Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

ZETA-CYPERMETHRIN

A mixture of the stereoisomers (S)-a-cyano-3-phenoxybenzyl (1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate where the ratio of the (S);(1RS,3RS) isomeric pair to the (S);(1RS,3SR) isomeric pair lies in the ratio range 45-55 to 55-45 respectively

2019

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

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

INTRODUCTION

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

From 2002, the development of FAO specifications follows the **New Procedure**, described in the 1st edition of the "Manual on 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 2000 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 (http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/ps-new/en/) OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

ZETA-CYPERMETHRIN

INFORMATION

ISO common name *zeta*-cypermethrin (ISO 1750, published)

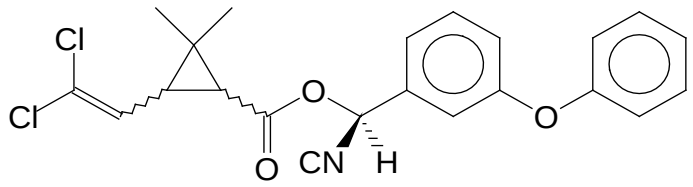
Chemical names

IUPAC Mixture of the stereoisomers (S)-α-cyano-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2 dimethylcyclopropane carboxylate
where the ratio of the (S);(1RS,3RS) isomeric pair to the (S);(1RS,3SR) isomeric pair lies in the ratio range 45-55 to 55-45 respectively.

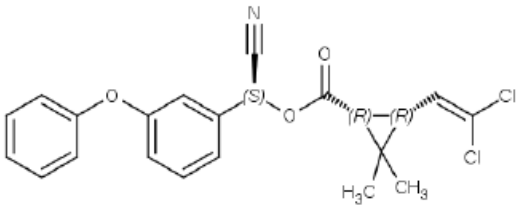
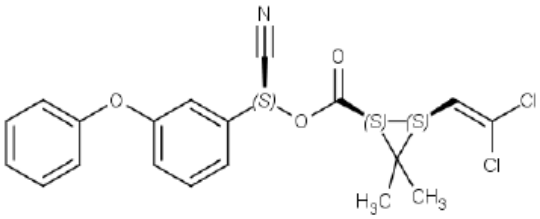
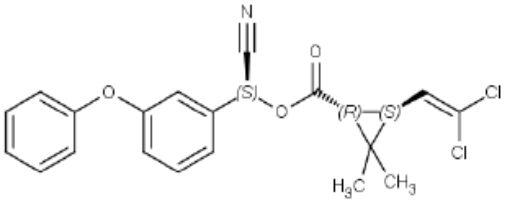
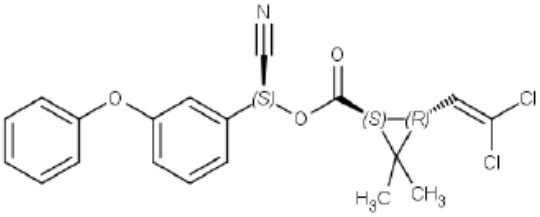
CA (S)-cyano(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

Synonyms none

Structural formula



Stereoisomers contained in *zeta*-cypermethrin according to the ISO common name definition:

Isomer designation[2] and CAS Number	Structure	%	Contained in diastereomer - see "Identity tests" below[3]
1*R*-*cis*-*aS* 65731-84-2		22	*cis*-2
1*S*-*cis*-*aS* 72204-43-4		22	*cis*-1
1*R*-*trans*-*aS* 65732-07-2		22	*trans*-4
1*S*-*trans*-*aS* 83860-31-5		22	*trans*-3

Molecular formula $C_{22}H_{19}Cl_2NO_3$

Molecular mass 416.3

CAS Registry number 52315-07-8 (undefined stereochemistry, as for cypermethrin)
See CAS numbers in table above for individual stereoisomers.

CIPAC number 733

[2] The Rothamstead designation for pyrethroid stereoisomers is used (M. Elliott, N. F. Janes & D. A. Pulman, J. Chem. Soc., Perkin Trans. I, 1974, p. 2470 (first footnote))
[3] The designation of cypermethrin diastereomers follows the elution order in normal phase HPLC, see e.g. CIPAC 332/TC/M/3.2 and Fig. 131, Handbook 1C, p. 2056

Identity tests

For total isomer content and ratio of *cis/trans*-isomers: normal phase HPLC with UV-detection, for quantification of all stereoisomers having *a-S* configuration in the presence of minor amounts stereoisomers having *a-R* configuration: enantioselective HPLC on a HiChrom Chiral D-PGC 5µm particle size.

Approximate retention times for the *cis*- and *trans*-cypermethrin diastereomers are:

Cypermethrin diastereomer	**Approximate retention time (min)**
cis1	15.1
cis2	17.1
trans1	20.5
trans2	23.0

ZETA-CYPERMETHRIN TECHNICAL MATERIAL

FAO Specification 733 / TC (July 2019*)

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 (733/2018). It should be applicable to TC produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation report (733/2018) as PART TWO forms an integral part of this publication.

1. Description

The material shall consist of technical *zeta*-cypermethrin together with related manufacturing impurities, in the form of a pale yellow viscous liquid, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (Cypermethrin 332/TC/M/3; CIPAC 1C, p. 2052, 1985 and *zeta*-cypermethrin HPLC method) (Note 1)

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

2.2 ***zeta*-Cypermethrin content** (Cypermethrin 332/TC/M/3; CIPAC 1C, p. 2052 **and** *zeta*-cypermethrin HPLC method) (Notes 1 & 2)

The zeta-cypermethrin content shall be declared (not less than 850 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

2.3. ***Cis-trans* isomer ratio** (Cypermethrin 332/TC/M/3; CIPAC 1C, p. 2052), The *cis/trans*-ratio should be in the range 55/45 to 45/55

Note 1 The peer validation of the quantitative stereospecific identity test for quantification of the individual zeta-cypermethrin stereoisomers in TC was presented and accepted at the 2018 CIPAC Meeting in Panama. Briefly, the a-S and a-R stereoisomers are separated by normal phase HPLC with UV detection on a HiChrom Chiral D- PGC 5µm column and quantified based on their peak area. Prior to the publication of the method in a next Handbook, copies of the method my be obtained through https://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 2 The *zeta*-cypermethrin content is calculated using the chemical purity of cypermethrin provided by the CIPAC method 332/M/2 multiplying with the enantiomeric purity expressed as a fraction of the sum of all stereoisomers having a-S configuration divided by the sum of all stereoisomers in the sample obtained by the stereoselective HPLC method.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/ps-new/en/

PART TWO

EVALUATION REPORTS

ZETA-CYPERMETHRIN

ZETA-CYPERMETHRIN

FAO/WHO EVALUATION REPORT 733/2018

Recommendations

The Meeting recommended the following:

the specification for zeta-cypermethrin TC, proposed by FMC and as amended, should be adopted by FAO, subject to acceptance of the peer validation of the analytical method by CIPAC and clarification of some points.

Appraisal

The Meeting considered data on zeta-cypermethrin submitted by FMC, in support of development of new FAO specifications for the technical material submitted in 2017.

The ISO common name *zeta*-cypermethrin designates a pyrethroid that can be considered as esterification product of the (*S*)-α-cyano-3-phenoxybenzyl alcohol and permethric acid. Whereas cypermethrin refers to a racemic mixture of the alcohol and acid moiety, *zeta*-cypermethrin is enriched with the *S*-alcohol and has a *cis/trans* ratio of 45.55 in the cyclopropane moiety.

zeta-Cypermethrin was evaluated by JMPR in 2006, together with cypermethrin and alpha-cypermethrin (Pesticide residues in food 2008, Joint FAO/WHO Meeting on Pesticide Residues, p. 169).

The conclusions of the toxicological evaluation were as follows (quote):

Cypermethrin has low to moderate acute oral toxicity in rats (LD_{50}, 163 to > 3000 mg/kg bw). This variability was only partly explicable by the vehicle used. The acute oral LD_{50} of *cis*-cypermethrin in rats was 160–300 mg/kg bw, indicating that it is considerably more toxic than trans-cypermethrin, for which the LD_{50} was > 2000 mg/kg bw under the same conditions. From these results, it would be predicted that *alpha*-cypermethrin is approximately twice as acutely toxic as cypermethrin. A wide range of acute oral LD_{50} values in rats was also reported for *alpha*-cypermethrin (LD_{50}, 64 to > 5000 mg/kg bw). Similar studies with *zeta*-cypermethrin gave fairly consistent results (LD_{50}, 86–367 mg/kg bw). The dermal toxicity of cypermethrin and *alpha*-cypermethrin was low in rats (LD_{50}, > 1600 mg/kg bw and > 2000 mg/kg bw per day, respectively), as was the dermal toxicity of zeta-cypermethrin in rabbits (LD_{50}, > 2000 mg/kg bw), and inhalation toxicity was moderate for cypermethrin (LC_{50}, 1.260 mg/l) and alpha-cypermethrin (LC_{50}, 1.590 mg/l). Overall, the three isomeric mixtures displayed qualitatively similar profiles for acute toxicity in rats. (...)

Cypermethrin, *alpha*-cypermethrin and *zeta*-cypermethrin gave negative results in an adequate battery of studies of genotoxicity in vitro and in vivo.

In the absence of any carcinogenic potential in rodents and the lack of genotoxic potential *in vitro* and *in vivo*, the Meeting concluded that the cypermethrins are unlikely to pose a carcinogenic risk to humans (unquote)."

The Meeting noted, that the hazard data package on *zeta*-cypermethrin contained some data gaps, e.g. no long-term / carcinogenicity studies had been provided. Later on, summaries of these studies were provided by FMC on request by the Meeting and are now included in the hazard summaries.

The JMPR deemed it appropriate to set a single ADI applying for cypermethrin, alpha-cypermethrin and zeta-cypermethrin, since racemic cypermethrin already includes a substantial proportion of alpha- and zeta-cypermethrin, and the cypermethrins are qualitatively similar in their toxicity and metabolism. From this it can be deduced, that the JMPR found it appropriate to read-across toxicity profiles from racemic cypermethrin, alpha- and zeta-cypermethrin toxicity profiles, where hazard data for a specific cypermethrin are missing. Likewise, in the EU read-across or “bridging” between cypermethrin and alpha-cypermethrin was also supported[4].

Furthermore, the Meeting noted that no specific guidance on toxicity read-across is provided in the FAO/WHO Specification Manual.

Taking into consideration the JMPR toxicological evaluation does not provide a specific rationale on read-across from racemic cypermethrin, alpha- and zeta-cypermethrin toxicity profiles, the need to look deeper into that subject was felt by the Meeting.

Under the assumption, that the cypermethrin stereoisomers in racemic-, *alpha*- and *zeta*-cypermethrin contribute most to the overall toxicity and the impurities that are related to intermediates and solvents play a minor role in the individual hazard profiles, hazard data of single stereoisomers including their ADME studies would allow to apportion a sum of hazard effects to defined stereoisomer compositions based on effect additivity. Such data is, however, not available for a number of obvious reasons like availability of sufficient amounts of these pure stereoisomers, animal welfare etc.

The EU draft assessment report on *zeta*-cypermethrin[5] provides the most comprehensive read-across on the hazard profiles of racemic, *alpha*- and *zeta*-cypermethrin so far. The common understanding seems to be that some cypermethrin stereoisomers exhibit more pronounced toxicity than others.

[4] Peer review of the pesticide risk assessment of the active substance alpha- cypermethrin, EFSA Journal 2018;16(9):5403
[5] Draft assessment report on zeta-cypermethrin, Volume 3, B.6, available from http://dar.efsa.europa.eu/dar-web/provision

According to a publication by Soderlund et al[6], for racemic cypermethrin, *alpha*- and *zeta*-cypermethrin, the mammalian neurotoxicity as important endpoint is governed by the configuration at the cyclopropane moiety and at the a-carbon atom, where

- the esters of the 1*R* carboxylates are neurotoxic whereas the respective 1*S* are not
- the esters of 1*R* trans carboxylates are toxic, the respective 1*R* cis are not
- and finally the isomers with *S*-configuration at the a-carbon atom show neurotoxicity, whereas the isomers with corresponding a- *R*-configuration are non-toxic

This conclusion is well in line with the conclusions of the JMPR report. Comparing the *cis-trans* ratio of cypermethrin and of *zeta*-cypermethrin respectively shows that they are similar, however *zeta*-cypermethrin has a significantly higher proportion of the a-S-isomer, leading to an approx. 2.5 times higher insecticidal activity and concurrently to a higher mammalian neurotoxicity. Therefore, some read-across from cypermethrin toxicity studies seems appropriate, using a correction factor of 2.5 for neurotoxicological endpoints.

The JMPR toxicological evaluation further concludes, that "the (JMPR) Meeting acknowledged that since racemic cypermethrin already includes a substantial proportion of alpha- and zeta-cypermethrin, and that all three cypermethrins are qualitatively similar in their toxicity and metabolism" a single ADI for these three cypermethrins can be set - this notwithstanding the quantitative differences in neurotoxicological effects in mammals. For that reason, JMPS concluded that for the majority of the toxicological properties the read-across from racemic and alpha-cypermethrin was deemed to be justified.

Technical *zeta*-cypermethrin has a fairly low volatility and a melting point of - 3 °C, it is therefore a viscous liquid at room temperature.

The compound is sparingly soluble in water with 0.05 mg/L and has an octanol/water partition coefficient (log P_{ow}) of 5 - 6. It does not dissociate at pH of 1 to 12 and is stable to hydrolysis. The Meeting noted some deficiencies in the physical-chemical data, as the main four diastereomers constituting *zeta*-cypermethrin are expected to show different water solubilities, octanol-water partition coefficients etc. and need to be characterized individually (see FAO/WHO Manual, Section 3.1).

The Meeting was provided with confidential information on the manufacturing process and specification limits for the technical material. The minimum purity of the active and maximum impurity limits as proposed by FMC were supported by 5 batch analysis data. *zeta*-Cypermethrin is produced in a three-step synthesis. The minimum purity of 980 g/kg was justified by the 5-batch data. Mass balances were high (99.76 – 100.52 %). 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.

[6] Soderlund *et al*. Mechanisms of pyrethroid neurotoxicity: implications for cumulative risk assessment, Toxicology 171, 1, pp. 3 - 59, 2002.

The company proposed to consider residues of an aromatic solvent used in the manufacturing process at 2 g/kg and high molecular weight substances as relevant impurities. However, according to current practice of the assessment of the relevance of aromatic solvents the Meeting concluded that neither the residues of that aromatic solvent nor the high molecular weight material should be considered as relevant impurities.

The determination of *zeta*-cypermethrin in TC is based on the combined use of a normal phase HPLC method on silica gel capable of separating and quantifiying all four diastereomers present in cypermethrin and is considered applicable to zeta-cypermethrin as well. The method is a CIPAC method published in Handbook D and allows to determine total cypermethrin content and the total *cis/trans* ratio.

As zeta-cypermethrin is enriched in the enantiomers having *a-S* configuration, a second method - a quantitative stereoselective identity test - is needed to complement the chemical purity result obtained in the normal phase HPLC assay with the actual content of those stereoisomers having *a-S* configuration. This is achieved by a second method that was peer validated in 2018 and accepted by CIPAC. That method allows to separate and quantify all 4 stereoisomers that compose *zeta*-cypermethrin.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 733/2018

USES

zeta-Cypermethrin is a pyrethroid insecticide, acting by contact and ingestion on the central and peripheral nervous system of target insects. It is used in agriculture against a broad range of foliar insects.

IDENTITY OF THE ACTIVE INGREDIENT

ISO common name *zeta*-cypermethrin (ISO 1750, published)

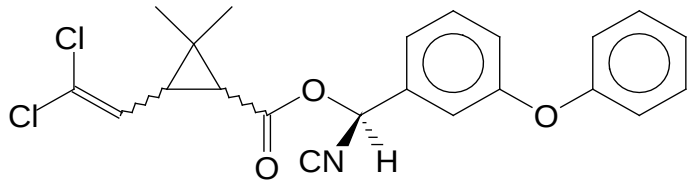
Chemical names

IUPAC *Mixture of the stereoisomers* (S)-α-cyano-3-phenoxybenzyl (1RS,3RS;1RS,3SR)- 3-(2,2-dichlorovinyl)-2,2 dimethylcyclopropane carboxylate *where the ratio of the (S);(1RS,3RS) isomeric pair to the (S);(1RS,3SR) isomeric pair lies in the ratio range 45-55 to 55-45 respectively.*

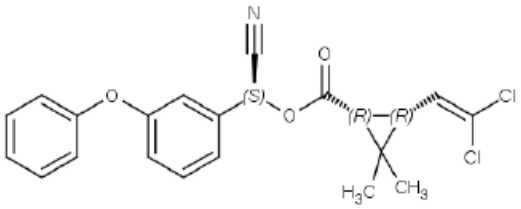
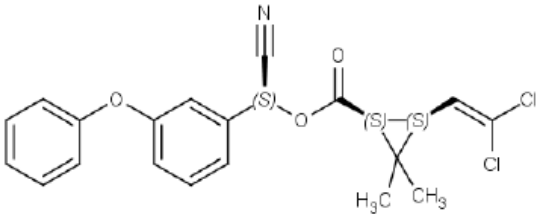
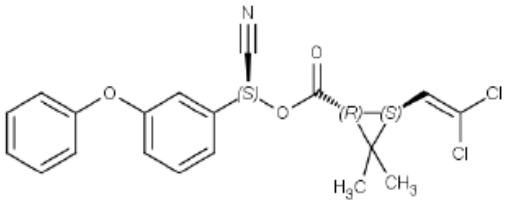
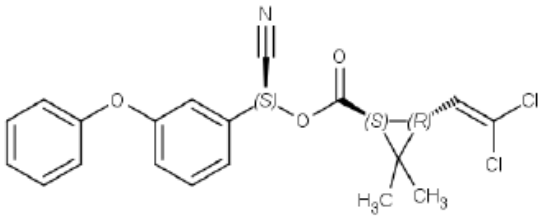
CA (S)-cyano(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

Synonyms none

Structural formula



Stereoisomers comprised in zeta-cypermethrin according to the ISO common name definition:

Isomer designation[7] and CAS Number	Structure	%	Contained in diastereomer - see "Identity tests" below[8]
1*R-cis-aS* 65731-84-2		22	*cis*-2
1*S-cis-aS* 72204-43-4		22	*cis*-1
1*R-trans-aS* 65732-07-2		22	*trans*-4
1*S-trans-aS* 83860-31-5		22	*trans*-3

Molecular formula

$C_{22}H_{19}Cl_2NO_3$

Relative molecular mass

416.3

CAS Registry number

52315-07-8 (undefined stereochemistry, as for cypermethrin)

See CAS numbers in table above for individual stereoisomers.

[7] The Rothamstead designation for pyrethroid stereoisomers is used (M. Elliott, N. F. Janes & D. A. Pulman, J. Chem. Soc., Perkin Trans. I, 1974, p. 2470 (first footnote))

[8] The designation of cypermethrin diastereomers follows the elution order in normal phase HPLC, see e.g. CIPAC 332/TC/M/3.2 and Fig. 131, Handbook 1C, p. 2056

CIPAC number 733

Identity tests

For total isomer content and R/S-enantiomers: HPLC, UV-detection, isocratic reversed (chiral) phase (For method, please refer to Test Method APG 240 in Report P-17-04-14)

For total isomer content and ratio of *cis/trans*-isomers: normal phase HPLC with UV-detection.

Approximate retention times for the *cis*- and *trans*-cypermethrin diastereomers are:

Cypermethrin isomer	Approximate retention time (min)
cis1	15.1
cis2	17.1
trans1	20.5
trans2	23.0

Table 1. Physical-chemical properties of pure *zeta*-cypermethrin

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	2.53×10^{-7} Pa at 25°C	86.8 (batch N° E7434:36)	Gas saturation method	194AF90196
Melting point.	-3 °C	85.3 cis/trans 51/49 (batch N° E6788:122B)	CIPAC MT 139, based on ASTM D97-66	FMC/FO20323/Ch.2386/2001/74
Temperature of decomposition	231 °C at 5 mm Hg (0.7 kPa) pressure	86.8 (batch N° E7434:36)	Vacuum distillation	194AF93264
Solubility in water	0.0387 mg/l at 20 °C at natural pH The *zeta*-cypermethrin molecule does not have moities that donate or accept protons.	85.3 cis/trans 51/49 (batch N° E6788:122B)	EEC A6 (column elution method with levelling vessel + GC-ECD analysis)	FMC/FO20323/Ch.2386/2001/74
Octanol/water partition coefficient	log P_{OW} = 5-6 at 24 °C at pH 2	85.3 cis/trans 51/49 (batch N° E6788:122B)	EEC A8, OECD 117 (RP-HPLC method + UV detection)	P/B 660 G

<table>
<tr><th>Parameter</th><th>Value(s) and conditions</th><th>Purity %</th><th>Method reference (and technique if the reference gives more than one)</th><th>Study number</th></tr>
<tr><td>Hydrolysis characteristics</td><td>Half-life[9] at 50 °C
<table>
<tr><th>pH</th><th>result</th></tr>
<tr><td>4</td><td>< 10% degradation in 5 days
Þ hydrolytically stable;
no further tests required</td></tr>
<tr><td>7</td><td>hydrolysis (first-order kinetics)
k = 0.1499 d^{-1}; DT_{50} = 4.6 d</td></tr>
<tr><td>9</td><td>DT_{50} = 1.5 hrs (i.e. < 2.4 hrs)
Þ hydrolytically labile; no further tests required</td></tr>
</table>
Further tests at pH 7
35°C : k = 0.0564 d^{-1}; DT_{50} = 12.3 d
25°C : k = 0.0278 d^{-1}; DT_{50} = 25 d (extrapolated using Arrhenius equation)</td><td>85.3 cis/trans 51/49 (batch N° E6788:122B)</td><td>EEC C7</td><td>P/B 669 G</td></tr>
<tr><td>Photolysis characteristics</td><td>DT_{50} = 3.05 d (k = 2.63 x 10^{-6} s^{-1}) at 20 °C
20-25°C; in pure water; sterile conditions, ≤ 1% acetonitrile co-solvent; continuous irradiation at wavelength 304 nm for 72 hrs. Significant degradation (approximately 70%) was observed in dark control samples (k_{hydr} = 1.20 x 10^{-6} s^{-1}). The experimentally observed transformation (about 90% degradation) in water under irradiation (k_{obs} = 3.83 x 10^{-6} s^{-1}; DT_{50} = 2.09 d) thus comprised both hydrolysis and direct phototransformation.</td><td>85.3 cis/trans 51/49 (batch N° E6788:122B)</td><td>UBA draft test guideline “Photo-transformation of chemicals in water, part A, direct photo-transformation” (similar to OECD draft guideline)</td><td>030382</td></tr>
</table>

[9] If estimated half-life exceeds twice the period of data observation, state the percentage of the compound remaining at the end of the observation period as an alternative to estimated half-life.

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Dissociation characteristics	Molecular structure of zeta-cypermethrin clearly shows that this compound will not dissociate in water to form ionic species.	Not applicable	Not applicable	Not applicable
Solubility in organic solvents	At 20 °C: 40.12 g/l n-heptane >1000 g/l p-xylene >1000 g/l 1,2-dichloroethane >1000 g/l acetone >1000 g/l ethyl acetate At 25 °C: >1000 g/l methanol >1000 g/l ethyl acetate	84.43 (batch N° PL98-0937) 85.3 cis/trans 51/49 (batch N° E6788:122B)	EEC A6 (flask method + HPLC-UV analysis for n-heptane)	FMC/FO2017 3/Ch.2125/20 01/9 194AF96343

Table 2. Chemical composition and properties of *zeta*-cypermethrin technical material (TC)

Manufacturing process, maximum limits for impurities ³ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 97.77-98.51 % and percentages of unknowns were 1.49-2.23 %.
Declared minimum *zeta*-cypermethrin content	≥850 g/kg
Relevant impurities ³ 1 g/kg and maximum limits for them	none
Relevant impurities < 1 g/kg and maximum limits for them:	none
Stabilisers or other additives and maximum limits for them:	none

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC and/or TK	Melting point: -3 °C Boiling point: 231 °C at 5 mm Hg (0.7 kPa) (with thermal decomposition)	85.3% pure – cis/trans 51/49 (batch N° E6788:122 B) 86.8% pure (batch N° E7434:36)	EEC A1 EEC A2	FMC/FO20323/Ch.2 386/2001/74 194AF93264
Solubility in organic solvents	At 20 °C: 40.12 g/l n-heptane >1000 g/l p-xylene >1000 g/l 1,2-dichloroethane >1000 g/l acetone >1000 g/l ethyl acetate At 25 °C: >1000 g/l methanol >1000 g/l ethyl acetate	84.43 (batch N° PL98-0937) 85.3 cis/trans 51/49 (batch N° E6788:122 B)	EEC A6 (flask method + HPLC-UV analysis for n-heptane)	FMC/FO20173/Ch.2 125/2001/9 194AF96343
Isomer ratio	*Cis/trans*-ratio should be in the range 55/45 to 45/55			Review Report for Zeta-cypermethrin. SANCO/142/08 final rev 1 , 20 November 2012.

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The present submission is for TC only.

METHODS OF ANALYSIS AND TESTING

The analytical method for the cypermethrin active ingredient (including identity tests) is 332/TC/M/3 (CIPAC 1C, p. 2052) and can be used to determine total cypermethrin content and the cis/trans ratio. Total cypermethrin is determined by GC and cis/trans ratio is determined by normal phase HPLC.

The method(s) for determination of relevant impurities are based on gel permeation chromatographic analysis for tar residues (>600 molecular weight) and high resolution gas chromatographic analysis for the determination of toluene.

Test methods for determination of physico-chemical properties of the technical active ingredient were EC approved methods (including CIPAC, EEC, and OECD methods).

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The content of the active ingredient *zeta*-cypermethrin is expressed as *zeta*-cypermethrin.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from *zeta*-cypermethrin having impurity profiles similar to those referred to in the table above. In certain cases, cypermethrin was used in toxicological evaluations. Those instances are noted in the tables and summaries below. The differences between zeta-cypermethrin and cypermethrin are further explained in the tables below.

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 3. Toxicology profile of *zeta*-cypermethrin technical material, based on acute toxicity, irritation and sensitization.

Species (Strain)	Test	Purity % Note[10]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study/Report number
Rat (Sprague Dawley)	N/A	N/A	Technical report comparing newer acute oral toxicological study Freeman 1999 (A99-5015) with previously conducted Freeman 1989 (A89-2914) and providing new WHO classification. Guideline: None	Freeman 1999 used larger group sizes, so therefore is statistically preferable to Freeman 1989. The technical active ingredient used in Freeman 1999 is representative of current material used for product formulations. Details for both studies are provided below. From these data, the most appropriate classification using WHO's latest criteria is Class II or moderately hazardous.	P-4145A
Rat (Sprague Dawley)	Oral[1]	86 Batch n° G0292-95	Acute, 10 fasted rats/ sex/group received by gavage, a single oral dose of zeta-cypermethrin as a 5% solution in corn oil at 100, 200 or 400 mg/kg bw. Guideline: Study is not fully in compliance with dir EEC 92/69 method B1, or 84/449 or OECD guideline 401(1987-81).	LD_{50}=269mg/kg bw for male and 285 mg/kg bw for female rats. Combined LD_{50}= 278 mg/kg bw.	A99-5015

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

Species (Strain)	Test	Purity % Note11	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study/Report number
Rat (Sprague Dawley)	Oral[1]	88.2 batch n° E6278-103	Acute, 5 fasted rats/ sex/group received by gavage, a single oral dose of zeta-cypermethrin as a 5% solution in corn oil at 50, 100, 150 mg/kg bw (females) and 100, 150, 200 mg/kg bw (males). Guideline: Study is not fully in compliance with dir EEC 92/69 method B1, or 84/449 or OECD guideline 401(1987-81)	LD_{50}=134.4mg/kg bw for male and 86 mg/kg bw for female rats. Combined LD_{50}= 105.8 mg/kg bw.	A89-2914
Rabbit (New Zealand White)	Dermal	88.2 Ref n° E6278-103	Acute. 5 rabbits/sex received 2000 mg/kg zeta-cypermethrin applied to shaved, intact skin beneath a 4X4 gauze pad. The entire trunk of the animals was wrapped with an occlusive wrap for 24 hrs. Guideline: Dir EEC 92/69 Annex V, method B.3 or OECD test guideline 402(1987-81).	LD_{50} > 2000 mg/kg bw	A89-3037
Rat (Sprague Dawley)	Inhalation	95.7 batch n° PL91-333	Acute. 5 rats/sex were exposed to cypermethrin as an aerosol (whole body exposure) at 1.32 mg/l for 4 hours. Two groups of 5 females were exposed to either 2.19 mg/l or 3.48 mg/l cypermethrin. Guideline: EEC 92/69 test method B2, dir 84/449 EEC or OECD test guideline 403 (1981).	[Cypermethrin[2]] LC_{50} = 2.5 mg/l	A91-3534

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

Species (Strain)	Test	Purity % Note11	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study/Report number
Rat (Alpk:ApfSD - Wistar)	Inhalation	72.9 CTL n° Y00334/104/001	Acute. 5 rats/sex/dose were exposed to cypermethrin by nose only to a liquid atomizer at target concentrations of 0.5, 1.0, 2.0 mg/l for 4 hours. Guideline: EEC 92/69 test method B2, dir 84/449 EEC or OECD test guideline 403 (1981).	[Cypermethrin[2]] LC_{50} = 1.26 mg/l	CTL/P/2531
Rabbit (New Zealand White)	Skin Irritation	88.2 lot E6278-103	3 rabbits/sex received 0.5 mL topical applications of zeta-cypermethrin applied to shaved, intact skin at two test sites under 2x2 inch gauze pads. The entire trunk of the animals was wrapped with a semi-occlusive wrap for 4 hrs. The application site was then wiped gently. Guideline: Study is not fully conforming to Dir. EEC 92/69 Annex V, method B.4 or 84/449/EEC or OECD test guideline 404(1992-81).	Non-irritating	A89-3039
Rabbit (New Zealand White)	Eye Irritation	88.2 batch E6278-103	3 male and 6 female rabbits received 0.1 ml zeta-cypermethrin into the right eyes. 30 and 15 min prior dosing, one drop of 0.5% tetracaine HCL was instilled in both eyes to minimize pain. Treated eyes of 3 rabbits were washed at 20-30 seconds after application. Guideline: Study not fully in compliance with dir EEC 92/69 method B.5, or dir 84/449/EEC or OECD 405 guideline.	Non-irritating	A89-3038

Species (Strain)	Test	Purity % Note11	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study/Report number
Species (Strain)	Test	Purity % Note12	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study/Report number
Guinea Pig (Hartley)	Buehler Skin Sensitisation	88.2 batch E6278-103	10 guinea pigs/sex were exposed to 0.3 ml undiluted zeta-cypermethrin applied to the left shoulders (previously clipped free of hair). Three induction treatments were given one week apart. 14 days after 3rd induction, the animals were challenged with the test material on a virgin test site. An additional 5 males and 5 females received 0.3 ml of test material (challenge control group). Skin was observed at 24 and 48 hrs after each application. Guideline: Dir EEC 96/54 method B6 or 92/69-84/449 or OECD 406 guideline (1981-1992).	Skin sensitizer	A89-3040

Footnotes:

1: Two rat acute oral studies were completed for zeta-cypermethrin dissolved in corn oil as a vehicle: Freeman 1989 (A89-2914) and Freeman 1999 (A99-5015). A99-5015 was conducted with a technical active ingredient that is representative of current material used for product formulations, followed more robust testing guidelines, and used a greater number of animals per sex, improving the statistical determination of the LD_{50}. The EU has reviewed A99-5015 and the study was concluded as "acceptable." Please refer to citation P-4145A.

2: The toxicological evaluation of zeta-cypermethrin is based in part on bridging to cypermethrin toxicity data. Cypermethrin is an ester pyrethroid having three chiral carbons and a total of eight isomers. Cypermethrin and zeta-cypermethrin contain the same eight isomers in different proportions, however the two differ in that cypermethrin has a 50:50 *αS*/αR ratio (at the cyano carbon bearing group) whereas zeta-cypermethrin is enriched in the *αS*-enantiomer with a ratio of 88/12 of the *αS*/αR. Both cypermethrin and zeta-cypermethrin have a *cis/trans* ratio of 50/50.

See table below.

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

Isomer	Cypermethrin %	Zeta-cypermethrin %
1. 1**R cis** aR	14	3
2. 1S **cis** a**S**	14	22
3. 1**R cis** a**S**	11	22
4. 1S **cis** aR	11	3
5. 1**R** trans aR	14	3
6. 1S trans a**S**	14	22
7. 1**R** trans a**S**	11	22
8. 1S trans aR	11	3
αS/αR ratio CN bearing carbon	50/50	88/12
Cis/trans ratio	50/50	50/50

Table 4: Neurotoxicological profile of *zeta*-cypermethrin

Species (Strain)	Test	Purity % Note[13]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study number
Rat (Long Evans)	Oral, Acute Neurotoxicity	84.4% Batch no° PL93-533	10 rats/sex/dose received a single dose of undiluted zeta-cypermethrin by gavage at 0, 10, 50 and 250 mg/kg bw. Guideline: Study in compliance with OECD test guideline 424 (1997).	NOAEL= 10 mg/kg bw LOAEL = 50 mg/kg bw	A97-4642
Rat (Long Evans)	Oral, 13-week Neurotoxicity	86% Batch no° G0292-95	10 rats/sex/dose received in their diet containing zeta-cypermethrin at 0, 75, 400, 750 ppm for 13 weeks. Guideline: Study in compliance with OECD test guideline 424 (1997) except for 1st functional test performed at week 4 and not during the 1st or 2nd week of exposure.	Males: NOAEL = 75 ppm (5 mg/kg bw/d) LOAEL = 400 ppm (26 mg/kg bw/d) Females: NOAEL = 400 ppm (31.5 mg/kg bw/d) LOAEL = 750 ppm (55.6 mg/kg bw/d)	A98-4874
Rat (Sprague Dawley	Oral, developmental neurotoxicity	81.8% batch n° PL03-0427	25 female rats/dose received diet containing zeta-cypermethrin at 0, 50, 125, 300 ppm from gestation day (GD) 6 through lactation day (LD) 21. Guideline: Study is in compliance with OECD test guideline 426 (2003).	NOAEL= 125 ppm (9 mg/kg bw/day during gestation and 21.4 mg/kg bw/day during lactation) LOAEL = 300 ppm 21.1 mg/kg bw/day during gestation and 48.7 mg/kg bw/day during lactation)	A2004-5809

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

Table 5. Toxicology profile of *zeta*-cypermethrin technical material based on repeated administration (subacute to chronic)

Species (Strain)	Test	Purity % Note[14]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study number
Rat (Fisher 344)	Oral, 28-day toxicity	88.2 batch n° E6278-103	5 rats/sex/dose received in their diet zeta-cypermethrin for 28 days at 0, 50, 100, 300, 600, 900 and 1500 ppm. Guideline: Study is not fully in compliance with dir EEC 96/54/EEC, B.7, dir EEC 92/69-84/449, or OECD 407 guideline (1995-1981).	NOAEL/NOEL= 300 ppm (26 mg/kg bw/d) LOAEL = 600 ppm (48 mg/kg bw/d)	A89-2819
Dog (Beagle)	Oral, 32-34 day study	95.7 batch n° PL 91-333	4 dogs/sex/dose received in their diet cypermethrin for 32-34 days at 0, 500, 800, 1000 and 1300 ppm Guideline: Study is not fully in compliance with dir EEC 96/54/EEC, B.7, dir EEC 92/69-84/449, or OECD 407 guideline (1995-1981).	[Cypermethrin[1]] NOAEL = 500 ppm (17.8 mg/kg bw/d) LOAEL = 800 ppm (29 mg/kg bw/d)	92-3111
Rat (Fisher)	Oral, 90-day toxicity	88.2 batch n° E6278-103	10 rats/sex/dose received in the diet zeta-cypermethrin at 0, 10, 50, 150, 250, 500, 900 ppm for 90 days. Guideline: Study is not fully in compliance with dir EEC 2001/59/EEC, Annex V B or 87/302 part B or OECD test guideline 408(1998-81).	NOAEL= 250 ppm (16.7 mg/kg bw/d) LOAEL = 500 ppm (33.7 mg/kg bw/d)	A89-2880

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

Species (Strain)	Test	Purity % Note[14]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study number
Dog (Beagle)	Oral, 90-day toxicity	95.7 batch n° PL91-333	4 dogs/sex/dose received in their diet cypermethrin dissolved in corn oil and added to the diet at 0, 300, 600, 800, 1100 ppm for 13 weeks. Guideline: Study is not fully in compliance with dir EEC 2001/59/EEC or 87/302 part B or OECD test guideline 409(1998-1981).	[Cypermethrin[1]] NOAEL = 600 ppm (20.7 mg/kg bw/d) LOAEL = 800 ppm (24.6 mg/kg bw/d)	A92-3706
Dog (Beagle)	Oral, 1 year toxicity	95.7 lot n° PL91-333	4 dogs/sex/dose received cypermethrin in diet at 100, 200, 600, and 1100 ppm for 52 weeks. Guideline: Study is not fully in compliance with dir EEC 87/302 part B or OECD test guideline 452 (1981).	[Cypermethrin[1]] NOAEL = 200 ppm (6 mg/kg bw/d) LOAEL = 600 ppm (18.1 mg/kg bw/d)	92-3115, A93-3821
Rat (Alpk:ApfSD - Wistar)	Inhalation, 21-day toxicity	87.1 batch n°. P36.R079383	5 rats/sex/dose were exposed nose-only to cypermethrin at target concentrations of 10, 50, 250 µg/L for 6 hr/day, for 15 days over a 21-day period. Guideline: Study is not fully in compliance with dir EEC 92/69 Annex V part B.9 or 84/449 or OECD test guideline 412 (1981).	[Cypermethrin[1]] NOAEL = 10 µg/L (2.7 mg/kg bw/d) LOAEL = 50 µg/L (13.5 mg/kg bw/d)	CTL/P/4534

Species (Strain)	Test	Purity % Note[14]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study number
Rat (Sprague-Dawley)	Dermal, 21-day toxicity	86 batch n° G-0292-95	10 rats/sex/dose were exposed to zeta-cypermethrin at doses of 100, 500 and 1000 mg a.i./kg bw/d which were applied undiluted to the intact skin. The doses were applied once daily for 6 hours over a 21 day period. Guideline: Study is not fully conforming to dir EEC 92/69 B.9 or EEC/84/449 or OECD test guideline 410(1981).	NOAEL local effects: < 100 mg/kg bw/d NOAEL systemic toxicity: ≥ 1000 mg/kg bw/d LOAEL = 100 mg/kg bw/d	A98-4885
Rabbit (New Zealand White)	Dermal, 3 week toxicity	91.5 batch n° P 19	10 rabbits/sex/dose were exposed to cypermethrin at doses of 2, 20 and 200 mg a.i./kg bw/d diluted in polyethylene glycol which were applied to the intact or abraded skin for 3 weeks (5 days/week). The doses were applied once daily for 6 hours. Guideline: Study is not fully conforming to dir EEC 92/69 B.9 or EEC/84/449 or OECD test guideline 410(1981).	[Cypermethrin[1]] NOAEL local effects=2 mg/kg bw/d LOAEL local effects=20 mg/kg bw/d NOAEL systemic toxicity= 20 mg/kg bw/d LOAEL systemic effects=200 mg/kg bw/d	CTL/P/588

Species (Strain)	Test	Purity % Note[14]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study number
Rat (Sprague-Dawley)	Two generation, reproductive toxicity	89.6 batch n° E-6539-78	30 male and 30 female rats received in their diet zeta-cypermethrin at 0, 7.5, 25, 100, 375, 750 ppm for 12 weeks prior to mating and throughout the reproduction phase. Guideline: Study protocol is not fully conforming to EEC 87/302 Annex V B.35 or OECD guideline 416 (1983).	NOAEL reproduction = P1: 750 ppm (43 mg/kg bw/d) F1: 375 ppm (22 mg/kg bw/d) NOAEL systemic toxicity parents = 100 ppm (5.9 mg/kg bw/d) NOAEL developmental toxicity = 100 ppm (5.9 mg/kg bw/d)	A89-2959
Rat (Sprague-Dawley)	Developmental toxicity, embryo-fetal toxicity and teratogenic potential	89.6 Batch nº E-6539-78	25 female rats were given zeta-cypermethrin at a dose of 0, 5, 12.5, 25 or 35 mg/kg b.w. per day in corn oil by gavage from day 6 to 15 of gestation. Guideline: study protocol is fully compliance with OECD guideline 426 (2001-1981).	NOAEL maternal tox= 12.5 mg/kg bw/d based on clinical signs of toxicity and transient effects on body weight, weight gain and food consumption occurring at 25 mg/kg bw/d. NOAEL developmental tox = 35 mg/kg bw/d, highest dose tested based on no evidence of effects on fetal development.	A89-2958

Species (Strain)	Test	Purity % Note[14]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin, unless otherwise noted in brackets]	Study number
Rat (Wistar-derived)	Combined Chronic and carcinogenicity dietary rat study	88.2-93.1 (cypermethrin) Batch nº P19, P24, P26	52 rats of each sex were fed diets containing cypermethrin at concentrations of 0, 20, 150 or 1500 ppm and 12 rats of each sex per dose (interim kill) were treated for 24 and 12 months respectively. Guideline: study protocol is not fully compliance with EEC 87/302 Annex V, B.30 or OECD guideline 453 (1981).	The NOAEL was 150 ppm, equivalent to 7.5 mg/kg bw per day, based on clinical signs and decreased body-weight gain at 1500 ppm, equivalent to 75 mg/kg bw per day	CTL/P/669 (FMC study No A82-761)
Mice (SPF-Swiss-derived)	Carcinogenicity dietary mice study	91.5-94.2 (cypermethrin) Batch nº P19, ACD/79/134, 47	70 males and 70 female mice received diets containing cypermethrin at concentrations of 0, 100, 400 or 1600 ppm for up to 101 weeks. Guideline: study protocol is not fully in compliance with EEC 87/302 Annex V B.32 or OECD guideline 453 (1981)	The NOAEL was 400 ppm, equivalent to 61 mg/kg bw per day, based on reduced body-weight gain at 1600 ppm, equivalent to 240 mg/kg bw per day. The NOAEL for carcinogenicity was 1600 ppm, equivalent to 240 mg/kg bw per day, the highest dose tested	CTL/P/687 (FMC study No. A82-762)

Footnote:

1: The toxicological evaluation of zeta-cypermethrin is based in part on bridging to cypermethrin toxicity data. Cypermethrin is an ester pyrethroid having three chiral carbons and a total of eight isomers. Cypermethrin and zeta-cypermethrin contain the same eight isomers in different proportions, however the two differ in that cypermethrin has a 50:50 *αS*/αR ratio (at the cyano carbon bearing group) whereas zeta-cypermethrin is enriched in the *αS*-enantiomer with a ratio of 88/12 of the *αS*/αR. Both cypermethrin and zeta-cypermethrin have a *cis/trans* ratio of 50/50. See table below.

Isomer	Cypermethrin %	Zeta-cypermethrin %
1. 1**R cis** aR	14	3
2. 1S **cis** a**S**	14	22
3. 1**R cis** a**S**	11	22
4. 1S **cis** aR	11	3
5. 1**R** trans aR	14	3
6. 1S trans a**S**	14	22
7. 1**R** trans a**S**	11	22
8. 1S trans aR	11	3
αS/αR ratio CN bearing carbon	50/50	88/12
Cis/trans ratio	50/50	50/50

Table 6. Mutagenicity profile of *zeta*-cypermethrin technical material based on *in vitro* and *in vivo* tests

Species (Strain)	Test	Purity % Note[15]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin]	Study number
Salmonella typhimurium	Bacterial mutagenicity assay	88.2 batch n° E6278-103	Strains TA 100, TA1535, TA 1538, TA98, TA 1537 were exposed to *zeta*-cypermethrin dissolved in DMSO using the plate incorporation assay. A preliminary toxicity test was performed at 10, 33, 67, 100, 333, 667, 1000, 3333, 6667, 10000 µg/plate. Five concentrations (100, 333, 1000, 3333, 10000 µg/plate) were tested with and without a microsomal enzyme preparation from liver from Arochlor 1254 pretreated rats in the first test and from 333 to 10000 µg/plate in the second test. Guideline: Dir 2000/32/EEC Annex 4D, or dir 92/69/EEC method B 14, dir 84/449 or OECD 471(1997-83).	Without metabolic activation system, a slight increased mutation rate was seen in tester strain TA 100 at 3333 and 10000 µg/plate with a maximum increase of 2-fold in mean revertants/plate at 10000 µg/plate. Negative results were observed in strain TA 1535, TA 1537, TA 1538 and TA 98 with/without metabolic activation system and in strain TA 100 with activation. *zeta*-cypermethrin was mutagenic in tester strain TA 100 without metabolic activation system.	A89-3012

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

Species (Strain)	Test	Purity % Note[16]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin]	Study number
Chinese Hamster ovary cells (CHO-K1-BH4)	CHO/HGPRT Mammalian cell forward gene mutation assay	88.2 batch n° E6278-103	Cells were exposed to *zeta*-cypermethrin dissolved in DMSO with or w/o metabolic activation system (S9 mix from Aroclor 1254 pretreated rat liver). The initial assay was conducted at dose levels of 50, 100, 400, 700, 1000 µg/ml with and w/o S9 mix. 5 x 10^5 cells/25 cm^2 flasks were used. The confirmatory assay was conducted at 1, 10, 25, 50, 100 µg/ml. Guideline: Study is conforming to dir 2000/32/EEC, Annex 4E or dir 87/302 or OECD guideline 476(1997-1984).	Non-mutagenic	A89-3013

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

Species (Strain)	Test	Purity % Note[17]	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin]	Study number
Chinese Hamster ovary cells	Chromosomal aberration test	88.1 batch n° E6278-103	Cells were exposed to zeta-cypermethrin dissolved in DMSO with or w/o metabolic activation system (S9 mix from rat liver induced with Aroclor 1254) at 0.0332 to 996 µg/ml in a range finding test with or w/o S9. Replicate cultures of CHO cells were incubated with 40-800 µg/ml in the 20 hr non-activation test and with 100 –1000 µg/ml in the 10 and 20 hr test with metabolic activation. Guideline: Study is not fully conforming to dir 2000/32/EEC, Annex 4A or dir 92/69-84/449 or OECD guideline 473(1997-1983).	Non-clastogenic	A89-3014

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

Species (Strain)	Test	Purity % Note18	Guideline, duration, doses and conditions	Result [Zeta-Cypermethrin]	Study number
Rat (Fischer 344 Hepatocytes)	Unscheduled DNA synthesis assay	88.2 lot n° E6278-103	Primary rat hepatocytes from a freshly perfused rat liver were used. *zeta*-Cypermethrin was solubilized in DMSO. DMBA was used as positive control and solvent was DMSO. Ten concentrations ranging from 14 µg/ml to 5000 µg/ml were used. However, due to a technical error, the dosing solution resulted in 4500 µg/ml. 5 $x10^5$ hepatocytes/plate were treated. Guideline: Study is not fully conforming to dir 87/302/EEC, Annex V B or OECD guideline 482 (1986).	*zeta*-Cypermethrin was considered to be inactive in the primary rat hepatocytes UDS assay.	T8853.380

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

Species (Strain)	Test	Purity % Note[19]	Guideline, duration, doses and conditions	Result [*zeta*-Cypermethrin]	Study number
Rat (Sprague-Dawley)	*In vivo*, chromosomal aberration test in bone marrow	90.7 n° PL92-81	5 rats/sex/dose/sacrifice time were used and were treated at 31.25, 62.5, and 125 mg/kg bw. Rats were sacrificed about 6, 18 and 30 hours after treatment and 30 hr after treatment with vehicle control. An additional group of rats were exposed at the top dose as replacements for any, which died. Bone marrow of tibiae were removed. Positive control, cyclophosphamide, was administered to 5 rats/sex as a single oral dose of 60 mg/kg and animals were sacrificed 18 and 30 hrs later. Guideline: Study is not fully conforming to dir 2000/32/EEC, or dir 92/69/EEC or 84/449/EEC or OECD guideline 475(1997-84).	*zeta*-cypermethrin, under the exposure conditions of the assay induced no significant increases in the percentage of chromosomally aberrant cells in either sex at any dose level over the level of aberrations observed in the vehicle control. *zeta*-cypermethrin did not induce *in vivo* chromosomal aberrations under these experimental conditions.	A92-3675

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

Table 7. Ecotoxicology profile of *zeta*-cypermethrin technical material

Species	Test	Purity % Note[20]	Guideline, duration, doses and conditions	Result [*zeta*-Cypermethrin, unless otherwise noted in brackets]	Study number
Pseudokirchneriella subcapitata (green alga)	Growth inhibition test	92.4 batch n°: PL98-0937	6 replicates per treatment, 1.0 x 104 cells/mL nominal: control; solvent control (acetone); 1.0 mg a.s./L. 96 hours static toxicity test Guidelines: C.3 (92/69/EEC) OECD Guideline 201: Alga, Growth Inhibition Test (1984)	EC_{50} > 0.144 mg a.s./L NOEC = 0.144 mg a.s./L	D17AG, A-17-02-19
Oncorhynchus mykiss (Rainbow trout)	Acute toxicity	88.2 batch n°: E6278-103	10 fish per test vessel, 2 replicates per treatment (total of 20 organisms per treatment, except for solvent control there were 19 organisms), 69-day old juveniles, no indication of weight, length or fish loading nominal: control; solvent control (dimethyl formamide); 0.70, 1.17, 1.94, 3.24, 5.40 µg *zeta*-cypermethrin/L mean measured: control; solvent control (dimethyl formamide); 0.47, 0.82, 1.65, 2.77, 5.27 µg *zeta*-cypermethrin/L, 96 hours flow-through test Guideline: FIFRA guideline 72-3 (1982)	LC_{50} = 0.00069 mg *zeta*-cypermethrin/L NOEC could not be determined as some of the test organisms were affected at the test substance lowest concentration used in this test.	3903026-0700-3140

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

Species	Test	Purity % Note[20]	Guideline, duration, doses and conditions	Result [*zeta*-Cypermethrin, unless otherwise noted in brackets]	Study number
Cyprinodon variegates (Sheepshead minnow)	Acute toxicity	88.2 batch n°: E6278-103	10 fish per test vessel, 2 replicates per treatment, at least 91 days old, no indication of weight, length or fish loading nominal: control; solvent control (dimethyl formamide); 0.70, 1.17, 1.94, 3.24, 5.40 µg zeta-cypermethrin/L mean measured: control; solvent control (dimethyl formamide); 0.28, 0.62, 0.91, 1.79, 3.00 µg zeta-cypermethrin/L 96 hours flow-through test Guideline: FIFRA guideline 72-3 (1982)	LC_{50} = 0.00237 mg zeta-cypermethrin/L NOEC = 0.00179 mg zeta-cypermethrin/L	3903026-0600-3140
Daphnia magna (water flea)	Acute toxicity	92.4 batch n°: PL98-0937	5 daphnids per test vessel, 4 replicates per treatment, 6 – 24 hours old 48 hours semi-static test (renewal after 24 hours). Tested concentrations: control; solvent control (acetone); 0.032, 0.071, 0.155, 0.342, 0.751, 1.653, 3.636, 8.00, 17.60 µg a.s./L Guideline: 92/69/EEC C.2.	EC_{50} = 0.000141 mg a.s./L NOEC = 0.000035 mg a.s./L	D15DA, A-17-02-01

Species	Test	Purity % Note[20]	Guideline, duration, doses and conditions	Result [*zeta*-Cypermethrin, unless otherwise noted in brackets]	Study number
Gammarus pulex (gammarids)	Acute toxicity	93.7 batch n°: PL97-1605	10 gammarids per test vessel, 2 replicates per treatment, less than 7 days old 96 hours static test Tested concentrations: control; solvent control (acetone); 0.19, 0.38, 0.75, 1.5, 3.0 ng a.s./L Guideline: EPA OPPTS 850.1020	EC_{50} = 0.0000013 mg a.s./L NOEC < 0.19 ng a.s./L = 0.00000019 mg a.s./L	282.0698.6126.179

Footnote:

1: The toxicological evaluation of zeta-cypermethrin is based in part on bridging to cypermethrin toxicity data. Cypermethrin is an ester pyrethroid having three chiral carbons and a total of eight isomers. Cypermethrin and zeta-cypermethrin contain the same eight isomers in different proportions, however the two differ in that cypermethrin has a 50:50 *αS*/αR ratio (at the cyano carbon bearing group) whereas zeta-cypermethrin is enriched in the *αS*-enantiomer with a ratio of 88/12 of the *αS*/αR. Both cypermethrin and zeta-cypermethrin have a *cis/trans* ratio of 50/50. See table below.

Isomer	Cypermethrin %	Zeta-cypermethrin %
1. 1**R cis** aR	14	3
2. 1S **cis** a**S**	14	22
3. 1**R cis** a**S**	11	22
4. 1S **cis** aR	11	3
5. 1**R** trans aR	14	3
6. 1S trans a**S**	14	22
7. 1**R** trans a**S**	11	22
8. 1S trans aR	11	3
αS/αR ratio CN bearing carbon	50/50	88/12
Cis/trans ratio	50/50	50/50

zeta-Cypermethrin was evaluated by the WHO IPCS for hazard classification in 2009. The WHO hazard classification of zeta-cypermethrin is Class Ib (adjusted classification for liquids).

It may be noteworthy that in 2009, the publication of revised classification of the WHO Hazard Classes included an alignment with the Globally Harmonized System (GHS) Acute Toxicity Hazard Categories for acute oral toxicity (http://www.who.int/ipcs/publications/pesticides_hazard_2009.pdf).

Under this alignment, certain inconsistencies in these two classification systems led to a classification of *zeta*-cypermethrin TC as "Class Ib Highly Hazardous" based upon the *liquid technical* (FMC Study Reference A89-2914). Furthermore, it should be noted that the zeta-cypermethrin (*Fury 10 EW*) formulation would be classified as Class II Moderately Hazardous.

As the classification of the TC was deemed to not properly reflect the hazard profile of the compound, FMC in 2012 submitted a more recent and robust data package to WHO on the *technical* material (references: FMC Study Reference No. A99-5015 and Study Report No. P-4145A) which would align the classification to that of the *end use formulation* to Class II Moderately Hazardous. The following table summarizes this information:

Study/Classification Scheme	***zeta*-cypermethrin**	**LD_{50} mg/kg bw/day***	**Resulting Classification**
1989 study under *former* (2004) WHO classification criteria for liquids (*20-200) (Freeman; A89-2914)	Technical material	86 (females)	WHO Highly Hazardous (Ib)
1989 study under GHS classification criteria (*50-300) (Freeman; A89-2914)	Technical material	86 (females)	GHS Category 3 (less toxic than WHO Ib)
If classification was correctly based upon the formulation under the *aligned* 2009 WHO/GHS classification (*50-2000)	Fury 10 EW formulation	385	Moderately hazardous (II)
1999 study under the *aligned* 2009 WHO/GHS classification (*50-2000) (Freeman; A99-5015) and (Gammon and Kikta; Report P-4145A)	Technical material	285 (females)	Moderately hazardous (II)

In the report (Gammon and Kikta; Report P-4145A) the acute oral toxicity studies for the technical material cited in the above table are reviewed, concluding that the most appropriate classification using the WHO recent (2009) classification criteria is Class II or moderately hazardous for zeta-cypermethrin. The report continues that, although current (2006) OECD guidelines allow fewer animals for assessing

acute toxicity, it is statistically preferable to use larger group sizes, as was done for the 1999 study. It is also important to note that the sample used in the 1999 study is representative of the technical active ingredient that is used in the current manufacturing of formulated product.

ANNEX 2

References

(sorted by study number)

Study number	Author	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
N/A	EC	2009	Commission Directive 2009/37/EC of 23 April 2009.
N/A	EC	2012	Final: Review report for the active substance zeta-cypermethrin. SANCO/142/08 rev 1 20 November 2012.
30382		2003	Determination of the direct phototransformation of Zeta-Cypermethrin and m-PB acid in water. Report 030382. GLP. C.A.U. GmbH, Germany. Unpublished.
194AF90196		1991	Physical properties of FMC 56701. Report 194AF90196. GLP. FMC Corporation, USA. Unpublished.
194AF93264		1994	Additional physical properties of Zeta-cypermethrin. Report 194AF93264. GLP. FMC Corporation, USA. Unpublished.
194AF96343		1996	Solubility of Zeta-cypermethrin in methanol and ethyl acetate. Report 194AF96343. GLP. FMC Corporation, USA. Unpublished.
282.0698.6126.179		1999	Zeta-cypermethrin - Acute toxicity to gammarids (*Gammarus pulex*) under static conditions. Report 282.0698.6126.179. GLP. Unpublished.
282.0698.6126.179		2003	Zeta-cypermethrin - Acute toxicity to gammarids (*Gammarus pulex*) under static conditions (Addendum to final report). Report 282.0698.6126.179. GLP. Unpublished.
3903026-0600-3140		1990	Cypermethrin-S (FMC 56701): Acute toxicity to sheepshead minnow (*Cyprinodon variegatus*) under flow-through test conditions. Report 3903026-0600-3140. GLP. Unpublished.
3903026-0700-3140		1990	Cypermethrin-S (FMC 56701): Acute toxicity to rainbow trout (*Oncorhynchus mykiss*) under flow-through test conditions. Report 3903026-0700-3140. GLP. Unpublished.
92-3111 (A92-3682)		1993	A 28-day oral toxicity study of FMC 30980 technical in the dog via dietary administration. Report 92-3111 (A92-3682). GLP. Unpublished.
92-3115 (A93-3821)		1995	A chronic (12 month) oral toxicity study of FMC 30980 technical in the dog via dietary administration. Report 92-3115 (A93-3821). GLP. Unpublished.
A89-2819		1990	28-day rangefinding study in rats. Report A89-2819. GLP. Unpublished.
A89-2880		1990	Ninety-day feeding study in rats. Report A89-2880. GLP. Unpublished.
A89-2914		1989	Acute oral toxicity study in rats. Report A89-2914. GLP. Unpublished.
A89-2959		1991	Multigeneration study with FMC 56701 technical administered orally via diet to Crl:CD (SD) BR rats. Report A89-2959. GLP. Unpublished.
A89-3012		1990	Salmonella/mammalian microsome plate incorporation mutagenicity assay (AMES test). Report A89-3012. GLP. Unpublished.
A89-3013		1990	CHO/HGPRT mutation assay with confirmation. Report A89-3013. GLP. Unpublished.

Study number	Author year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
A89-3014	1990	In an in vitro cytogenetic assay measuring chromosomal aberration frequencies in chinese hamster ovary (CHO) Cells: With multiple harvests under conditions of metabolic activation with a confirmatory assay. Report A89-3014. GLP. Unpublished.
A89-3037	1990	Acute dermal toxicity study in rabbits. Report A89-3037. GLP. Unpublished.
A89-3038	1990	Primary eye irritation study in rabbits. Report A89-3038. GLP. Unpublished.
A89-3039	1990	Primary skin irritation study in rabbits. Report A89-3039. GLP. Unpublished.
A89-3040	1990	Skin sensitization study in guinea pigs. Report A89-3040. GLP. Unpublished.
A91-3534	1992	Acute inhalation toxicity study in rats. Report A91-3534. GLP. USA.
A92-3675	1993	Mutagenicity test on FMC 56701-technical measuring chromosomal aberrations in vivo in rat bone marrow cells. Report A92-3675. GLP. Unpublished.
A92-3706	1994	A subchronic (3-month) oral toxicity study of FMC 30980 technical in the dog via dietary administration. Report A92-3706. GLP. Unpublished.
A98-4885	1999	Zetacypermethrin technical 21-day repeated-dose dermal study in rats. Report A98-4885. GLP. Unpublished.
A99-5015	1999	Zetacypermethrin technical - Acute oral toxicity study in rats. Report A99-5015. GLP. Unpublished.
CTL/P/2531	1989	Cypermethrin: 4-hour acute inhalation toxicity study in the rat. Report CTL/P/2531. Unpublished.
CTL/P/4534	1994	Cypermethrin: 21 day sub-acute inhalation toxicity study in the rat. Report CTL/P/4534. GLP. Unpublished.
CTL/P/588	1981	Cypermethrin technical: Subacute dermal toxicity study in rabbits. Report CTL/P/588. Not GLP. Unpublished.
D15DA, A-17-02-01	2002	A study on the Daphnia acute toxicity of Zeta-cypermethrin according to the EEC directive 92/69 method C.2, "Acute toxicity for Daphnia." Report D15DA, A-17-02-01. GLP. Unpublished.
D17AG, A-17-02-19	2002	A study on the toxicity of Zeta-cypermethrin to algae (*Pseudokirchneriella subcapitata*). Report D17AG, A-17-02-19. GLP. Unpublished.
FMC/FO20173/Ch.2125/2001/9	2001	Solubility of Zeta-Cypermethrin technical in organic solvents. Report FMC/FO20173/Ch.2125/2001/9. GLP. Departement de Phytopharmacie, Belgium. Unpublished.
FMC/FO20323/Ch.2386/2001/74	2001	Physico-chemical data on pure Zeta-cypermethrin. Report FMC/FO20323/Ch.2386/2001/74. GLP. Departement de Phytopharmacie, Belgium. Unpublished.
P/B 669 G	2003	Zeta-Cypermethrin and its degradates: Hydrolysis as a function of pH. Report P 669 G. GLP. PTRL Europe, Germany. Unpublished.
P/B 660 G	2003	Zeta-Cypermethrin and its degradates: Determination of partition coefficients (log Pow). Report P/B 660 G. GLP. PTRL Europe, Germany. Unpublished.

Study number	Author year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
P-4145A	2012	Zeta-Cypermethrin: WHO reclassification based upon a new acute toxicity study. Report P-4145A. Not GLP. Unpublished.
T8853.380 (A89-3015)	1989	Unscheduled DNA synthesis in rat primary hepatocytes. Report T8853.380 (A89-3015). GLP. Unpublished.
A89-2958	1990	Developmental toxicity (Embryo-fetal toxicity and teratogenic potential) study of FMC 56701 technical administered orally via gavage to Crl:CD (SD) BR presumed pregnant rats.
CTL/P/669 (A82-761)	1982	Cypermethrin – 2 year feeding study in rats. CTL/P/669 (A82-761). Unpublished.
CTL/P/687 (A82-762)	1982	Cypermethrin – lifetime feeding study in mice. CTL/P/687 (A82-762). Unpublished
A97-4642	1998	FMC 56701 technical acute neurotoxicty screen in rats. Report A97-4642. GLP. Unpublished.
A98-4874	1999	Zeta-cypermethrin technical subchronic neurotoxicty screen in rats. Report A98-4874. GLP. Unpublished.
A2004-5809	2005	A dietary developmental neurotoxicity study of zeta-cypermethrin technical in rats. Unpublished.