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 31st October, 2019

**Application for FAO/WHO Specification Development:**

**Application number: JMPS2020-001**

**Lambda-cyhalothrin WHO Specification 463/CS**

Dear Dr Muller,

Further to our bilateral discussions in Braunschweig in June this year Syngenta has the pleasure of submitting a package of data to support its proposal to update lambda-cyhalothrin WHO Specification 463/CS.

Syngenta periodically reviews the quality control (QC) data associated with specified products for compliance and also to identify any issues that may require the specification to be updated, to ensure the relevance of specification limits to the quality of the product.

Specifically, in relation to WHO Specification 463/CS, Syngenta will propose a change to the release-rate clause ***2.4 (Release of lambda-cyhalothrin)*** in light of a stewardship exercise involving a review of:

* existing release-rate and biological efficacy data
* new release-rate data (four laboratories)
* new biological efficacy data (laboratory)

Furthermore, during review of the noted data and definition of a proposal to update of the specification it has become clear that there is also a need to update CIPAC method MT 190 (The Determination of Release Properties of Lambda-cyhalothrin CS Formulations). Discussions are currently underway with CIPAC to determine the way forward and it is expected that an updated MT method and supporting data will be presented at the 2020 CIPAC meeting.

Therefore, in the following pages Syngenta will present its rationale for updating the specification and a summary of the supporting data. The updated specification proposal and supporting study reports are referenced and will be submitted separately to this letter.

If you have any questions or would like me to clarify anything please let me know.

Yours sincerely,

**Simon Baker**
Product Chemistry Manager

**Enclosed:**

Lambda-cyhalothrin WHO specification 463/CS proposal (Word format)

Release rate reports as noted below (in pdf format)

Biological efficacy reports as noted below (in pdf format)

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| **Report number**  | **Author(s)** | **year** | **Report title. Report identification number. Report identification number. GLP [if GLP]. Company conducting the study.**  |
| **CONFIDENTIAL DATA: Biological Efficacy Reports**  |
| VV-716726 | Hoppe M., Hofer D., Spycher C. | 2019 | Evaluation of the Residual Insecticidal Performance of Five ICON 10CS Batches, Report No.PPMG18309, Unpublished, Non-GLP, Syngenta Crop Protection, Stein, Switzerland  |
| VV-716724 | Hoppe M., Hofer D., Spycher C. | 2018 | Evaluation of the Insecticidal Performance of Five ICON 10CS Batches, Report No. PH WST 18/013, Unpublished Non-GLP, Syngenta Crop Protection, Stein, Switzerland  |
| **NON-CONFIDENTIAL DATA: Release Rate Reports** |
| VV-716674 | Baes M. | 2019 | Certificate of Analysis, Report No. 24861/Ch.7130/2019/A 25.04.2019. Unpublished, Non-GLP, Walloon Agricultural Research Centre (CRA-W), Gembloux, Belgium |
| VV-716675 | Jutsum P. | 2019 | A12690P Chemical Analysis of 10 Lambda-cyhalothrin CS Formulations, Report No. CEMS-8958, 18.03.2019, Unpublished, Non-GLP, CEM Analytical Services Ltd (CEMAS), Wokingham, UK |
| VV-716671 | Simonin C. | 2019a | A12690P – Analysis of Ten Representative Formulation Batches Produced at Syngenta Chemicals B.V., Belgium, 30.10.2019, Unpublished, Non-GLP, QC Laboratory - Syngenta Chemicals B.V. Rue de Tyberchamps, 37 B-7180 Seneffe Belgium |
| VV-716669 | Simonin C. | 2019b | A12690P – Analysis of Ten Representative Formulation Batches Produced at Syngenta Chemicals B.V., Belgium, 30.10.2019, Unpublished, Non-GLP, Analytical Development & Product Chemistry Breitenloh 5 4333 Münchwilen, Switzerland |

**Technical Letter - WHO Specification 463/CS**

**Introduction**

Since development of the lambda-cyhalothrin slow-release capsule suspension specification (WHO 463/CS) in 2003 there has been no systematic review of the specification clauses or routine quality control (QC) data that support those clauses.

Specifically, in relation to the release-rate clause - ***2.4 Release of lambda-cyhalothrin*** - the limits within the specification clause are restrictive, difficult to achieve, don’t correlate well with biological activity and are time consuming.

Therefore, following a stewardship exercise involving a review of:

* existing release-rate and biological efficacy data
* new release-rate data (four laboratories)
* new biological efficacy data (laboratory knockdown and residual assays)

Syngenta will propose a change to the release rate clause 2.4 that it believes provides an adequate quality benchmark that can be assessed in a timely manner compared to the current limits in the specification clause.

Furthermore, during review of the noted data and definition of a proposal to update of the specification it has become clear that there is also a need to update CIPAC method MT 190 (The Determination of Release Properties of Lambda-cyhalothrin CS Formulations). Discussions are currently underway with CIPAC to determine the way forward and it is expected that an updated MT method and supporting data will be presented at the 2020 CIPAC meeting.

**Background - Existing Release-rate and Biological Efficacy Data (2014)**

Production batches of slow release lambda-cyhalothrin CS formulation routinely fail one or more parts of the release rate specification clause, however these batches demonstrate perfectly acceptable biological activity which is at least equivalent to the standard sample and expectation of performance from many years of testing. It appears that there is no direct relationship between the current release rate specification clauses and efficacy of a particular batch.

Therefore, in 2014 Syngenta conducted a study where fifteen production batches of slow release CS formulations were tested for release rate profile and biological performance in order to:

* Investigate the reproducibility of the release rate method (CIPAC MT190),
* Demonstrate that batches which failed the release rate clauses remained efficacious
* Provide data to propose a more appropriate specification clause for release rate

The release rate profile was analysed at three Syngenta analytical sites and by an independent laboratory (CEMAS, UK).

The biological performance was assessed at Syngenta’s Stein site in Switzerland.

Following statistical data analysis Syngenta concluded that the release rate results showed that the greatest source of variability was due to batch to batch variation i.e. variability inherent of the manufacturing process. Additionally, with respect to the analytical method (CIPAC MT190) random analytical variability appeared greater than site to site variability i.e. the method, providing it was followed carefully according to the specified conditions, was robust between laboratories.

Finally, it was concluded that the release rate method itself was considered to be fit for purpose, again with the proviso that the method conditions were strictly adhered too (see below – **Method Variability CIPAC MT190**).

Analysis of the results demonstrated two important points regarding the current release rate clause:

* The data suggested that the most confident prediction of an “in-specification” result would be at the 15minute time assessment point i.e. the variability at the 15minute point was lower than for the later assessment points.
* A large proportion of the results would be expected to fall below the current specification limit at the 180minute assessment time point.

The results from the release rate study suggested that further investigations could be beneficial. However, the release rate methodology remains a complex analytical process and micro-encapsulated formulations and themselves inherently complex to manufacture, therefore the potential for uncertain, variable results is clear.

Biological performance of the fifteen batches was assessed under two protocols; a knock-down test using German cockroaches (*Blattella germanica*) exposed to dilute spray dispersions of the production samples and a residual efficacy test where mosquitoes (*Ades aegypti*) were exposed to a substrate treated again with the dilute dispersions. Assessment of knock-down and mortality were then made at different time points.

Conclusions from the two tests demonstrated that for the fifteen production batches:

* Knock-down time was no different to the standard sample; under the conditions of the test the KD50, the time taken to knock-down (immobilize) 50% of the cockroaches, was within the expected range.
* Residual biological activity was excellent with greater than 90% mortality of mosquitoes at least 6months after application of the spray dilutions to a standard cement substrate.

Overall, it was concluded that all fifteen production batches were efficacious irrespective of the measured differences in release rate profile, which strongly suggests that intrinsic release rate, as measured *in vitro* is not a good predictor of biological activity.

Taking into account the release rate and biological efficacy data, Syngenta postulated that the current release rate clause in the WHO specification 463/CS is not appropriate and should be modified, in principle, to a single measurement at 15minutes with a modified “% released range” for lambda-cyhalothrin, to be defined.

**Additional Release-rate and Biological Efficacy Data (2017/2018)**

During the years 2017 and 2018 further studies were conducted to look again at the method variability (CIPAC MT190), release rate and biology of a further set of production samples of ICON 10CS.

**Method Variability (CIPAC MT190)**

During the 2014 release rate investigation with five different laboratories analysing fifteen production batches of ICON 10CS, Syngenta became concerned about variability in the results generated across the laboratories.

When a new study was initiated in 2018 involving four different laboratories discussions at laboratory level as to the precise procedure followed, revealed that the preparation of the Internal Standard (IS) solution was not clear in the respective CIPAC Handbook. As a consequence, a different volume of ethanol was used for the preparation of the IS across the laboratories; two laboratories used 100ml and three laboratories were using 50ml. An erratum (below) was published by CIPAC but not all laboratories were aware, leading to the use of different volumes of ethanol being used.

**Fig 1. Erratum to CIPAC MT190**

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The consequence of the use of different volumes of ethanol is highly significant with respect to the measured release rate. Ten production batches of ICON 10CS were analysed using CIPAC MT190 by CRA-W, Belgium using 50 and 100mls ethanol during the IS preparation and subsequent rolling/extraction. The results are given graphically in Fig 2.

**Fig 2. Release-rate (CIPAC MT190) *vs* Ethanol Volume**

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References: Baes M., (2019)

Clearly the volume of ethanol used during IS preparation has a significant effect on the magnitude of the released lambda-cyhalothrin under the conditions of the test and is therefore a major potential source of variability in the measured data. The greater volume of ethanol (100 vs. 50ml gives rise to a greater amount of lambda-cyhalothrin released. The conclusion being that the correct amount to be used (100ml) should be clearly stated in method CIPAC MT190.

**Release rate “Round-robin” Exercise**

A small scale study was organised with four laboratories with ten production batches of ICON 10CS using the correct amount of ethanol (100ml) for IS preparation, to understand how the data relates to the current WHO specification 463/CS.

Ten batches of ICON10CS were analysed according to CIPAC MT190 by:

* Walloon Agricultural Research Centre, Gembloux, Belgium(CRA-W)
* CEM Analytical Services Ltd, Wokingham, UK (CEMAS)
* Syngenta Seneffe Quality Control Laboratory, Seneffe, Belgium (Seneffe)
* Syngenta Analytical Sciences and Product Chemistry, Munchwilen, Switzerland (CHMU)

According to CIPAC MT190 and subsequent rolling/extraction and analysis a summary of the results are given graphically below in Figs 3 and 4, for the 15 and 180minute time points.

The black horizontal bars indicate the minimum and maximum specification limits according to the current WHO 463/CS specification and the batch numbers for the ten production batches are given on the x-axis e.g. BSN7D2980 etc.

**Fig 3. Release-rate at 15minutes *cf.* Lambda-cyhalothrin Released at 180minutes**

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References: Baes M., (2019), Jutsum P., (2019), Simonin C., (2019a, b)

**Fig 4. Release-rate at 180minutes *cf.* Total Lambda-cyhalothrin Content**

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References: Baes M., (2019), Jutsum P., (2019), Simonin C., (2019a, b)

The key conclusions from the round-robin study are:

* At the 15minute assessment point: several of the batches could be outside the specification range limits but it is unclear because it is laboratory dependent.
* At the 180minutes assessment point: all ten batches are outside the specification range limits

Finally, it appears that when release rate data is calculated against the total lambda-cyhalothrin content of each formulation, that the variability of the data across the four laboratories is reduced compared to calculating against the amount released after the 180minute assessment point, which is of course subject to its own analytical variability. This is the same conclusion that was reached for the pirimiphos-methyl capsule suspension specification[[1]](#footnote-1) where the release rate is calculated with reference to the total pirimiphos-methyl content of the formulation.

The release rate data for the round-robin was re-calculated with reference to the total lambda-cyhalothrin content of each formulation and is summarised graphically in Fig 5.

**Fig 5. Release Rate at 15minutes *cf.* Total Lambda-cyhalothrin Content**

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References: Baes M., (2019), Jutsum P., (2019), Simonin C., (2019a, b)

**Biological Efficacy Data (2018 and 2019)**

Biological performance of five of the production batches, selected randomly, was assessed under the standard two protocols; a knock-down test using German cockroaches (*Blattella germanica*) exposed to dilute spray dispersions of the production samples and a residual efficacy test where mosquitoes (*Ades aegypti*) were exposed to a substrate treated again with the dilute dispersions. Assessment of knock-down and mortality were then made at different time points and graphical summaries are given in Figs 6 and 7.

Conclusions from the two tests demonstrated that for the five production batches:

* Knock-down time was not significantly different to the standard sample; under the conditions of the test the KD50, the time taken to knock-down (immobilize) 50% of the cockroaches, was within the expected range
* All batches provided 100% control of *Aedes aegypti* adult female mosquitoes for a minimum of 12 weeks post application to an unglazed porous ceramic substrate
* No significant differences were observed in the performance of the five batches during the 12 week study.
* All batches provided knockdown and residual performance within the ranges historically observed with ICON 10CS under the noted testing protocols.

**Fig 6. Knock-down of German Cockroaches at Minutes after Application**

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References: Hoppe M., Hofer D and Spycher C. (2018)

**Fig 7. Knock-down and Residual Activity of Aedes aegypti at Time after Application**

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References: Hoppe M., Hofer D and Spycher C. (2019)

It was concluded that the biological performance of all five production batches was acceptable and as expected, irrespective of the measured differences in release rate profile.

Overall in summary, the release rate and biological efficacy studies from 2014 and 2019, point towards the same conclusions:

* Production batches of ICON 10CS have acceptable biological performance irrespective of the differences in release rate as measured according to the CIPAC MT190 method i.e. there is no simple relationship between the biological performance and release rate profile.
* The release rate limits within the current specification (WHO 463/CS) clause are difficult to achieve, don’t correlate well with biological activity and are time consuming. In summary, they current limits do not add value to the quality assessment of the encapsulated products.

In relation to the release rate, the formulation chemical composition and process (reaction time) effectively define the macro variables that effect the rate of release from the micro-capsules and these input parameters are effectively fixed for a given formulation.

Therefore, after analysis of a wider data set Syngenta has postulated that the current release rate clause in the WHO specification 463/CS is not appropriate and should be modified, to a single measurement at 15minutes with a modified “% released range” for lambda-cyhalothrin as per Table 1.

**Table 1. Current and Proposed Release Rate Clause for WHO 463/CS**

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| **WHO 463/CS Specification Clause** | **Current limit** | **Proposed New Limit** |
| Release of lambda-cyhalothrin [2.4] | The release of lambda-cyhalothrin from the capsules shall be:at 15 min, 30 to 75% of that released at 180 min; and at 30 min, 50 to 90% of that released at 180 min; and at 180 min, a minimum of 80% of the total lambda-cyhalothrin content, determined according to clause 2.2. | The release of lambda-cyhalothrin measured from the capsules at 15 min, shall be 15 to 60% of the total lambda-cyhalothrin content determined according to clause 2.2. |

An updated, draft lambda-cyhalothrin WHO specification 463/CS proposal in Word format is included with this submission.

Syngenta believes that this new proposal provides an adequate quality benchmark that can be assessed in a timely manner compared to the current limits in the specification clause. It is consistent with the approach taken for the pirimiphos-methyl capsule suspension (WHO 239/CS) and will ensure a saving in resource for quality control laboratories without compromising quality.

With respect to CIPAC MT190 the strict dependence of the release rate on the ethanol volume used in the IS preparation should be emphasized through CIPAC in relation to the communication of the erratum. Finally, should the proposed specification limit be accepted then there is a need to update the method CIPAC MT190 so that it is consistent with the new specification limits. Discussions are currently underway with CIPAC to determine the way forward and it is expected that an updated MT method and supporting data will be presented at the 2020 CIPAC meeting.

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1. WHO Specification 239/CS (August 2016) <https://www.who.int/pq-vector-control/prequalified-lists/actellic_300cs/en/> [↑](#footnote-ref-1)