Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

PROTHIOCONAZOLE

(RS)-2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-1,2,4-triazole-3-thione

2021

TABLE OF CONTENTS

PROTHIOCONAZOLE

DISCLAIMER[1]

FAO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

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.

FAO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may be arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

Additionally, FAO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.
FAO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, FAO does not in any way warrant or represent that any pesticide claimed to comply with a FAO specification actually does so.

[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.

*NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (https://www.fao.org/pest-and-pesticide-management/guidelines-standards/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/)

PART ONE

SPECIFICATIONS

PROTHIOCONAZOLE

PROTHIOCONAZOLE INFORMATION

ISO common name: Prothioconazole (ISO 1750, approved)

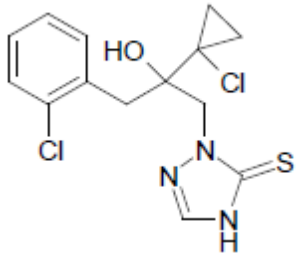
Chemical names:

IUPAC: (*RS*)-2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2- hydroxypropyl]-2,4-dihydro-1,2,4-triazole-3-thione

CA: 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

Synonyms: PTZ, JAU 6476

Structural formula:



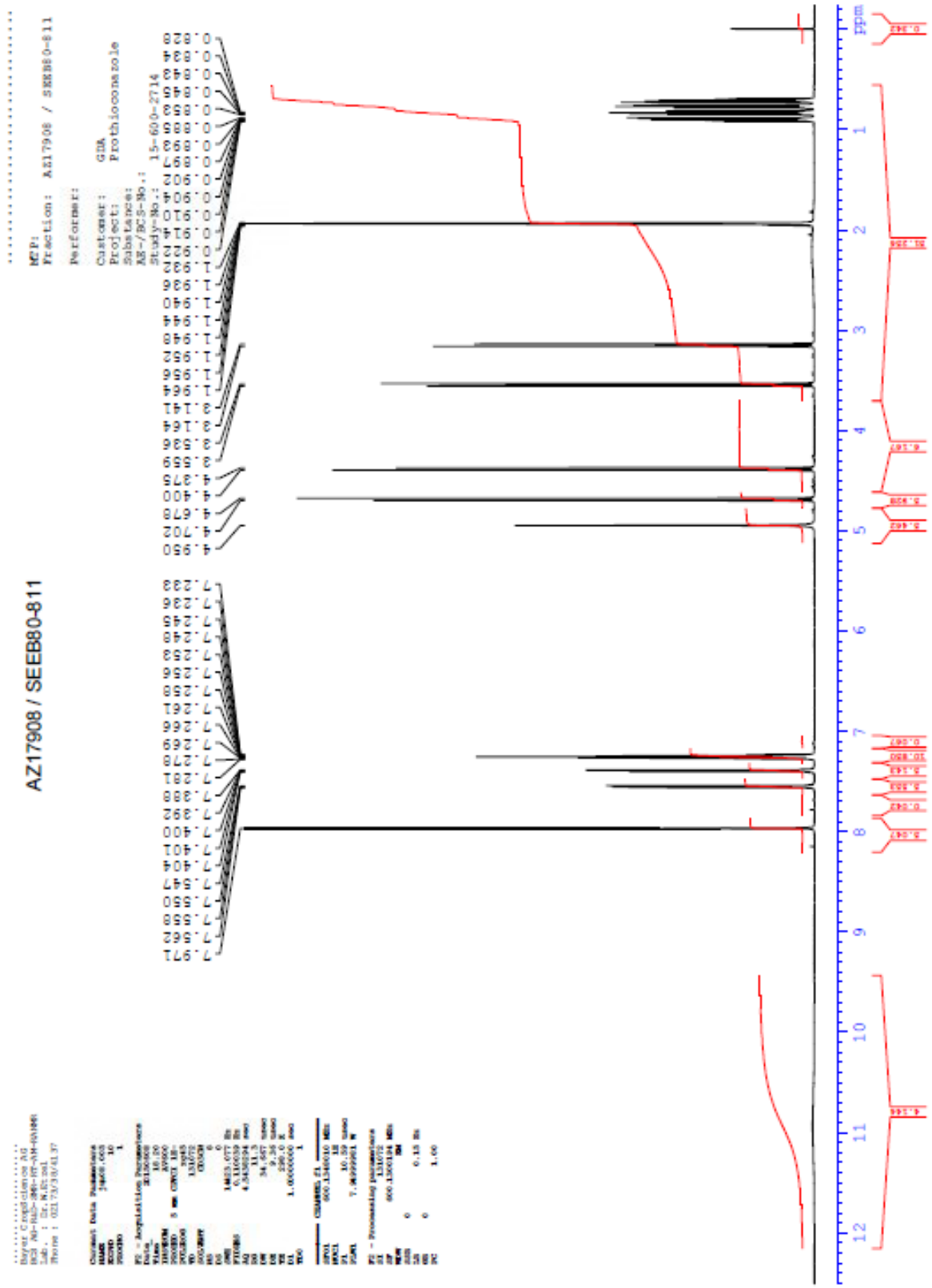
Relative molecular mass: 344.26

CAS Registry No.: 178928-70-6

CIPAC No.: 745

Identity tests: Retention time in HPLC-UV, ^{1}H-NMR

Figure 2: ^{1}H - NMR - Spectrum of Prothioconazole



PROTHIOCONAZOLE TECHNICAL MATERIAL

FAO Specification 745 / TC (October 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 (745/2020). 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 specifications. The specification may not be appropriate for TC produced by other manufacturers. The evaluation report (745/2020) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of prothioconazole together with related manufacturing impurities and shall be white to beige powder free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 745/TC/M/2, CIPAC Handbook P, p. 165, 2021)

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 **Prothioconazole content** (CIPAC 745/TC/M/3, CIPAC Handbook P, p. 165, 2021) (Note 1)

The prothioconazole content shall be declared (not less than 970 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

3 Relevant impurities

3.1 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol (Note 1)
Maximum: 0.5 g/kg.

.

Note 1 Abbreviation for 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol: PTZ-desthio. A peer-validated method for the determination of PTZ-desthio in TC, EC, FS and SC based on HPLC-MS (ESI-MS/MS in MRM mode) was noted and adopted. Copies of the methods are available through the CIPAC free imethods for impurities scheme https://www.cipac.org/index.php/methods-publications/free-methods/free-relevant-impurities-methods

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: https://www.fao.org/pest-and-pesticide-management/guidelines-standards/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/

PROTHIOCONAZOLE EMULSIFIABLE CONCENTRATE

FAO Specification 745 / EC (October 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 (745/2020). It should be applicable to EC of this manufacturer, and those of any other formulators who use only TC from the evaluated sources. The specification 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 who use TC from other sources. The evaluation report (745/2020) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of technical prothioconazole, complying with the requirements of FAO specification 745/TC (October 2021) together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

2 Active ingredient

2.1 Identity tests (CIPAC 745/EC/M/2, CIPAC Handbook P, p. 169, 2021)

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 Prothioconazole content (CIPAC 745/EC/M/3, CIPAC Handbook P, p. 169, 2021)

The prothioconazole content shall be declared in g/l at 20 ± 2ºC (Note 1) and, when determined, the average content measured shall not differ from that declared by more than the appropriate tolerance, given in the table of tolerances.

Declared content in g/l at 20 ± 2°C	Tolerance
above 25 up to 100	± 10% of the declared content
above 100 up to 250	± 6% of the declared content
above 250 up to 500	± 5% of the declared content
Note: the upper limit is included in each range	

*Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: https://www.fao.org/pest-and-pesticide-management/guidelines-standards/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/

3 **Relevant impurities** (Note 2)

3.1 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol
Maximum: 0.05 % w/w of the prothioconazole content found under 2.2.

4 **Physical properties**

4.1 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p. 137, 2003)

The formulation, when diluted at 25 ± 2 °C (Note 3) with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.3
0 h	Initial emulsification complete
0.5 h	"Cream" or “Sediment”, maximum: 1 ml
2.0 h	"Cream" or “Sediment”, maximum: 2 ml; "Free oil", maximum: 0.5 ml
24 h	Re-emulsification complete
24.5 h	"Cream" or “Sediment”, maximum: 1 ml "Free oil", maximum: 0.5 ml
Note: in applying MT 36.3, tests after 24 h are required only where results at 2 h are in doubt	

4.2 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 117, 2017) (Note 4)

Maximum: 60 ml after 1 min.

5 **Storage stability**

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

After storage at 0 ± 2°C for 7 days, the volume of solid and/or liquid which separates shall not be more than 0.3 ml.

5.2 **Stability at elevated temperature** (MT 46.4, CIPAC Handbook P, p. 232, 2021)

After storage at 54 ± 2°C for 14 days (Note 5), 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:

- by-products of manufacture or storage (3.1)
- emulsion stability and re-emulsification (4.1),

Note 1 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 2 Abbreviation for 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol: PTZ-desthio. A peer-validated method for the determination of PTZ-desthio in TC, EC, FS and SC based on HPLC-MS (ESI-MS/MS in MRM mode) was noticed and adopted. Copies of the methods are available through the CIPAC free impurities methods scheme https://www.cipac.org/index.php/methods-publications/free-methods/free-relevant-impurities-methods

Note 3 As outlined in CIPAC MT 36.3, the test concentrations should be based on those in the recommended directions for use supplied with the product. Where several concentrations are recommended, the highest and lowest concentrations within the scope of the method should be used.Note 4 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 5 When a prothioconazole EC coformulated with other active ingredient(s) is tested in MT 46.4, lower temperatures according to that MT should be considered in cases where one or more of the coformulated active ingredients are not stable at 54 °C.

Note 6 Samples of the formulation taken before and after the storage stability test should be protected from light during handling and storage. The time to analysis after sampling from the sealed container should be kept to a minimum, especially in cases where samples of the formulation before and after storage are intended to be analyzed concurrently after the test in order to reduce the analytical error.

PROTHIOCONAZOLE SUSPENSION CONCENTRATE FOR SEED TREATMENT

FAO Specification 745 / FS (October 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 (745/2020). It should be applicable to FS of this manufacturer, and those of any other formulators who use only TC from the evaluated sources. The specification 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 who use TC from other sources. The evaluation report (745/2020) as PART TWO forms an integral part of this publication.

1 **Description**

The material shall consist of a suspension of fine particles of technical prothioconazole, complying with the requirements of FAO specification 745/TC (October 2021), in an aqueous phase together with suitable formulants, including colouring matter. After gentle stirring or shaking, the material shall be homogeneous (Note 1) and suitable for further dilution with water if necessary.

2 **Active ingredient**

2.1 **Identity tests** (CIPAC 745/FS/M/2, CIPAC Handbook P, p. 169, 2021)

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 **Prothioconazole content** (CIPAC 745/FS/M/3, CIPAC Handbook P, p. 170, 2021)

The prothioconazole content shall be declared (g/l at 20 ± 2ºC, note 2) and, when determined, the average content measured shall not differ from that declared by more than the appropriate tolerance, given in the table of tolerances:

Declared content in g/L	Tolerance
Up to 25	± 15% of the declared content
above 25 up to 100	± 10% of the declared content
above 100 up to 250	± 6% of the declared content
above 250 up to 500	± 5% of the declared content
Note: In each range the upper limit is included	

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: https://www.fao.org/pest-and-pesticide-management/guidelines-standards/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/

3 Relevant impurities

3.1 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol (Note 3)

Maximum: 0.05 % w/w of the prothioconazole content found under 2.2.

4 Physical properties

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

Maximum "residue": 7 %.

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

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

4.3 **Adhesion to seeds** (MT 194, CIPAC Handbook N, p. 145, 2011)

Wheat: A minimum of 95 % of the prothioconazole shall remain on the seeds after the test.

Barley: A minimum of 85 % of the prothioconazole shall remain on the seeds after the test.

Maize: A minimum of 95 % of the prothioconazole shall remain on the seeds after the test.

5 Storage stability

5.1 **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 the clause for: wet sieve test (3.2).

5.2 **Stability at elevated temperature** (CIPAC 745/FS/M/2, CIPAC Handbook P, p. 169, 2021)

After storage at 54 ± 2°C for 2 weeks (Note 4), the determined average active ingredient content must not be lower than 95 % relative to the determined average content found before storage (Note 5) and the formulation shall continue to comply with the clauses for:

- by-products of manufacture or storage (3.1)
- pourability (4.1),
- wet sieve test (4.2),
- adhesion to seeds (4.3)

Note 1 Before sampling, homogenize the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, gently shake 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 laboratory sample taken after the recommended homogenization procedure.

Note 2 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 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 3 The abbreviation for this relevant impurity is PTZ-desthio. A peer-validated method for the determination of PTZ-desthio in TC, EC, FS and SC was presented at i2020 CIPAC Meeting and accepted. Copies of the methods will be available through the CIPAC free impurities methods scheme https://www.cipac.org/index.php/methods-publications/free-methods/free-relevant-impurities-methods

Note 4 When a prothioconazole FS coformulated with other active ingredient(s) is tested in MT 46.4, lower temperatures according to that MT should be considered in cases where one or more of the coformulated active ingredients are not stable at 54 °C.

Note 5 Samples of the formulation taken before and after the storage stability test should be protected from light during handling and storage. The time to analysis after sampling from the sealed container should be kept to a minimum, especially in cases where samples of the formulation before and after storage are intended to be analyzed concurrently after the test in order to reduce the analytical error.

PROTHIOCONAZOLE SUSPENSION CONCENTRATE

FAO Specification 745 / SC (October 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 ((*745/2020*). It should be applicable to SC of this manufacturer, and those of any other formulators who use only TC from the evaluated sources. The specification 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 who use TC from other sources. The evaluation report (*745/2020*) as PART TWO forms an integral part of this publication.*

1 Description

The material shall consist of a suspension of fine particles of technical prothioconazole, complying with the requirements of FAO/WHO specification 745/TC (October 2021), in the form of white to beige powder, 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 (CIPAC 745/SC/M/2, CIPAC Handbook P, p. 170, 2021)

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 Prothioconazole content (CIPAC 745/SC/M/3, CIPAC Handbook P, p. 171, 2021)

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

Declared content in g/L	Tolerance
above 100 up to 250	± 6% of the declared content
above 250 up to 500	± 5% of the declared content
Note: In each range the upper limit is included	

3 Relevant impurities (Note 3)

3.1 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol

Maximum: 0.05 % w/w of the prothioconazole content found under 2.2.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: https://www.fao.org/pest-and-pesticide-management/guidelines-standards/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/

4 Physical properties

4.1 **Pourability** (MT 148.1, CIPAC Handbook F, p. 348, 1995)

Maximum residue: 5%.

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

A minimum of 80% of the prothioconazole content found under 2.2 shall be in suspension after 5 minutes in CIPAC Standard Water D at 30 ± 2°C.

4.3 **Suspensibility** (MT 184.1) (Note 4)

A minimum of 80% of the prothioconazole content found under 2.2 shall be in suspension after 30 minutes in CIPAC Standard Water D at 25 ± 5°C.

4.4 **Wet sieve test** (MT 185, CIPAC Handbook K, p.148, 2003) (Note 5)

Maximum: 0.2% of the formulation shall be retained on a 75 µm test sieve.

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

Maximum: 60 ml after 1 minute.

5 Storage stability

5.1 **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 (4.4),
- wet sieve test (4.5).

5.2 **Stability at elevated temperature** (CIPAC 745/FS/M/2, CIPAC Handbook P, p. 169, 2021)

After storage at 54 ± 2°C for 14 days (Note 7), the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 8) and the formulation shall continue to comply with the clauses for:

- by-products of manufacture or storage (3.1)
- pourability (4.1),
- spontaneity of dispersion (4.2),
- suspensibility (4.3),
- wet sieve test (4.4),

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 laboratory sample taken after the recommended homogenization procedure.

Note 2 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 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 3 The abbreviation for this relevant impurity is PTZ-desthio. A peer-validated method for the determination of PTZ-desthio in TC, EC, FS and SC was presented at i2020 CIPAC Meeting and accepted. Copies of the methods will be available through the CIPAC free impurities methods scheme https://www.cipac.org/index.php/methods-publications/free-methods/free-relevant-impurities-methods

Note 4 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric and solvent extraction determination may be used on a routine basis provided that these methods have been shown to give equal results to those of the chemical assay method. In case of dispute, the chemical method 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 correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 7 When a prothioconazole SC coformulated with other active ingredient(s) is tested in MT 46.4, lower temperatures according to that MT should be considered in cases where one or more of the coformulated active ingredients are not stable at 54 °C.

Note 8 Samples of the formulation taken before and after the storage stability test should be protected from light during handling and storage. The time to analysis after sampling from the sealed container should be kept to a minimum, especially in cases where samples of the formulation before and after storage are intended to be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

PROTHIOCONAZOLE

PROTHIOCONAZOLE

FAO/WHO EVALUATION REPORT 745/2020

Recommendations

The Meeting recommended that the specifications for prothioconazole TC, FS and SC, proposed by Bayer AG, Division Crop Science and as amended, should be adopted by FAO, subject to clarification of some points.

Appraisal

The Meeting considered data on prothioconazole submitted by Bayer AG, Division Crop Science (BCS) in December 2019, in support of new FAO specifications for TC, EC, FS and SC.

The ISO common name prothioconazole designates a molecule consisting of a thio-triazole ring attached to a tertiary alcohol with a cyclopropane and phenyl moiety, each with a chlorine atom attached at C-1 (cyclopropane) or C-2 (phenyl-moiety), respectively. The carbon atom carrying the alcohol moiety is a stereogenic center, and prothioconazole therefore has two enantiomeric forms. The ISO common name however stands for a racemate of (*R*)- and (*S*)-prothioconazole. The method of manufacture is expected to lead to a racemate.

Prothioconazole has been evaluated for its toxicology and residues in 2008 (JMPR, 2008).

An ADI of 0–0.05 mg/kg bw was established for prothioconazole based on the NOAEL of 5 mg/kg bw per day, identified on the basis of gross and microscopic changes in the liver and kidneys in a 2-year study of toxicity and carcinogenicity in rats treated by gavage, and a safety factor of 100.

An ARfD of 0.8 mg/kg bw was established for women of childbearing age based on a NOAEL of 80 mg/kg bw per day, identified on the basis of a marginally increased incidence of supernumerary rudimentary ribs that might be attributable to a single exposure at 750 mg/kg bw per day in a study of developmental toxicity in rats, and with a safety factor of 100. The Meeting concluded that the establishment of an ARfD for the general population was not necessary on the basis of its low acute toxicity, the lack of evidence for any acute neurotoxicity and absence of any other toxicologically relevant effect that might be attributable to a single dose.”

There is an IPCS hazard classification of prothioconazole. Prothioconazole was evaluated by the WHO IPCS in 2009 and classified with a GHS classification number 5 (LD50 > 6200 mg/kg bw) as Class “U”, i.e. “unlikely to present acute hazard in normal use”.

An ADI of 0–0.01 mg/kg bw was established for prothioconazole-desthio based on the NOAEL of 1.1 mg/kg bw per day, identified on the basis of microscopic changes in the liver

and ovaries in a 2-year dietary study of toxicity and carcinogenicity in rats, and with a safety factor of 100. An ARfD of 0.01 mg/kg bw was established for women of childbearing age based on a NOAEL of 1 mg/kg bw per day, identified on the basis of increased incidence of supernumerary rudimentary ribs that might be attributable to a single exposure at 3 mg/kg bw per day in a study of developmental toxicity in rats, and with a safety factor of 100. Although the increased incidence at 3 mg/kg bw per day was only significant on the basis of the number of foetuses, this was the lower limit of a clear dose-related response curve.

The Meeting also established an ARfD of 1 mg/kg bw for the general population based on a NOAEL of 100 mg/kg bw, identified on the basis of clinical signs in studies of toxicity in mice and rats given single doses, and a safety factor of 100."

The Meeting noted that a full toxicological data package on PTZ-desthio is available and recommended, that the hazard summary section should cover the relevant impurity as well. BCS agreed and submitted a full updated hazard summary that now covers both prothioconazole and PTZ-desthio.

Prothioconazole has a low volatility and a melting point of 140 and 137 °C (pure compound and TC, respectively). It has water solubility that is low (0.02 g/L under acidic conditions and increases to 3.2 g/l at pH 9. It has an acid-base constant (pKa) of 6.8 and hence also shows a pH-dependence in its octanol-water partition coefficient: 3.4 at pH 4, 0.2 at pH 9.

It is stable to hydrolysis at all pH values but shows a moderate stability to aquatic photolysis with an experimental half live of approx. 2 days.

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 and maximum impurity limits as proposed by the BCS were supported by 5 batch analysis data. Prothioconazole is produced at several different production sites. One of the production sites is considered as the reference profile, and the others as equivalence cases. All production sites produce prothioconazole TC supported with 5 batch analysis and compliant to a common manufacturing specification.

The minimum purity of 970 g/kg was justified by the available 5-batch data. Mass balances were high (981.6 to 996.6 g/kg %). The analytical methods for the majority of organic impurities are based on HPLC and are fully validated and support the results in the 5-batch study. The limits of quantitation were determined as part of the validation.

A CIPAC method based on reversed phase HPLC has been developed for determination of PTZ in TC, EC, FS and SC formulations and was presented at the 2018 CIPAC Meeting. The method was provisionally adopted as CIPAC method and is published in Handbook P (2021).

The Meeting concluded that none of the impurities included in the manufacturing specification beside PTZ-desthio should be considered as relevant.

A CIPAC method (5251/m) based on reversed phase HPLC MS/MS detection has been developed and peer validated for determination of PTZ-desthio in TC, EC, FS and SC

formulations. Method was presented and adopted at the 2020 CIPAC Meeting and is available on CIPAC website.

The proposed specification for TC, EC, FS and SC were essentially in accordance with the requirements of the Manual (3rd revision of the 1st edition, FAO/WHO 2016). As PTZ is hydrolytically stable independent of pH value, no clause for pH or acidity was proposed in any of the formulation specification. This was accepted by the Meeting.

Certain specific issues were identified in the specifications for formulations as follows:

Draft specifications for TC, EC, FS and SC:

The draft TC specification had two subclauses for relevant impurities:

- a clause for "material insoluble in acetone" A closer examination of the 5-batch studies indicated that this material in fact a well known non-toxic inorganic salt well soluble in water. This material will readily dissolve when the EC is mixed with water and does not interfere when the active ingredient is formulated as FS or SC. The Meeting therefore concluded that this clause is not required.
- a second for PTZ-desthio impurity. Whereas the need for the clause for limiting the desthio in TC, EC, FS and SC was well understood, BCS had proposed sub-clauses in MT 46.4 on compliance of the formulation with the limit for PTZ-desthio after storage as well. Considerung the thermal stability of prothioconazole, PZ-desthio is not expected to increase in storage.

  BCS responded that the understanding of the Meeting was correct assuming that properly formulated products are packaged and stored with suitable measures and packaging protecting from light. However BCS explained that even if light is the main contributor for formation of PTZ-desthio, other ways of formation may contribute as well. As FAO specifications are the international reference for equivalence material assessment for quality control after storage or handling, PTZ-desthio should be controlled also after storage. Measuring the PTZ-desthio content after accelerated storage shall efficiently reveal suboptimum quality so the sub-clause for the relevant impurity after storage should be kept.

  The Meeting noted that this is a kind of borderline case: the criterion for including a relevant impurity after storage - that it may be formed under storage conditions - is only partially met, but when the whole procedure for MT 46.4 is considered, the inclusion of the subclause for compliance for PTZ-desthio after accelerated storage was deemed justified. For this reason, the footnotes in the accelerated storage test were somewhat amended with a cautionary sentence that samples of the formulation taken before and after the storage stability test should be protected from light and kept with minimal headspace volume during handling and storage, and the time to analysis after sampling from the sealed container should be kept to a minimum.

Suspension concentrate for seed treatment (FS)

- Dilution rate and applicability of the suspensibility and persistent foam clauses: The formulation is intended to be used with minimal dilution. The minimal dilution (e.g. 50 % concentration) is out of the scope of the test to determine suspensibility (MT 184.1) which is approximately 10 %. For that reason, the suspensibility clause was removed.
- Adhesion to seed (FS): The proposed limit for adhesion to rapeseed was 90 %, a value that was considered as very low by the Meeting. Even though for the moment no general limits are given in the Manual, experience of last years with a number of FS formulations has shown that typical adhesion/seed retention values are around 95 % or higher. The Meeting challenged the 90 % on rape seed - in morphological terms these seeds are not more difficult to coat than cereal seed like maize. The company then proposed a higher value (95 %) that was accepted by the Meeting.
- As other FS formulations, some prothioconazole FS formulations seem to be sensitive to higher temperatures. These formulations tend to show an increase in viscosity under the conditions of the accelerated storage test. The proposed conditions in accelerated storage were a combination of 35 °C and duration of 12 weeks. This extended duration is expected to cause problems in quality control would need and to be carefully justified. The studies on two existing prothioconazole FS formulations that had been exposed to 54 °C for two weeks however show, that with exception of the pourability, which is slightly above 5 %, all other parameters are within acceptable ranges and limits. The Meeting therefore suggested to specify the standard 54 °C and 2 weeks conditions for accelerated storage and to accept somewhat higher residue in the pourability test (7 %) as a trade-in. The company agreed to set 54 °C and 2 weeks conditions for accelerated storage and the higher residue in the pourability test.

The Meeting considered the responses provided by BCS and concluded, that all open points had been satisfactorily addressed and recommended, that the specifications and evaluation for prothioconazole proposed by Bayer AG, Division Crop Science should be adopted by FAO.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 745/2020

USES

Prothioconazole is a systemic fungicide of the chemical class of triazolinethione for seed treatment and foliar application in cereals and many other arable crops. As a de-methylation-inhibitor (DMI), the mode of action is based on the inhibition of the demethylation of lanosterol at position 14- or 24-methylene dihydrolanosterol and it belongs to the FRAC code group 3. It provides excellent control of all relevant cereal pathogens, including stem base and ear diseases (eg. *Oculimacula yallundae/acuformis or Fusarium spp.*), as well foliar diseases(eg. *Mycosphaerella graminicola, Blumeria graminis, Puccinia recondite*) and possesses protective, curative and eradicative activity [2] [3].

IDENTITY OF THE ACTIVE INGREDIENT

ISO common name prothioconazole (ISO 1750, accepted)

Chemical name(s)

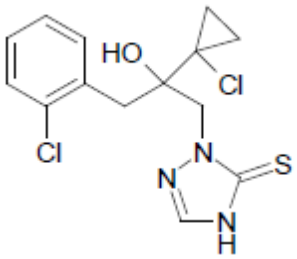
IUPAC (RS)-2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-1,2,4-triazole-3-thione

CA 3H-1,2,4-Triazole-3-thione, 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro- (9CI, ACI)

Synonyms

PTZ, JAU 6476

Structural formula



Racemate (50:50)

Molecular formula

$C_{14}H_{15}Cl_2N_3OS$

Relative molecular mass

344.26

CAS Registry number

178928-70-6

CIPAC number

745

[2] Dutzmann, S., and A. Suty-Heinze. "Prothioconazole: a broad spectrum demethylation-inhibitor (DMI) for arable crops." Pflanzenschutz-Nachrichten Bayer 57.2 (2004): 249-264.

[3] Kuck, Karl-Heinz, Klaus Stenzel, and Jean-Pierre Vors. "Sterol biosynthesis inhibitors." Modern crop protection compounds 1 (2012): 761-805.

Table 1. Physico-chemical properties of pure prothioconazole

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	7.4×10^{-10} Pa at 20 °C (extrapolated) 1.8×10^{-9} Pa at 25 °C (extrapolated]) 1.1×10^{-7} Pa at 50 °C (extrapolated)	99.8	OECD 104 EC method A 4	M-498988-01-1
Melting point.	140.3°C	99.8	OECD 102 EC method A 1 (DSC)	M-491727-01-1
Temperature of decomposition	220 – 395 °C exothermic effect	99.8	OECD 113	M-491727-01-1
Solubility in water	0.0022 g/l at 20°C pH 4 buffer 0.0225 g/l at 20°C pH 7 buffer 1.24 g/l at 20°C pH 9 buffer	99.8	OECD 105 EC method A 6 (column elution method and flask method)	M-503425-01-1
Octanol/water partition coefficient	log P_{OW} = 3.4 at 25°C at pH 4 log P_{OW} = 2.0 at 25°C at pH 7 log P_{OW} = 0.2 at 25°C at pH 9	99.8	OECD 117 EC method A 8 (HPLC method)	M-492539-01-1
Hydrolysis characteristics	Half-life[4] = > 1 year at 50 °C at pH 7 and 9 120 days at 50 °C at pH 4 > 1 year at 25 °C at pH 9, 7 and 4 Stable with respect to hydrolysis under environmental conditions.	radio-chemical purity: >99 chemical purity: >98	EEC C7; SETAC-Europe Procedures, 1995; US EPA, Subdivision N, 161-1	M-005117-01-1

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Aquatic photolysis characteristics	**Quantum yields** Φ of 0.0638 (pH 4) and 0.0047 (pH 9) were calculated. Environmental direct photolysis half-lives were in the range: - 50 to > 200 days at pH 4 and - 7 to 20 days at pH 9 for the periods of main use.	99.9	German UBA, 1992	M-051279-01-1
Aquatic photolysis characteristics	**Photolysis in sterile aqueous buffer**: experimental half-lives: phenyl label: 44.3 hours triazol label: 51.4 hours mean: 47.7 hours predicted environmental half-life Phoenix AZ in June: 7.1 days Athens in June: 11 days <u>Indirect photochemical degradation:</u> No study has been performed and is not required	radio-chemical purity: >99 chemical purity: >98	US EPA 162-1, 1982 SETAC, 1995	M-064326-01-1
Dissociation characteristics	pK_a = 6.8	99.8	OECD 112	M-498202-01-1
Solubility in organic solvents	132 g/l Methanol at 20°C 0.027 g/l Heptane at 20°C 10 g/l Toluene at 20°C 89 g/l Dichloromethane at 20°C >280 g/l Acetone at 20°C 215 g/l Ethyl acetate at 20°C 208 g/l Dimethyl sulfoxide at 20°C	99.8[5]	OECD 105 EC method A 6 (flask method and HPLC method)	M-503064-01-1

Table 2. Chemical composition and properties of prothioconazole technical materials (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances at the three production sites ranged from 981.6 to 996.6 g/kg with no unknowns detected.
Declared minimum prothioconazole content	970 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	none
Relevant impurities **<** 1 g/kg and maximum limits for them:	Prothioconazole-desthio (PTZ-desthio): (CAS name: 1H-1,2,4-Triazole-1-ethanol, α-(1-chlorocyclopropyl)-α-[(2-chlorophenyl)methyl]-, (+/-)) [120983-64-4]. 0.5 g/kg max
Stabilisers or other additives and maximum limits for them:	none

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC	137.3 °C	97.9	OECD Guideline 102	M-525909-01-1
Solubility in organic solvents	See Table 1			

FORMULATIONS

The main formulation types available are EC, SC and FS. Prothioconazole is mainly co-formulated with e.g. clothianidin, bixafen, fludioxonil, fluopyram, fluoxastrobin, imidacloprid, metalaxyl, pencycuron, penflufen, proquinazid, spiroxamine, tebuconazole and trifloxystrobin.

These formulations are registered and sold in many countries throughout the world.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) is CIPAC 745/M, published in Handbook P. Prothioconazole is determined by HPLC, using UV detection at 254 nm and external standardisation.

The method(s) for determination of impurities is based on HPLC, using UV detection and external standardisation.

The method for determination of the relevant impurity (PTZ-desthio) is based on HPLC with MS/MS detection. This method will was presented at the CIPAC 2020 Annual Meeting, adopted and available as download from www.cipac.org.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD and EC, while those for the formulations were CIPAC, as indicated in the specifications.

PHYSICAL PROPERTIES

The physical properties of the SC, EC, FS and EC formulations, the test methods and specification limits proposed, comply with the requirements of the Manual (FAO/WHO Manual 2016, 3rd revision of the 1st edition)

CONTAINERS AND PACKAGING

Do not use translucent packaging. Products are light-sensitive.

EXPRESSION OF ACTIVE INGREDIENT

The active ingredient is expressed as prothioconazole in g/kg or g/l at 20 ± 2ºC.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer confirmed that the toxicological data included in the summary below were derived from prothioconazole 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.

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

Species	**Test**	**Purity % Note6**	**Guideline, duration, doses and conditions**	**Result**	**Study number**
Acute toxicity studies					
Rat M F	acute oral toxicity	99.8	**Guideline:** OECD Guideline 423 (1996) Dose(s) of test item: = 6200 mg/kg bw Animals were observed for 14 days prior to necropsy.	LD_{50} >6200 mg/kg bw	M-012312-01-1
Rat M F	acute dermal toxicity	98.8	**Guideline:** OECD Guideline 402 (1987) Dose(s) of test item: 2000 mg/kg bw The test substance was applied to shorn skin for 24 hours under a semi-occlusive dressing	LD_{50} >2000 mg/kg bw	M-009688-01-1
Rat M F	acute inhalation toxicity	98.8	**Guideline:** OECD Guideline No. 403 4-hour nose-only exposure, dynamic exposure conditions, -week observation period	LC_{50} > 4990 mg/m^3	M-008846-01-1

6 Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Species	Test	Purity % Note6	Guideline, duration, doses and conditions	Result	Study number
Rabbit M	acute skin irritation	99.8	**Guideline:** EC guideline B.4. and OECD guideline 404 Dose(s) of test item: 500 mg of JAU 6476/patch and animal, once epicutaneous 4-hour exposure, examination time-points 60 min, 24, 48 and 72 hours after patch removal	No irritation recorded	M-009890-02-1
Rabbit M	acute eye irritation	99.8	**Guideline:** EC guideline B.5. and OECD guideline 405 Dose(s) of test item: single application of 100 mg JAU 6476 per animal into the conjunctival sac.	Minimal irritation recorded	M-009893-02-1
Guinea pig M	skin sensitisation M&K method	99.8	**Guideline:** OECD Guideline No. 406, EC Guideline 92/69, Method B.6., Pesticide Assessment Guidelines, §81-6 Concentration(s) of test item: 5% (intradermal induction), 25% (topical induction), 15% (challenge) Exposure period: 45h	Negative	M-009898-03-1

Species	Test	Purity % Note6	Guideline, duration, doses and conditions	Result	Study number
Mouse F	skin sensitisation LLNA	97.2	**Guideline:** OECD Guideline No. 406, Section 4, No. 429, EC Guideline 96/54/EC, Method B.6, Health Effects Test Guidelines, OPPTS 870.2600 Dose(s) of test item: 0 (vehicle control), 2, 10 and 50%.	Negative	M-291490-01-1
BALB/c 3T3 cells	In vitro 3T3 NRU phototoxicity test	96.7	**Guideline:** EC No. 440/2008 B 41 CPMP Note for Guidance on Photosafety testing, EMEA, CPMP/SWP/398/01, OECD Guideline 432 Dose(s) of test item: 1.95, 3.91, 7.81, 15.63, 31.25, 62.5, 125, 250 µg/mL, Irradiation: artificial sunlight for 50 minutes with 1.65 mW/cm2 UVA	Not phototoxic	M-498655-01-1

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

Species	Test	Purity % Note7	Guideline, duration, doses and conditions	Result	Study number
Short-term studies					
Rat, M F	subacute oral toxicity (feeding study)	99.5	**Guideline:** Directive 67/548/EE, Method B 7 (1992); OECD 407(1995) **Dose(s) of test item**: 0, 196, 1480 and 9250 ppm **Duration**: 4 weeks	**NOAEL** = 1480 ppm [146 mg/kg/d (m)] [151 mg/kg/d (f)] **LOAEL** = 9250 ppm [952 mg/kg/d (m)] [1033 mg/kg/d (f)]	M-012338-01-1
Rat M F	subacute dermal toxicity	98.5	**Guideline:** OECD 410 (1981); Directive 92/69/EEC, Annex V, Part B.9 (1992); USA-EPA 712-C-98-201, OPPTS 870.3200 (1998) **Dose(s) of test item**: 0, 100, 300 and 1000 mg/kg/d **Duration**: 4 weeks	**NOAEL** = 1000 mg/kg/d	M-044301-01-1
Rat M F	subchronic toxicity (administration by gavage)	97.6	**Guideline:** OECD 453 (1981); Directive 88/302/EEC (1987); US-EPA FIFRA §83.5 (1984); JMAFF (1985) **Dose(s) of test item**: 0, 20, 100 and 500 mg/kg bw/d **Duration**: Administration by gavage over 14 weeks, subsequent recovery period of 4 weeks	**NOAEL** = 100 mg/kg bw/d **LOAEL** = 500 mg/kg bw/d	M-011757-01-1

7 Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Species	Test	Purity % Note7	Guideline, duration, doses and conditions	Result	Study number
Mouse M F	dose range-finding study (administration by gavage)	97.6	**Guideline:** US-EPA Series 82-1; OECD 408 (1981); Directive 88/302/ EEC, Annex V, Part B (1987); JMAFF 59 Nohsan No. 4200 (1985) **Dose(s) of test item**: 0, 25, 100 and 400 mg/kg/d **Duration**: 14 weeks	**NOAEL** = 25 mg/kg/d **LOAEL** = 100 mg/kg bw/d	M-012244-01-1
Dog M F	subchronic oral study (administration by gavage)	98.1-98.8	**Guideline:** US-EPA-FIFRA Guideline 82-1 (1984); US-EPA OPPTS 870.3150 (1998); OECD 409 (1981); JMAFF 59 NohSanNo. 4200 (1985); US-FDA Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (1982) **Dose(s) of test item**: 0, 25, 100 and 300 mg/kg/d **Duration**: 13 weeks	**NOAEL** = 25 mg/kg/d **LOAEL** = 100 mg/kg bw/d	M-035825-01-1

Species	Test	Purity % Note7	Guideline, duration, doses and conditions	Result	Study number
Long-term and carcinogenicity studies					
Dog M F	chronic oral study (administration by gavage)	98.1-98.8	**Guideline:** US-EPA-FIFRA Guideline 83-1 (1984); US-EPA-TSCA, 40 CFR Section 798.3260 (1989); OECD 452 (1981) JMAFF 59 NohSan No. 4200 (1985); US-EPA-OPPTS OPPTS 870.4100 (1998). US-FDA Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food, Appendix TI Guidelines For Toxicological Testing (1982); Health Canada PMRA DACO 4.4.5 **Dose(s) of test item**: 0, 5, 40 and 125 mg/kg/d **Duration**: 1 year	**NOAEL** = 5 mg/kg/d **LOAEL** = 40 mg/kg bw/d	M-035967-01-1
Rat M F	chronic toxicity (administration by gavage)	98.8-99.4	**Guideline:** OECD 452 (1981); Directive 88/302/EEC (1987); US-EPA 712-C-98-210, OPPTS 870.4100 (1998); JMAFF (1985) **Dose(s) of test item**: 0, 5, 50 and 750 mg/kg bw/d **Duration**: 1 year	**NOAEL** = 50 mg/kg bw/d **LOAEL** = 750 mg/kg bw/d	M-030441-01-1

Species	Test	Purity % Note7	Guideline, duration, doses and conditions	Result	Study number
Rat M F	study on carcinogenicity (administration by gavage)	98.5-99.1	**Guideline:** OECD 451 (1981), Directive 88/302/EEC (1987), US-EPA OPPTS 870.4200 (1998), JMAFF (1985) **Dose(s) of test item**: 0, 5, 50 and 750/500 (m) / 750/625 (f) mg/kg bw/d **Test duration**: 2 years	**NOAEL** = 5 mg/kg bw/d **LOAEL** = 50 mg/kg bw/d	M-084962-01-1
Mouse M F	Oncogenicity Study in CD-1-Mice (administration by gavage)	98.2-98.8%	**Guideline:** OECD 451 (1981), Directive 88/302/EEC (1987), US-EPA OPPTS 870.4200 (1998); JMAFF (1985) **Dose(s) of test item**: 0, 10, 70 and 500 mg/kg body weight/day **Duration**: 557 days (80 weeks).	**$NOAEL_{carcinogenic\ potential}$** 500 mg/kg bw/d **NOAEL**=10 mg/kg bw/d **LOAEL** = 70 mg/kg bw/d	M-085068-01-1

Species	Test	Purity % Note7	Guideline, duration, doses and conditions	Result	Study number
Reproductive- & developmental toxicity studies					
Rats	Reproductive toxicity study (Pilot study; administration by gavage)	98.1-98.8	**Guideline:** US EPA FIFRA Guideline 83-4. US-EPA-TSCA 40 CFR Section 798.4700, 87/302/EEC, OECD 416 (1983), JMAFF 4200 (1985) **Dose(s) of test item**: 0, 10, 100, 250 and 500 mg/kg bw/d	**NOAEL:** Parental toxicity: 250 mg/kg bw/d Offspring: 250 mg/kg bw/d Reproductive effects: 500 mg/kg bw/d **LOAEL:** Parental toxicity: 500 mg/kg bw/d Offspring: 500 mg/kg bw/d Reproductive effects: >500 mg/kg bw/d	M-018760-01-1

Species	Test	Purity % Note7	Guideline, duration, doses and conditions	Result	Study number
Rats	two-generation reproductive toxicity study (administration by gavage)	98.1-98.8	**Guideline:** OPPTS Guideline No. 870.3800, OECD Guideline No. 416, PMRA DACO No. 4.5.1, JMAFF Guideline 59 NohSan No. 4200 **Dose(s) of test item**: 0, 10, 100 and 750 mg/kg bw/d **Duration**: 2 generations	**NOAEL:** Parental toxicity: 10 mg/kg bw/d Offspring: 100 mg/kg bw/d Reproductive effects: 100 mg/kg bw/d **LOAEL:** Parental toxicity: 100 mg/kg bw/d Offspring: 750 mg/kg bw/d Reproductive effects: 750 mg/kg bw/d	M-036206-01-1

Species	Test	Purity % Note7	Guideline, duration, doses and conditions	Result	Study number
Rat	developmental toxicity (administration by gavage)	99.5–99.8	**Guideline:** OECD 414 (1981); US-EPA Series 83-3, (1984); JMAFF (1984); US-EPA 712-C-96-207, OPPTS 870.3700 (1996); Directive 88/302/EEC (1988) **Dose(s) of test item**: 0, 80, 500 and 1000 mg/kg bw/d **Treatment**: gestation days 6-19	**NOAEL:** Maternal toxicity: 80 mg/kg bw/d Feto- and developmental toxicity: 80 mg/kg bw/d[8] **LOAEL:** Maternal toxicity: 500 mg/kg bw/d Feto- and developmental toxicity: 500 mg/kg bw/d	M-012279-01-1
Rat	Developmental toxicity (administration by gavage)	97.8-98.7%	**Guideline:** OPPTS 870.3700; OECD 414 (2001); Health Canada PMRA DACO 4.5.2; JMAFF 12-Nousan no. 8147; Guideline 88/302/EEC **Dose(s) of test item**: 0, 20, 80, or 750 mg kg bw/day **Treatment**: gestation days 6-19	**NOAEL:** Maternal toxicity: 80.0 mg/kg bw/d Developmental toxicity: 80.0 mg/kg bw/d **LOAEL:** Maternal toxicity: 750.0 mg/kg bw/d Developmental toxicity: 750.0 mg/kg bw/d	M-067839-01-1

8 conservative

Species	Test	Purity % Note7	Guideline, duration, doses and conditions	Result	Study number
Rabbit F	Developmental toxicity (administration by gavage)	99.5 - 99.7%	**Guideline:** OECD 414 (1981), Directive 67/548/EEC (1987), EPA Health Effects Test Guidelines - OPPTS870.3700, EPA 712-C-96-207 (1997) **Dose(s) of test item**: 10, 30, 80 or 350 mg/kg body weight. **Treatment**: gestation days 6-27	**NOAEL:** Maternal toxicity: 80 mg/kg bw/d Feto- and developmental toxicity: 80 mg/kg bw/d Prothioconazole did not reveal any teratogenic potential up to and including 350 mg/kg body weight/day.	M-012237-01-1

Species	Test	Purity % Note7	Guideline, duration, doses and conditions	Result	Study number
Neurotoxicity studies					
Rat M F	acute neurotoxicity screening (oral administration)	97.6%-98.8%	**Guideline:** U.S. EPA OPPTS 870.6200 guideline (1998), **Dose(s) of test item**: 0 (vehicle), 200, 750 and 2000 mg/kg **Duration**: 17 days	**$NOEL_{clinical\ signs}$:** M: 200 mg/kg F: 200 mg/kg **$NOEL_{decreased\ (loco)motor\ activity}$:** M: 200 mg/kg F: 750 mg/kg	M-023861-01-1
Rat M F	subchronic neurotoxicity screening (administration by gavage)	97.6-98.8%	**Guideline:** US-EPA 540/09-91-123, PB 91-154617, OPPTS 870.6200 **Dose(s) of test item**: 0, 98, 505 and 1030 mg/kg/day **Duration**: 13 weeks	**$NOEL_{clinical\ signs}$:** M: 100 mg/kg/day F: 100 mg/kg/day	M-053225-01-1

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

Species	**Test**	**Purity % Note9**	**Guideline, duration, doses and conditions**	**Result**	**Study number**
			***In vitro* studies**		
S. typhimurium strains (TA1535, TA100, TA1537, TA98, TA102)	Bacterial point mutation assay (Ames test)	99.5	**Guideline:** OECD 471 (1983), EEC Directive 92/69/EEC B.14, US-EPA PB 84-233295 (1984) Plate incorporation assay: 16 - 5000 µg /plate (±S9) Pre-incubation assay: 1.6 - 500 µg/tube (±S9)	**Negative**	M-012254-01-1
In vitro (HPRT locus, V79 CHL cells)	Mammalian cell gene mutation assay	99.8	**Guideline:** OECD 476 (1984); EEC Directive 88/302/EEC; US-EPA OPPTS 870.5300 (1996) 1st gene mutation assay: 25 - 175 µg/ml (-S9) 75 - 200 µg/ml (+S9) 2nd gene mutation assay: 5 - 150 µg/ml (-S9) 75 - 200 µg/ml (+S9)	**Negative**	M-012273-01-1

9 Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Species	Test	Purity % Note9	Guideline, duration, doses and conditions	Result	Study number
Rat	Rat liver UDS assay *in vitro*	99.7	**Guideline:** EEC Directive 88/302/EEC; OECD 482 (1986); US-EPA712-C-96-230, OPPTS 870.5550 (1996) 1st UDS assay: 1.0 – 40.0 µg/ml 2nd UDS assay: 0.5 - 20.0 µg/ml	**Equivocal**	M-012317-01-1
In vitro (V79 CHL cells)	Mammalian chromosomal aberration assay	99.8-99.9	**Guideline:** OECD 473 (1983); EEC Directive 92/69/EEC B.10.; US-EPA "In vitro mammalian cytogenetics" (1986) 1st chromosome aberration assay: 18 h harvest: 25 - 150 µg/ml (±S9) 30 h harvest: 75 - 150 µg/ml (±S9) 2nd chromosome aberration assay: 8 h harvest time: 75 - 150 µg/ml (±S9) 18 h harvest time: 50 - 100 µg/ml (-S9)	**Positive**	M-012277-01-1

Species	Test	Purity % Note9	Guideline, duration, doses and conditions	Result	Study number
in vitro (human lymphocytes)	Micronucleus test	97.6	**Guideline:** OECD 487 (2016) 1st micronucleus assay (4 h exposure): 30.1, 52.7, 119 µg/ml (-S9) 30.1, 52.7, 79 µg/ml (+S9) 2nd micronucleus assay (20 h exposure): 43,4, 57.8, 69.9 µg/ml (-S9)	**Negative**	M-588628-01-1
***In vivo* studies**					
Rat M	Rat liver UDS assay *in vivo*	99.5 and 99.7	**Guideline:** OECD 486 (1997) 2500, 5000 mg/kg bw (oral gavage)	**Negative**	M-007155-01-1
Mouse M F	Micronucleus assay *(In vivo* mouse bone marrow)	99.9	**Guideline:** OECD 474 (1983), EEC Directive 92/69/EEC B.12, US-EPA OPPTS 870.5395 (1996) 250 mg/kg bw (i.p.)	**Negative** (PCE/NCE ratio not altered)	M-012265-01-1
Mouse M	Micronucleus assay (I*n vivo* mouse bone marrow)	95.7	**Guideline:** OECD 474 (1997), Commission Directive 2000/32/EC B-12 (2000); US-EPA712-C-98-226, OPPTS 870.5395 (1988) 2 x 50, 2 x 100, 2 x 200 mg/kg bw (i.p.)	**Negative** (PCE/NCE ratio altered)	M-102790-01-1

Table 6. Ecotoxicology profile of prothioconazole technical material

Species	**Test**	**Purity % Note10**	**Guideline, duration, doses and conditions**	**Result**	**Study number**
Daphnia magna (water flea)	48h acute toxicity test under static conditions	98.4%	Based on OECD 202, EPA 72-2, GLP-study without reported deviations. In a static test system young *Daphnia magna* were exposed for 48 h to nominal concentrations of 0, 0.56, 1.0, 1.8, 3.2, 5.6 and 10 mg AI/L.	EC_{50} (24h) = 2.5mg/l EC_{50} (48h) = 1.3mg/l LOEC (24h) = 1.8 mg/l LOEC (48h) = 1.8 mg/l NOEC (24h) = 1.0 mg/l NOEC (48h) = 1.0 mg/l	M-013690-01-1
Daphnia magna (water flea)	21d reproductive toxicity test in a static renewal test system	98.8%	Based on OECD 211, EPA 72-4, GLP-study with reported deviations. Young *Daphnia magna* were exposed in a static renewal test system (renewal of test solution 3 times a week) to nominal concentrations of control, 0.56, 1.0, 1.8, 3.2, 5.6, 10.0, and 18.0 mg AS/L. Endpoints recorded were mortality, reproduction and body length of the parent animals at the end of the test.	Inhibition of reproduction: EC_{10} (21d) = 0.61 mg a.s./L EC_{20} (21d) = 1.09 mg a.s./L NOEC = 0.56 mg/L.	M-055997-01-1 and M-625860-02-1

10 Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
Chironomus riparius	28d developmental toxicity test in a water-sediment system under static conditions	98.6%	Based on proposal for a new OECD Guideline 219 (2000) and BBA proposal "Effects of PPPs on development of sediment-dwelling larvae of Chironomus riparius" (1995), GLP study without deviations. Larvae of Chironomus riparius were exposed for 28 days in a static test system to concentrations of 1.14, 2.29, 4.57, 9.14, 18.3, 36.6 and 57.1 mg a.i./L (nominal) in a water-sediment system (spiked water).	Emergence rate: NOEC: 9.14mg a.i./L LOEC: >9.14 mg a.i./L Development rate: NOEC: 9.14mg a.i./L LOEC: >9.14 mg a.i./L	M-047356-01-1
Mysidopsis bahia (saltwater mysid)	96h acute toxicity test under flow-through conditions	98.4%	Based on EPA 850, OPPTS Number 850.1035, GLP study without reported deviations, Mysidopsis bahia were exposed to nominal test concentrations of 0.25 mg a.i./L, 0.50 mg a.i./L, 1.0 mg a.i./L, 2.0 mg a.i./L, 4.0 mg a.i./L, neg. control and solvent control.	96h LC_{50}: 2.4 mg a.i./L NOEC: 0.99 mg a.i./L	M-083057-01-1
Crassostrea virginica (eastern oyster)	96h acute toxicity (shell deposition) test under flow-through conditions	98.4%	Based on EPA 850, OPPTS Number 850.1025 and ASTM Standard E729-88a, GLP study without deviation. Nominal test concentrations were 0.31, 0.63, 1.3, 2.5 and 5.0 mg a.i./L.	96h EC_{50}: 2.9 mg a.i./L NOEC: 0.76 mg a.i./L	M-055051-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
Oncorhynchus mykiss (Rainbow trout)	96h acute toxicity test under static conditions	98.4%	Based on EG C.I, EPA § 72-1, OECD 203, GLP-study without deviations reported. In a static test system *Oncorhynchus mykiss* were exposed for 96 h to nominal concentrations of 1.17 (0.99), 1.94 (1.70), 3.24 (3.08), 5.40 (5.26) and 9.00 (8.02) mg test substance (a.i.)/l.	LC_{50} (96h) = 1.83 mg/l LOEC (96h) = 1.70 mg/l NOEC (96h) = 0.99 mg/l	M-015215-01-1
Lepomis macrochirus (Bluegill sunfish)	96h acute toxicity test under static conditions	98.4%	Based on EG C.I, EPA § 72-1, OECD 203, GLP-study without deviations reported. In a static test system *Lepomis macrochirus* were exposed for 96 h to nominal concentrations of 1.94 (1.69), 3.24 (2.81), 5.40 (4.81), 9.00 (6.65) and 15.0 (8.88) mg test substance (a.i.)/l.	LC_{50} (96h) = 4.59 mg/l LOEC (96h) = 2.81 mg/l NOEC (96h) = 1.69 mg/l	M-020269-01-1
Cyprinus carpio (Common Carp)	96h acute toxicity test under static conditions	98.6%	Based on EG C.I, OECD 203, GLP-study without deviations reported.In a static test system *Cyprinus carpio* were exposed for 96 h to nominal concentrations of 1.00,2.00,4.00, 8.00 and 16.0 mg test substance (a.i.)/l	LC_{50} (48h) = 8.00 mg/l LC_{50} (96h) = 6.91 mg/l LOEC (48h) = 2.00 mg/l LOEC (96h) = 2.00 mg/l NOEC (48h) = 1.00 mg/l	M-037387-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
				NOEC (96h) = 1.00 mg/l	
Cyprinodon variegatus (Sheepshead Minnow)	96h acute toxicity test under static-renewal conditions	97.8%	Based on EPA-FIFRA 72-3a, GLP study without reported deviations. Fish were exposed to the following nominal (measured concentrations): control (<0.075), solvent control (<0.075), 0.75 (0.69), 1.5 (1.34), 3.0 (2.51), 6.0 (5.42), and 12.0 (10.3) mg a.i./L.	LC_{50} (96h) = >10.3 mg a.i./L LOEC (96h) = >10.3 mg a.i./L NOEC (96h) = >10.3 mg a.i./L	M-107721-01-1
Oncorhynchus mykiss (Rainbow trout)	91d Early Life Stage Toxicity test under flow-through conditions	98.3%	Based on EPA-FIFRA Guideline 72-4, OPPTS Guideline 850.1400 (draft), OECD Guideline 210, GLP study with no reported deviations. Freshly fertilized rainbow trout (Oncorhynchus mykiss) eggs were exposed to concentrations (mean measured) of control (<0.005), solvent control (<0.005), 0.0625 (0.052), 0.125 (0.107), 0.25 (0.22), 0.50 (0.49) and 1.00 (0.94) mg a.i./L.	NOEC $_{\text{Fry Survival}}$ 0.49 mg a.i./L LOEC $_{\text{Fry Survival}}$ 0.94 mg a.i./L NOEC $_{\text{Percent Hatch}}$ 0.94 mg a.i./L LOEC $_{\text{Percent Hatch}}$ > 0.94 mg a.i./L NOEC $_{\text{Time to Hatch}}$ 0.94 mg a.i./L LOEC $_{\text{Time to Hatch}}$ > 0.94 mg a.i./L NOEC $_{\text{Time to Swim-up}}$ 0.49 mg a.i./L LOEC $_{\text{Time to Swim-up}}$ 0.94 mg a.i./L NOEC $_{\text{Growth/Length}}$ 0.94 mg a.i./L LOEC $_{\text{Growth/Length}}$ > 0.94 mg a.i./L NOEC $_{\text{Growth/Dry Weight}}$ 0.94 mg a.i./L LOEC $_{\text{Growth/Dry Weight}}$ > 0.94 mg a.i./L NOEC $_{\text{Morphological \& Behavioral Effects:}}$ 0.49 mg a.i./L LOEC $_{\text{Morphological \& Behavioral Effects:}}$ 0.94 mg a.i./L	M-291414-01-1

<table>
<tr><th>Species</th><th>Test</th><th>Purity % Note10</th><th>Guideline, duration, doses and conditions</th><th>Result</th><th>Study number</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Maximum Acceptable Toxicant:
Concentration (MATC): 0.68 mg a.i./L
(based on fry survival, swim-up and morphological / behavioral effects)</td><td></td></tr>
<tr><td>Lepomis macrochirus
(Bluegill sunfish)</td><td>Bioconcentration and Biotransformation under flow-through Conditions</td><td>98.0%</td><td>Based on OECD 305, EPA-FIFRA § 72-6, EPA-FIFRA § 165-4, GLP study without reported deviations. Lepomis macrochirus, with a mean body weight of 3.3 g and a mean body length of 6.2 cm) were exposed to two treatment levels (5 µg and 50 µg [14C]- JAU 6476/L , one control) for 28 days for bioconcentration; For a period of 7 and 14 days 30 fish were exposed additionally in order to investigate the biotransformation of JAU 6476 (one treatment group) in fish and water.</td><td>Residue bioconcentration factor of about 43.9 to 57.8 X for whole fish (sum of all radiolabelled compounds, JAU 6476 parent, metabolites and mineralization products).
Residues depuration: half-life of 0.47 - 0.80 days, after 14 days in uncontaminated water 91 % (5 ug/L) and 95 % (50 ug/L),
<table>
<tr><th>Parameter</th><th colspan="2">5µg/L</th><th colspan="2">50µg/L</th></tr>
<tr><td></td><td>Edible part</td><td>Whole fish</td><td>Edible part</td><td>Whole fish</td></tr>
<tr><td>BCF_{trr}</td><td>19.1</td><td>57.8</td><td>15.1</td><td>43.9</td></tr>
<tr><td>T (1/2) for clearance (days)</td><td>1.1</td><td>0.80</td><td>0.42</td><td>0.47</td></tr>
<tr><td>Uptake rate const. (Ku)(1/day)</td><td>12.4 (±3.04)</td><td>50.03 (±6.44)</td><td>25.2 (±4.31)</td><td>65.2 (±6.70)</td></tr>
<tr><td>Clearance rate const. (Kd)(1/day)</td><td>0.65 (±0.00)</td><td>0.87 (±0.00)</td><td>1.67 (±0.00)</td><td>1.49 (±0.00)</td></tr>
</table></td><td>M-087902-01-1</td></tr>
<tr><td>Selenastrum capricornutum
(green alga)</td><td>96h algal growth test under static conditions</td><td>98.3%</td><td>Based on EEC Directive 79/831/E, EG C.3, OECD 201, ISO 8692, ASTM E 1218, US-EPA FIFRA § 123-2 Tier 2, GLP study with minor deviations. These deviations do not</td><td>EC_{50} = 2.18 mg/L
NOEC = 0.295 mg./L</td><td>M-027625-01-1
recalculated endpoints:</td></tr>
</table>

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
			influence the results of this study. Selenastrum capricornutum was exposed under static conditions (shake cultures) for 96 h. to nominal test concentrations of 0.10, 0.20, 0.40, 0.80, 1.60, 3.20 mg test substance/L		M-634695-01-1
Skeletonema costatum (Saltwater Diatom)	96h Growth and Reproduction test under static conditions	98.2%	Based on USEPA Guideline 123-2, Growth and Reproduction of Aquatic Plants (Tier2): GLP study without deviations. Skeletonema costatum were exposed under static conditions (shaken cultures) for approximately 96 hours to the following nominal concentrations: Control (<0.5), Solvent Control (<0.5), 3.1 (3.0), 7.7 (7.3), 19.2 (17.5), 48.0 (46.8), and 120 (117) µg a.i./L (ppb).	96h EC_{50} (cell density) = 25.6 µg a.i./L 96h EC_{50} (cumulative biomass) = 20.1 µg a.i./L 96h EC_{50} (growth rate) = 49.9 µg a.i./L 96h NOEC (cumulative biomass) = 7.3 µg a.i./L	M-000954-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
Navicula pelliculosa (Freshwater Diatom)	96h Growth and Reproduction test under static conditions	97.5%	Based on USEPA Guideline 123-2, Growth and Reproduction of Aquatic Plants (Tier2): Navicula pelliculosa were exposed under static conditions (shaken cultures) for approximately 96 hours to the following nominal concentrations (Day 0 measured): Control (<2.6), Solvent Control (<2.6), 26 (23.5), 64 (56.6), 160 (146.3), 400 (356.4) and 1000 (889.5) µg a.i./L	96h EC_{50} (cell density) = 215.0 µg a.i./L 96h EC_{50} (cumulative biomass) = 163.8 µg a.i./L 96h EC_{50} (growth rate) = 395.3 µg a.i./L	M-001064-02-1
Anabaena flos-aquae (blue-green alga)	96h Growth and Reproduction test under static conditions	98.2%	Based on USEPA Guideline 123-2, Growth and Reproduction of Aquatic Plants (Tier2): Anabaena flos-aquae were exposed under static conditions (shaken cultures) for approximately 96 hours to the following nominal concentrations (Day 0 measured): Control (<0.5), Solvent Control (<0.5), 0.02 (0.02), 0.08 (0.08), 0.27 (0.22), 0.90 (0.82), 3.00 (2.97), and 10.00 (9.12) mg a.i./L.	96h EC_{50} (cell density) = 3.71 mg a.i./L 96h EC_{50} (cumulative biomass) = 3.55 mg a.i./L 96h EC_{50} (growth rate) = 9.12 mg a.i./L 96h NOEC (cell density and growth rate) = 0.82 mg a.i./L	M-000348-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
Lemna gibba (Duckweed)	7d Growth inhibition test under static-renewal conditions	98.2%	Based on USEPA. 1996. Series 850 - Ecological Effects test Guidelines (draft), OPPTS Number 850.4400: Aquatic Plant Toxicity Test Using Lemna spp., Tiers I and II., GLP study without significant deviations.	7d EC_{50} (standing crop) = 74 ug a.i./L 7d EC_{50} (growth rate) = > 404 ug a.i./L 7d EC_{50} (cummulative biomass) =404 ug a.i./L 7d EC_{50} (frond dry weight) = 404 ug a.i./L LOEC = 10.4 ug a.i./L NOEC = 3.34 ug a.i./L	M-000532-01-1
Eisenia fetida (Earthworm)	14d acute toxicity test in artificial soil	98.3%	Based on OECD 207, "OECD-Guideline for Testing Chemicals," "Earthworm, Acute Toxicity Tests", GLP-study without deviations reported. Earthworms were exposed in an artificial soil for 14 days to the concentrations of 100, 178, 316, 562 and 1000 mg test substance / kg dry weight soil (nominal concentrations).	LC_{50} = >1000 mg/ kg dry weight soil LOEC = 1000 mg / kg dry weight soil NOEC = 562 mg / kg dry weight soil	M-031137-02-1
Folsomia candida (Collembola)		97.1%	Based on OECD 232, collembolans were exposed to control (water treated), 62.5, 125, 250, 500 and 1000 mg test item/kg artificial soil dry weight at 20 ± 2°C, 400 –800 lux, 16h light: 8h dark.	NOEC $_{Reproduction}$ = ≥1000mg a.i./kg dry soil LOEC $_{Reproduction}$ = >1000 a.i./kg dry soil	M-405273-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
Apis mellifera (honey bee)	48h acute oral- and contact toxicity	98.4%	Based on EPPO No. 170, GLP study without major deviations. Honeybees were exposed to concentration levels of 12.5 - 25 - 50 -100 -200 ug a.i. per bee for oral (feeding) and for topical (contact) application under laboratory conditions. The control was treated with tap water or tap water + detergent (oral), C02-paralysation or CO2-paralysation + acetone (contact). 605 FORTE (Parathion: 0.3833 ug a.i./bee (oral), 0.156 ug a.i./bee (contact)) was used as reference treatment.	LD_{50} [ug a.i. / bee] (48h): Oral = >71.0 Contact = >200	M-023105-01-1
Apis mellifera (honey bee)	48h acute oral- and contact toxicity (limit test) under laboratory conditions	96.7 % (w/w)	Based on OECD 213 and 214 (1998), GLP study without deviations to the guideline reported. Apis mellifera worker bees were exposed for 48 hours to a single dose of 100.0 µg a.i. per bee by topical application (contact limit test) and 50 worker bees to a single dose of 105.1 µg a.i. per bee by feeding (oral limit test, value based on the actual intake of the test item).	LD_{50} µg a.i./bee: Contact => 100.0 Oral = > 105.1 NOED µg a.i./bee: Contact = ≥ 100.0 Oral = ≥ 105.1	M-505379-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
Bombus terrestris (Bumble bee)	48h acute oral toxicity test (limit test) under laboratory conditions	96.7%	No specific guidelines available. Based on OECD Guidelines No. 213 (1998), OEPP/EPPO 170 (4) (2010), review article of Van der Steen (2001) Controls: pure 50 % (w/v) aqueous sucrose solution (C) 50 % (w/v) aqueous sucrose solution containing 5 % acetone and 0.1 % Xanthan (Csol) Test item: 214.32 µg a.s./bumble bee (actual uptake)	Oral toxicity test [µg a.s./bumble bee] LD_{50} (24h) = > 214.32 LD_{50} (48h) = > 214.32 NOED (48h) = > 214.32 Conclusion: According to the study results, the 48-hour oral LD_{50} (Lethal Dose causing 50 % mortality) was determined to be > 214.32 µg a.s./bumble bee.	M-557946-01-1
Bombus terrestris (Bumble bee)	48h acute contact toxicity test (limit test) under laboratory conditions	96.7%	No specific guidelines available. Based on OECD Guidelines No. 213 (1998), OEPP/EPPO 170 (4) (2010), review article of Van der Steen (2001) In the laboratory, the bumble bees were exposed to 100 µg Prothioconazole /bumble bee by topical application. Mortality and sub-lethal effects were assessed.	Contact toxicity test [µg a.s./bumble bee] LD_{50} (24h) = > 100 LD_{50} (48h) = > 100 NOED (48h) = > 100 Conclusion: The 48-hour contact LD_{50} value for Prothioconazole technical was determined to be > 100 µg Prothioconazole /bumble bee. The contact NOED (48 h) was determined as 100 µg Prothioconazole technical/bumble bee.	M-521802-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
Apis mellifera (honey bee)	Honey Bee larvae study, repeated exposure under laboratory conditions	96.7%	Based on OECD 239, GLP study without deviations reported. Larvae were exposed to 5 concentrations of prothioconazole tech. via the larval diet on 4 consecutive days (D3 to D6). Assessments of larval mortality were done on D4, D5, D6, D7 and D8. Additionally, other observations such as small body size or unconsumed food on D8 were noted. Pupal mortality was assessed at D15 and emergence of adults was evaluated at D22.	ED_{50} [µg a.s./larva] = >25.0 EC_{50} [mg a.s./kg food] = >159 LOEC [mg a.s./kg food] = >159 NOEC [mg a.s./kg food] = ≥159	M-615696-01-1
Soil microorganisms	Microbial Mineralization of Nitrogen in Soils	98.3%	Based on BBA Part VI1-1 (2•anido ed), ISO/DIS 1036-6, GLP study, Deviations: Following BBA recommendations of 19 Jan. 1999, 1 instead of 2 soils was used in the experiments. Silty sand soil was exposed for 28 d to concentrations of 0.27 and 2.71 mg a.i. /kg d.wt. soil. Lucerne-grass-green meal was added to the soil (5 g/kg d.wt. soil) to stimulate nitrogen transformation.	During the 28-day experiments the maximum field rate and the 10-fold overdose of JAU 6476 technical ingredient had no influence on the turnover of nitrogen in a silty sand soil amended with lucerne-grass-green meal.	M-024673-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
Soil microorganisms	Glucose Stimulated Respiration in Soils	98.3%	Based on BBA Part VI1-1 (2nd ed), ISO/DIS 1036-6, GLP study, Deviations: Following BBA recommendations of 19 Jan. 1999, 1 instead of 2 soils was used in the experiments. silty sand soil was exposed for 28 d to concentrations of 0.27 and 2.71 mg a.i./ kg d.wt. soil; glucose was added to soil samples to induce maximum respiration rate (3 g/kg d.wt. soil).	During the 28-day experiments, JAU 6476 technical ingredient had no influence on soil respiration after addition of glucose to a silty sand soil.	M-024679-01-1
Activated sludge (mixed population of different microorganisms)	Inhibition of oxygen consumption	98.4%	Commission Directive 88/302/EEC; Official Journal of the ECL 133, Part C: Biodegradability: Test for inhibition of oxygen consumption (corresponds for the most part to the test method OECD 209) Test concentrations: 1000, 1800, 3200, 5600, 10000 mg a.i./ L; Test temperature: 20 ±2°, Incubation time: 3 hours with permanent aeration	EC_{50} = 10.000 mg a.i./L	M-012578-01-1
Colinus virginianus (Bobwhite quail)	14d Acute oral toxicity test	98.4%	EPA § 71-1, MAFF-Working Document No. 7/5, Draft-OECD guideline "Avian Acute Toxicity Test – Oral Toxicity" (1992), GLP study without deviation from EPA § 71-1. Single oral administration	LD_{50} = >2000 mg a.i./kg body weight LLD = >2000 mg a.i./kg body weight LOEL = 650 mg a.i./kg body weight NOEL = 200 mg a.i./kg body weight	M-013030-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
			in gelatin capsules, treatment level (5 per sex) at 200 mg ai/kg, 650 mg ai/kg, and 2000 mg ai/kg b.w. and control		
Serinus canaria (Canary)	14d Acute oral toxicity test (limit dose test)	98.3%	Based on OPPTS 850.2100, OECD 223, GLP studies without reported deviations. Adult canaries were orally dosed based on body weight with the a.i. at a limit dose level of 2000 mg active ingredient (ai)/kg body weight. Five males and five females were tested per treatment level and observed daily for clinical symptoms for 14 days post-dose administration. Study endpoints of bird body weight and daily feed consumption were also monitored during the study period.	LD_{50} = > 2000 mg ai/kg body weight LOAEL = > 2000 mg ai/kg body weight NOAEL = 2000 mg ai/kg body weight	M-364387-01-1
Colinus virginianus (Bobwhite quail)	5d Avian Dietary Toxicity Test	98.4%	Based on U.S.EPA Pesticide Assessment Guidelines-Subdivision E, § 71-2, OECD guideline for testing of chemicals "Avian Dietary Toxicity Test (1984). GLP study without reported deviation Young Bobwhite Quails (10-day-old chicks, 10 per diet group, two	LC_{50} = >5000 mg ai/kg food LLC = >5000 mg ai/kg food LOEC = 1250 mg ai/kg food NOEC = 625 mg ai/kg food	M-054770-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
			controls) were exposed for 5 days to nominal dietary concentrations of 313, 625, 1250, 2500 and 5000 mg a.i./kg food corresponding to 299. 622, 1215, 2380 and 4983 mg measured a.i./kg food; exposure was followed by a subsequent 3-day observation period with untreated food.		
Anas platyrhynchos (mallard duck)	5d Avian Dietary Toxicity Test	98.7%	Based on U.S.EPA Pesticide Assessment Guidelines-Subdivision E, § 71-2, OECD guideline for testing of chemicals "Avian Dietary Toxicity Test (1984). GLP study without deviation. Young mallard ducks (10-day-old chicks, 10 per diet group, two controls) were exposed for 5 days to nominal dietary concentrations of 313, 625, 1250, 2500 and 5000 mg a.i./kg food corresponding to 256, 555, 1180, 2532 and 5567 mg measured a.i./kg food; exposure was followed by a subsequent 3-day observation period with untreated food.	LC_{50} = >5000 mg ai/kg food LLC = >5000 mg ai/kg food NOEC = 5000 mg ai/kg food	M-055523-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
Colinus virginianus (Bobwhite quail)	Avian reproduction toxicity study (22 weeks)	98.7%	EPA guidelines (TSCA par. 797.2130 and FIFRA Ref. No. 71-4, OPPTS Par. 850.2300), OECD Testing Guideline No. 206 (parental treatment period). GLP study without reported deviation. A.i. was administered in the daily diet to Bobwhite quails aged approx. 6 months over a period of 22 weeks. The birds were treated for 8 weeks under short-day light conditions (7 hrs). Afterwards, the lighting period was prolonged to 17 hrs light per day to induce reproductive performance (study week 11 - 22).	Based on the findings, the Lowest Observed Effect Concentration (LOEC) for parent birds, reproductive parameters and 14-day old survivors was considered to exceed 1000 mg/kg diet. The overall No Observed Effect Concentration (NOEC) was considered to be 1000 mg/kg diet.	M-042334-01-1
Anas platyrhynchos (mallard duck)	Avian reproduction toxicity study (21 weeks)	98.7%	EPA guidelines (TSCA par. 797.2130 and FIFRA Ref. No. 71-4, OPPTS Par. 850.2300), OECD Testing Guideline No. 206 (parental treatment period). GLP study without reported deviation. A.i. was administered in the daily diet to Mallard ducks aged approximately 7 months over a period of 21 weeks. The birds were treated for 8 weeks under short-day light conditions (7 hrs). Afterwards, the lighting period	Based on these findings, the Lowest Observed Effect Concentration (LOEC) for parental toxicity, reproductive parameters and 14-day old survivors was considered to be 2000 mg/kg diet. The overall No Observed Effect Concentration (NOEC) was considered to be 700 mg/kg diet.	M-035123-01-1

Species	Test	Purity % Note10	Guideline, duration, doses and conditions	Result	Study number
			was prolonged to 17 hrs light per day to induce reproductive performance (study week 11 - 21).		

Addendum: Summary of toxicological data for the relevance assessment of the impurity prothioconazole-desthio (JAU 6476-desthio / AE 1194888)

Prothioconazole-desthio is considered a relevant impurity because it shows additional and more severe toxic properties (e.g. developmental toxicity potential) compared to prothioconazole. A comprehensive toxicological study package is available for prothioconazole-desthio and an overview is presented below.

An acute oral rat toxicity study and a complete in vitro and in vivo genotoxicity data package performed with PTZ-desthio resulted in a low acute oral toxicity (LD50 > 2000 mg/kg bw [M-008355-01-1] similar to prothioconazole and non-mutagenicity in two Ames tests [M-031136-01-1], [M-588632-01-1], in an in vitro Chromosome aberration test [M-031119-01-1], a mammalian cell mutation assay [M-009104-01-1], in a vitro UDS [M-031126-01-1] and a MNT in vivo [M-031124-01-1]. PTZ-desthio has no skin or eye irritation or sensitisation potential [M-031139-01-1], [M-031139-01-1].

A (Q)SAR analysis of PTZ-desthio was conducted and revealed an additional alert for hepatotoxicity compared to prothioconazole. This was confirmed in the short-term toxicity studies performed with PTZ-desthio in rats, mice and dogs revealing the liver as common most sensitive target organ in all three species [M-008365-01-1], [M-008029-03-1], [M-026972- 01-1], [M-018496-01-1], [M-023192-02-1], [M-136735-01-1]. As in the short-term studies the liver was also the target organ in the chronic toxicity and carcinogenicity studies. In both species tested, liver weights were increased, and there were also liver histopathological changes. The test material was not carcinogenic in either of these studies [M-027339-01-1], [M-044458-02-1].

In addition, the reproductive toxicity of PTZ-desthio was assessed in several studies:
Effects on reproduction in rats comprised reduced litter size, reduced pup viability, pre-weaning growth retardation and some incidents of cleft palate [M- 036130-01-1] and[M-031146-01-2]. In the main 2-generation study, a number of P and F1 generation females exhibited dystocia correlating with the occurrence of slight to moderate liver necrosis in the P and F1 maternal livers. In both the pilot and the main study the parental NOAEL values were comparable to, or lower than, NOAEL values for reproductive and neonatal effects.

In the developmental studies the prime effects were increased incidences of cleft palate in the rat and rabbit and supernumerary 14^{th} ribs in the rat only [M-008329-01-1], [M-008334-01-1], [M-008322-01-1], [M-026431-01-1]. Where frank malformations and fully formed supernumerary 14^{th} ribs tended to occur at higher dose levels, rudimentary supernumerary 14^{th} ribs occurred at substantially lower doses and were considered indicative of a developmental toxicity in rats as they occurred in the absence of maternal toxicity in the supplementary oral study in rats [M-026445-01-1], [M-008317-01-1]. In rabbits the oral NOAEL for maternal toxicity coincided with that for fetotoxicity.

PTZ-desthio was contained in several toxicologically tested batches of prothioconazole including batches used for repeated dose and reprotoxicity studies. PTZ-desthio was contained in batch 06233/0031 at a concentration of 0.06% (i.a. short-term rat and dog, carcinogenicity mouse, two-generation study rat, developmental toxicity rat) in batch 06233/0044 at a concentration of 0.07% (chronic and carcinogenicity rat) and in batch 898 803 005 at a concentration of 0.04% (i.a. subchronic rat & mouse).

Therefore, based on the available studies the originally specified concentration limit of < 0.05 % for PTZ-desthio is justified and of no toxicological concern.

Table 3-1. Toxicology profile of the impurity prothioconazole-desthio, based on acute toxicity, irritation and sensitization

Species	Test	Purity % Note11	Guideline, duration, doses and conditions	Result	Study number
Acute toxicity studies					
Rat M F	acute oral toxicity	93.7	**Guideline:** US EPA-OPPTS guideline 870.1100, conform to OECD Guideline 401 (1987) Dose(s) of test item: = 2500, 4000, 3150, 4000 mg/kg bw Animals were observed for 14 days prior to necropsy.	LD_{50}: 2806 mg/kg (M) 2506 mg/kg (F)	M-008355-01-1
Mouse M F	Acute oral toxicity	94.7	**Guideline:** OECD 401 (1987); US-EPA Series: 81-1 (1984) **Dose(s) of test item**: = 100 – 5000 mg/kg bw Animals were observed for 14 days prior to necropsy.	LD_{50}: 2235 mg/kg (M) 3459 mg/kg (F)	M-008521-01-1
Rat M F	Acute dermal toxicity	93.7	**Guideline:** OECD 402 (1987); US-EPA Series 81-2:(1984) **Dose(s) of test item:** = 5000 mg/kg **Exposure:** 24 hrs	LD_{50}: >5000 mg/kg	M-008350-01-1
Rat M F	Acute inhalation toxicity	95.4	**Guideline:** Guideline 84/449/EC, B.2. (1984); OECD 403 (1981); US-EPA FIFRA §81-3 (1984)	LC_{50}: >5077 mg/m^3 (dust)	M-008361-01-1

11 Note: Purity of the technical material, expressed as a percentage.

Species	Test	Purity % Note11	Guideline, duration, doses and conditions	Result	Study number
			Dose(s) of test item: =256, 520, 5077 mg/m^3 **Exposure:** 4 hrs		
Rabbit M F	Skin irritation	95.4	**Guideline:** OECD Guideline 404 (1981) **Dose(s) of test item:** = 500 mg **Exposure:** 4 hrs	Not irritant	M-031139-01-1
Rabbit M F	Eye irritation	95.4	**Guideline:** OECD Guideline 405 (1981) **Dose(s) of test item:** = 45 mg **Exposure:** 24 hrs	Slightly irritating	M-031139-01-1
Guinea pig M	Skin sensitisation	94.7	**Guideline:** OECD Guideline 406 (1992) **Dose(s) of test item:** = 0.5 ml 60% conc. **Exposure:** 6 hrs at weekly intervals	Not skin sensitising	M-008358-01-1

Table 4-1. Toxicology profile of the impurity prothioconazole-desthio based on repeated administration (subacute to chronic)

Species	Test	Purity % Note12	Guideline, duration, doses and conditions	Result	Study number
Short-term studies					
Rat M F	subacute toxicity (feeding study)	93.7	**Guideline:** PMRA DACO 4.3.3, conform to OECD 407 (1981) **Dose(s) of test item**: 0, 100, 300, 1000 ppm **Duration**: 4 weeks	**NOAEL:** < 100 ppm [<11 mg/kg/d] **LOAEL:** 100 ppm [11 mg/kg/d]	M-008365-01-1
Dog M F	Sub-acute toxicity (feeding study)	94.7	**Guideline:** OECD 409 (1981) **Dose(s) of test item**: 0, 10, 100, 1000, 5000 ppm **Duration**: 6-weeks	**NOAEL:** 10 ppm [0.37 mg/kg/d] **LOAEL:** 100 ppm [3.7 mg/kg/d]	M-008029-03-1
Dog M F	Sub-chronic toxicity (feeding study)	94.3	**Guideline:** OECD 409 (1981) **Dose(s) of test item**: 0, 40, 200, 1000 ppm **Duration**: 13 weeks	**NOAEL:** 200 ppm [7.8 mg/kg/d] **LOAEL:** 1000 ppm [38 mg/kg/d]	M-026972-01-1
Mouse M F	subchronic toxicity (feeding study)	93.7	**Guideline:** OECD 408 (1981) **Dose(s) of test item**: 0, 40, 200, 1000, 5000 ppm **Duration**: 13 weeks	**NOAEL:** <40 ppm [<12 mg/kg/d] **LOAEL:** 40 ppm [12 mg/kg/d]	M-023192-02-1

12 Note: Purity of the technical material, expressed as a percentage.

Species	Test	Purity % Note12	Guideline, duration, doses and conditions	Result	Study number
Rat M F	subchronic toxicity (feeding study)	93.1	**Guideline:** OECD 408 (1981) **Dose(s) of test item**: 0, 30, 125, 500, 2000 ppm **Duration**: 14 weeks	**NOAEL:** 30 ppm [2.2 mg/kg/d] **LOAEL:** 125 ppm [9.7 mg/kg/d]	M-018496-01-1

Species	Test	Purity % Note12	Guideline, duration, doses and conditions	Result	Study number
Long-term and carcinogenicity studies					
Dog M F	Chronic toxicity (feeding study)	92.8% / 93.1%	**Guideline:** OECD 452 (1981) **Dose(s) of test item**: 0, 40, 300, 2000 ppm **Duration**: 30-week	**NOAEL:** 300 ppm [10 mg/kg/d] **LOAEL: 2000 ppm** [70 mg/kg/d]	M-136735-01-1
Mouse M F	Oncogenicity study (feeding study)	93.1	**Guideline:** OECD 452 (1981) **Dose(s) of test item**: 0, 12.5, 50 and 200 ppm **Duration**: 2 years	**NOAEL: 12.5** ppm [3.1 mg/kg/d] **LOAEL:** 50 ppm [13 mg/kg/d]	M-044458-02-1
Rat M F	Long-term toxicity and carcinogenicity (feeding study)	92.8 - 95.4 %	**Guideline:** OECD 453 (1981) **Dose(s) of test item**: 0, 20, 140, 980 ppm **Duration**: 106 weeks	**NOAEL:** 20 ppm [1.1 mg/kg/d] **LOAEL:** 140 ppm [8.0 mg/kg/d]	M-027339-01-1
Reproductive- & developmental toxicity studies					
Rat M F	Pilot reproductive toxicity (dietary)	95.5	**Guideline:** n.a. , pilot study **Dose(s) of test item**: 0, 10, 50, 1000, 1500 ppm **Duration**: 28 days pre-mating + 20 days gestation +21 days lactation	**NOAEL:** 50 ppm (M)/ 10 ppm (F) (parental) 50 ppm (reproductive) **LOAEL:** 1000 ppm (M) / 50 ppm (F) (parental) 1000 ppm (reproductive)	M-031146-01-2

Species	Test	Purity % Note12	Guideline, duration, doses and conditions	Result	Study number
Rat F	Two-generation study (feeding study)	92.8-95.6	**Guideline:** conducted in accordance with the contemporary OECD 416 (1983) **Dose(s) of test item**: 0, 40, 160, 640 ppm **Duration**: 28 days pre-mating + 20 days gestation +21 days lactation	**NOAEL:** 2.513 mg/kg/d (parental); 10 mg/kg/d (reproduction/development); 18.614 mg/kg/d (offspring)/ **LOAEL:** 10.4 mg/kg/d (parental male) 41.2[14] mg/kg/d (parental female); 41.2[14] mg/kg/d (reproduction/development); 72.615 mg/kg/d (offspring)/	M-036130-01-1
Rat F	Embryotoxicity (oral gavage)	97.4	**Guideline:** EPA OPPTS 870.3700, compliant with OECD 414 (1981) **Dose(s) of test item**: 0, 10, 30, 100 mg/kg bw/d **Duration**: 16 days gestation	**NOAEL:** 10 mg/kg bw/d (maternal)/ < 10 mg/kg bw/d (foetal) **LOAEL:** 30 mg/kg bw/d (maternal)/ 10 mg/kg bw/d (foetal)	M-026431-01-1
Rabbit F	Embryotoxicity study (oral gavage)	94.0	**Guideline:** OECD 414 (1981) **Dose(s) of test item**: 0, 2, 10, 50 mg/kg bw/day **Duration:** 18 days gestation	**NOAEL:** 2 mg/kg bw/d (maternal)/ 2 mg/kg bw/d (foetal) **LOAEL:** 10 mg/kg bw/d (maternal)/ 10 mg/kg bw/d (foetal)	M-008334-01-1

13 the overall NOAEL for parental effects was 40 ppm, equivalent to approximately **2.5** mg/kg bw/day
14 mean value of achieved dose level during pre-mating and gestation periods
15 mean achieved dose level during days 0 - 14 of lactation

Species	Test	Purity % Note12	Guideline, duration, doses and conditions	Result	Study number
Rat F	Embryotoxicity study on postnatal development (supplementary study to investigate the post-natal reversibility of supernumerary ribs) (oral gavage)	93.9	**Guideline:** n.a., mostly compliant with OECD 414 **Dose(s) of test item**: 0, 30 mg/kg bw/d **Duration**: 20 days gestation +21 days lactation +42-44 days weaining	**NOAEL:** > 30 mg/kg bw/d (maternal)/< 30 mg/kg bw/d (foetal) **LOAEL** (foetal)**:** 30 mg/kg bw/d	M-008329-01-1
Rat F	Supplementary embryotoxicity study to specify NOAEL upon study above (M-026431-01-1) (oral gavage)	94.7	**Guideline:** OECD 414 (1981) **Dose(s) of test item**: 0, 1, 3 mg/kg bw/d **Duration**: 21 days gestation	**NOAEL:** > 3 mg/kg bw/d (maternal)/ > 3 mg/kg bw/d (foetal)[16]	M-026445-01-1
Rat F	Embryotoxicity study (dermal)	93.7	**Guideline:** OECD 414 (1981) **Dose(s) of test item**: 0, 100, 300, 1000 mg/kg bw/day **Duration:** 15 days gestation	**NOAEL:** >1000 mg/kg bw/d (maternal)/ < 100 mg/kg bw/d (foetal) 300 mg/kg bw/d (teratogenicity) **LOAEL:** 100 mg/kg bw/d (foetal) 1000 mg/kg bw/d (teratogenicity)	M-008322-01-1

16 proposed value in EU renewal process of prothioconazole

Species	Test	Purity % Note12	Guideline, duration, doses and conditions	Result	Study number
Rat F	Supplementary embryotoxicity (dermal)	94.0-94.7	**Guideline:** broadly followed OECD guideline 414 (1981) **Dose(s) of test item**: 0, 10, 30 mg/kg/d **Duration**: gestation days 6-15, 6 hrs/day	**NOAEL:** >30 mg/kg/d, (maternal); > 30 mg/kg/d (foetal)	M-008317-01-1

Table 5-1. Mutagenicity profile of the impurity prothioconazole-desthio based on in vitro and in vivo tests

Species	Test	Purity % Note17	Guideline, duration, doses and conditions	Result	Study number
***In vitro* studies**					
S. typhimurium strains (TA1535, TA1537, TA98, TA100)	Bacterial point mutation assay (Ames test)	93.7	**Guideline:** OECD 471 (1983) 1st assay: 0, 8, 40, 200, 1000, 5000 µg/plate (± 30% S9 mix) 2nd assay: 0, 150, 300, 600, 1200, 2400 µg/plate (-S9 mix) / (+10 or 30% S9 mix)	**Negative**	M-031136-01-1

17 Note: Purity of the technical material, expressed as a percentage.

Species	Test	Purity % Note17	Guideline, duration, doses and conditions	Result	Study number
S. typhimurium strains (TA1535, TA1537, TA98, TA100, TA102)	Bacterial reverse mutation assay (Ames test)	98.3	**Guideline:** OECD 471 (1997) Plate incorporation assay: 0, 3, 10, 33, 100, 333, 1000, 2500, 5000 µg /plate (±S9) Pre-incubation assay: 0, 33, 100, 333, 1000, 2500, 5000 µg /tube (±S9)	**Negative**	M-588632-01-1
Chinese hamster cells, *in vitro*	Mammalian cell gene mutation assay (HPRT locus, V79 CHL cells)	92.7-93.1	**Guideline:** OECD 475 (1984); US-EPA OPPTS 870.5300 Gene mutation assay: 12.5 - 250 µg/ml (-S9) 50 - 500 µg/ml (+S9**)**	**Negative**	M-009104-01-1
Rat hepatocyte cells, *in vitro*	Rat liver UDS assay *in vitro*	93.7	**Guideline:** compliant to OECD 482 (1986) UDS assay: 5.0 - 60.0 µg/ml	**Negative**	M-031126-01-1

Species	Test	Purity % Note17	Guideline, duration, doses and conditions	Result	Study number
Chinese hamster cells, *in vitro*	Chromosome aberration assay *(ovary)*, *in vitro*	93.1	**Guideline:** OECD 473 (1983), US-EPA 'In vitro mammalian cytogenetics' (1986) Chromosome aberration assay: 8 h harvest: 125 µg/ml (±S9) 24 h harvest: 5 - 125 µg/ml (±S9) 30 h harvest: 125 µg/ml (±S9)	**Negative**	M-031119-01-1
			***In vivo* studies**		
Mouse M F *in vivo*	Bone marrow, micronucleus (intraperitoneal injection)	93.1	**Guideline:** OECD 474 (1983), 350 mg/kg Exposure: 16, 24 or 48 hrs	**Negative** not clastogenic or aneugenic	M-031124-01-1

Prothioconazole was evaluated by the

- WHO IPCS in 2009[18] and classified with a GHS classification number 5 (LD_{50} > 6200 mg/kg bw) as Class "U", i.e. "unlikely to present acute hazard in normal use"
- FAO/WHO JMPR in 2008 with the following conclusions:
    - On the basis of the results of the submitted studies of toxicity, the acute oral toxicity of prothioconazole was low and the compound did not show any mutagenic or carcinogenic potential
    - The Meeting concluded that the existing database on prothioconazole was adequate to characterize the potential hazards to foetus, infants and children.
      Prothioconazole showed effects on the reproductive system in a two-generation study in rats only at dose levels toxic to the parent animals and caused developmental toxicity only at dose levels toxic to the dams.
      The reproduction toxicity and developmental effects seen with prothioconazole are related to parental/maternal toxicity.
    - An ADI of 0.05 mg/kg bw was established for prothioconazole based on the NOAEL of 5 mg/kg bw per day, identified on the basis of gross and microscopic changes in the liver and kidneys in a 2-year study of toxicity and carcinogenicity in rats treated by gavage, and a safety factor of 100.
    - An ARfD of 0.8 mg/kg bw was established for women of childbearing age based on a NOAEL of 80 mg/kg bw per day, identified on the basis of a marginally increased incidence of supernumerary rudimentary ribs that might be attributable to a single exposure at 750 mg/kg bw per day in a study of developmental toxicity in rats, and with a safety factor of 100. The Meeting concluded that the establishment of an ARfD for the general population was not necessary on the basis of its low acute toxicity, the lack of evidence for any acute neurotoxicity and absence of any other toxicologically relevant effect that might be attributable to a single dose.

The IPCS states that since the publication of the above mentioned reference[18], "the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) has been further developed and is now being widely used for the classification and labelling of chemicals worldwide. For this revision of the classification, the WHO Hazard Classes have been aligned in an appropriate way with the GHS Acute Toxicity Hazard Categories for acute oral or dermal toxicity as the starting point for allocating pesticides to a WHO Hazard Class. As has always been the case, the classification of some pesticides has been adjusted to take account of severe hazards to health other than acute toxicity. The GHS Acute Toxicity Hazard Category for each pesticide is now presented alongside the existing information."19

18 The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2009, WHO 2010, Geneva, Switzerland
19 https://www.who.int/ipcs/publications/pesticides_hazard/en/

Hazard classification of prothioconazole according to GHS[20] is:

Name	Classification	Hazard statement Code(s)
Prothioconazole	Aquatic Acute 1; H400	Very toxic to aquatic life
	Aquatic Chronic 1; H410	Very toxic to aquatic life with long-lasting effects

20 Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355

ANNEX 2

REFERENCES

Non-confidential data (prothioconazole) - (sorted by reference number)

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-000348-01-1	Kern, M. E.; Roberts, J. A.; de Haan, R. A.	2004	Toxicity of JAU 6476 technical to the blue-green alga Anabaena flos-aquae Bayer Report No.: 200497 MRID#: 46246103 Date: 2004-02-23 GLP/GEP: Yes, unpublished
M-000532-01-1	Kern, M. E.; Banman, C. S.; Lam, C. V.	2004	Toxicity of JAU 6476 technical to duckweed (Lemna gibba G3) under static-renewal conditions Bayer Report No.: 200488 MRID#: 46246101 Date: 2004-03-03 GLP/GEP: Yes, unpublished
M-000954-01-1	Kern, M. E.; DeHaan, R. A.	2004	Toxicity of JAU 6476 technical to the saltwater diatom Skeletonema costatum Bayer Report No.: 200434 MRID#: 46246110 Date: 2004-03-10 GLP/GEP: Yes, unpublished
M-001064-02-1	Bowers, L. M.	2018	Amendment no. 1 to final report - Toxicity of JAU 6476 technical to the freshwater diatom Navicula pelliculosa Bayer Report No.: J6883401 MRID#: 46246109 Date: 2004-03-12 **... amended: 2018-07-30** GLP/GEP: Yes, unpublished
M-005117-01-1	Riegner, K.	1998	Hydrolysis of [phenyl-UL-14C]JAU 6476 in sterile aqueous buffer solutions Bayer Report No.: MR-623/98 Date: 1998-11-16 GLP/GEP: Yes, unpublished
M-007155-01-1		1999	JAU 6476 - Test on unscheduled DNA synthesis with rat liver cells in vivo Bayer Report No.: 28905 Date: 1999-06-30 GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-008846-01-1		1999	JAU 6476 (c.n.: not yet available) - Study on acute inhalation toxicity in rats according to OECD no. 403 Bayer Report No.: 28954 Date: 1999-07-20 GLP/GEP: Yes, unpublished
M-009688-01-1		1999	JAU 6476 - Study for acute dermal toxicity in rats Bayer Report No.: 28495 Date: 1999-02-22 GLP/GEP: Yes, unpublished
M-009890-02-1		1999	Acute skin irritation test (patch test) of JAU 6476 in rabbits LPT Laboratory of Pharmacology and Toxicology, Hamburg, Germany Bayer Report No.: R6505 Date: 1996-01-15 **... amended: 1999-03-02** GLP/GEP: Yes, unpublished
M-009893-02-1		1999	Acute eye irritation study of JAU 6476 by instillation into the conjunctival sac of rabbits LPT Laboratory of Pharmacology and Toxicology, Hamburg, Germany Bayer Report No.: R6506 Date: 1996-01-16 **... amended: 1999-03-02** GLP/GEP: Yes, unpublished
M-009898-03-1		1999	JAU 6476 - Study for the skin sensitization effect in guinea pigs (guinea pig maximization test method according Magnusson and Kligman) Bayer Report No.: 25027 Date: 1996-05-07 **... amended: 1999-03-25** GLP/GEP: Yes, unpublished
M-011757-01-1	Wirnitzer, U.; Hartmann, E.	1999	JAU 6476 - Study on subchronic toxicity in Wistar rats. Administration by gavage over 14 weeks with a subsequent recovery period of 4 weeks. Bayer Report No.: 28760 Date: 1999-05-18 GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-012237-01-1	Becker, H.; Biedermann, K.	1998	Developmental toxicity study with JAU 6476 in the rabbit RCC, Research and Consulting Company AG, Itingen, Switzerland Bayer Report No.: R7235 Date: 1998-07-16 GLP/GEP: Yes, unpublished
M-012244-01-1	Wirnitzer, U.; Hartmann, E.	1999	JAU 6476 - Dose-range-finding study in CD-1-mice (administration by gavage over 14 weeks) Bayer Report No.: 28579 Date: 1999-03-17 GLP/GEP: Yes, unpublished
M-012254-01-1	Herbold, B.	1996	JAU 6476 - Salmonella/microsome test plate incorporation and preincubation method Bayer Report No.: 24859 Date: 1996-03-05 GLP/GEP: Yes, unpublished
M-012265-01-1	Herbold, B.	1996	JAU 6476 - Micronucleus test on the mouse Bayer Report No.: 25572 Date: 1996-10-25 GLP/GEP: Yes, unpublished
M-012273-01-1	Brendler-Schwaab, S.	1996	JAU 6476 - Mutagenicity study for the detection of induced forward mutations in the V79- HPRT assay in vitro Bayer Report No.: 25605 Date: 1996-11-05 GLP/GEP: Yes, unpublished
M-012277-01-1	Herbold, B.	1996	JAU 6476 - In vitro mammalian chromosome aberration test with Chinese hamster V79 cells Bayer Report No.: 25718 Date: 1996-12-05 GLP/GEP: Yes, unpublished
M-012279-01-1		1997	JAU 6476 - Developmental toxicity study in rats after oral administration Bayer Report No.: 25827 Date: 1997-01-20 GLP/GEP: Yes, unpublished
M-012312-01-1		1998	JAU 6476 - Study for acute oral toxicity in rats Bayer Report No.: 27500 MRID#: 46246230 Date: 1998-05-22 GLP/GEP: Yes, unpublished

Reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP/GEP status *(where relevant)*, published or not
M-012317-01-1		1998	JAU 6476 - Test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro Bayer Report No.: 27417 Date: 1998-04-23 GLP/GEP: Yes, unpublished
M-012338-01-1		1997	JAU 6476 - Study for subacute oral toxicity in rats feeding study for 4 weeks) Bayer Report No.: 26398 Date: 1997-06-24 GLP/GEP: Yes, unpublished
M-012578-01-1	Mueller, G.	1999	Investigation of the ecological properties of JAU 6476 Bayer Report No.: 839 N/99 Date: 1999-05-17 GLP/GEP: Yes, unpublished
M-013030-01-1		1999	JAU 6476 techn.ai.: Acute oral toxicity for bobwhite quail (Colinus virginianus) Bayer Report No.: BAR/LD 028 Date: 1999-06-17 GLP/GEP: Yes, unpublished
M-013690-01-1		1999	Acute toxicity of JAU 6476 (tech.) to water fleas (Daphnia magna) Bayer Report No.: HBF/DM 212 Date: 1999-08-13 GLP/GEP: Yes, unpublished
M-015215-01-1		1999	JAU 6476 - Acute toxicity (96 hours) to Rainbow trout (Oncorhynchus mykiss) in a static test Bayer Report No.: DOM 99076 Date: 1999-09-01 GLP/GEP: Yes, unpublished
M-018760-01-1		1999	A pilot reproductive toxicity study with JAU 6476 technical in the Wistar rat Bayer Report No.: 109079 MRID#: 46246334 Date: 1999-10-18 GLP/GEP: Yes, unpublished
M-020269-01-1		1999	JAU 6476 - Acute toxicity (96 hours) to bluegill (Lepomis macrochirus) in a static test Bayer Report No.: DOM 99090 Date: 1999-11-02 GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-023105-01-1		1999	JAU 6476 a.i. - Acute effects on the honeybee Apis mellifera Bayer Report No.: IBA64051 Date: 1999-11-10 GLP/GEP: Yes, unpublished
M-023861-01-1		2000	An acute oral neurotoxicity screening study with technical grade JAU 6476 in Wistar rats Bayer Report No.: 109250 MRID#: 46246417 Date: 2000-02-03 GLP/GEP: Yes, unpublished
M-024673-01-1	Anderson, J. P. E.	1999	Influence of JAU 6476 technical ingredient on the microbial mineralization of nitrogen in soils Bayer Report No.: AJO/203199 Date: 1999-12-08 GLP/GEP: Yes, unpublished
M-024679-01-1	Anderson, J. P. E.	1999	Influence of JAU 6476 technical ingredient on glucose stimulated respiration in soils Bayer Report No.: AJO/203099 Date: 1999-12-08 GLP/GEP: Yes, unpublished
M-027625-01-1	Dorgerloh, M.	2000	JAU 6476 - Influence on the growth of the green alga, Selenastrum capricornutum Bayer Report No.: DOM 99107 Date: 2000-10-25 GLP/GEP: Yes, unpublished
M-030441-01-1		2000	JAU 6476 - Study on chronic toxicity in Wistar rats. Administration via gavage over 1 year. Bayer Report No.: 30536 Date: 2000-12-15 GLP/GEP: Yes, unpublished
M-031137-02-1		2000	Acute toxicity of JAU 6476 (tech.) to earthworms (Eisenia fetida) Bayer Report No.: MPE/RG 326/00 Date: 2000-04-10 **... amended: 2000-04-10** GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-035123-01-1		2000	Reproduction study in mallard duck with JAU 6476 (by dietary admixture) Bayer Report No.: 259919 Date: 2000-11-07 GLP/GEP: Yes, unpublished
M-035825-01-1		2001	Technical grade JAU 6476 - A subchronic oral gavage study in the Beagle dog Bayer Report No.: 109442 MRID#: 46246313 Date: 2001-11-30 GLP/GEP: Yes, unpublished
M-035967-01-1		2001	Technical grade JAU 6476 - A chronic oral gavage study in the Beagle dog Bayer Report No.: 110921 MRID#: 46246336 Date: 2001-12-07 GLP/GEP: Yes, unpublished
M-036206-01-1		2001	A two-generation reproductive toxicity study with JAU 6476 in the Wistar rat Bayer Report No.: 110500 MRID#: 46246331 Date: 2001-01-04 GLP/GEP: Yes, unpublished
M-037387-01-1		2000	JAU 6476 - Acute toxicity (96 hours) to common carp (cyprinus carpio) in a static test Bayer Report No.: DOM 20010 Date: 2000-06-05 GLP/GEP: Yes, unpublished
M-042334-01-1		2000	Reproduction study in bobwhite quail with JAU 6476 (by dietary admixture) Bayer Report No.: 259842 Date: 2000-06-29 GLP/GEP: Yes, unpublished
M-044301-01-1		2000	JAU 6476 - Study for subacute dermal toxicity in rats (four-week treatment period) Bayer Report No.: 30115 Date: 2000-08-02 GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-047356-01-1		2000	Influence of JAU 6476 (tech.) on development and emergence of larvae of Chironomus riparius in a water-sediment system Bayer Report No.: HDB/CH 42 Date: 2000-09-14 GLP/GEP: Yes, unpublished
M-051279-01-1	Hellpointner, E.	2001	Determination of the quantum yield and assessment of the environmental half-life of the direct photodegradation in water of JAU 6476 Bayer Report No.: MR-101/01 Date: 2001-04-10 GLP/GEP: Yes, unpublished
M-053225-01-1		2001	A subchronic oral neurotoxicity screening study with technical grade JAU 6476 in Wistar rats Bayer Report No.: 738484 MRID#: 46246416 Date: 2001-04-12 GLP/GEP: Yes, unpublished
M-054770-01-1		2001	JAU 6476 techn.: 5 day-dietary LC50 for bobwhite quail (Colinus virginianus) Bayer Report No.: BAR/LC 005 Date: 2001-04-18 GLP/GEP: Yes, unpublished
M-055051-01-1		2001	JAU 6476: A 96-hour shell deposition test with the eastern oyster (Crassostrea virginica) Bayer Report No.: 110956 Edition Number: MRID#: 46246014 Date: 2001-11-20 GLP/GEP: Yes, unpublished
M-055523-01-1		2001	JAU 6476 techn.: 5-day-dietary LC50 to mallard duck (Anas platyrhynchos) Bayer Report No.: BAR/LC 010 Date: 2001-02-13 GLP/GEP: Yes, unpublished
M-055997-01-1		2001	Influence of JAU 6476 (tech) on the reproduction rate of water fleas Bayer Report No.: HDB/RDM 67 MRID#: 46246028 Date: 2001-04-11 GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-067839-01-1		2004	Technical grade JAU 6476: A supplementary prenatal developmental toxicity study in the Wistar Hanover (Crl:WI(HAN) rat to investigate ocular abnormalities and supernumerary ribs Bayer Report No.: 201037 MRID#: 46923601 Date: 2004-05-10 GLP/GEP: Yes, unpublished
M-083057-01-1		2002	JAU 6476: A 96 hour flow-through acute toxicity test with the saltwater mysid (Mysidopsis bahia) Wildlife International, Ltd., Easton, MD, USA Bayer Report No.: 110983 MRID#: 46246016 Date: 2002-05-28 GLP/GEP: Yes, unpublished
M-084962-01-1		2001	JAU 6476 - Study on carcinogenicity in Wistar rats. Administration by gavage over 2 years. Bayer Report No.: 31512 Date: 2001-11-20 GLP/GEP: Yes, unpublished
M-085068-01-1	Schladt, L.	2001	JAU 6476 - Oncogenicity study in CD-1 mice. Administration via gavage for 18 months. Bayer Report No.: 31510 Date: 2001-11-19 GLP/GEP: Yes, unpublished
M-087902-01-1	Dorgerloh, M.; Weber, E.	2001	(14C)-JAU 6476 - Bioconcentration and biotransformation in bluegill (Lepomis macrochirus) under flow-through conditions Bayer Report No.: DOM 21003 Date: 2001-11-13 GLP/GEP: Yes, unpublished
M-102790-01-1	Herbold, B.	2003	JAU 6476 - Micronucleus-test on the male mouse Bayer Report No.: AT00605 Date: 2003-08-01 GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-107721-01-1	Kern, M. E.; Lam, C. K.	2004	Acute toxicity of JAU 6476 technical to the Sheepshead minnow (Cyprinodon variegatus) under static-renewal conditions Bayer Report No.: 200615 MRID#: 46246027 Date: 2004-01-22 GLP/GEP: Yes, unpublished
M-291414-01-1	Matlock, D.; Lam, C. V.	2007	Early life stage toxicity of prothioconazole technical to the rainbow trout (Oncorhynchus mykiss) under flow through conditions Bayer Report No.: EBJAX313 MRID#: 50489201 Date: 2007-08-06 GLP/GEP: Yes, unpublished
M-291490-01-1	Vohr, H. W.	2007	Prothioconazole (Project: Prothioconazole (JAU 6476)) - Local lymph node assay in mice (LLNA/IMDS) Bayer Report No.: AT04016 Date: 2007-08-14 GLP/GEP: Yes, unpublished
M-364387-01-1		2010	Toxicity of JAU 6476 technical (prothioconazole) during an actue oral LD50 with the canary (Serinus canaria) Bayer Report No.: EBJAL065 MRID#: 48024801 Date: 2010-02-25 GLP/GEP: Yes, unpublished
M-405273-01-1		2011	Prothioconazole a.s.: Influence on the reproduction of the collembolan species Folsomia candida tested in artificial soil Bayer Report No.: FRM-COLL-118/11 Date: 2011-04-12 GLP/GEP: Yes, unpublished
M-491727-01-1	Nau, M.	2014	Prothioconazole (JAU6476, AE 1344248), pure substance: Melting point, boiling point, thermal stability Siemens AG, Frankfurt am Main, Germany Bayer Report No.: 20140193.01 Date: 2014-07-11 GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)***, published or not**
M-492539-01-1		2014	Prothioconazole (JAU6476, AE 1344248), pure substance: Partition coefficients 1-octanol / water at pH 4, pH 7 and pH 9 (HPLC method) Bayer Report No.: PA14/071 Date: 2014-07-22 GLP/GEP: Yes, unpublished
M-498202-01-1		2014	Prothioconazole (JAU6476, AE 1344248), pure substance: Dissociation constant in water Bayer Report No.: PA14/083 Date: 2014-10-02 GLP/GEP: Yes, unpublished
M-498655-01-1		2014	Prothioconazole, technical: Cytotoxicity assay in vitro with BALB/c 3T3 cells: Neutral red (NR) test during simultaneous irradiation with artificial sunlight Harlan Cytotest Cell Research GmbH (Harlan CCR), Rossdorf, Germany Bayer Report No.: 1646000 Date: 2014-09-25 GLP/GEP: Yes, unpublished
M-498988-01-1	Dreisch, S.	2014	Prothioconazole (JAU6476, AE 1344248), pure substance: Vapour pressure consilab Gesellschaft fuer Anlagensicherheit mbH, Frankfurt am Main, Germany Bayer Report No.: CSL-14-0898.01 Date: 2014-09-23 GLP/GEP: Yes, unpublished
M-503064-01-1	Eyrich, U.; Ziemer, F.	2014	Prothioconazole (JAU6476, AE 1344248), pure substance: Solubility in organic solvents Bayer Report No.: PA14/084 Date: 2014-11-20 GLP/GEP: Yes, unpublished
M-503425-01-1	Ziemer. F.; Strunk, B.	2014	Prothioconazole (JAU6476, AE 1344248), pure substance: Water solubility at pH 4, pH 7 and pH 9 Bayer Report No.: PA14/078 Date: 2014-11-20 GLP/GEP: Yes, unpublished
M-505379-01-1		2014	Effects of prothioconazole tech. (Acute contact and oral) on honey bees (Apis mellifera L.) in the laboratory Report No.: 89491035 Date: 2014-12-09 GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-521802-01-1		2015	Prothioconazole technical: Acute contact toxicity to the bumble bee, Bombus terrestris L. under laboratory conditions Bayer Report No.: S14-00616 Date: 2015-04-30 GLP/GEP: Yes, unpublished
M-525909-01-1	Winkler, S.	2015	Prothioconazole (JAU6476, AE 1344248), technical substance: Melting point, boiling point, thermal stability Siemens AG, Frankfurt am Main, Germany Bayer Report No.: 20150184.01 Date: 2015-06-19 GLP/GEP: Yes, unpublished
M-534563-01-1	Gondol, D.	2015	Spectral data (UV / VIS, IR, 1H-NMR, 13C-NMR, MS) and molar extinction coefficients of prothioconazole, pure substance Bayer Report No.: 15-600-2714 Date: 2015-09-29 GLP/GEP: Yes, unpublished
M-557946-01-1		2016	Prothioconazole technical: Acute oral toxicity to the bumble bee, bombus terrestris L. under laboratory conditions Bayer MRID#: 50521802 Date: 2016-06-14 GLP/GEP: Yes, unpublished
M-588628-01-1		2017	Prothioconazole, technical: Micronucleus test in human lymphocytes In vitro Bayer Report No.: 1825700 Date: 2017-05-17 GLP/GEP: Yes, unpublished
M-615696-01-1		2018	Prothioconazole tech. - Repeated exposure to honey bee (Apis mellifera) larvae under laboratory conditions (in vitro) - Final Report BioChem agrar GmbH, Cunnersdorf, Germany Bayer Report No.: 17 48 BLC 0029 MRID#: 50633903 Date: 2018-02-27 GLP/GEP: Yes, unpublished
M-625860-02-1		2018	Statistical re-evaluation of the Daphnia magna reproduction study with prothioconazole technical (M-055997-01-1) Bayer Date: 2018-06-29 GLP/GEP: n.a., unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant)*, **published or not**
M-634695-01-1		2018	Statement - Re-evaluation of green algae growth inhibition study with prothioconazole (M-027625-01-1) Bayer Date: 2018-09-06 GLP/GEP: n.a., unpublished

Addendum: References Section 2. Non-confidential data (prothioconazole-desthio) - (sorted by reference number)

Reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP/GEP status *(where relevant),* published or not
M-008029-03-1		1999	SXX 0665 - Subacute toxicity study in the beagle dog - revised version - Bayer Report No.: 28890 Date: 1999-06-25 GLP/GEP: No, unpublished
M-008317-01-1		1991	SXX 0665 - Supplementary study for embryotoxic effects in rats following dermal exposure Bayer Report No.: 20582 Date: 1991-08-29 GLP/GEP: Yes, unpublished
M-008322-01-1		1992	SXX 0665 - Study for embryotoxic effects in rats following dermal exposure Bayer Report No.: 21058 Date: 1992-02-07 GLP/GEP: Yes, unpublished
M-008329-01-1		1992	SXX 0665 - Embryotoxicity study on postnatal development of supernumerary ribs in rats following oral administration Bayer Report No.: 21792 Date: 1992-10-27 GLP/GEP: Yes, unpublished
M-008334-01-1		1992	SXX 0665 - Study for embryotoxic effects in rabbits following oral administration Bayer Report No.: 21091 Date: 1992-02-17 GLP/GEP: Yes, unpublished
M-008355-01-1		1991	SXX 0665 - Study for acute oral toxicity in rats Bayer Report No.: 20098 Date: 1991-03-22 GLP/GEP: Yes, unpublished
M-008358-01-1		1991	SXX 0665 - Study for skin-sensitizing effects in guinea pigs (Buehler Patch Test) Bayer Report No.: 20719 Date: 1991-10-07 GLP/GEP: Yes, unpublished

Reference number	Author(s)	Year	Title **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant),* **published or not**
M-008350-01-1		1991	SXX 0665 - Study for acute dermal toxicity in rats Bayer Report No.: 20094 Date: 1991-03-22 GLP/GEP: Yes, unpublished
M-008521-01-1		1991	SXX 0665 - Study for acute oral toxicity in mice Bayer Report No.: 20097 Date: 1991-03-22 GLP/GEP: Yes, unpublished
M-008361-01-1		1992	SXX 0665 - Study for acute inhalation toxicity in the rat Bayer Report No.: 21087 Date: 1992-02-17 GLP/GEP: Yes, unpublished
M-008365-01-1		1992	SXX 0665 - Subacute oral toxicity study in rats Bayer Report No.: 21173 Date: 1992-03-13 GLP/GEP: Yes, unpublished
M-009104-01-1		1999	SXX 0665 - Mutagenicity study for the detection of induced forward mutations in the V79-HGPRT assay in vitro Bayer Report No.: 28965 Date: 1999-07-22 GLP/GEP: Yes, unpublished
M-018496-01-1		1999	SXX 0665 - Study on subchronic toxicity in Wistar rats. Dietary administration over 14 weeks with a subsequent recovery period over 5 weeks. Bayer Report No.: 29336 Date: 1999-11-29 GLP/GEP: Yes, unpublished
M-023192-02-1		1999	SXX 0665 - Dose-range-finding study in B6C3F1-mice. Dietary administration for about 14 weeks Bayer Report No.: 29235 Date: 1999-10-25 **... amended: 1999-11-06** GLP/GEP: Yes, unpublished
M-026445-01-1		1991	Supplementary study to the embryotoxicity study (including teratogenicity) with SXX 0655 technical in the rat Bayer Report No.: R5437 Date: 1991-12-06 GLP/GEP: Yes, unpublished

Reference number	Author(s)	Year	Title **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant),* **published or not**
M-026431-01-1		1991	Embryotoxicity study (including teratogenicity) with SXX 0665 technical in the rat Bayer Report No.: R5436 Date: 1991-12-03 GLP/GEP: Yes, unpublished
M-026972-01-1		2000	SXX 0665 - Subchronic toxicity study in beagle dogs (13 week feeding study) Bayer Report No.: 29616 Date: 2000-02-24 GLP/GEP: Yes, unpublished
M-027339-01-1		1999	SXX 0665 - Combined study on chronic toxicity and carcinogenicity in Wistar rats. Dietary administration over 2 years. Bayer Report No.: 29419 Date: 1999-12-22 GLP/GEP: Yes, unpublished
M-031119-01-1		1995	SXX 0665 - In vitro mammalian chromosome aberration test with chinese hamster ovary (CHO) cells Bayer Report No.: 24457 Date: 1995-11-08 GLP/GEP: Yes, unpublished
M-031124-01-1		1993	SXX 0665 - Micronucleus test on the mouse Bayer Report No.: 22089 Date: 1993-02-22 GLP/GEP: Yes, unpublished
M-031126-01-1		1992	SXX 0665 - Mutagenicity test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro Bayer Report No.: 21187 Date: 1992-03-16 GLP/GEP: Yes, unpublished
M-031136-01-1		1990	SXX 0665 - Salmonella/microsome test Bayer Report No.: 19539 Date: 1990-09-20 GLP/GEP: Yes, unpublished
M-031146-01-2		1992	Pilot study to establish dose levels for a two-generation reproduction study in rats using technical grade SXX 0665 adminstered via the diet Bayer Report No.: 103274 Date: 1992-09-08 GLP/GEP: Yes, unpublished

Reference number	**Author(s)**	**Year**	**Title** **Source** *(where different from company)* **Company name, Report No., Date, GLP/GEP status** *(where relevant),* **published or not**
M-036130-01-1		2001	A two-generation dietary reproduction study in rats using SXX 0665 Bayer Report No.: 109835 Date: 2001-12-04 GLP/GEP: Yes, unpublished
M-044458-02-1		2002	SXX 0665 - Oncogenicity study in B6C3F1-mice. Dietary administration over 2 years Bayer Report No.: 30045 Date: 2000-07-24 **... amended: 2002-10-28** GLP/GEP: Yes, unpublished
M-031139-01-1		1991	SXX 0665 - Study for skin and eye irritation/corrosion in rabbits Bayer Report No.: 19945 Date: 1991-02-04 GLP/GEP: Yes, unpublished
M-136735-01-1		2001	SXX 0665 - Chronic toxicity study in beagle dogs (30 week feeding study) Bayer Report No.: 31148 Date: 2001-07-05 GLP/GEP: Yes, unpublished
M-588632-01-1		2017	AE 1194888, pure substance (JAU 6476-desthio): Salmonella typhimurium reverse mutation assay Bayer Report No.: 1825400 Date: 2017-05-15 GLP/GEP: Yes, unpublished