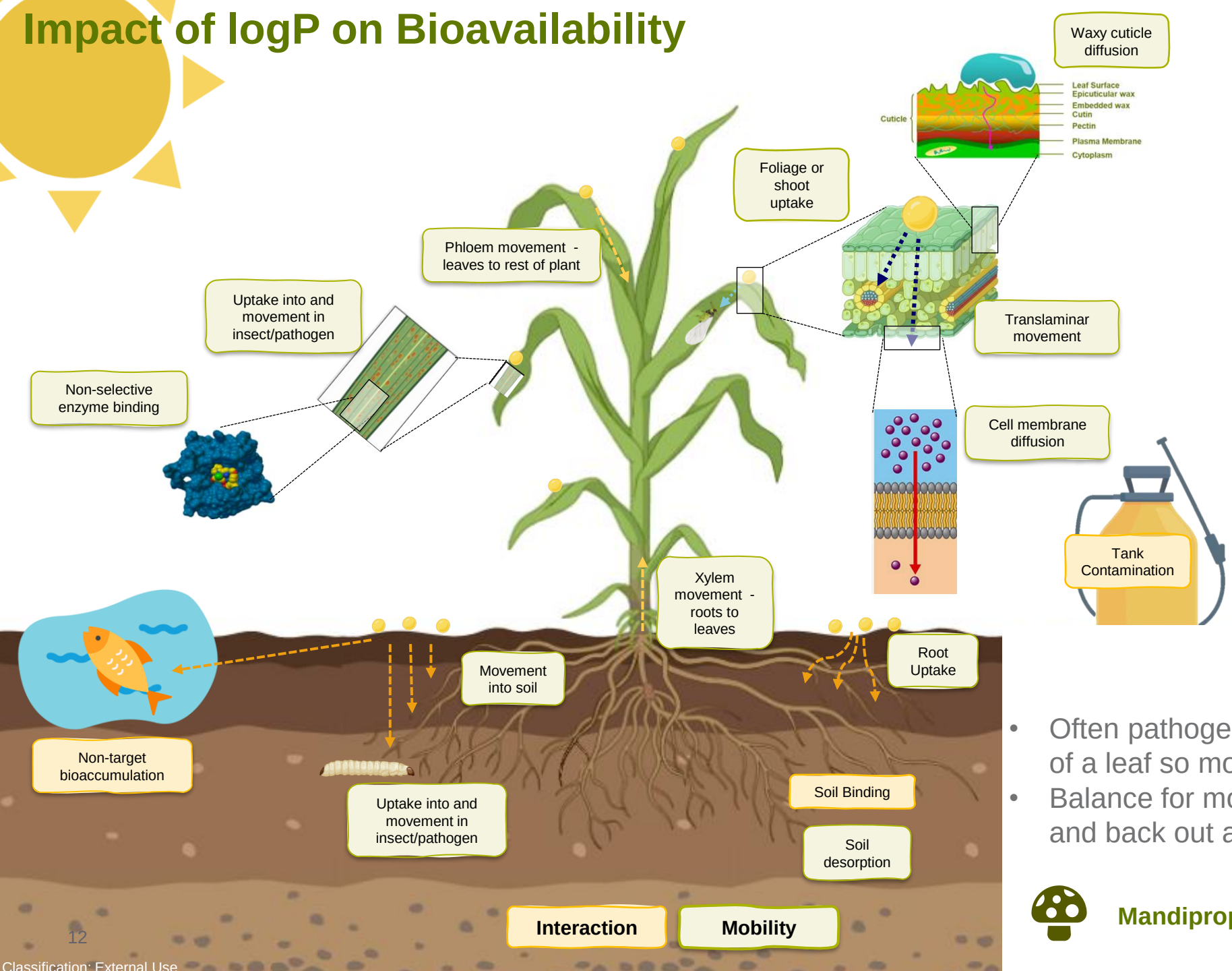
- PhysChem properties can be used to model many complicated biological processes.
  - Understanding these are fundamental for AgChem design.

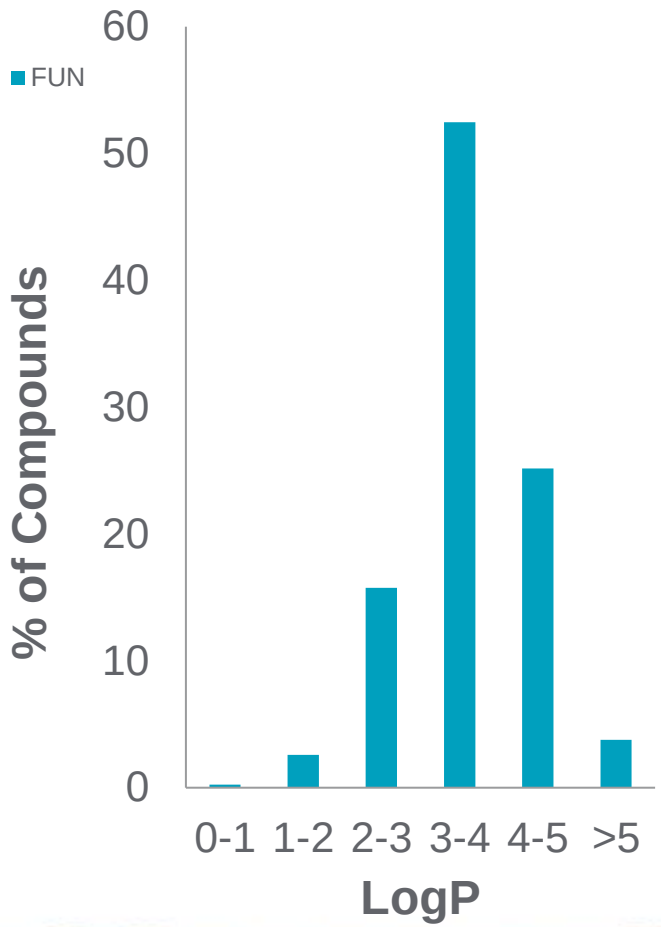
- Actively developing *in vitro* assays to better measure and understanding ADME processes.
  - Multiple learnings from Pharma.
  - AgChem PAMPA/ Droplet Interface Bilayers (DIBs).
    - Need different membranes to represent all species of interest (plants, insects, pathogens and mammalian).

- logP, pKa and water solubility are key to understanding ADME.



Impact of logP on Bioavailability

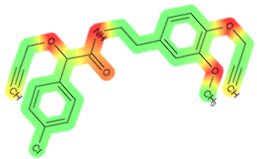




logP ~ 2 - 4

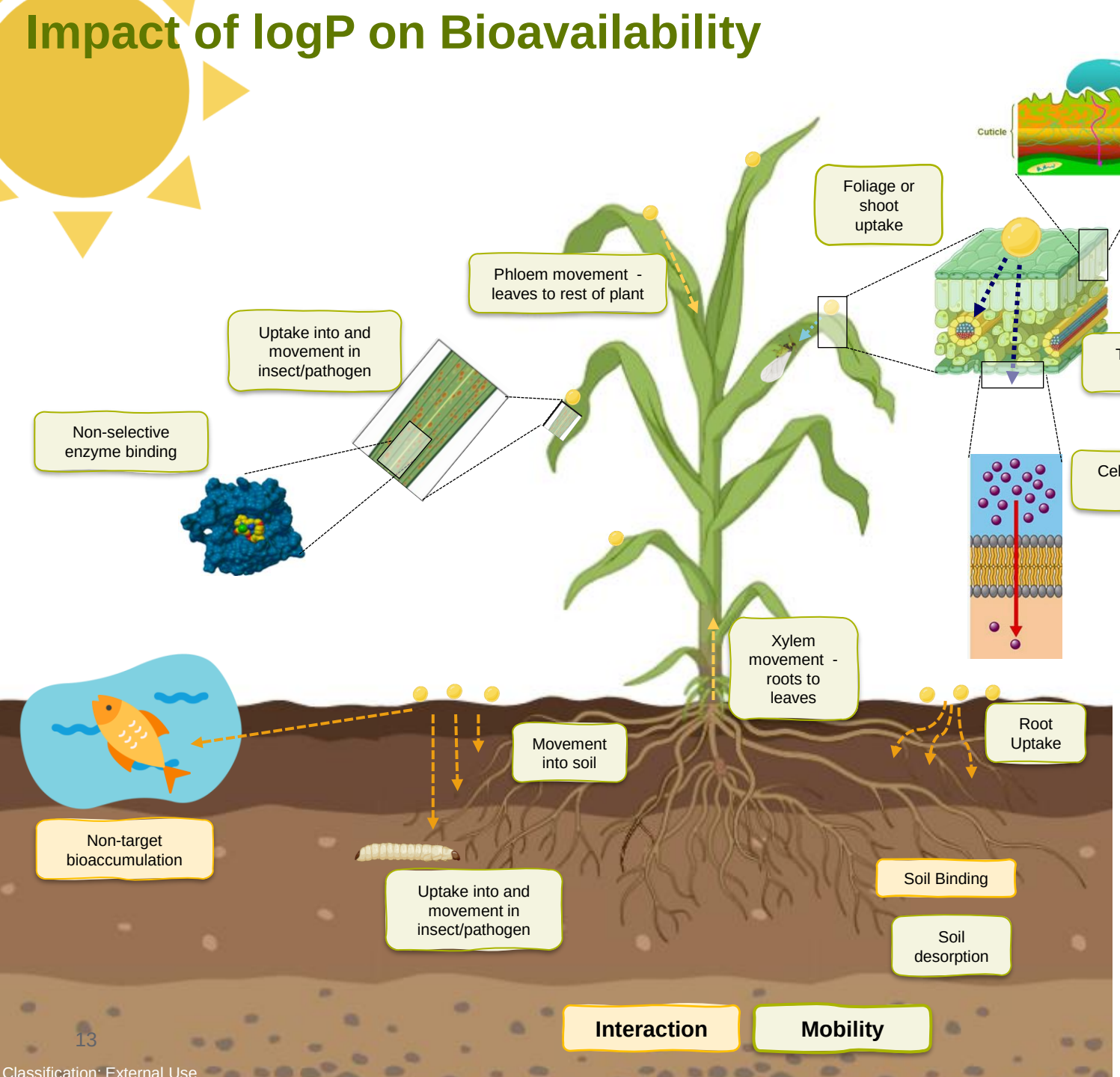
- Often pathogens are located in the topmost layers of a leaf so moderate movement is ideal.
- Balance for movement through lipid membranes – and back out again!

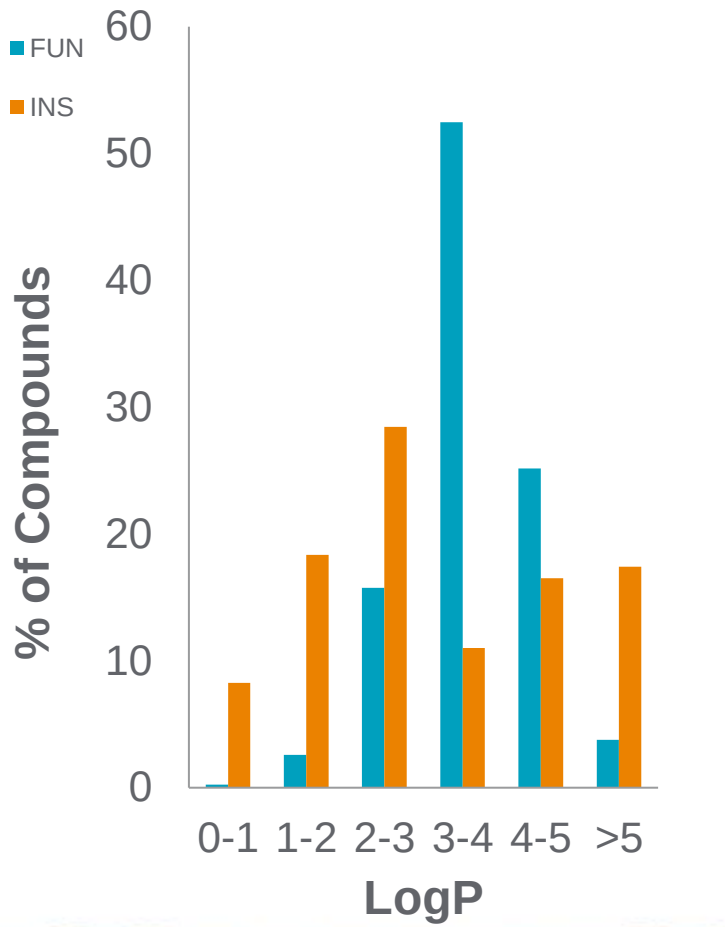
Mandipropamid



LogP: 3.2

Impact of logP on Bioavailability

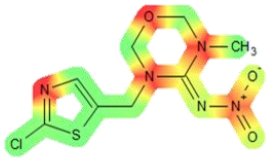




logP < 0

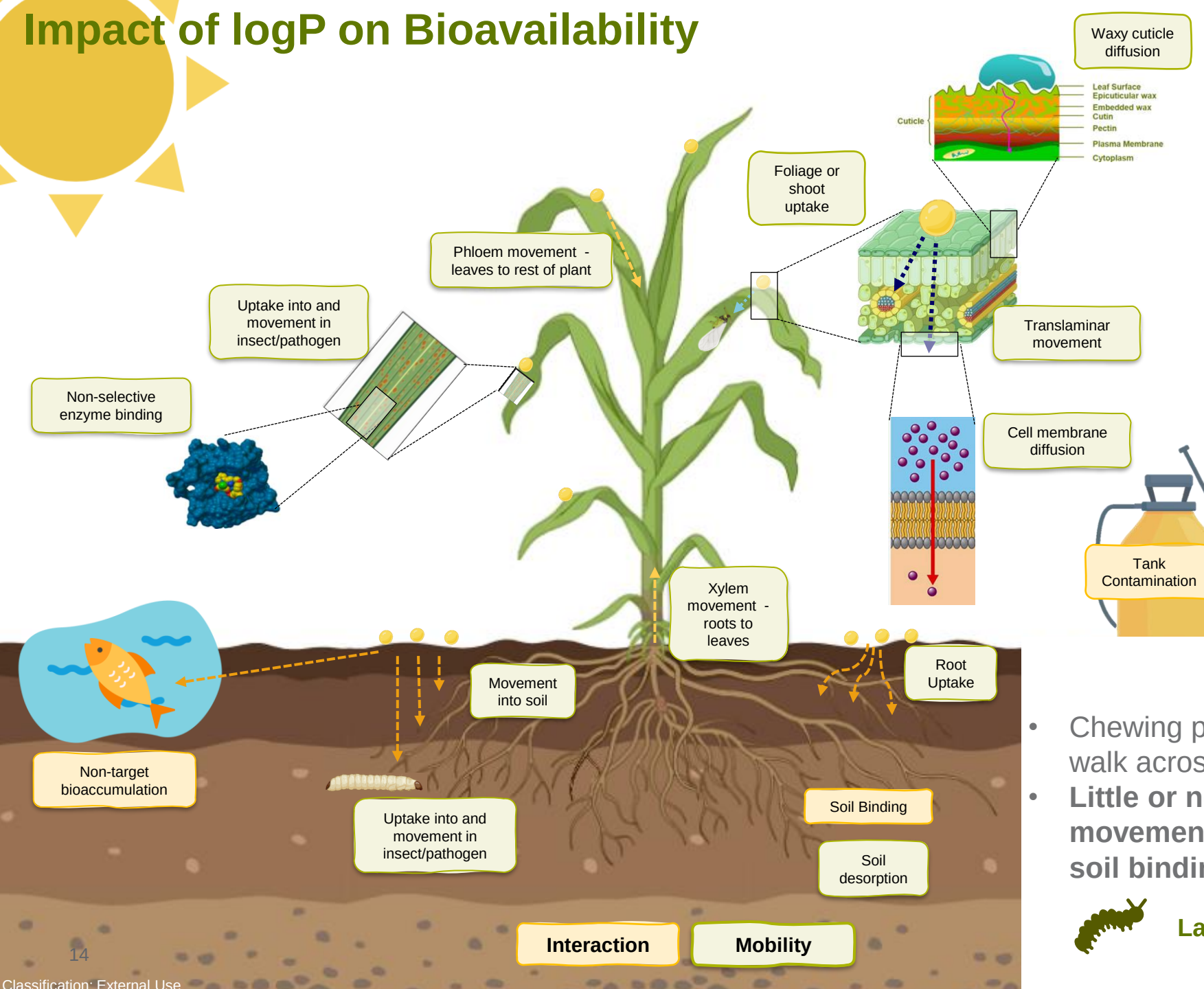
- Sucking pests need the compound to be in the right vascular tissues.
- Very hydrophilic, **high-water** solubility but **slow absorption** through lipid membranes.

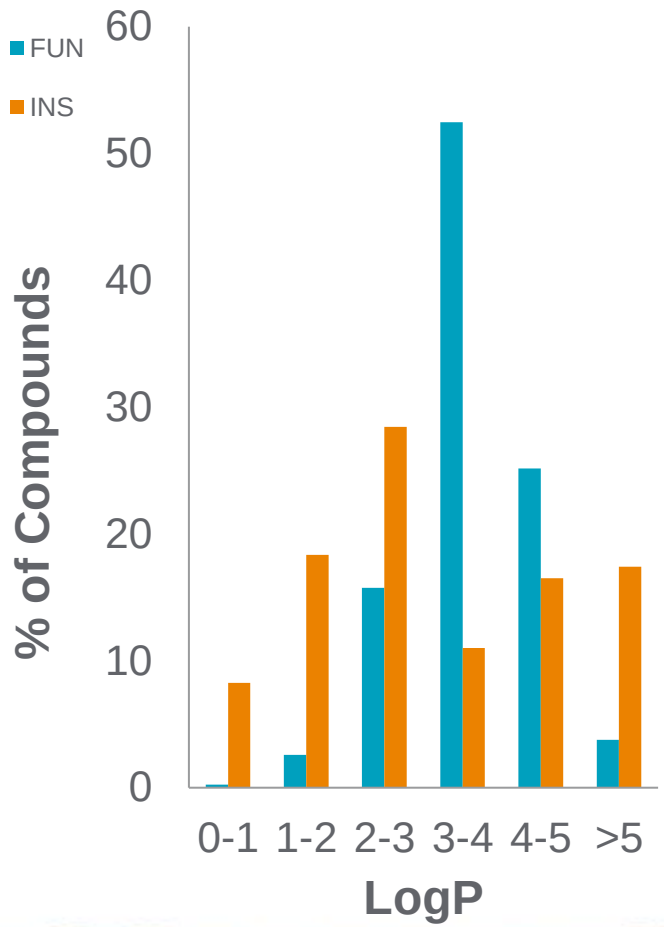
Thiamethoxam



LogP: -0.13

Impact of logP on Bioavailability

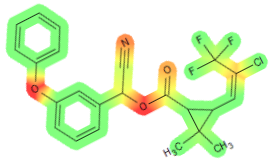




logP ≥ 4

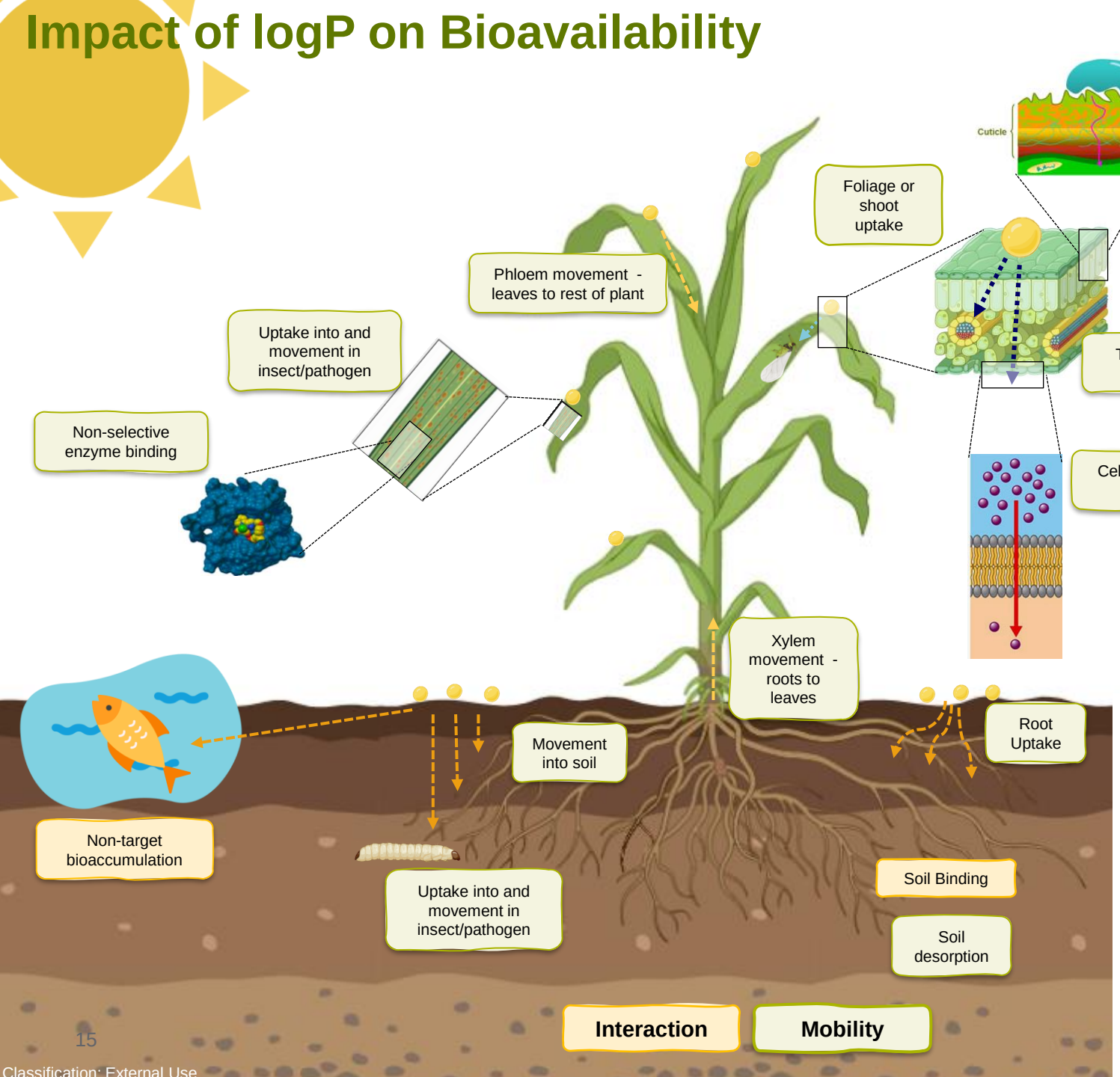
- Chewing pests have contact activity whilst they walk across the leaf or root and eat it.
- **Little or no mobility** in plants and soil and **rapid movement** into lipid membranes. Potentially **high soil binding.**

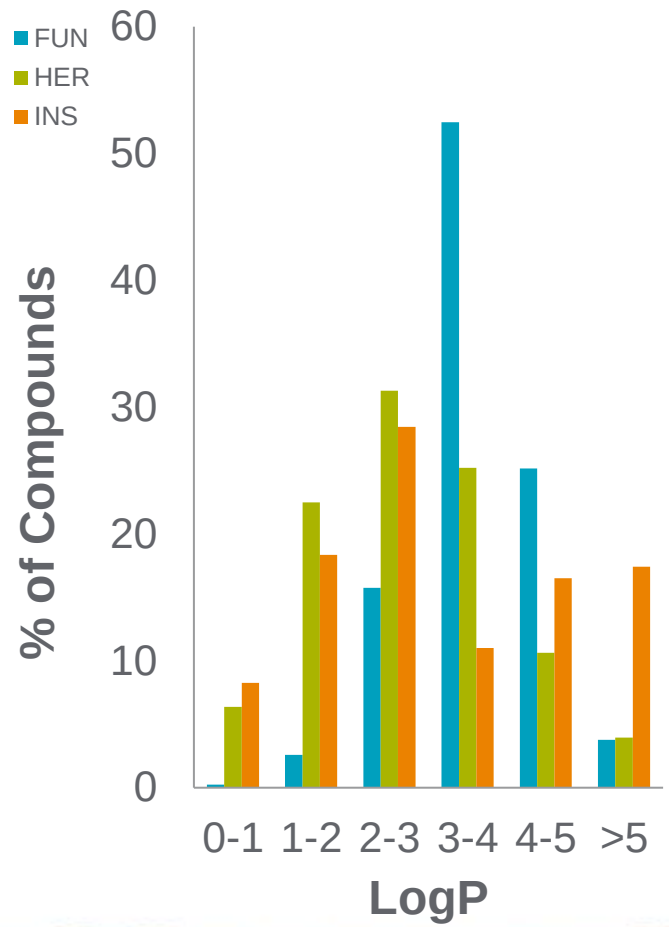
Lamdacyhalothrin



LogP: 7.0

Impact of logP on Bioavailability

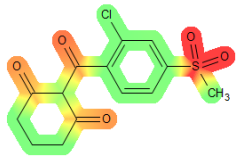




logP ~ 0 - 2

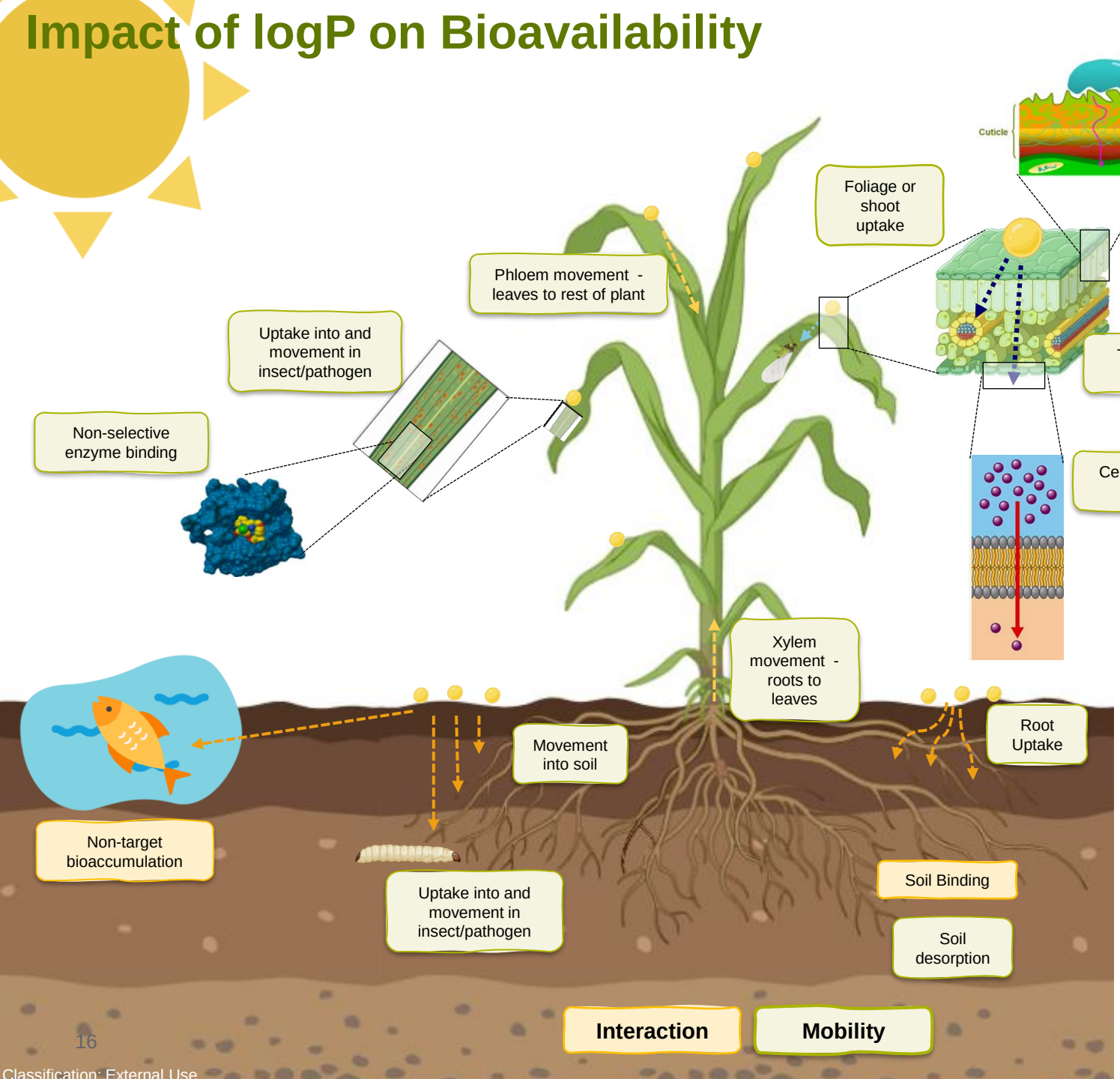
- Uptake into the vascular system and further translocation to the active site is required.
- **Balance** of properties for **absorption** through lipid membranes and **movement** in vascular tissue.

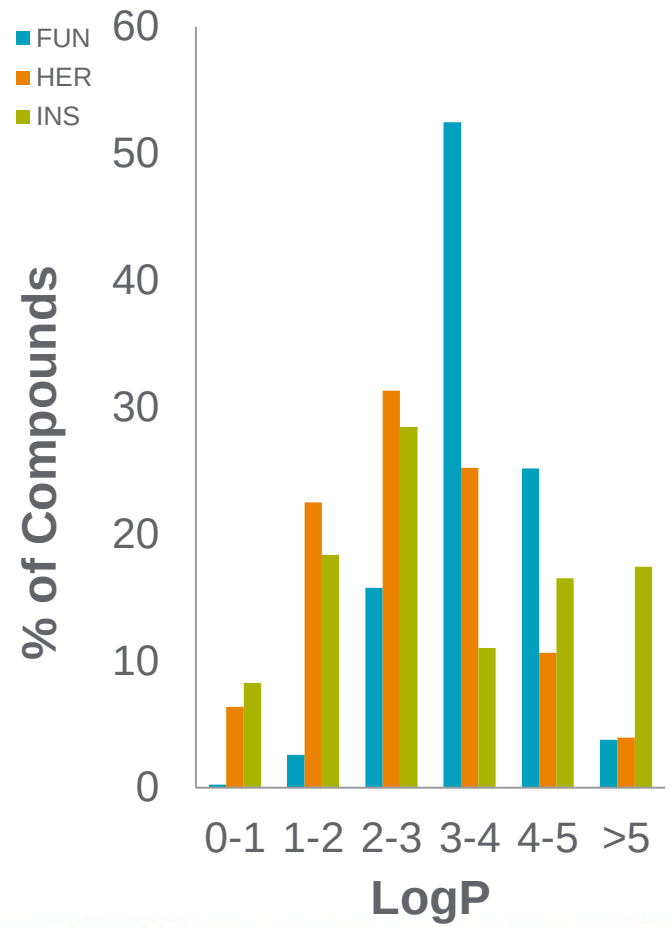
Sulcotrione



LogP: 1.3

Impact of logP on Bioavailability

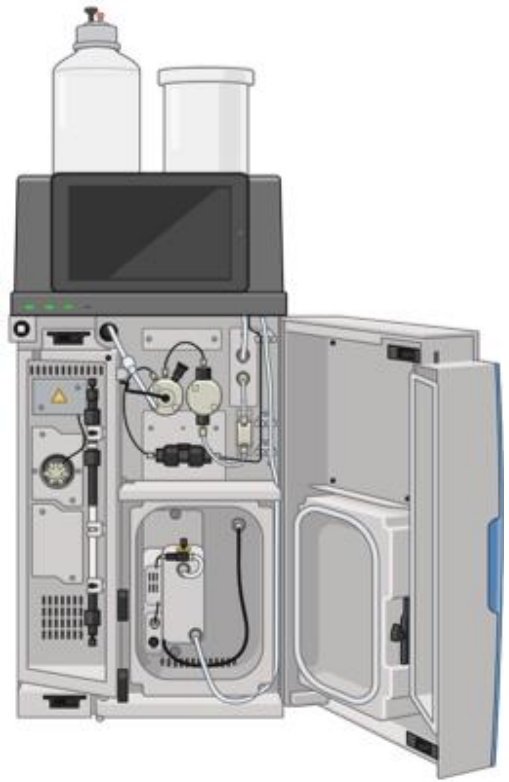


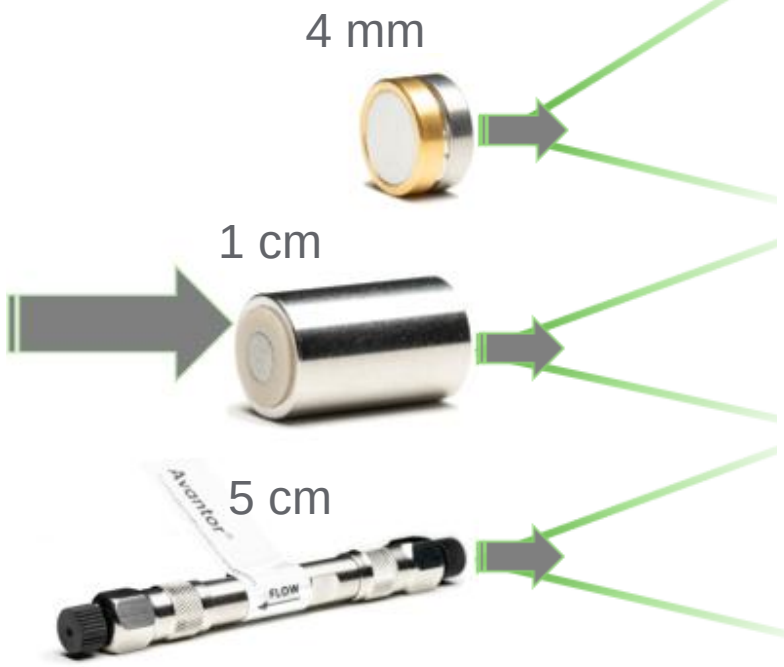


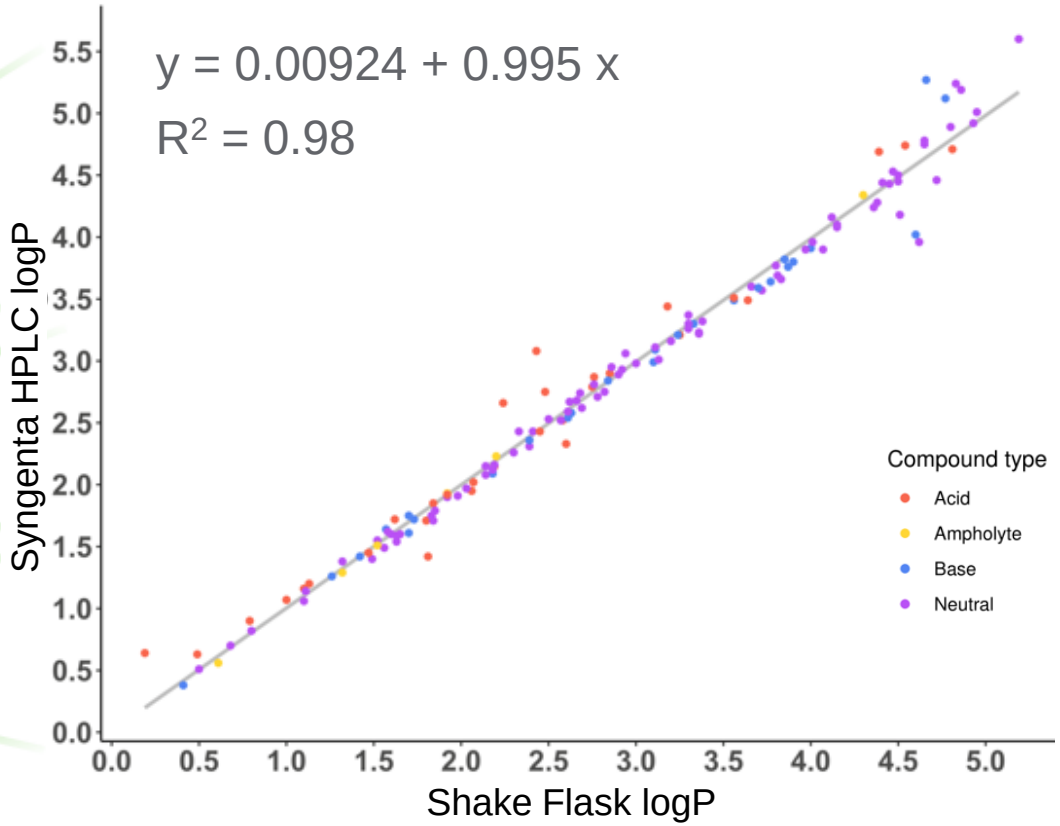
Often LogP requires a balance to optimise against multiple endpoints!

How We Measure logP

- Octanol-coated column HPLC is the primary method for logP/logD measurement using specific pH (2-10) octanol saturated buffers.
- A series of small short alkyl chain analytical HPLC columns/ guard columns are used.
- The octanol coated column HPLC method can provide fast and accurate measurement of logD from 0 to 5.6.

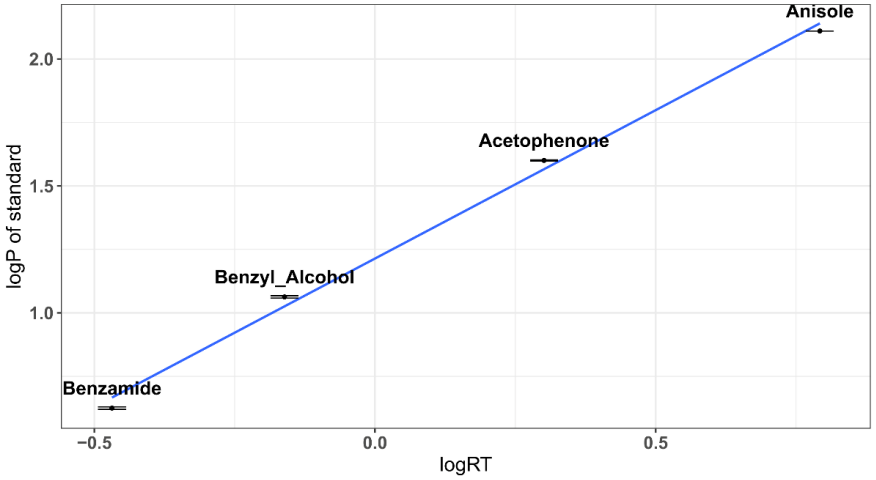


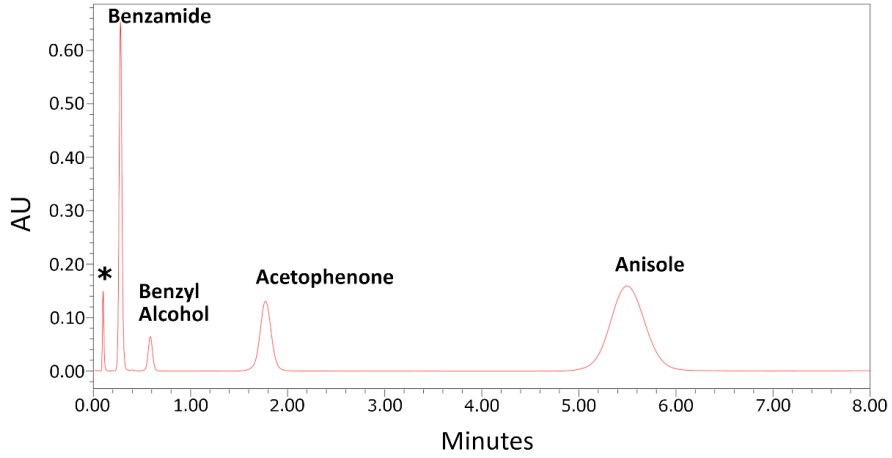




Data currently under review for publication J.Med.Chem

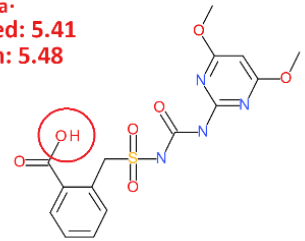
How We Measure logP





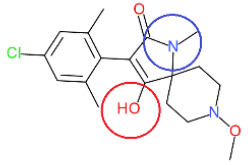
Bensulfuron-methyl

Acid pK_a:
extracted: 5.41
titration: 5.48



Spiropidion acid

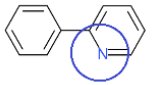
Acid pK_a:
extracted: 5.54
titration: 5.53

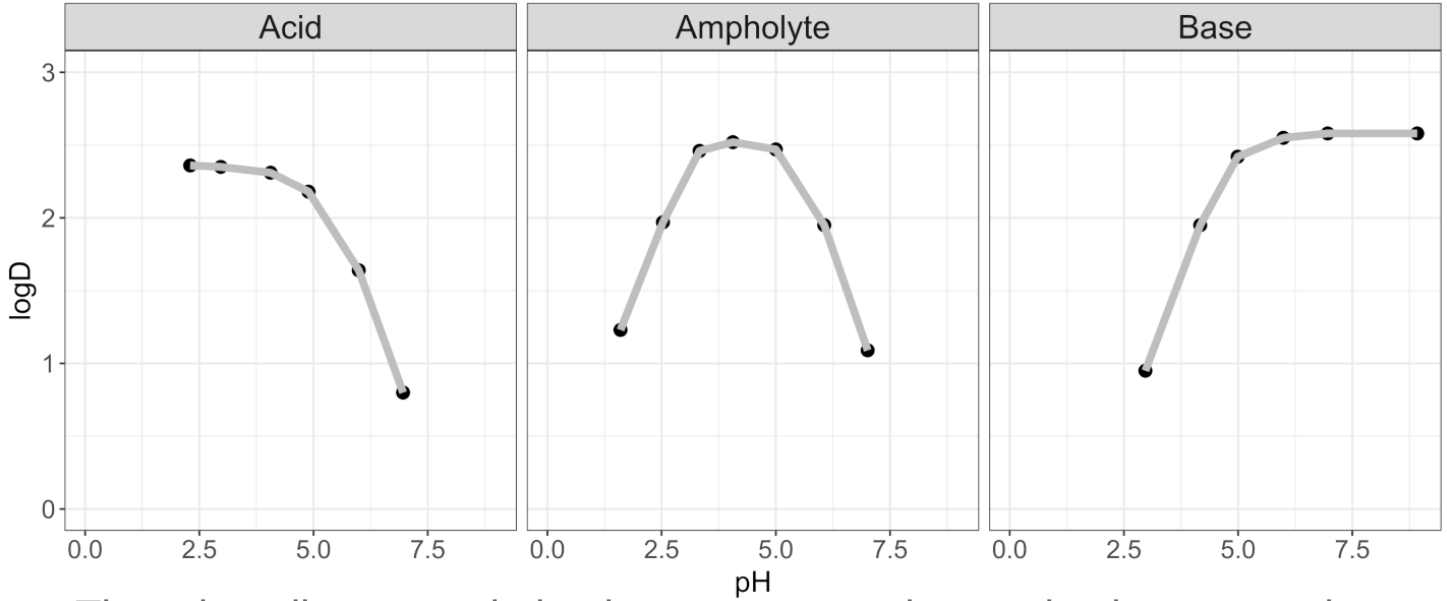


Base pK_a:
extracted: 2.96
titration: 3.02

2-phenylpyridine

Base pK_a:
extracted: 4.61
titration: 4.62





- There is a direct correlation between octanol coated column retention time and logP/logD.
  - Retention time is a function of genuine octanol-aqueous partitioning.
  - Peaks become broader as retention time increases.
- Can plot logD vs pH for any pKa type.

Data currently under review for publication J.Med.Chem

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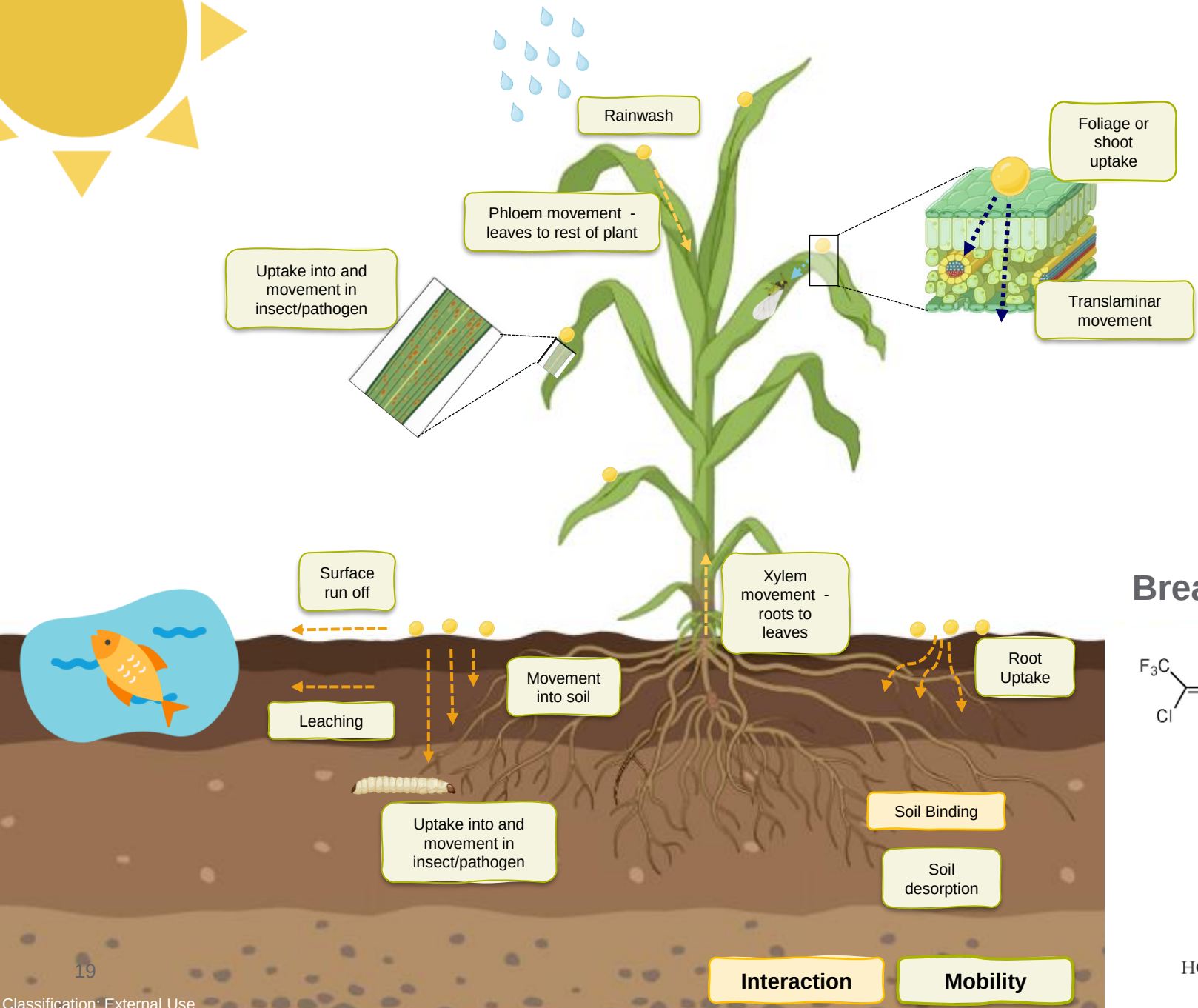
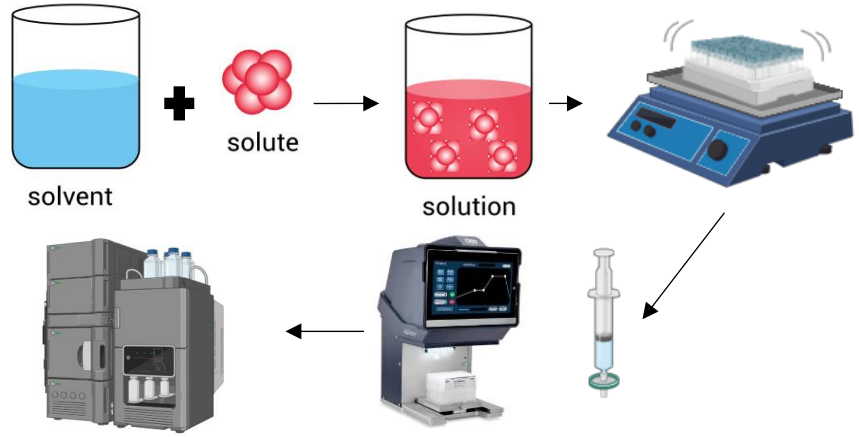
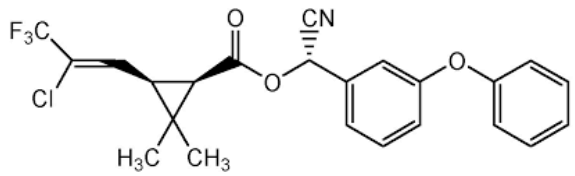
Impact of Water Solubility on Bioavailability



We routinely measure the thermodynamic solubility of compounds in aqueous buffer and in simple alkanes (heptane).



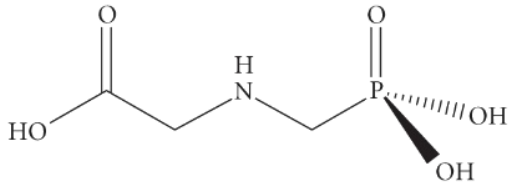
Breadth of AgChem Solubility Space:



Lambda-cyhalothrin

Aq sol 0.005 ppm

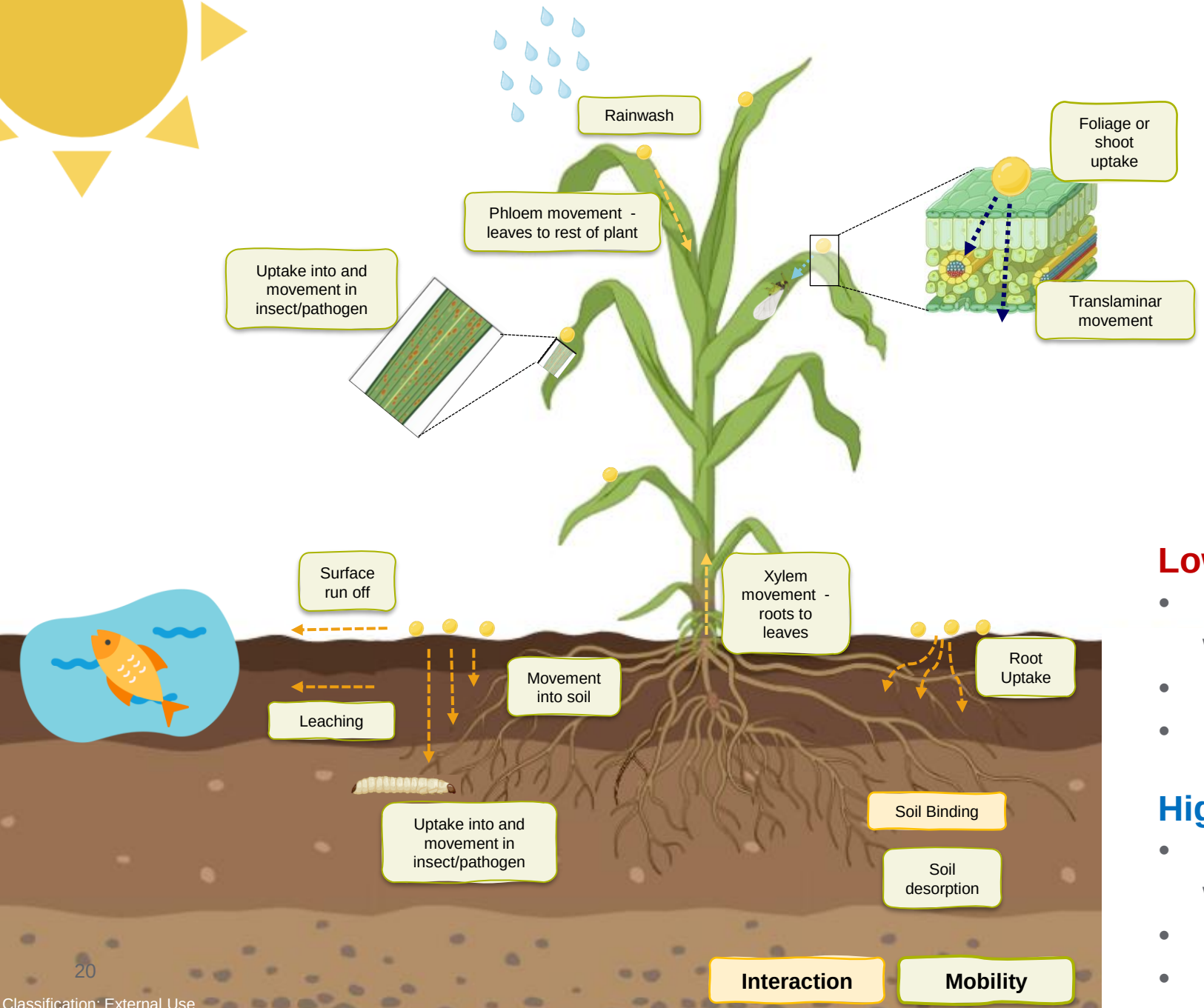
>100,000,000 fold difference!



Glyphosate

Aq sol 900,000 ppm

Impact of Water Solubility on Bioavailability



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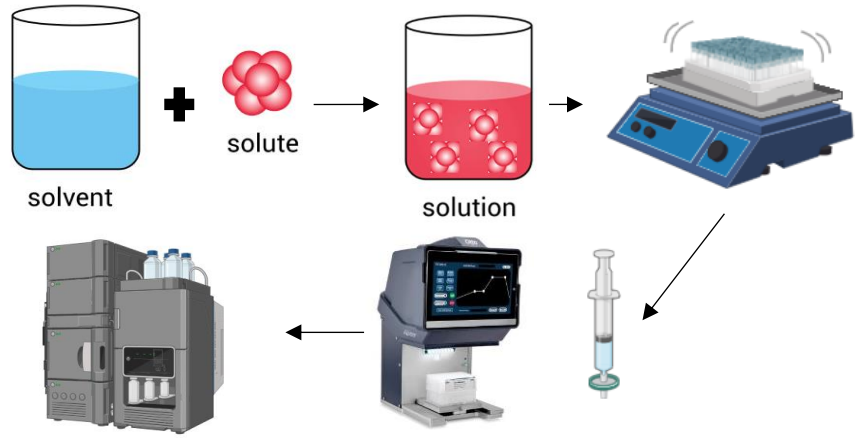


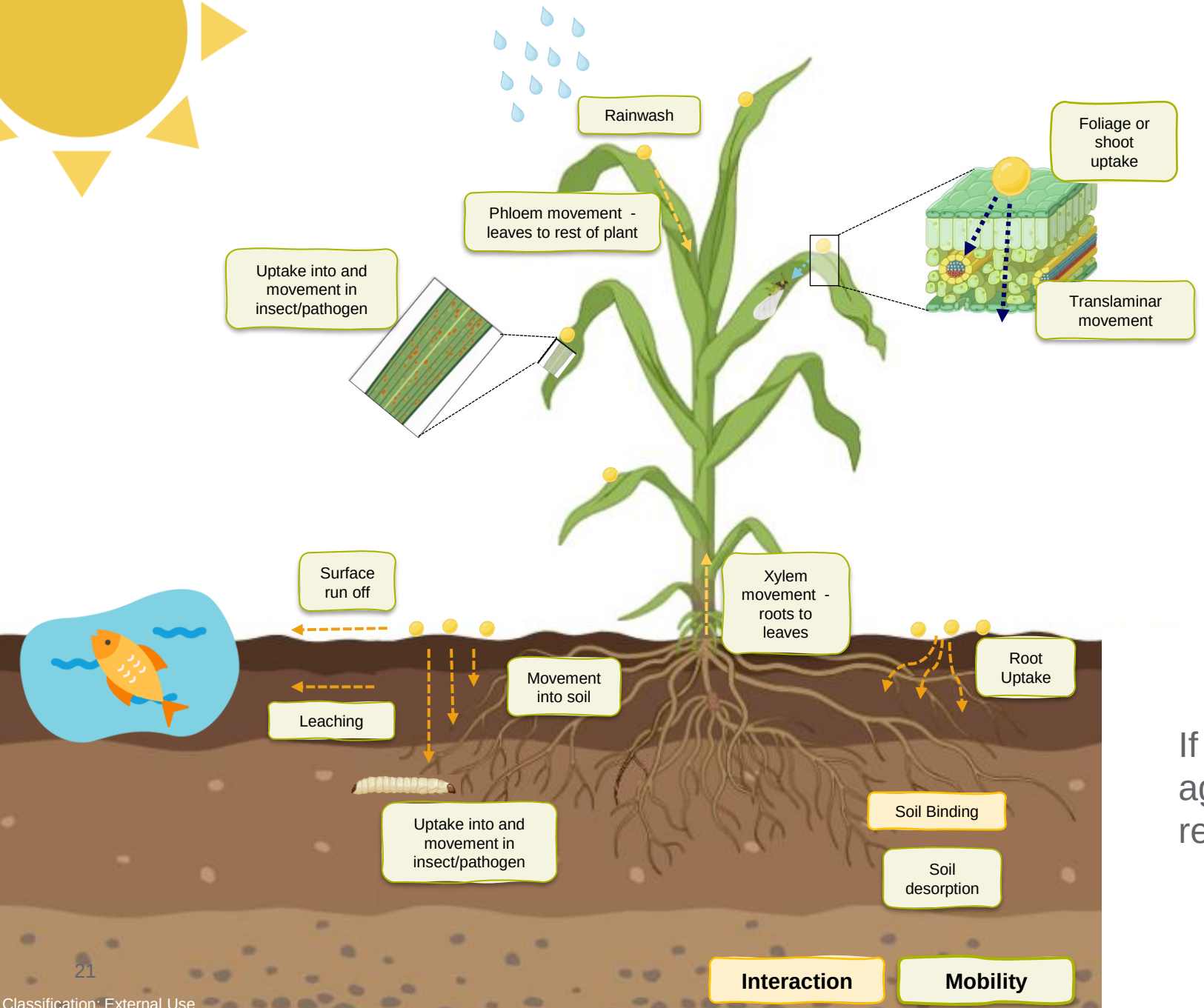
Low water solubility (<1 ppm):

- Lower chance of leaching and moving with surface run off
- Bind to soil surface
- High probability of precipitation

High water solubility (>50 ppm):

- Higher chance of leaching and movement with surface run off
- More potential to be washed off crop
- Higher mammalian exposure

Impact of Water Solubility on Bioavailability



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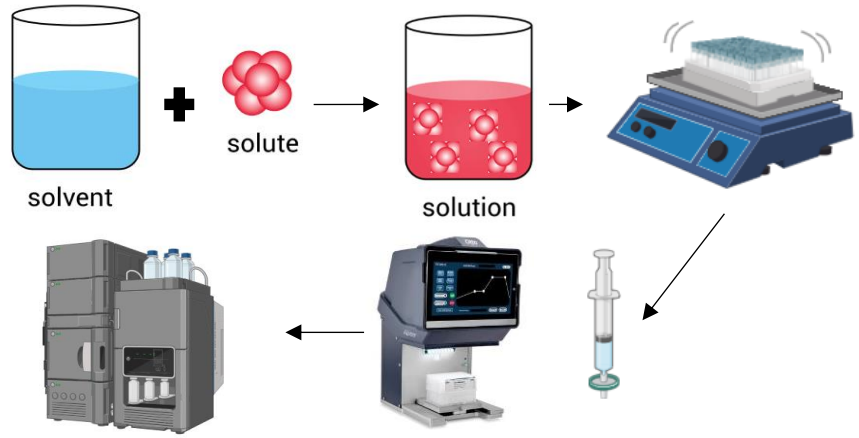
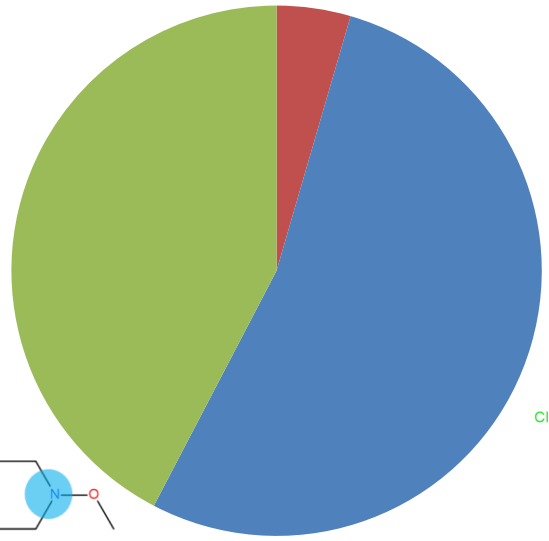


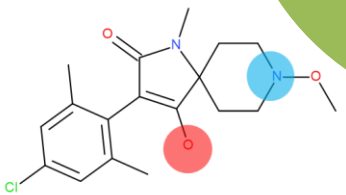
If solubility is too high or too low, agrochemicals have less chance of reaching the target – a balance is required!

pKa in AgChem

- Automated spectrophotometric or potentiometric titration using Sirius/Pion T3 instruments is the primary method for pKa measurement.
- Use Syngenta custom assay settings can provide accurate, automated measurement of acid and base pKa from 2-10.

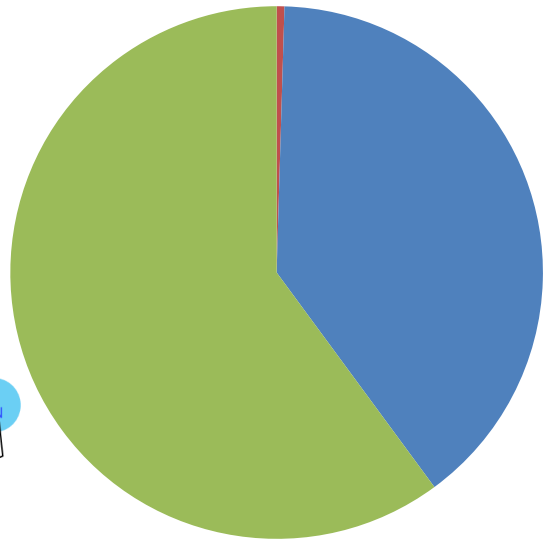
INS

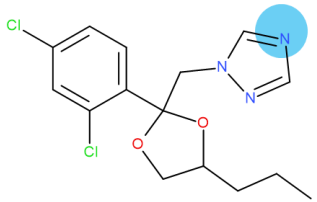




Spiropidion Acid (INS)
Acid pK_a 5.53
BASE pKa: 2.97

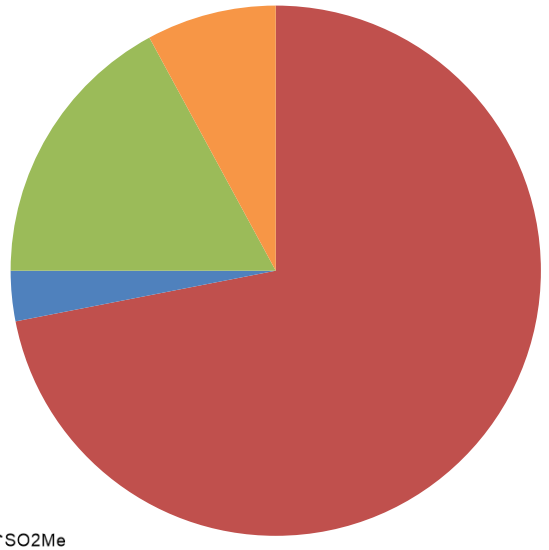
FUN

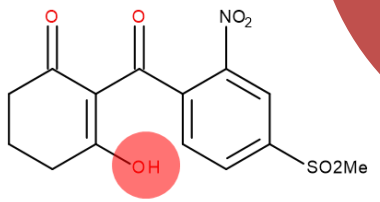




Propiconazole (FUN)
BASE pKa: 1.09

HER



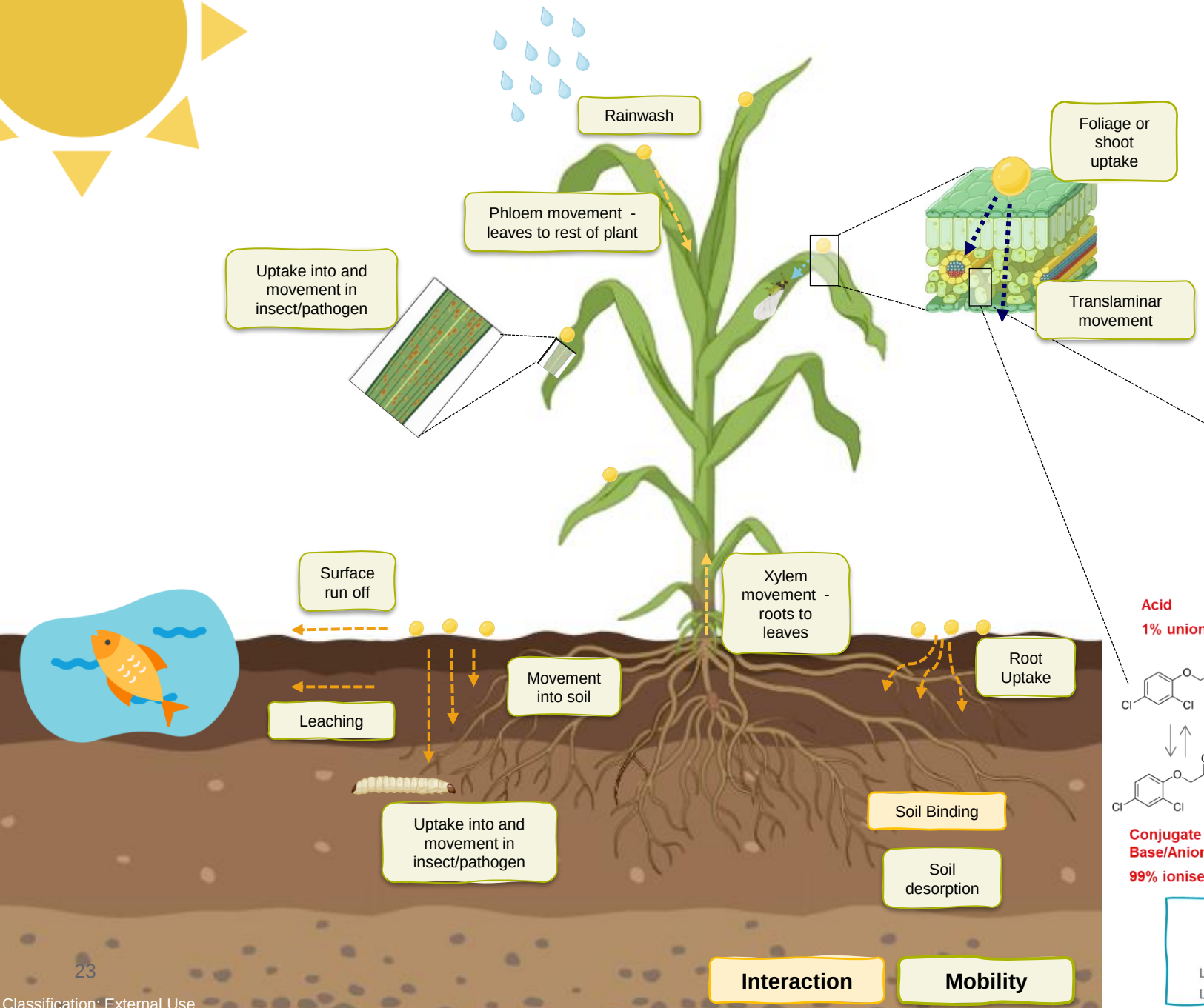


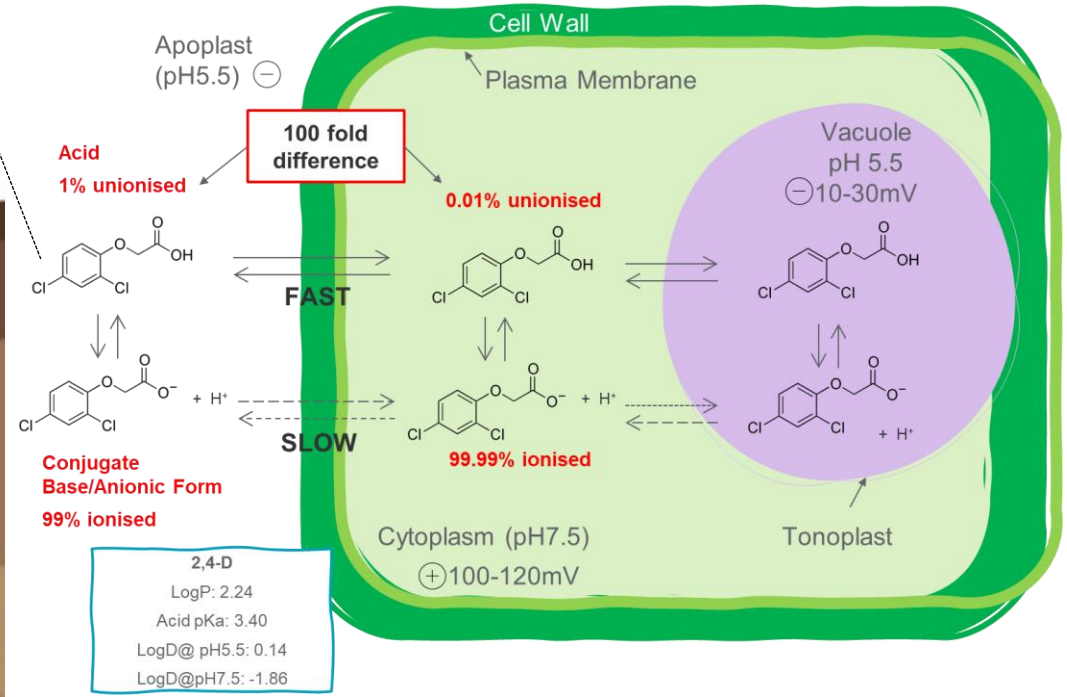
Mesotrione (HER)
Acid pK_a 3.12

ACID BASE NEUT ZWIT

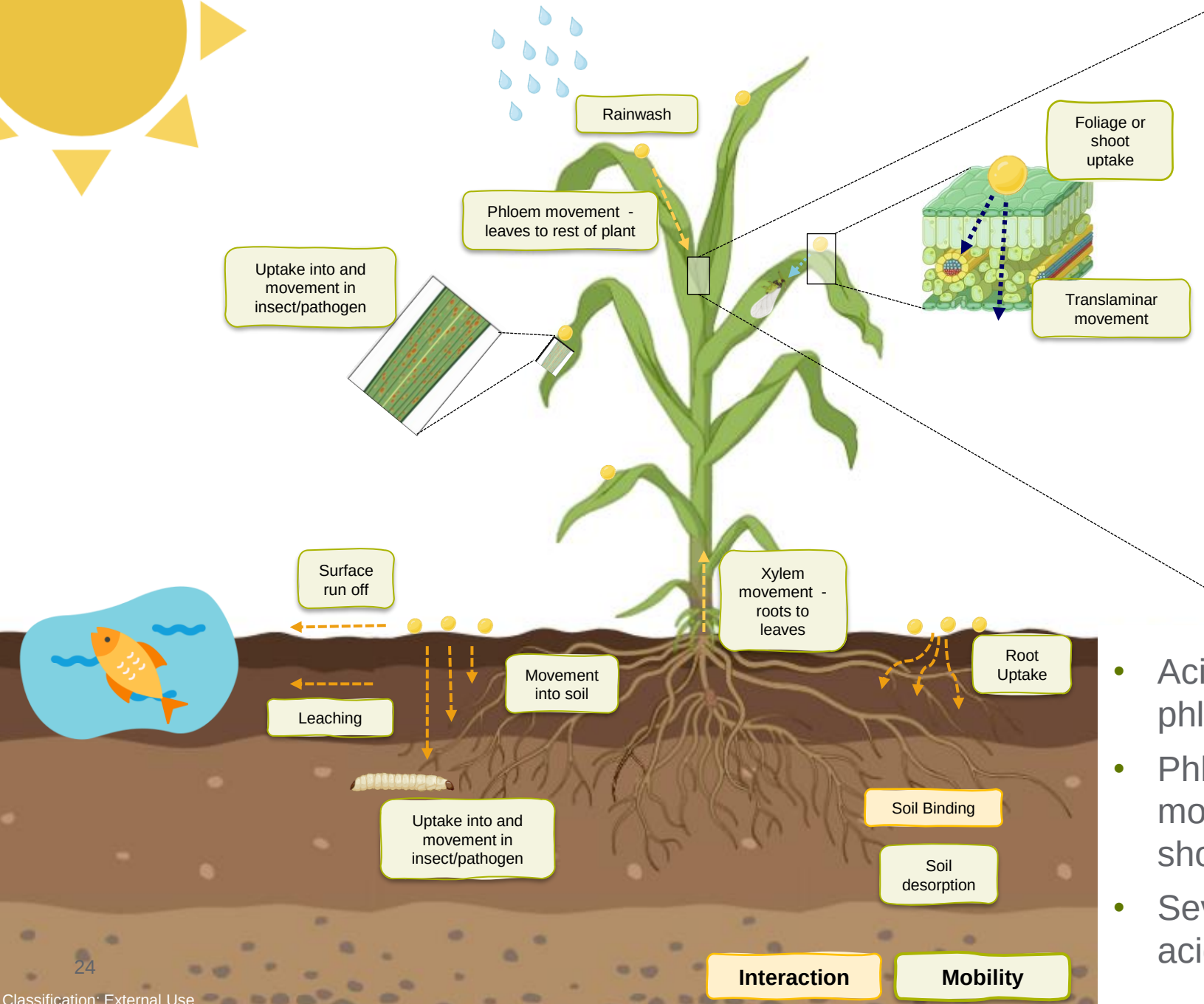
Impact of pKa on Bioavailability

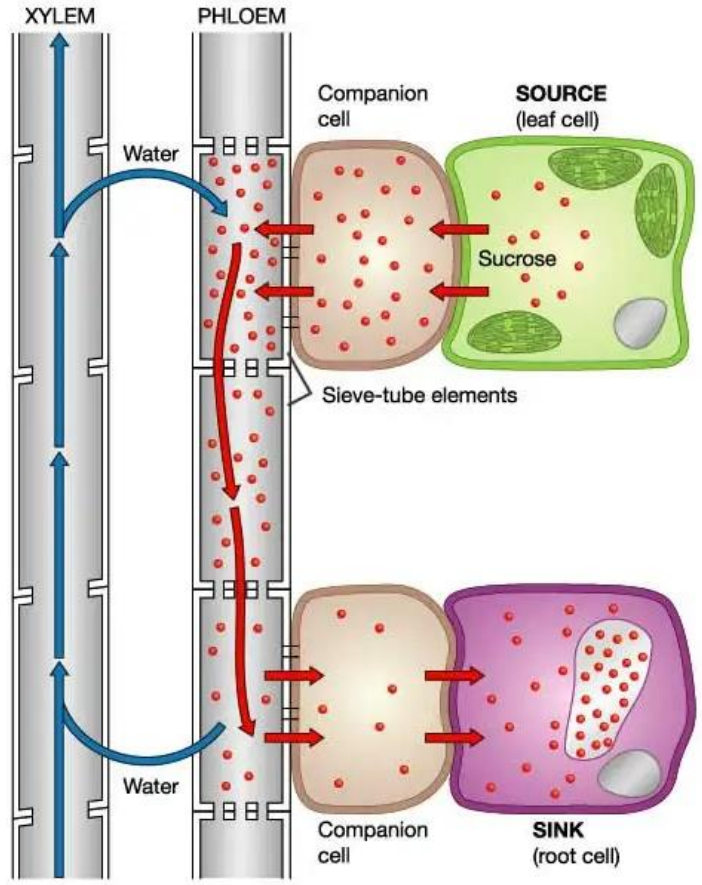
- A variety of pH's across the different biological systems of interest (target and non-target).
- Behaviour of compounds impacted by pKa value and type.
- Compound charge also impacts movement in the environment:
  - Movement in soil
  - Solubility in water bodies





Impact of pKa on Bioavailability





pH5.5 pH8.0

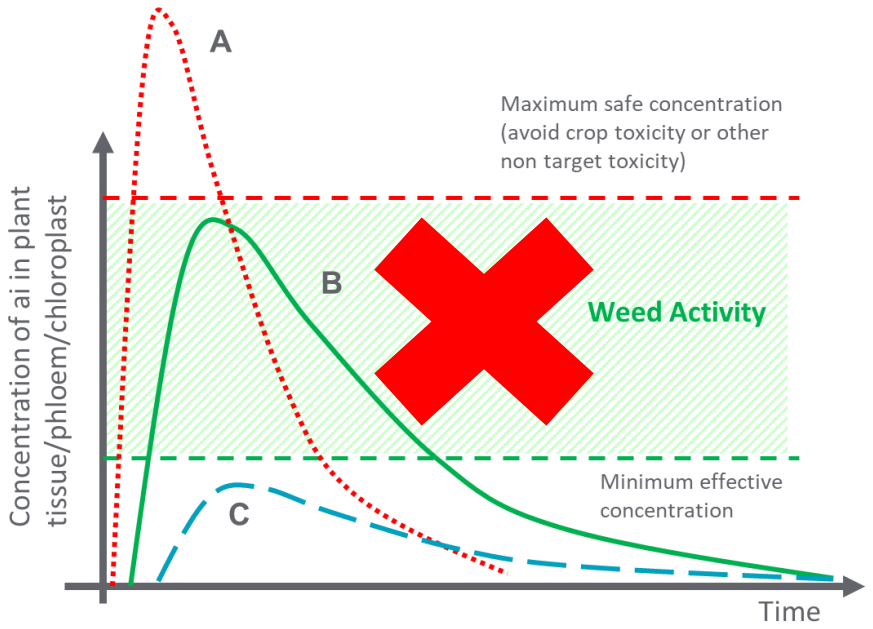
- Acid trapping/accumulation phenomena in phloem due to the pH differences.
- Phloem mobile compounds are key for moving compounds to growing tips (roots & shoots meristematic tissues).
- Several models theorise an ideal logP and acid pKa space for best phloem mobility.

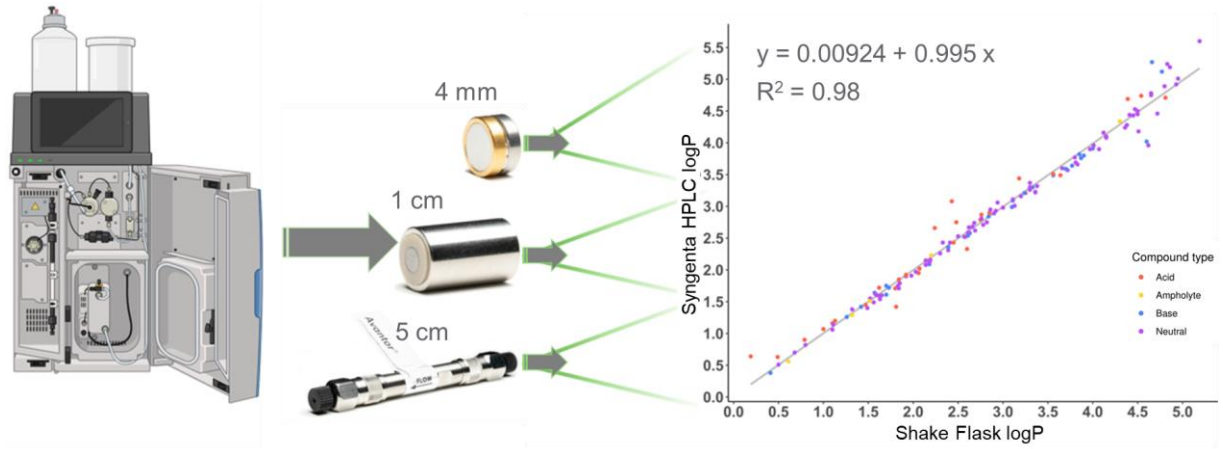
ADME and PhysChem in AgChem

- ADME understanding is still evolving within the AgChem industry.
  - Multiple targets = multiple ADME processes

- PhysChem properties are essential for understanding ADME.
  - logP, pKa and water solubility are the key mobility properties.
  - Different targets have different property profiles.

- We measure high quality experimental PhysChem data.
  - Often using bespoke methodology due to AgChem PhysChem space.





Experiments are great, but….

- We can’t measure the physical properties of every compound we make

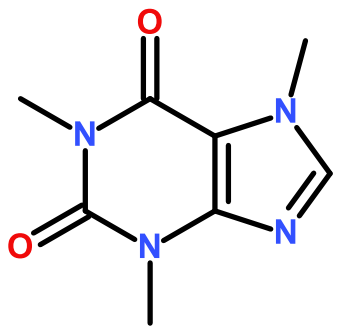
- And we don’t want to anyway

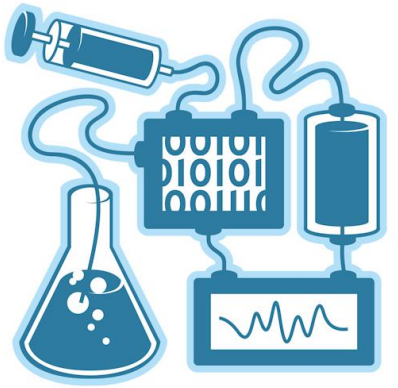
- Actually, we’d like to know the properties of compounds ***before*** we make them

- We want to be able to predict the physical properties of any compound

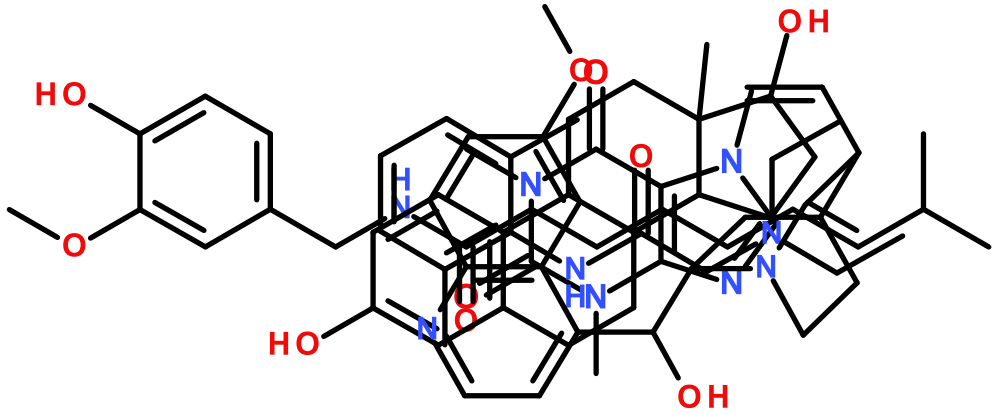
Ensure that every Syngenta scientist has routine access to physical property data of the highest possible quality

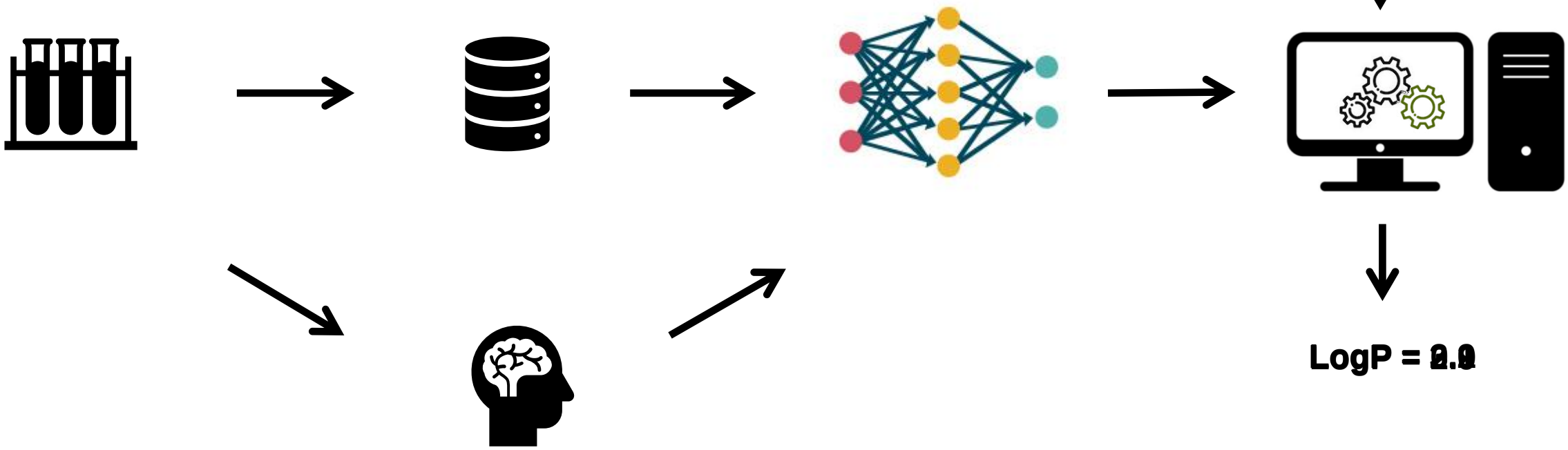
- at the moment when they need it





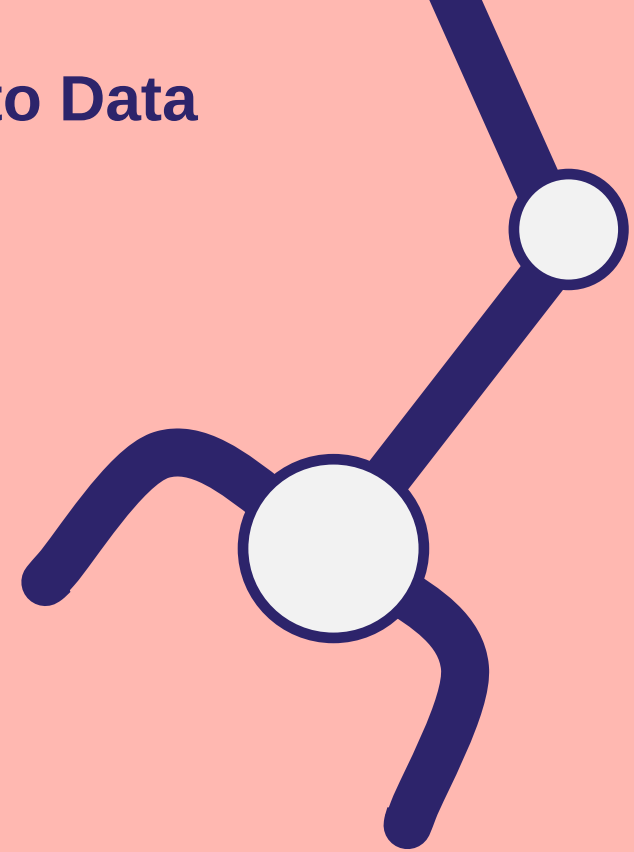
Data Driven Predictive Modelling

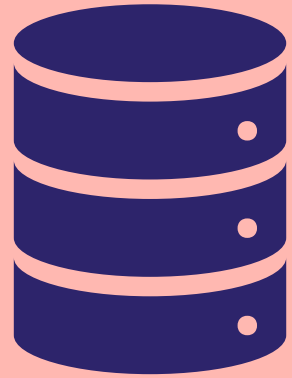




LogP = 2.0

Turning Knowledge into Data with Crowdsourcing





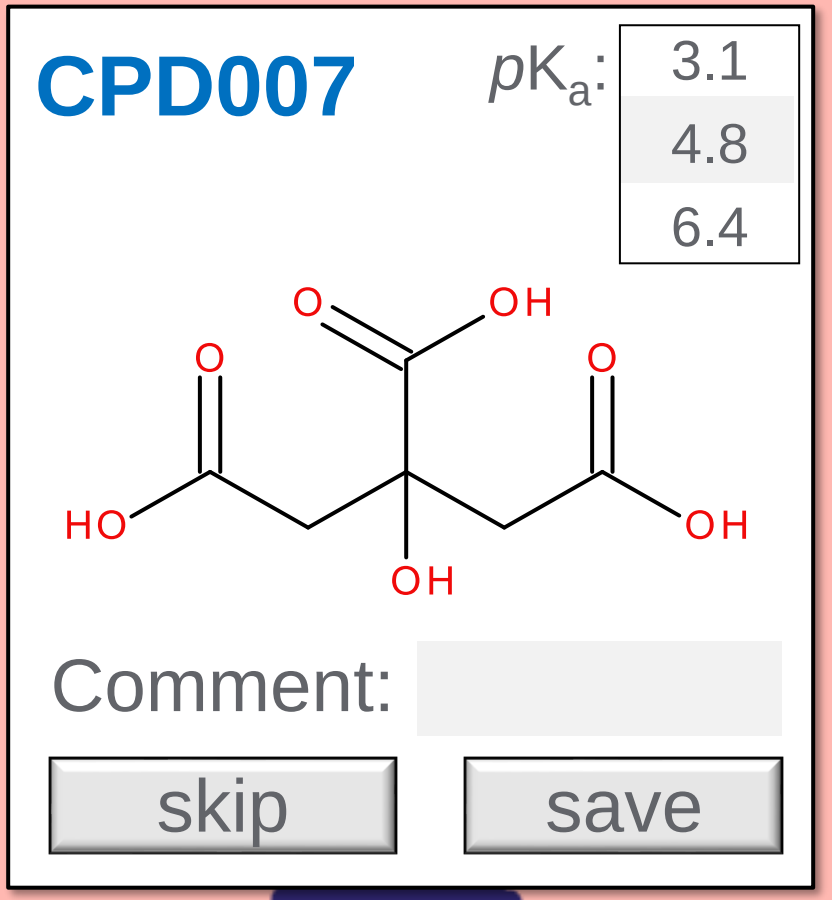
Turning Knowledge into Data with Crowdsourcing

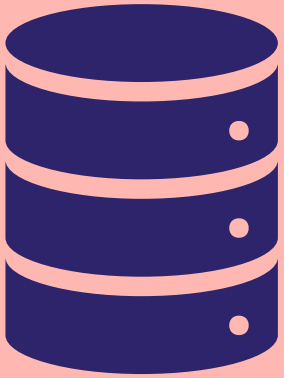
Turning Knowledge into Data with Crowdsourcing

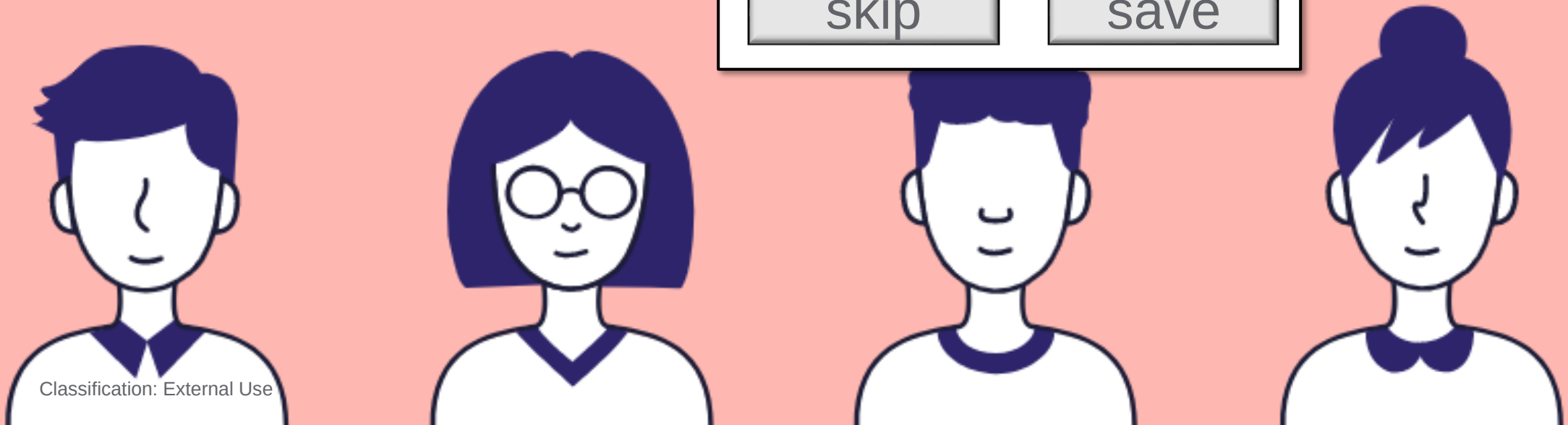
Turning Knowledge into Data with Crowdsourcing

> 35 Syngenta experts

> 4,200 assignments



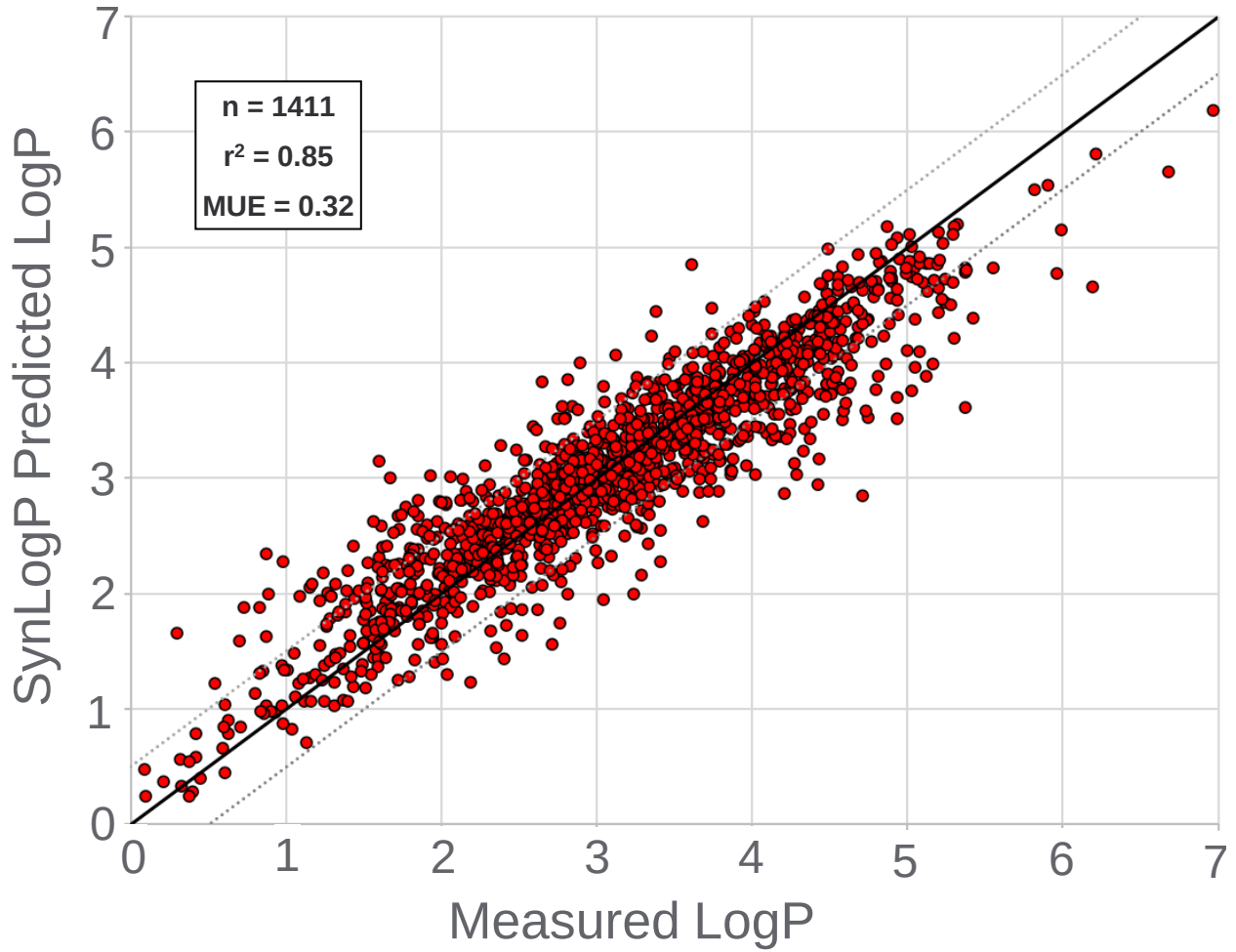




SynLogP

- Algorithm:
  - Support Vector Machine
- Training set:
  - ~25k internal data points
  - ~10k literature data points

- Hosted on internal modelling platform
- Automatically retrained every week
- Deployed to end-user tools (and available via API)

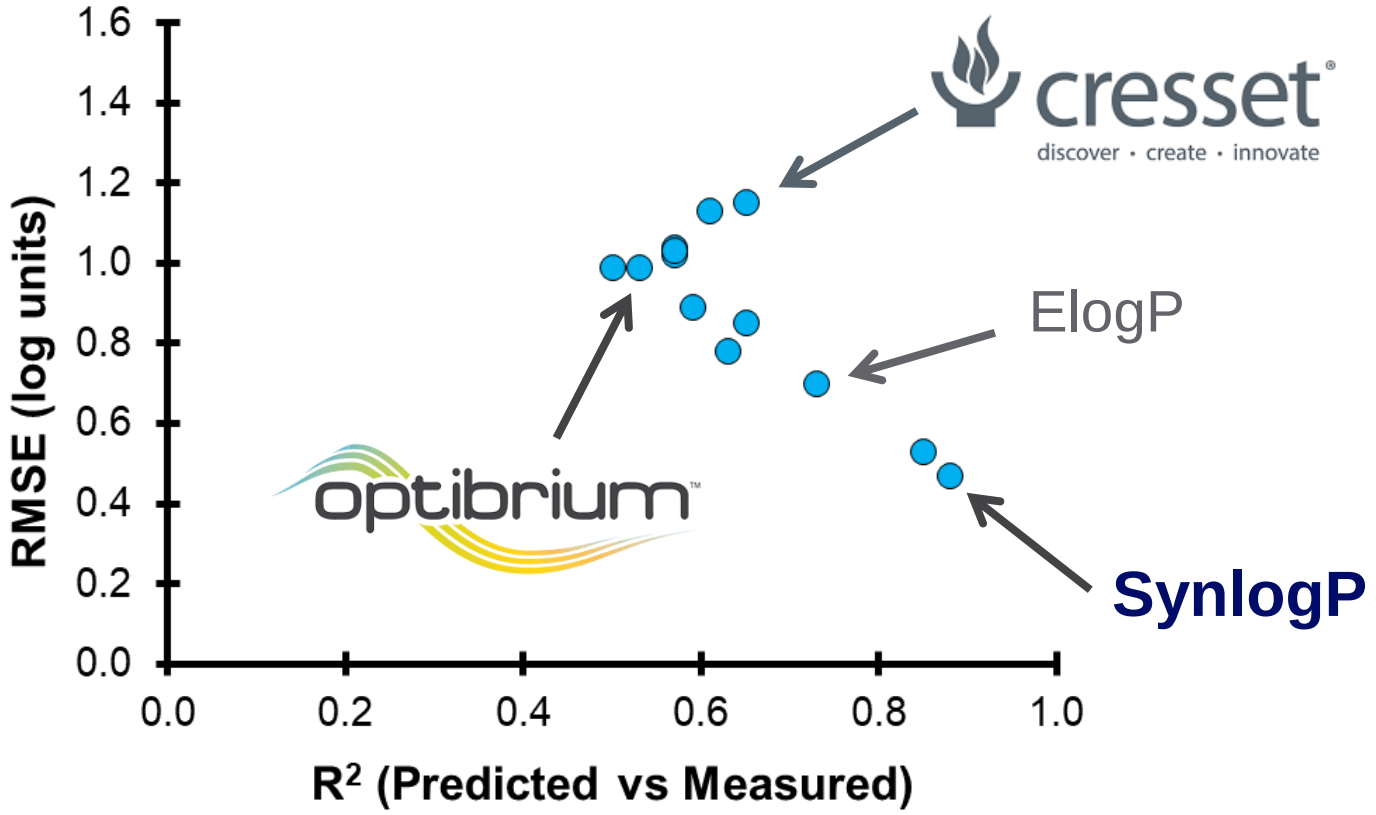


1411 Measurements

80% of predictions within 0.5 log units

97% of predictions within 1 log unit

Building High-Performing Models



Uptake and Use

2018

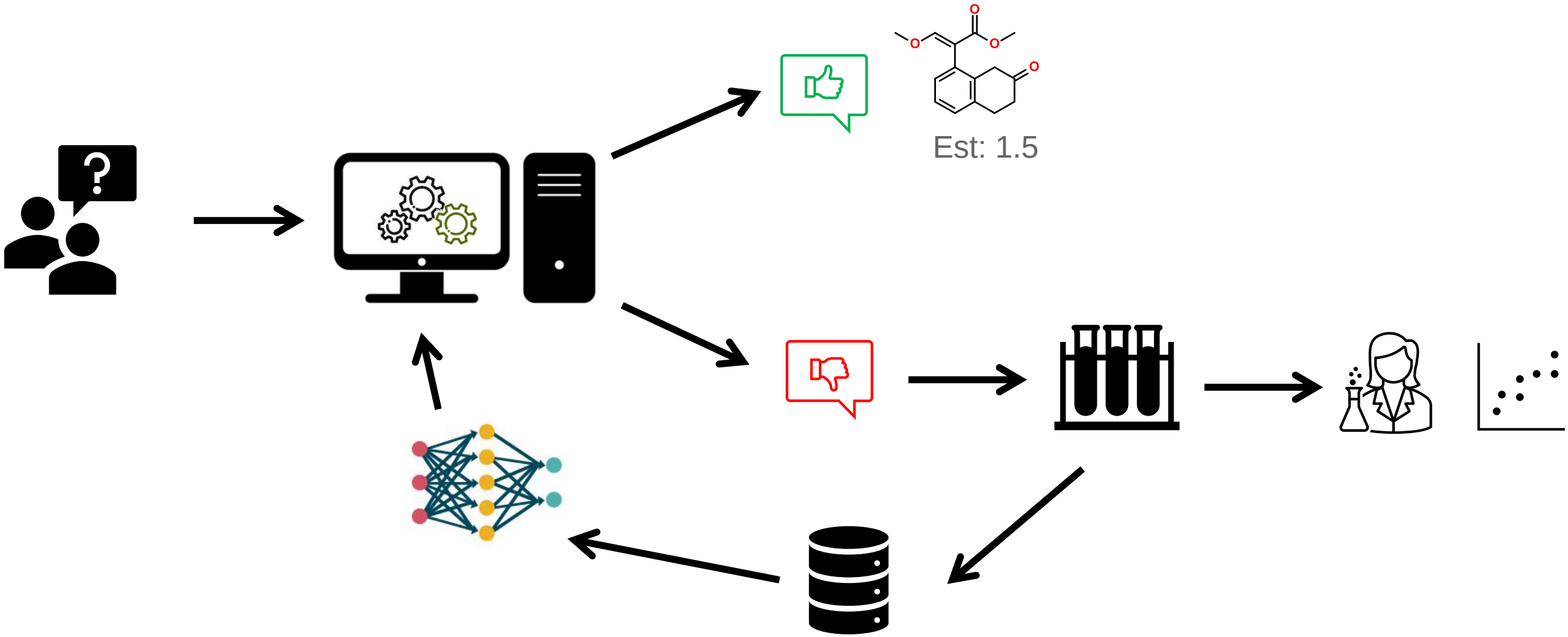
38%

2022

80%

Of scientists working in Research Projects use predictive models to obtain Physical Property Data

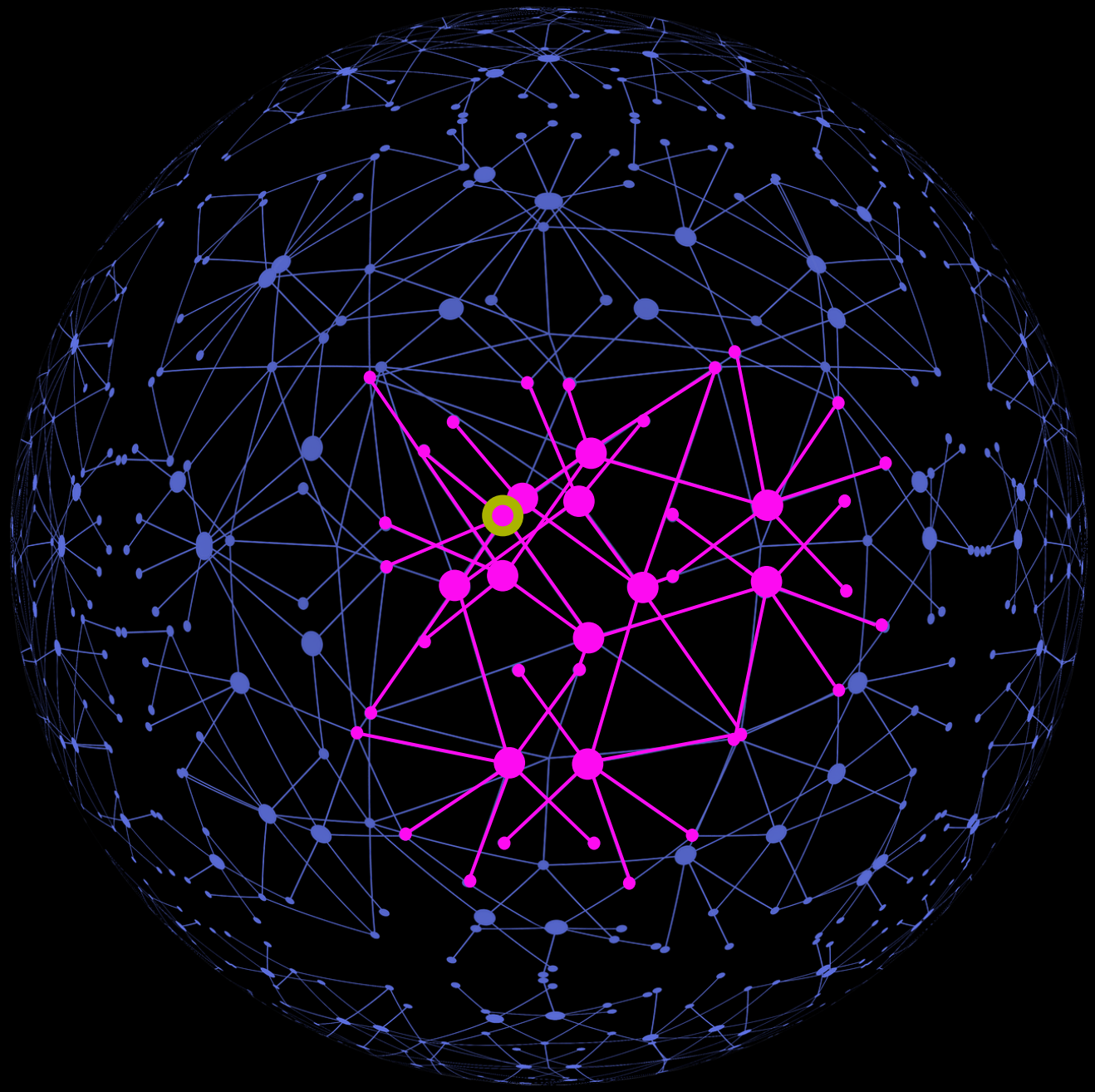
Impact – Active Learning



A single compound can be highly connected in chemical space…

18 measurements informed predictions for 3118 compounds

Advancing knowledge by 3 years

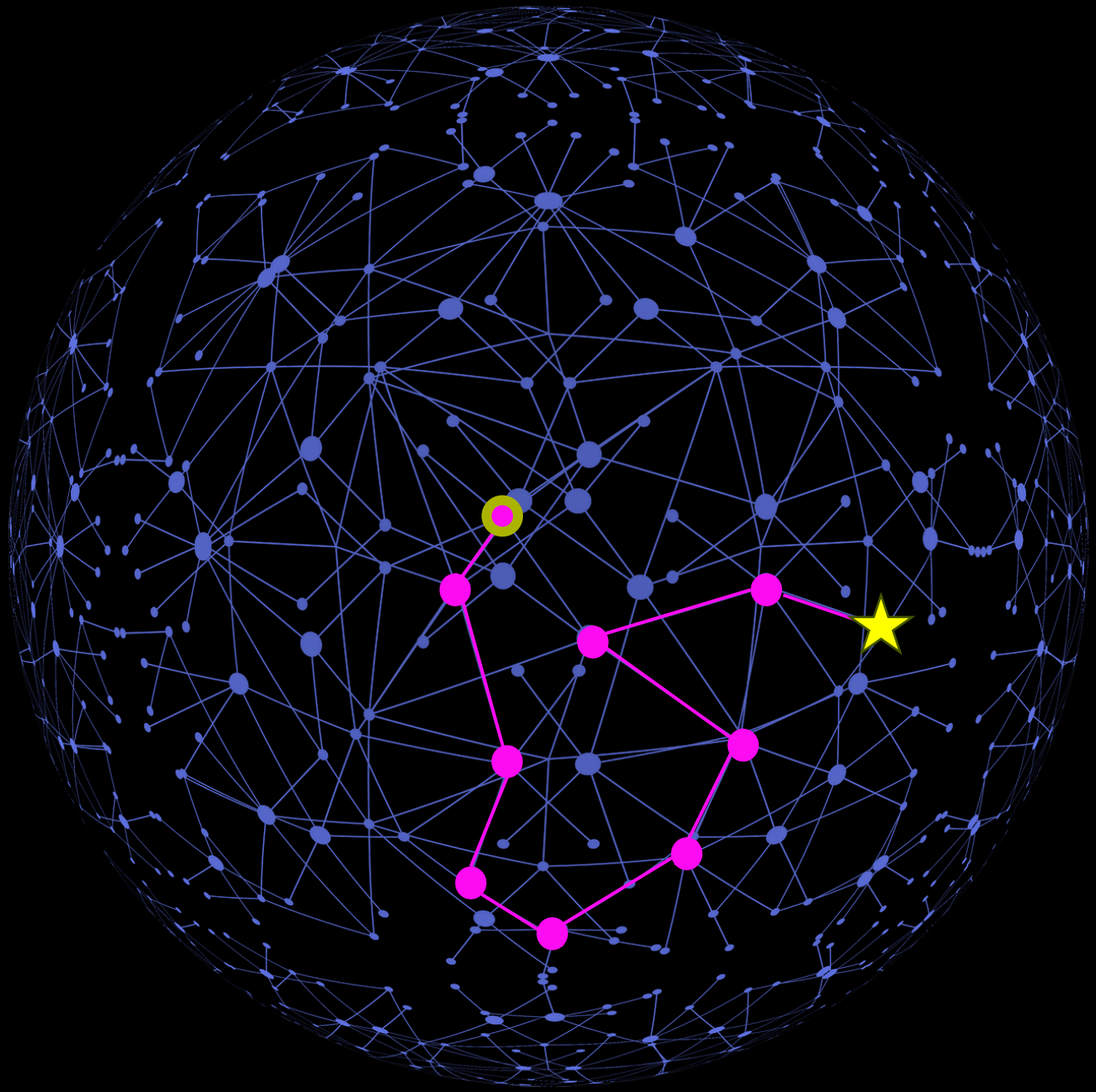


Chemical Design

Design target: reduce logP

Lead Compound
logP = 3.0

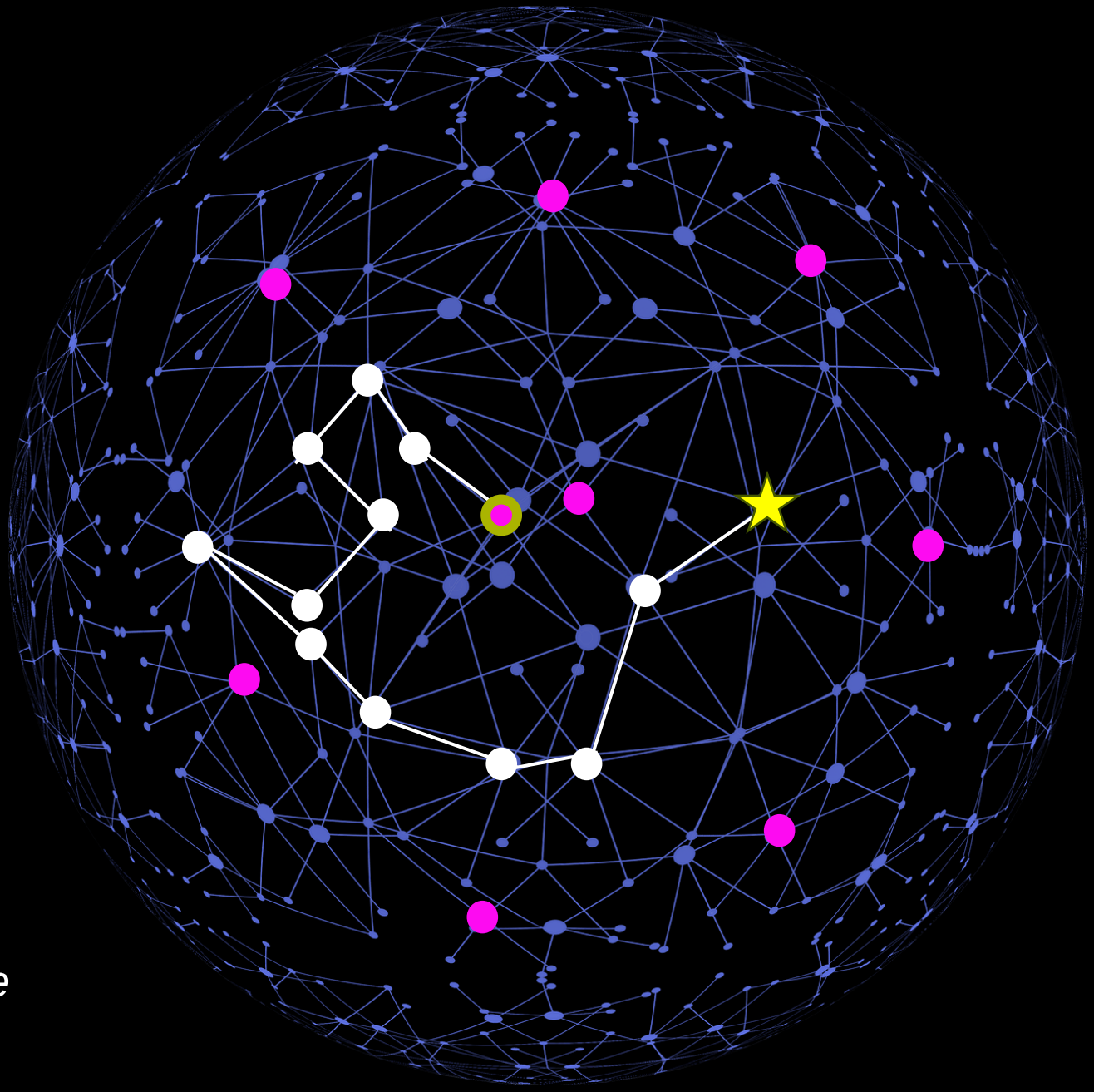
New Compound
logP = 0.8



Enabling Generative Chemistry

Design target: reduce logP

- Profile Chemical Space
- Lead Compound
  logP = 3.0
- New *virtual* Compound
  Predicted logP = 0.4



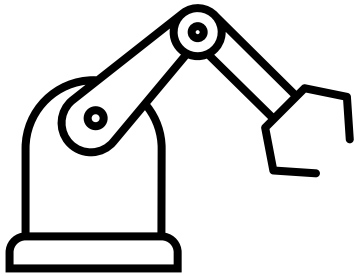
High quality predictive models are essential for inverse design

Active Learning Workflows

In 2023, we trialled an automated, closed loop workflow within projects

- Aiming to deliver more high-quality data, more quickly by improving Syngenta models for logP and pKa.

- All newly registered compounds were automatically evaluated
  - a subset was selected for measurement every week.

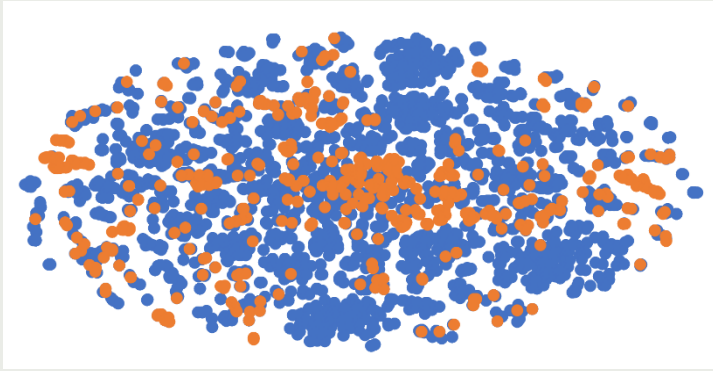
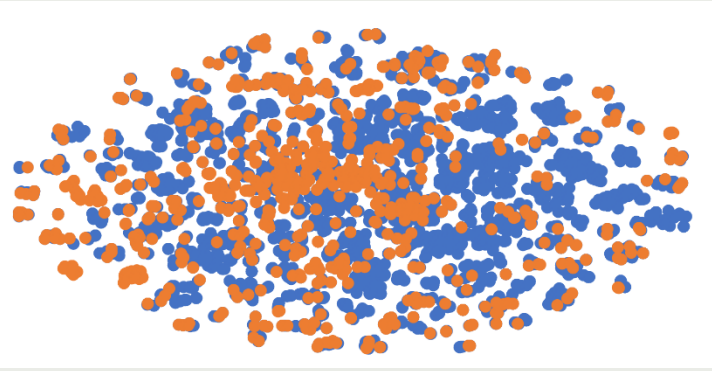


Compounds were selected based on the following criteria;

- Confidence of the existing algorithm
- Compound availability (>15mgs)
- Assay requirements (presence of a chromophore, measurable logP range etc)

- A small selection of well predicted compounds will also be measured to test the model performance.

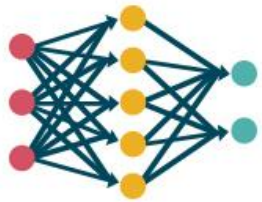
Active Learning: Performance

Measurement Metrics	Before Active Learning (6-month period)	With Active Learning (6-month period)
LogP Requests Completed	684	919
Median time between sample registration and logP request completion	102 days	76 days
% of compounds with a logP measurement within 60 days of sample registration	16%	36%
Chemical Space coverage		

* Comparing 6 months prior to AL implementation (June-Dec 2022) to 6 month trial of AL (June-Dec 2023).

Conclusions.

- ADME understanding is still evolving within the AgChem industry.
- PhysChem properties are essential for understanding ADME.
- We measure high quality experimental PhysChem data.
- Which enables us to building high quality predictive PhysChem models.
- These models allow us to provide PhysChem data at scale, on demand.
- And coupling models with measurements drives efficiency in the lab.
- Freeing time and resource for the development of new methods in the ADME space.




Partnership between computational, physical and medicinal chemists is essential!

Acknowledgements

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