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# Integrating Innovation: Novel Approaches to Developing New Products

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**Summary:** The framework for innovation in pesticide formulation is a network of climatic, geographic, social, cultural, and economic influences. While value changes with the opportunity, the basic rules about what creates value continue to apply where a critical element of success is increasing the effectiveness of control in each generation of technology. Advanced formulation approaches will provide the enabling technology to add this value and are critical to differentiation as new active ingredient numbers decline. Successful innovation also depends on understanding the formulation in detail, using the appropriate tools, and applying proper design while ensuring sustainability by selecting and incorporating safer formulants. The growing demand for flexible and robust formulants will continue to drive innovation toward new classes of functional polymer while increasing biological performance demands will guide formulation design to accommodate adjuvants. The analysis provided highlights a range of approaches using past, present, and potential future examples of innovation.

## Introduction

What does it mean to innovate within pesticide formulations? The question is specific to the complex environment of agricultural production which is not uniform. Instead, it is fragmented with differing opportunities to innovate appearing in different regions at different times. In order to begin, we first need to acknowledge that production differs greatly around the world and that this presents the primary level of complexity. Opportunities to innovate within this complexity are driven by factors like climate and geography (water and soil) that shape the agricultural economy.

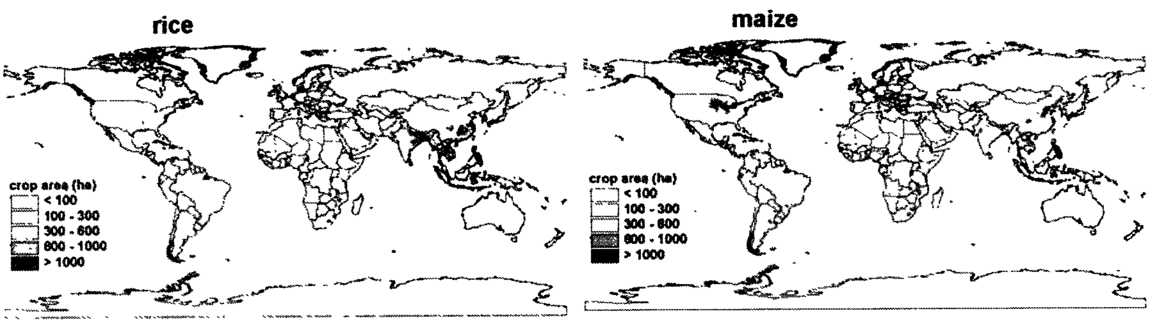
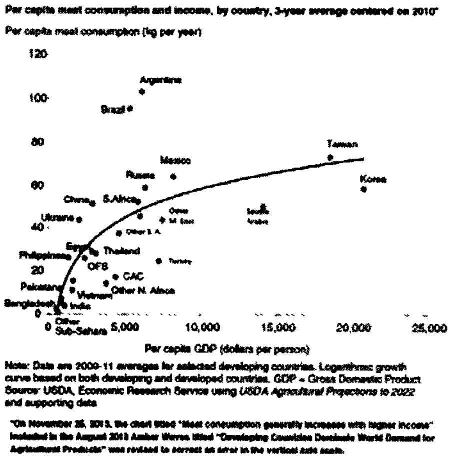



**Figure 1. Global Rice and Maize Production** (*Pixels are on a scale of 5x5 minutes or about 9x9 km2 on the equator).*
[Source: Generating Global Crop Distribution Maps: From Census to Grid, IAAES Conference 2006. Copyright 2006 by Liangzhi You, Stanley Wood, Ulrike Wood-Sichra.]

These factors go on to include man-made influences where geopolitics or local economics add further complexity. Along with crops planted and cropping systems employed, these strongly influence the choice of active ingredients and how they are formulated. The state of "local" economic development and political stability is critically important to how each market operates.

Its behavior is a selector of inputs in a basic way: the economics of production have to be desirable for the grower at the point of application. This provides the next layer of complexity.



Consumer influences include demand for meat in the developing world and increased demand for non-genetically modified organism (GMO) or organic produce in many developed nations.

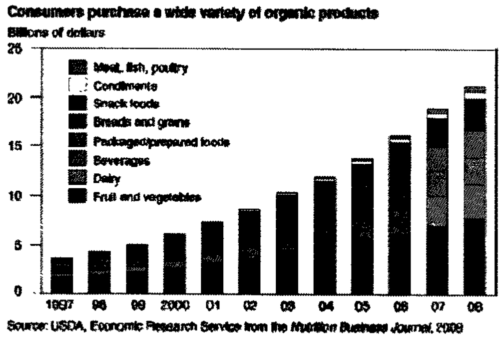



**Figure 2. Changes in Consumer Demand for Meat and Organic Food.**

The sum of natural and human influences drives agronomics. Agronomics drive commodity production which shapes the demand for specific agronomic inputs such as chemicals (fertilizers and pesticides) and seeds. The technologies selected to enhance production (including GMO and the use of biopesticides) are critically important in driving change. They are linked to specific choices of which pesticide or adjuvant formulations are used and how they will be applied. In the case of genetically modified crop cultivation, seed genetics provide economic advantages that are dependent on the use of specific formulated active ingredients. This choice changes the demand for chemical inputs including pesticides and adjuvants and therefore significantly influences the agricultural formulation targets of innovation.

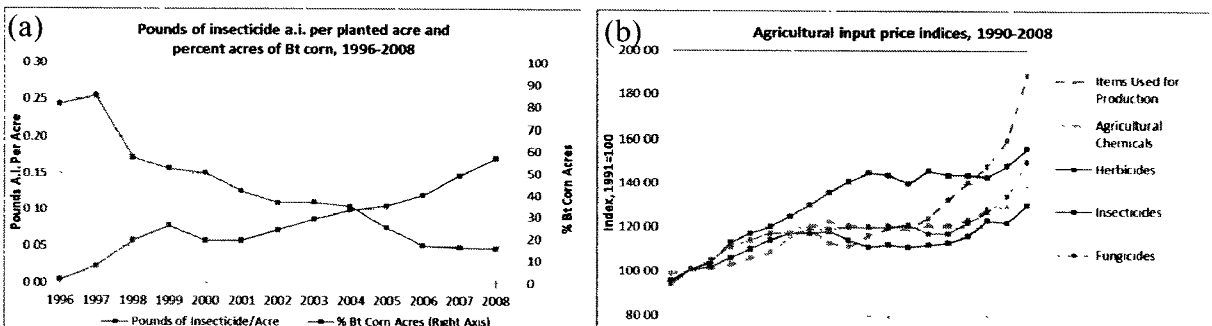



**Figure 2. (a) Bt Cotton Impact on Insecticide Use and (b) Agricultural Input Price Trends [Source USDA ERS 2014]**

The result is an overlapping network of climatic, geographic, social, cultural, and economic influences presenting complex challenges to accurately identifying when and where to invest in differentiation. It includes hard economic parameters such as market size, liquidity, and profitability as well as touching on social imperatives such as improved human or environmental safety and continues on to be concerned with enhanced sustainability and genetic diversity. It considers distribution channel efficiency and sophistication for chemicals input as well as commodities produced.

The graph of price indexes provided indicates other production costs have risen faster than pesticides so there is space for value creation in many markets. It will be primarily the available room for value growth that changes although the basic rules about what creates value from formulation innovation will apply in much the same way. Advanced formulations are seen as enabling technology which adds significant value and attractive presentations to pesticide products. It is critical for innovation and differentiation as new active ingredient numbers decline.

In order to be successful, innovation must be directed at the target of delivering positive "return on investment" for research and development. Value has to be created so how do we formulate that? The goal of this analysis is to highlight a range of approaches to innovation in agricultural formulations that incorporate this target by design using a variety of examples including past, present, and potential future innovations.

## Impact of Regulation

The environment within which innovation is conducted is heavily regulated so in addition to accommodating the physical and organic chemistry of the materials formulated and maximizing their biological effect, managing their toxicology becomes a primary objective. Regulatory trends in Europe and the United States have driven research toward development of fewer new active ingredients due to increasingly stringent criteria for safety in use in what was until recently a relatively crowded market. As this continues, there will be net loss of existing technologies.

The change from risk to hazard based criteria in Europe has been a particularly clear example of how this change can impact available technology. The elimination of exposure as a variable in assessment threatens to drive many existing active ingredients out of the market since modifying use rates is no longer a feasible strategy to maintain its viability. Recently we saw the outcome of one of such processes with the appearance of regulations implementing Article 80(7) of Regulation (EC) No 1107/2009 of the European Parliament in the EU as appears below and providing a "List of Active Substances which are Candidates for Substitution":

**Table 1. List of Active Substances which Are Candidates for Substitution.**

| |
|---|
| Methyl cyclopropene, amitrole, diclofop, dimethoate, ethoprophos, fenamiphos, fipronil, fluometuron, haloxyfop, metam, oxamyl, sulcotrione, triazoide, bromadiolone, difenacoum, diquat, warfarin, fluquinconazole, bifenthrin, bromuconazole, chlorotoluron, copper, cyproconazole, cyprodinil, diflufenican, dimoxystrobin, epoxiconazole, fenbutatin oxide, fludioxonil, flufenacet, flupicolide, imazamox, imazosulfuron, isoproturon, isopyrazam, lenacil, lufenuron, metconazole, metribuzin, metsulfuron-methyl, myclobutanil, nicosulfuron, oxadiazon, oxyfluorfen, paclobutrazol, primicarb, prochloraz, propiconazole, propoxycarbazone, prosulfuron, quinoxyfen, tebuconazole, tebufenpyrad, tepraloxydim, triallate, triasulfuron, ziram, aclonifen, esfenvalerate, etofenprox, famoxadone, lambda-cyhalothrin, pendimethalin, mecoprop, metalaxyl, carbendazim, flumioxazine, glufosinate, linuron, oxadiargyl, quizalofop, molinate, profoxydim, and thiacloprid, |

There is change on the horizon for these active ingredients although the priority and timing for change is unclear. In contrast, the impact of changing the risk assessment process under FQPA was apparent in the availability of active ingredients effective for controlling corn rootworm in a declining market for soil-applied pesticides. The decline was accelerated by a transition to genetically expressed Bt as the primary means of agronomic soil insect control which now struggles to deliver it in the presence of increasing pest resistance with fewer effective active ingredients. The outcome opposite challenges to regain control of resistant corn rootworm has been an increased focus on formulation innovation for the remaining active ingredients, specifically pyrethroid insecticides like bifenthrin.

1. **Start with Bt expression** in corn as one of several traits appearing in genetically modified varieties and which removed value from the soil applied insecticide market and beginning its deterioration.
2. **Add the loss of organophosphates** from the "risk cup" assessment, i.e. "cumulative and aggregate exposure". The market was not valuable enough to absorb the cost of new data and risk assessments.
3. **Consider the withdrawal of carbamates** such as carbofuran (FURADAN, FMC) or aldicarb (TEMIK, Bayer) from the market due to increasing concerns over toxicity in a shrinking market.
4. **Remove large portions of the capacity to deliver toxic insecticide granules** to soils as growers retire and do not replace obsolete soil application equipment.
5. **Add the risk-based decision not to permit some active formulation types**, specifically no solvent based fipronil formulations in the US or EU due to heightened risk concerns.
6. From this eroded market **subtract control lost from increasing resistance** to the expressed Bt trait...
7. Yielding the **development of solvent based pyrethroid (bifenthrin) formulations compatible with concentrated fertilizers** (10-34-0 type) and stable during application to improve pest control.
8. This **new use is in addition to neonicotinoids applied as seed treatments** although pressure is now increasing against the continued use of this formulation. Innovation has been critical here as well.

As this process continues, the effect will drive innovation in replacement technology toward multiple formulated products, many containing multiple active ingredients and adjuvants. These formulations will need to be safer than the products they are designed to replace. The incorporation of safer formulants is integral to developing safer pesticide formulations. This makes component selection critical to delivering safer products.

Initiatives such as REACH and FQPA have significantly changed the depth of formulant hazard assessment so more is known about their toxicology. Formulators must understand more about their contribution to risk and apply this knowledge to the development of new products. Change in regulation does not specifically limit innovation, but instead shapes it. This process changes across regions changing new active and formulant demand and availability around the world and changes the opportunities for innovation as a result.

**Formulation Evolution**

A key element of increasing innovation's chances of success, regardless of driver, is to increase the effectiveness of agronomic pest control available from each successive generation of technology. This is accomplished using a core set of approaches that starts with the development of more effective active ingredients and the incorporation of multiple modes of action into a single product. These products may also include adjuvants that increase the effectiveness of the product. Increases in effectiveness can be used to maximize performance, reduce the required application rate, or both.

**Table 2. Response of Innovation Emphasis to Technology Change**

| Technology | Principal Drivers | Responses |
|---|---|---|
| **Chemical** | Control Pests, Maximize Yield<br>Improve Quality/Value | Introduce New Modes of Action and Active Ingredients<br>Develop New Formulations and Combinations<br>Apply Adjuvants and Mitigate Off-Target Drift, Treat Seeds |
| **Biopesticide (extract)** | Enhance Safety<br>Treat Closer to Harvest<br>Reduce Chemical Residues | Facilitate IPM Adoption<br>Improve Formulations, Apply Adjuvants<br>Facilitate Organic Production |
| **Biological (microbe)** | Reduce Chemical Agent Use<br>Enhance Safety<br>Protect Beneficials | Introduce New Formulations<br>Enhance Organism Viability (Adjuvancy)<br>Treat Seeds |
| **GMO – siRNA (repeat cycle)** | Reduce Chemical Agent Use<br>Control Pests<br>Manage Resistance | Introduce New Modes of Action and Active Ingredients<br>Develop New Formulations and Combinations<br>Apply Adjuvants, Treat Seeds |

Frequently the approach will consider combining several formulated products, pesticide and and adjuvant in nature, into a single spray mixture in order to further increase the effectiveness of a single treatment. The approach may also consider different active ingredients, modes of action, and altogether different control technologies into pest control programs. These take the form of Integrated Pest Management (IPM) solutions where chemical, biochemical, and biological control agents are applied over the production cycle to increase yield and manage resistance. All are different facets of the same innovation process that combine to provide an integrated approach.

**Table 3. New Active Ingredients and Their Prominent Global Marketers.**

- **Flupyradifurone**: Insecticide; **Flubendiamide**: Insecticide (Bayer CropScience)
- **Halauxyfen**: Herbicide; **Sulfoxaflor**: Insecticide (Dow Agrosciences)
- **Bicyclopyrone**: Herbicide; **Benzovindiflupyr**: Fungicide (Syngenta)
- **Fluxapyoxad**: Fungicide; **Ametoctradin**: Fungicide (BASF)
- **Renaxapyr**: Insecticide; **Cyazapyr**: Insecticide; **Penthiopyrad**: Fungicide (DuPont)

**Table 4. Combinations with Multiple Modes of Action and/or Adjuvants.**

- **O-Teq/ODEsi** (Bayer CropScience) Oil dispersions of pesticides with adjuvants to enhance uptake.
- **STELLAR** (Dow Agrosciences) Dual active herbicide for improved weed control in small grains.
- **TOUCHDOWN Total** (Syngenta) Optimized adjuvant system for glyphosate solution formulation.
- **SELECT Max** (Valent USA) Improved control of glyphosate tolerant corn in glyphosate mixtures.

The high costs, extended timelines, and unquantified risks associated with the development of new active ingredients makes formulation a more attractive target for innovation. The resulting preference is to innovate with limited introduction of new active ingredients, reliance on more effective combinations of existing active ingredients, and incorporate adjuvants and alternative control agents wherever possible into more effective control programs targeting higher yields, lower risks, and managed resistance. The examples below indicate this approach is already in practice.

**Table 5. New Registrations for Active Ingredients, Combinations, Biopesticides, and Formulations.**

| | | | |
|---|---|---|---|
| Fungicide | Benzovindiflupyr | Syngenta | Terrestrial food crops; Turf and Greenhouse, |
| | Benzovindiflupyr + Difenoconazole | | Terrestrial food crops;Turf |
| Insecticide/ Miticide | *Streptomyces microflavus strain AQ 6121.* | Bayer CropSciences | Terrestrial food crops |
| Herbicide | Benzobicyclon | Gowan | For use in California: Post-flooding rice paddies |
| Fungicide | Isofetamid | ISK Biosciences | Almonds; Lettuce (head and leaf); Small Fruit Vine Climbing, Low growing Berry, Rapeseed |
| Insecticide | *Helicoverpa ZeaNucleopolyhedrovirus.* | AgBiTech | Agriculture (outdoors). |
| Insecticide | *Bacillus thuringiensis subsp. galleriae strain SDS-502 at 85.0%.* | Phyllom | For control of certain beetle pests, ornamentals and crops for food and animal feed, poultry premises. |

To minimize the potential for developing resistance too soon after introduction, an approach gaining preference includes formulation of the active with other active ingredients expressing different modes of action. The commonly encountered differences in active ingredient physical form, chemical stability, and solubility increase the complexity of employing this approach. Complexity tends to peak when one of the active ingredients is dissolved in the continuous phase (most frequently water) or where the formulation must be a non-aqueous suspension (oil dispersion or OD) to accommodate the sensitivity of one of more of the active ingredients and still deliver a liquid formulation.

**Table 6. Liquid Formulation Systems of Increased Complexity by Formulation Type.**

***Oil Dispersions***

- **GOLDSKY** (Dow Agrosciences) *Three active oil dispersion* (plus safener) for broad spectrum postemergence grass and broadleaf weed control in wheat.
- **HUSSAR** (Bayer CropScience) Convenient and cost-effective postemergence *herbicide oil dispersion with safener* for use on a unique combination of grass and broadleaf weeds.
- **REVOLVER** (Bayer CropScience) *Herbicide oil dispersion* for control of grass weeds in turf.

**Suspensions (SC), Emulsions (EW), and Suspoemulsions (SE) in Soluble Liquid (SL)**

- **SURESTART** (Dow Agrosciences) *Triple active herbicide* for improved weed control in maize.
- **HALEX GT** (Syngenta) *Triple active herbicide* for improved control of resistant weeds in maize.
- **FLEXSTAR GT** (Syngenta) *Dual active herbicide* for improved control of resistant weeds in soybean.

With this understanding, evolution toward more innovative formulations is associated with resolving more complex challenges in formulation technology. The effects required will vary and may not overlap significantly so their solutions may not be interchangeable. Instead, successful innovation depends on understanding the formulation in detail and using the appropriate tools and approach to assure proper design. What appears consistent is that the demand for flexible and robust formulants will continue to drive innovation toward new classes of functional polymer while increasing biological performance demands will guide formulation design to accommodate adjuvants.

This is the case with chemicals and appears consistent for biopesticides, but it is reasonable to question whether this will remain accurate after the emergence of nucleotide based products that modulate gene expression. Although the outcome may not be known for some time, it is likely formulation innovation will continue to support this approach.

## Reducing Off-Target Movement

Spray droplet and vapor drift control have become targets of increasing importance to formulation innovation due to (1) regulatory concerns about off-target movement and (2) the demand for increasing treatment effectiveness. Volatility management is primarily through formulation technology but its relative effectiveness can be significantly modified by decisions on spray mixture composition. In contrast, control of droplet size distribution and spray quality is predominantly the domain of agricultural spray engineering (nozzles, pressure, boom height etc.) although the need to maintain control in complex spray mixtures relies on a much more multidisciplinary approach. Variable application conditions and mixture compositions have driven development of formulated products targeted at refinement of spray quality to provide both reduced risk and improved efficacy.

**Table 7. Examples of New Pesticide and Adjuvant Formulations Claiming Improved On-Target Delivery.**

- **ENLIST Duo** (Dow): Dual herbicide salt soluble liquid formulation containing drift reduction agent.
- **ENGENIA** (BASF) Low volatility amine dicamba salt formulation for use with DHT crops.
- **INTERLOCK** (WinField) Oil emulsion based drift control adjuvant.
- **LI-700**: (Loveland/UAP) Nonionic surfactant and drift control adjuvant.

If we include the complexity encompassing final application technologies, we can consider broader approaches to assure success through innovation. Delivering each element to a new formulation adds value; the more elements we include, the more incremental value we add and the greater the potential return on investment available.

## Alternative Solvents

The data on transition in formulation technologies between 1994 and 2012 confirms steady migration away from traditional solvent-based concentrates, dusts, and wettable powders. Approximately 65% of active ingredients in 2012 remained in older formulation types and approximately 35% of actives formulated appeared in water based suspensions and emulsions, dispersible granules, and oil dispersions which are considered advanced formulation technologies. Although solvent-based concentrates remained relatively stable in use, the solvents used are changing with development driven by the demand for safer products (e.g. avoiding the chronic toxicity of alkyl pyrollidones and the physical and health hazards of aromatic fractions).

**Table 8. Examples of Innovation Response to the Demand for Alternate Solvents.**

- **Alkyl Lactates**, e.g. Purasolv EL (Purac)
- **Alkylmethyl Formamide**, Armid FMPC (Akzo)
- **Bis(difuranyl)ethers**, e.g. Atlox Solvall BDE-1 (Croda)
- **Dibasic Acid Esters and Amides**, e.g. Rhodiasolv IRIS, STRIP, etc. (Solvay)
- **Dimethyl Alkylamides**, e.g. Hallcomide M 8-10 and others (Stepan, Clariant, BASF)
- **Morpholine Alkylamide**, e.g. Jeffsol AG1730 (Huntsman)

Counterbalancing avoidance of traditional solvents has been the demand to increase efficacy. It is accepted that solvated active ingredients are more bioavailable (other forms include "sub-micron" dispersions, amorphous solids, and cocrystals) so the demand for safer, lower water miscibility solvents offering useful solvation properties for important active classes remains a development driver. Solvent specialization for specific actives or classes is becoming more apparent as development considers (1) solvency, (2) adjuvancy, and (3) toxicology concurrently.

## Dry Formulations

Changes in dry formulations have been led by movement away from dispersible dry powders to water dispersible solids. While there was little change in the relative number of dry broadcast granule formulations, there was an increase in water dispersible granule formulations. One explanation for the shift may be toward reducing risk through the delivery of non-friable solids. The basic formulation technologies applied have not changed significantly although there have been some advances in the use of polymeric surfactants in high performance water dispersible granule products.

**Table 9. Formulants Used in Water Dispersible Granule and Wettable Powder Products are Dominated by Anionic Surfactants.**

| |
|---|
| **Dispersants** *(polymers)* |
| *Styrenic carboxylate copolymer salts*, alkylnaphthalene sulfonate condensate salts, *lignin sulfonate salts*, and alkyl ether sulfates and/or phosphates on soluble (sodium sulfate/sodium benzoate) or insoluble (silica) carriers |
| **Wetting agents** |
| Sulfonated alkylnaphthalenes, sulfosuccinates, alkyl ether sulfates and phosphates on soluble (sodium sulfate/sodium benzoate) or insoluble (silica) carriers. |

Frequently for reduction of dust and to minimize friability, low pressure basket extrusion is applied as this generally increases compaction and produces stronger granules. While strength increases, dispersibility may deteriorate making the selection of highly effective formulants critical to maintain dissolution performance and granule durability.

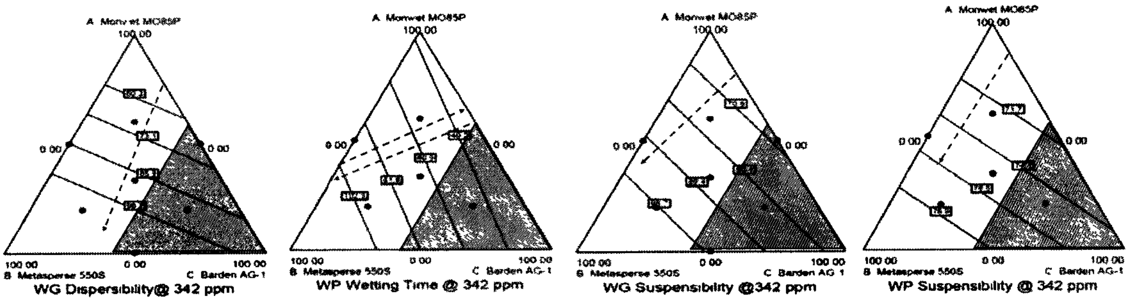



**Figure 4. Properties of Captan Granules Formulated with Styrenic Carboxylate Polymer Salts.**

As an improvement over previously applied technologies, anionic polymer dispersants such as styrenic carboxylate copolymer salts provide increased granule strength which reduces dust generation incidental to handling and use. Other desirable properties include exceptional granule shelf life as observed in stable dispersibility and suspensibility.

## Seed Coatings

The expanded use of seed coatings has been driven by both regulation and economics. With direct application of the control agent to seed, the risk of off target delivery and use rate relative to treated area both decrease while control effectiveness increases. The innovative product benefit desired for pesticide products applied to seed includes an ideal balance between the opposing need for (1) active ingredient adhesion to seed and (2) maintaining seed flowability.

Suspension formulations developed for use on seeds may frequently include higher use rates of polymeric dispersants or additional materials such as latex emulsions and suspended fillers to deliver the desired mixture of properties. Binders that are more traditional include natural products like waxes and lanolin while more traditional fillers include mineral products such as clay, talc, titanium dioxide and calcium carbonate.

**Table 1. Examples of Innovative Seed Coating and Treatment Additives.**

| |
|---|
| **Dispersant Polymers** |
| **Atlox 4913** (Croda) Acrylic comb graft copolymer: maintains low viscosity; promotes adhesion to seed surfaces |
| **Atlox Metasperse 500L** (Croda) Styrenic carboxylate polymer solution; improves dispersion flow and coverage |
| **Flo Rite Polymers** (BASF) keep products on the seed, reduces dust-off, enhances flow, improves plantability. |
| **Binding Polymers** |
| **CF Clear** (BASF): Low-rate binding polymer. |
| **CF Neutral** (BASF): Binding polymer with glossy appearance. |
| **Atlox SemKote E-135** (Croda): Low-rate high-tack flexible adhesive polymer. |
| **OMRI Listed** |
| **Polymer 1172–O** (BASF): Dry polymer that binds organic seed treatments and controls dust-off. |

In formulations containing polymeric binding and adhesive agents we see preference for flexible adhesive polymer latexes with low glass transition temperatures. When this material is not present, in some cases suitable adhesion may be provided by the nonionic polymeric dispersant used to formulate the suspension. Investigation of natural polymers such as starch has also been advanced in a combined role and more recently polyethylene wax based additives have been developed to manage the generation of duct and replace more traditional materials like talc. Future development in seed coating formulation technology must consider a growing range of materials that will be applied including biochemical agents, inoculants, nutrients, water management technology, biological agents, wetting agents, etc.

## Built-In Adjuvants

Adjuvants appear in spray mixtures through incorporation into formulated pesticides or by direct addition to the spray mixture. The choice of how to make the adjuvant available is complex, so the decision making process needs to be thorough. There is increasing awareness that adjuvant materials present in the spray mixture affect physical properties, stability, pest control, residue levels, and potentially toxicity. Tank added adjuvants effectively modulate performance of pesticides in spray mixtures but placing adjuvants into the pesticide formulation offers greater control over their use. The incorporation of adjuvants increases pesticide formulation complexity which demands an innovative response.

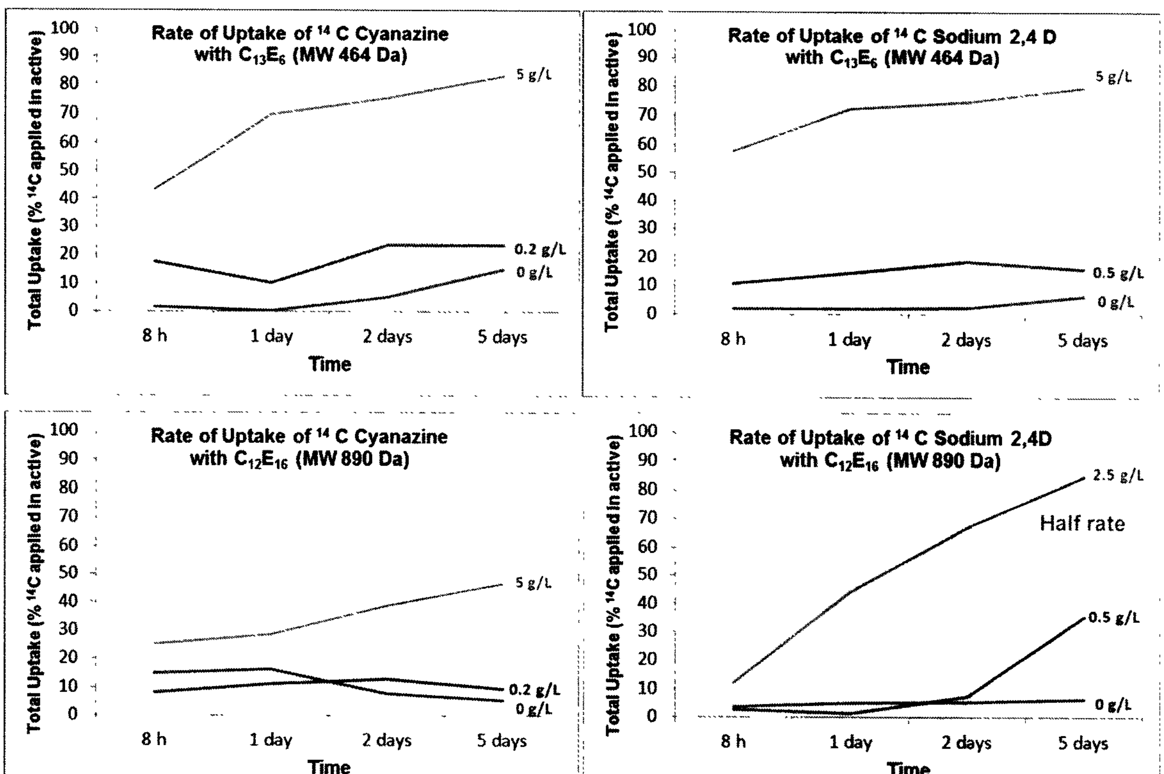



**Figure 5. Selection of the Appropriate Adjuvant Substance Relies on Bioassay Data.**

Once the appropriate adjuvant material is selected, adjuvant combinations with active ingredients in formulated products may require specialized formulation tools. This is due to the presence of high concentrations of specific types of oils and/or surface active agents which present unique challenges to maintaining stability and performance.

Surfactants adjuvants may be built into either (1) water-based liquid suspensions or (2) oil or solvent-borne liquid concentrates. In either case their inherent properties and interactions with other components may present problems in the concentrate or upon dilution. Aggregation and phase behavior may be especially problematic in water based dispersions since viscosity and instability generally increase in proportion to the amount of surfactant adjuvant present. Micellizing surfactants may also partially solubilize the active and contribute to mass transfer and crystal growth.

For pesticide suspensions and emulsions containing oil or oil-like adjuvants, there may be practical limitations on the volume of adjuvant contained in the final product due to "space" limitations. The need for large volumes of oil may present problems with volume fraction of disperse to continuous phase which may drive formulation type away from aqueous dispersion or suspoemulsion to an oil dispersion to avoid phase inversion and further concentrate the product. Partial solubility of an active ingredient in its adjuvant system also increases instability and there is also the potential incompatibility of the adjuvant dispersion stabilizers with stabilizers for the active ingredient or ingredients.

Mitigating the instability inherent in these formulations obligates the use of more advanced and innovative high molecular weight polymeric stabilizers. One example of an effective polymeric stabilizer technology providing a foundation tool for producing stable complex dispersions in water is the acrylic comb graft copolymer (introduced to the market as Atlox 4913). Although this formulant generally has higher unit cost, stability improvement and enhanced biological performance commonly justify its cost-effective use.

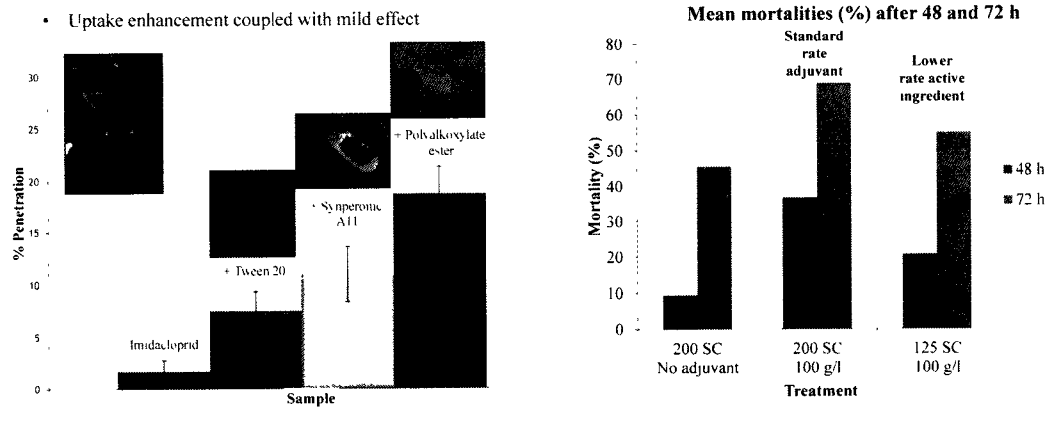



**Figure 6. Enhanced Adjuvant Performance with Reduced Phytotoxicity as Built-in.**

Adjuvant phytotoxicity is a concern when formulating high concentrations of traditional surfactants and some oils, notably vegetable oil methyl esters. Polymeric uptake-enhancing adjuvants are a technology recently developed to avoid this outcome and provide a useful alternative to traditional surfactants. In the case of formulant and adjuvant development, increasing molecular weight within a specific framework of structural modification provides very specific benefits. That this change increases flexibility and effectiveness while reducing toxicological concern makes it a preferred approach for formulation technology tool development in supporting innovation.

## Tank-Added Adjuvants

Building adjuvancy into a product is attractive but there may be conflicts appearing between the pesticide marketer and the marketer of formulated adjuvant technology added to spray mixtures. This risk is limited to the US and perhaps Australia although the markets are significant. There are also instances where adjuvant use would add value but the full spectrum of adjuvant substances cannot be properly formulated into the concentrate. Development of innovative tank added adjuvant solutions can offer valuable differentiation. By using "stand-alone" formulated adjuvant compositions, fewer interaction challenges appear and in many cases product registration may be avoided.

A drawback of separating the adjuvant from the pesticide formulation is that there must be justification for investment in developing the adjuvant separately. Commercial complexity and risk may also increase as additional products are developed that require management. In the US, conflicts are avoided when recommending adjuvants for use with formulated pesticides by referencing tank added adjuvant terminology that is managed by The American Society for Testing Materials (ASTM) where adjuvants generally fall within standard ranges of composition.

**Table 2. Examples of Traditional Formulated Adjuvant Systems Used to Enhance Performance.**

| |
|---|
| **Methylated Seed Oil Fatty Acid** ("MSO") adjuvant with surfactant concentration of 10-15% to be used at a rate of 1.0% v/v with saflufenacil (DESTINY ex. WinField Solutions). |
| **Crop Oil Concentrate** ("COC") adjuvant with surfactant concentration of 15-20% to be used at a rate of 1.0% v/v with clethodim (AGRIDEX ex. Helena). |
| **High Surfactant Crop Oil Concentrate** (HS-COC) adjuvant with surfactant concentration of 50% to be used at a rate of 0.5% to 1.0% v/v with fungicide combinations to control Asian soybean rust (NIMBUS ex. Syngenta). |
| **Ammonium Sulfate** ("AMS") or **Dipotassium Phosphate** ("DKP") water conditioners in 40-50% solution to be used at a rate of approximately 1-2% w/w with either glyphosate or its spray mixture with dicamba. |

As with pesticide innovation, formulated adjuvant innovation involves combining multiple materials including materials with multiple functions to provide more broadly functional and effective premixes. This is analogous to incorporation of multiple effective modes of action when combining multiple formulated products in a single application to address efficacy, safety, residue, or IPM concerns or when combining multiple actives into a single formulated product. When multiple actives are applied together, adjuvancy complexity increases and frequently requires several classes of material or effect to be provided in order to maximize effectiveness.

In the field of stand-alone or "tank added" adjuvants, innovation includes combining effects like drift control, foam control, and compatibility with adjuvant surfactants, oils, or water conditioners. Individual combinations are determined by the target active ingredients and types of application. In addition to convenience, innovation in formulated adjuvants should provide greater control over how the mixture performs. Managing key interactions with formulation technology in an innovative multifunctional concentrate creates fewer opportunities for unexpected outcomes such as incompatibility or antagonism that could result from the use of a larger range of formulated products.

**Table 3. Examples of Innovative Formulated Adjuvant Systems That Address Significant Compatibility Concerns.**

**High Surfactant Oil "Hybrids"**

**DESTINY HC** (WinField Solutions) High surfactant methyl ester adjuvant containing high-fructose corn syrup.
**VOLARE OC** (Precision Laboratories) High surfactant oil concentrate with drift control and deposition.

**Surfactant and Drift Reduction**

**ATPLUS DRT-NIS** (Croda) Nonionic surfactant adjuvant containing oily ester drift reduction agent.
**BORDER AQ** (Precision Laboratories): Liquid suspension of drift reduction agent, retention aid, and surfactant.

**High Surfactant Oil in Water Conditioner**

**ATPLUS AL-3330 and ATPLUS AL-3383** (Croda) Soy methyl ester microemulsion with surfactant adjuvant in concentrated ammonium sulfate water conditioner.

**Drift Reduction in Water Conditioner**

**BORDER Xtra 8L** (Precision Laboratories) Spray retention polymer with ammonium sulfate water conditioner.

**Surfactant and Drift Reduction in Water Conditioner**

**ATPLUS AL-3354** (Croda) Drift reduction ester suspension with surfactant adjuvant in concentrated dipotassium phosphate water conditioner.

Developments in formulated adjuvant stability and multifunctionality have helped to advance the formulant technology available to address similar challenges presented by the combination of oils, surfactants, electrolytes, and polymers into pesticide containing products. While there are gaps in understanding how these adjuvant tools behave and how they may best be applied to effect stabilization in active ingredient-containing products, they are innovative tools for developing complex adjuvants that also appear amenable to the development of complex pesticides.

Pesticide manufacturers protect innovative active ingredients and formulations with patents; other members of the value chain such as adjuvant marketers and pesticide distributors pursue patents protecting adjuvant products that are important to their ability to generate value. Adjuvant marketers generally pursue patent protection for formulated adjuvants while formulant suppliers primarily pursue intellectual property around the underlying materials although this has been changing. Protection that relies on multiple patents covering (1) active ingredients, (2) pesticide formulations, (3) novel formulants, (4) innovative adjuvant components, and/or (5) adjuvant formulations captures additional value.

Innovative approaches to create or expand patent protection may be applied to a number of traditional formulated adjuvant products marketed by pesticide manufacturers. Many of these are well known branded products.

**Table 4. Example Co-Packed and/or Co-Marketed Formulated Adjuvants Developed by Pesticide Manufacturers.**

**Agral 90:** Nonionic surfactant adjuvant based on ethoxylated nonylphenol (Syngenta, others)
**Nimbus, Supercharge, and Turbocharge:** High surfactant paraffinic oil concentrate containing oleyl alcohol and ethoxylated nonylphenols (Syngenta)
**Dash and Merge:** High surfactant aromatic and paraffinic oil concentrates containing surfactants (BASF)
**Nominee:** Nonionic surfactant adjuvants based on alkoxylated alcohols (Bayer)
**Aureo:** High surfactant methyl fatty acid ester adjuvant containing uptake enhancing polymers (Bayer)
**Amigo:** Alkyl ether phosphate surfactant adjuvant solution (Arysta).
**Sure-Mix:** High surfactant paraffinic oil concentrate containing sorbitan esters and polysorbates (Dupont).

A commercial variation of tank added adjuvant is a co-packed adjuvant that is sold in a separate container within a single package alongside a formulated pesticide. The decision whether to introduce a co-packed adjuvant is frequently dictated by (1) the adjuvancy requirements of a specific active and (2) most likely appears where the proportion of adjuvant required in relation to the active ingredient cannot be provided within the formulated materials in either a chemically or physically stable system or at suitable economy. This occurs most frequently in regions such as Brazil and Canada where regulation of both tank added and co-packed stand-alone adjuvants is highly restrictive.

Dow AgroSciences

**Turbocharge® D Adjuvant**

A Spray Tank Adjuvant for use with Liquid Achieve™ SC Herbicide or Achieve Liquid Herbicide

**Figure 7. Example Co-Packed Adjuvant Labeling.**

The formulated adjuvant products provided by registrants for use either as co-packed adjuvants or marketed separately to supplement performance have been static for decades. Development of a multifunctional formulated adjuvant to market alongside aging formulated pesticides for improving performance enables registrants to test innovative approaches while relying on traditional pesticide concentrates with a reliable history of use. Separation can afford time needed to develop adjuvant and combination targets while technologies are identified to enable formulation of a robust formulated product containing all the required elements. It can hold a market position from which to accomplish this.

**Patent Expiration**

Core to commercial success is the development of products that demonstrate competitive advantage. The goal of prioritization is to select innovation projects that best support the strategy for succeeding although agrochemical companies may struggle to prioritize innovation at times. This may occur when there are more projects that could deliver value than can practically be executed with available resources and within the available time.

As discussed, prioritizing innovation investment requires we understand crops and control technologies (insecticide, fungicide, and herbicide) that are agronomically important within their niches. This includes genetic and chemical approaches that are in practice as well as those that are likely to be introduced in the future. The decision on where and how to innovate must consider how value may shift as a result of changes in the intellectual property landscape.

We can define areas of innovation emphasis based on changes in the life cycle of key active ingredients, primarily where patents are expiring. Some years ago this was glyphosate, after that imidacloprid, then azoxystrobin, specific sulfonylurea herbicides, then more neonicotinoids, and further on additional strobilurin fungicide technology.

**Table 5. Expiring Pesticide Patents Alphabetically by Active Ingredient.**

| *Active | EU Expiry | US Expiry | Active | EU Expiry | US Expiry |
|---|---|---|---|---|---|
| Benthiavalicarb | 5/23/2015 | 8/4/2015 | Mesosulfuron-methyl | 10/12/2014 | 10/13/2014 |
| Benzobicyclon | | 6/14/2014 | Metaflumizone | 6/6/2011 | 8/6/2013 |
| Bifenazate | 11/17/2012 | 8/1/2012 | Methoxyfenozide | 11/8/2013 | 11/23/2012 |
| Bistrifluron | 11/7/2016 | 11/7/2016 | Oxasulfuron | 1/16/2012 | 1/21/2012 |
| Boscalid | 11/7/2012 | 11/9/2012 | Oxazicomefone | 12/4/2016 | 12/4/2016 |
| Chromafenozide | 1/21/2012 | 1/15/2012 | Penthiopyrad | 4/3/2016 | 4/3/2016 |
| Cyflufenamid | 12/18/2015 | 12/18/2015 | Proquinazid | 5/10/2014 | 5/12/2013 |
| Diflovidazin | 7/20/2014 | 7/20/2014 | Prothioconazole | 11/8/2015 | 11/8/2015 |
| Dimethenamid-P | | 11/16/2012 | Pyraclostobin | 6/21/2015 | 6/21/2015 |
| Dimoxystobin | 6/21/2015 | 6/21/2015 | Pyribenzoxim | 11/11/2014 | 11/10/2014 |
| Dinotefuran | 10/26/2014 | 10/26/2014 | Pyridalyl | 10/12/2015 | 10/12/2015 |
| Ethaboxam | 8/12/2014 | 8/9/2014 | Silthiofam | 10/16/2012 | 3/12/2013 |
| Etoxazole | 4/28/2012 | 12/26/2012 | Simeconazole | 1/28/2014 | |
| Fentrazamide | 2/14/2014 | 2/24/2014 | Spirodiclofen | 7/3/2012 | 7/7/2012 |
| Flonicamid | 7/16/2013 | 7/23/2013 | Spiromesifen | 7/3/2012 | 7/7/2012 |
| Fluoxastrobin | 1/15/2017 | 1/15/2017 | Spirotetramat | 7/23/2017 | 7/23/2017 |
| Foramsulfuron | 4/12/2015 | 4/27/2015 | Thiamethoxam | 7/13/2013 | 12/22/2015 |
| Indoxacarb | 12/17/2012 | 10/31/2012 | Trifloxysulfuron | 3/13/2014 | 11/12/012 |
| Iodosulfuron | 2/12/2012 | 11/18/2014 | Zoxamide | 11/15/2013 | 12/1/2012 |
| Isoxaflutole | 8/4/2012 | 9/11/2010 | | | |

While the post-patent market is commonly approached with attempts to gain share through price, there is demand for innovation even among generic products due to the need for differentiation as a tool to protect value. In some cases actives that are facing exposure to the post-patent marketplace are being formulated with new, patented actives or into new, patented formulations in an attempt to gain extended protection in the marketplace.

**Table 6. Examples of New Active Ingredients Introduced within Complex Premixtures.**

- **Halauxifen** (ARYLEX, Dow Agrosciences) will be introduced in both PARADIM as one component in a two herbicide water dispersible granule containing florasulam, and in PIXXARO as one component in a two herbicide water dispersible granule containing fluoroxypyr.
- **Bicyclopyrone** will be introduced as ACRON (Syngenta) as one component of a four herbicide premix also containing atrazine, mesotrione and S-metolachlor

Innovation is an excellent way to protect value in the post-patent market. While specific active ingredient, crop, and adjuvant combinations present complex targets, we can simplify the task by focusing on how the toolkit or formulation technology used to support formulation innovation can facilitate differentiation. By employing such tools, the view is that the targets we set should become more approachable through:

- Enabling formulated systems not otherwise possible,
- Facilitating improvement of robustness and convenience to meet critical performance standards, and/or
- Manage down the cost and time needed to deliver practical versions of challenging formulations systems.

Core drivers of innovation remain (1) improved cost-effectiveness and (2) convenience. Cost-effectiveness includes reducing the cost of control, not necessarily the unit cost of the formulation or the active, and delivering greater value in pest control. This may include migration to more advanced and often more costly formulations when examined on a cost per unit mass or volume basis. Increased unit cost may be leveraged to competitive advantage through the delivery of greater control which itself may be defined in terms of breadth or consistency or both.

Convenience incorporates actual and perceived reduction of cost where the benefit is defined using measurements other than material cost. Reduction of service "overhead", increased simplification, and enhanced robustness contribute to value described as "trouble free operation". An example can be found in the description of user benefits in the PARADIGM formulation as announced by Dow Agrosciences:

> "Paradigm introduces another breakthrough with GoDRI™ Rapid Dispersion Technology (RDT). GoDRI RDT makes Paradigm unlike any of the old dry products growers may have used in the past. Newly developed coformulants are the key to the technology's rapid dispersion. With Paradigm, growers can fill a sprayer tank and cover a lot of acres – fast."

To deliver innovative solutions like this, development approaches are needed that facilitate crossover of multiple technologies to deliver functional innovation. Once there is access to suitable tools, we can target innovation at a few areas where there is greater potential to create value based on changes in technologies and market positions. Pesticide formulation innovation needs to identify intersecting common interests between end users, marketers, formulators, and component developers. These provide focal points for developing innovative technology.

**Polymeric Dispersion Stabilizers**

There are several complex systems where advanced formulants provide the most effective option for placing a desired pesticide product into commerce quickly and with a high probability of success. They rely on formulation tools that enable effective "mixing and matching" of simpler materials into higher value offerings. Combinations of active ingredients in concentrated water-based liquid dispersions are among the more complex systems, although they demonstrate flexibility and reliability as well as improved safety. Their successful development requires formulants that produce highly stable mixtures of dispersed particles and droplets.

The key formulant technologies employed to support innovation in aqueous dispersions tend to be polymeric in nature since higher molecular weight formulants provide advantages in maintaining stability in storage, especially at higher temperatures encountered in warmer growing regions and over extended periods in the supply chain. These attributes generate value in terms of longer product shelf life and greater logistic flexibility. Trends in formulation confirm that water based dispersions and emulsions are frequently used to innovative formulations.

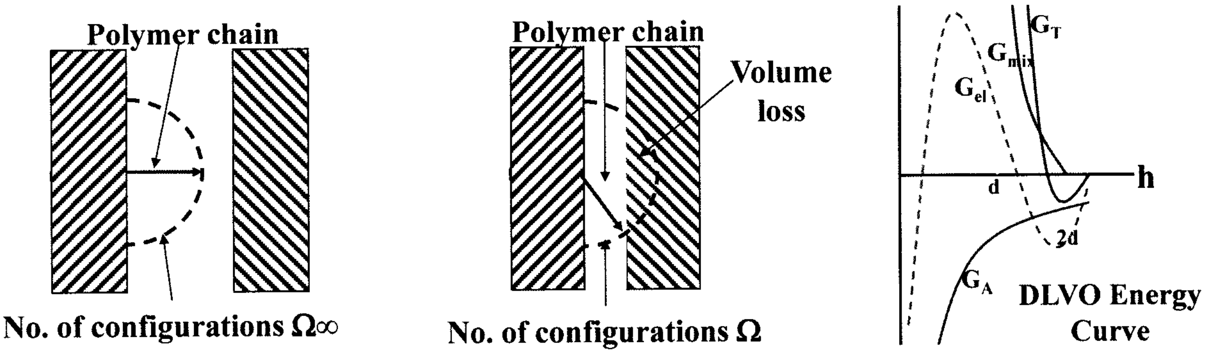



**Figure 8. Graphic Representation of Entropic and Enthalpic Aspects of Seric Stabilization.**

Benefits from the use of nonionic steric stabilizing polymers include improved first-pass quality, reduced disposal cost for failed material, and minimized rework for off-specification manufacturing. Polymeric surfactants that rely on nonionic steric stabilizing chains provide improved dilution stability when dispersed into complex spray mixtures. This is due to increased compatibility because of their chemical nature as nonionic surfactants and their high molecular weight increases their affinity for surfaces of dispersed liquids and solids. It is not uncommon for these benefits to generate positive customer experiences that reinforce the perception of quality.

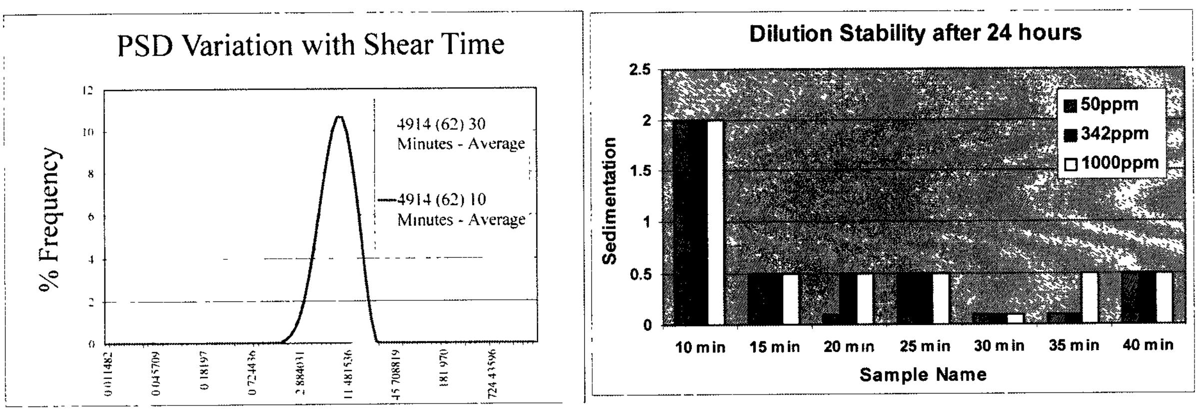



**Figure 9. 2,4-D Emulsion Droplet Size Distribution and Dilution Performance of Atlas G-5000 and Atlox 4914 Mixtures (1:1)**

Recently, the range of demands placed upon water based suspensions has expanded to include tolerance to high concentrations of dissolved (water soluble) active ingredients. While each different dissolved active ingredient presents different degrees of difficulty when incorporated into formulation development, a common demand has become the production of stable dispersions of one or more herbicidal active ingredients into concentrated solutions of phenoxy herbicides (2,4-D or dicamba), paraquat, isopropylamine glyphosate, or potassium glyphosate.

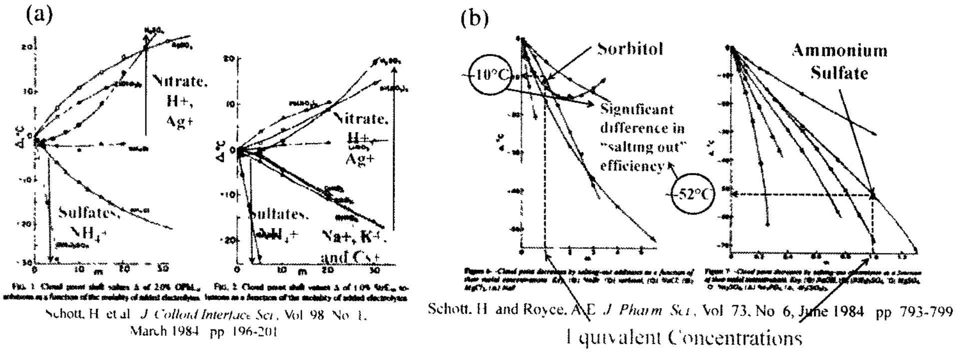



**Figure 10. Dissolved Electrolyte Effect Based on (a) Ion Composition and (d) Concentration.**

One example of an actual formulation target for this performance would be for crops that are genetically modified to be herbicide tolerant. At least one active ingredient included in every control technology placed in this niche is formulated as a soluble liquid. While there is a short list of technologies in use today, they are very successful and the list of such materials as well as the herbicides included in them is growing. There is only the increasing likelihood of greater complexity opposite the development of combination herbicide products needed to address this market segment.

There are examples of these systems in commerce and new purpose-designed polymeric stabilizers continue to be introduced to facilitate development of such products. One example of a new purpose-designed material intended specifically for use in advanced glyphosate formulations is highlighted with examples including stable dispersions of atrazine and diuron in concentrated glyphosate salts (also containing a surfactant adjuvant) that were produced using a novel amphoteric graft polymer stabilizer utilizing a unique electrosteric stabilization mechanism.

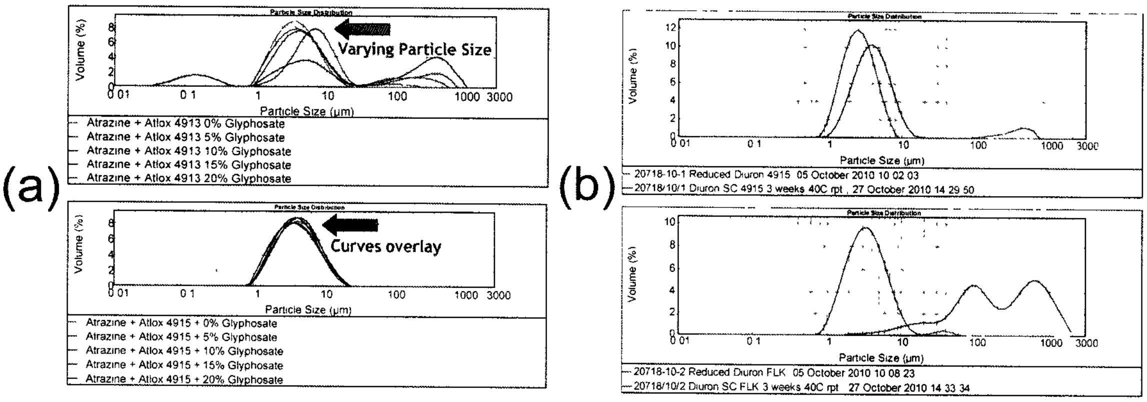



**Figure 3. Particle Size Distribution Change (a) in Increasing Glyphosate Concentration for an Atrazine Suspension and (b) between Dispersants in a Diuron Suspenion in Glyphosate. Stable Systems are Seen with Atlox 4915 Stabilizer ex. Croda.**

As a new formulant with specialized performance targeting complex heterodispersion-solution formulations, the technology represents an expansion of the accessible toolkit for developing high value soluble liquid based dispersions. It is designed to address changing formulation requirements opposite the increasing appearance of resistant pests and the increased demand to combine active ingredients for enhanced control. Formulation innovation enabled by purpose-designed tools such as this remains an important target since it provides critical capability. More formulants are in development although there remains the need to understand what other effects they provide in order to apply them to greatest effect. In some cases additional functionality such as adjuvancy with increased safety may be present.

The selection and use of suitable rheology modifiers also presents challenges in that the materials selected present specific advantages and disadvantages. A common approach is the use of either natural or synthetic structuring polymers to produce sufficient zero shear viscosity to keep dispersions from separating under the force of gravity. An alternate approach to the use of polymers includes the incorporation of structuring clays. Polymers and clays present different rheology profiles, have differing tolerance to other formulation components, and respond differently to microbial degradation, which is a common challenge when developing water based products.

The inclusion of dissolved materials in aqueous dispersions as well as the possible need to maintain the aqueous environment at a particularly high or low pH to accommodate the chemical sensitivity of an active ingredient can strongly influence the performance of rheology modifiers. These conditions can make them less effective requiring their substitution and/or the use of higher rates to maintain the desired rheological properties or by reducing their chemical stability over time thus shortening shelf life. The change in complexity to include dissolved materials in aqueous dispersions may limit the use of traditional materials and present opportunities to innovate with new tools.

**Dispersions in Oil**

A growing target for innovation is with suspension of pesticides in fluids other than water, commonly referred to as oil dispersions. Although these formulations are among the most complex and difficult to produce commercially, the approach provides important differentiation. A primary benefit is the delivery of water sensitive active ingredients in a liquid product and a second benefit is incorporation of adjuvant fluids to afford better control. There are successful oil dispersion formulations in the market although they tend to be provided in smaller pack sizes due to stability concerns.

The use of fluids other than water such as oils, esters, or similar materials presents special problems. One of the most significant hurdles in the development and adoption of oil dispersions tends to be physical stabilization to prevent particle flocculation and resist sedimentation. Recent work suggests that some of the variable physical stability can be traced to variability in properties and composition of many materials used to formulate oil based suspensions.

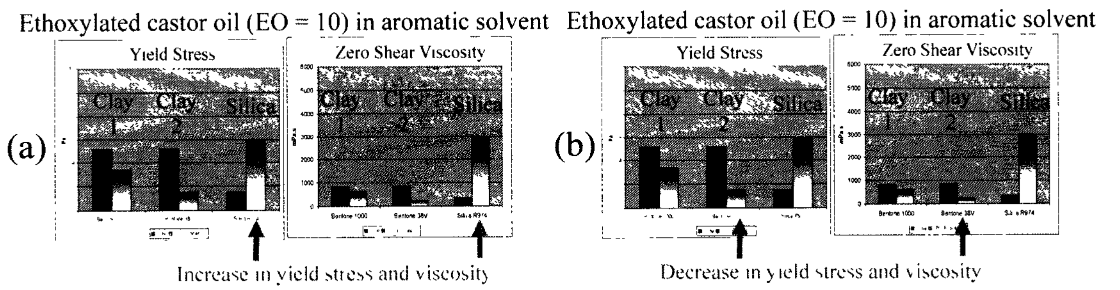



**Figure 4. Introduction of a Formulant into the Same Fluid at Constant Concentration (10% w/w) Can Have Significantly Different Effects on Fluid Rheology Showing either (a) Increased or (b) Decreased Structuring Dependig on the Structurant.**

Successful development depends on examining the performance of systems containing high concentrations of surface active materials which are required to (1) stabilize the concentrate and (2) facilitate dispersion into spray mixtures, including compatibility with other agents in the fluid and emulsion upon dilution. A more detailed understanding of interactions between surface active materials and rheology modifiers is helping to produce more stable formulations.

**Table 7. Materials Applied to Modify the Rheology of Fluid Oil Dispersions.**

| |
|---|
| **Non-aqueous Rheology Modifiers:** |
| Hydrophobically treated bentonite clay (**Bentone 760 or 1000** ex. Elementis) |
| Hydrophobically modified silica (**Aerosil 972 and 974** ex. Evonik) |
| Trihydroxystearin(**Thixcin R**, Elementis) |
| Polyester wax polymer (**Rheostrux 100**, Croda) |
| Polyester polyamide polymer (**Rheostrux 200**, Croda) |

Improving the tools available to formulate oil dispersions, especially rheology modifiers, is critical to making the technology more accessible to product developers. A number of materials have been applied to the problem of rheology modification starting with clays and silica and progressing through several classes of polymer. Successful formulation of simple dispersions can provide the insight needed to develop highly loaded dispersions containing several actives and adjuvants, although the stabilization complexity increases with the number components included.

## Outlook and Way Forward

An integrated approach to innovation described in this paper has been outlined to characterize opportunities for value generation with active ingredients, formulants, and adjuvant substances. Success at each stage of innovation captures additional value, maximizing total value returned when selecting and developing combinations of actives and/or adjuvants, either in the same product or marketed separately, when using a "full market access" approach.

Each innovative technology employed (complex combination, built-in adjuvant, tank added or co-pack adjuvant, electrolyte solution, oil dispersion etc.) may be individually more or less valuable to the end user based on how much each element contributes to meeting the need that exists at the point of use. Ensuring the investment has a long return cycle and contributes quickly after development depends on (1) how carefully the product and its components were designed to avoid risks, and (2) how well the impact of changing regulations are managed over the life of the product.

**Table 8. Safer Formulants Including Solvents, Polymers, and Adjuvants for Built-in and Tank-Added Use.**

- **Atlox Solvall BDE-1**: Bis(difuranyl) methyl ether nonvolatile cosolvent and solubilizer.
- **Atplus UEP-100:** Nonionic polymer ester adjuvant.
- **Tween 20, 21, 22, 23, 24, and 28:** Polyoxyethylene sorbitan monolaurate; wetting agent; adjuvant improved food and environmental safety; suitability for organic production.

With the shift toward complex formulations is an increase in required skill necessary to produce them. As new tools are introduced, available experience will be challenged to learn new techniques. While polymeric stabilizers that provide safer and more robust products will remain applicable to many new formulation problems, its underlying principles are challenged by the demand to incorporate highly concentrated solutions as a more common element of development.

**Table 9. Polymers for Developing Complex Formulations with Improved Physical and Biological Control.**

- **Atlox 4913:** Acrylic comb graft stabilizer for highly loaded and multiple active aqueous dispersions.
- **Atlox 4915:** Amphoteric graft copolymer stabilizer for solids dispersed into soluble liquid pesticides.
- **Atlox SemKote E-135:** Latex polymer binding agent and adhesive for coating seeds.
- **Atlox Metasperse 550S:** Modified styrene acrylic copolymer for low dusting concentrated granules.
- **Atplus UEP-100:** Uptake enhancing polymer adjuvant to increasing transfer across leaf cuticles.

Important changes in the effects needed from the formulants required to produce a finished product are occurring. The industry supplying the materials to address changing technology are extending the range of effects available to build formulated pesticide and adjuvant products. They must provide clear guidance on how to employ new effects reliably. Effective communication around critical needs must take place to ensure success.

**Table 19. Materials Providing more than One Function.**

- **Atlox 4915:** Amphoteric polymeric dispersion stabilizer; electrolyte tolerant surfactant ; adjuvant.
- **Atplus 310:** High electrolyte microemulsifier; compatibility aid; adjuvant.
- **Atplus DRT-NIS:** Nonionic surfactant wetting agent; drift reduction agent; adjuvant.
- **Crovol PK70:** Ethoxylated glyceride adjuvant; emulsifier, low irritation; reduced toxicity.

When the delivery systems targeted by innovation are well defined and the technologies available to produce them are properly understood, we should expect targeted opportunities for applying novel technology to yield successful formulated products. The approach needed to deliver successful innovation includes:

- Clear understanding of the specific markets where we plan to conduct innovation,
- Accurate identification of critical performance attributes including the full range of agronomic targets,
- Delivery of reliable, cost-effective, and convenient control in the targeted application,
- Application of advanced materials and expert technical development to create novel and protected products,
- Routinely apply formulants that deliver more functionality or perform with less health/environmental impact.

By overlaying changes in (1) regional market preferences, (2) effect of local value channel behavior, (2) change in pesticide and adjuvant use, (3) regulatory changes, (4) proprietary-to-generic value shift, and (5) value shift from the chemical-to-biotechnology transition we are best able to define specific paths to successful and balanced innovation.

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