

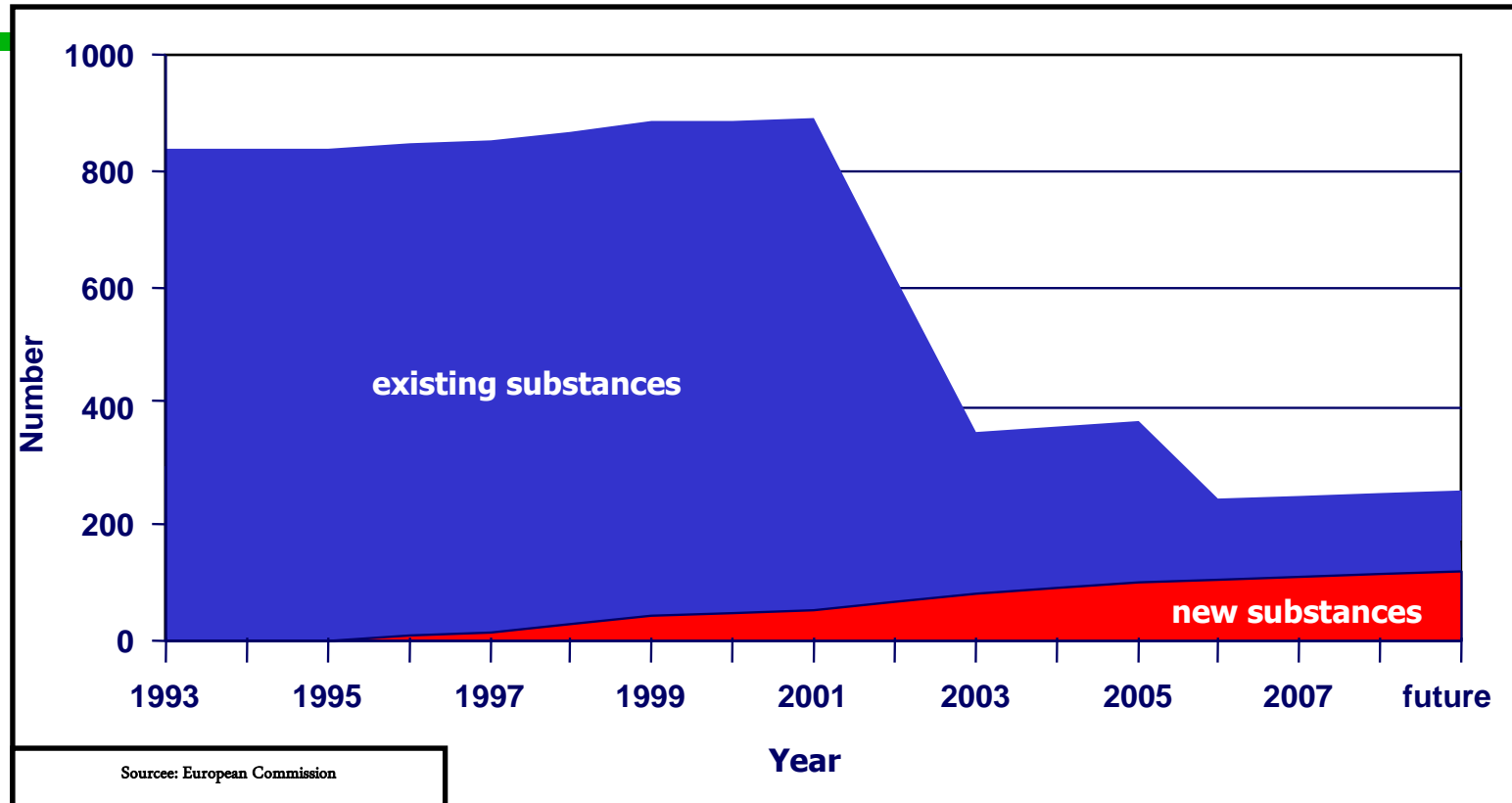
Dynamics to develop a new molecule and product Stewardship matters

DAFF Minor Crops 2018 Stakeholders Workshop, ARC VOPI

Andre Broeksma



Regulatory pressure at European level



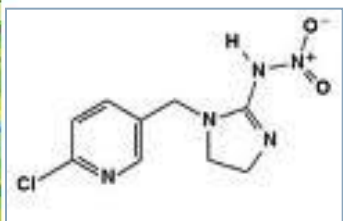
▶ Many active substances being lost due to the review programme



The Challenge of developing Plant Protection Products



From the molecule...



...to the final product

▶ Development: The challenging task of transferring Research into Products



Optimal profile for crop protection product

High and sustainable efficacy:

- New Mode of Action
- Broad and high efficacy
- High selectivity
- Knock down effect
- Residual efficacy
- High plant compatibility
- Systemicity
- Low resistance risk

Favourable environmental profile:

- Beneficial friendly
- Good degradation (metabolism)
- Low application rate
- Low drift
- Low mobility in soil
- Low residues

Innovative agricultural product

High operator safety:

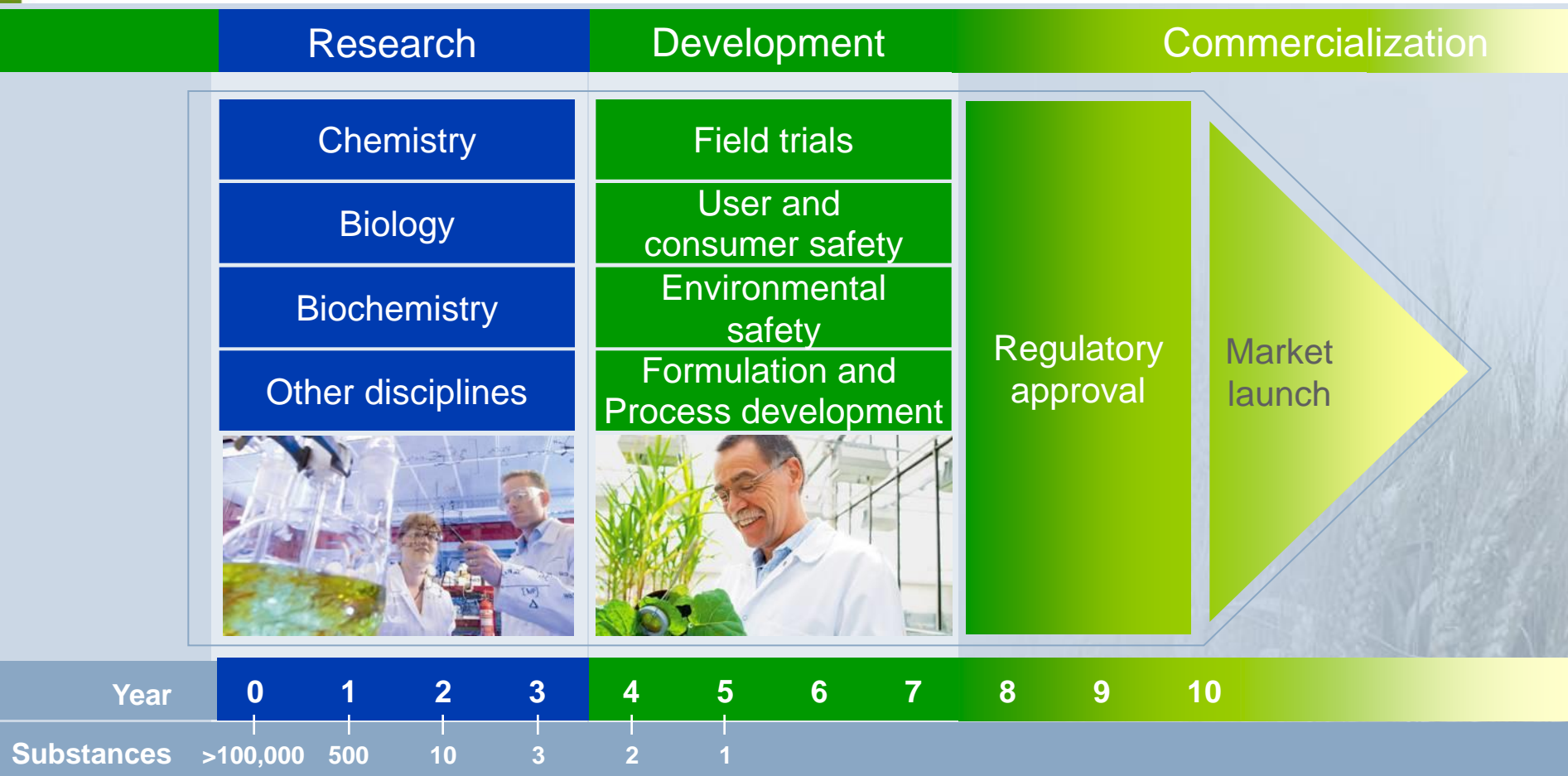
- Low application rates
- Low acute toxicity
- Ease of application
- Suitable for formulations
- Compatibility to other pesticides
- Storage stability

High profitability:

- Favourable cost-benefit ratio
- Adapted to IPM programs
- Unique selling propositions
- Portfolio fit
- Competitiveness
- Fast registration
- Patent protection



From Idea to Market



▶ After 8 to 10 years and an average investment of about €200 million, one compound out of 100,000 substances reaches the market

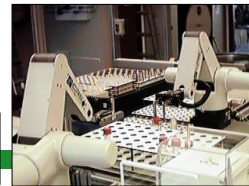


The general process of identification and optimization of active ingredient

virtual screening



Test Libraries



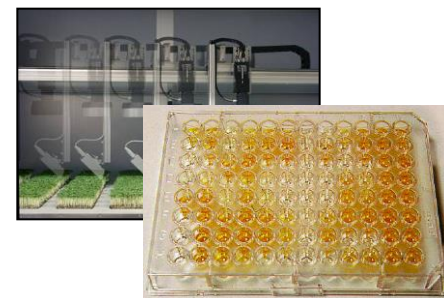
chemical synthesis



Target based HTBS



Vivo Screen



in vivo HTS



Research Projects

Lead Structures

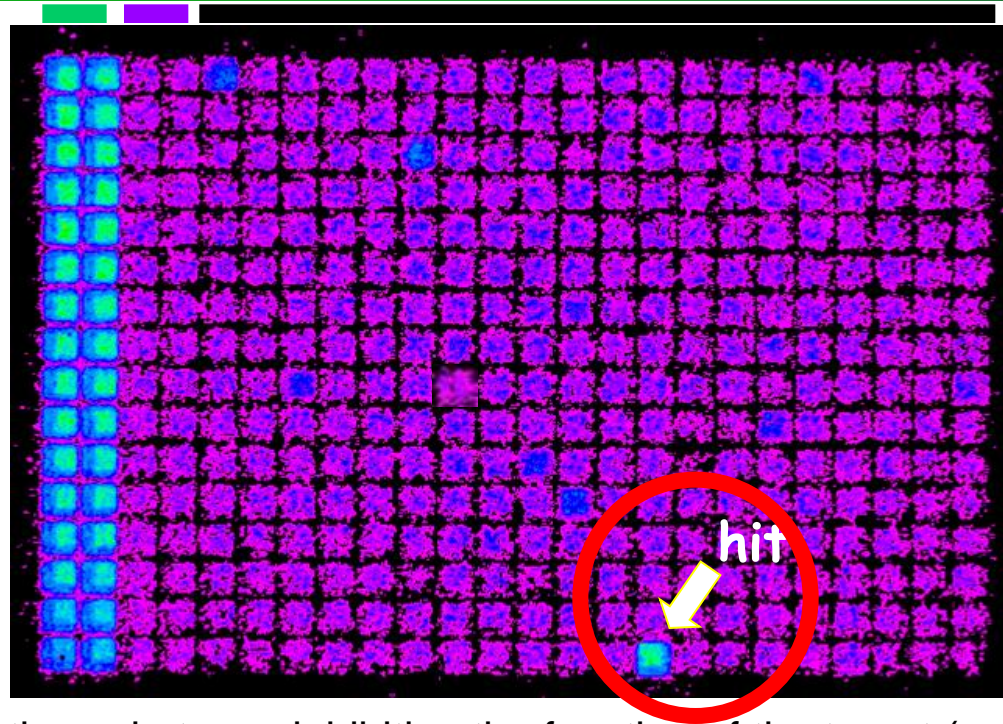
Development Projects



Example of a test plate in target based screening

positive controls

test compounds



Hit = active substance inhibiting the function of the target (mode of action)

- The target based approach is fully integrated and is one part of the early discovery workflow – but hits have to overcome the *in vivo* hurdle



Primary Screening – Spray booth system



Fieldscreening in Early Phases - Insights into Potency of Compounds under Natural Conditions



Peter Oberkötter

- Important tool for differentiation of top ranking compounds in a chemical class – direct guidance for chemistry in optimization



Development processes

- Formulation
- Biological profiling
- Toxicology
- Metabolism and E-Fate (MEF)
- Residues, Operator and Consumer Safety (ROCS)
- Ecotoxicology



Working Areas in Product Development

Formulation Technology

Convenient and Robust
Allowing registration
Producible at industrial scale
Compatible with applications



Biological profiling

Demonstrating technical profile
Basis for marketing concepts
Demonstration of additional
benefits e.g. Plant health



Human Safety

Residues of active ingredients /
metabolites in animals &
plants
Risk of products for operator
& consumer



Environmental Safety

Metabolism of active ingredients /
metabolites in animals & plants
Environmental fate
Ecotoxicological behavior



Regulatory Affairs

Active ingredients and products
Compilation of dossiers
Aligning with regulatory community
Influencing external regulatory community



Formulation – Why do we need it?



How can we treat an area of a rugby field (>1 ha) with a few grams of active ingredient?

**Agrochemical
+ supplementary components
= Formulation**



Formulation - Major challenges

Water is the most common carrier for the distribution of agrochemicals

Problem: Most active ingredients are not easily soluble in water

Solution: Formulation technology must provide the active for:

- easy dilution in water**
- even distribution on the crop**
- optimal biological performance**
- easy and safe handling**
- lowest environmental impact**



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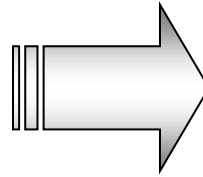
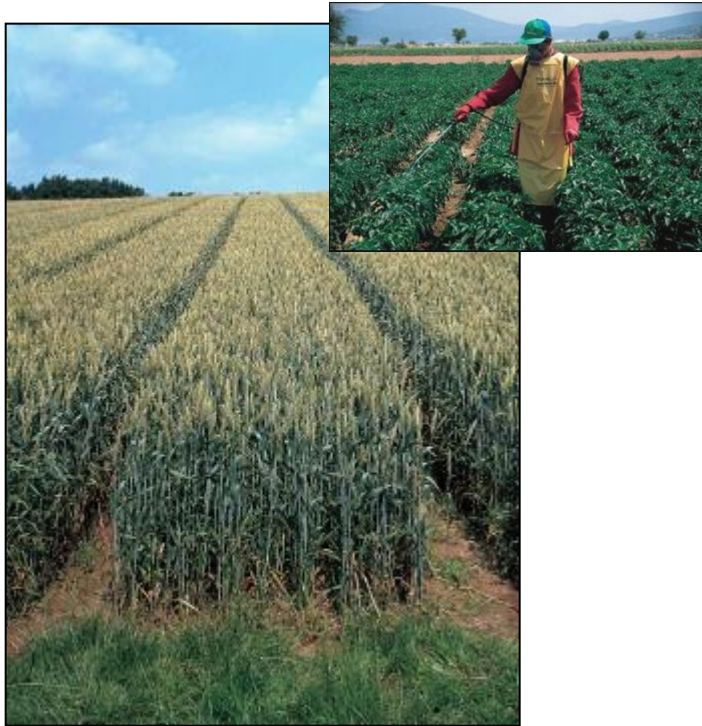
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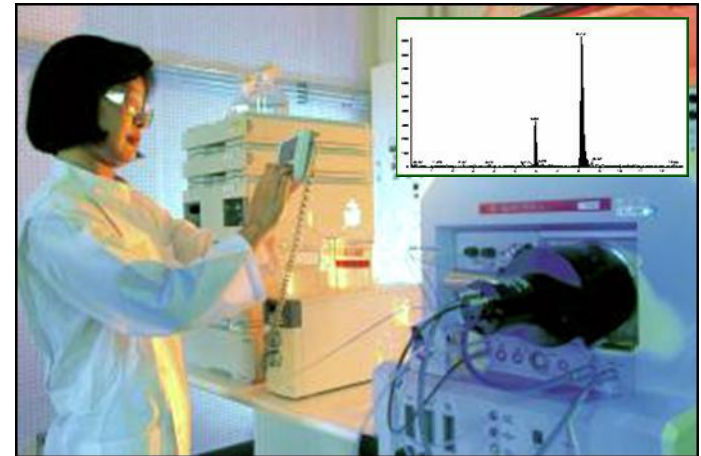


Human Safety: Conduct of Residue Studies

Application & Sampling



Residue Analysis



under practical conditions on test plots
trial sites all across South Africa
24 items, at least 2 kg

5 trial locations (1x rate)
4-5 points (breakdown curve)
1 $\mu\text{g}/\text{kg}$ = 1 ppb =
1 part in 1 billion
1 mm of 1000 km
1 wrong letter in 4000 bibles



Human Safety: Conduct of Operator Exposure Studies

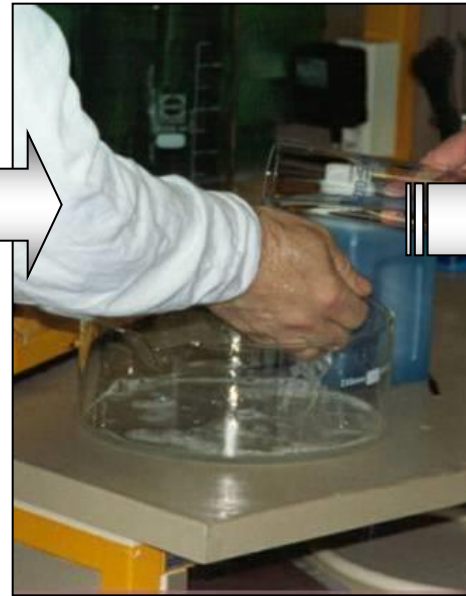
“Artificial skin”



Normal use



Controlled washes



**Clothes and
“skin”**



Human Safety: Exposure and the Food Chain

Exposure scenarios cover the entire Food chain
Residues are measured in all affected food types

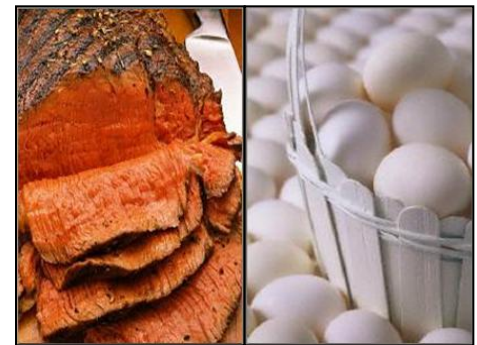
**Food of plant
origin**



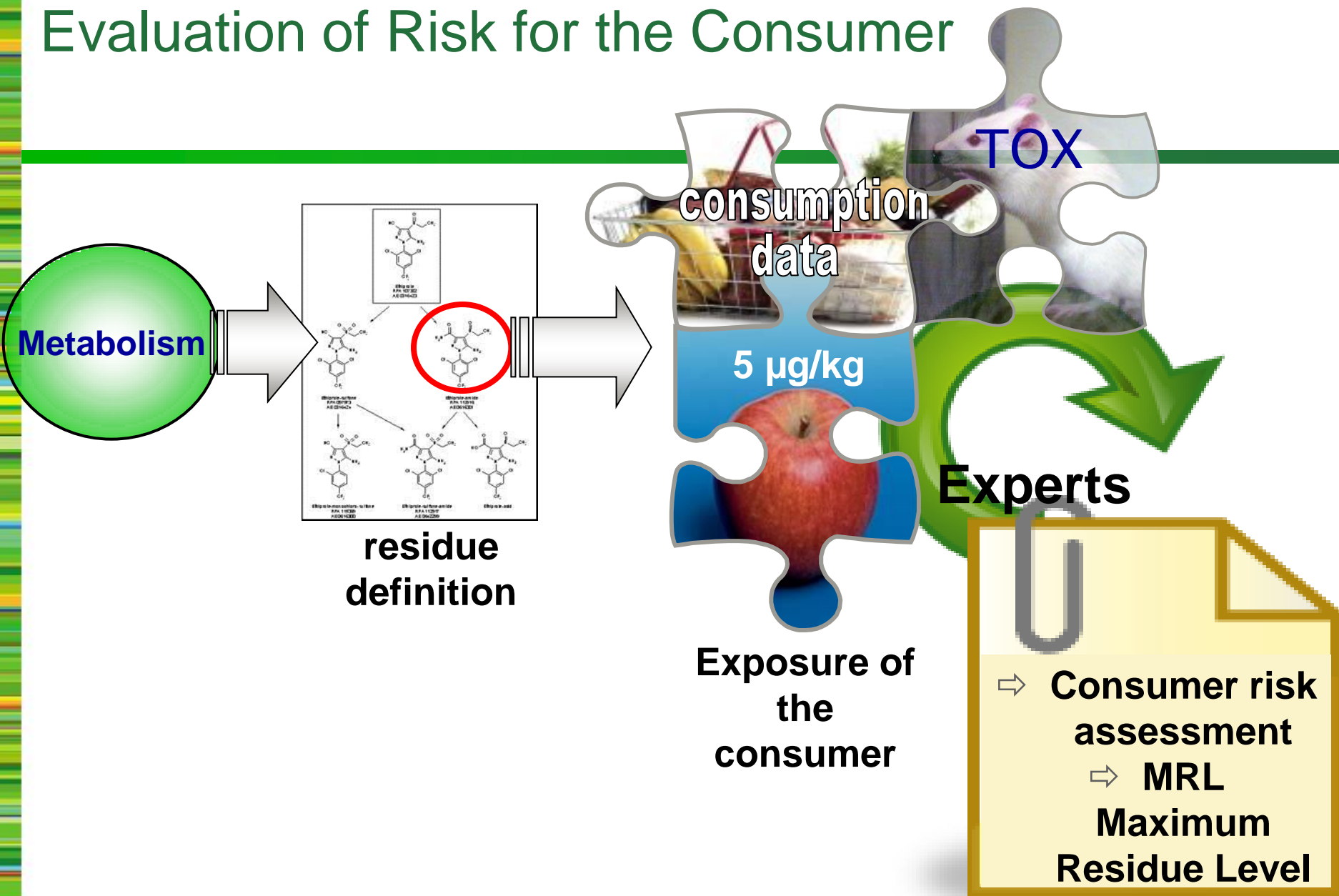
Processed food



**Food of animal
origin**



Human Safety: Evaluation of Risk for the Consumer



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Ecotoxicology: Studies and Risk Assessment to Demonstrate Environmental Safety of Products

Aquatic Organisms



Outdoor pond facility

Non-Target Arthropods & Bees



Semi-field honey bee study

Soil Organisms



Earthworm field study

Non-Target Plants



Aquatic macrophytes pond study

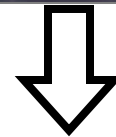


Terrestrial Vertebrates



Arthropods = “Gliederfüßer”;
Insects, spiders etc.

Vertebrates = “Wirbeltiere”,
amphibia, reptiles, birds, mammals



Project Discovery
0 1 1.1 1.2 2

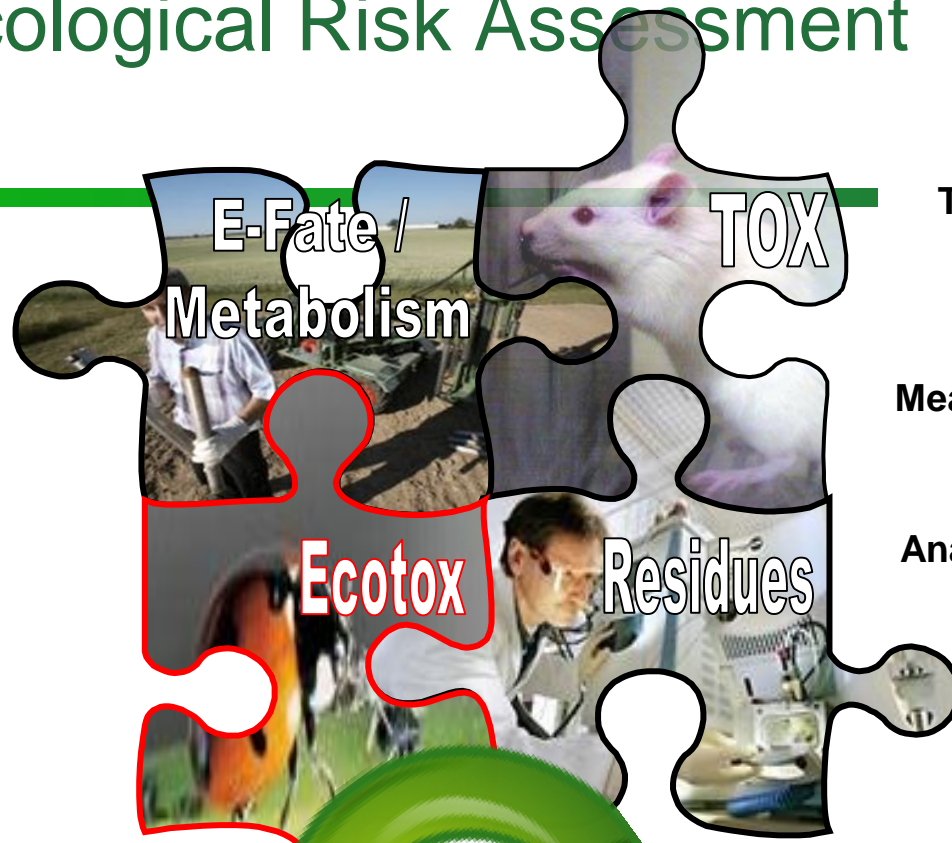
Project Realization
Phase 3

Business Realization
Phase 4



Ecotoxicological Risk Assessment

Metabolic pathways
Relevant metabolites
Behavior of compound and metabolites in the environment
PEC: Predicted environmental concentrations



Toxicological effects
Tox endpoints

Measured concentrations in the environment:
soil, water

Analysis of animals from ETX studies: birds, mice, earth worm, etc...

Ecotoxicological effects

⇒ Ecotoxicological risk assessment



Acceptable uses may involve minimal exposure to a product during application

- Terrestrial, foliar application via downward-directed boom sprayers (either tractor-driven or self-propelled), in which the applicator is protected within a closed cabin or wearing appropriate PPE.
- Professional seed treatment (including on-farm) performed with dedicated seed treatment equipment.
- Aerial application outside of populated areas if carried out by professional applicators, without the use of human flaggers, and where workers and local populations are adequately protected from spray (drift) and/or deposits.
 - Chemigation in North America



To be avoided: Potential higher risk of operator, worker and bystander exposure due to use pattern parameters

- Greenhouse uses and all permanently or temporarily covered crop uses
- Knapsack sprayer and mist blower atomizer applications
- Aerial application in populated areas
 - Hand-harvested crops,
 - Orchard, plantation and vineyard crops
- Fruiting vegetables (e.g. cucumbers, tomatoes, aubergines)
- Non-professional / non-agricultural uses, (Home and amenity uses including lawns, gardens and turf greens) ornamentals and forestry



Bayer has avoided registrations in ALL of A...



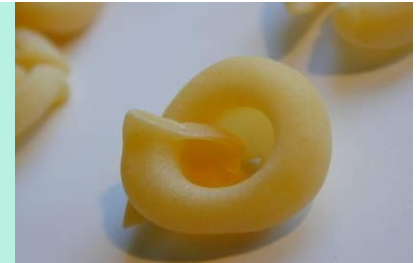
Additional impact on Food Quality & Final Produce

Not only efficacy needs to be determined...

- **Yield**



- **Quality of pasta**



- **Quality of food and feed**



- **Quality in brewing and malting**



- **Quality of baking**



- **Germination rate**



➔ Healthy food of high quality requires innovation



Regulatory Affairs

The registration - our license to sell...



Compilation of core Dossiers for submission and coordination of submissions & registrations worldwide



Changing Regulatory Environment

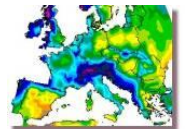
Increasing co-operation between authorities

- EU and US-EPA 'sell' their regulations
- Worksharing, information exchange



Increasing data requirements

- New study types, more complex risk assessments
- Local study requests, introduction of GLP ('good laboratory practice')



Growing importance of global trade

- Countries forced to adapt global standards
- Need for global strategy to achieve Maximum Residue Levels (MRLs)



Increased data transparency

- Evaluations available in the internet
- Accessible to the public



Strong and increasing pressure by NGOs

- Perceived in public as having more credibility
- In contrast to industry accepted as negotiation partner



Increasing political influence

- 'Green thinking', protectionism



Changing Regulatory Environment –AIR process

- Stringent renewal AIR process (AIR1, AIR2, AIR3, AIR4)
- Example: Period Jan–Sept 2017:
 - >10 substances with non–renewal decision
 - >10 substances with critical EfSA conclusio
 - >20 substances not submitted in AIR 4
- Re–registration not requested by applicant, Commission non–renewal decision, EFSA non–renewal proposal, Critical ECHA classification decision
- Over 30 substances are pending decisions, several non–approvals expected
- Products thus needs to be handled responsibly & with care
 - Not overuse (risk of resistance)
 - Manage crop uses – resistance



Minor crop registrations: Risks we are facing

- **We have to acknowledge the efforts of all (Industries and Regulators) to address the issue**
- **Adopting and implementing Global label recommendations and Global residues is risky:**
 - Products act differently on different crops and under different conditions
 - Residue levels can differ (extrapolating Apricot -> Nectarines -> Peach risky because of skin differences)
 - Rates in SA often differ from Global rates
- **Are we (Manufacturer, Authorities, Industry) willing to take these risks ?**



Thank you for your attention

Our Websites

CropLife Africa Middle East

www.croplifeafrica.org

CropLife International

www.croplife.org

