

# The trouble with CTL

“Chlorothalonil is the most effective multisite.”

## Technical Disease control

The future of chlorothalonil hangs in the balance in light of the recommendation by EFSA for non-renewal of its approval. *CPM* finds out why this is and looks at the implications of its potential loss.

By Lucy de la Pasture

It's been a decade since the European Commission moved from a risk-based assessment to a hazard-based one under directive EC 1107/2009. But it's only relatively recently the industry has been feeling the bite of the new system, with several important pesticides (most recently diquat and metaldehyde) feeling the teeth of the new regulations during their passage through the renewal process.

Now the goalposts have moved, much of the older chemistry is struggling to meet the new standards and it's a problem chlorothalonil is currently facing as it's considered for renewal of approval. The process has been complex and frustrating, according to Maureen Smith, head of regulatory affairs (N Europe) at Syngenta, who are approval holders for Bravo 500.

“One of the main areas of difficulty has been around the metabolites of chlorothalonil

and their effect on the environment. It's a very simple but reactive molecule, so it forms a lot of metabolites and it's impossible to test for them all.

“If you imagine chlorothalonil as being the trunk of a tree, then each branch a first level metabolite, as that branches a second level metabolite is formed and so on,” she explains.

### Best approach

“We agreed with the rapporteur Member State, the Netherlands that the best approach was to group similar metabolites into clusters and then test one or two metabolites from each group. This is in line with current accepted guidance. Once the dossier was submitted, some of the Member State experts reviewing the information within the European Food Standards Agency (EFSA) peer review process disagreed with this approach and consequently found data gaps in the information presented to them.”

In addition, the EFSA peer review process identified other areas of concern, including genotoxicity of metabolites, and ecological concern regarding a high risk to amphibians and fish, she adds.

Chlorothalonil has been one of several active substances caught out by a change of approach to the genotoxic assessments by EFSA in the current round of renewals, which was made without notifying approval holders, explains Maureen, which explains some of the data gaps identified in its dossier following the EFSA peer review process.

“Chlorothalonil is a multisite so, by its

definition, it has the potential to affect many biochemical processes. There's also an element of interpretation of the data around some of the key issues such as the metabolites in groundwater, genotoxic risk assessments and ecotoxic risk assessments.

“One of the other data gaps identified is chronic risk to fish and amphibians but because chlorothalonil is a molecule that has a short half-life in water and typically an acute effect, i.e. it either kills something or doesn't, the standard chronic studies, and consequently risk assessments, tend to exaggerate the reality of the risk.”

Ordinarily interpreting challenges such as these are often left for Member States to take a view on, but chlorothalonil is facing another major hurdle in its path to renewal ▶



Hazel Doonan explains that if chlorothalonil were to go, it may not have the usual six months use-up period.

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*Chlorothalonil is the 'last man standing' when it comes to ramularia control, points out David Ranner.*

► which may prove unsurmountable, explains Maureen.

EFSA also proposed a new classification for chlorothalonil. It should be noted that classification is outside the remit of EFSA, being the accountability of ECHA.

"Under harmonisation, chlorothalonil was classified as a carcinogen Category 2.0 but the European Chemicals Agency (ECHA) are currently considering a proposal to reclassify it as Category 1b. Under 1107, Category 1b triggers a 'cut-off criteria' and this would mean an automatic revocation of chlorothalonil's approval. To further complicate matters, the ECHA process is running behind the decision-making process for chlorothalonil's renewal."

With so many things looking uncertain, the recommendation from EFSA to the European Commission (EC) has been for a non-renewal of chlorothalonil's approval and on Dec 4 2018, a World Trade Organisation technical barrier to trade notification was issued. The procedure is to then allow 60 days from the date of its publication before chlorothalonil can be discussed at the next meeting of the EC Standing Committee on Plants, Animals, Food and Feed (SCoPAFF), which at the earliest will be during the third week of March 2019.

While the industry waits for SCoPAFF to give its verdict, there's plenty going on behind the scenes to inform Member States of the importance of chlorothalonil because of the important role it plays in resistance management in wheat and the control of ramularia in barley, adds Maureen.

Hazel Doonan, AIC's sector head of crop protection, has been involved in submitting data to support the case for chlorothalonil in the UK. Even though the outlook is 'unfavourable', she stresses chlorothalonil's future is still to be decided.

Under EC law, when the proposal for non-renewal is put to a SCoPAFF vote it has to be backed by a qualified majority. That means the outcome is weighted so the majority must represent 55% of Member States, representing 65% of the EU population, so much will depend on the views of Germany, France, Italy, Spain and Poland as well as the UK, explains Hazel.

Ireland and the UK have the greatest pressure from septoria due to their rainfall, but Germany has a big problem with ramularia in barley. But even if the numbers were to add up in favour of chlorothalonil based on industry needs, its completely unknown whether any particular Member State's view would consider this or would be political when it comes to how they cast their vote.

If ECHA decide to reclassify chlorothalonil, meaning it meets EC 1107/2009 cut-off criteria and has to be removed regardless of any of the other issues it faces, then Hazel says AIC would lobby to give the UK enough time to manage stocks in the supply chain following any decision, provided there was no unacceptable risk to human health or the environment.

## Quick revocation

"We can't assume that chlorothalonil will have the normal six-month sale period and a 12-month use-up period if it is revoked, it could well be less. For growers with chlorothalonil in store ready for the start of fungicide programmes, they could find themselves with a disposal problem if there's a quick revocation," she explains.

So what would the impact be on growers? David Ranner, Syngenta's UK cereal fungicides marketing manager, says that chlorothalonil provides cost-effective septoria control as well as being an essential tool in resistance management. But in reality, there are multisite alternatives available which could be used in its place, albeit at greater cost.

"The biggest challenge would be ramularia control in barley because alternative options don't exist. The SDHIs and azoles are now doing very little on ramularia and the strobos aren't working at all. Chlorothalonil really is the last man standing," he says.

"Although breeders are working hard,

there currently isn't a known source of genetic resistance and no effective seed treatments for the disease. The biggest threat is to malting barley where ramularia affects quality as well as yield."

Plant pathologist Prof Fiona Burnett agrees with David's concerns. "Chlorothalonil has been a win-win in terms of giving effective disease control and a useful anti resistance measure, all at a cheap price for growers.

Other multisites such as folpet and mancozeb could help for septoria control if there's a move to more restricted chlorothalonil usage, believes Fiona.

"Going forward removal of chlorothalonil, particularly if almost immediately, would give us a lot of concern. For wheat, other multisites will offer some recourse, although other multisites like mancozeb are also under scrutiny. All in all, chlorothalonil is the most effective multisite, so it will still be a loss in efficacy," says Fiona.

"But on barley, it's critical as folpet doesn't offer effective ramularia control. Since ramularia developed resistance to SDHI, strobilurin and azoles, chlorothalonil is the sole effective active. If we move to restricted use then T2 would be the one we must retain," she says.

"Broadly, removing chlorothalonil puts other single site actives, existing and new, at greater risk of resistance development. We need to keep working on better varieties and new actives but that's a longer game, so a quick removal before we have other solutions would be a big deal. In the best sense chlorothalonil has propped up programs and covered declines in other chemistry."

Irish growers face the highest septoria challenge and would be the worst affected if there was an outright ban on chlorothalonil. Dr Steven Kildea, senior research officer at Teagasc, says in Ireland chlorothalonil has become much more than a partner product for resistance management. It's needed for the added septoria control it brings to the ►



*Chlorothalonil has the most efficacy of all the multisites as far as septoria is concerned.*

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*Without chlorothalonil Irish growers would see net margin reduced by over 50% in wheat and 65% in barley, says Steven Kildea.*

► mix since the efficacy expected from SDHI + azole mixes has declined to around 65-70% control in Teagasc trials.

"In barley applying chlorothalonil at T2 is standard practice for ramularia control. In trials last year (2018), the two highest yield losses were due to ramularia (15%) and occurred in winter barley where just SDHI + azole mixes were applied. In barley that's your profit gone and in spring crops the impact could be even bigger," he comments.

In anticipation that the dose of chlorothalonil may be restricted, Steven's been looking at restricted doses of chlorothalonil in trials to find out how this would affect control and when in the programme it's best to target them.

"If doses were restricted to 1000g then we could manage septoria by using chlorothalonil at T1 and T2. At 750g, there's a question whether you load the programme early or late but the news that chlorothalonil may go completely leaves us with a problem," he says.

Teagasc have also been looking at folpet, mancozeb and sulphur as alternatives to chlorothalonil and Steven admits that when folpet's used as part of a good programme,



*Ramularia has evolved resistance to all the currently available single site modes of action.*

its performance is hard to pull apart from chlorothalonil but in a high septoria pressure or risk situation he would have less confidence in the alternative multisite.

To assess the probable impact the loss of chlorothalonil would have on the economics of barley and wheat production in Ireland, Steven reviewed trials data from 2016 and 2017, both regarded as moderate disease pressure seasons, with the addition of a small number of trials from 2018. He found within the trials data set, the addition of chlorothalonil to fungicide programmes on wheat had a significant impact on yield, adding on average 0.58 t/ha.

## Net margin reduction

He came to the conclusion that if chlorothalonil was no longer available, the most likely scenario for Irish growers would be an average net margin reduction of over 50% in wheat and 65% in barley, for growers achieving national average yields at or just above break even. There would also be an increase in costs of production of between 8-12%.

"In the medium term the introduction of new fungicides will be welcome and increase disease control options, however in the absence of chlorothalonil a more rapid loss of efficacy of these fungicides is expected due to high disease pressure."

Barley growing is Steven's biggest concern because it's not yet known whether new chemistry will be successful in providing sufficient control of ramularia in the field, he says.

The good news is BASF's pipeline azole, Revysol, does have good intrinsic activity on ramularia, says Ben Freer, BASF business development manager for the UK.

"We saw Revysol in wheat and barley field trials in New Zealand. It's clear that Revysol is a step forward in controlling ramularia from what we saw, in a very challenging disease year. Our observations from trials in Scotland and Ireland would very much support what we saw in the southern hemisphere, even in situations where prothioconazole was under pressure," he comments.

"Whilst it isn't BASF's place to comment on active ingredients other than our own, we know that chlorothalonil is under pressure through the re-registration process, and if it does go, we lose a very valuable tool for controlling foliar cereal diseases.

"Revysol, a fungicide innovation, is coming and as a result, programmes will change with its inclusion. We're working with other organisations in the industry to look at the implications of these changes



*Removing chlorothalonil puts other single site actives, existing and new, at greater risk of resistance development, says Fiona Burnett.*

in available chemistry, integrated crop management and for programme choices for the future, in which Revysol will be a key component."

Inatreq, the pipeline molecule from Corteva Agriscience, will offer a completely new mode of action but it's not yet clear whether it has any potential activity on ramularia. According to the company, the initial registration will be for wheat with barley to follow.

"The level of control of barley diseases is still under evaluation and it would be unfair to offer a speculative answer to this question at this stage," comments Mike Ashworth, Corteva's fungicide product manager.

Protecting the new chemistry is a key concern for the industry and to help protect a mode of action, a partner with an equally



*Ben Freer was impressed by Revysol's performance on ramularia in New Zealand, where resistance is also a problem with other fungicides.*

strong efficacy on the target disease is needed to mix with it, according to the researchers. The trouble in barley is that there's no such partner for the pipeline

chemistry where ramularia's concerned if chlorothalonil goes.

Even though there's overwhelming support for continued use of chlorothalonil

from an agronomic perspective, the industry is united from manufacturer to researcher that if the science indicates chlorothalonil has had its day, then it should go. ■

## Resistance rise 'may be overstated'

The shift in septoria resistance to prothioconazole may not be taking place at a rate as high as anecdotal reports suggest. Figures released following routine sampling carried out by Bayer show the resistance of the isolate population is hovering at around the same level in the UK as it was in 2015.

"Our work shows there's been a slower evolution of resistance in recent years than perhaps some of the published data show," says Dr Andreas Mehl, Bayer's global resistance management specialist for fungicides. "But it still has to be managed — indeed it may be the very responsible approach UK growers are taking to resistance management that has contributed to the apparent slow down."

Bayer's survey work involves taking septoria samples from across Europe and assessing them in the lab for their EC<sub>50</sub> value — that's the rate of prothioconazole needed to control 50% of the isolates. As the proportion and virulence of the resistant population grows, so the EC<sub>50</sub> value rises. "In the test system we used, a value of 4mg/l is quite sensitive, while 9-10mg/l is too high," says Andreas.

These are compared with reference samples — populations known to be sensitive to prothioconazole — to give a resistance factor. "So a population with an EC<sub>50</sub> value of 6mg/l compared with a reference sample averaging 0.3mg/l has a resistance factor of 20. A factor of 30-40 will give acceptable field performance, but 50 or above is problematic," he explains.

"In the UK and Ireland, compared with the rest of Europe, there is a very high disease pressure and we see the most frequent use of fungicides, so a high resistance factor is not a surprise."

Although this then appeared to drop in 2016 (see table right), Andreas notes the EC<sub>50</sub> values of the reference samples were relatively high in that year.

Disease pressure influences the results, he points out. "In a year of high disease pressure, we have a lot of isolates to test, but in a dry year, we get a limited number of samples, which may skew results.

"But given the UK and Ireland have the highest disease pressure in Europe, a resistance factor of 20-22 is a good number. Prothioconazole is Bayer's most important fungicide molecule and we want to ensure it is effective for as long as possible. The data suggest that there's a responsible approach to resistance management being taken by UK growers."

The picture with SDHIs is somewhat different. The first signs of a shift took place in Ireland in 2015, reports Andreas. "We saw 19 septoria strains with a higher EC<sub>50</sub> value for bixafen, but the resistance factor was no more than 20, so we weren't too concerned.

"Not all of the mutant isolates identified are causing a sensitivity shift, and they may also have a fitness penalty. So mutations are worth monitoring, but they're not necessarily impacting on SDHI performance."

In 2016, less sensitive strains showed up again in the Irish population, and also in the Netherlands, and then showed up in the UK in 2017, along with one highly resistant strain.

"Last year, there was no sign of the highly resistant mutant, but there was a slight shift in resistance of the population of 'softer' mutants. Importantly there's no evidence of a decrease in field performance of bixafen, but it's worth monitoring these populations," he notes.

Fluopyram has a lower intrinsic activity against septoria, but it's complementary, Andreas reasons. "Most problematic strains for bixafen show much lower resistance factors for fluopyram. The strategy of using these two SDHIs with different cross-resistance in Aspra is working."

His advice is to keep rates of azole high, but



Andreas Mehl attributes the apparent slow down to the responsible approach UK growers are taking to resistance management.

tailor the SDHI dose to disease risk. "The azole shift is generated by using too low a rate. SDHI resistance is a mutation, and selection is driven by the number of applications you make. So in a low disease year, by all means reduce your use of SDHI, but keep azole rates robust."

Dr Paul Gosling of AHDB believes growers and agronomists should treat the information with some caution. "AHDB-funded fungicide performance research has also shown a pause in the shift of azole resistance in the past few years, but we don't know if it will last.

"There may be some cross-resistance benefit using fluopyram, but the practical significance is less clear. Our monitoring shows Aspra doesn't stand out as a product that's less affected by shifts in efficacy."

### Mean resistance factor

|         | 2015 | 2016 | 2017 | 2018 |
|---------|------|------|------|------|
| UK      | 20   | 5    | 34   | 22   |
| Ireland | 19   | 7    | 33   | 23   |

*Source: EpiLogic (Germany); 851 isolates.*

## New UPL commits to "open" agriculture

UPL has completed its \$4.2bn (£3.2bn) acquisition of Arysta LifeScience. The deal catapults the new company into the top five global agrochemical players with approximately \$5bn (£3.82bn) in combined sales.

UPL's global CEO Jai Shroff has launched what he calls 'OpenAg' — a commitment to open-minded and "win-win" partnerships.

"Through our purpose of OpenAg, we aim

to transform agriculture by creating an open agriculture network that feeds sustainable growth for all," says Jai.

"We believe that UPL can offer a portfolio of technologies in the field from crop protection to innovative hybrid platforms. Our combined biosolutions pipeline signals the dawn of a new era in sustainable agriculture as a part of integrated pest and nutrition

management programmes."

UPL says it has received unconditional regulatory approval for the acquisition from authorities in the countries in which it trades — more than 130 worldwide. The company has a portfolio of over 13,000 registrations, with 27 formulation labs and 48 manufacturing plants. Its brands include Advanta Seeds and its mancozeb fungicide Unizeb Gold.