Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

SPINETORAM

a mixture of two main components, 3'-O-ethyl, 5,6-dihydro spinosyn J (XDE-175-J, major factor, 50-90%) and 3'-O-ethyl-spinosyn L (XDE-175-L, minor factor, 50-10%)

2021

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DISCLAIMER[1]

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Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides that are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

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[1] This disclaimer applies to all specifications published by FAO.

INTRODUCTION

FAO establishes and publishes specifications for technical material and related formulations of agricultural pesticides, with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 1999 onward, the development of FAO specifications follows the **New Procedure**, described first in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products" and later in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) - currently available as 3rd revision of the 1st edition (2016) - , which is available only on the internet through the FAO and WHO web sites.

This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPM, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 1999 onwards the publication of FAO specifications under the **New Procedure** has changed. Every specification consists now of two parts namely the specifications and the evaluation report(s):

Part One: **The Specification** of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the "Manual on development and use of FAO and WHO specifications for pesticides".

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the "FAO/WHO Manual on Pesticide Specifications" and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

FAO specifications developed under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. FAO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Evaluations bear the date (year) of the Meeting at which the recommendations were made by the JMPS.

PART ONE
SPECIFICATIONS

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SPINETORAM

SPINETORAM

INFORMATION

ISO common name (ISO 1750, published)

Spinetoram: a mixture of two main components, 3′-O-ethyl, 5,6-dihydro spinosyn J (XDE-175-J, major factor, 50-90%) and 3′-O-ethyl-spinosyn L (XDE-175-L, minor factor, 50-10%)

Chemical names
IUPAC
XDE-175-J
(2*R*,3a*R*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-[(6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-α-L-mannopyranosyl)oxy]-13-{[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methylpyran-2-yl]oxy}-9-ethyl-2,3,3a,4,5,5a,5b,6,9,10,11,12,13,14,16a,16b-hexadecahydro-14-methyl-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecine-7,15-dione

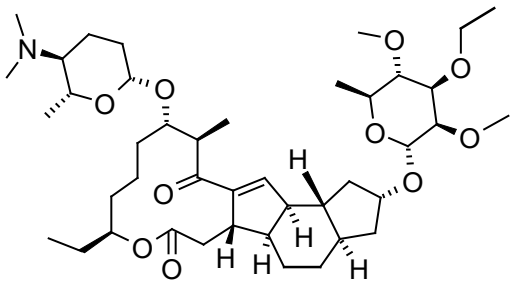
XDE-175-L
(2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-2-[(6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-α-L-mannopyranosyl)oxy]-13-{[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methylpyran-2-yl]oxy}-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecine-7,15-dione

CA
XDE-175-J
(2*R*,3a*R*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-[(6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-α-L-mannopyranosyl)oxy]-13-[[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methyl-2*H*-pyran-2-yl]oxy]-9-ethyl-2,3,3a,4,5,5a,5b,6,9,10,11,12,13,14,16a,16b-hexadecahydro-14-methyl-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecin-7,15-dione
XDE-175-L
(2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-2-[(6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-α-L-mannopyranosyl)oxy]-13-[[(2*R*,5*S*,6*R*)-5-(dimethylamino)tetrahydro-6-methyl-2*H*-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecin-7,15-dione

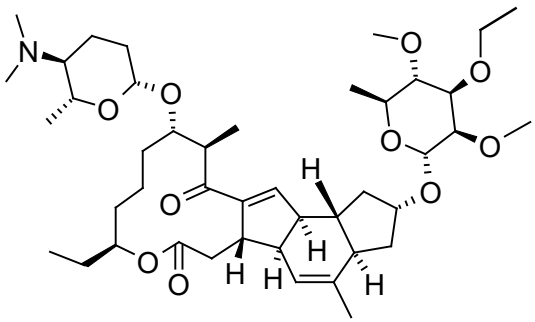
Synonyms
XDE-175, X574175, Factor J+L,

Structural formula

3'-*O*-ethyl-5,6-dihydro spinosyn J (XDE-175-J)



3'-*O*-ethyl-spinosyn L (XDE-175-L)



Molecular formula
XDE-175-J: $C_{42}H_{69}NO_{10}$
XDE-175-L: $C_{43}H_{69}NO_{10}$

Relative molecular mass
XDE-175-J 748
XDE-175-L 760

CAS Registry number
XDE-175-J: 187166-40-1
XDE-175-L: 187166-15-0
XDE-175 (Spinetoram): 935545-74-7

CIPAC number
802

Identity tests
Retention time of XDE-175-J factor and XDE-175-L factor in the HPLC chromatogram,
Infra-red spectroscopy
Nominal ratio is 75:25 (J:L)
Ratios of factors typically range from 70:30 to 90:10 (J:L)

SPINETORAM TECHNICAL MATERIAL

FAO/WHO Specification 802 / TC (February 2021)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (*802/2020). *It should be applicable to TC produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation report (*802/2020*), as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of spinetoram together with related manufacturing impurities and shall be a white to grey powdery material free from visible extraneous matter and added modifying agents.

.2 Active ingredient

2.1 **Identity tests** (802/TC/M/2) (Note 1)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Spinetoram content** (802/TC/M/3) (Note 1)

The spinetoram content shall be declared (not less than 830 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

Note 1 The reversed phase HPLC method (CIPAC/5249) for the determination of spinetoram in TC, SC, WG, and DT formulations was accepted as provisional CIPAC method in 2020. Prior to its publication in a next Handbook, the method is available through the CIPAC prepublishment scheme from https://www.cipac.org/index.php/methods-publications/pre-published-methods

SPINETORAM WATER DISPERSIBLE GRANULES

FAO Specification 802 / WG (February 2021)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (*802/2020). *It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers. The evaluation report (*802/2020*), as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of an homogeneous mixture of technical spinetoram, complying with the requirements of FAO Specification 802/TC (February 2020), together with carriers and any other necessary formulants. It shall be in the form of pale brown granules in the size range of 0.5 to 1 mm, for application after disintegration and dispersion in water. The formulation shall be dry, free-flowing, nearly dust free or essentially non-dusty, and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (802/WG/M/2) (Note 1)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Spinetoram content** (802/WG/M/3) (Note 1)

The spinetoram content shall be declared (g/kg) and, when determined, the average content measured shall not differ from that declared by more than the following tolerances:

Declared content, g/kg	Tolerance
Above 100 up to 250 Above 250 up to 500 Note: in each range the upper limit is included.	± 6% of the declared content ± 5% of the declared content

3 Physical properties

3.1 **pH range** (MT 75.3, CIPAC Handbook J, p.131, 2000)

pH range: 7.5 to 9.5

3.2 **Wettability** (MT 53.3, CIPAC Handbook F, p.165, 1995)

The formulation shall be completely wetted in 1 min without swirling.

3.3 **Wet sieve test** (MT 185, CIPAC Handbook K, p.149, 2003)

Maximum: 0.5% retained on a 75 µm test sieve.

3.4 **Dispersibility** (MT 174, CIPAC Handbook F, p. 435, 1995)

Dispersibility: minimum 90% after 1 min of stirring.

3.5 **Suspensibility** (MT 184.1, Handbook P, p. 245, 2021) (Notes 2 and 3)

Suspensibility: minimum 80% after 30 min in CIPAC Standard Water D at 25 ± 5°C

3.6 **Persistent foam** (MT 47.3, CIPAC Handbook O, p.177, 2017) (Note 4)

Maximum: 60 ml after 1 min.

3.7 **Dustiness** (MT 171.1, Handbook P, p. 235, 2021) (Note 5)

Essentially non-dusty.

3.8 **Flowability** (MT172.2, Handbook P, p. 241, 2021)

At least 99% of the formulation shall pass through a 5 mm test sieve after 20 drops of the sieve.

3.9 **Attrition resistance** (MT 178.2, CIPAC Handbook K, p.140, 2003)

Minimum: 95 % attrition resistance.

4 Storage stability

4.1 **Stability at elevated temperature** (MT 46.4, Handbook P, p. 22 , 2021)

After storage at 54 ± 2 C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 6) and the formulation shall continue to comply with the clauses for:

- wet sieve test (3.3),
- dispersibility (3.4),
- suspensibility (3.5),
- dustiness (3.7),
- attrition resistance (3.9),

Note 1 The reversed phase HPLC method (CIPAC/5249) for the determination of spinetoram in TC, SC, WG, and DT formulations was accepted as provisional CIPAC method in 2020. Prior to its publication in a next Handbook, the method is available through the CIPAC prepublishment scheme from https://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 2 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in method MT 184.1.

Note 3 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method may be used on a routine basis provided that it has been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the referee method.

Note 4 The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D at 25 ± 5°C.

Note 5 Measurement of dustiness must be carried out on the sample “as received” and, where practicable, the sample should be taken from a newly opened container, because changes in the water content of samples may influence dustiness significantly. The optical method of MT 171.1, usually shows good correlation with the gravimetric method, and can, therefore, be used as an alternative where the equipment is available. Where the correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute the gravimetric method shall be used.

Note 6 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

SPINETORAM SUSPENSION CONCENTRATE

FAO Specification 802 / SC (February 2021)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (*802/2020). *It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for SC produced by other manufacturers. The evaluation report (*802/2020*), as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of a suspension of fine particles of technical spinetoram, complying with the requirements of FAO Specification 802/TC (February 2021), in an aqueous phase together with suitable formulants. After gentle agitation the material shall be homogeneous (Note 1) and suitable for further dilution in water.

2 Active ingredient

2.1 **Identity tests** (802/SC/M/2) (Note 2)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Spinetoram content** (802/SC/M/3) (Note 2)

The spinetoram content shall be declared (g/kg or g/l at 20 ± 2ºC, Note 3) and, when determined, the average content measured shall not differ from that declared by more than the following tolerances:

Declared content, g/kg or g/l at 20±2ºC	Tolerance
Above 25 up to 100	± 10% of the declared content
Above 100 up to 250	± 6% of the declared content
Note: in each range the upper limit is included.	

3 Physical properties

3.1 **pH range** (MT 75.3, CIPAC Handbook J, p.131, 2000)

pH range: 6 to 8

3.2 **Pourability** (MT 148.1, CIPAC Handbook J, p.133, 2000)

Maximum “residue”: 5%.

3.3 **Spontaneity of dispersion** (MT 160, CIPAC Handbook F, p.391, 1995) (Note 4)

Spontaneity of dispersion: minimum 75% after 5 min in CIPAC Standard Water D at 30 ± 2°C

3.4 **Suspensibility** (MT 184.1, Handbook P, p. 245, 2021) (Note 4)

A minimum of 70% of the spinetoram content found under 2.2 shall be in suspension after 30 min in CIPAC Standard Water D at 25 ± 5°C

3.5 **Wet sieve test** (MT 185, CIPAC Handbook K, p.149, 2003) (Note 5)

Maximum: 0.5% of the formulation shall be retained on a 75 µm test sieve.

3.6 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 6)

Maximum: 60 ml after 1 min.

4 Storage stability

4.1 **Stability at 0°C** (MT 39.3, CIPAC Handbook J, p.126, 2000)

After storage at 0 ± 2°C for 7 days, the formulation shall continue to comply with clauses for:
- suspensibility (3.4),
- wet sieve test (3.5)

4.2 **Stability at elevated temperature** (MT 46.4, Handbook P, p. 22 , 2021)

After storage at 54 ± 2 °C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 7) and the formulation shall continue to comply with the clauses for:
- pourability (3.2),
- spontaneity of dispersion (3.3),
- suspensibility (3.4),
- wet sieve test (3.5),

Note 1 Before sampling to verify the formulation quality, inspect the commercial container carefully. On standing, suspension concentrates usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or of sediment on the bottom. Therefore, before sampling, homogenize the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example by inverting the closed container several times). Large containers must be opened and stirred adequately. After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer ("cake") is by probing with a glass rod or similar device adapted to the size and shape of the container. All the physical and chemical tests must be carried out on a sample taken after the recommended homogenization procedure.

Note 2 The reversed phase HPLC method (CIPAC/5249) for the determination of spinetoram in TC, SC, WG, and DT formulations was accepted as provisional CIPAC method in 2020. Prior to its publication in a next Handbook, the method is available through the CIPAC prepublishment scheme from https://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 3 Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre and in calculation of the active ingredient content (in g/l) if methods other than OECD 109 or MT 3.3 are used. If the buyer requires both g/kg and g/l at 20 °C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 4 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method may be used on a routine basis provided that it has been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the referee method.

Note 5 This test detects coarse particles (e.g. caused by crystal growth) or agglomerates (crust formation) or extraneous materials which could cause blockage of spray nozzles or filters in the spray tank.

Note 6 The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D at 25 ± 5°C.

Note 7 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

SPINETORAM

SPINETORAM

FAO/WHO EVALUATION REPORT 802/2020

Recommendations

The Meeting recommended that:

(i) the specifications for spinetoram TC, WG and SC, proposed by Corteva Agriscience and as amended, should be adopted by FAO.

(ii) the specifications for spinetoram TC and DT, proposed by Corteva Agriscience (TC) and Clarke International (DT) and as amended, should be adopted by WHO.

Appraisal

The Meeting considered data on spinetoram submitted by Corteva Agriscience (Corteva[2]), in support of new FAO specifications for TC, WG and SC and new WHO specifications for TC and DT, respectively.

The ISO common name spinetoram designates a mixture of two structurally related macrocyclic lactones - 3′-*O*-ethyl, 5,6-dihydro spinosyn J (XDE-175-J major factor, "factor J") and 50-10 % 3′-*O*-ethyl-spinosyn L (XDE-175-L minor factor "factor L"). XDE-175-J and -L are the development codes allocated by Dow AgroSciences. These two codes in their abbreviated form are used in this evaluation for brevity when individual properties of the two components need to addressed. The Meeting noted that Corteva declares a typical range of factors J and L, respectively, that is somewhat narrower than in the ISO common name definition (70-90 % and 30-10 % for factors J and L instead of 50-90 and 50-10%). The Meeting concluded that, as long as the typical ranges of J and L cover the range defined in the ISO common name definition, this is up to the discretion of the company and deemed acceptable.

In the JMPR report (see below), it was concluded that "the ratio of factor J to factor L ranges from 70 : 30 to 90 : 10. Unless otherwise stated, the studies of toxicity described in the present monograph were conducted with factor J and factor L in a ratio equal to 75 : 25. Some studies were repeated with factor J and factor L in the ratio of 85 : 15; this was done to demonstrate that the 85 : 15 ratio produces a toxicity profile that is essentially the same as that seen with a 75 : 25 ratio".

Spinetoram has been evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) for its toxicology and residues in 2008 (JMPR, 2008). The JMPR concluded that spinetoram is of low acute toxicity and an ADI of 0 - 0.05 mg/kg bw was established, based on an overall NOAEL of 5.0 mg/kg bw per day, identified on the basis of arteritis, accompanied by necrosis of the arterial walls in the affected organ(s), in studies of toxicity in dogs, and with a safety factor of 100.

[2] Corteva Agriscience is the agriculture division of DowDuPont formed in a merger of the complementary portfolios of Dow and DuPont effective Aug. 31, 2017, see e.g. https://corporate.dow.com/en-us/news/press-releases/dowdupont-merger-successfully-completed

JMPR further concluded that it was not necessary to establish an acute reference dose (ARfD) for spinetoram on the basis of its low acute toxicity, the absence of neurotoxic potential and of developmental or any other effects of relevance for acute exposure in studies of longer duration.

The IPCS hazard classification of spinetoram is U, unlikely to present acute hazard in normal use.

Factors J and L expectedly show low volatilities due to their high molecular weights and a melting point of 143°C (ratio of J and L of 3:1). Spinetoram as a whole has a rather low and somewhat pH dependent water solubility. This pH dependence is due to the amphoteric nature of factors J and L: they act as weak acids (pKa of 7.86 and 7.59) and possess a tertiary amine group that can be protonated. Accordingly, water solubility increases with lower pH values, and the log K_{ow} values are pH-dependent and increase with higher pH-values, e.g. from 2.4 at pH 5 to 4.2 at pH 9.

Whereas factors J and L are not susceptible to hydrolysis at all pH values investigated, direct photolysis is a fast process and may rapidly degrade both factors under natural sunlight conditions (half lives of ≈ 0.5 days under artificial conditions). Spinetoram is readily soluble in apolar and medium-polarity organic solvents.

The Meeting was provided with confidential information on the manufacturing process and specification limits for the technical material as manufactured. The minimum purity of the active ingredient spinetoram (expressed as sum of factors J and L) and maximum impurity limits as proposed by Corteva were supported by 5- batch analysis data.

Spinetoram is produced at two different sites according to the same process and nominally the same manufacturing specification. One of the sites belongs to Corteva, the other is a toll manufacturer. The minimum purity proposed by Corteva was 812 g/kg. The Meeting noted that the company had used the analytical results of two sets of 5 typical batches of both production sites and had calculated a minimum purity based on the estimation (average - 3 standard deviations) as described in the Manual.

Yet, one site consistently produces a somewhat higher content and the other a lower one. This leads to a higher standard deviation when an overall average is calculated and hence to an unrealistically low minimum purity. A separate estimation of the minimum purities of spinetoram produced at site one and two leads to a justifiable minimum purity of 830 and 890 g/kg. The Meeting concluded that 830 g/kg should be considered as typical minimum purity that can be achieved at both production sites. This value is in the same range as the purity of spinetoram that had been produced in pilot scale and used in the toxicity studies.

Mass balances in the 5-batch studies were high (99.76 – 100.52 %). The analytical methods for the majority of organic impurities are based on HPLC and are adequately validated and support the results in the 5-batch study. The limits of quantitation were determined as part of the validation.

The Meeting noted that certain noble metals are used as hydrogenation catalysts to selectively hydrogenate the C 5-6 double bond in the Spinosyn backbone[3], what may lead to trace residues of these metals in the finished TC. When contacted, the company explained that they indeed monitor possible residues of these noble metals and submitted a quality control document that demonstrated that the levels detected are at the low sub-ppm to low-ppm-range.

[3] Spinetoram: How Artificial Intelligence Combined Natural Fermentation with Synthetic Chemistry to Produce a New Spinosyn Insecticide, 2008 Plant Management Network, published 27 August 2008.

For both noble metals that are used in the process, no health based guidance values are available. Instead, a comparison with the TTC-values for DNA-reactive carcinogens was made. The theoretical uptake of both metals was estimated when assuming an exposure to spinetoram at the ARfD-level of 0.1 mg/kg bw (ARfD listed by EFSA; no JMPR value available) and would be orders of magnitude below the TTC-values for DNA-reactive carcinogens. The Meeting therefore concluded that the presence of trace residues of certain noble metals does not significantly contribute to the hazard of spinetoram TC and these residues should be considered as non-relevant.

A CIPAC method based on reversed phase HPLC has been developed for determination of spinetoram as sum of factors J and L in TC, WG, SC and DT formulations. The results of the full scale collaborative trial were presented at the 2020 CIPAC Meeting and the method was accepted as provisional CIPAC method.

The proposed specifications for TC, WG, SC and DT were essentially in accordance with the requirements of the Manual (3rd revision of the 1st edition, FAO/WHO 2016 and its amendments). Appropriate studies on the physical-chemical properties including storage stability were submitted for the WG SC and DT formulations.

Certain issues were identified in some formulation specifications as follows:

TC specification. Corteva had proposed a minimum purity of 812 g/kg. Based on the evaluation of the two 5-batch studies, a minimum purity of 830 g/kg is deemed acceptable by the Meeting and does better reflect the quality of the TC. Corteva responded in writing that a minimum purity of 830 g/kg was acceptable to them.

SC specification. The Meeting questioned the necessity of a pH range, as the two factors of spinetoram are not susceptible to hydrolysis. The Meeting noted that the formulation, when mixed with water, produces a fairly high amount of persistent foam, so the limit of 60 ml after 1 min was deemed justified.

Tablets for direct application (DT). The formulation was developed by Clarke Mosquito Control (Clarke). The Meeting noted that the proposer suggested a narrower tolerance for the declared content (10 g/kg, ± 10 %, whereas the default tolerance would be ± 25 % for that concentration range and inhomogeneous formulation). Indeed, the study on physical-chemical properties of the DT formulation shows an RSD for the tablet dose uniformity well below 10 %. The Meeting concluded that a well documented lower tolerance for active ingredient content and tablet dose uniformity was acceptable. Furthermore, the proposers initially suggested to carry out the accelerated storage test in the original packaging to better protect the tablets from humidity. The Meeting concluded that this deviation from MT 46.3 was acceptable. In the meantime, the harmonized and revised MT method for accelerated storage, MT 46.4, was adopted. This method allows storage of formulations in commercial containers ("Alternatively, formulations in commercial packs can be stored as delivered"). Therefore, a footnote was added to instruct the user that the tablets should be stored in the commercial container or pouch, and obviously without pressure.

Furthermore, Clarke also proposed to test tablet friability according to MT 193. As this method is obsolete and the tablets do not meet the criteria for being tested by MT 178.2, the Meeting agreed that neither a friability nor attrition clause was necessary in the specification.

WG specification. The water dispersible granules do not readily wet when mixed with water, probably due to the hydrophobic nature of spinetoram. Yet, the study data show that the WG is completely wetted after 60 sec without swirling.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 802/2020

Table 1. Physical-chemical properties of pure XDE-175-J and -L, respectively, the components of spinetoram

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	XDE-175-J : 5.3×10^{-5} Pa at 20 °C 6.0×10^{-5} Pa at 25 °C	99.0	EEC Method A4 Knudsen-Effusion/Weight Loss Method	PC1 Comb A.L. (2005a)
Vapour pressure	XDE-175-L : 2.1×10^{-5} Pa at 20 °C 4.2×10^{-5} Pa at 25 °C	99.1%	EEC Method A4 Knudsen-Effusion/Weight Loss Method	PC2 Comb A.L. (2005c)
Melting point, boiling point and/or temperature of decomposition	XDE-175-J: 143.4 °C Decomposes before boiling (at 298 °C)	99.0	EEC Method A1	PC3 Madsen S, Jennings C (2005)
Melting point, boiling point and/or temperature of decomposition	XDE-175-L: 70.8 °C Decomposes before boiling (at 291 °C)	99.1	EEC Method A1	PC4 Madsen S, Jennings C (2005)
Solubility in water	XDE-175-J Purified water 10.0 mg/L pH 5 buffer solution 423 mg/L pH 7 buffer solution 11.3 mg/L pH 9 buffer solution ca 8 mg/L pH 10 buffer solution 6.27 mg/L	99.0	EEC Method A6 Flask method at 20°C	PC5 Comb A.L. (2005d)
Solubility in water	XDE-175-L Purified water 31.9 mg/L pH 5 buffer solution 1.63 g/L pH 7 buffer solution 46.7 mg/L pH 9 buffer solution 1.98 mg/L pH 10 buffer solution 0.71 mg/L	99.1	EEC Method A6 Flask method at 20°C	PC6 Comb A.L. (2005e)
Octanol/water partition coefficient	XDE-175-J Log Kow = 2.44 at pH 5 Log Kow = 4.09 at pH 7 Log Kow = 4.22 at pH 9	99.0	EEC Method A8 (20°C)	PC7 Comb A.L. (2005g)
Octanol/water partition coefficient	XDE-175-L Log Kow = 2.94 at pH 5 Log Kow = 4.49 at pH 7 Log Kow = 4.82 at pH 9	99.1	EEC Method A8 (20°C)	PC8 Comb A.L. (2005h)

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Hydrolysis characteristics	XDE-175-J stable at 25 °C, at pH 5 and pH 7. At pH 9 slow degradation* at 25°C XDE-175-L stable at 25 °C, at pH 5 and pH 7. At pH9 DT_{50} = 156 d at 25 °C *Actual degradation rate and DT_{50} was not calculated because 91.9 % radioactivity remained as parent at study termination	98.6 (^{14}C) 97.3 (^{14}C)	OECD Method 111	PC9 Rutherford et al (2005)
Photolysis characteristics	Sterile aqueous buffer solution – pH 7 (Direct phototransformation). XDE-175-J: Photochemical half-life = 0.5 days XDE-175-L: Photochemical half-life = 0.5 days Quantum yield of direct phototransformation in water at > 290 nm XDE-175-J: 4.2×10^{-2} XDE-175-L: 6.6×10^{-2}	98.6 (^{14}C) 97.3 (^{14}C)	US EPA Guideline 161-2 (Aqueous photolysis in sterile buffer at pH7 conducted using Xenon lamb, 25°C for 19 days)	PC10 Yoder R.N. et al (2005)
Dissociation characteristics	XDE-175-J pKa = 7.86 ± 0.04 at 25 °C	99.0	OECD Guideline 112 (Capillary electrophoresis method)	PC11 Madsen S, Holley R (2005a)
Dissociation characteristics	XDE-175-L pKa = 7.59 ± 0.06 at 25 °C	99.1	OECD Guideline 112 (Capillary electrophoresis method)	PC12 Madsen S, Holley R (2005b)
Solubility in organic solvents	XDE-175-J + XDE-175-L - technical >250g/l Methanol at 20°C >250g/l Acetone at 20°C >250g/l Xylene at 20°C >250g/l 1,2-dichloroethane at 20°C >250g/l ethyl acetate at 20°C 61g/l n-heptane at 20°C 132g/l n-octanol at 20°C	85.6	Shake flask method based on EEC A6	PC13 Comb A.L. (2005)

Table 2. Chemical composition and properties of spinetoram technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 99-100.5 % and percentages of unknowns were <0.5 % maximum
Declared minimum spinetoram content	830 g/kg (Total, XDE-175-J + XDE-175-L)
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them	None
Stabilisers or other additives and maximum limits for them:	None
Estimated Melting temperature range of the TC	XDE-175-J + XDE-175-L , Ratio 3.3:1 of J:L Study reference number: PC18 Melting point: 143.5C

USES

Spinetoram is an insecticide used in agriculture to control *Lepidoptera* larvae (e.g., worms, caterpillars), various *Diptera*, thrips, sawfly larvae, certain beetles and psyllids, some *Orthoptera*, fleas on various crops like fruits and vegetables. It is used in public health to control early life stages of certain malaria vectors.

Spinetoram is classified by the Insecticide Resistance Action Committee to act as allosteric modulator of the nicotinic acetylcholine receptor (nAChR) Site I.

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The main formulation types available are suspension concentrate (SC), and water dispersible granules (WG) for agricultural uses.

Spinetoram may be co-formulated with other insecticide active ingredients.

These formulations are registered and sold in more than 75 countries throughout the world including U.S.A (2007), Australia, Brazil, Canada, India, Japan, New Zealand, Switzerland and South Africa. Spinetoram was approved in the EU in 2014 as a new active substance and is currently approved in 13 EU Member States. A direct application tablet (DT) has been developped by Clarke International, for use as a larvicide to control mosquitoes in potable water containers.

METHODS OF ANALYSIS AND TESTING

The analytical method(s) for the active ingredient (including identity tests) is validated and the principle of the method for spinetoram content is reverse phase HPLC using UV detection and external standardisation (References MA1 to MA3). The method for determination of spinosyn derived impurities are based on reverse phase HPLC with UV detection. The method for determination of residual solvents in technical is based on GC with FID detection.

Test methods for determination of physical-chemical properties of the technical active ingredient were OECD/EC, while those for the formulations were CIPAC as indicated in the specifications (References PC14 – PC17).

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The content of spinetoram active ingredient is expressed as sum of the factors XDE-175-J and XDE-175-L.

ANNEX 1
HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from spinetoram having impurity profiles similar to those referred to in the table above.

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified. The %-ratio of factor J to factor L ranges from 70:30 to 90:10 (568-730 g/kg for factor J; 82 - 244 g/kg) for factor L). The majority of studies of toxicity in the summary tables below were conducted with factor J and factor L in a ratio of 75 : 25. However, some studies were duplicated with factor J and factor L in the ratio of 85 : 15; the reason was to confirm that the toxicity profile of the mixture does not depend on a specific ratio, e.g. 85 : 15.

Table 3. Toxicology profile of spinetoram technical material, based on acute toxicity, irritation and sensitization

Species	Test	Purity % (J:L ratio) Note[4]	Guideline, duration, doses and conditions	Result	Study number
Rat, female, F344/DuCrl	Acute oral	85.8% (75:25)	OECD 425 (2001), up and down procedure, 14 days	LD_{50} = >5000 mg/kg bw	TC1 (2005a)
Rat, female, F344	Acute oral	86.3% (85:15)	OECD 425 (2001), up and down procedure, 14 days	LD_{50} = >5000 mg/kg bw	TC2 (2007a)
Rat, male and female, F344/DuCrl	Acute dermal	85.8% (75:25)	OECD 402 (1987), topical application, limit test, 14 days	LD_{50} = >5000 mg/kg bw	TC3 (2005b)
Rat, male and female, F344	Acute dermal	86.3% (85:15)	OECD 402 (1987), topical application, limit test, 14 days	LD_{50} = >5000 mg/kg bw	TC4 (2007b)
Rat, male and female, F344/DuCrl	Acute inhalation	85.8% (75:25)	OECD 403 (1981), 4hr nose only exposure, 14d evaluation	LC_{50} = >5.50 mg/L air	TC5 (2005)
Rat, male and female, F344	Acute inhalation	86.3% (85:15)	OECD 403 (1981), 4hr nose only exposure, 14d evaluation	LC_{50} = >5.44 mg/L air	TC 6 (2005)
Rabbit, male and female, New Zealand White	Skin irritation	85.8% (75:25)	OECD 404 (2002), 500 mg application for 4h, 72 hours observation	No irritation	TC 7 (2005a)
Rabbit, male and female, New Zealand White	Skin irritation	86.3% (85:15)	OECD 404 (2002), 500 mg application for 4h, 72 hours observation	Slight (reversible) irritation	TC8 (2007b)
Rabbit, male and female, New Zealand White	Eye irritation	85.8% (75:25)	OECD 405 (2002), 50 mg application, 72 hours observation	Transient irritation, reversible after 24 hours	TC9 (2005b)

[4] Note: Purity is the content of pure active ingredient (Total of XDE-175-J + XDE-175-L factors) in the technical material, expressed as a percentage.

Species	Test	Purity % (J:L ratio) Note[4]	Guideline, duration, doses and conditions	Result	Study number
Rabbit, male and female, New Zealand White	Eye irritation	86.3% (85:15)	OECD 405 (2002), 50 mg application, 72 hours observation	Transient irritation, resolved at 72 hours	TC10 (2007d)
Mouse, Female, Balb/cAnNCrl	Skin sensitization, LLNA (local lymph node assay)	85.8% (75:25)	OECD 429 (2002), 0/2.5/10/40% doses, evaluation after 3 exposures	Moderate sensitization	TC11 (2006)
Mouse, Female, CBA/J	Skin sensitization, LLNA (local lymph node assay)	86.3% (85:15)	OECD 429 (2002), 0/5/25/75% doses, evaluation after 3 exposures	No sensitization	TC12 (2007)

Table 4. Toxicology profile of spinetoram technical material based on repeated administration (subacute to chronic)

Species	Test	Purity % (J:L ratio) Note[5]	Guideline, duration, doses and conditions	Result	Study number
Rat, male and female, Fischer 344	Rat dietary, 28d	95% (67:33)	OECD 407 (1995), 28d, 0 to 185 mg/kg bw/d	NOAEL,11.7(F) mg/kg bw/d LOAEL, 48.2(F) mg/kg bw/d Effects at the LOAEL Vacuolation (thyroid, kidney), macrophage aggregates (spleen)	TC13 (2004)
Mice, male and female, CD-1	Mouse dietary, 28d	95% (67:33)	OECD 407 (1995), 28d, 0 to 226 mg/kg bw/d	NOAEL, 24.5 (M) mg/kg bw/d LOAEL, 75.1(M) mg/kg bw/d Effects at the LOAEL Vacuolation (several organs), macrophage aggregates (lung), stomach lesions	TC14 (2005)
Rat, male and female, Fischer 344	Rat dermal, 28d	85.8% (75:25)	OECD 410 (1981), 28d, 1000 mg/kg bw/d	NOAEL, 1000 (M/F) mg/kg bw/d LOAEL, >1000 (M/F) mg/kg bw/d Effects at the LOAELNo adverse systemic or local effects	TC15 (2005)

[5] Note: Purity is the content of pure active ingredient (Total of XDE-175-J + XDE-175-L factors) in the technical material, expressed as a percentage.

Species	Test	Purity % (J:L ratio) Note[5]	Guideline, duration, doses and conditions	Result	Study number
Rat, male and female, Fischer 344	Rat dietary, 90d + recovery	83% (75:25)	OECD 408 (1998), 90d, 0 to 159 mg/kg bw/d	NOAEL, 9.5 (F) mg/kg bw/d LOAEL, 39.6 (F) mg/kg bw/d Effects at the LOAE: Vacuolation (thyroid, kidney), macrophage aggregates (several organs), reduced serum triglycerides	TC16 (2008)
Rat, male and female, Fischer 344	Rat dietary, 90d	86.3% (85:15)	OECD 408 (1998), 90d, 0 to 142 mg/kg bw/d	NOAEL, 9.0 (F) mg/kg bw/d LOAEL, 35.0 (F) mg/kg bw/d Effects at the LOAEL: Vacuolation (thyroid) macrophage aggregates (several organs)	TC17 Stebbins, Card (2007)
Mice, male and female, CD-1	Mouse dietary, 90d	83% (75:25)	OECD 408 (1998), 90d, 0 to 90mg/kg bw/d	NOAEL, 7.5 (M) mg/kg bw/d LOAEL, 22.8 (M) mg/kg bw/d Effects at the LOAEL Vacuolation (epididymides)	TC18 (2005)
Dogs, male and female, Beagles	Dog dietary, 90d	85.8% (75:25)	OECD 409 (1998), 90d, 0 to 31.0 mg/kg bw/d	NOAEL,5.0 (F) mg/kg bw/d LOAEL, 9.8 (M) mg/kg bw/d Effects at the LOAEL macrophage vacuolation, arteritis, perivascular inflammation, bone marrow necrosis	TC19 (2005)

Species	Test	Purity % (J:L ratio) Note[5]	Guideline, duration, doses and conditions	Result	Study number
Dogs, male and female, Beagles	Dog dietary, 1 year	85.8% (75:25)	OECD 452 (1981), 1 year, 0 to 5.8 mg/kg bw/d Effects at the LOAEL Arteritis (epididymides)	NOAEL, 2.5 (F) mg/kg bw/d LOAEL, 5.4 (M) mg/kg bw/d	TC20 (2006)
Rat, male and female,	2 year carcinogenic and chronic toxicity, dietary	85.8% (75:25)	OECD 453 (1981), 2 year, 0 to 40 mg/kg bw/d Effects at the LOAEL Vacuolation (thyroid), macrophage aggregates (lymphoid tissue)	Toxicity NOAEL, 10.8 (M) mg/kg bw/d LOAEL, 21.6 (M) mg/kg bw/d Carcinogenicity NOAEL, 32.9 mg/kg bw/d Not carcinogenic	TC21 (2007)
Mice, male and female, CD-1	18 months carcinogenicity, Mouse dietary	85.8% (75:25)	OECD 451(1981), 18m, 0 to 46.6mg/kg bw/d Effects at the LOAEL Vacuolation (epididymides), macrophage aggregates (lung), lesions (glandular stomach)	NOAEL,18.8 (M) mg/kg bw/d LOAEL, 37.5 (M) mg/kg bw/d Carcinogenicity NOAEL, 37.5 mg/kg bw/d Not carcinogenic	TC22 (2007)

Species	Test	Purity % (J:L ratio) Note[5]	Guideline, duration, doses and conditions	Result	Study number
Rat, male and female,	Multi-generation rat, dietary	85.8% (75:25)	OECD 451(1981), , 0 to 75mg/kg bw/d, fed 10 weeks prior to breeding Effects at the LOAEL (Reproductive) Dystocia Effects at the LOAEL (Adults) Thyroid cytoplasmic vacuolation, dystocia (F) Effects at the LOAEL (Offspring) No adverse effects except in dams with dystocia at 75 mg/kg bw/d (reduced litter size and weight due to parturition rather than developmental effects)	**Reproductive** NOAEL, 10 mg/kg bw/d LOAEL, 75 mg/kg bw/d **Adults** NOAEL, 10 mg/kg bw/d LOAEL, 75 mg/kg bw/d **Offspring** NOAEL, 75 mg/kg bw/d LOAEL, >75 mg/kg bw/d	TC23 (2006)

Species	Test	Purity % (J:L ratio) Note[5]	Guideline, duration, doses and conditions	Result	Study number
Rat, female,	Rat Developmental gavage	85.8% (75:25)	OECD 414(2001), , 0 to 300 mg/kg bw/d, Effects at the LOAEL (Maternal) Reduced b/w gain and food consumption	**Maternal** NOAEL, 100 mg/kg bw LOAEL, 300 mg/kg bw **Developmental** NOAEL, 300 mg/kg bw LOAEL, >300 mg/kg bw Effects at the LOAEL (Developmental) No adverse effects	TC24 (2005b)
Rabbit, female,	Rabbit Developmental gavage	85.8% (75:25)	0 to 60 mg/kg bw/d,	**Maternal** NOAEL, 10 mg/kg bw LOAEL, 60 mg/kg bw **Developmental** NOAEL, 60 mg/kg bw LOAEL, >60 mg/kg bw Effects at the LOAEL (Maternal) Reduced b/w gain and food consumption Effects at the LOAEL (Developmental) No adverse effects	TC25 (2008)

Species	Test	Purity % (J:L ratio) Note[5]	Guideline, duration, doses and conditions	Result	Study number
Rat, male and female,	Acute neurotoxicity, oral gavage	85.8% (75:25)	OECD 424(1997), 14d, 0 to 2000 mg/kg bw/d,	NOAEL, 2000 mg/kg bw LOAEL, 2000 mg/kg bw No evidence of neurotoxicity Effects at the LOAEL Reduced b/w gain and food consumption	TC26 (2005)
Rat, male and female,	Chronic neurotoxicity, dietary	85.8% (75:25)	OECD 424(1997), 1 year, 0 to 44.3 mg/kg bw/d, Effects at the LOAEL No adverse effects at highest rate tested	NOAEL, 36.7 (F) mg/kg bw LOAEL, >36.7 mg/kg bw No evidence of neurotoxicity	TC27 (2007)

Table 5. Mutagenicity profile of spinetoram technical material based on *in vitro* and *in vivo* tests

Species	Test	Purity % Note[6]	Guideline, duration, doses and conditions	Result	Study number
S. typhimurium TA 98, TA 100 , TA 1535,TA 1537 And *E. coli* WP2uvrA	Ames test, preincubation *in vitro* , plate incorporation *in vitro*	85.8% (75:25)	OECD 471 (1997) Dose levels up to 1,000 and 5,000 ug/plate analysed for gene mutation	Negative (+/- S9)	TC28 (2005)
S. typhimurium TA 98, TA 100 , TA 1535,TA 1537 And *E. coli* WP2uvrA	Ames test, preincubation *in vitro* , plate incorporation *in vitro*	86.3% (85:15)	OECD 471 (1997) Dose levels up to 1,000 and 5,000 ug/plate analysed for gene mutation	Negative (+/- S9)	TC29 (2007e)
Chinese hamster ovary (CHO-WB_L) cells	mammalian cells *in vitro*, cytogenic assay	85.8% (75:25)	OECD 473 (1997) Dose levels up to 30-80 ug/ml analysed for aberrations.	Negative (+/- S9)	(2008)
Chinese hamster ovary (CHO-WB_L) cells	mammalian cells *in vitro*, cytogenic assay	86.3% (85:15	OECD 473 (1997) Dose levels up to 30-50 ug/ml analysed for aberrations.	Negative (+/- S9)	TC31 (2007)
mouse lymphoma cell L5178Y	mammalian cells *in vitro*, gene mutations, TK assay	85.8% (75:25)	OECD 476 (1997) Dose levels up to 40-200 ug/ml analysed for gene mutation	Negative (+/- S9)	TC32 (2006)
mouse lymphoma cell L5178Y	mammalian cells *in vitro*, gene mutations, TK assay	86.3% (85:15)	OECD 476 (1997) Dose levels up to 60-200 ug/ml analysed for gene mutation	Negative (+/- S9)	TC33 (2007)

[6] Note: Purity is the content of pure active ingredient (Total of XDE-175-J + XDE-175-L factors) in the technical material, expressed as a percentage.

Species	Test	Purity % Note[6]	Guideline, duration, doses and conditions	Result	Study number
Mouse	*In vivo* micronucleus test	85.8% (75:25)	OECD 474 (1997), Male CD-1 mice, bone marrow Gavage dose of up to 2000 mg/kg bw/day on 2 consecutive days.	Negative	TC34 (2005)

Based on these results, spinetoram is considered to be non-genotoxic.

Table 6. Ecotoxicology profile of spinetoram technical material

Species	Test	Purity % Note[7]	Guideline, duration, doses and conditions	Result	Study number
Daphnia magna (water flea)	48hrs Static	85.8	OECD 202, 48h, 0 TO 1.05 mgas/L	EC_{50} = 0.228 mg as/L	EC1 Hicks S.L. (2007)
Daphnia magna (water flea)	21-d Flow through	83.0	OECD 211, 21d, 0 to 2 µg as/L	NOEC = 0.0624 µg as/L	EC2 Hicks S.L. (2005b)
Daphnia magna (water flea)	21d single pulsed dose (static renewal at 2, 4, 8, 24 hrs and daily thereafter)	85.8	OECD 211, 21d, 0 to 0.95 µg as/L	NOEC = 0.95 µg as/L	EC3 Hughes C.I. (2005)
Daphnia magna (water flea)	21d static renewal with peak concentrations renewal on days 0, 5, 10, and 15)	85.8	OECD 211, 21d, 0 to 2.2 µg as/L	NOEC = 0.33 µg as/L	EC 4 Sayers L.E. (2010a)
Lepomis macrochirus Bluegill sunfish	96 hrs flow through	85.8	OECD 203, 96hrs, 0 – 4.12 mgas/L	LC_{50} = 2.69 mg as/L	EC5 (2005a)
Pimephales promelas Fathead minnow	32d ELS flow through	85.8	OECD 210, 32d, 0 – 1.61 mgas/L	NOEC = 0.182 mg as/L	EC6 (2005b)
Chironomus riparius Chironomid midge	28d spiked water chronic toxicity	85.8	OECD 219, 28d, 0 – 6.0 µg as/L	NOEC =0.75 µg as/L	EC7 Currie R.J. et al (2007)
Chironomus riparius Chironomid midge	28d spiked sediment chronic toxicity	85.8	OECD 218, 28d, 0 – 200 µg as/kg	NOEC = 97.2 µg as/kg	EC8 Henry K.S. et al (2005)

[7] Note: Purity is the content of pure active ingredient (Total of XDE-175-J + XDE-175-L factors) in the technical material, expressed as a percentage.

Species	Test	Purity % Note[7]	Guideline, duration, doses and conditions	Result	Study number
Algae *Navicula Pellicolosa*	96h static toxicity, growth inhibition	83.0	OECD 218, 28d, 0 – 800 µg as/L	72h EC_{50} = 77.9 µg as/L	EC9 Hicks S.L. (2004b)
Aquatic plants Duckweed *Lemna Gibba*	7d static renewal, growth inhibition	83.0	US EPA OPPTS guideline 850.4400, 7d, 0 – 16 mgas/L	EC_{50} = 14.2 mg as/L (biomass and growth rate)	EC10 Hicks S.L. (2005c)
Bobwhite quail	Avian, acute oral toxicity	85.8	OPPTS guideline 850.2100, 17d, 0 to 2250 mg/kg bw,	LD_{50} = >2250 mg a.s/kg bw	EC11 (2005a)
Mallard Duck	Avian, acute oral toxicity	85.8	OPPTS guideline 850.2100, 14d, 0 to 2250 mg/kg bw,	LD_{50} = >2250 mg a.s/kg bw	EC12 (2005b)
Bobwhite quail	Avian, short term dietary toxicity	85.8	OECD 205, 14d, 0 to 5620 ppm diet	LC_{50} = >5620 ppm diet LD_{50} = >2044 mg a.s/kg bw/day	EC13 (2005c)
Mallard Duck	Avian, short term dietary toxicity	85.8	OECD 205, 14d, 0 to 5620 ppm diet	LC_{50} = >5620 ppm diet LD_{50} = >1981 mg a.s/kg bw/day	EC14 (2005d)
Bobwhite qua*il*	Avian, long term dietary toxicity	85.8	OECD 206, 0 to 1000 ppm diet	NOEC = 1000 ppm diet NOEL = 95 mg a.s/kg bw/day	EC15 (2005a)
Mallard Duck	Avian, long term dietary toxicity	85.8	OECD 206, 0 to 1000 ppm diet	NOEC = 1000 ppm diet NOEL = 1495 mg a.s/kg bw/day	EC16 (2005b)

Species	Test	Purity % Note[7]	Guideline, duration, doses and conditions	Result	Study number
Apis mellifera (honey bee)	acute oral toxicity	83.0	OECD 213, 0 to 1.0 µg as/bee	48h LD_{50} = 0.14 µg as/bee 72h LD_{50} = 0.11 µg as/bee	EC17 Hughes C (2004c)
Apis mellifera (honey bee)	acute contact toxicity	83.0	OECD 214, 0 to 100 µg as/bee	24h LD_{50} = 0.039 µg as/bee 48h LD_{50} = 0.024 µg as/bee	EC18 Hughes C (2004d)
Apis mellifera (honey bee)	Laboratory Foliar residue toxicity test	83.0	US EPA guideline 41.2, foliar residue at treatment rate of 110 g/ha – exposure 3,6,24 hrs after spraying foliage	No mortality or significant adverse effects to bees when exposed to foliar residues.	EC19 Hughes C (2004e)
Earthworms	Acute toxicity	85.8	OECD 207, 14d, exposure to dry soil 1000mg/kg a.s.	$LC_{50=}$ 1000 mg/kg dry soil	EC20 Warbritton R (2004b)
Earthworms	Chronic toxicity	85.8	OECD 222, 56d, exposure to dry soil 0 to 18.65 mg/kg a.s.	$LC_{50=}$ 18.65 mg/kg dry soil NOEC = 18.65 mg/kg dry soil	EC21 Warbritton R (2004)

ANNEX 2
REFERENCES

(sorted by Study reference list number)

Study Number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
Published references			
JMPR, Part II		2008	Joint FAO/WHO Meeting on Pesticide Residues, Evaluations 2008, Part II – Toxicological, pps 327-368
IPCS		2009	The WHO Recommended classification of pesticides by Hazard, and guidelines to classification 2009.
EFSA		2013	Conclusion on the peer review of the pesticide risk assessment of the active substance spinetoram, EFSA Journal (2013); 11(5):3220.
Methods of Analysis			
MA1 Attach-ment 8	Madsen S	2007	Analytical Method and Validation for the Determination of XDE-175 (Spinetoram) in GF-1587, GF-1629 and GF-1640 Formulations and in XDE-175 Technical Grade Active Ingredient DAS Report No.: DAS-AM-07-15 GLP/GEP (Y/N): Y
MA2 Attach-ment 9	King K	2018	Analytical Method for the Determination of Spinetoram in tablets Clarke Method SPTM-001 Rev.1 GLP/GEP (Y/N): Y
MA3 Attach-ment 10	King K	2018	Method validation for HPLC Determination of Spinetoram Content in Tablets Clarke Report No.: AN 1072 GLP/GEP (Y/N): Y
Phys-chem studies			
PC1	Comb A.L.	2005a	Determination of Vapour Pressure for XDE-175-J DAS Report No.: NAFST-05-073 (Masterfile Number): Derbi 208969 GLP/GEP (Y/N): Y
PC2	Comb A.L.	2005c	Determination of Vapour Pressure for XDE-175-L DAS Report No.: NAFST-05-074 (Masterfile Number): Derbi 208970 GLP/GEP (Y/N): Y
PC3	Madsen S, Jennings C	2005a	Determination of the Melting and Decomposition Temperatures of XDE-175-J DAS Report No.: FAPC-052-002 (Masterfile Number): Derbi 219997 GLP/GEP (Y/N): Y
PC4	Madsen S, Jennings C	2005b	Determination of the Melting and Decomposition Temperatures of XDE-175-L DAS Report No.: FAPC-052-003 (Masterfile Number): Derbi 219998 GLP/GEP (Y/N): Y
PC5	Comb A.L.	2005d	Determination of Water Solubility for XDE-175-J DAS Report No.: NAFST-05-071

Study Number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
			(Masterfile Number): Derbi 220048 GLP/GEP (Y/N): Y
PC6	Comb A.L.	2005e	Determination of Water Solubility for XDE-175-L DAS Report No.: NAFST-05-072 (Masterfile Number): Derbi 220047 GLP/GEP (Y/N): Y
PC7	Comb A.L.	2005g	Determination of Octanol/Water Partition Coefficient for XDE-175-J DAS Report No.: NAFST-05-075 (Masterfile Number): Derbi 220045 GLP/GEP (Y/N): Y
PC8	Comb A.L.	2005h	Determination of Octanol/Water Partition Coefficient for XDE-175-L DAS Report No.: NAFST-05-076 (Masterfile Number): Derbi 220049 GLP/GEP (Y/N): Y
PC9	Rutherford et al	2005	Hydrolysis of XDE-175-J and XDE-175-L DAS Report No.: 040108 (Masterfile Number): Derbi 208213 GLP/GEP (Y/N): Y
PC10	Yoder R.N. et al	2005	Aqueous Photolysis of XDE-175 in Natural Water under Xenon Light DAS Report No.: 060089 (Masterfile Number): Derbi 244914 GLP/GEP (Y/N) : Y
PC11	Madsen S, Holley R	2005a	Determination of the Dissociation Constant of XDE-175-J using Capillary Electophoresis DAS Report No.: FOR-05-043 (Masterfile Number): Derbi 220155 GLP/GEP (Y/N): N
PC12	Madsen S, Holley R	2005b	Determination of the Dissociation Constant of XDE-175-L using Capillary Electrophoresis DAS Report No.: FOR-05-044 (Masterfile Number): Derbi 220154 GLP/GEP (Y/N): N
PC13	Comb A.L.	2005f	Determination of Organic Solubility for XDE-175 DAS Report No.: NAFST-05-078 (Masterfile Number): Derbi 208976 GLP/GEP (Y/N): Y
PC14a Attach-ment 12a	Comb A.L	2007	Accelerated Storage Stability for GF-1640 WG in Commercial Containers (1 L PET, 1 L HDPE and Foil-Lined Bag), DAS Report No.: NAFST-07-058 GLP/GEP (Y/N): Y
PC14b Attach-ment 12b	McKeown S	2013	GF-1640 WG, 2 weeks at 54C, Accelerated Storage Stability DAS Report No.: NAFST-13-168 GLP/GEP (Y/N): Y

Study Number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
PC15 Attach-ment 13	Latham A	2005	Storage Stability and Package Corrosion Characteristics of GF-1587; Accelerated Study DAS Report No.: NAFST-05-022 GLP/GEP (Y/N): Y
PC16 Attach-ment 14	Stock M	2009	Two-Week Accelerated Storage Stability of GF-1587 DAS Report No.: FOR-09-07 GLP/GEP (Y/N): Y
PC17 Attach-ment 11	King K	2018	Product Properties Study for CMP128-005 Clarke Report No.: AN 1074 GLP/GEP (Y/N): Y
PC18 Attach-ment 15	Dow AgroSciences	2005	Personal communication on DSC (Differential Scanning Calorimetry) determination of melting point, pure XDE-175-J, XDE-175-L and Spinetoram (J+ L) Dow AgroSciences GLP/GEP (Y/N): N
Toxicology studies			
TC1		2005a	XDE-175: Acute Oral Toxicity Study in F344/DUCRL Rats (Up-Down Procedure) DAS Report No.: 051040 (Masterfile Number): Derbi 208478 GLP/GEP (Y/N): Y
TC2		2007a	XDE-175 TGAI 85:15: Acute Oral Toxicity Up and Down Procedure in Rats DAS Report No.: 070052 (Masterfile Number): Derbi 242758 GLP/GEP (Y/N): Y
TC3		2005b	XDE-175: Acute Dermal Toxicity Study in F344/DUCRL Rats DAS Report No.: 051041 (Masterfile Number): Derbi 208479 GLP/GEP (Y/N): Y
TC4		2007b	XDE-175 TGAI 85:15: Acute Dermal Toxicity Study in Rats - Limit Test DAS Report No.: 070053 (Masterfile Number): Derbi 243006 GLP/GEP (Y/N): Y
TC5		2005	XDE-175: Acute Dust Aerosol Inhalation Toxicity Study in F344/DUCL Rats DAS Report No.: 051021 (Masterfile Number): Derbi 207665 GLP/GEP (Y/N): Y

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TC6		2005	XDE-175 (85:15): Acute Dust Aerosol Inhalation Toxicity Study in F344/DUCRL Rats DAS Report No.: 071163 (Masterfile Number): N/A GLP/GEP (Y/N): Y
TC7		2005a	XDE-175: Acute Dermal Irritation Study in New Zealand White Rabbits DAS Report No.: 051042 (Masterfile Number): Derbi 208480 GLP/GEP (Y/N): Y
TC8		2007b	XDE-175 TGAI 85:15: Acute Dermal Toxicity Study in Rats - Limit Test DAS Report No.: 070053 (Masterfile Number): Derbi 243006 GLP/GEP (Y/N): Y
TC9		2005b	XDE-175: Acute Eye Irritation Study in New Zealand White Rabbits DAS Report No.: 051043 (Masterfile Number): Derbi 208481 GLP/GEP (Y/N): Y
TC10		2007d	XDE-175 TGAI 85:15: Primary Eye Irritation Study in Rabbits DAS Report No.: 070055 (Masterfile Number): Derbi 243492 GLP/GEP (Y/N): Y
TC11		2006	Revised Report for: XDE-175: Local Lymph Node Assay in BALB/cAnNCrl Mice DAS Report No.: 051023R (Masterfile Number): Derbi 223921 GLP/GEP (Y/N): Y
TC12		2007	XDE-175 (85:15): Local Lymph Node Assay in CBA/J Mice DAS Report No.: 071025 (Masterfile Number): Derbi 243491 GLP/GEP (Y/N): Y
TC13		2004	X574175: 28-Day Dietary Toxicity Study in Fischer 344 Rats DAS Report No.: 031151 (Masterfile Number): Derbi 147922 GLP/GEP (Y/N): Y
TC14		2005	Report Revision for X574175: 28-Day Dietary Toxicity Study in CD-1 Mice DAS Report No.: 031081R

Study Number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
			(Masterfile Number): N/A GLP/GEP (Y/N): Y
TC15		2005	XDE-175: 28-Day Dermal Toxicity Study in F344/DuCrl Rats DAS Report No.: 051052 (Masterfile Number): Derbi 209245 GLP/GEP (Y/N): Y
TC16		2008	XDE-175: 90-Day Dietary Toxicity Study with a 4-Week Recovery in Fischer 344 Rats DAS Report No.: 041029R (Masterfile Number): Derbi 220011 GLP/GEP (Y/N): Y
TC17		2007	XDE-175 (85:15 Ratio): 90-Day Dietary Toxicity Study in F344/DUCRL Rats DAS Report No.: 061077 (Masterfile Number): Derbi 239527 GLP/GEP (Y/N): Y
TC18		2005	XDE-175: 90-Day Dietary Toxcity Study in Crl:CD-1 (ICR) Mice DAS Report No.: 041045 (Masterfile Number): Derbi 209238 GLP/GEP (Y/N): Y
TC19		2005	XDE-175: 90-Day Dietary Toxicity Study in Beagle Dogs DAS Report No.: 041114 (Masterfile Number): Derbi 207612 GLP/GEP (Y/N): Y
TC20		2006	XDE-175: One-Year Dietary Toxicity Study in Beagle Dogs DAS Report No.: 051072 (Masterfile Number): Derbi 240687 GLP/GEP (Y/N): Y
TC21		2007	XDE-175: Two-Year Chronic Toxicity/Oncogenicity and Neurotoxicity Study in F344/DuCrl Rat DAS Report No.: 041155 (Masterfile Number): Derbi 241324 GLP/GEP (Y/N): Y
TC22		2007	XDE-175: 18-Month Dietary Oncogenicity Study in Crl:CD1(ICR) Mice DAS Report No.: 041164 (Masterfile Number): N/A GLP/GEP (Y/N): Y
TC23		2006	XDE-175: Two Generation Dietary Reproductive Toxicity Study in CD Rats

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			DAS Report No.: 041147 (Masterfile Number): Derbi 223959 GLP/GEP (Y/N): Y
TC24		2005b	XDE-175: Developmental Toxicity Probe Study in New Zealand White Rabbits DAS Report No.: 041062 (Masterfile Number): Derbi 207611 GLP/GEP (Y/N): Y
TC25		2008	XDE-175: Oral Gavage Developmental Toxicity Study in New Zealand White Rabbits DAS Report No.: 041125R (Masterfile Number): Derbi 208477 GLP/GEP (Y/N): Y
TC26		2005	XDE-175: Acute Neurotoxicity Study in F344/DUCRL Rats DAS Report No.: 051037 (Masterfile Number): Derbi 209243 GLP/GEP (Y/N): Y
TC27		2007	XDE-175: Chronic Neurotoxicity Study in F344/DuCrl Rat DAS Report No.: 041155N (Masterfile Number): Derbi 241324 GLP/GEP (Y/N): Y
TC28		2005	Salmonella-Escherichia Coli/Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with XDE-175 DAS Report No.: 051020 (Masterfile Number): Derbi 209009 GLP/GEP (Y/N): Y
TC29		2007e	Salmonella-Escherichia Coli/Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with XDE-175 85:15 DAS Report No.: 071024 (Masterfile Number): N/A GLP/GEP (Y/N): Y
TC30		2008	Evaluation of XDE-175 in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay DAS Report No.: 051027R (Masterfile Number): Derbi 208581 GLP/GEP (Y/N): Y

Study Number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
TC31		2007	Evaluation of XDE-175 (85:15) in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay DAS Report No.: 071028 (Masterfile Number): N/A GLP/GEP (Y/N): Y
TC32		2006	Revised Report for: XDE-175: Local Lymph Node Assay in BALB/cAnNCrl Mice DAS Report No.: 051023R (Masterfile Number): Derbi 223921 GLP/GEP (Y/N): Y
TC33		2007	XDE-175 (85:15): Local Lymph Node Assay in CBA/J Mice DAS Report No.: 071025 (Masterfile Number): Derbi 243491 GLP/GEP (Y/N): Y
TC34		2005	Evaluation of XDE-175 in the Mouse Bone Marrow Micronucleus Test DAS Report No.: 051034 (Masterfile Number): Derbi 208647 GLP/GEP (Y/N): Y
Ecotoxicology studies			
EC1	Hicks S.L.	2007	Side-by-Side Static Acute Toxicity Test of Three Test Substances (XDE-175, N-Demethyl-XDE-175-J, and N-Demethyl-XDE-175-L) Exposed to the Water Flea, Daphnia magna DAS Report No.: 070295 (Masterfile Number): N/A GLP/GEP (Y/N): Y
EC2	Hicks S.L.	2005b	XDE-175: Chronic Toxicity Test with the Water Flea, Daphnia magna, Conducted Under Flow-Through Conditions DAS Report No.: 040400 (Masterfile Number): Derbi 208593 GLP/GEP (Y/N): Y
EC3	Hughes C.I.	2005	XDE-175: Chronic Toxicity Test with the Water Flea, Daphnia magna, Exposed Under Static-Renewal Conditions DAS Report No.: 050481 (Masterfile Number): Derbi 209010 GLP/GEP (Y/N): Y
EC4	Sayers L.E.	2010a	XDE-175 (Spinetoram)- Acute Toxicity Test with Water Fleas (*Daphnia magna*) Under Static-Renewal Conditions, Following OPPTS Draft Guideline 850.1010 DAS Report No.: 090427 (Masterfile Number): N/A

Study Number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
			GLP/GEP (Y/N): Y
EC5		2005a	XDE-175: Flow-Through Acute Toxicity Test with the Bluegill Sunfish, Lepomis Macrochirus DAS Report No.: 050012 (Masterfile Number): Derbi 208292 GLP/GEP (Y/N): Y
EC6		2005b	XDE-175: Early Life-Stage Toxicity Test with the Fathead Minnow, Pimephales Promelas, Under Flow-Through Conditions DAS Report No.: 050013 (Masterfile Number): Derbi 209244 GLP/GEP (Y/N): Y
EC7	Currie R.J. et al	2007	XDE-175: 28-Day Chronic Toxicity Study with the Midge, Chironomus riparius, using Spiked Water in a Sediment-Water Exposure System DAS Report No.: 071056 (Masterfile Number): . GLP/GEP (Y/N): Y
EC8	Henry K.S. et al	2005	XDE-175: 28-Day Chronic Toxcity Study with the Midge, Chironomus riparius, using Spiked Sediment in a Sediment-Water Exposure System DAS Report No.: 051035 (Masterfile Number): Derbi 209242 GLP/GEP (Y/N): Y
EC9	Hicks S.L.	2004b	XDE-175: Growth Inhibition Test with the Freshwater Diatom, Navicula pelliculosa DAS Report No.: 040369 (Masterfile Number): Derbi 205755 GLP/GEP (Y/N): Y
EC10	Hicks S.L.	2005c	XDE-175: Growth Inhibition Test with the Freshwater Aquatic Plant, Duckweed, Lemna gibba DAS Report No.: 040368 (Masterfile Number): Derbi 205754 GLP/GEP (Y/N): Y
EC11		2005a	XDE-175: An Acute Oral Toxicity Study with the Northern Bobwhite DAS Report No.: 050003 (Masterfile Number): Derbi 207613 GLP/GEP (Y/N): Y
EC12		2005b	XDE-175: An Acute Oral Toxicity Study with the Mallard DAS Report No.: 050004 (Masterfile Number): Derbi 209171 GLP/GEP (Y/N): Y
EC13		2005c	XDE-175: A Dietary LC50 Study with the Northern Bobwhite DAS Report No.: 050005 (Masterfile Number): Derbi 208582 GLP/GEP (Y/N): Y

Study Number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
EC14		2005d	XDE-175: A Dietary LC50 Study with the Mallard DAS Report No.: 050006 (Masterfile Number): Derbi 208583 GLP/GEP (Y/N): Y
EC15		2005a	XDE-175: A Reproduction Study with the Northern Bobwhite DAS Report No.: 040346 (Masterfile Number): Derbi 208579 GLP/GEP (Y/N): Y
EC16		2005b	XDE-175: A Reproduction Study with the Mallard DAS Report No.: 040347 (Masterfile Number): Derbi 208580 GLP/GEP (Y/N): Y
EC17	Hughes C	2004c	XDE-175: Acute Toxicity Test with the Honeybee (Apis mellifera) DAS Report No.: 040179 (Masterfile Number): Derbi 204279 GLP/GEP (Y/N): Y
EC18	Hughes C	2004d	XDE-175: Acute Contact Toxicity Test with the Honeybee, Apis mellifera DAS Report No.: 040178 (Masterfile Number): Derbi 145380 GLP/GEP (Y/N): Y
EC19	Hughes C	2004e	XDE-175: Toxicity of Residues on Foliage to the Honeybee, *Apis mellifera* DAS Report No.: 040345 (Masterfile Number): N/A GLP/GEP (Y/N): Y
EC20	Warbritton R	2005b	XDE-175: Acute Toxicity Test with the Earthworm, Eisenia fetida DAS Report No.: 050007 (Masterfile Number): Derbi 207234 GLP/GEP (Y/N): Y
EC21	Reynolds S.E.	2005	XDE-175: Effects on Reproduction and Growth in the Earthworm Eisenia fetida DAS Report No.: 050008 (Masterfile Number): Derbi 219912 GLP/GEP (Y/N): Y