Phase III. Registration

Phase III of ag-chemical research & development is the last stage before a chemical becomes a product and is the subject of the fourth part of this series. This phase is the preparation for product registration.

Registration Data

Only one compound in every one to three years makes it to Phase III. Field testing for efficacy is completed on the intended crop and pests. If new chemistry is involved, the patent has already been submitted and revisions are in progress.

During Phase III (Preparation for Registration), active compounds are tested in 10 categories such as Toxicology, Wildlife and Aquatic Protection, Botanical Protection, Environmental Fate, and Residue. Some 142 studies dealing with potential dangers are conducted on every potential product.

Acute toxicity are 90-day studies looking for potential poisoning such as inhalation, feeding and excretion, nervous system reaction, dermal exposure.

Then, chronic or repeated, and long-term feeding exposure studies are conducted on mammals. Meanwhile, studies continue on determining any dangers to wildlife and aquatic animals, both acute and chronic exposure studies. There are even tests to find out if there is in bad effect on pollinating insects such as bees.

Many and intensive, long-term (years) studies on any cancerous potential are conducted and safe levels are determined. Food residue and ‘breadbasket’ studies are now intensely surveyed. Residue tolerances are determined and set by the Environmental Protection Agency (EPA).

Metabolic studies are conducted on the compounds and their breakdown products. The breakdown products are each tested for their health safety and their fate in the environment. Environmental fate studies include leaching and run-off, drift, and microbial breakdown of the materials in soil. What happens to any residue on the plants and in the soil are identified.

Large scale farm trials are conducted by growers under an ‘emergency use permit’ (EUP). The company begins large scale manufacturing research in anticipation that the product will be registered and in preparation for building a manufacturing facility.

After all studies are completed, the registration package containing many thousands of pages of test data is submitted to the EPA’s Office of Pesticide Programs (CPP) for evaluation and comments.

Risk Assessment

A major determination done by the EPA, not the company, is to determine the potential risk of a new active ingredient. Risk equals the hazard times the exposure. This is the most important part and the key to registration.

Hazard is evaluated from the toxicology studies. From laboratory animal feeding studies a “No Observable Effect Level” (NOEL) in the diet is determined. The NOEL is divided by a safety factor of at least one-hundred (100). This hazard level is the “Reference Dose” (RfD) also called the “Acceptable Daily Intake” (ADI). This (ADI = RfD) is the amount of the compound or material or active ingredient which may be ingested by the average person every day for a lifetime without causing any ill effects. This level is well below anything that showing an effect on even the most sensitive animal.

The exposure part of the above equation is determined by all the residue studies. Residue levels are determined by combining the levels for all treated crops. Then, the tolerance is set by the EPA at a level falling well below (usually a tenth) the ADI.

Phase IV and Beyond

During and after EPA’s analysis for product approval, the manufacturing company looks for additional uses of the potential product, the “me too” phases. “Minor crop” uses usually fruits and vegetables are explored. Each added use must go through additional research including efficacy, residue and metabolism. Each must be scrutinized by the EPA and approval given. Residue levels are calculated into the risk assessment equation above.

Part V of this series will review the time lines for this process. It takes 7 to 10 years to go from initial discovery to registration and label.
1. Seed inoculated with the late blight fungus shortly before planting performs poorly. Inoculated seed emerged more slowly and final plant stands were reduced by 42% (year 1) and by 99% (year 2) compared to the non-inoculated healthy seed.

2. Beneficial fungicide effects were most obvious when fungicides were applied to seedpieces immediately after they were inoculated with the late blight fungus (year 2) versus when fungicide applications were delayed until several days after seed tubers were inoculated and late blight was allowed to become established (year 1). Treatments that included thiophanate-methyl, mancozeb and cymoxanil were most effective at restoring the ability of inoculated seed to establish plants.

During year 1, TOPS 5D and TOPS-MZ 2.5D improved final stands by an average of 7% while addition of cymoxanil to the fungicide increased final stands by an average of 21%. If seed was inoculated with late blight within several hours prior to fungicide applications (year 2), TOPS MZ and fungicide treatments containing cymoxanil resulted in emergence rates and final stands equivalent to those of non-inoculated healthy seed.

3. Once plants were established in the field, no late blight stem or foliar lesions resulted from the seedborne inoculum. However, these research plots received weekly applications of protestant fungicide which may have reduced our ability to detect infection, and conditions were not always favorable for late blight development. Yield effects were a function of treatment effects on stand; if stand was increased then yields were also increased. No phytotoxicity from any treatment was detected in the plots.

In conclusion, several seedpiece fungicide treatments available to growers during 1999 are proven to reduce the late blight spread that occurs during seed handling and cutting. The specific formulations available are based on the labeling efforts for each State; label directions must be followed. It is important to realize that you cannot cure an infected seedlot by applying seedpiece fungicide treatments and also that seedpiece treatment will not protect the foliage. Although most growers agree that increased emergence is a desirable benefit of seedpiece treatment, don't forget that plants that emerge from late blight-infected seedpieces may ultimately serve as a source of inoculum from which late blight spreads.

Therefore, is it really desirable to increase emergence by applying fungicide to seed, or should every late blight-carrying seedpiece rot in the ground before it produces a plant? Although the answer is not immediately obvious, if you always start with a seedlot that has no known prior exposure to late blight, application of fungicide will provide an added layer of protection that prevents the inadvertent spread of late blight inoculum in your seed. In other words, since it is not possible to certify that a seedlot is late blight-free, labeled seedpiece fungicide treatments will ultimately reduce the risk of planting infected seed. Seed treatment fungicides will become an important component of an integrated late blight management program.
Blight Highlights

from Winter Workshops

LATE BLIGHT
(from the British Isles)

Stem and tuber late blight - During rains, late blight spores may wash down stem and 'funnel' into the ground around the base, going through the soil to the tubers. For affecting stem blight, triphenyltin-OH (SuperTin) worked better than the mancozebs. Fungicides were applied foliar every 10-14 days with a ground rig at 25 gpa. Chlorothalonil were not in the trials. An Irish researcher pointed out that the phytotoxicity associated with SuperTin is related to late and wet season applications. In Aug. and Sep. A Scottish researcher reported that stem blight was a better predictor of tuber blight than is foliar blight. UK research shows that late blight barely grows in tissues, not skin, on infected tubers stored below 43F.

(from the U.S.)

Center-pivots - The area under center-pivot irrigation most susceptible to late blight is the first 100 feet out from the pivot (center tower). This area comprises about one-third of an acre. In an Idaho survey, late blight always appeared within the radius of the first tower when the field was infested, i.e., all fields with late blight had it in this area. Dennis Johnson of Washington St. U. recommended not planting this area.

Forecasting - Besides the need to monitor winds coming from regions of the country with late blight, predicting the lag period before late blight occurrence may be related to the speed of crossing the threshold level of 18. Wet periods which are followed by long dry spells prior to accumulating 18 severity points may allow a low level development of late blight. When the threshold is crossed, late blight appears sooner, within a week. On the other hand, following a sudden, rapid accumulation of severity values resulting in an immediate crossing of 18, late blight may take three weeks before appearing. It would need that time to undergo its developmental and population process. Data supporting this was presented by Alexander Pavlista, U Nebraska-Lincoln. More on this in later this year.

EARLY BLIGHT

Even with increased fungicide usage, there is an increase in early blight over the past couple of years. Why? Some possible reason discussed are a/ There are more applications at shorter intervals but the rates have been lowered to marginal levels. b/ There is less fungicide alternation, 'locking' into programs. c/ There is a high usage of chlorothalonil versus EBDCs. Are there new, more virulent strains of early blight? Neil Gudmestad, NDSU, reported some loss of sensitivity of early blight, primarily to chlorothalonil as the growing season progresses. The population seems to shift and mot be due to a mutational change, i.e., new strain. Why the shift? It could be due to sub-lethal (below maximum label rate) use of chlorothalonil zinc applied in 5-day intervals.

Economics-based studies by Gary Secor, NDSU, show that chlorothalonil zinc (Bravo Zn) plus copper hydroxide (Kocide 2000) gave the best return for blight control based on per acre cost and yield. Some highlights for application are a/ High pressure ground sprayers work "wonderful" while airblast et al. are not any better. b/ Applications under wet conditions or on leaves with early morning dew give better coverage against both blights. c/ The low-volume irrigation ("drop booms") system giving 50-100 gpa gives the best fungicide coverage on the plant.

Around the time of first flower is usually when the first early blight lesions appear on lower leaves and time for first fungicidal treatment. Early blight on tubers surfaces move internally after a few months of storage. Gary Franc, U Wyoming, emphasized that research is needed on pre-harvest treatment of soil to reduce inoculum, maybe treating just ahead of harvesters. Early blight tuber decay over months is related to bruising during harvest in the presence of spores. A key observation is that there is NO correlation between early blight on seed and subsequent early blight on foliage.

Updates

Full registrations have been granted for late blight control to Curzate DF (DuPont) and Acrobat MZ (American Cyanamid). No word on the status of Tattoo C (AgrEvo); a Section 18 ("emergency use") on this product will not be filed this year.

Bravo Zn and other Bravos will be marketed this year by Zeneca which has acquired ISK BioScience.

Manex C8 will no longer be marketed as announced by ICL.

Quadris is still expected to get full registration for early and late blights on potato this Spring (March-April). If not achieved, I'll begin filing for a Section 18 on it like last year.

Section 24c (SLN) registrations are in the pipeline for MZ cymoxanil (Gustafson) for control of late blight spread on cutting knives. Late blight has been added to the TOPS MZ label.

Maxim MZ (Novartis) is likewise expected to receive a section 24c clearance in Nebraska soon.

Dual II Magnum (Novartis), a granular herbicide, received full registration on potatoes last year and first introduced on corn and soybeans last fall. Some key targets are pigweeds and Eastern black nightshade. Also included are many grasses such as the foxtails. It must be applied prior to potato emergence. Note: if cool, wet soil conditions occur shortly after application, the product may delay maturity of early season varieties especially chippers. Plant-back restrictions after application include 4 months for alfalfa and 4.5 months for small grains.
Seed-Borne Late Blight
Sources of Information

Continued from Page 2


Windbreaks and Potato Yields

Recent research in tropical north Australia, showed that treed windbreaks greatly reduce wind velocity and increased potato yields by 6% over the whole field. A model was developed to determine yields at differing distances from the tree line and the heights of the tree windbreak.

Highest yields were reported for potatoes grown away from the windbreak from 2 to 10 times the height of the windbreak. The yield of potatoes grown at 8 times windbreak height was 18% greater than yields of potatoes grown 30 times windbreak height away. In other words, if the trees in the windbreak are 25 feet tall, then the yield 200 feet away is 18% greater than that of potatoes grown 750 feet away from the windbreak. Note an acre is 208 feet by 208 feet.

Check out the Nebraska Potato Eyes on the WWW at: http://lanrwww.unl.edu/lanr/phrec/Peyes.htm