Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

PARAQUAT DICHLORIDE[1]

1,1'-dimethyl-4,4'-bipyridinium dichloride

2021

[1] Paraquat is the ISO common name for the 1,1'-dimethyl-4,4'-bipyridyldinium dication

TABLE OF CONTENTS

PARAQUAT DICHLORIDE

DISCLAIMER[1]

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

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

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

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

Additionally, FAO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

FAO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, FAO does not in any way warrant or represent that any pesticide claimed to comply with a FAO specification actually does so.

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

INTRODUCTION

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

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

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

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

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

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

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

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

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

PART ONE

SPECIFICATIONS

PARAQUAT DICHLORIDE

PARAQUAT DICHLORIDE

INFORMATION

Common name (dication): paraquat (E-ISO, (m)F-ISO, BSI, ANSI, WSSA, JMAF)

Synonym: methyl viologen

Chemical names:

dication -
IUPAC, 1,1'-dimethyl-4,4'-bipyridinium [1]
CA, 1,1'-dimethyl-4,4'-bipyridinium

dichloride -
IUPAC, 1,1'-dimethyl-4,4'-bipyridinium dichloride [1]
CA, 1,1'-dimethyl-4,4'-bipyridinium dichloride

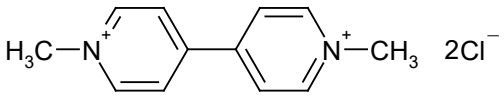
CAS No:

1910-42-5 (dichloride); 4685-14-7 (dication)

CIPAC No:

56 (dication); 56.302 (dichloride)

Structural formula (dichloride):



Molecular formula:

$C_{12}H_{14}Cl_2N_2$ (dichloride); $C_{12}H_{14}N_2$ (dication)

Relative molecular mass:

257.2 (dichloride); 186.3 (dication)

Identity tests (CIPAC G 56/SL/M-):
HPLC retention time; UV spectrum; addition of alkaline sodium dithionite to a dilute solution, where a blue colour indicates the presence of paraquat. The presence of the dichloride salt is tested with silver nitrate solution or, in the presence or absence of diquat dibromide, by capillary electrophoresis.

[1] The IUPAC name for the bipyridinium moiety is alternatively expressed as “bipyridinediium” or “bipyridilium”.

PARAQUAT DICHLORIDE TECHNICAL CONCENTRATE (Note 1)

FAO Specification 56.302/TK (October 2021*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation reports 56.302/2003, 56.302/2020, 56.302/2021*). It should be applicable to TK 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 TK produced by other manufacturers. The evaluation reports (*56.302/2003, 56.302/2020, 56.302/2021*), as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of paraquat dichloride, together with related manufacturing impurities, in the form of an aqueous solution, free from visible extraneous matter, and must contain an effective emetic (Note 2). The material may also include colorants and olfactory alerting agents.

2 Active ingredient

2.1 **Identity tests** (56/SL/M/2, CIPAC Handbook G, p.128, 1995)

The active ingredient (paraquat and chloride, Note 3) shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Paraquat dichloride content** (56/SL/M/3, CIPAC Handbook E, p.167, 1993)

The paraquat dichloride content (Note 4) shall be declared (not less than 500 g/l at 20 ± 2ºC, Note 5) and, when determined, the average measured content shall not differ from that declared by more than ± 25 g/l.

3 Relevant impurities

3.1 **Free 4,4'-bipyridyl** (56/13/M/7.4, CIPAC Handbook 1A, p.1317, 1980)

Maximum: 1.0 g/kg (1000 ppm).

3.2 **Total terpyridines** (56/SL/M/5, CIPAC Handbook M, p. 141, 2009)

Maximum: 0.001 g/kg (1.0 ppm).

4 Physical properties

4.1 **pH range** (MT 75.3, CIPAC Handbook J, p. 131, 2000) (Note 1)

pH range: 2.0 to 6.0.

* 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/

Note 1 The product must not be allowed to come into direct contact with metal. Containers may be manufactured from suitable polymeric materials or metal and must comply with pertinent national and international transport and safety regulations. If metal is used, containers must be lined with suitable polymeric material, or the internal surfaces treated to prevent corrosion of the container and/or deterioration of the contents.

Note 2 An effective emetic, having the following characteristics, must be incorporated into the TK.

- It must be rapidly absorbed (more rapidly than paraquat) and be quick acting. Emesis must occur in about half an hour in at least 50% of cases.
- It must be an effective (strong) stimulant of the emetic centre of the brain, to produce effective emesis. The emetic effect should have a limited 'action period', of about two to three hours, to allow effective treatment of poisoning.
- It must act centrally on the emetic centre in the brain.
- It must not be a gastric irritant because, as paraquat is itself an irritant, this could potentiate the toxicity of paraquat.
- It must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).
- It must be compatible with, and stable in, the paraquat formulation and not affect the herbicidal efficacy or occupational use of the product.

The paraquat TK, SL and SG produced by the manufacturer mentioned in the evaluation reports 56.302/2003, 56.302/2020 and 56.302/2021 contain the emetic 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazole-(1,5-a)pyrimidin-5-one (PP796). The method for determination of PP796 content in TK and formulated products is provided in Appendix 1.

Note 3 Chloride in paraquat dichloride TK may be identified by means of the white precipitate produced on reaction of a solution of the TK with silver nitrate solution. Alternatively or in addition, the method for identification of chloride in mixed formulations of diquat dibromide and paraquat dichloride may be used. This method is provided in Appendix 2.

Note 4 To obtain the paraquat dichloride content, multiply the paraquat ion content (as determined by CIPAC method 56/SL/M/3) by 1.38.

Note 5 The lower limit of 500 g/l corresponds nominally to 442 g/kg and thus the tolerance of ± 25 g/l corresponds to ± 5% on a g/kg basis. If, in a particular case, the declared concentration exceeds 566 g/l (>500 g/kg), the tolerance shall be ± 25 g/kg, not ± 25 g/l (± 22 g/kg). If the buyer requires specification of both g/l at 20°C and g/kg, then in case of dispute the analytical results shall be calculated as g/kg.

PARAQUAT DICHLORIDE SOLUBLE CONCENTRATE (Notes 1, 2 and 3)

FAO Specification 56.302/SL (October 2021*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation reports (*56.302/2003, 56.302/2020, 56.302/2021*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TK from the evaluated source. 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 TK from other sources. The evaluation reports (*556.302/2003, 56.302/2020, 56.302/2021*), as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of technical paraquat dichloride, complying with the requirements of FAO Specification 56.302/TK (October 2021), in the form of an aqueous solution (Notes 1 and 2), together with any other necessary formulants, and must contain an effective emetic (Note 3). The material may also include colorants, olfactory alerting agents and thickeners. It shall contain not more than a trace of suspended matter, immiscible solvents and sediment.

2 Active ingredient

2.1 **Identity tests** (56/SL/M/2, CIPAC Handbook G, p.128, 1995)

The active ingredient (paraquat and chloride components, Note 4) shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Paraquat dichloride content** (56/SL, CIPAC Handbook E, p.167, 1993) (Note 1)

The paraquat dichloride content (Note 5) shall be declared (g/kg and/or g/l at 20 ± 2ºC, Note 6) and, when determined, the average content measured shall not differ from that declared by more than the following tolerances.

Declared content, g/kg or g/l at 20 ± 2ºC	Permitted tolerance
25 up to 100	± 10% of the declared content
Above 100 up to 250	± 6% of the declared content
Above 250 up to 500	± 5% of the declared content
Note: the upper limit is included in each range.	

3 Relevant impurities

3.1 **Free 4,4'-bipyridyl** (56/13/M/7.4, CIPAC Handbook 1A, p.1317, 1980)

Maximum: 1 g/kg (1000 ppm).

---

* 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/

3.2 **Total terpyridines** (56/SL/M/5, CIPAC Handbook M, p. 141, 2009)

Maximum: 0.001 g/kg (1.0 ppm).

4 Physical properties

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

pH range: 4.0 to 8.0.

4.2 **Dilution stability** (MT 41.1, CIPAC Handbook O, p. 174, 2017)

The formulation, after the stability test at 54°C (see 5.2) and following dilution (Note 7) with CIPAC Standard water D and standing at 30 ± 2°C for 24 h, shall give a clear or opalescent solution, free from more than a trace of sediment and visible solid particles. Any visible sediment or particles produced shall pass through a 75 μm test sieve (Note 8).

4.3 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 9)

Maximum: 60 ml after one minute.

5 Storage stability

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

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

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

After storage at 54 ± 2ºC 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 10), and the product shall continue to comply with the clause for:

- pH range (4.1).

Note 1 FAO specifications 55/SL and 56/SL are applied to mixed SL formulations, containing both paraquat and diquat. Emetic is added to all formulations containing paraquat and the extra precautions required for handling solutions of paraquat must be observed when handling the mixed formulation. If the SL contains both diquat and paraquat, CIPAC method 55+56/SL/M/3 (CIPAC Handbook E, p.75, 1993) should be used for determination of active ingredient content.

Note 2 The product must not be allowed to come into direct contact with metal. Containers may be manufactured from suitable polymeric materials or metal and must comply with pertinent national and international transport and safety regulations. If metal is used, containers must be lined with suitable polymeric material, or the internal surfaces treated to prevent corrosion of the container and/or deterioration of the contents.

Note 3 An effective emetic, having the following characteristics, must be incorporated into the SL.

- It must be rapidly absorbed (more rapidly than paraquat) and be quick acting. Emesis must occur in about half an hour in at least 50% of cases.
- It must be an effective (strong) stimulant of the emetic centre of the brain, to produce effective emesis. The emetic effect should have a limited ‘action period’, of about two to three hours, to allow effective treatment of poisoning.
- It must act centrally on the emetic centre in the brain.
- It must not be a gastric irritant because, as paraquat is itself an irritant, this could potentiate the toxicity of paraquat.

— It must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).
— It must be compatible with, and stable in, the paraquat formulation and not affect the herbicidal efficacy or occupational use of the product.

The paraquat TK, SL and SG produced by the manufacturer mentioned in the evaluation reports 56.302/2003, 56.302/2020 and 56.302/2021 contain the emetic 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazole-(1,5-a)pyrimidin-5-one (PP796). The method for determination of PP796 content in TK and formulated products is provided in Appendix 1.

Note 4 Chloride in paraquat dichloride SL may be identified by means of the white precipitate produced on reaction with silver nitrate solution. Alternatively or in addition, the method for identification of bromide and chloride in mixed formulations of diquat dibromide and paraquat dichloride may be used. This method is provided in Appendix 2.

Note 5 To obtain the paraquat dichloride content, multiply the paraquat ion content (as determined by CIPAC method 55/SL/M/3) by 1.38.

Note 6 If the buyer requires specification of both g/l at 20°C and g/kg, then in case of dispute the analytical results shall be calculated as g/kg.

Note 7 The concentration for the test should not be higher than the highest concentration recommended for use.

Note 8 Some formulations containing additional wetter may show signs of layering and produce a trace of oily precipitate under the test conditions defined in MT 41.1. This is acceptable and does not affect biological efficacy or spray characteristics at normal spray dilution.

Note 9 The mass of sample to be used in the test should correspond to the highest concentration recommended for use by the supplier. The test is to be conducted in CIPAC standard water D.

Note 10 Samples of the product taken before and after the storage stability test may be analyzed concurrently after the test to reduce the analytical error.

PARAQUAT DICHLORIDE WATER SOLUBLE GRANULES (Note 1)

FAO Specification 56.302/SG (October 2021*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation reports (*56.302/2003, 56.302/2020, 56.302/2021*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TK from the evaluated source. 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 TK from other sources. The evaluation reports (*56.302/2003, 56.302/2020, 56.302/2021*), as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of granules containing technical paraquat dichloride complying with the requirements of the FAO Specification 56.302/TK (October 2021) and suitable carriers, if required, and it must contain an effective emetic (Note 2). The material may also contain colorants and olfactory alerting agents. It shall be homogeneous, free from visible extraneous matter and/or hard lumps, free flowing, and nearly dust-free. Insoluble carriers and formulants shall not interfere with compliance with clause 4.2.

2 Active ingredient

2.1 **Identity tests** (56/SL/M/2, CIPAC Handbook G, p.128, 1995)

The active ingredient (paraquat and chloride components, Note 3) shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Paraquat dichloride content** (55+56/SG/M/4, CIPAC Handbook E, p.78, 1993)

The paraquat dichloride content (Note 4) shall be declared (g/kg) and, when determined, the content measured shall shall not differ from that declared by more than the following tolerances:

Declared content, g/kg	Permitted tolerance
25 up to 100	± 10% of the declared content
Above 100 up to 250	± 6% of the declared content
Note: the upper limit is included in each range.	

3 Relevant impurities

3.1 **Free 4,4'-bipyridyl** (56/13/M/7.4, CIPAC Handbook 1A, p.1317, 1980)

Maximum: 1.0 g/kg (1000 ppm).

* 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/

3.2 **Total terpyridines** (56/SL/M/5, CIPAC Handbook M, p. 141, 2009)

Maximum: 0.001 g/kg (1.0 ppm).

4 Physical properties

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

pH range of a 1% w/v dispersion: 6.0 to 8.0.

4.2 **Degree of dissolution and solution stability** (MT 179.1, CIPAC Handbook O, p.189, 2017)

Residue of formulation retained on a 75 µm test sieve after dissolution in CIPAC Standard Water D at 30 ± 2°C.

Maximum: 2% after 5 minutes.

Maximum: 2% after 24 h.

4.3 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 5)

Maximum: 30 ml after 1 minute.

4.4 **Dustiness** (MT 171.1, CIPAC Handbook P, p. 235, 2021) (Note 6)

Nearly dust-free, with a maximum of 1 mg (0.0033% by weight) dust collected by the gravimetric submethod.

4.5 **Flowability** (MT 172.2, CIPAC Handbook P, p.240, 2021)

At least 98% of the formulation shall pass through a 5 mm test sieve after 20 drops of the sieve.

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

Minimum 99.5% attrition resistance.

5 Storage stability

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

After storage at 54 ± 2°C for 14 days the determined average active ingredient content shall not be lower than 97% relative to the determined average content found before storage (Note 7) and the formulation shall continue to comply with the clauses for:

- pH range (4.1),
- degree of dissolution and solution stability (4.2),
- dustiness (4.4),
- flowability (4.5),
- attrition resistance (4.6).

Note 1 Containers may be manufactured from suitable polymeric materials or metal, and must comply with pertinent national and international transport and safety requirements. Where metal is used containers shall be lined with suitable polymeric material, or the internal surfaces treated to prevent corrosion of the container and/or deterioration of the contents. The product must not be allowed to come into direct contact with metal.

Note 2 An effective emetic, having the following characteristics, must be incorporated into the SG.

- It must be rapidly absorbed (more rapidly than paraquat) and be quick acting. Emesis must occur in about half an hour in at least 50% of cases.
- It must be an effective (strong) stimulant of the emetic centre of the brain, to produce effective emesis. The emetic effect should have a limited 'action period', of about two to three hours, to allow effective treatment of poisoning.
- It must act centrally on the emetic centre in the brain.
- It must not be a gastric irritant because, as paraquat is itself an irritant, this could potentiate the toxicity of paraquat.
- It must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).
- It must be compatible with, and stable in, the paraquat formulation and not affect the herbicidal

The paraquat TK, SL and SG produced by the manufacturer mentioned in the evaluation reports 56.302/2003, 56.302/2020 and 56.302/2021 contain the emetic 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazole-(1,5-a)pyrimidin-5-one (PP796). The method for determination of PP796 content in TK and formulated products is provided in Appendix 1.

Note 3 Chloride in paraquat dichloride SG may be identified by means of the white precipitate produced on reaction of a solution of the SG with silver nitrate solution. Alternatively or in addition, the method for identification of chloride in mixed formulations of diquat dibromide and paraquat dichloride may be used. This method is provided in Appendix 2.

Note 4 To obtain the paraquat dichloride content, multiply the paraquat ion content (as determined by CIPAC method 55+56/SG/M/4) by 1.38.

Note 5 The mass of sample to be used in the test should correspond to the highest concentration recommended for use by the supplier. The test is to be conducted in CIPAC standard water D.

Note 6 The optical method of MT 171.1 would not give reliable values for dust at levels around the specified limit and should therefore not be used.

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

PART TWO
EVALUATION REPORTS

PARAQUAT

PARAQUAT

FAO/WHO EVALUATION REPORT 56.302/2021

Recommendations

The Meeting recommended the following:

(i) the revised FAO specifications for paraquat TK, SL and SG proposed by Syngenta Crop Protection AG, and as amended, should be adopted by FAO.

Appraisal

The FAO specifications for paraquat TK, SL and SG proposed by Syngenta were considered by the Meeting in 2003, published in 2003 and 2008 and revised in 2020 (TK, SL and SG). In 2019, the Meeting established a systematic review programme for FAO and WHO specifications developed under the new procedure and the FAO specifications for paraquat TK, SL and SG were ranked among the FAO specifications with the highest priority for review. Among other reasons, the way the information on the emetic present in the TK and formulated products gave rise to some concerns and led to a revision in 2020, where an amended disclaimer and a footnote on the minimum concentration were added.

Noting that mentioning the identity of emetic and its concentration is outside the scope of specifications and hence the mandate of the JMPS, the Meeting reconsidered the disclaimers preceding the TK, SL and SG specifications and the footnotes related to the emetic. The 2021 Meeting concluded that only the fact that an emetic should be present and the criteria for its effectiveness should be kept in the footnotes, but without recommendation of any particular emetic concentration. The Meeting referred to a paragraph in Section 1.1 of the Manual on development and use of FAO and WHO specifications for chemical pesticides [The evaluation of the hazards and risks associated with pesticides for specifications purposes is based primarily on the assessment of the national registration authorities, and is carried out by a WHO-designated unit or other international organization].

The emetic is considered as a coformulant and not related to the quality itself of paraquat TK, SL and SG. The evaluation of the risks and benefits of adding an emetic falls into the remits of national pesticide registration authorities that obviously have to consider national regulations as well. Taking these considerations into account, the Meeting recommended to remove all references to a certain concentration of an emetic that is contained in Syngenta's products. However, the Appendix 1 that provides an analytical method to determine that particular emetic added by Syngenta should be kept.

PARAQUAT

FAO/WHO EVALUATION REPORT 56.302/2020

Recommendations

The Meeting recommended the following:

(i) the updated FAO specifications for paraquat TK, SL and SG proposed by Syngenta Crop Protection AG, and as amended, should be adopted by FAO.

(ii) the disclaimer preceding the specifications for paraquat TK, SL and SG should be amended to reflect the current understanding of the role of the emetic in paraquat TK and formulated products.

Appraisal

The FAO specifications for paraquat TK, SL and SG were considered by the Meeting in 2003 and published in 2003 and 2008 (TK, SL and SG, respectively). In 2019, the Meeting established a systematic review programme for FAO and WHO specifications developed under the new procedure and the FAO specifications for paraquat TK, SL and SG were ranked among the FAO specifications with the highest priority for review. Concurrently, some concerns regarding the nature and concentration of the emetic PP796 in paraquat TK and formulated products were brought to the attention of the Meeting, yet without robust scientific evidence that could demonstrate that the emetic concentration does not represent a best effort of the company to reduce risks and fatalities associated with accidental or self-harm ingestion of paraquat SL and SG.

The Meeting therefore contacted Syngenta Crop Protection AG (Syngenta) in early 2020 with a request to provide background information regarding the choice of the emetic and its concentration in paraquat TK and formulated products - information that was not accessible to JMPS in 2003 and 2008. Syngenta promptly responded in writing and provided several documents and studies (see "References") that were considered by the Meeting in Closed Meeting in October 2020.

Briefly, the Meeting noted that:

- The emetic PP 769 was initially developed as antiasthmatic drug, acts on the central nervous system and may lead to considerable side effects in humans when exposed to higher doses,
- The type and concentration of the emetic in paraquat (PP 796) has been chosen to be a reasonable compromise between efficacy in terms of fast and reliable induction of vomiting after accidental or self-harm uptake of paraquat formulations, minimization of unwanted toxicological side effects of higher concentrations of the emetic and the solubility / stability of PP796 in paraquat TK and formulated product.
- The recommended concentration of PP 796 is expected to induce vomiting after short time and reduce uptake of paraquat with a reasonable probability.

The Meeting agreed that an in-depth assessment of the risks and benefits associated with a possible absence or changed concentrations of the emetic would clearly be outside the scope

of specifications and hence the mandate of the JMPS[1]. The Meeting concluded that the disclaimer preceding the FAO specification for paraquat TK and formulated products should be amended to explain that the emetic present may lead to only a partial reduction of the toxic effect of an uptake of paraquat.

Furthermore, the Meeting recommended that the specifications for paraquat TK, SL and SG should be editorially updated to reflect the current CIPAC analytical methods for paraquat and terpyridines now published in Handbook M. Furthermore, newer MT methods replacing previous versions while providing equivalent results should be referenced in the appropriate clauses and the peer-validated methods for determination of the emetic PP796 in TK and formulated products and for chloride and bromide should be provided in Appendices 1 and 2 to the specifications and evaluations.

References

Study number	Author (s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
		2020	Syngenta submission to JMPS re paraquat, unpublished
		2020	Technical Feasibility Assessment: Incorporation of PP796 Emetic into Paraquat Dichloride Technical Material at high loading. Syngenta, Unpublished
SMN11335, CA3575		2016	Solubility in Water. Unpublished.
		2020	"The Use of Emetics and Relevant Emetic Dose Considerations for Preventing Harm From Paraquat Ingestion", unpublished
RSA/CPD2019_009_001		2020	Analysis of the Efficacy of the Emetic PP796 in Paraquat Formulations, Regulatory Science Associates. Unpublished.

[1] For more information on FAO and WHO specifications and remits of the JMPS, see Section 1.1 "Scope of specifications" FAO/WHO Manual, 3rd edition of the 1st Edition.

PARAQUAT

FAO EVALUATION REPORT 56.302/2003

Explanation

The data for paraquat dichloride were evaluated in support of a review of existing FAO specifications (AGP:CP/344, Rome,1996).

Paraquat dichloride is not under patent.

Paraquat was reviewed by the World Health Organization (WHO) and the United Nations Environment Programme (UNEP) in 1983, resulting in the publication of Environmental Health Criteria 39 (WHO, 1984), and by the International Programme on Chemical Safety (IPCS, 1991), resulting in IPCS Health & Safety Guide No 51. Paraquat was reviewed by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) in 1986 and was scheduled for periodic re-evaluation in 2003. It has been evaluated by US EPA (USEPA, 1996) and is currently under evaluation by the European Commission.

The draft specification and the supporting data were provided by Syngenta Crop Protection AG, in 2002.

Uses

Paraquat dichloride is a non-selective contact herbicide, which is absorbed by foliage, with some translocation in the xylem. It is used in broad-spectrum control of broad-leaved weeds and grasses, in a wide range of agricultural applications, for general weed control on non-crop land and also for pasture restoration.

Identity

Common name (dication):

paraquat (E-ISO, (m)F-ISO, BSI, ANSI, WSSA, JMAF)

Synonyms:

methyl viologen

Chemical names:

dication -
IUPAC, 1,1'-dimethyl-4,4'-bipyridinium [1]
CA, 1,1'-dimethyl-4,4'-bipyridinium

dichloride -
IUPAC, 1,1'-dimethyl-4,4'-bipyridinium dichloride [1]
CA, 1,1'-dimethyl-4,4'-bipyridinium dichloride

CAS No:

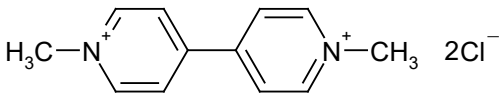
1910-42-5 (dichloride); 4685-14-7 (dication)

CIPAC No:

56 (dication); 56.302 (dichloride)

[1] The IUPAC name for the bipyridinium moiety is alternatively expressed as “bipyridinediium” or “bipyridilium”.

Structural formula (dichloride):



Molecular formula:

$C_{12}H_{14}Cl_2N_2$ (dichloride); $C_{12}H_{14}N_2$ (dication)

Relative molecular mass:

257.2 (dichloride); 186.3 (dication)

Identity tests (CIPAC G 56/SL/M-):

HPLC retention time; UV spectrum; addition of alkaline sodium dithionite to a dilute solution, where a blue colour indicates the presence of paraquat. The presence of the dichloride salt is tested with silver nitrate solution or, in the presence or absence of diquat dibromide, by capillary electrophoresis.

Physicochemical properties

Table 1. Physicochemical properties of pure paraquat dichloride

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure	<<1x10-8kPa at 25ºC (extrapolated)	99.5	OECD 104
Melting point, boiling point and/or temperature of decomposition	Melting point: >400ºC Boiling point: not applicable Decomposition temperature: 340ºC	99.5	OECD 102
Solubility in water	620g/l at 20 °C across pH range	99.5	OECD 105 (flask method)
Octanol/water partition coefficient	log P_{ow} = -4.5 at 20ºC	99.5	OECD 107 (flask method)
Hydrolysis characteristics	Paraquat dichloride is hydrolytically stable under acidic, neutral and alkaline conditions, no significant decrease in concentration having been recorded at pH 5, 7 and 9 after 30days at 25ºC and 40ºC.	Not stated	Analysis of sterile aqueous buffer solutions containing known amounts of paraquat dichloride before and after storage.
Photolysis characteristics	The environmental half-life of paraquat dichloride in water under mid-European conditions was calculated to be between 2 and 820 years, depending upon seasonal sunlight and depth of water.	99.7	Measurement of molar extinction coefficients and quantum yield, then these data used in the Frank and Klöpffer model to obtain an estimate of half-life.
Dissociation characteristics	In aqueous solution the paraquat dichloride is completely dissociated.	Not applicable	-

Table 2. Chemical composition and properties of paraquat dichloride (TK)

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 98.1-99.3% and percentages of unknowns were 1.9-0.7%.
Declared minimum paraquat dichloride content	500 g/l (442 g/kg).
Relevant impurities ≥ 1 g/kg and maximum limits for them	4,4 bipyridyl, 1 g/kg (1000 ppm).
Relevant impurities < 1 g/kg and maximum limits for them	Total terpyridines 0.001 g/kg (1.0 ppm)
Stabilisers or other additives and maximum limits for them	An effective emetic (reference to effective emetic criteria) – see below. PP796, 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazole-[1,5-a]pyrimidin-5-one is the only emetic known to meet these effective emetic criteria. If PP796 is the effective emetic employed, it must be present at a minimum level of 0.23% by weight of the paraquat ion content[0.17% on a paraquat dichloride basis]
Melting or boiling temperature range	340°C, at which decomposition occurs

Criteria for effective emesis.

- The emetic must be rapidly absorbed (more rapidly than paraquat) and be quick acting. Emesis must occur in about half an hour in at least 50% of cases.
- The emetic must be an effective (strong) stimulant of the emetic centre, to produce effective emesis. The emetic effect should have a limited “action period” of about two to three hours, to allow effective treatment of poisoning.
- The emetic must be act centrally on the emetic centre in the brain.
- The emetic must be not be a gastric irritant because, as paraquat is itself an irritant, this could potentiate the toxicity of paraquat.
- The emetic must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).
- The emetic must be compatible with, and stable in, the paraquat formulation and not affect the herbicidal efficacy or occupational use of the product.

Toxicological summaries

Notes. (i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from paraquat dichloride having impurity profiles similar to those referred to in the table above.
(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 3. Toxicology profile of paraquat dichloride TK, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions or guideline adopted	Result (paraquat dichloride technical / paraquat cation).
Rat, Alpk:ApfSD, male	oral	OECD 401, 14 day observation	MLD = 344 [246 – 457] mg paraquat dichloride technical/kg bw, equivalent to 113.5 mg/kg bw expressed as paraquat cation.
Rat, Alpk:ApfSD, female	oral	OECD 401, 14 day observation	MLD = 283 [182 – 469] mg paraquat dichloride technical/kg bw, equivalent to 93.4 mg/kg bw expressed as paraquat cation.

Table 3. Toxicology profile of paraquat dichloride TK, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions or guideline adopted	Result (paraquat dichloride technical / paraquat cation).
Rat, Alpk:ApfSD, male and female	dermal	OECD 402, 24 hour, occluded, 14 day observation	MLD = >2000 mg paraquat dichloride technical/kg bw equivalent to >660 mg/kg bw expressed as paraquat cation.
Rat, Alpk:Ap, male and female	inhalation	OECD 403, 4 hour nose only*, 14 day observation	LC_{50} = 0.83 – 1.93 mg/m^3 expressed as paraquat cation.
Rabbit, New Zealand White, female	skin irritation	OECD 404, 4 hour, occluded, 34 day, observation	Slight but persistent skin irritant.
Rabbit, New Zealand White, female	eye irritation	OECD 405, 28 day observation	Persistent, moderate to severe irritant to the rabbit eye [Class 5 on a 1-8 scale].
Guinea pigs, Dunkin Hartley, female	skin sensitization	OECD 406, Magnusson and Kligman maximization test, 24 hour, occluded, 48 hour observation	Negative, not a skin sensitizer.

* Paraquat dichloride is non-volatile and formulations containing paraquat are not applied through equipment which will generate a significant proportion (>1% w/w) of spray droplets of diameter less than 50 µm. Therefore, respirable vapour or droplets of paraquat dichloride will not be produced in practice and these toxicity data are not relevant to assessment of human risks.

Table 4. Toxicology profile of paraquat TK, based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions or guideline adopted	Result
Rabbit, New Zealand White, male and female	Short-term dermal toxicity	21-day dermal toxicity	NOEL = 1.57 mg paraquat dichloride/kg bw/day equivalent to 1.15 mg/kg bw/day, expressed as paraquat cation. LOEL = 3.61 mg paraquat dichloride /kg bw/day, equivalent to 2.6 mg/kg bw/day, expressed as paraquat ion.
Mouse, ICR-CRJ SPF, male and female	Short-term toxicity	13-week dietary	NOEL = 100 ppm, equivalent to approximately 12 and 14 mg/kg bw/day, expressed as paraquat ion in males and females, respectively. LOEL = 300 ppm, equivalent to approximately 36 and 42 mg/kg bw/day, expressed as paraquat ion in males and females, respectively.
Rat, Fischer CDF (F344), male and female	Short-term toxicity	13-week dietary	NOEL = 100 ppm, equivalent to approximately 6 and 7 mg/kg bw/day, expressed as paraquat ion in males and females, respectively. LOEL = 300 ppm, equivalent to approximately 20 and 21 mg/kg bw/day, expressed as paraquat ion in males and females, respectively.

Table 4. Toxicology profile of paraquat TK, based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions or guideline adopted	Result
Dog, Beagle, male and female	Short-term toxicity	13-week dietary	NOEL = 20 ppm, equivalent to approximately 0.6 and 0.7 mg/kg bw/day, expressed as paraquat ion in males and females, respectively. LOEL = 60 ppm, equivalent to approximately 2 mg/kg bw/day, expressed as paraquat ion in males and females.
Dog, Beagle, male and female	Short-term toxicity	1-year dietary	NOEL = 15 ppm, equivalent to approximately 0.45 and 0.48 mg/kg bw/day, expressed as paraquat ion in males and females, respectively. LOEL = 30 ppm, equivalent to approximately 0.9 and 1.0 mg/kg bw/day, expressed as paraquat ion in males and females, respectively.
Mouse, Alpk Swiss-derived, male and female	Carcinogenicity	99-week dietary	Not tumorigenic. NOAEL = 12.5 ppm, equivalent to approximately 1.5 mg/kg bw/day, expressed as paraquat ion in males. NOEL = 37.5 ppm, equivalent to approximately 4.3 mg/kg bw/day, expressed as paraquat ion in females.
Rat, Fischer 344, male and female	Chronic toxicity / carcinogenicity	113-117 weeks for males and 122-124 weeks for females	Not carcinogenic. NOEL = 25 ppm, equivalent to approximately 1.25 mg/kg bw/day, expressed as paraquat ion. LOEL = 75 ppm, equivalent to approximately 3.75 mg/kg bw/day, expressed as paraquat ion.
Rat, Alpk:APfSD, male and female	Reproductive toxicity	3-generation, 2 litters per generation	No effect on reproductive parameters. NOEL for toxicity = 25 ppm, equivalent to approximately 2.3 mg/kg bw/day, expressed as paraquat ion. NOEL for reproductive effects = >150 ppm, equivalent to approximately 13 mg/kg bw/day, expressed as paraquat ion.
Mice, Crl:CD1 (ICR) BR, female	Developmental toxicity	Gavage	NOEL for both maternal and developmental toxicity = 15 mg/kg bw/day expressed as paraquat ion.
Mice, Alpk SPF, female	Developmental toxicity	Gavage	Not teratogenic. No significant influence on embryonic or foetal development. NOEL for developmental toxicity = >10 mg/kg bw/day expressed as paraquat ion.
Rat, Alpk:SPF, female	Developmental toxicity	Gavage	Not teratogenic. NOEL for maternal and developmental toxicity > 1mg/kg bw/day expressed as paraquat ion.
Rat, Alpk:APfSD	Developmental toxicity	Gavage	Not teratogenic. NOAEL for maternal and developmental toxicity = 3 mg/kg bw/day expressed as paraquat ion.

Table 5. Mutagenicity profile of paraquat dichloride TK, based on *in vitro* and *in vivo* tests

Species	Test	Conditions	Result
Mouse, lymphocytes (L5178Y)	OECD 476, L5178Y mouse lymphoma assay (*in vitro*)	Doses of 23 – 361 µg/ml	Negative
Human lymphocytes	OECD 473, Cytogenetic study (*in vitro*)	Dosed at 90, 903 and 1807 µg/ml	Positive
Chinese hamster lung fibroblasts	OECD 479, Sister chromatid exchange assay (*in vitro*)	Dosed at 0.9, 1.8, 9, 18, 90 and 177 µg/ml	Positive
Rat hepatocytes	OECD 482, DNA damage and repair/unscheduled DNA synthesis (*in vitro*)	Dosed at 0.19 ng/ml to 1.86 mg/ml	Negative
Rat somatic cells	Rat cytogenetic assay (*in vivo*)	Male and female Wistar rats given a single oral dose at 15, 75 and 150 mg/kg	Negative
Mouse somatic cells	OECD 474, Micronucleus test (*in vivo*)	Male and female C57BL/6J/Alpk mice given a single oral dose at 52 and 83 mg/kg	Negative
Rat somatic cells	UDS assay (*in vivo*)	Single oral dose at 42 to 120 mg/kg	Negative
Mouse germ cells	Dominant lethal (*in vivo*)	Male CD1 mice dosed orally at 0, 0.04, 0.4 and 4.0 mg/kg for 5 days.	Negative

Table 6. Ecotoxicology profile of paraquat dichloride TK.

Species	Test	Duration and conditions	Result
Daphnia magna, (water flea)	Acute toxicity	EEC Method C2, Static system, 20-21°C, 48-hour observation	24 and 48 hour EC_{50} = 11.8 and 4.4 mg/l, expressed as paraquat ion, respectively. 48 hour NOEC = 2.2 mg/l expressed as paraquat ion.
Daphnia magna, (water flea)	Chronic toxicity	21-day exposure, based on OECD Guideline 202, modified by individually separating the Daphnia static system, growth and reproduction monitored	NOEC = 0.12 mg/l expressed as paraquat ion.
Oncorhynchus mykiss, (rainbow trout)	Acute toxicity	EEC Method C1, static system at 15°C	24, 48, 72 and 96 hour LC_{50} = 33, 22, 22 and 19 mg/l, expressed as paraquat ion, respectively. 96 hour NOEC = <0.3 mg/l, expressed as paraquat ion
Cyprinus carpio, (mirror carp)	Acute toxicity	EEC Method C1, static system at 22°C	24, 48, 72 and 96 hour LC_{50} = >112, >112, >112 and 98 mg/l expressed as paraquat ion, respectively. 96 hour NOEC = 60 mg/l expressed as paraquat ion.

Table 6. Ecotoxicology profile of paraquat dichloride TK.

Species	Test	Duration and conditions	Result
Oncorhynchus mykiss, (rainbow trout)	Chronic toxicity	21-day fish juvenile growth test, based upon OECD Method 204, with the exposure period extended to 21 days. Broadly in agreement with the draft OECD guideline 'Fish, juvenile growth test - 28 days', except that the exposure was for 21 days. Flow through system at 15°C	NOEC = 8.5 mg/l expressed as paraquat ion.
Selenastrum capricornutum, (green alga)	Effect on growth	Based on OECD Guideline 201 but with an extension of the exposure period to 96 hours. Static system at 24°C, biomass and growth rate observed	EbC_{50} = 0.075 mg/l expressed as paraquat ion. ErC_{50} = 0.20 mg/l expressed as paraquat ion. NOEC = 0.016 mg/l expressed as paraquat ion.
Eisenia foetida, (earthworm)	Acute toxicity	Laboratory study in artificial soil	LC_{50} = >1000 mg/kg dry soil, expressed as paraquat ion
Apis mellifera (honey bee)	Acute oral toxicity	Based on UK data requirements for approval under the Control of Pesticides Regulations, Working Document D3 (revised 1979). Consistent with EPPO guideline 170. Controlled environment at 22°C	24, 48, 72, 96 and 120 hour LD_{50} = 154, 50.9, 26.3, 19.5 and 11.2 µg/bee, expressed as paraquat ion, respectively.
Apis mellifera (honey bee)	Acute contact toxicity	Based on UK data requirements for approval under the Control of Pesticides Regulations, Working Document D3 (revised 1979). Consistent with EPPO guideline 170. Controlled environment at 22°C	72, 96 and 120 hour LD_{50} = 108, 89.1 and 50.9 µg/bee, expressed as paraquat ion, respectively.
Colinus virginianus, (bobwhite quail)	Acute toxicity	Oral intubation in distilled water, 14 day observation	LD_{50} = 127 mg/kg bw expressed as paraquat ion. LLD = 115 mg/kg bw expressed as paraquat ion. NOEL = 72 mg/kg bw expressed as paraquat ion.
Anas platyrhynchos, (mallard duck)	Acute toxicity	Oral intubation in propylene glycol, 14 day observation	LD_{50} = 144 mg/kg bw expressed as paraquat ion.
Colinus virginianus, (bobwhite quail)	Short-term toxicity	5 days treatment, 3 days observation	LC_{50} = 711 mg/kg diet expressed as paraquat ion.
Anas platyrhynchos, (mallard duck)	Short-term toxicity	5 days treatment, 3 days observation	LC_{50} = 2932 mg/kg diet expressed as paraquat ion.
Coturnix japonica, (Japanese quail)	Short-term toxicity	5 days treatment, 3 days observation	LC_{50} = 703 mg/kg diet expressed as paraquat ion

Table 6. Ecotoxicology profile of paraquat dichloride TK.

Species	Test	Duration and conditions	Result
Colinus virginianus, (bobwhite quail)	Reproductive toxicity	18 week dietary treatment. Egg laying and collection started after 10 weeks on treated diet and lasted for 8 weeks.	NOEC for toxicity and reproduction = 100 mg/kg diet expressed as paraquat ion.
Anas platyrhynchos, (mallard duck)	Reproductive toxicity	18 week dietary treatment. Egg laying and collection started after 10 weeks on treated diet and lasted for 8 weeks.	NOEC for toxicity = 100 mg/kg diet expressed as paraquat ion. NOEC for reproduction = 30 mg/kg diet expressed as paraquat ion.

Paraquat dichloride was evaluated by WHO (WHO, 1984), by IPCS (IPCS, 1991) and by the FAO/WHO JMPR in 1986 (by which it is subject to a periodic re-evaluation in 2003). The IPCS (1991) review concluded that residue levels of paraquat in food and drinking-water, resulting from its normal use, are unlikely to pose a health hazard for the general population.

The WHO/PCS hazard classification (WHO 2002) of paraquat dichloride is: moderately hazardous, class II.

The US EPA concluded, from acute toxicity studies on laboratory animals, that paraquat is highly toxic by the inhalation route and was placed in Toxicity Category I (the highest of four levels) for acute inhalation effects. However, the EPA established that the large droplets arising in agricultural practice (400 to 800 µm) are well beyond the respirable range and therefore inhalation toxicity is not a toxicological endpoint of concern. Paraquat is moderately toxic (Category II) by the oral route and slightly toxic (Category III) by the dermal route. Paraquat will cause moderate to severe eye irritation and minimal dermal irritation and has been placed in Toxicity Categories II and IV for these effects (USEPA, 1997). Paraquat was classified as a “Group E” chemical, i.e. one showing evidence of non-carcinogenicity to humans. The no observed effect levels (NOEL) for maternal toxicity are equal to, or more conservative (protective) than, the NOEL based on developmental toxicity. There is no evidence that paraquat is associated with reproductive effects. Paraquat also shows no evidence of causing mutagenicity. The US EPA has determined that there is a reasonable certainty that no harm will result to infants and children or to the general population from aggregate exposure to paraquat dichloride residues. The EPA does not believe that the effects produced by paraquat would be cumulative with those of other, structurally related, compounds.

Formulations

The main formulation types available are SL and SG.

The SL formulations are registered and sold in many countries throughout the world. SG formulations are registered in Europe and sold mainly in the UK.

Methods of analysis and testing

Analytical methods for the active ingredient (including identity tests) were published in CIPAC Handbook E, pp. 75 and 167, and utilise a colorimetric procedure based on the blue free-radical ion produced by paraquat. The method(s) for determination of impurities are based on GC-FID, GC-MS and CE.

Relevant impurity, 4,4'-bipyridyl, is determined by GC-FID (CIPAC 56/13) the group of relevant impurities, the terpyridines, are determined by GC-MS.

The methods for the terpyridines and the emetic have been peer evaluated for the TK but peer validation for the analysis of formulations is still to be finalized[1][2].

Test methods for determination of physico-chemical properties of the technical active ingredient were essentially OECD methods, with CIPAC procedures being used for formulation assessment (as indicated in the specifications).

Physical properties

The physical properties, the methods for testing them and the limits proposed for the SL and SG formulations, comply with the requirements of the FAO Manual (5th edition).

Containers and packaging

Detailed requirements for containers are given in the specifications, as a note, but it is important to prevent paraquat dichloride from coming into contact with metals.

Expression of the active ingredient

The active ingredient is expressed as paraquat dichloride.

Appraisal

Data submitted were in accordance with the FAO/WHO Manual (2002, 1st edition) and supported the proposed specifications.

Paraquat dichloride specifications were previously developed under the old FAO procedure in 1994 (TK and SL) and published by FAO. Revised FAO specifications (TK and SL) and an additional specification (SG) for paraquat dichloride were proposed under the new procedure by Syngenta Crop Protection AG.

Paraquat dichloride is no longer under patent.

Paraquat dichloride is a non-selective contact herbicide, highly soluble and stable in water (pH 5-9), only very slowly subject to photolysis and essentially non-volatile. It very readily, and essentially irreversibly, binds to soils and sediments.

The proposer provided the meeting with commercially confidential information on the two manufacturing processes (a third manufacturing process was no longer in use) for paraquat dichloride and concomitant impurities. Data for five batches from each of the two manufacturing processes were provided for the TK. Addition of water and an emetic (after reactions are complete) complete the TK manufacturing process. Other safening additives, such as warning colorants, stenching agents and thickeners (for liquid formulations) are also incorporated. Mass balances were good: 99.0-99.3% characterized one manufacturing process, while 98.1-99.0% characterized the second process.

The proposer identified two relevant impurities of manufacturing (4,4'-bipyridyl and total terpyridines), both of which are normally below 0.5 g/kg. Minimum levels were specified for

[1] The method for determination of total terpyridines in technical and formulated paraquat dichloride was accepted by CIPAC in 2007.

[2] The method for determination of the emetic in technical and formulated paraquat was peer-validated in 2003.

the emetic additive, and maximum levels for the two proposed relevant impurities, in the draft specifications for paraquat dichloride TK, SL and SG. Data submitted to FAO for TK purity, impurities and emetic content were similar to those submitted for registration of paraquat dichloride in the UK. A difference between the two sets of data was that terpyridines were not included in the UK data, because the concentrations are well below 1 g/kg. Both the terpyridines and 4, 4' bipyridyl were below 1 g/kg in batch analysis data submitted to FAO, regardless of which of the two current manufacturing processes was employed. The proposer noted that terpyridines are highly toxic, whilst, in some respects, 4,4'-bipyridyl is rather more toxic than paraquat dichloride. WHO/PCS opinion was to accept these views. The proposed new limit of 1 g/kg for 4,4'-bipyridyl is below the level of the previous FAO Specification (56/TK/S/F-1994). The Meeting agreed that the two impurities should be considered as relevant.

The method of analysis for paraquat dichloride is based on a colorimetric procedure, in which the blue paraquat radical, formed upon addition of alkaline sodium dithionite, is measured (CIPAC Handbook E, pages 75-78 and 167-168). The presence of paraquat as the dichloride salt may be identified by a check for chloride, using silver nitrate solution.

Methods for impurities are based on GC-FID (4,4' bipyridyl, CIPAC Handbook E, p.168 and CIPAC Handbook 1A, p. 1245) or GC-MS (terpyridines). Determination of the content of emetic, PP796, is based on capillary GC. The methods for the emetic and terpyridines have under gone satisfactory peer validation for the TK but further validation is underway for analysis of the formulations.

The proposer stated that physiochemical properties of paraquat dichloride were essentially determined using OECD methods, with CIPAC procedures used for assessment of formulation characteristics, as indicated in the specifications.

Paraquat dichloride was evaluated by WHO IPCS (1983 and 1991) with a classification of moderately hazardous assigned. The acceptable daily intake estimated by the FAO/WHO JMPR is 0-0.004 mg/kg. The US EPA has assigned a Category II acute toxicity to paraquat dichloride, which indicates it is moderately toxic. However, once paraquat is ingested and absorbed in sufficient amount, poisoning is essentially irreversible, with death as the probable end-point. Thus, all paraquat products must contain an effective emetic, to reduce the risk of accidental or deliberate ingestion and absorption. Paraquat is of low dermal toxicity but the US EPA classified paraquat dichloride in its highest toxicity class, Category I, for inhalation hazard. Nonetheless, the agency noted that, because the spray droplets produced in normal agricultural uses are too large to be respirable, the inhalation risk is actually very low. Paraquat dichloride is moderately toxic to aquatic invertebrates, slightly toxic to fish, moderately toxic to avian species and relatively non-toxic to bees.

As a result of evaluation of paraquat under Directive 91/414/EEC, the European Commission is proposing to make a colorant, an effective emetic and a stenching (or other olfactory alerting) agent, mandatory requirements for paraquat formulations. The proposer recommended the revised specifications be amended to reflect these same standards. The Meeting accepted the requirements for a stenching agent and emetic in paraquat product descriptions. The Meeting also agreed that a note to the specifications should identify the only emetic currently known to be satisfactory and provide both a minimum concentration and a suitable analytical method for it. The Meeting agreed that the note on emetic content should allow for a possible alternative compound, by describing the characteristics required for an effective emetic.

Paraquat dichloride is not mutagenic and EPA placed it in Group E for chemicals showing evidence of being non-carcinogenic to humans. Further, the evidence available indicates that paraquat dichloride has no effect on reproduction parameters and is non-teratogenic.

Certain amendments were made to the draft specifications, as agreed between the Meeting and the proposer. Apart from the exceptional requirements identified in the appraisal, the specifications were in accordance with the normal requirements of the FAO/WHO Manual.

Recommendations

The Meeting recommended that the specification for paraquat dichloride TK, as amended, should be adopted by FAO. The Meeting recommended that the specifications for SL and SG, as amended should be adopted by FAO, subject to satisfactory completion of peer validation of the analytical method for terpyridines and the emetic.

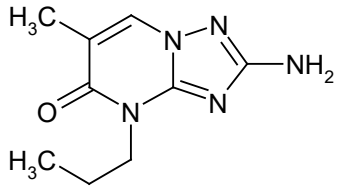
References

Text reference	Publication details
FAO/WHO 2006	Section 2.9, p. 16. Manual on development and use of FAO and WHO specifications for pesticides. March 2006 revision of the first edition. Available only on the internet at http://www.fao.org/ag/agp/agpp/pesticid/ and http://www.who.int/whopes/quality.
IPCS, 1991	Health and Safety Guide No. 51. Paraquat Health and Safety Guide. World Health Organization, Geneva. 1991.
US EPA, 1996	Reregistration Eligibility Decision (RED), Paraquat dichloride. List A Case 0262. United States Environmental Protection Agency, 1996.
USEPA, 1997	R.E.D. Facts. Paraquat dichloride (EPA-738-F-96-018). United States Environmental Protection Agency, 1997.
WHO, 1984	Environmental Health Criteria 39: Paraquat and diquat. World Health Organization, Geneva, 1984.
WHO, 2002	The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2000-2002 (WHO/PCS/01.5). World Health Organisation, Geneva, 2002.

Determination of PP796 (emetic) in paraquat dichloride technical concentrates (TK)

Information

IUPAC name: 2-amino-4,5-dihydro-6-methyl-4-propyl-*s*-triazole-[1,5-a]pyrimidin-5-one
CA name: 2-amino-6-methyl-4-propyl-(1,2,4)triazolo[1,5-a]pyrimidine-5-(4*H*)-one (9CI)
CAS Registry No: *[27277-00-5]*
Molecular structure:



Molecular formula: $C_9H_{13}N_5O$
Relative molecular mass: 207.2

Scope of method

This capillary gas chromatography (GC) method is for the determination of PP796 emetic, as % w/w, in paraquat dichloride technical concentrates.

Summary of method

A portion of the TK (aqueous solution) is made basic with NaOH and partitioned into dichloromethane, containing octadecane as an internal standard. The extract is analyzed by capillary GC-FID, measuring peak areas.

Safety information

Paraquat dichloride salts are toxic, particularly by inhalation of particulates or ingestion, and, because there is no antidote or treatment for the progressive symptoms which can develop, exposure must be avoided. Paraquat dichloride solutions are irritant if splashed in the eyes and harmful if allowed to contact the skin or open cuts. Wear eye protection and protective gloves when handling paraquat dichloride analytical standards, the TK or formulated materials. Solid paraquat materials must only be handled in a fume cupboard.

If in any doubt about the nature and hazards of the chemicals used in this method, consult the Material Safety Data Sheet (MSDS) or an appropriate safety manual such as:

> "Hazards in the Chemical Laboratory", Luxon, Ed., Royal Society of Chemistry, 5th Edn, 1992, London, ISBN 0-85186-220-2.
>
> "The Sigma-Aldrich Library of Chemical Safety Data", Lenga, Ed., 2nd Edn, 1999, Milwaukee, WI, ISBN 0-941633-16-0.

Chemicals

Dichloromethane, HPLC grade.

Octadecane, laboratory reagent grade. Weigh approximately 50 mg into a 100 ml volumetric flask and add about 80 ml dichloromethane. Shake to dissolve, make to the mark with dichloromethane and mix well, to produce an internal standard solution of approximately 0.5 mg/ml.

Sodium hydroxide solution, 1M.

PP796 emetic, analytical standard grade (obtainable from Syngenta). Weigh accurately about 10 mg into two separate 25 ml volumetric flasks and add 5.0 ml of internal standard solution. Shake to dissolve, make to the mark with dichloromethane and mix well, to produce two solutions (Solutions A_1 and A_2) containing PP796 at 0.4 mg/ml.

Laboratory detergent, non-ionic, e.g.

Decon Neutracon.

Dimethyldichlorosilane (DMCS), laboratory reagent grade.

Hexane, laboratory reagent grade.

Methanol, water-free.

Acetone, laboratory reagent grade

Apparatus

Gas chromatograph, equipped with split/splitless injection system and flame ionisation detection, operated in split mode, with automatic injector and electronic data capture and handling system. All gases should be purified through molecular sieves. The carrier gas should be further purified through an oxygen trap.

Injection Liner, straight silica liner (4 mm ID) packed with silanized fused silica wool plug (e.g. Restek cat No. 20790). Contaminated split injection liners should be treated as follows.

Immerse in detergent (10% solution) for about 1 hour, then wash in purified water and dry in an oven at 120°C. Take the liner, while still warm, and immerse in a 5% solution of dimethylchlorosilane in hexane for 5 min. Remove the liner and immerse in fresh dry methanol for 1 hour. Wash the liner with acetone and dry thoroughly. The fused silica liner is ready for packing with silanized fused silica wool.

Column, 25 m x 0.25 mm ID fused silica capillary column with 0.25 μm film of BPX-5 (ex SGE) or Chrompack CP-Sil 8CB, or equivalent. Maximum programmed operating temperature 350ºC.

Typical operating conditions

Oven temperature programme:	initial temperature 50ºC for 2 min. programme 1, rate 20ºC min^{-1} to 100ºC, held for 2 min. programme 2, rate 20ºC min^{-1} to 280ºC, held for 10 min. total run time, 25.5 min.
Injector temperature:	300ºC
Detector temperature:	325ºC
Gas flow rates:	hydrogen carrier gas, 50 cm/sec (e.g. 10 psi head pressure) nitrogen make-up gas, 30 ml/min. hydrogen flame gas, 30 ml/min. air, 450 ml/min. Split flow , 50 ml/min.
Injection volume:	1 μl (by autosampler)
Typical retention times:	octadecane, 12-14 min; PP796, 13-15 min.

Sample extraction

Weigh accurately, in duplicate, about 2 g of paraquat dichloride technical concentrate into two 100 ml separating funnels. In each case, add 0.5 ml 1M sodium hydroxide solution and swirl the separating funnel taking care not to foul the stopper. Add 2.0 ml octadecane internal standard solution and swirl the separating funnel, taking care not to foul the stopper. Carefully release the gas pressure, shake well and again carefully release the gas pressure. Leave standing until two clear layers are obtained.

Collect the lower (dichloromethane) layer into a 14 ml glass screw-capped (trident) vial and retain the aqueous layer in the separating funnel. Add 2 ml dichloromethane to the separating funnel and shake well. Leave standing until two clear layers are obtained. Combine the lower (dichloromethane) layer with the initial extract in the glass vial and retain the aqueous layer in the separating funnel. Repeat the extraction with a further 2 ml dichloromethane, combining all three extracts in the glass vial and add 5 ml dichloromethane to the glass vial. Identify the duplicate extracts as Solutions B_1 and B_2.

Determination

Make replicate injections of Solution A_1 and/or A_2 at about 2 min. intervals, to equilibrate the GC system. Wait 19 min. then inject Solution A_1 or A_2 again and check that the retention times of the octadecane (12-14 min.) and PP796 (13-15 min.) are within the expected time windows. If not, the column head pressure may be adjusted ± 1 psi, or column temperature programme 1 final temperature may be adjusted ± 10°C. If column performance deteriorates substantially during use, check the condition of the split injection liner and replace if necessary.

Perform replicate injections of calibration and sample solutions in an appropriate sequence, such as: A_1, B_1, A_1, B_1, A_1, B_1, A_2, B_2, A_2, B_2, A_2, B_2. Measure peak areas.

Confirm the identity of PP796 in Solution B by GC-MS or, alternatively, by spiking an aliquot of Solution B with an aliquot of Solution A and check for exact co-elution.

Calculations

Calculate the relative response factor, RF, for each injection of the standard Solution A as follows.

$$RF = \frac{A \times VI \times 100}{P \times I \times WR}$$

Where: WR = weight of PP796 standard (mg);
VI = volume of internal standard added in ml;
A = peak area of PP796 peak;
I = peak area of octadecane peak;
P = % w/w purity of PP796 standard.

Calculate the percentage PP796 content (w/w) of each sample Solution B as follows.

$$\% \text{ w/w} = \frac{A' \times VI \times 100}{I' \times WS \times RF}$$

Where: WS = weight of sample (mg);
VI = volume of internal standard added in ml;
A' = peak area of PP796 peak;
I' = peak area of octadecane peak;
RF = relative response factor for PP796 obtained from the preceding standard Solution A.

Calculate the average PP796 content from Solutions B_1 and B_2.

Semi-Quantitative Determination and Identity Test for Chloride and BromideAnions in Paraquat Dichloride Technical and Formulation, Diquat DibromideTechnical and Formulation, and Paraquat Dichloride and Diquat Dibromide Formulation Mixtures

OUTLINE OF METHOD

The weight percent content of chloride anion and bromide anion can be estimated in bipyridinium samples by capillary electrophoresis (CE), using an external standard procedure. The key parameters of this method include the use of an Agilent polyvinyl alcohol (PVA) coated capillary column with indirect ultra-violet (UV) detection and calculation of the chloride anion and bromideanion contents with reference to standards.

The identity of chloride anion and bromide anion can be established by using the CE instrument tofortify samples with calibration solutions.

REAGENTS

0.1N Orthophosphoric acid, aqueous diluted from HPLC grade Orthophosphoric acid (ex Fluka)

Sodium chromate, 98% (ex Aldrich)

*Water***,** purified conforming to ASTM type

II *Sodium chloride,* standard of known

purity *Potassium Bromide*, standard of

known purity

Electrolyte preparation

Prepare a solution containing approximately 20mM sodium chromate at pH 8.0. For example, to prepare 1 litre: Weigh approximately 3.2g of sodium chromate into a 1 litre plastic bottle. Add 1 litre of ASTM Type II water. Sonicate until completely dissolved and mix thoroughly. Adjust thepH of the electrolyte by gradually adding 0.1N Orthophosphoric acid until pH 8.0 is obtained.
Filter the solution using a 0.45µm membrane filter. Degas the electrolyte before use.

Calibration solutions – preparation of solutions for injection

For chloride anion determination or identification: Weigh approximately 40 mg Sodium Chloride standard (WCAL*Cl* mg) into a glass bottle (60 ml). Add 50 ml ASTM Type II and shake the bottle until all the sodium chloride has dissolved. Call this solution CCl. Transfer approximately 200µl (using e.g. Gilson Microman pipette) of solution CCl to a CE autosampler vial.

For bromide anion determination or identification: Weigh approximately 50 mg Potassium Bromidestandard (WCAL*Br* mg) into a glass bottle (60 ml). Add 50 ml ASTM Type II and shake the bottle until all the potassium bromide has dissolved. Call this solution CBr. Transfer approximately 200µl (using e.g. Gilson Microman pipette) of solution CBr to a CE autosampler vial.

These are the solutions to be injected as calibration solutions, if a semi-quantitative analysis is required. In addition, they can be used as fortifying solutions if an identity test is required.

APPARATUS

The apparatus listed below was that used to establish the method. Consideration must be given to confirmation of the method on other makes of equipment, providing equivalent performance, to ensure that they are suitable.

Capillary Electrophoresis Instrument equipped with a diode array detector (DAD)

Capillary Column 64.5 cm x 50µm (effective length 56 cm) fused silica capillary coated with PVA

Data system

PROCEDURE

(a) Chromatographic conditions (typical)

Capillary 64.5 cm x 50µm (effective length 56 cm) fused silica capillarycoated with PVA ex Agilent part no.: G1600-61219. Green interface required for Agilent 3D CE

Capillary Temperature 20°C

Electrolyte Replenishment For quantitative, reproducible results, replenishment of electrolyte vials is recommended prior to each injection. This can be doneby filling vials manually or by using the Replenishment capability, if the instrument can do this. For example:

Function	cm	Vial
REPLENISH	1.8	InHomeVial
REPLENISH	1.8	OutHomeVial

Capillary Preconditioning For quantitative, reproducible results, capillary preconditioning is required. An example of the typical entries in the capillary preconditioning table is shown below:

Function	Time	Inlet	Outlet
FLUSH	2.00 min	I : InHomeVial	O : 48: Waste

Injection Parameters For semi-quantitative analyses use the following:

Vial	Pressure (mbar)	Time (s)
Calibration/Sample	20	15
I : InHomeVial	20	10

Where identification of an anion is required use the following:

Vial	Pressure (mbar)	Time (s)
Sample	20	15
Calibration (chloride or bromide anion)	20	10

Electrical Parameters

Negative Polarity

Time (min)	*Voltage (kV)*
0	*0*
0.2	*25*

This voltage will generate a current of approximately minus 30-36 μA

Run Time 5 minutes

Detector Settings Wavelength 500 nm, Bandwidth 60 nm
Reference 374 nm, Bandwidth 30 nm

Retention times Bromide anion approximately 3.4 min
Chloride anion approximately 3.5 min

(b) Equilibration

Inject portions of the CA or CB solution and check that two consecutive electropherograms are similar to the typical electropherograms shown at the end of the method.

(a)Preparation of sample

WARNING: Bipyridinium salts and their solutions are highly poisonous. Bipyridinium salt solutions are corrosive if splashed in the eyes and harmful if allowed to contact the skin or open cuts. Wear eye protection and protective gloves when handling bipyridinium salts, aqueous concentrates and formulated materials.

Weigh approximately 200-250 mg (200µl) of sample (WS mg) into a bottle (60 ml). Add 50 ml ASTM Type II water and mix well. Call this sample solution S. Transfer approximately 200µl (using e.g. Gilson Microman pipette) of each sample solution S to separate CE autosampler vials.

(b) Determination

Make at least duplicate injections of each calibration and sample in the following sequence:

CCl, S, CCl, S …for chloride anion analyses and

CBr, S, CBr, S …for bromide anion analyses

Measure time corrected peak areas in calibration and sample solution injections. The limit of determination for this method is approximately 0.1% w/w for chloride anion and 0.2% w/w for bromide anion in bipyridinium samples.

Confirmation of identity can be established by fortification using the CE instrument. Fortificationis achieved by loading a portion of sample solution S onto the capillary followed by a portion ofCCl or CBr calibration solution. This can be done by using the appropriate CE instrument injection parameters described earlier in this method. On comparison of an electropherogram resulting from an injection made without fortification with an electropherogram resulting from an injection with fortification, the identity of the anion will be confirmed if the anion peak in question is greater in size for the fortified injection electropherogram and there is an absence of an additional peak.

Calculation

When not calculated by a data system, time corrected peak areas can be calculated as follows:

$$\text{Time corrected peak area} = \frac{\text{Peak area}}{\text{Migration time (s)}}$$

The following calculation is appropriate for the semi-quantitative determination of chloride anioncontent using the weights and dilutions of standard and samples specified in this method:

For each sample injection solution, the percentage chloride anion content (w/w) is:

$$\% \text{ w/w} = \frac{A' \times P \times 0.607 \times WCAL_{Cl} \times 100}{A \times WS \times 100}$$

where:

A' = Time corrected peak area of chloride anion in the sample solution injectionP = Purity of the Sodium Chloride Standard (% w/w)

0.607 = Factor for the proportion of chloride anion in the standard
WCAL*Cl* = Weight taken of Sodium Chloride Standard (mg)
A = Time corrected peak area of chloride anion in the calibration solution injection
WS = Weight taken of sample (mg)

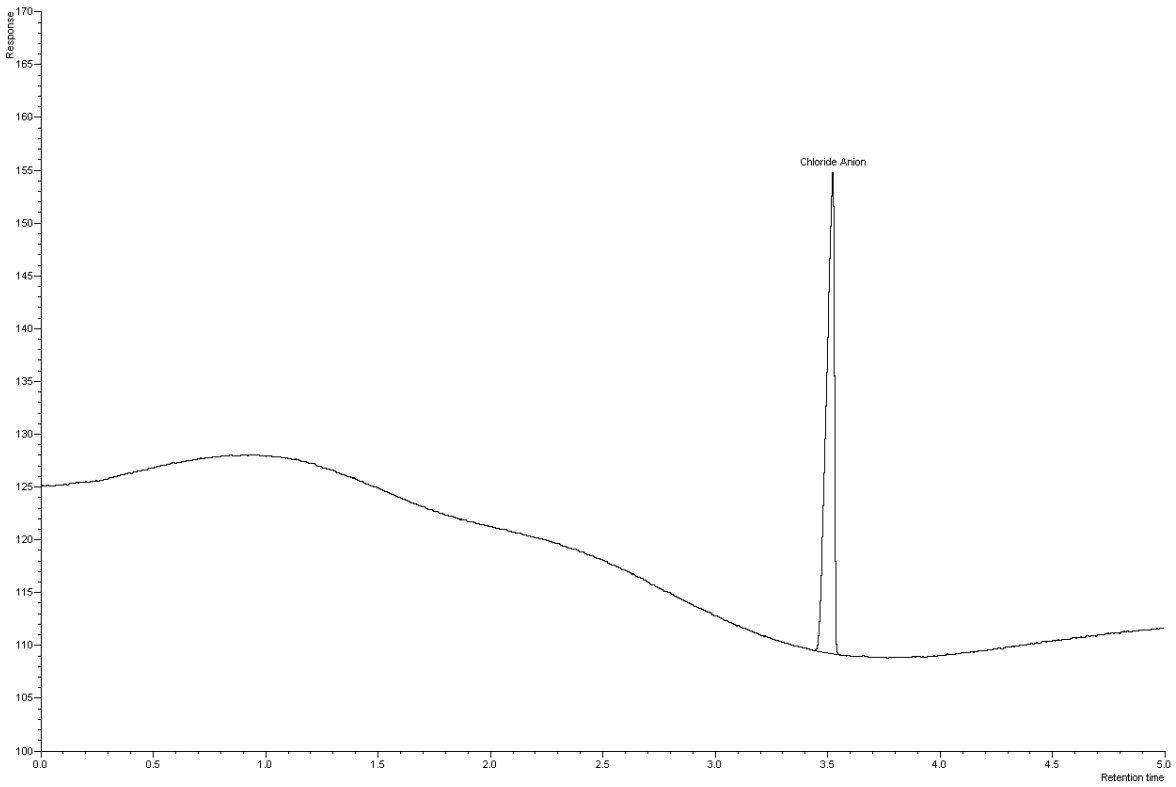
The following calculation is appropriate for the semi-quantitative determination of bromide anioncontent using the weights and dilutions of standard and samples specified in this method:

For each sample injection solution, the percentage bromide anion content (w/w) is:

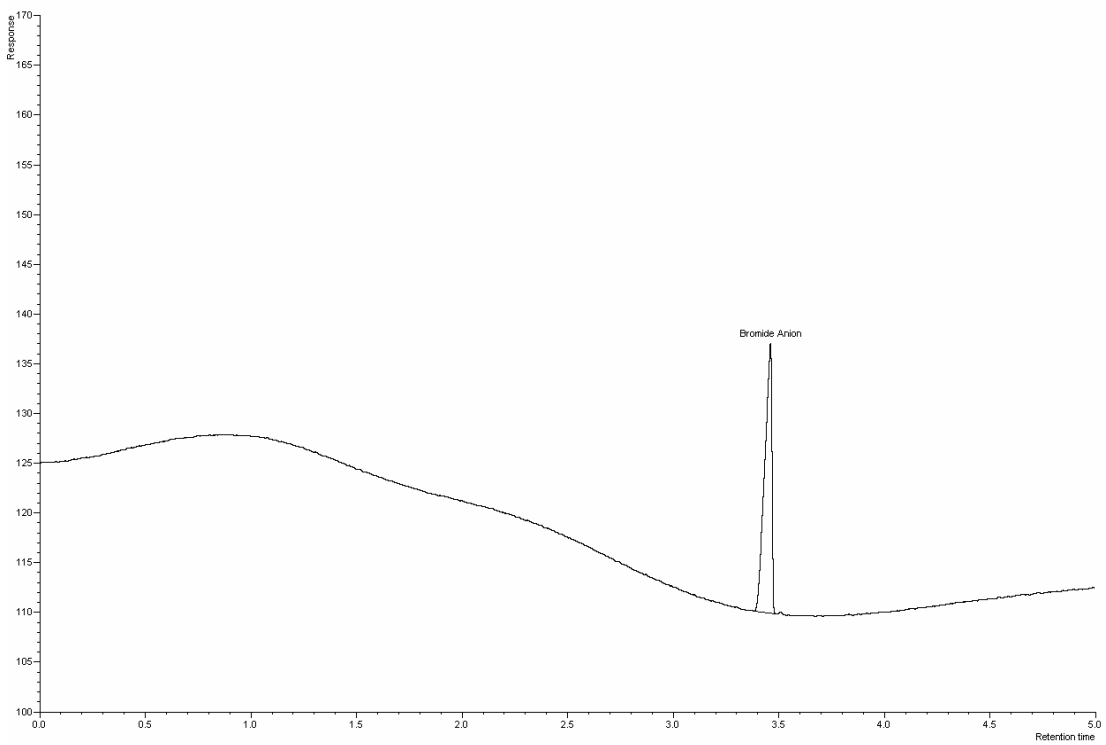
$$\% \text{ w/w} = \frac{\text{A' x P x 0.671 x WCAL}Br \text{ x}}{100\text{A x WS x 100}}$$

where:

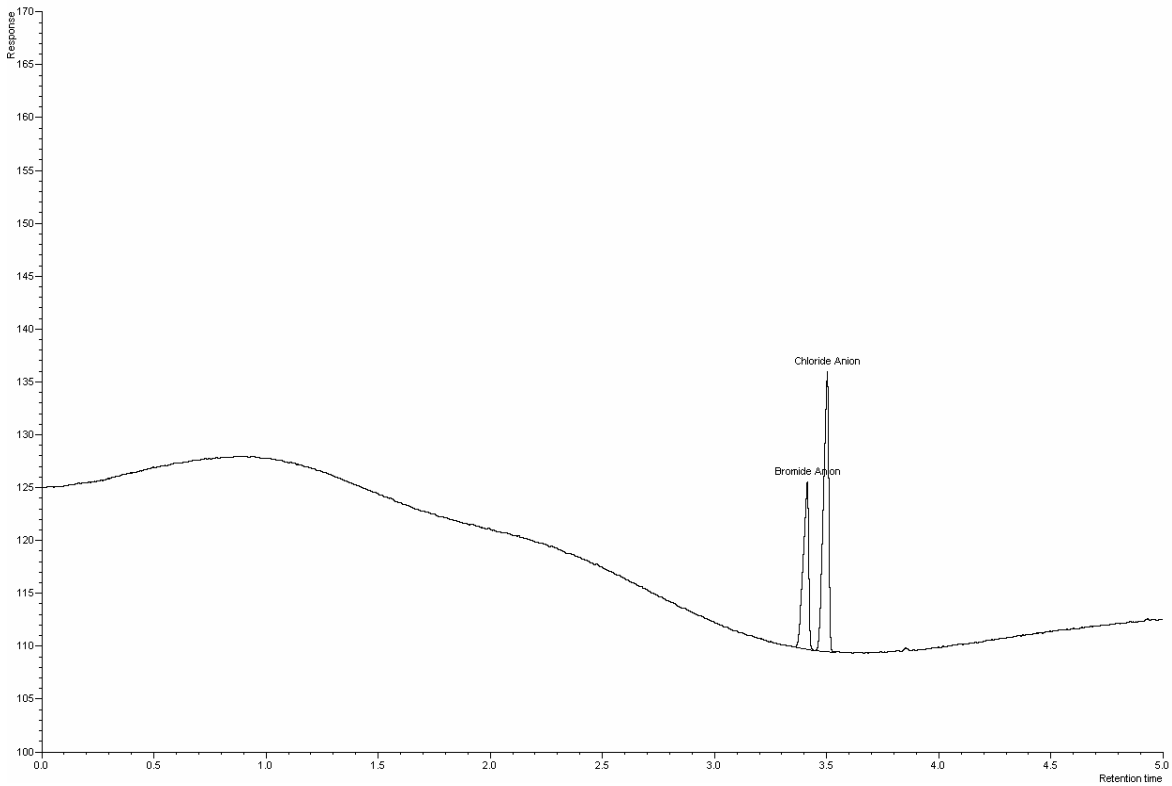
A' = Time corrected peak area of bromide anion in the sample solution
injectionP = Purity of the Potassium Bromide Standard (% w/w)
0.671 = Factor for the proportion of bromide anion in the standard
WCAL*Br* = Weight taken of Potassium Bromide Standard (mg)
A = Time corrected peak area of bromide anion in the calibration solution injection
WS = Weight taken of sample (mg)



Typical Electropherogram Of Sodium Chloride Calibration Solution



Typical Electropherogram Of Potassium Bromide Calibration Solution



Typical Electropherogram Of Paraquat Dichloride and Diquat Dibromide Formulation MixtureSolution