Carboxylic Acid Amides (CAA) Working Group

Annual Meeting Season 2023 on January 16th, 2024

Protocol of the discussions and recommendations of the CAA Working Group of the Fungicide Resistance Action Committee (FRAC)

Participants

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Venue:
Meeting at Lindner Hotel, Frankfurt

Anti-trust guidelines (from FRAC constitution) were shown at the start of the meeting

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1. Introduction

The FRAC CAA Working Group was set up in 2005 to generate common resistance management recommendations for the Oomycete fungicides dimethomorph, flumorph, pyrimorph, benthiavalicarb, iprovalicarb, valifenalate and mandipropamid.

All of the above-mentioned fungicides exhibit cross resistance and are grouped under the FRAC Code No. 40 in the FRAC Code List.

CODE	TARGET SITE OF ACTION	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS
40	Cellulose synthesis	**CAA**-fungicides (**C**arboxylic **a**cid **a**mides)	cinnamic acid amides	dimethomorph flumorph pyrimorph	Low to medium risk. Resistance management required.
			valinamide carbamates	benthiavalicarb iprovalicarb valifenalate	
			mandelic acid amides	mandipropamid	

As shown in the table, the group name **C**arboxylic **A**cid **A**mides (**CAA**) has been chosen. This name best represents compounds from three different chemical groups. The mode of action of CAA compounds is directly linked to the inhibition of cellulose synthesis in the Oomycete plant pathogen (Blum *et al.* 2010, Molecular Plant Pathology 11, 227-243).

Uptake studies with ^{14}C labeled mandipropamid (MPD) showed that this Oomycete control agent acts on the cell wall and does not enter the cell. Furthermore, ^{14}C glucose incorporation into cellulose was perturbed in the presence of MPD. Gene sequence analysis of cellulose synthase genes in laboratory mutants, insensitive to MPD, revealed two point mutations in the *PiCesA3* gene, known to be involved in cellulose synthesis. Both mutations in the *PiCesA3* gene result in a change to the same amino acid (Glycine-1105) in the protein.

Sensitivity monitoring studies over several years revealed that in populations of the late blight pathogen, *Phytophthora infestans*, all isolates were fully sensitive to CAA fungicides. In monitoring studies from 2021 first suspicious cases were identified and in the seasons 2022 CAA resistance in this species was confirmed. In populations of the grape downy mildew pathogen, *Plasmopara viticola*, resistant isolates can be found in many grape growing regions in Europe. There is cross-resistance to all CAA fungicides.

Inheritance studies (Gisi *et al.* 2007, Plant Pathology 56, 199-208) showed that sexual crosses between sensitive and CAA resistant isolates of *Plasmopara viticola* lead to a co-segregation of resistance to dimethomorph, iprovalicarb, benthiavalicarb and mandipropamid, but not to the phenylamide, mefenoxam, which was tested in parallel as an independent marker.

Further, the inheritance studies showed that the gene(s) for resistance to CAA fungicides are inherited in a recessive manner. Therefore, the entire F1 generation of crosses between sensitive and CAA resistant isolates was sensitive, and only in the F2 progeny did CAA resistance reappear in some isolates. These results suggest that the resistance risk can be classified as moderate (as compared to high for phenylamide and CAA fungicides) and that it can be managed by appropriate product use strategies (see below).

2. CAA – Resistance Monitoring

2.1. CAA – *Plasmopara viticola* – Grape downy mildew

Disease incidence

In 2023, disease pressure was different in European regions with high disease pressure especially in France and Italy.

Monitoring results

(BASF, Bayer, Certis-Belchim, K-I Chemical and Syngenta)

The following estimations are based on the data provided by the different companies. These data were generated by different laboratories including external service providers. Different methods such as *in vivo* tests, zoospore germination tests and molecular genetic analysis were used for sensitivity assessment.
The latest assessments for each country are provided. These are from populations from the 2023 season, besides another year is mentioned. Regions of interest which are not listed here, may be found in previous meeting minutes.

France
As in the years before, CAA resistant isolates have been detected consistently in most areas. High frequencies of resistance were detected in Cognac; moderate to high frequencies in Armagnac, Champagne, Languedoc, Sud-Est and Val de Loire. Moderate frequencies were detected in Alsace/Lorraine, Bordeaux, Bourgogne and Beaujolais, Midi-Pyrenees and Valle du Rhone.

Germany
High frequencies of resistance were found in the regions Baden, Main, Mosel and Neckar.

Switzerland
A limited number of samples was analysed in 2021 from Ticino, Vaud and Geneva with high frequency values of CAA resistance. In Wallis, frequency was moderate.

Austria

Samples were analysed from Niederösterreich which showed as in the year before heterogenous frequencies from low to high, and from Steiermark with high frequencies of CAA resistance.

Italy
High frequencies of resistance were observed in Lazio, Lombardia, Marche, Piemonte, and Puglia, while moderate to high values were found in Veneto. Moderate frequencies were detected in Emilia Romagna, Friuli and Trentino. Monitoring in Abruzzo was limited to single samples, which showed no CAA resistance. Limited monitoring with some samples from Sicilia showed a heterogenous picture of samples with full sensitivity or high resistance frequency.

Spain:
A heterogenous situation with low or high frequency of CAA resistance was detected in Cataluna. Monitoring in Basque, Galicia and Leon resulted in a high frequency of CAA resistance.

Portugal
CAA resistance was heterogenous in Portugal with low to high frequencies of CAA resistance in the populations.

Greece
A heterogenous situation has been detected in the Peloponnese area with low to high frequencies of CAA resistance.

Croatia
Samples from 2022 from Croatia showed moderate to high frequency of CAA resistance.

Hungary
In 2022, samples from Hungary were heterogenous and contained no to moderate frequency of CAA resistance.

Romania:
Monitoring of samples across Romania showed a heterogenous situation with no to high values of CAA resistance.

Turkey
As in the seasons before, samples from the regions Dogu Marmara and Ege were fully sensitive to CAAs.

Bulgaria
Samples from 2022 were full sensitive.

Slovenia
Samples from 2022 showed overall high values of CAA resistance.

Slovakia
The sites, which were analysed in a limited CAA monitoring in 2020 were full sensitive.

2.2. CAA – *Phytophthora infestans* – Late blight

Disease incidence

In 2023, disease pressure was high in the many potato growing areas of Europe.

Monitoring results

(Certis-Belchim, K-I Chemical and Syngenta)

In 2023 samples were taken from potatoes and tomatoes from Belgium, Croatia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Sweden and UK. Analysis was done with sensitivity tests using isolates or populations from leaf samples and/or with genetic analysis from these samples. Complementary studies were conducted to elucidate the SSR genotype and target-site mutation (G1105S) presence using FTA cards.
Extensive monitoring showed full sensitivity in most European countries.
Resistance was found in potato samples in Belgium, Germany, Netherlands and Portugal; preliminary data from Denmark showed lower frequency of resistance compared to 2022; further studies are still ongoing.
All samples from tomatoes (France, Portugal, Italy, Croatia and Romania) were sensitive. A single sample from Slovakia was resistant.
In 2023 the G1105S mutation in CesA3 in homozygous stage was found as the responsible resistance mechanism as in the years before. All resistant isolates were characterized as the genotype EU_43_A1, but also sensitive isolates with this genotype have been identified (Genotypes are classified by Euroblight (https://agro.au.dk/forskning/internationale-platforme/euroblight). These genotypes could express variable aggressiveness, but are not necessarily linked to fungicide resistance, which is genetically independent).
For the first time in 2023, heterozygous strains were detected and phenotyped as sensitive confirming the recessive inheritance of CAA resistance as reported for *Plasmopara viticola* (Gisi et al. 2007, Plant Pathology 56, 199-208)

In 2022 and 2023 monitoring studies were carried out with samples from tomatoes from Vietnam using FTA cards for molecular analysis of the presence of the G1105S mutation. In 2022 all samples were sensitive (homozygous wildtype), in 2023 most samples were sensitive (homozygous wildtype), single samples were heterozygous (sensitive) and homozygous (resistant) for the G1105S mutation.

Historic background:

Further analysis of suspicious isolates from 2021 confirmed resistance to CAAs. The mechanism is the G1105S mutation in the CesA3 gene. All isolates having CesA3 G1105S mutation were genotype EU_43_A1.

Monitoring studies were carried out in 2022 in potatoes in Belgium, Denmark, Germany, France, Hungary, Ireland, Latvia, Norway, Netherlands, Poland, Portugal, Sweden and United Kingdom. Single resistant isolates have been detected in Germany, Netherlands, Sweden, Norway and with higher frequency in Denmark. Full sensitivity was monitored in Belgium, France, Hungary, Ireland, Latvia, Poland, Portugal and United Kingdom.

All samples from tomatoes from Europe (Croatia, Italy, Poland) and Vietnam were fully sensitive.

Sensitivity monitoring programs in 2021 showed generally a full sensitive picture over Europe. Samples were taken from tomatoes and potatoes originating from Belgium, Czech Republic, Denmark, Germany, France, Spain, Greece, Italy, Portugal, Slovakia, Netherlands, Poland, Romania, United Kingdom. However, few suspicious isolates with higher EC_{50} values have been detected. Further molecular analysis conducted in 2022 identified the mechanism of resistance, which is related to the G1105S mutation in the CesA3 gene.

Sensitivity monitoring programs in previous years showed full sensitivity for *Phytophthora infestans* collected from potatoes and tomatoes in Europe (Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Latvia, Netherlands, Poland, Portugal, Slovakia, Spain, Sweden, UK). From China, data are available from 2016 (Hebei, Inner Mongolia) and all samples were sensitive.

2.3. CAA – *Pseudoperonospora cubensis* - Downy mildew of cucurbits

(Syngenta)

In 2022 and 2023, genetic monitoring was carried out with samples from Vietnam. Low frequency of resistance (responsible mutation was V1109L) was detected in Ha-Nam. Southern regions showed full sensitivity.

In 2020 and 2021 full sensitivity was monitored in samples collected from cucumber, melon and zucchini in Croatia, Germany, Hungary, France, Greece, Poland, Switzerland. Single strains showing CAA resistance were detected in Italy in 2020 and in Spain from 2021, however most of the samples from both countries were sensitive.

All samples collected from China (6 provinces) between 2019 and 2020 confirmed full sensitivity based on molecular analysis.

Two trial sites from US (South Carolina and Florida) confirmed the presence of the previous published mutation G1105W in the cesA3 associated to CAA resistance (Blum *et al.* 2011, *Pest Management Science* 67, 1211-1214).

2.4 CAA – *Bremia lactucae* – Downy mildew of lettuce

(Syngenta, BASF)

Full sensitivity was monitored in 2020 and 2021 from samples collected in Belgium, Germany, Spain, Greece, Croatia, Hungary and Italy.

Sensitivity studies were done with samples from 2013-2015 from France, Italy, Germany and Spain. All samples tested were sensitive.
In 2016, genetic analysis of the cesA3 gene showed that all samples from Spain, Germany and UK did not contain any known mutation potentially causing CAA resistance and were therefore classified as sensitive.
In 2018 and 2019 samples collected from France, Greece, Germany, Netherlands and Italy were sensitive.

2.5 CAA – *Peronospora destructor* - Downy mildew of onions

(BASF)

Genetic analysis of the cesA3 gene in 2016 showed that all samples from Germany did not contain any known mutation potentially causing CAA resistance and were therefore classified as sensitive.

3. CAA – Use Recommendations

3.1. CAA – *Plasmopara viticola* – Grape downy mildew

Plasmopara viticola is classified by FRAC as a high-risk pathogen. Long-term experience with CAA fungicides demonstrates that the resistance risk of *Plasmopara viticola* to this fungicide group is moderate and can be managed through appropriate use strategies.

CAA – Use Recommendations:

- Apply CAA fungicides preferably in a preventive manner
- Apply a maximum of 50% of the total number of intended applications for disease control not exceeding a total of 4 CAA fungicide sprays during one crop cycle. In areas of high resistance, the total number should not exceed a maximum of 3 applications during one crop cycle
- Always apply CAA fungicides in mixture with effective partners such as multi-site or other non-cross resistant fungicides
- An effective partner for a CAA fungicide is one that provides satisfactory disease control when used alone at the mixture rate
- Alternation with fungicides having other modes of action is recommended in spray programs

For more detailed product recommendations refer to the use guidelines published by the respective CAA manufacturers.

3.2. CAA – *Phytophthora infestans* – Late blight of potato and tomato

CAA were introduced into the market in 1993. No resistant isolates from field populations have been found until 2021.

Phytophthora infestans is classified by FRAC as a medium risk pathogen. Long-term experience with CAA fungicides demonstrates that the resistance risk of *Phytophthora infestans* to this fungicide group is low to moderate. For effective resistance management, appropriate use strategies should be implemented.

Use Recommendations:

- Apply CAA fungicides preferably in a preventive manner
- Apply a maximum of 50% of the total number of intended applications for late blight control
- Apply CAA fungicides always at recommended dose rates
- Apply CAA fungicides using not more than 2 consecutive applications
- Apply CAA fungicides preferably in mixtures with effective partners belonging to different modes of action

- An effective partner for a CAA fungicide is one that provides satisfactory disease control when used alone at the mixture rate
- Alternation with fungicides having other modes of action is recommended in spray programs
- Good agricultural practices must be considered to reduce source of inoculum, disease pressure and resistance risk, *e.g.* consider to plant resistant varieties and refer to disease prediction models

In countries with reported cases of resistance:

- CAA fungicides must be used in mixtures, with not more than 2 consecutive applications
- In case mixtures cannot be applied for regulatory reasons, apply CAA fungicide in strict alternation

For more detailed product recommendations refer to the use guidelines published by the respective CAA manufacturers.

3.3. CAA – *Pseudoperonospora cubensis* – Downy mildew of cucurbits

Pseudoperonospora cubensis is classified by FRAC as a high-risk pathogen.

Use Recommendations:

- Apply CAA fungicides preferably in a preventive manner
- Apply a maximum of 50% of the total number of intended applications for disease control not exceeding a total of 4 CAA fungicide sprays during one crop cycle. In areas of high resistance, the total number should not exceed a maximum of 3 applications during one crop cycle
- Always apply CAA fungicides in mixture with effective partners such as multi-site or other non-cross resistant fungicides
- An effective partner for a CAA fungicide is one that provides satisfactory disease control when used alone at the mixture rate
- Alternation with fungicides having other modes of action is recommended in spray programs

For product recommendations refer to the use guidelines published by the respective CAA manufacturers.

3.4. CAA – Other Oomycete pathogens

Some of the downy mildew pathogens are classified by FRAC as moderate risk pathogens (*e.g. Bremia lactucae*). Despite of the use of CAA fungicides for more than 20 years against a range of such Oomycete pathogens, no reports on the occurrence of less sensitive field populations are available.

For effective resistance management, a precautionary strategy has to be implemented.

Use Recommendations:

- Apply CAA fungicides preferably in a preventive manner
- Apply a maximum of 50% of the total number of intended applications for disease control
- Alternation with fungicides having other modes of action is recommended in spray programs

For more detailed product recommendations refer to the use guidelines published by the respective CAA manufacturers.

4. Next Meeting

Next annual meeting is scheduled for March 2025.