The Development of a Chemical Compound

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Residue Chemistry

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Disclaimer

Forward-Looking Statements

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At Bayer CropScience, we serve agriculture

23,100 employees
Full year sales: € 9,494m
> 120 countries
Innovative solutions in three business segments

**Seeds**
- Vegetable seeds
- Seeds for agricultural crops (e.g. cotton, canola, rice, wheat, soybean)
- Traits

**Crop Protection***
- Insecticides
- Fungicides
- Herbicides
- SeedGrowth

**Environmental Science**
- Products for professional users (pest and vegetation management)
- Products for consumers (home and garden use)

* with both chemical and biological modes of action
We serve our customers worldwide

A global network of manufacturing, R&D and seed processing sites

- Manufacturing sites
- Major R&D sites
- Major seed processing sites

*Research Triangle Park
Integrated crop solutions

Services and consultancy

- Seeds & Traits
- Seed Treatment
- Weed Management
- Pest Management
- Disease Management

Goal: Healthy, high yielding and high-quality plants

Healthy, high yielding and high-quality plants
BCS Product Launches

- 2003: Ignite, Calypso, Silverado, Osprey
- 2004: REASON, SCALA
- 2005: Olympus
- 2006: TRILEX, AERIS, BAYTHROID XL, RADIUS
- 2007: Huskie, PROVOST, AUSTRUM, Synapse, Ignite
- 2008: BELT, SYNAPSE, Ignite, LAUDIS
- 2009: BalanceFLEXX, CORVUS, VOTIVO
- 2010: UTOR, HBK SEEDS, Capreno
- 2011: Alion, Luna COMPLETE
- 2012: Luna TRAUNQUILITY, Luna SENSATION
- 2013: Luna EXPERIENCE, Propulse, Luna EXPERIENCE
2014 – 2015 BCS Product Launches

ST Fluency Agent
2015 Product Launches

- **VELUM TOTAL**: A new solution for nematode and early insect management in southern row crops.

- **SIVANTO**: Fast-acting, long-lasting residual insecticide for horticulture crops.

- **Credenz**: Utilizes high-performing, smart genetics to maximize soybean yields.

- **ILEVO**: Seed treatment that protects against Sudden Death Syndrome (SDS) and nematodes.

- **DiFlexx**: Combines Bayer’s superior CSI Safener with Dicamba for fast, effective, crop-safe control of broadleaf weeds (including those resistant to glyphosate).
From Idea to Market – Developing a Crop Protection Product*

After 8 to 10 years and an average investment of about €200 million, one compound out of 100,000 substances reaches the market.
Discovery/Hits (phase 0)
Discovery – Pre-project (phase 1-2)
Agronomic Development - Demonstrating Efficacy of New Products

Example: Movento (Launched in 2007)

- New insecticide with broad pest control
- 2-way systemicity & long-lasting control
- Bee and beneficial safety

1 application targeted against *Eriosoma lanigerum*
Agronomic Development - Demonstrating Efficacy of New Products

**Example**: Movento (Launched in 2007)

- New insecticide with broad pest control
- 2-way systemicity & long-lasting control
- Bee and beneficial safety

**Untreated vs. Treated**

- **Untreated**: aphids + callus reaction
  - Giant cells after sucking
  - *E. lanigerum*

- **Treated**: branches protected
  - (no callus, no infestation)
The Formulation Challenge

How to uniformly treat a large area (1 ha) with a small amount (a few grams) of active ingredient?

How to make it convenient to use?

Agrochemical
+ supplementary components
= Formulation
Project – Commercial (phase 3-4)
DNA Field Operations

- Technology Centers
  - Screening phase 1.2 through 3
  - Development of phase 3 & 4 products
  - Facilities for sales support & training
  - BS & ES testing & support

- Field Development
  - Phase 2-4 testing & development
  - Product label & use directions
  - Regional & local fit
  - BS testing & support

- Tech Service
  - Pre-launch & launch activities
  - Influencer contact
  - Product positioning & sales support
  - Training

- SeedGrowth Tech Reps
  - Early Development
  - Sales Support / Training
  - Collaborate w/ seed companies
The Research & Development Process

Phase 0: Discovery
- Gate 1: Research Targets

Phase 1: Technical Concept Testing
- Gate 2: Technical Proof of Concept

Phase 2: Commercial Concept Testing
- Gate 3: Commercial Proof of Concept

Phase 3: Development
- Gate 4: Clearance for Sales

Phase 4: Life cycle Mgmt.
- Gate 5: Maintenance or Discontinuation

Selection → Validation → Registration → Commercialization
## Development of a Crop Protection Product

### CHEMISTRY
- **Active ingredient**
  - Synthesis
  - Process development
  - Synthesis optimisation
  - Pilot plant production
  - Formulation / Packaging
- **Formulation**
  - Laboratory/greenhouse
  - Pilot trials
  - Field trials for development and registration
- **Costs in $**
  - $80-108 million

### BIOLOGY
- **Research**
  - Laboratory/greenhouse
  - Pilot trials
- **Development**
  - Field trials for development and registration
  - Optimization of application
- **Costs in $**
  - $80-108 million

### TOXICOLOGY
- **Mammals**
  - Acute, sub-chronic, chronic toxicity/mutagenicity/carcinogenicity/teratogenicity/reproduction
- **Environment**
  - Algae/daphnies/fish/birds/micro-organisms/bees/non-target organisms
  - Regulatory evaluation of registration documents/registration/first sales
- **Costs in $**
  - $80-108 million

### ENVIRONMENT
- **Metabolism**
  - Plants/animals/soil/water and air
- **Residues**
  - Plants/animals/soil/water and air
  - Costs in $240-338 million

### Substances
- >>100,000
- 500
- 10
- 3
- 2
- 1
- 1
- 1
- 1
- 1

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*Note: The image contains a table and a flowchart illustrating the stages of developing a crop protection product.*
Environmental Safety/Human Safety

We ensure the human and environmental safety of our technologies to maximize current and future value for our company, our customers and our communities.

Mindful Matters

Mission Statement in Development North America
Regulatory Science is about Risk Management defined by Federal Laws

**United States**

**FQPA:** *Reasonable certainty of no harm* (to humans consuming food produced or imported into the US with special focus on risk to infants and children).

**FIFRA:** *No unreasonable adverse effects* (to the environment) with consideration given to “benefits” (reliable food production, public health, etc.)

**Endangered Species:** *Not likely to jeopardize the continued existence of any endangered species or threatened species or result in the destruction or adverse modification of habitat*
Regulatory Science is about Risk Management defined by Federal Laws

**Canada**

**Pest Control Products Act (PCPA):** Acceptable Human and Environmental Risk with consideration given to the value to end users and society (includes efficacy).

**Mexico**

**DECREE** amending, supplementing or repealing certain provisions of Regulation in Matter of Registration, Import and Export Authorizations and Export Certificates for Pesticides, Nutrients for Plants and Toxic or Dangerous Substances and Materials: Acceptable human and environmental safety and biological efficacy
Principle of Risk Assessment

Risk = Exposure + Toxicity/Hazard

High Hazard \times \text{Minimal Exposure} = \text{Negligible Risk}
Environmental Safety in North America

Support the North American Business and Global Development by quantifying the intrinsic toxicity, environmental exposure, and risk of adverse effects from the use of BCS products to “all species other than man”.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Risk</th>
<th>Hazard</th>
<th>Outreach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental Fate</td>
<td>Residue Chemistry</td>
<td>Exposure Modeling</td>
<td>BATRA/ETRA</td>
</tr>
<tr>
<td>Determine the fate, transport, and potential accumulation of BCS compounds in the environment</td>
<td>Determine the magnitude of residues in food, feed, soil, water, and pollinator-relevant matrices.</td>
<td>Predict environmental concentrations and exposures via air, water, soil, and sediment</td>
<td>BATRA/ETRA</td>
</tr>
<tr>
<td></td>
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<td>NA Bee Care Center</td>
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Regulatory process is risk based in NA: "No unreasonable adverse effect"
Environmental Safety

Environmental Fate and Residue Chemistry Activities: Regulatory Studies

Determination of the Conceptual Model in the Lab for Fate and Transport in Air, Soil & Water

Testing the Conceptual Model in the Field

Aerobic Soil Metabolism

Anaerobic Soil Metabolism

Aerobic Aquatic Metabolism

Anaerobic Aquatic Metabolism

Degradation Pathway

Soil volatilization

Runoff / erosion

Plant uptake/washoff

Degradation in plants/soil

Leaching

Soil sorption

Sediment sorption

Degradation in water

Hydrolysis

Photolysis

Aqueous photolysis

Soil column leaching

Adsorption / desorption

Soil volatilization

Soil sorption

Degradation in sediment

Degradation in plants/soil

Degradation in water

Water monitoring study

Prospective groundwater study

Terrestrial field dissipation

Aquatic field dissipation

Direct measurement in the field of potential exposure to aquatic species and humans

Aerobic soil metabolism

Anaerobic soil metabolism

Aerobic aquatic metabolism

Anaerobic aquatic metabolism
Environmental Fate to Exposure Assessment

Routes of Exposure – *per conceptual model*

- Direct deposition
- Spray Drift
- Volatilization
- Runoff and subsurface flow
- Systemic plant residues – relevant matrices (e.g., pollen, nectar, guttation, young vegetation….)

Direct contact

Ingestion (Food and Water)

Inhalation and Dermal

Irrigation water

Simulation models are used to define environmental concentrations
Human Safety Process

*Identical Core Principle of Risk*

\[
\text{Risk} = \text{Hazard} \times \text{Exposure}
\]

**Hazard Assessment**
(defines is the safe level)

**Exposure Assessment**
(food, residential, non-occupational)

(likelihood of an adverse outcome to Humans)
### Human Safety in North America

**HuSa Scope**: Support the North American Business and Global Development by quantifying the intrinsic toxicity, aggregated exposure, and risk of adverse effects from the use of BCS products to humans.

<table>
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<tr>
<th>Exposure</th>
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</thead>
<tbody>
<tr>
<td>Dietary Exposure Assessment</td>
<td>Occupational Exposure</td>
<td>Residential Exposure</td>
</tr>
<tr>
<td>Define metabolism and crop/animal residue trials needed for registration at a country level.</td>
<td>Define and manage studies needed to quantify exposure to workers</td>
<td>Define and manage studies needed to quantify exposure outside the workplace.</td>
</tr>
<tr>
<td>Calculate dietary exposure via food and drinking water</td>
<td>Derive exposure assessments from study data and models</td>
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Regulatory process is risk based in NA: *Reasonable Certainty of No Harm*.
Human Safety Functions

Key Responsibilities:

- Evaluate potential toxicological effects associated with all possible routes and life-stages of exposure.
- Determine potential exposures during product use, e.g. to consumers via dietary and non-dietary sources and to workers from application and reentry.
- Evaluate associated risks, identify potential issues and define safe use conditions.
Aggregate/Cumulative Exposure

**Aggregate Exposure:**
all sources and routes of exposure

**Cumulative Exposure:**
joint occurrence of multiple chemicals with a common mechanism of toxicity for the same individual on the same day by all sources and routes of exposure

Multiple Sources
- Dietary
- Drinking Water
- Residential

Multiple Routes
- Oral Ingestion
- Respiratory Exposure
- Dermal Exposure

Statement of Risk to Humans (may trigger refinement of exposure and regulation of competitive products)
Dietary Safety Experts: Process (simplified)

- Defined use patterns (GAPs)

- Metabolism Studies (Plant, CRC and Animal)
  - Definition of Residue (DoR) for Data Generation

- Residue trials (1st Year)
- Field Rotational Crop Studies
- Feeding studies

- Processing Trials
- Residue trials (2nd Year)
- Storage Stability Studies

- Methods for Plants and for Animals (data generation)
- Methods for Plants and for Animals (enforcement)
- Independent Laboratory Validations

- Data evaluation and preparation of registration dossiers
  - Definition of Residue for Risk Assessment and for Monitoring (enforcement)
    - Risk assessments
    - Proposition / Harmonisation of MRLs
    - Product defence
Dietary Safety Experts: What is risk assessment?

Risk = Hazard x Exposure

- **Level of exposure**
  - Magnitude of residues:
    - Level of residues
    - Consumer diets
  - Nature of residue:
    - Metabolism
    - Residue definitions

- **Acute Reference Dose (ARfD)**
- **Acceptable Daily Intake**

The risk of each product is a combination of the toxicity and the level of exposure.
Maximum Residue Levels (MRLs) - Basic Principles

**MRL** is defined as the upper legal level of a concentration for a pesticide residue in or on food or feed, based on **Good Agricultural Practice (GAP)** and the lowest consumer exposure necessary to protect vulnerable consumers;

**MRLs are set as high as necessary**
- To cover the critical GAP leading to the highest residue level (cGAP)
- To allow **Free Trade**

**MRLs are set as low as possible**
- To avoid unnecessary exposure of consumers to residues
- To support monitoring that plant protection products are used according to the authorised GAP

**MRL’s are not safety limits as often mixed up in the public domain**
Actual Residues are much lower than MRL’s

Maximum Levels → 0.2 ppm
Set MRL’s

Average Residues from Field Trials → 0.082 ppm Average

Percent of Crop Treated
25%

25% of US Crop

Market Basket Surveys
0.01 ppm

Processing Studies Residues
0.005 - 0.041 ppm

Bayer CropScience
Putting Dietary Risk into Perspective: Example Insecticide

LoAEL

NOAEL

ADI

MRL

21040

Reaching “lowest observable adverse effect level” (LoAEL):
Eating 21040 tomatoes per day

7054

Reaching “no observable adverse effect level” (NOAEL):
Eating 7054 tomatoes per day

74

Reaching “acceptable daily intake level” (ADI)
Eating 74 tomatoes per day

1

Reaching MRL-Level:
Eating 1 tomato per day (during your entire lifetime containing residues of the insecticide)

A factor of at least 100 is applied between NOAEL and ADI/ARfD.
From Idea to Market – Developing a Crop Protection Product*

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

*Ag-Industry View as published by IVA
We are well prepared to address the CHALLENGES in agriculture

Thank You!