Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

FOSETYL-ALUMINIUM

aluminium tris-O-ethylphosphonate

2022

TABLE OF CONTENTS

FOSETYL-ALUMINIUM

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.

FAO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may 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 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. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

PART ONE

SPECIFICATIONS

FOSETYL-ALUMINIUM

INFORMATION

ISO common names

fosetyl (E-ISO, (m) F-ISO, BSI), refers to the acid, ethyl hydrogen phosphonate
fosetyl-aluminium, modified ISO 1750 (published)

Synonyms

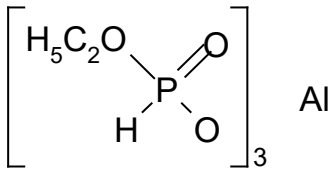
fosetyl: efosite
fosetyl-aluminium: efosite-Al; EPAL

Chemical names

IUPAC fosetyl: ethyl hydrogen phosphonate
fosetyl-aluminium: aluminium *tris*-*O*-ethylphosphonate

CA fosetyl: ethyl hydrogen phosphonate
fosetyl-aluminium: aluminium *tris*-*O*-ethylphosphonate

Structural formula (fosetyl-aluminium)



Empirical formula

fosetyl: $C_2H_7O_3P$
fosetyl-aluminium: $C_6H_{18}AlO_9P_3$

Relative molecular mass

fosetyl: 110.03
fosetyl-aluminium: 354.14

CAS Registry number

fosetyl: 15845-66-6
fosetyl-aluminium: 39148-24-8

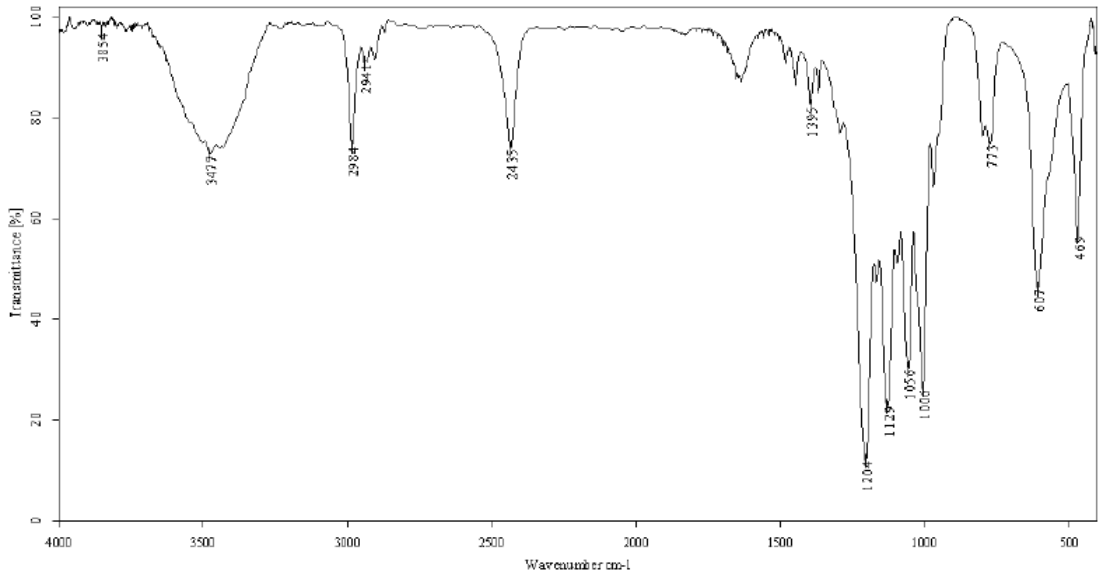
CIPAC number

fosetyl: 384
fosetyl-Aluminium: 384.013

Identity tests

HPLC retention time; IR spectrum (see below)

Bayer CropScience



Echantillon : EA 11678D5 TV3169B	Chemin : D:\Données IR\IFS 48\Data\Full service\Autres\Etude	Appareil : IFS48
Technique : KBr	Fichier : E99_188.0	Nombre de scans : 32
Opérateur et N° danalyse : JVAS-94136	Gamme spectrale : 3999.64-400.157	Résolution : 2
Mesurée le : 8/9/1999	Méthode : ETU	Zerofilling : 2

FOSETYL-ALUMINIUM TECHNICAL MATERIAL

FAO Specification 384.013 / TC (December 2021*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (384/2010, 384.013/2012 & 384/2020). It should be applicable to TC produced by these manufacturers 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 reports (384/2010, 384.013/2012 and 384/2020), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of fosetyl-aluminium, together with related manufacturing impurities, and shall be a white crystalline powder, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (384/TC/M/2, CIPAC Handbook J, p.66, 2000: 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 **Fosetyl-aluminium content** (384/TC/M/3, CIPAC Handbook J, p.66, 2000)

The fosetyl-aluminium content shall be declared (not less than 960 g/kg, equivalent to 895 g/kg fosetyl) and, when determined, the average measured content shall not be lower than the declared minimum content.

3 Relevant impurities

3.1 **Water** (MT 30.6, CIPAC Handbook P, p. 222, 2021)

Maximum: 7 g/kg.

4 Physical properties

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

pH range: 3.0 to 6.0

Note 1 To identify the TC as fosetyl-aluminium by the CIPAC method, IR spectra obtained from the sample and an authentic standard must be compared. The CIPAC HPLC method identifies only the fosetyl moiety. Fosetyl-aluminium contains 7.6 % (w/w) aluminium and, to confirm that the active ingredient is in the form of fosetyl-aluminium (and not some other salt), a semi-quantitative method for determination of aluminium content by chelatometric titration is provided in Appendix 1.

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

FOSETYL-ALUMINIUM WETTABLE POWDER

FAO Specification 384.013 / WP (December 2021*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose names are listed in the evaluation report (384.013/2010). It should be applicable to relevant products 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 (384.013/2010), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of technical fosetyl-aluminium, complying with the requirements of FAO specification 384/TC (December 2021), together with filler(s) and any other necessary formulants. It shall be in the form of a fine powder, free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (384/TC/M/2, CIPAC Handbook J, p.66, 2000: 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 **Fosetyl-aluminium content** (384/WP/M2, CIPAC Handbook J, p.68, 2000)

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

Declared content in g/kg	Tolerance
above 250 up to 500 above 500 Note: the upper limit is included in the lower range	± 5 % of the declared content ± 25 g/kg

3 Relevant impurities

3.1 **Water** (MT 30.6, CIPAC Handbook P, p.222, 2021)

Maximum: 15 g/kg.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://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 **pH range** (MT 75.3, CIPAC Handbook J, p.131, 2000)

pH range: 3.0 to 5.0.

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

Maximum: 1 % retained on a 75 µm test sieve.

4.3 **Suspensibility** (MT 184.1, CIPAC Handbook P, p. 245, 2021) (Notes 2 & 3)

A minimum of 70 % of the fosetyl-aluminium content found under 2.2 shall be in suspension after 30 min in CIPAC standard water D at 25 ± 5 °C.

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

Maximum: 50 ml after 1 min.

4.5 **Wettability** (MT 53.3, CIPAC Handbook F, p.164, 1995)

The formulation shall be completely wetted in 2 min without swirling.

5 Storage stability

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

After storage at 54 ± 2 °C for 14 days, the determined average active ingredient content must not be lower than 97 %, relative to the determined average content found before storage (Note 5), and the formulation shall continue to comply with the clause for:

- pH range (4.1),
- wet sieve test (4.2),
- suspensibility (4.3),
- wettability (4.5).

Note 1 To identify the TC as fosetyl-aluminium by the CIPAC method, IR spectra obtained from the sample and an authentic standard must be compared. The CIPAC HPLC method identifies only the fosetyl moiety. Fosetyl-aluminium is 7.6 % aluminium and, to confirm that the active ingredient is in the form of fosetyl-aluminium (and not some other salt), a semi-quantitative method for determination of aluminium content by a chelatometric titration is provided in Appendix 1.

Note 2 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in method MT 184.

Note 3 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 chemical assay. In case of dispute, chemical assay shall be the "referee method".

Note 4 The test should be carried out at the highest application concentration. The test is to be conducted in CIPAC standard water D.

Note 5 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

FOSETYL-ALUMINIUM WATER DISPERSIBLE GRANULES

FAO Specification 384.013 / WG (December 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 (384 / 2010). It should be applicable to relevant products 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 (384 / 2010), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of a homogeneous mixture of technical fosetyl-aluminium, complying with the requirements of FAO specification 384/TC (December 2021), together with carriers and any other necessary formulants. It shall be in the form of granules for application after disintegration and dispersion in water. The formulation shall be dry, free-flowing, essentially non-dusty, and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (384/TC/M/2, CIPAC Handbook J, p.66, 2000, 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 **Fosetyl-aluminium content** (384/WG/M/3, CIPAC Handbook J, p.69, 2000)

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

Declared content in g/kg	Tolerance
above 250 up to 500 above 500 Note: the upper limit is included in the lower range	± 5 % of the declared content ± 25 g/kg

3 Relevant impurities

3.1 **Water** (MT 30.6, CIPAC Handbook P, p.222, 2021)

Maximum: 10 g/kg.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://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 **pH range** (MT 75.3, CIPAC Handbook J, p.131, 2000)

pH range: 3.0 to 5.0.

4.2 **Wettability** MT 53.3, CIPAC Handbook F, p.164, 1995)

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

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

Maximum: 1 % of the formulation shall be retained on a 75 µm test sieve.

4.4 **Degree of dispersion** (MT 174, CIPAC Handbook F, p.435, 1995)

Dispersibility: minimum 80 % after 1 minute of stirring.

4.5 **Suspensibility** (MT 184.1, CIPAC Handbook P, p. 245, 2021) (Notes 2 & 3)

A minimum of 70 % shall be in suspension after 30 min in CIPAC standard water D at 25 ± 5 °C.

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

Maximum: 50 ml after 1 min.

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

Essentially non-dusty.

4.8 **Flowability** (MT 172.2, CIPAC Handbook P, p. 241, 2021)

100 % of the formulation shall pass through a 5 mm test sieve after 20 drops of the sieve.

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

Minimum: 98 % attrition resistance.

5 Storage stability

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

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

- pH range (4.1),
- wet sieve test (4.3),
- degree of dispersion (4.4),
- suspensibility (4.5),
- dustiness (4.7)
- attrition resistance (4.9),

Note 1 To identify the TC as fosetyl-aluminium by the CIPAC method, IR spectra obtained from the sample and an authentic standard must be compared. The CIPAC HPLC method identifies only the fosetyl moiety. Fosetyl-aluminium consists of 7.6 % aluminium and, to confirm that the active ingredient is in the form of fosetyl-aluminium (and not some other salt), a semi-quantitative method for determination of aluminium content by a chelatometric titration is provided in Appendix 1.

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

Note 3 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 4 The test should be carried out at the highest application concentration. The test is to be conducted in CIPAC standard water D.

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

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

PART TWO

EVALUATION REPORTS

FOSETYL-ALUMINIUM

FOSETYL-ALUMINIUM

FAO/WHO EVALUATION REPORT 384.013/2020

Recommendations

The Meeting recommended the following.

(i) The fosetyl-aluminium TC as proposed by Limin Chemical Co.,Ltd. should be accepted as equivalent to the fosetyl reference profile.

(ii) The FAO specification for fosetyl-aluminium TC should be extended to encompass the material produced Limin Chemical Co.,Ltd.

Appraisal

The data for fosetyl-aluminium (fosetyl-Al) were evaluated in support of the extension of the existing FAO specification 384.013/TC (2013).

Fosetyl-Al is not under patent and has not been evaluated by the FAO/WHO JMPR.
The first specification for fosetyl-Al was developed and published in the year 2000 still under the old procedure. In 2009, Bayer CropScience submitted new draft specifications and supporting data to revise the old procedure specifications according to the new procedure. The reference specifications and supporting data for fosetyl-Al TC had been submitted by Bayer CropScience and the FAO/WHO specifications had been published in 2013.

The Meeting considered a data package on fosetyl-aluminium, submitted by Limin Chemical Co.,Ltd (Limin) in December 2019, in support of an extension of the published FAO specification for fosetyl-Al TC. A statement has been provided confirming that the confidential data on the manufacturing process and declaration of composition submitted to the FAO were the same as those submitted to SALUD (the Mexican ministry of public health).

The Meeting was provided with confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1g/kg, as well as any relevant impurities below 1g/kg, supported by 5 batch analysis data. The mass balance range is 989 - 992 g/kg. The maximum limits for the impurities were supported by the 5-batch data and are statistically justified. The data provided supported a minimum fosetyl-Al content of 975 g/kg and complies with the existing FAO specifications. On request by the Meeting, the pH of batches and the identity test were provided. The pH results comply with the pH range in the FAO TC specification (pH : 3-6).

The manufacturing process, impurity profile and five batch analyses were compared with the data submitted in the reference profile. Limin's manufacturing process of fosetyl-Al is similar

as that of the reference material. However, the impurity profile was found to differ from the reference source with the potential for one new inorganic impurity (see below).

Water was proposed as a relevant impurity to be in line with the FAO specification published in 2011; however the actual level is lower than the limit in the FAO TC reference specification. The analytical batch data indicated that a lower level that complies with the current FAO specification would be appropriate

A low-molecular weight inorganic compound was quantified in all batches at levels below 1 g/kg and was specified by Limin at 1.2 g/kg. That compound was not detected in the reference TC. The possible relevance of this impurity has been assessed by the JMPS meeting.

The Meeting compared the possible human exposure to fosetyl-Al at the ADI of 1 mg/kg and caused by fosetyl-Al containing 1.2 mg/kg of that impurity and concluded, that the exposure with that impurity would amount at approx. 0.1 % of its "modified Theoretical Added Maximum Daily Intake" (mTAMDI). Since this contribution is negligible compared to other uptakes the Meeting concluded that the contribution by the fosetyl-Al is not relevant and that compound should not be considered as relevant.

A mutagenicity study (Ames test) for fosetyl-Al has been submitted as Tier-1 data. Fosetyl-Al TC from Limin does not show mutagenicity in this *in vitro* bacterial assay (OECD 471).

The analytical method to determine the content of fosetyl-Al in the TC was not the CIPAC method 384/TC/M/3 published in Handbook J but an in-house HPLC method. A number of differences were noted with regard to the extraction solvent used, type of mobile phase and operating conditions. Regardless the in-house method for fosetyl-Al content being adequately validated, the FAO/WHO Manual requests that collaboratively validated analytical methods - in reality mostly CIPAC methods - are used.

Therefore, the Meeting requested Limin to provide a bridging study for comparison of the results of the fosetyl-Al content in the 5 batches elaborated with the in-house method with the results produced by the CIPAC method. Limin provided a bridging study and the results were deemed comparable. The determination of impurities was achieved using a spectrophometry method, LC-ID/CD and by titration. These method were properly validated. The content of residual water was determined using the CIPAC method MT 30.1 (Karl Fischer titration, Handbook F).

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, CIPAC, EEC and OPPTS test methods, where appropriate.
The confirmation of structural identity of fosetyl-Al and its related impurities was by comparing retention times of the sample and an authentic standard in HPLC and FT-IR- , NMR- and UV spectroscopy.

Based on the evidence described above, the Meeting concluded that Limin's fosetyl-Al TC can be considered as equivalent to the fosetyl-aluminium reference TC based on a Tier-1 evaluation.

Therefore, the Meeting recommended that the existing FAO specification for fosetyl-Al should be extended to the material produced by Limin.

Limin had also submitted summaries of acute toxicity studies (acute oral toxicity, acute inhalation etc) - studies that are either no longer required at all or only in case of a Tier-2 evaluation. These summaries and their studies had not been further considered by the Meeting.

In addition, the Meeting recommended that the FAO specifications for for fosetyl-Al TC, WP and WG should be editorially updated, such as for the determination of residual water in the formulations - now the harmonised method MT 30.6 -, the reference to the revised MT 184.1 for determination of suspensibility and the use of MT 46.4 for accelerated storage all published in Handbook P.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 384/2020

Table 1. Chemical composition and properties of fosetyl-aluminium 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 ranged from 98.9– 99.2 % and percentages of unknowns were 0.8 – 1.1 %.
Declared minimum fosetyl-aluminium content	975 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	Water: 7g/kg
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	209℃	97.5	OECD102	G016-2019

Formulations and co-formulated active ingredients
Not relevant

Background information on toxicity and ecotoxicity
Limin Chemical Co.,Ltd provides also the Meeting with summary data supported by GLP studies on the physical-chemical properties of pure fosetyl-Al TC, and also summary data on the toxicology profile of the fosetyl-Al TC, based on acute toxicity, irritation and skin sensitization. These data were not considered by the Meeting as it is not requested by the FAO/WHO Manual for equivalence assessment in Tier-1.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Toxicological summaries

Notes.

(i) The proposer confirmed that the toxicological data included in the summary below were derived from fosetyl-aluminium having impurity profiles similar to those referred to in the Table above 1.

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

Table 2. Mutagenicity profile of fosetyl-Aluminium technical material based on an *in vitro* test

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number 4
Salmonella typhimurium TA1535, TA1537, TA98, TA100 and *Escherichia coli* strain WP2uvrA	In vitro, Ames Test, reverse mutation assay	97.5%	OECD Guideline 471 50,150,500,1500 and 5000(µg.plate-1), using the direct plate incorporation method and using fresh bacterial cultures, test item and control solution	non-mutagenic	41104063

ANNEX 2

REFERENCES

(sorted by study number)

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
CH-0711/2019	E. Rigamonti	2019	Fosetyl-aluminium TECH:Validation of the Analytical Method for the Determination of the Fosetyl Active Ingredient Content ChemService S.r.l Controlli e Ricerche, GLP
CH-0712/2019	E. Rigamonti	2019	Fosetyl-aluminium TECH:Validation of the Analytical Method for the Determination of the Aluminium Active Ingredient Content ChemService S.r.l Controlli e Ricerche, GLP.
CH-0713/2019	E. Rigamonti	2019	Fosetyl-aluminium TECH:Validation of the Analytical Method for the Determination of the Anionic Significant Impurities Content ChemService S.r.l Controlli e Ricerche,GLP.
CH-0714/2019	E. Rigamonti	2019	Fosetyl-aluminium TECH:Validation of the Analytical Method for the Determination of the Ammonium Significant Impurity Content ChemService S.r.l Controlli e Ricerche GLP
CH-0715/2019	E. Rigamonti	2019	Fosetyl-aluminium TECH:Complete Analysis of Five Batch Samples. ChemService S.r.l Controlli e Ricerche, GLP.
CH-0716/2019	E. Rigamonti	2019	Fosetyl-aluminium TECH: Spectroscopic Characterisation of Five Batch Samples ChemService S.r.l Controlli e Ricerche, GLP
41104063		2012	Reverse mutation assay “Ames test” using *Salmonella Typhimurium* and *Escherichia Coli* GLP
G016-2019	E. Zhang	2019	Determination of melting point of fosetyl-aluminium TC Jiangsu Limin Laboratory Co.,Ltd. GLP: Yes
NCW-2021-003	Ms Jing Gao	2021	Five batch analysis of fosetyl-Aluminium TC : Quantitation of active ingredient and pH Nutrichem Laboratory Co.,Ltd. GLP: No
CH-0717/2019	E. Rigamonti	2019	Fosetyl-aluminium TECH: Screening for Impurities and Residual Solvents Content in Five Batch Samples ChemService S.r.l Controlli e Ricerche GLP

FOSETYL-ALUMINIUM

FAO/WHO EVALUATION REPORT 384.013/2012

Recommendations

The Meeting recommended that the fosetyl-aluminium TC as proposed by Helm AG be accepted as equivalent to the fosetyl-aluminium reference profile and that the existing specification for fosetyl-aluminium TC should be extended to include the TC from Helm AG.

Appraisal

The data for fosetyl-aluminium were evaluated in support of the extension of the existing FAO specification 384.01/TC (2011).

Fosetyl-aluminium is not under patent. Fosetyl-aluminium has not been evaluated by the FAO/WHO JMPR or the WHO IPCS. It was evaluated / reviewed by the European Commission in 2005 and by the US EPA in 1990.

The first specification for fosetyl-aluminium was developed and published in the year 2000 still under the old procedure. In 2009, Bayer CropScience submitted new draft specifications and supporting data to revise the old procedure specifications according to the new procedure.

Data on fosetyl-aluminium, submitted by Helm AG in 2009, in support of extension of existing FAO specifications for fosetyl-aluminium TC were considered by the JMPS. The data from Helm AG could not be considered fully for procedural reasons until the review of the reference specification from BayerCropScience had been completed and the specifications and the evaluation report had been published.

The meeting were provided with commercially confidential information on the manufacturing process and manufacturing specification for purity and impurities, supported by 5 batch analysis data. Mass balances were >990 g/kg and no unidentified impurities greater than 1 g/kg were reported. A statement has been provided confirming that the confidential data on the manufacturing process and declaration of composition submitted to the FAO were the same as those submitted to the French national regulatory authority for pesticides. The data provided supported a minimum fosetyl-aluminium content of 960 g/Kg.

Water was proposed as a relevant impurity to be in line with the FAO specification published in 2011; however the level originally proposed exceeded the limit in the FAO TC specification. The analytical batch data indicated that a lower level that complies with the current FAO specification would be appropriate. The proposer confirmed in writing that their product would comply with the limit stated in the FAO specification and that they would amend their specification accordingly.

The data submitted was sufficient to conclude on equivalence of Helm AG technical fosetyl-aluminium with the reference profile. The meeting concluded that Helm AG fosetyl-aluminium TC was equivalent to the fosetyl-aluminium reference TC based on Tier-1 evaluation as detailed in the FAO and WHO specification manual (2010 edition).

The Tier-1 is mainly based on chemical evidence (impurity profile, manufacturing specifications etc.) and includes only an *in-vitro* mutagenicity study to detect the presence of

exceptionally hazardous - mutagenic - impurities, which could go undetected by chemical analysis. For that reason, the hazard data package is reduced. This reduced data package is reflected in the Annex 1 Hazard summary. As with the reference material, the reverse mutation tests with *S. typhimurium* and *E. coli* were negative and did not show a mutagenic activity in the TC produced by Helm.

The proposer confirmed that their technical material complies with the current FAO specification.

The meeting noted that the proposer was seeking equivalence to the existing TC specification only, but not for the specifications for the WP and WG formulations.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 384.013/2012

Table 1. Chemical composition and properties of fosetyl-aluminium technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 99 – 102%.
Declared minimum [a.i.] content	960 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	Water: Max 7 g/kg
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 of the TC	Not available	-	-	-
Solubility in organic solvents	Not available	-	-	-

USES

Fosetyl-aluminium is a phosphonate compound but has a structure and mode of action that are different to other organophosphorus compounds used as pesticides. It was first commercialised as an agricultural systemic fungicide in 1977 and, although perhaps most well known for the protection of grape vines against mildew, it is registered for use on more than 100 crops.

Fosetyl-aluminium is a fungicide with systemic activity. It is used to control diseases e.g. *Phytophthora, Pythium, Plasmopara, Bremia* spp., etc. on a variety of crops, including vines, fruit (citrus, pineapples, avocado, stone fruit and pome fruit), berries, vegetables, hops, ornamentals and turf.

FORMULATIONS

Helm AG did not apply for extension of the existing FAO specification to its formulated products.

METHODS OF ANALYSIS AND TESTING

The analytical method for fosetyl-aluminium (including identity tests) is CIPAC method 384 (CIPAC J), which encompasses TC, WP and WG. Identification of fosetyl-aluminium is by means of its IR spectrum and identification of fosetyl is by means of its HPLC retention time. Fosetyl (calculated as fosetyl-aluminium but detected as dissociated fosetyl in solution) in a buffered solution is separated by ion chromatography and determined with a conductimetric detector and external standardization.

The analytical method for determination other impurities is also based on ion chromatography with conductimetric detection. The test method for determination of water as an impurity is CIPAC MT 30.5.

The analytical method used by the proposer was a validated ion chromatography method using conductivity detection and internal standardisation. The method for determination of impurities was also a validated ion chromatography method using conductivity detection and internal standardisation. Water was determined by CIPAC MT 30.5.

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient is expressed as fosetyl-aluminium.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Helm AG provided written confirmation that the toxicological data included in the following summary were derived from fosetyl-aluminium having impurity profiles similar to those referred to in Table 1, above.

Table 2. Mutagenicity profile of the technical material based on an in vitro test

Species	Test	Purity % Note[1]	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium *Escherichia coli*	*In vitro* bacterial reverse mutation tests 3; 10; 33; 100; 333; 1,000; 2,500 & 5,000 µg/plate (with and without S-9)	99.6	OECD 471; 4 *Salmonella* strains 1 *E. coli* strain	No genotoxic potential	1
Mouse lymphoma cells	mouse lymphoma assay 180; 360; 720; 1,440; 2,880 & 3,600 µg/mL (without S-9) 22.5; 45; 90; 180 & 360 µg/mL (with S-9)	99.6	OECD 476; Clastogenicity test	No genotoxic potential	2

ACUTE TO CHRONIC TOXICITY

No information was available on acute to sub acute to chronic toxicity of the fosetyl-aluminium technical material produced by Helm AG.

MUTAGENICITY

No information was available on the mutagenicity profile of the fosetyl-aluminium technical material produced by Helm AG beside the mutagenicity tests provided in Table 2. The tests based on bacterial reverse mutation with S. typhimurium and E. coli without and with the addition of rat liver homogenate (S9) and the mouse lymphoma test do not show a mutagenic or genotoxic potential of the material produced by Helm AG.

ECOTOXICITY

No information was available on ecotoxicity profile of the fosetyl-aluminium technical material produced by Helm AG

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

ANNEX 2

REFERENCES

Ref number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
1		2007	*Salmonella typhimurium* and *Escherichia coli* - Reverse Mutation Assay with Fosetyl-Al TC. 04.04.2007, 33 pp. Unpublished Confidential Report of Helm AG. GLP: Yes
2		2007	Cell Mutation Assay at the Thymidine Kinase Locus (TK +/-) in Mouse Lymphoma L5178Y Cells with Fosetyl-Al TC. 16.04.2007, 43 pp. Unpublished Confidential Report of Helm AG. GLP: Yes

FOSETYL-ALUMINIUM

FAO/WHO EVALUATION REPORT 384.013/2010

Recommendations

The Meeting recommended that the proposed new specifications for fosetyl-aluminium TC, WP and WG, proposed by Bayer CropScience and as amended, should be adopted by FAO.

Appraisal

Data for fosetyl-aluminium were submitted by Bayer CropScience in support of a revision of existing FAO specifications for TC, WP and WG (FAO 2000), which were developed under the old procedure. The revision was conducted at the request of Bayer CropScience, partly because a change in analytical methodology for impurities had prompted a minor change in the manufacturing specification. The data submitted were in accordance with the requirements of the Manual (FAO/WHO 2010) and the proposed specifications were similar to the existing specifications.

Fosetyl-aluminium is no longer under patent.

Fosetyl-aluminium has not been evaluated by the FAO/WHO JMPR but is has been reviewed in the EU (Directive 91/414/EEC, Annex 1 listing granted in Directive 2006/64/EC dated 18 July 2006).

Fosetyl-aluminium is an odourless white powdery-crystalline solid, which melts at 215 °C and has a very low vapour pressure. It is poorly soluble in most organic solvents, with exception of methanol. Fosetyl-aluminium is fairly soluble in water but it dissolves rather slowly and, following dissociation of the salt, the liberated ions undergo various reactions. This complex behaviour in water has important implications for the specifications and the data given in Table 1 for water solubility, octanol/water partition coefficient, hydrolysis and pK_a. The Meeting questioned the meaning of these data but the manufacturer explained that the behaviour of fosetyl-aluminium in water is not completely understood and therefore the data in Table 1 should be interpreted with precaution. Broadly, when fosetyl-aluminium dissolves in water it dissociates and the aluminium (Al^{3+}) ions, which are liberated, tend to form aluminium hydroxide (which may precipitate or flocculate), while the liberated acidic fosetyl ions tend to be hydrolyzed, with the formation of inorganic phosphite[1*] and ethanol. The given values in table 1 for water solubility and partition coefficient only refer to the organic moiety, i.e. the fosetyl.

---

[1] Inorganic phosphite is a convenient term describing the dianion of a rather strong acid, which exists as an equilibrium mixture of two tautomers, phosphonic acid and phosphorous acid (the former tending to be predominant).

Inorganic phosphite is a fungicidally active component and its various salts have also been registered as pesticides but not in the EU. However, inorganic phosphite can be phytotoxic at high concentrations and fosetyl-aluminium minimizes this problem by generating inorganic phosphite relatively slowly.

Inorganic phosphite (as the free acid) may accelerate the hydrolysis of fosetyl in formulations, or in the spray-tank, but rapid neutralization in the environment means that this effect is not a problem following application in the field.

The Meeting was provided with commercially confidential information on the manufacturing process for fosetyl-aluminium, the manufacturing specifications for the TC and 5-batch analytical data on the purity and impurities ≥1 g/kg. Mass balances were high (99.1 - 102.0 %) and no unidentified impurities were detected. The data were identical to those submitted for registration in the Federal Republic of Germany.

The existing and proposed specifications were similar, and generally in accordance with the requirements of the Manual (FAO/WHO 2006), but the Meeting considered the following points.

TC, WP, WG. Inorganic phosphite was limited by a clause in the existing specifications for fosetyl-aluminium TC, WP and WG and the manufacturer considered that it should be designated as a relevant impurity in the proposed specifications. Although it is potentially phytotoxic, the Meeting noted that its concentration should be adequately limited by control of the water and active ingredient content and therefore agreed that inorganic phosphite should not be designated as a relevant impurity. The manufacturer agreed and specified the pH value for TC instead to control hydrolysis.

Water was limited by a clause in the existing specifications for the TC, WP and WG, because it hydrolyzes fosetyl-aluminium, with the formation of inorganic phosphite. The Meeting agreed with the manufacturer that it should be designated as a relevant impurity.

WP, WG. Given that fosetyl-aluminium is water-soluble (and subject to further degradation in water), the Meeting questioned whether the WP and WG should be designated SP and SG, respectively. The manufacturer stated that dissolution occurs only slowly in water (about 80 % of Aliette WP is dissolved after 60 min). Initially, almost all of the active ingredient is in the form of a suspension. The Meeting therefore accepted the proposed designations.

The Meeting questioned the proposed pH range (3.0 - 5.0) because, although fosetyl-aluminium was considered to be stable at pH 5-7, its half-life at pH 3 is only 5 days (at 22 ºC). The manufacturer explained that the apparently low pH range represents a compromise for optimum product shelf-life: at pH < 3, the active ingredient is too unstable and at pH > 5 flocculation can occur upon dispersal in water, prior to application. The Meeting accepted the explanation and the proposed range.

The Meeting questioned the wettability limits of 2 min and 1 min for WP and WG, respectively, which appeared to indicate very slow wetting of the water-soluble active ingredient. The manufacturer explained that fosetyl-aluminium dissolves very slowly in water. The crystalline solid has a relatively low affinity for water and it is important not to increase this, to avoid increasing the uptake of water during product storage and the consequent increased degradation of the active ingredient. The Meeting accepted the explanation and the proposed limits.

As a consequence of the complex behaviour of fosetyl-aluminium in water, the Meeting questioned the meaning of the proposed clauses and limits for degree of dispersion (WG) and suspensibility (WP and WG). The manufacturer acknowledged that both chemical and gravimetric measurements may be rendered somewhat inaccurate by the dissolution and degradation that occurs but stated that the proposed limits take into account this behaviour. The Meeting therefore accepted the proposed limits.

WG. The Meeting questioned the apparently low limit of 90 % for flowability. The manufacturer stated that clumping can occur, even at low water content. The Meeting noted that if this happened then the product would not comply with the description. After checking available data the manufacturer raised the value to 100 %.

Analytical methods for determination of fosetyl-aluminium in the TC, WP and WG are full CIPAC methods, in which the fosetyl moiety is determined by ion chromatography, using conductivity detection and external standardization. The retention time in ion chromatography provides a mean for identifying the fosetyl moiety. Confirmation of identity of the fosetyl moiety may further be accomplished by LC-MS.

The CIPAC method for identification of fosetyl-aluminium is based on the IR spectrum, which is suitable for the TC but could be questionable for use with the formulations. The Meeting agreed that a second identity test is required to ensure correct identification as fosetyl-aluminium and the manufacturer provided an analytical method, where aluminium (fosetyl-aluminium contains 7.6 % w/w aluminium) is determined by chelatometric titration.

The method for determination of water, as a relevant impurity, is a CIPAC MT 30.5, Karl Fischer method using pyridine-free reagent published in Handbook J.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 384.013/2010

USES

Fosetyl-aluminium is a phosphonate compound but has a structure and mode of action which are unlike those of most other organophosphorus compounds used as pesticides. It was first commercialised as an agricultural systemic fungicide in 1977 and, although perhaps most well known for the protection of grape vines against mildew, it is registered for use on more than 100 crops. Fosetyl-aluminium is used for control of various plant pathogenic phycomycetes and ascomycetes in various crops, and it is also used to control certain plant pathogenic bacteria (e.g. *Erwinia*, *Xanthomonas*). Modes of application are very varied, including foliar, root, soil, dip, trunk paint/injection, and seed treatments.

Fosetyl-aluminium is a preventative fungicide, inhibiting fungal spore germination and penetration of the pathogen into plants, but it also acts indirectly by stimulating the plant's natural defence mechanisms. For these reasons, its effects are relatively long-lasting and resistance rarely occurs.

IDENTITY

ISO common names

fosetyl (E-ISO, (m) F-ISO, BSI), refers to the acid, ethyl hydrogen phosphonate
fosetyl-aluminium, derived common name for the aluminium salt

Synonyms

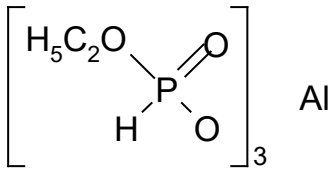
fosetyl: efosite
fosetyl-aluminium: efosite-Al; EPAL

Chemical names

IUPAC fosetyl: ethyl hydrogen phosphonate
fosetyl-aluminium: aluminium *tris*-*O*-ethylphosphonate

CA fosetyl: ethyl hydrogen phosphonate
fosetyl-aluminium: aluminium *tris*-*O*-ethylphosphonate

Structural formula (fosetyl-aluminium)



Empirical formula

fosetyl: $C_2H_7O_3P$
fosetyl-aluminium: $C_6H_{18}AlO_9P_3$

Relative molecular mass

fosetyl: 110.03
fosetyl-aluminium: 354.14

CAS Registry number

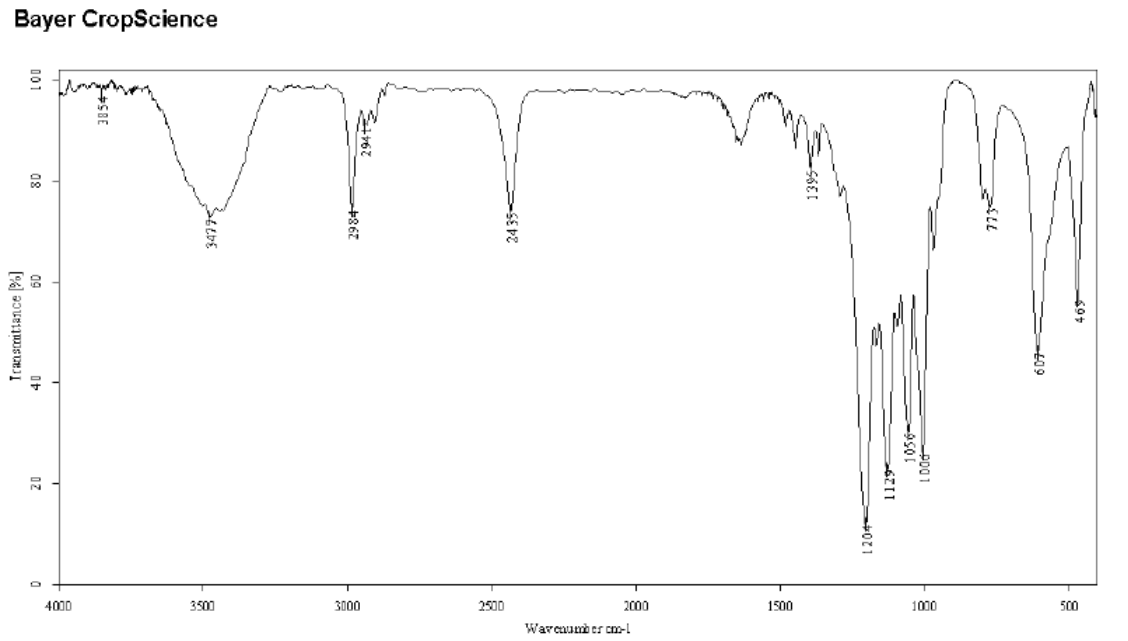
fosetyl: 15845-66-6
fosetyl-aluminium: 39148-24-8

CIPAC number

fosetyl: 384
fosetyl-aluminium: 384.013

Identity tests

HPLC retention time; IR spectrum (see below)



Echantillon : EA 11678D5 TV3169b	Chemin : D:\Données IR\IFS 48\Data\Full service\Autres\Etude	Appareil : IFS48
Technique : KBr	Fichier : E99_188.0	Nombre de scans : 32
Opérateur et N° danalyse : JVAS-94136	Gamme spectrale : 3999.64-400.157	Résolution : 2
Mesuréle : 8/9/1999	Méthode : ETU	Zerofilling : 2

PHYSICAL AND CHEMICAL PROPERTIES

Table 1. Physical and chemical properties of pure fosetyl-aluminium

Parameter	Value(s) and conditions	Purity %	Method reference	Reference
Vapour pressure	< 10^{-7} Pa at 25°C	98.0	EEC A.4 gas saturation method; OECD 104	M-179047-01-1
Melting point	215 °C	99.1	EEC A1	M-179033-01-1
Boiling point	not measurable	99.1	-	M-179033-01-1
Decomposition temperature	> 277 °C	99.1	OECD 113	M-163556-01-1
Solubility in water	111.3 g/L at 20°C (pH 7.7) not influenced by pH in the range pH 5.1-8.6	99.3	EEC A.6, OECD 105, flask method	M-179038-01-1
Octanol/water partition coefficient	log P K_{OW} = -2.11 at 21°C (pH 6.8) not influenced by pH in the range pH 4-10	99.1	EEC A.8, OECD 107, flask shaking method	M-184417-01-1
Hydrolysis characteristics	Half-life = 5 d at 22°C at pH 3 Half-life = 13.4 d at 22°C at pH 13 Stable at 22°C at pH 5-9	99.7	EPA Vol 43 No.132	M-159693-01-1
Photolysis characteristics	Based on the absence of absorption in the range 190-800 nm, the influence of photolysis on decomposition is expected to be negligible	-	-	-
Dissociation characteristics	At 20-25°C, the measured pKa was 4.7 (average of 3 measurements). This represents the pKa of neither fosetyl nor inorganic phosphite but is an artefact due to the presence of aluminium hydroxide, generated when fosetyl-aluminium is dissolved in water	99.1	OECD 112, potentiometric method	M-179042-01-1

Table 2. Chemical composition and properties of technical fosetyl-aluminium (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 were 991.1 – 1020.2 g/kg.
Declared minimum [a.i.] content	960 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	Water, 7 g/kg
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 reference
Melting temperature range of the TC and/or TK	207 – 210 °C	97.6	OECD 102	M-179033-01-1
Solubility in organic solvents (at 20 °C)	< 1 mg/L n-heptane < 1 mg/L ethyl acetate 1 mg/L xylene 1 mg/L acetonitrile 4 mg/L dichloromethane 6 mg/L acetone 10 mg/L n-octanol 807 mg/L methanol	97.6	EEC A.6 OECD 105 Flask method	M-179038-01-1

HAZARD SUMMARY

Fosetyl-aluminium has not been evaluated by the FAO/WHO JMPR or IPCS.

The WHO classification of fosetyl is class U, unlikely to present acute hazard in normal use (WHO 2002).

The EU hazard classification for labelling of technical active according to regulation EC/790/2009 is Xi (irritant) and R41 (risk of severe eye irritation) and “serious eye damage”, Category 1 (H 318).

FORMULATIONS

The active substance fosetyl-aluminium is sold under different trade names. The most common trade name is ALIETTE® and it is used world-wide mainly for the grape, fruit and vegetable foliar market segment.

The main formulation types available are: WGs & WPs.

Fosetyl-aluminium can be co-formulated with: benalaxyl, captan, carbendazim, chlorothalonil, copper oxychloride, cymoxanil, dimethoate, fenamidone, fluopicolide, folpet, iprovalicarb, mancozeb and metiram zinc.

METHODS OF ANALYSIS AND TESTING

The analytical method for fosetyl-aluminium (including identity tests) is CIPAC method 384 (CIPAC Handbook J), which encompasses TC, WP and WG. The method is based on ion chromatography with conductivity detection and quantifies the fosetyl moiety. Identification of fosetyl-aluminium is by means of its IR spectrum in the TC and identification of the fosetyl moiety is by means of its HPLC retention time. Fosetyl (calculated as fosetyl-aluminium but detected as dissociated fosetyl in solution) in a buffered solution is separated by ion chromatography and determined with a conductometric detector and external standardization.

The test method for determination of aluminium-ion is by chelatometric titration.

The analytical method for determination of inorganic phosphite and other impurities is also based on ion chromatography with conductivity detection. The test method for determination of water as an impurity is CIPAC MT 30.5

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

PHYSICAL PROPERTIES

The physical properties, the methods for testing them and the limits proposed for the TC, WP and WG formulations complied with the requirements of the Manual (FAO/WHO, 2010).

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient is expressed as fosetyl-aluminium.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: The proposer provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from fosetyl-aluminium having impurity profiles similar to those referred to in Table 2, above.

Table 3 Toxicology profile of fosetyl-aluminium technical material, based on acute toxicity, irritation and sensitization

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rat (m, f)	oral	97.0	single application; OECD 401	LD_{50} > 7080 mg/kg bw (m,f)	M-179086-01-1
Rat	dermal	97.0	single application, 24 h; OECD 402	LD_{50} > 2000 mg/kg bw	M-179084-01-1
Rat	inhalation	97.0	dust, 4 h exposure; OECD 403	LC_{50} > 5.11 mg/l	M-178978-01-1
Rabbit	skin irritation	97.0	OECD 404	Non-irritating	M-179080-01-1
Rabbit	eye irritation	97.0	OECD 405	Severe irritation	M-179082-01-1
Guinea pig	skin sensitization	97.0	Maximization test, OECD 406	Non-sensitizing	M-179051-01-1

Table 4 Toxicology profile of fosetyl-aluminium technical material, based on repeated administration (sub-acute to chronic)

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Mouse (m,f)	sub-acute, oral	97.8	6 weeks, guideline unspecified	NOAEL = 40000 ppm 7390 (m), 9361 (f) mg/kg bw/day	M-159695-01-1
Rat	sub-acute, dermal	98.1	28 day, OPPTS 870.3200 (1998) (EPA FIFRA 82.2)	NOAEL = 1050 mg/kg/day	M-178986-01-1
Rat	sub-chronic, oral	98.1	90 day, OECD 408	NOAEL = 20000 ppm 1269 (m) & 1580 (f) mg/kg bw/day 1424 mg/kg bw/day (both sexes)	M-184588-01-1
Dog	sub-chronic, oral	99.7	90 day, guideline unspecified	NOAEL = 50000 ppm 1309 (m) & 1446 (f) mg/kg bw/day 1377 mg/kg bw/day (both sexes)	M-231272-01-2
Rat	chronic toxicity & oncogenicity, feeding	99.7	24 months, OECD 453	NOAEL = 8000 ppm, 348 (m) & 450 (f) mg/kg bw/day	M-249664-02-1
Mouse	chronic toxicity & oncogenicity, feeding	96.9	24 months, OECD 451	NOAEL = 30000 ppm, 3956 (m) & 4549 (f) mg/kg bw/day Not carcinogenic	M-159267-01-1
Dog	chronic toxicity & oncogenicity, feeding	96.9	24 months, OECD 452	NOAEL = 10000 ppm, 309 (m) & 288 (f) mg/kg bw/day 298 mg/kg bw/day (both sexes) Not carcinogenic	M-159302-01-1
Rat	multi-generation reproduction toxicity	97.3	Over 3 generations, guideline unspecified	NOAEL maternal & foetal = 6000 ppm (23) 439 (m) & 520 (f) mg/kg bw/day (F0) NOAEL reproduction = 24000 ppm 1782 (m) & 1997 (f) mg/kg/day (F0)	M-159087-01-1

Table 4 Toxicology profile of fosetyl-aluminium technical material, based on repeated administration (sub-acute to chronic)

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rat	developmental toxicity	99.8	From Gestation Day 6 to 15, considered to meet requirement OECD 414	NOAEL maternal = 1000 mg/kg bw/day NOAEL developmental = 1000 mg/kg bw/day	M-158819-01-1
Rabbit	developmental toxicity	98.1	From Gestation Day 4 to 28, OECD 414	NOAEL maternal = 300 mg/kg bw/day NOAEL developmental = 300 mg/kg bw/day	M-205472-01-1

Table 5 Mutagenicity profile of fosetyl-aluminium technical material based on *in vitro* and *in vivo* tests

Species	Test	Purity %	Conditions and doses	Result	Reference
Salmonella typhimurium TA 98, 100, 1535 & 1537, *Escherichia coli* WP2 uvrA	Ames test	97.0	OECD 471	negative	M-184456-01-1
Salmonella typhimurium TA 98,100,1535 & 1538	Ames test	99.7	OECD 471	negative	M-159301-01-1
Chinese hamster ovary cells (CHO-HGPRT)	*In vitro* chromosome aberration test	97.5	conducted according to a method described by Natarajan *et al.*	negative	M-231739-01-2
Mouse lymphoma assay	*In vitro* mammalian cell gene mutation test	97.0	OECD 476	negative	M-184459-01-1
Mouse, CD1 (m,f)	*In vivo* micronucleus test	97.0	OECD 474	negative	M-178982-01-1
Escherichia coli K12	*In vitro,* induct test	99.7	conducted according to a method described by Moreau P. *et al.*	negative	M-159301-01-1
Escherichia coli W3478–W3110	DNA repair test	99.7	conducted according to a method described by Rosenkrantz H.S. *et al.*	negative	M-159301-01-1

Table 6 Ecotoxicology profile of fosetyl-aluminium technical material

Species	Test	Purity %	Duration and conditions	Results	Reference
Daphnia magna (water flea)	acute	95.9	OECD 202, 48 h, 21°C, static	EC_{50} > 100 mg/l	M-170914-01-1
Daphnia magna (water flea)	chronic toxicity	95.9	OECD 202, 21 d, 21°C, static renewal	NOEC = 17 mg/l	M-189214-01-1

Table 6 Ecotoxicology profile of fosetyl-aluminium technical material

Species	Test	Purity %	Duration and conditions	Results	Reference
Oncorhynchus mykiss (rainbow trout)	acute toxicity	97.8	OECD 203, 96 h, 14°C, semi-static	LC_{50} > 122 mg/l	M-189219-01-1
Lepomis macrochirus (bluegill sunfish)	acute toxicity	97.0	OECD 203, 96 h, 21°C	LC_{50} > 60 mg/l	M-184477-01-1
Oncorhynchus mykiss (rainbow trout)	chronic toxicity	97	28 d, 14°C	EC_{50} = 100 mg/l	M-184572-01-1
Scenedesmus subspicatus (green alga)	chronic toxicity	97.8	OECD 201, 72 h, 23°C	E_rC_{50} > 16 mg/l NOEC = 1.4 mg/l	M-189220-01-1
Earthworm	acute toxicity	97.0	OECD 207, 14 d	LC_{50} > 1000 mg/kg dry soil	M-179078-01-1
Apis mellifera (honey bee)	acute contact toxicity	98.6	96 h	LD_{50} > 1000 µg/bee	M-189217-01-1
Apis mellifera (honey bee)	acute oral toxicity	98.6	96 h	LD_{50} = 461.8 µg/bee	M-189217-01-1
Bobwhite quail	acute toxicity	97.5	14 d, single dose	LD_{50} > 8000 mg/kg bw	M-159690-01-1
Japanese quail	acute toxicity	95	14 d, single dose	LD_{50} = 4997 mg/kg bw	M-158803-01-1
Bobwhite quail	short-term dietary toxicity	97.5	US EPA 163.71-2, 11 d, 5 d dosing	LC_{50} > 20000 ppm diet	M-159687-01-1
Mallard duck	short-term dietary toxicity	97.5	US EPA 163.71-2, 11 d, 5 d dosing	LC_{50} > 20000 ppm diet	M-159685-01-1
Japanese quail	sub-chronic reproduction toxicity	99.6	OECD, 6 weeks	NOEC ≥ 1500 ppm diet	M-189216-01-1

ANNEX 2
REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
M-158803-01-1		1977	The acute oral toxicity (LD 50) of LS 74 783 to the Japanese Quail Unpublished
M-158819-01-1		1977	Effect of LS 74-783 on pregnancy of the rat Unpublished
M-159087-01-1		1981	Effect of LS 74-783 on reproductive function of multiple generations in the rat GLP Unpublished
M-159267-01-1		1981	Fosetyl-Al : 24 month carcinogenicity study in mice GLP Unpublished
M-159301-01-1		1981	Fosetyl-Al (32545 R.P., aluminium salt) Supplementary studies of mutagenisis in micro-organisms; Unpublished
M-159302-01-1	.	1981	Fosetyl-Al: Two-year dietary toxicity study in dogs GLP Unpublished
M-159685-01-1		1981	The sub acute dietary toxicity (LC 50) of LS 74 783 to the Mallard duck GLP Unpublished
M-159687-01-1		1982	The sub acute dietary toxicity (LC 50) of LS 74 783 to the Bobwhite Quail GLP Unpublished
M-159690-01-1		1981	The acute oral toxicity (LD_{50}) of LS 74 783 to the Bobwhite Quail GLP
M-159696-01-1		1997	Fosetyl aluminium Hydrolysis study Rhone-Poulenc Agrochimie, Lyon, France Unpublished
M-159695-01-1		1978	Efosite-Al: 6 Week range finding study in mice. Unpublished
M-163556-01-1		1996	Fosetyl aluminium active ingredient – Stability GLP Rhone-Poulenc Agro Unpublished
M-170914-01-1		1996	Fosetyl Al: Acute toxicity to Daphnia magna GLP Unpublished
M-178978-01-1		1997	Fosetyl-Al: acute inhalation toxicity (nose only) study in the rat.

		GLP Unpublished
M-178982-01-1	1998	Fosetyl-Al : Induction of micronuclei in the bone marrow of treated mice GLP
M-178986-01-1	1999	28-day dermal toxicity study with fosetyl-Al in rats GLP Unpublished
M-179033-01-1	1996	Fosetyl aluminium active ingredient – Physical characteristics GLP Rhone-Poulenc Agro, Lyon, France Unpublished
M-179038-01-1	1996	Fosetyl aluminium active ingredient – Water and solvent solubility GLP Rhone-Poulenc Agro, Lyon, France Unpublished
M-179042-01-1	1997	Fosetyl aluminium active ingredient – pH and pKa GLP Rhone-Poulenc Agro, Lyon, France Unpublished
M-179047-01-1	1997	Fosetyl aluminium active ingredient – Vapour pressure GLP Rhone-Poulenc Agro, Lyon, France Unpublished
M-179051-01-1	1998	Skin sensitization test in guinea-pigs GLP Unpublished
M-179078-01-1	1997	Fosetyl-Al. Acute toxicity (14-day) to earthworms (Eisenia foetida). Artificial soil method. Unpublished
M-179080-01-1	1997	Fosetyl-Al. Skin irritation test in the rabbit GLP Unpublished
M-179082-01-1	1997	Fosetyl-Al. Eye irritation test in the rabbit. GLP Unpublished
M-179084-01-1	1997	Fosetyl-Al. Acute dermal toxicity in the rat. GLP Unpublished
M-179086-01-1	1997	Fosetyl-Al. Acute oral toxicity in the rat. GLP Unpublished
M-184417-01-1	1997	Fosetyl aluminium active ingredient – n-Octanol/Water partition coefficient GLP Unpublished
M-184456-01-1	1997	Fosetyl-Al : Reverse Mutation in four histidine-requiring strains of Salmonella typhimurium and one tryptophan-requiring strain of Escherichia coli. GLP

		Unpublished
M-184459-01-1	1997	Fosetyl-Al : Mutation at the Thymidine Kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the microtitre fluctuation technique GLP Unpublished
M-184477-01-1	1997	Fosetyl-Al : Acute toxicity to bluegill sunfish (Lepomis macrochirus) GLP Unpublished
M-184572-01-1	1997	Fosetyl-Al: fish, juvenile growth test - 28 days. GLP Unpublished
M-184588-01-1	1999	Fosetyl-Al : 90-day toxicity study in the rat by dietary administration GLP Unpublished
M-189214-01-1	1996	Fosetyl Al: Daphnia magna reproduction test GLP Unpublished
M-189216-01-1	1999	Fosetyl-Aluminium; a reproduction study with the Japanese quail (Coturnix coturnix japonica) GLP Unpublished
M-189217-01-1	1999	Laboratory testing on the acute contact and oral toxicity of fosetyl-al to honey bees (Apis mellifera L.) (Hymenoptera, Apidae). GLP Unpublished
M-189219-01-1	1999	Fosetyl-Al. Acute Toxicity for Rainbow Trout (Oncorhynchus mykiss) GLP Unpublished
M-189220-01-1	1999	Fosetyl-Al: Algal growth inhibition assay on Scenedesmus subspicatus. GLP Unpublished
M-205472-01-1	2000	Technical Fosetyl-Al: oral range finding study of embryo-fetal development in rabbits GLP Unpublished
M-231272-01-2	1977	LS 74-783 (Aluminium ethyl phosphite) 3 month oral toxicity study in the dog Unpublished
M-231739-01-2	1982	Report on in vitro assay of chromosomal aberrations in "CHO" cell line, with and without metabolic activation, carried out on the product Fosetyl-Al of Ravit Co., Rome Unpublished
M-249664-02-1	1981	Fosetyl-Al (LS 74-783) Chronic toxicity (2 year) and carcinogenicity study in rats. Unpublished
M-360260-01-1 FAO	1995	FAO Specifications for Plant Protection Products

			Fosetyl-aluminium (AGP: CP/326) Food and Agriculture Organization of the United Nations Published
M-360262-01-1	FAO	2000	FAO Specifications for Plant Protection Products Fosetyl-aluminium - ethyl hydrogen phosphonate, aluminium salt (AGP: CP/368) Food and Agriculture Organization of the United Nations Published
M-360693-02-1	FAO/WHO	2006	Manual on the development and use of FAO and WHO specifications for pesticides, 1st edition, FAO Plant production and protection paper 173, FAO, Rome, 2002 amended in 2006.
EFSA (2005)		2005	EFSA Scientific Report (2005) 54, 1-79, Conclusion on the peer review of fosetyl

Appendix 1: Determination of aluminium in active ingredient and in fosetyl-Al containing formulations

Bayer CropScience

ANALYTICAL METHOD

Determination of Aluminium in Active Ingredient and in Fosetyl-AL Containing Formulations

Assay - Titrimetric

AUTHOR

W. Zitzmann

COMPLETION DATE

2007-06-25

PERFORMING LABORATORY

Bayer CropScience AG
Development
Formulation Technology
D-40789 Monheim
Germany

ANALYTICAL METHOD NO.

AM010107MF1

M-289853-01-1

Certification of Authenticity

AUTHOR
BAYER CROPSCIENCE AG

Dr. W. Zitzmann: W. Zitzmann

Date: 2007-06-25

LAB RESPONSIBLE SCIENTIST
BAYER CROPSCIENCE AG

Dr. E. Seidel: E. Seidel

Date: 2007-06-21

Annotation

This analytical method was drawn up in good faith. Nonetheless we do not undertake to guarantee the correctness of the analytical method nor the success of its application. Application is the sole responsibility of the user. Furthermore, the user is not released from the obligation to examine for himself the legal requirements governing the implementation of the analytical method.

Table of Contents Page

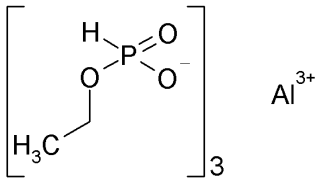
Determination of Aluminium in Active Ingredient and in Fosetyl-AL Containing Formulations

1. Formulas

1.1. Aluminium

Atomic Symbol: Al
Atomic mass: 26.98

1.2. Fosetyl-AL



Empirical formula: (C2 H6 O3 P)3 Al
Molecular weight (g/mole): 354.1
Other names: AE F053616, LS 74783, FEA
CAS no.: 39148-24-8

CAS Index name: Phosphonic acid, monoethylester

2. Principle

The aluminium ions of the sample are determined by chelatometric titration.

The aluminium ions are complexed under acidic conditions by heating in the presence of an excess of CDTA standard solution.

The remaining CDTA is back-titrated using a zinc sulfate standard solution.

3. Reagents

1. Perchloric acid 70-72 %, A.R., e.g. Merck Art. no. 1.005.191.000
2. Xylenol orange tetra sodium salt, A.R., e.g. Merck Art. no. 1.086.770.005
3. Hexamethylen tetramine (HMTA), A.R., e.g. Merck Art. no. 4343
4. Diamino-cyclohexane tetra acetate monohydrate (CDTA), A.R., e.g. Merck Art. no. 1.084.240.100
5. NaOH, A.R., e.g. Merck Art. no. 6498
6. Zinc sulfate A.R. (concentrated standard solution, available as a 60 ml ampoule which is appropriate for the preparation of 1.0 L of a 0.1 molar standard) e.g. KMF Laborchemie Art. no. 88-343.0001
7. KNO_3, A.R., e.g. Merck Art. no. 1.05063.0500
8. Deionized water

4. Apparatus

1. 150 ml beaker
2. Volumetric pipette 20 ml
3. Dosimat, e.g. Metrohm 665
4. Magnetic stirrer with heating

5. Procedure

5.1. Preparation of CDTA standard solution

Dissolve 8.5 g sodium hydroxide in 500 ml deionized water in a 2 L volumetric flask. Add 36.4 g CDTA and dissolve by heating.

Adjust to the calibration mark with deionized water, after the solution has cooled.

5.2. Preparation of dilute perchloric acid

Add 100 ml of perchloric acid to 300 ml deionized water while stirring.

5.3. Preparation of 0.05 molar zinc sulfate standard solution

Use an ampoule containing concentrated zinc sulfate standard solution (3.6) and adjust the volume to 2.0 L with deionized water (final concentration is 0.05 mol zinc sulfate).

5.4. Grinding of indicator

0.1 g Xylenol orange are thoroughly grinded together with 9.9 g potassium nitrate in a mortar.

5.5. Determination of the titer of the CDTA standard solution

Transfer 10 ml of the CDTA standard solution into a 250 ml Erlenmeyer flask and dilute by adding 20 ml deionized water. Add 5 ml dilute perchloric acid and heat to boiling for approx. 1 min.

After cooling to ambient temperature, add 6.0 g HMTA.

After the HMTA has dissolved completely, add 30-50 mg of grinded indicator (5.4) and titrate using the zinc sulfate standard solution (5.3) until the colour changes from yellow to red.

Repeat the procedure at least twice.

Calculate the mean of the 3 values.

5.6. Determination in the sample

Transfer an amount of the sample containing approx. 0.1 g of fosetyl-AL, accurately weighed to 0.1 mg, into a 250 ml beaker and add 10 ml of deionized water.

Add 5 ml perchloric acid and heat to boiling for approx. 1 min.

Add 20 ml of the CDTA standart solution and heat to boiling for approx. 1 min.

After cooling to ambient temperature, add 6.0 g HMTA.

After complete dissolution, add 30-50 mg of grinded indicator (5.4) are added. Titrate using the zinc sulfate standard solution (5.3) until the colour changes from yellow to red.

6. Calculation of content aluminium ions

6.1. Titer t of CDTA standard solution (5.1)

$$\frac{V_1}{10} = t$$

Where V_1 = ml of zinc sulfate standard solution. Calculate the mean from at least 3 determination of the factor.

6.2. Content aluminium ions in the sample

$$(20 \times t - V_2) \times 0.05 \times \frac{26.98}{1} \times \frac{100}{W \times 1000} = [\%] \text{ aluminium ions}$$

or

$$\frac{20 \times t - V_2}{W} \times 0.1349 = [\%] \text{ aluminium ions}$$

t : Titer of CDTA standard solution
V_2 : ml zinc sulfate standard
W : g sample weight

7. Notes

1. Based on the content of aluminium ions, the fosetyl-AL content of a sample can be determined according to the following equation:

$$\text{Fosetyl-AL [\%]} = [\%] \text{ aluminium} \times \frac{354.1}{26.98}$$

2. The specified conditions are obligatory. If, in exceptional cases, the specific situation in the laboratory (e.g. equipment, reagents not available etc.) necessitates the adaptation of individual parameters of the method, this can be recorded on a supplementary page in conformity with all QA and GLP requirements. This does not change the official analytical method, its code number or its general validity. The conditions to be listed on the supplementary page of the method documentation (see chapter 8) are only valid after approval by the signature of the head of laboratory or study director and only for the specified laboratory. Before approval, it must be verified that the changes are not relevant for the results. The supplementary page of the method documentation is not intended to correct errors in the method or in cases of fundamental changes. In these cases, a new version or a new analytical method must be drawn up and the author of the method should be consulted.