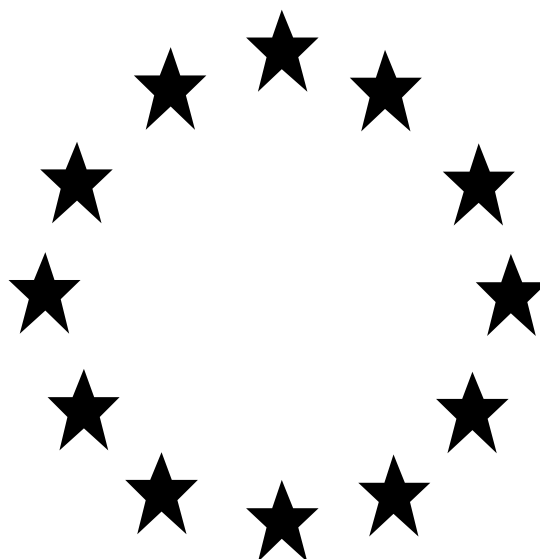




Additional Report to the DAR

- public version -

**Risk assessment provided by the rapporteur Member State
Italy for the existing active substance**

CHLOROPICRIN

**upon resubmission in the framework of the accelerated procedure in
accordance with Commission Regulation (EC) No 33/2008**

**Volume 3
Annex B1-B5**

March 2010

Ministry of Health

Rome

Italy

**Addendum to Draft Assessment Report
regarding resubmission of Chloropicrin**



Chloropicrin

Volume 3

Volume 3 – Annex B

Summary, Scientific Evaluation and Assessment

March 2010

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Rome
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Chloropicrin

**Volume 3
Annex B.1: Identity**

March 2010

B.1 IDENTITY

B.1.1 Identity of the active substance (Annex IIA 1)

B.1.1.1 Name and address of the applicant for inclusion of the active in Annex I (Annex IIA 1.1)

Name: European Chloropicrin Group
Address: 1805-45th Street N.W., Washington D.C., 20007-2070,
U.S.A.
Contact name: [REDACTED]
Contact address: [REDACTED]
Telephone number: [REDACTED]
Telefax number: [REDACTED]

EU contact company Rivendell Consulting Ltd.
EU contact company address : Rivendell House, Stamullen, Co. Meath, Ireland
EU contact name: [REDACTED]
Telephone number [REDACTED]
Telefax number: [REDACTED]
e-mail: [REDACTED]
Alternative EU contact name: [REDACTED]
Telephone number [REDACTED]
e-mail: [REDACTED]

B.1.1.2 Manufacturers of the active substance (Annex IIA 1.2)

Name: [REDACTED]
Address [REDACTED]
Contact name: [REDACTED]
Telephone number: [REDACTED]
Telefax number: [REDACTED]
Location of plants: [REDACTED]

B.1.1.3 Common name and synonyms (Annex IIA 1.3)

Please refer to the DAR from 2006.

B.1.1.4 Chemical name (Annex IIA 1.4)

Please refer to the DAR from 2006.

B.1.1.5 Manufacturer's development code number (Annex IIA 1.5)

Please refer to the DAR from 2006.

B.1.1.6 CAS, EEC and CIPAC Numbers (Annex IIA 1.6)

Please refer to the DAR from 2006.

B.1.1.7 Molecular and structural Formula, molecular mass (Annex IIA 1.7)

Please refer to the DAR from 2006.

B.1.1.8 Method or methods of manufacture (Annex IIA 1.8)

Please refer to the DAR from 2006.

B.1.1.9 Specification of purity of the active substance (Annex IIA 1.9)

Please refer to the DAR from 2006.

B.1.1.10 Identity of isomers, impurities and additives (Annex IIA 1.10)

Please refer to the DAR from 2006.

B.1.1.11 Analytical profile of batches (Annex IIA 1.11)

Please refer to the DAR from 2006.

B.1.2 Identity of the plant protection product (Annex IIIA.1)

B.1.2.1 Name and address of applicant and manufacturer of the plant protection product (Annex IIIA 1.1, 1.2)

Applicant

Name: European Chloropicrin Group
Address: 1805-45th Street N.W., Washington D.C., 20007-2070,
U.S.A.

Contact name: [REDACTED]
Contact address: [REDACTED]
Telephone number: [REDACTED]
Telefax number: [REDACTED]

EU contact company Rivendell Consulting Ltd.
EU contact company address : Rivendell House, Stamullen, Co. Meath, Ireland
EU contact name: [REDACTED]
Telephone number [REDACTED]
Telefax number: [REDACTED]
e-mail: [REDACTED]
Alternative EU contact name: [REDACTED]

Telephone number

e-mail:

Manufacturer

Name:

Address

Contact name:

Telephone number:

Telefax number:

Location of plants:

B.1.2.2 Current former and proposed trade names and development code numbers (Annex IIIA 1.3)

Please refer to the DAR from 2006.

B.1.2.3 Composition of the plant protection product (Annex IIIA 1.4)

Please refer to the DAR from 2006.

B.1.2.4 Type of the preparation and code (Annex IIIA 1.5)

Please refer to the DAR from 2006.

B.1.2.5 Function (Annex IIIA 1.6, Annex IIA 3.1)

Fungicide, insecticide, nematocide, bactericide

B.1.3 Reference relied on

No references

**Ministry of Health
Rome
Italy**

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Chloropicrin

Volume 3

Annex B.2: Physical and chemical properties

March 2010

B.2 PHYSICAL AND CHEMICAL PROPERTIES

B.2.1 Physical and chemical properties of the active substance (Annex IIA.2)

The physical and chemical properties of the active substance are given in the DAR from 2006.

Comments made on the active substance data by the Member States during the review of the DAR on the physical chemical properties were addressed by the notifier and are summarized below.

The relative density was corrected in this addendum to the DAR.

The purity of Chloropicrin was provided for the vapour pressure, the water solubility and the flammability studies.

The Henry's law was recalculated based on the vapour pressure and solubility data.

New data was generated to address the data gaps for Mass and IR spectra and are evaluated in Table B.2.1.

Further information on the water solubility study and surface tension studies was also given to address the queries from some Member States.

A new study on oxidizing properties was submitted by the notifier and is evaluated in the Table B.2.1.

A study was submitted to address the data gap on hydrolysis.

Information on the explosive property study was provided by the notifier.

The notifier also explained that in most cases both the US and EU methods are based on the same OECD guideline and are therefore considered equivalent. Where no EC method is available, the US method is considered to be appropriate in addressing the data points. In the case of the method used for determining hydrolysis rates, the US method differs slightly from the prescribed EC method, however the deviation is not considered to affect the scientific validity of the study. Therefore studies carried out according to US guidelines were deemed to be acceptable.

The above data gaps/additional information/corrections to the original DAR are provided in Table B.2.1.

Table B.2.1 Summary of the physical and chemical properties of the active substance

Test or Study & Annex Point	Guideline and GLP	Findings	Comment	Reference
B.2.1.4 Relative density purified active substance (IIA 2.2/01)	US EPA Guideline 63-7 GLP	1.667 at 25.7 °C Purity: 99.5%		IIA, 2.2/01 Charles M. Sparacino, 1994
B.2.1.5 Vapour pressure purified active substance (IIA 2.3.1/01)	US EPA Guideline 63-9 GLP	2670 Pa at 20.8°C (n=3) Purity: 99.5%		IIA, 2.3.1/01 Charles M. Sparacino, 1994
B.2.1.6 Volatility, Henry's law constant (IIA 2.3.2/01)	Calculation from vapour pressure and water solubility	43.89 Pa.m ³ .mol ⁻¹	Calculated based on available solubility data and vapour pressure	

Test or Study & Annex Point	Guideline and GLP	Findings	Comment	Reference
B.2.1.9 UV/Vis, IR, NMR, MS spectra (IIA 2.5.1/03)	IR, To comply with Directive 94/37/EC and US EPA Guidelines: 830 Mass spectrum, To comply with Directive 94/37/EC and US EPA Guidelines: 830 GLP	IR (KBr): 2500 – 3000 cm ⁻¹ : N=O combination bands 1609 cm ⁻¹ : NO ₂ (symmetric) 1280 – 1350 cm ⁻¹ : NO ₂ (asymmetric) 870 – 900 cm ⁻¹ : N-O, C-N stretches < 800 cm ⁻¹ : C-Cl stretch GC-MS: m/z: 201, 164, 117 Purity: 99.9 %	The infrared spectrum and mass spectrum were consistent with the assigned structure of Chloropicrin.	IIA, 2.5.1/03 A.L. Comb, 2007a
B.2.1.11 Solubility in water (IIA 2.6/01)	US EPA Guideline: 63-8 GLP	10 g/L at 25.7 °C Purity: 99.5%		IIA, 2.6/01 Charles M. Sparacino, 1994
B.2.1.14 Hydrolysis rate at pH 4,7 and 9 under sterile conditions in the absence of light (IIA 2.9.1/01)	California Notice 21021 GLP	No hydrolytic products formed at level >10% at pH 5, 7 (acetate and phosphate systems) and 9 at 25 °C Purity: 99.9%	No hydrolysis rate and half-life time were determined as no hydrolysis was observed.	IIA 2.9.1/01 T.-Y. Chang, 1989

Test or Study & Annex Point	Guideline and GLP	Findings	Comment	Reference
B.2.1.19 Flammability and auto-flammability (IIA 2.11/02)	EEC Method A15 GLP	Flammability: Non flammable Auto flammability: No auto ignition occurred up to a temperature of 402 °C at 98.4 kPa Purity: > 99.5 %		IIA, 2.11/02 J. Greenwood, 2003
B.2.1.22 Surface tension (IIA 2.14)	EEC Method A5, OECD Method 115 GLP	71.0 mN/m (1g/L solution) at 20°C. As the result is greater than 60 mN/m, Chloropicrin is not considered to be surface active. Chloropicrin is not considered to be surface active Purity 99.88%		IIA, 2.14 A.L. Comb, 2003
B.2.1.23 Oxidising properties (IIA 2.15/02)	EEC Method A21 GLP	No oxidizing or reducing properties Purity > 99.9%		IIA, 2.15/02 A.L. Comb, 2007b

B 2.2 Physical, chemical and technical properties of the plant protection product (Annex IIIA 2)

Product name: Chloropicrin 99 containing 990 g/kg active substance

The physical and chemical properties of the plant protection product are given in the DAR from 2006.

Comments made on the active substance data by the Member States during the review of the DAR on the physical chemical properties were addressed by the notifier and are summarized below.

The notifier clarified that the determination of the pH is not required for Chloropicrin since Chloropicrin is a non-polar organic substance and Chloropicrin is insufficiently soluble in water.

The notifier also clarified that the physical stability of Chloropicrin in the storage stability and shelf life study was confirmed in a 35 month storage stability study and a 7-day study. Both provide sufficient information with regard to effects of elevated temperatures on Chloropicrin content, moisture content and change in acidity.

A new study on oxidizing properties was submitted by the notifier and is evaluated in the Table B.2.2.

The above data gaps/corrections to the original DAR are provided in Table B.2.2.

Table B.2.2 Summary of the physical and chemical properties of the plant protection product, Chloropicrin 99

Test or Study & Annex Point	Guideline and GLP	Findings	Comments	Reference
B.2.2.4 Oxidising properties (IIIA 2.2.2/02)	EEC Method A21 GLP	Not oxidizing or reducing properties		IIIA, 2.2.2/02 A.L. Comb, 2007

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B.2.3 Summary of physical and chemical properties

B.2.3.1 Active substance

Chloropicrin is a colourless non-viscous liquid with a freezing point of -70°C and a vapour pressure of 2670 Pa at 20.8 °C. It is sparingly soluble in water (<0.01 g/ml at 25.7°C) and its partition coefficient of 2.5 would not suggest a high affinity for n-octanol. The photolytic degradation half-life is 31.1 hours at 25°C, pH 7 and the quantum yield is 0.5699. It does not dissociate in water, is not surface-active and shows no flammable, oxidising or explosive properties.

B.2.3.2 Plant protection product

Chloropicrin 99 is a colourless liquid. It is non-explosive, non-autoflammable and has a flash point of > 100°C. It has been shown to have a shelf life of > 35 months at ambient temperatures. Its technical properties indicate that no particular problems are to be expected when used as recommended. It does not exhibit any oxidising properties.

B.2.4 References relied on

B.2.4.1 Active substance

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection claimed Y/N	Owner
IIA 2.2/01	Sparacino, C.M.	1994	Product Chemistry for Chloropicrin Research Triangle Institute Report No.70C-5630-001 GLP, Unpublished	Y	Trinity Manufacturing Inc.
IIA 2.3.1/01	Sparacino, C.M.	1994	Product Chemistry for Chloropicrin Research Triangle Institute Report No. 70C-5630-001 GLP, Unpublished	Y	Trinity Manufacturing Inc.
IIA 2.5.1/03	Comb, A.L.	2007a	Chloropicrin: Infrared and Mass Spectra Huntington Life Sciences Ltd. Report No. SXC/0003/072428 GLP, Unpublished	Y	European Chloropicrin Group
IIA 2.6/01	Sparacino, C.M.	1994	Product Chemistry for Chloropicrin Research Triangle Institute Report No. 70C-5630-001 GLP, Unpublished	Y	Trinity Manufacturing Inc.
IIA 2.9.1/01	Chang, T-Y.	1989	Hydrolysis Study With Chloropicrin As A Function Of pH At 25° C Bolsa Research Associates, Inc. Report No. BR 51:89 GLP, Unpublished	Y	The Chloropicrin Industry Panel
IIA 2.11.2/01	Greenwood, J.	2003	Chloropicrin: Evaluation of the Spectroscopic Properties and Auto-ignition Temperature (EC Test A15) Covance Laboratories Ltd. Report No. 2194/001-D2149 GLP, Unpublished	Y	European Chloropicrin Group
IIA 2.14/01	Comb, A.L.	2003	Determination of the nuclear magnetic resonance (NMR) spectrum, freezing temperature, surface tension, flash point and explosive properties of Chloropicrin Huntington Life Sciences Ltd. Report No. RDB004 / 022843 GLP, Unpublished	Y	European Chloropicrin Group
IIA, 2.15/02	Comb, A.L.	2007b	Chloropicrin: Oxidising Properties Huntingdon Life Sciences Ltd. Report No. SXC/0002/072562 GLP, Unpublished	Y	European Chloropicrin Group

B.2.4.2 Plant protection product

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection claimed Y/N	Owner
IIIA 2.2.2/02	Comb, A.L.	2007b	Chloropicrin: Oxidising Properties Huntingdon Life Sciences Ltd. Report No. SXC/0002/072562 GLP, Unpublished	Y	European Chloropicrin Group

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**Addendum to Draft Assessment Report
regarding resubmission of Chloropicrin**



Chloropicrin

Volume 3

Annex B.3:

Data on application and Further information

March 2010

B.3 DATA ON APPLICATION AND FURTHER INFORMATION

B.3.1 Data on application relevant to active substance (Annex IIA 3.1 to 3.6)

B.3.1.1 Function (Annex IIA 3.1)

Fungicide, insecticide, nematocide, bactericide

B.3.1.2 Effect on harmful organisms (Annex IIA 3.2)

Chloropicrin is a pre-plant fungicide, insecticide, nematocide and bactericide which kills fungi, nematodes and germinating weed seeds by contact action. The specific mode of action is not understood, but chloropicrin is a strong irritant that is very toxic to all biological systems; affecting body surfaces and interfering with the respiratory system and the cellular transport of oxygen.

B.3.1.3 Field of use (Annex IIA 3.3)

Please refer to the DAR from 2006.

B.3.1.4 Harmful organisms controlled and crops or products protected or treated (Annex IIA 3.4)

Chloropicrin is recommended as a pre-planting treatment to control fungi such as *Fusarium*, *Verticillium*, *Rhizoctonia*, *Phytophthora*, *Pyrenochaeta*, *Pythium*, *Sclerotinia*, *Sclerotium*, *Didymella*, and *Armillaria*. Also controlled are nematodes, insects and germinating weed seeds.

B.3.1.5 Mode of action (Annex IIA 3.5)

Please refer to the DAR from 2006.

B.3.1.6 Possible occurrence of the development of resistance or cross resistance (Annex IIA 3.6)

Please refer to the DAR from 2006.

B.3.2 Data on application relevant to the plant protection product - Chloropicrin 99 (Annex IIIA 3.6)

B.3.2.1 Field of use (Annex IIIA 3.1)

Please refer to the DAR from 2006.

B.3.2.2 Effect on harmful organisms (Annex IIIA 3.2)

Please refer to the DAR from 2006.

B.3.2.3 Details of intended use (Annex IIIA 3.3)

Please refer to the DAR from 2006.

B.3.2.4 Application rate (Annex IIIA 3.4)

Please refer to the DAR from 2006.

B.3.2.5 Concentration of active substance in material used (Annex IIIA 3.5)

Please refer to the DAR from 2006.

B.3.2.6 Method of application (Annex IIIA 3.6)

The notifier provided a more detailed explanation of the method application of Chloropicrin by soil injection.

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

Chloropicrin is applied directly into soil with specialized equipment through shanks pulled behind a tractor (Shank injection). Chloropicrin is supplied directly from the manufacturer to professional applicators and is applied from a returnable steel cylinder (see pictures 1 + 2).



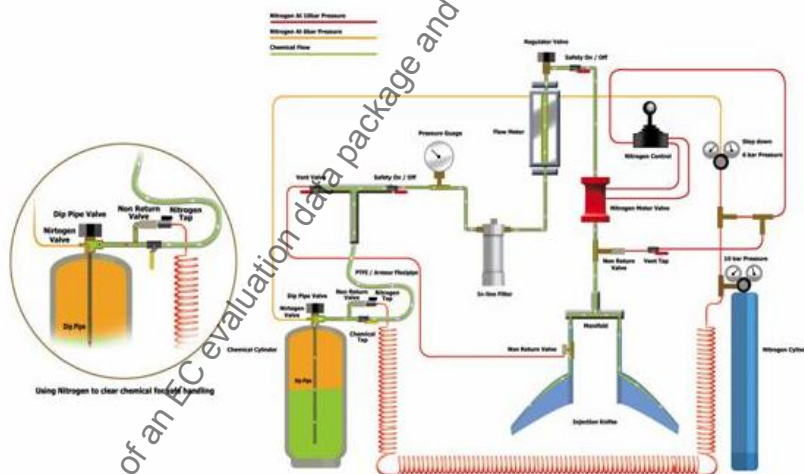
Picture 1



Picture 2

Equipment used for application of Chloropicrin to the soil use nitrogen, an inert gas, under low-pressure to push liquid chloropicrin through a closed application system. Treatment lines are securely connected and tested for leaks prior to the introduction of Chloropicrin. Chloropicrin passes from the cylinder through reinforced braded steel hose or copper pipes, valves, and filters.

The product then passes through a "flow meter" used as a gauge to regulate the predetermined amount that is applied to the soil beneath a retentive "barrier" film designed specifically for this purpose (see picture 3). Specially trained professional applicators maintain control of the rate at which chloropicrin is applied and keep a constant vigil throughout the treatment period. On completion of an application, the rig is purged, the cylinder sealed with all the valves closed in sequence, and delivery lines are de-pressurized into the soil and beneath the retentive film.

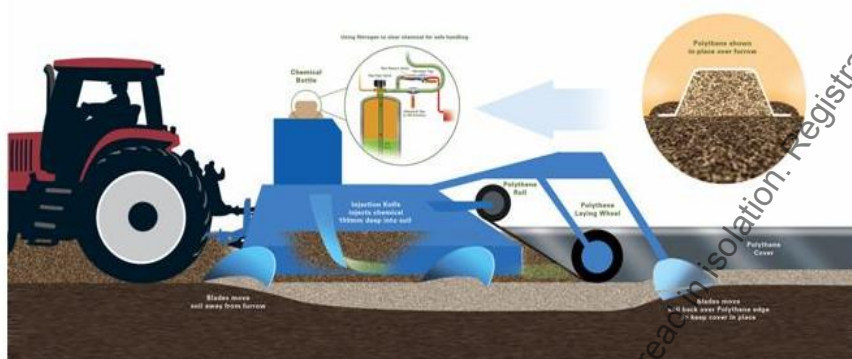


Picture 3

A custom program has been put in place to manage and audit the supply, storage, distribution and safe use of Chloropicrin. The program involves tracking cylinders through the supply chain from the Manufacturer to the applicator. This program includes the training and qualifying of professional fumigators. In this way Chloropicrin is managed and applied by a restricted number of individuals specifically qualified for this task.

Application by soil injection:

- This treatment is carried out using a tractor-mounted rig that simultaneously lays the virtually impermeable barrier film whilst applying the Chloropicrin.
- The tractor is regulated to a constant speed in order to stabilise the application rate. This speed is equivalent to walking speed.
- Inert N₂ gas is used to stabilise the pressure of the flow and to flush the delivery system.
- Chloropicrin cylinders are secured to a tractor on specially designed racks. Once a cylinder is opened and the system is charged with nitrogen, the product passes through a flow meter and control valves, then passes through additional lengths of hose or piping to the injection shanks, which are pulled by the tractor through the soil (see picture 4).



Picture 4

- Prior to the start of application, the injection shanks are placed in the soil to a depth of 20cm. The plough shears/discs used to bury the edges of the barrier film, used to retain the product following injection, are also adjusted to a depth of 25/30cm.
- As the tractor pulls forward, the flow of fumigant is turned on. Simultaneous to the injection process the barrier film is unrolled (see picture 5).

The front plough shear/disc of the rig creates furrows in which the sides of the roll of barrier film are pinned with the rear plough shear/disc covering the barrier film edges with soil and sealing the fumigant in the treatment zone.



Picture 5

- When the front of the tractor reaches the end of the treatment row the fumigant flow is switched off and the delivery system purged into the soil.
- The roll of barrier film is cut and buried.
- The tractor is turned around and set adjacent to the previous pass and the process is repeated. Each successive pass of barrier film is simultaneously glued to the previous pass, as it travels down the field, by means of a specialized gluing apparatus on the tractor.
- The last row to be treated is used to completely purge the delivery system into the soil before the tractor leaves the field.
- Empty cylinders are secured and returned to the manufacturer.

Table B.3.1 outlines a summary of the uses of Chloropicrin to be considered as part of the 91/414/EEC submission.

Table B.3.1 Summary of Application Processes used for Chloropicrin

Application Process	Full Field/ Partial Field	Maximum Application Rate	Duration of Tarping	Pre-planting Interval from removal of tarp
Soil Injection	Full Field	448 kg/ha	8 days	7 – 14 days

Summary of Key Points

- Closed System – Regardless of application method all fumigants are applied through a Closed System
- Returnable Steel Cylinders – Fumigants are packaged in steel cylinders and returned to the formulator for refilling
- Cylinder Tracking System – An accounting of all fumigant cylinders is maintained
- Trained Personnel – Chloropicrin fumigant products are only supplied to and applied by trained individuals
- No Residues – Soil treatment is carried out prior to planting and leaves no chemical residues in crops
- Stewardship - Products are managed following prescribed procedures under controlled conditions:
 - Appropriate sites and weather
 - Properly prepared soil
 - Properly maintained and calibrated equipment
 - Careful consideration of worker and bystander safety

The notifier also submitted a letter from a UK distributor which explains the advantages of using Chloropicrin and which demonstrates that the explanation provided above is supported by actual use of the product.

B.3.2.7 Number and timing of applications and duration of protection (Annex III 3.7)

A maximum of 1 application is recommended at least 22 ± 2 days prior to planting of the treated area. Chloropicrin 99 has no long-lasting fumigation activity in soil, however, due to the high volatility of Chloropicrin 99 tarping of the soil is used to prolong its activity in the soil.

B.3.2.8 Waiting period to avoid phytotoxicity on succeeding crops (Annex IIIA 3.8)

Please refer to the DAR from 2006.

B.3.2.9 Proposed instructions for use (Annex IIIA 3.9)

Please refer to the DAR from 2006.

B.3.3 Summary of data on application

Chloropicrin is applied pre-planting to soil by soil injection or drip irrigation with a single application per annum at a maximum application rate of 272 l/ha (448 kg as/ha)

B.3.4 Further information on the active substance

B.3.4.1 Recommended methods and precautions controlling handling, storage, transport and fire (Annex IIA 3.7)

Please refer to the DAR from 2006.

Transport:

The notifier provided an updated transport classification according to the ADR 2009.

Chloropicrin is regulated under U.S. DOT (land), ADR (road), IMO/IMDG (sea) or ICAO/IATA (air).

ADR: UN 1580, Chloropicrin, 6.1, T1, PG I

B.3.4.2 Nature of Combustion Products (Annex IIA 3.8)

Please refer to the DAR from 2006.

B.3.4.3 Emergency measures in case of accident (Annex IIA 3.9)

Please refer to the DAR from 2006.

B.3.5 Further information on the plant protection product-chloropicrin 99 (Annex IIIA 4)

B.3.5.1 Packaging (type, materials, size etc), compatibility of the preparation with the proposed packaging materials (Annex IIIA 4.1)

Please refer to the DAR from 2006.

B.3.5.2 Procedures for cleaning equipment (Annex IIIA 4.2)

Please refer to the DAR from 2006.

B.3.5.3 Re-entry periods (Annex IIIA 4.3)

Please refer to the DAR from 2006.

B.3.5.4 Recommended methods and precautions concerning handling, storage, transport or fire (Annex IIIA 4.4)

As for active substance, see section B.3.4.1.

B.3.5.5 Emergency measures in case of an accident (Annex IIIA 4.5)

Please refer to the DAR from 2006.

B.3.5.6 Procedures for the destruction or decontamination of the plant protection product and its packaging (Annex IIIA 4.6)

Please refer to the DAR from 2006.

B.3.6 References relied on

Please refer to the DAR from 2006.

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

**Ministry of Health
Rome
Italy**

**Addendum to Draft Assessment Report
regarding resubmission of Chloropicrin**



Chloropicrin

Volume 3

Annex B.4:

Proposal for classification and labelling

March 2010

**Addendum to
Draft Assessment Report**

B.4 PROPOSAL FOR CLASSIFICATION AND LABELLING

B.4.1 Proposals for the classification and labelling of the active substance

Hazard symbol:	T+, N	Classification For labelling purposes
Indication of danger:	Very toxic Dangerous for the environment	
Risk Phrases:	R22 R26 R36/37/38 R48/22 R50/53	Harmful if swallowed Very toxic by inhalation Irritating to eyes, skin and respiratory system Harmful: danger of serious damage to health by prolonged exposure if swallowed Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety Phrases:	S1/2 S4 S7 S9 S26 S36/37 S38 S45 S60 S61	Keep locked up. Keep out of the reach of children. Keep away from living quarters. Keep container tightly closed. Keep container in a well-ventilated place. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice Wear suitable gloves and protective clothing. In case of insufficient ventilation wear suitable respiratory equipment In case of accident or you feel unwell seek medical advice immediately (show the label where possible). This material and its container must be disposed of as hazardous waste. Avoid release to the environment. Refer to special instructions / safety data sheets.

B.4.2 Proposals for the classification and labelling of the plant protection products

As the active substance is equivalent to the formulated product, the classification and labelling is identical.

Ministry of Health

Rome

Italy

**Addendum to Draft Assessment Report
regarding resubmission of Chloropicrin**



Chloropicrin

Volume 3

Annex B.5: Methods of analysis

March 2010

B.5 METHODS OF ANALYSIS

B.5.1 Analytical methods for formulation analysis (Annex IIA 4.1; Annex IIIA 5.1)

B.5.1.1 Analytical methods for pure active substance

Arndt, T., Analysis and Certification of Product Ingredients in Five Batches of Chloropicrin. PTRL West, USA. Unpublished report No. 1801W. Owner European Chloropicrin Group. 2009. (IIA 4.2.1/02)

GLP: Yes

Principle of the method

A method for the determination of Chloropicrin in five batches of Chloropicrin technical as manufactured was carried out. The analytical method used gas chromatography with flame ionisation detection (GC/FID) with an external Chloropicrin reference standard and a chlorobenzene internal standard. The identity of Chloropicrin was confirmed by gas chromatography with mass spectral detection (GC/MS).

Linearity

Ten calibration standards were prepared and injected onto the GC to establish linearity of response in the range 13.16 to 23.54 mg/mL with a coefficient of determination (R^2) of 0.9998.

Specificity

No significant (<30%) peak interference was detected in the chromatograms at the retention time of Chloropicrin. Specificity was confirmed by GC/MS.

Limit of determination

The limit of detection (LOD) for Chloropicrin was 0.15 mg/mL (0.15 µg injected). The limit of quantification (LOQ) for Chloropicrin was 0.51 mg/mL (0.51 µg injected).

Repeatability

Accuracy of the method was demonstrated to be acceptable as the RSD of each of nine calibrant injections was less than ±0.6%.

Five injections of test substance solution resulted in an RSD 0.45%, demonstrating acceptable precision. Precision analysis using triplicate calibrant solutions prepared at the high end and low end of the calibration curve resulted in a RSD of 0.22%. Ten single calibrant injections resulted in a RSD of 0.28%.

The results are presented in Tables B.5.1.1-01 and B.5.1.1-02.

Conclusions:

The method was suitably validated for the analysis of Chloropicrin in Chloropicrin technical as manufactured.

Table B.5.1.1-01: Accuracy validation results for Chloropicrin

Theoretical concentration (mg/mL)	Found concentration (mg/mL)	RSD (%)	% Found/theoretical
13.16	13.19	0.23	100.2
14.12	14.15	0.21	100.2
14.12	14.15	0.21	100.2
15.79	15.71	-0.51	99.49
18.83	18.80	-0.16	99.84
19.30	19.29	-0.05	99.95
21.93	21.86	-0.32	99.68
21.93	21.95	0.09	100.1
23.54	23.62	0.34	100.3

Table B.5.1.1-02: % active ingredient results for sample injection of Chloropicrin technical

Lot number	Chloropicrin (%)	Mean Chloropicrin (%)	RSD (%)
007-044-A	100.1	99.61	0.42
	99.40		
	99.34		
007-044-A	99.58	99.77	0.38
	99.52		
	100.2		
007-164-A	100.2	99.74	0.50
	99.82		
	99.21		
007-197-A	100.1	99.71	0.36
	99.40		
	99.64		
007-235-B	99.11	99.51	0.43
	99.46		
	99.76		
	100.1		
	99.10		

B.5.1.2 Methods for the determination of significant and/or relevant impurities and additives (e.g. stabilisers) in the active substance as manufactured Impurities

Analysis of impurities in technical Chloropicrin is by GC with FID or MS detection. The methodology to fulfill the requirement is regarded as being confidential in nature. Details of the procedures used and validation data are provided under confidential information in Annex C.

There are no relevant metabolites or other components included in the residue definitions.

B.5.1.3 Analytical method for formulation analysis (Annex IIIA 5.1)

As the product, Chloropicrin 99, is equivalent to the active substance in this case, the methods described for the active substance can apply to both.

Table B.5.2 – B.5.6: Summary Table of Analytical Methods

Matrix ¹	Method	Limit of quantification	Reference
Tomato	GC-ECD	0.01 mg/kg	IIA, 4.3/01 (Gatti, 2001a)
Melon	GC-ECD	0.01 mg/kg	IIA, 4.3/02 (Gatti, 2001b)
Tomato (ILV)	GC-ECD	0.01 mg/kg	IIA, 4.3/03 (Todd, M, 2007a)
Tomato	GC-ECD	0.005 mg/kg	IIA 4.3/04 (Zoboli, G., 2009a)
Tomato (ILV)	GC-MS	0.005 mg/kg	IIA 4.3/05 (Gandhi, J., 2009)
Tomato (Dichloronitromethane)	GC-ECD	0.005 mg/kg	IIA 4.3/06 (Zoboli, G., 2009b)
Strawberries, lettuce, orange pulp, orange peel, almonds, potatoes	GC-ECD (PAM MRM test)	Not determined (Chloropicrin not recovered by PAM test)	IIA, 4.3/07 (Conrath, Koch, 1996)
Soil	GC-ECD	0.05 mg/kg	IIA, 4.4/01 (Todd, M, 2007b)
Water (ground, drinking and surface)	GC-ECD	0.1 µg/L all types	IIA, 4.5/01 (Todd, M, 2007c)
Air	GC-ECD	0.1 µg/tube (0.83 µg/m ³)	IIA, 4.7/01 (Todd, M, 2007d)
Body fluids and tissues: Fresh urine	GC-MS	0.05 mg/L	IIA, 4.8/01 (Wimbush, J, 2004)
Body fluids and tissues: Blood, muscle, liver	GC-ECD	0.01 mg/kg muscle 0.01 mg/kg liver 0.05 mg/L blood	IIA, 4.8/02 (Airs, D, 2009)

¹ – All methods for parent compound, Chloropicrin, unless stated

B.5.2 Analytical methods (residue) for plants, plant products, foodstuffs of plant and animal origin, feeding stuffs (Annex IIA 4.3 (EU 4.2.1); Annex IIIA 5.2)

Overview of available analytical methods

- Reports IIA 4.3/01 Gatti, G.C., Residue Determination of Chloropicrin in Tomato according to the OECD Principles of GLP, Residue Study LN78-01, May 2001a
- IIA 4.3/02 Gatti, G.C., Residue Determination of Chloropicrin in Melon according to the OECD Principles of GLP, Residue Study LN76-01, May 2001
- IIA 4.3/03 Todd, M., Chloropicrin: Independent Laboratory Validation of methodology for the determination of residues of Chloropicrin in tomatoes, report number SXC 0006/072457, July 2007
- IIA 4.3/04 Zoboli, G., Residue Determinations of Chloropicrin in Tomatoes According to the OECD Principles of GLP (Good Laboratory Practice), report number LN93-08, May 2009
- IIA 4.3/05 Gandhi, J., Analysis of Residues of Chloropicrin in Outdoor Grown Tomatoes with Associated Validation in Compliance with Good Laboratory Practice, report number QA01626, April 2009
- IIA 4.3/06 Zoboli, G., Determination of Residues of Dichloronitromethane In Tomato. Validation of the Analytical Method, report number LN95 (validation), May 2009
- Multi-residue method
IIA 4.3/07 Conrath B.A., Koch, D.A., Multiresidue method testing for Chloropicrin according to PAM I, Appendix II, as Updated January, 1994, ABC Laboratories Final Report #42878, February, 1996.

US FDA multi-residue methods of analysis were found to be not suitable for the determination of Chloropicrin residues in food of plant origin.

Single residue method - IIA 4.3/03

Todd, M., Chloropicrin: Independent Laboratory Validation of Methodology for the Determination of Residues of Chloropicrin in Tomatoes. Huntingdon Life Sciences, Ltd., UK. Unpublished report No. SXC 0006/072457. Owner European Chloropicrin Group. 2007a. (IIA 4.3/03)

GLP: Yes

Principle of the method

The analytical method for determination of residues of Chloropicrin in tomatoes was supplied by Neutron (reference IIA 4.3/01, Gatti 2001a) and was independently validated in this study. Samples were extracted with acetone: 25% phosphoric acid (20:80 v:v) containing 5% sodium chloride, and partitioned into isoctane prior to determination by gas chromatography with electron capture detection (GC-ECD). Confirmatory analysis was performed by gas chromatography with mass specific detection (GC-MS).

Recovery findings

Tomato samples were fortified at 0.01 and 0.1 mg/kg Chloropicrin. Mean recovery was determined at each fortification level. Mean recoveries were within the required range (70 to 110%), with actual values between 71 and 76%

The results are presented in Table B.5.2-01 and Table B.5.2-02.

Table B.5.2-01: Recovery results from the independent laboratory validation of a method for the determination of Chloropicrin in tomatoes using GC-ECD (reference IIA 4.3/03, Todd, 2007)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Tomatoes	0.01	71	70 – 74	2.3	5
		0.1	76	75 - 78	1.8	5

Table B.5.2-02 Recovery results from the independent laboratory validation of a method for the determination of Chloropicrin in tomatoes using confirmatory GC-MS (reference IIA 4.3/03, Todd, 2007)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Tomatoes	0.01	76	74 – 77	1.6	5
		0.1	73	70 - 76	2.9	5

Linearity

The GC-ECD system showed a linear response to Chloropicrin for eight concentrations in the range 1 to 100 ng/mL. The GC-MS system showed a linear response to Chloropicrin for seven concentrations in the range 1 to 80 ng/mL. The coefficient of determination (r^2) was 0.996, with the equation $y = 387.1x - 439.9$ using GC-ECD and 0.996, with the equation $y = 55530x - 109500$, using confirmatory GC-MS.

Specificity

Control samples determined according to the method showed that there was no apparent response >30% of the LOQ in the region corresponding to the retention time of Chloropicrin using either GC-ECD or GC-MS.

Limit of determination

The limit of detection (LOD) was 1 ng/mL, equivalent to 0.0005 mg/kg Chloropicrin in tomatoes. The limit of quantification (LOQ) was 0.01 mg/kg Chloropicrin in tomatoes.

Repeatability

The accuracy of the method was determined by the recoveries compared to the controls. The precision of the method was determined from the relative standard deviation (RSD) of the recovery results. The overall RSD was 3.6% in tomatoes. Precision was within the required specified limit, i.e. $RSD \leq 20\%$.

Stability

The final extract stability samples indicated that Chloropicrin was stable in the final extract for a period of three days when stored at -18°C. Day 0 stability samples indicated that there were no significant enhancement or suppression effects for Chloropicrin in tomatoes.

Conclusions:

The independent laboratory validation of the analytical method for the determination of Chloropicrin in tomatoes was validated and found to be acceptable, with an LOQ of 0.01 mg/kg. The analytical method is appropriate for post-registration enforcement monitoring.

Single residue method

Zoboli, G., Residue Determinations of Chloropicrin in Tomatoes According to the OECD Principles of GLP (Good Laboratory Practice). Neutron S.p.A., Italy. Unpublished report No. LN93-08. Owner European Chloropicrin Group. 2009a. (IIA 4.3/04)

GLP: Yes

Principle of the method

The analytical method for determination of residues of Chloropicrin in tomatoes previously validated (reference IIA 4.3/01, Gatti 2001a) was subject to further validation at the same Test Facility in this study with the aim of reducing the Limit of Quantification (LOQ) from 0.01 mg/kg to 0.005 mg/kg. Samples were extracted with acetone: 25% phosphoric acid (20:80 v:v) containing 5% sodium chloride, and partitioned into isooctane prior to determination by gas chromatography with electron capture detection (GC-ECD). Confirmatory analysis was performed by GC-ECD using a capillary column of different selectivity.

Recovery findings

Tomato samples were fortified at 0.005 and 0.05 mg/kg Chloropicrin. Mean recovery was determined at each fortification level. Mean recoveries were within the required range (70 to 110%), with actual values between 67 and 79%.

The results are presented in Table B.5.2-03 and Table B.5.2-04

Table B.5.2-03 Recovery results from the extended validation of a method for the determination of Chloropicrin in tomatoes using GC-ECD (reference IIA 4.3/04, Zoboli, 2009a)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Tomatoes	0.005	76	74 – 79	2.4	5
		0.05	74	67 - 76	4.4	5

Table B.5.2-04 Recovery results from the extended validation of a method for the determination of Chloropicrin in tomatoes using confirmatory GC-ECD conditions (reference IIA 4.3/04, Zoboli, 2009a)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]	CV (RSD) (%)	n
Chloropicrin	Tomatoes	0.005	75	-	1
		0.05	86	-	1

Linearity

The GC-ECD system showed a linear response to Chloropicrin for five concentrations in the range 2.5 to 100 ng/mL. The coefficient of determination (r^2) was 0.9975, with the equation $y = 1153524x$, using GC ECD.

Specificity

Control samples determined according to the method showed that there was no apparent response >30% of the LOQ in the region corresponding to the retention time of Chloropicrin with GC-ECD using two different columns.

Limit of determination

The limit of detection (LOD) was 0.0005 mg/kg Chloropicrin in tomatoes. The limit of quantification (LOQ) was 0.005 mg/kg Chloropicrin in tomatoes.

Repeatability

The accuracy of the method was determined by the recoveries compared to the controls at two fortification levels (0.005 and 0.05 mg/kg). The precision of the method was determined from the relative standard deviation (RSD) of the recovery results. Precision was within the required specified limit, i.e. $RSD \leq 20\%$.

Conclusions:

The extended validation of the analytical method for the determination of Chloropicrin in tomatoes was validated and found to be acceptable, with a reduced LOQ of 0.005 mg/kg. The analytical method is appropriate for data generation and post-registration enforcement monitoring.

Single residue method - ILV

Gandhi, J., Analysis of Residues of Chloropicrin in Outdoor Grown Tomatoes with Associated Validation in Compliance with Good Laboratory Practice. Oxford Analytical Ltd., UK. Unpublished report No. OA01626. Owner European Chloropicrin Group. 2009. (IIA 4.3/05)

GLP: Yes

Principle of the method

The analytical method for determination of residues of Chloropicrin in tomatoes previously validated (reference IIA 4.3/01, Gatti 2001a) was subject to further independent validation in this study using the reduced Limit of Quantification (LOQ) of 0.005 mg/kg. Samples were extracted with acetone: 25% phosphoric acid (20:80 v:v) containing 5% sodium chloride, and partitioned into hexane prior to determination by gas chromatography with mass selective detection (GC-MSD).

Recovery findings

Tomato samples were fortified at 0.005 and 0.01 mg/kg Chloropicrin. Mean recovery was determined at each fortification level. Mean recoveries were within the required range (70 to 110%), with values between 84 and 101%.

The results are presented in Table B.5.2-05.

Table B.5.2-05 Recovery results from the extended validation of a method for the determination of Chloropicrin in tomatoes using GC-MSD (reference IIA 4.3/05, Gandhi, 2009)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Tomatoes	0.005	96	92 – 101	3.9	5
		0.01	88	84 - 91	3.9	5

Linearity

The GC-MSD system showed a linear response to Chloropicrin for five concentrations in the range 1 to 56 ng/mL (injected in duplicate). The correlation coefficient (r) was 0.9995, with the equation $y = 47030.68604x + 63157.91403$.

Specificity

Control samples determined according to the method showed that there was no apparent response >30% of the LOQ in the region corresponding to the retention time of Chloropicrin using GC-MSD. The combination of chromatographic separation with representative selected GCMS ions gives confirmation of identity.

Limit of determination

The limit of quantification (LOQ) was 0.005 mg/kg Chloropicrin in tomatoes.

Repeatability

The accuracy of the method was determined by the recoveries compared to the controls. The precision of the method was determined from the relative standard deviation (RSD) of the recovery results.

Conclusions:

The independent validation of this analytical method for the determination of Chloropicrin in tomatoes was performed and found to be acceptable, with an LOQ of 0.005 mg/kg. The analytical method is appropriate for post-registration enforcement monitoring.

Single residue method for Dichloronitromethane

Zoboli, G., Determination of Residues of Dichloronitromethane In Tomato. Validation of the Analytical Method. Neutron S.p.A., Italy. Unpublished report No. LN95 (validation). Owner European Chloropicrin Group. 2009b. (IIA 4.3/06)

GLP: Yes

Principle of the method

An analytical method for determination of residues of the potential metabolite of Chloropicrin, Dichloronitromethane (DCNM), in tomatoes was developed and validated. Samples were extracted with acetone: 17% phosphoric acid (40:60 v/v) containing 5% sodium chloride, and 1 mL of glycerine solution. Toluene (5 mL) is included so that any residue is partitioned into this organic layer during extraction. After separation by centrifugation to determination is by gas chromatography with electron capture detection (GC ECD). Confirmatory analysis was performed by GC-ECD using a capillary column of different selectivity.

Recovery findings

Tomato samples were fortified at 0.005 and 0.05 mg/kg DCNM. Mean recovery was determined at each fortification level. Mean recoveries were within the required range (70 to 110%), with values between 72 and 97%.

The results are presented in Table B.5.2-06 and Table B.5.2-07

Table B.5.2-06 Accuracy and precision results from the validation of a method for the determination of DCNM in tomatoes using GC-ECD (reference IIA 4.3/06, Zoboli, 2009b)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Tomatoes	0.005	94	91 – 97	2.3	5
		0.05	74	72 - 75	1.4	5

Table B.5.2-07 Recovery results from the validation of a method for the determination of DCNM in tomatoes using confirmatory GC-ECD conditions (reference IIA 4.3/06, Zoboli, 2009b)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]	CV (RSD) (%)	n
Chloropicrin	Tomatoes	0.005	98	-	1
		0.05	88	-	1

Linearity

The GC-ECD system showed a linear response to DCNM for seven concentrations in the range 5.0 to 83 ng/mL. The coefficient of determination (r^2) was 0.9986, with the equation $y = 15.9x + 0$, using GC-ECD.

Specificity

Control samples determined according to the method showed that there was no apparent response >30% of the LOQ in the region corresponding to the retention time of DCNM using either GC-ECD. Confirmation was shown to be possible by GC-ECD using a capillary column of different selectivity.

Limit of determination

The limit of detection (LOD) was 0.00065 mg/kg DCNM in tomatoes. The limit of quantification (LOQ) was 0.005 mg/kg DCNM in tomatoes.

Repeatability

The accuracy of the method was determined by the recoveries compared to the controls. The overall mean recovery was 84%. The precision of the method was determined from the relative standard deviation (RSD) of the recovery results. The overall RSD was 12.7%. Precision was within the required specified limit, i.e. $RSD \leq 20\%$.

Conclusions:

The developed analytical method for the determination of DCNM in tomatoes was validated and found to be acceptable with an LOQ of 0.005 mg/kg. The analytical method is appropriate for data generation purposes.

B.5.3 Analytical methods (residue) soil (Annex IIA 4.4 (EU 4.2.2); Annex IIIA 5.2))

Single residue method

Todd, M., Chloropicrin: Validation of Methodology for the Determination of Residues of Chloropicrin in Two Soil Types. Huntingdon Life Sciences, Ltd., UK. Unpublished report No. SXC/0004/072450. Owner European Chloropicrin Group. 2007b. (IIA 4.4/01)

GLP: Yes

Principle of the method

Samples were extracted with acetonitrile followed by liquid-liquid partition using hexane prior to quantitation by gas chromatography using electron capture detection (GC-ECD). Confirmatory analysis was performed by gas chromatography with mass specific detection (GC-MS).

Recovery findings

Soil samples were fortified at 0.05 and 0.5 mg/kg Chloropicrin. Two soil types were investigated; clay and sandy soil. Mean recovery was determined at each fortification level. Mean recoveries were within the required range (70 to 110%), with values between 81 and 93%.

The results are presented in Tables B.5.3-01 and Table B.5.3-02

Table B.5.3-01 Recovery results from method validation of a method for the determination of Chloropicrin residues in soil using GC-ECD (reference IIA 4.4/01, Todd, 2007b)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Sandy soil	0.05	87	84 – 90	3.4	5
		0.5	84	81 – 86	2.7	5
	Clay soil	0.05	91	90 – 93	1.6	5
		0.5	87	86 – 89	1.5	5

Table B.5.3-02 Recovery results from method validation of a method for the determination of Chloropicrin residues in soil using confirmatory GC-MS (reference IIA 4.4/01, Todd, 2007b)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Sandy soil	0.05	91	84 – 98	6.5	5
		0.5	80	74 – 86	5.3	5
	Clay soil	0.05	99	91 – 108	7.3	5
		0.5	90	84 - 99	7.2	5

Linearity

The GC-ECD and GC-MS systems showed a linear response to Chloropicrin for ten concentrations in the range 0.5 to 100 ng/mL. The coefficient of determination (r^2) was 1.000, with the equation $y = 440.5x - 151.8$, using GC-ECD and 0.997, with the equation $y = 405800x - 269700$, using confirmatory GC-MS.

Specificity

Control samples determined according to the method showed that there was no apparent response >30% of the LOQ in the region corresponding to the retention time of Chloropicrin using either GC-ECD or GC-MS.

Limit of determination

The limit of detection (LOD) was 0.5 ng/mL, equivalent to 0.0125 mg/kg Chloropicrin in both soil types. The limit of quantification (LOQ) was 0.05 mg/kg Chloropicrin in both soil types.

Repeatability

The accuracy of the method was determined by the recoveries compared to the controls. The precision of the method was determined from the relative standard deviation (RSD) of the recovery results. Overall precision (RSD) was 2.9% in sandy soil and 3.5% in clay soil. Precision was within the required specified limit, i.e. RSD $\leq$ 20%

Stability

The final extract stability samples indicated that Chloropicrin was stable in the final extract for a period of three days when stored at -18°C. Day 0 stability samples indicated that there were no significant enhancement or suppression effects for Chloropicrin in either soil type.

Conclusions:

The analytical method for the determination of Chloropicrin in two soil types (clay and sandy) was validated and found to be acceptable for the analysis of Chloropicrin in soil, with a LOQ of 0.05 mg/kg.

B 5.4 Analytical methods (residue) water (Annex IIA 4.5 (EU 4.2.3))

Single residue method

Todd, M., Chloropicrin: Validation of Methodology for the Determination of Residues of Chloropicrin in Ground, Drinking and Surface Water. Huntingdon Life Sciences, Ltd., UK. Unpublished report No. SXC/0007/072387. Owner European Chloropicrin Group. 2007c. (IIA 4.5/01)

GLP: Yes

Principle of the method

Samples of ground, drinking or surface water were extracted with acetonitrile followed by liquid:liquid partition using hexane prior to determination by gas chromatography using electron capture detection (GC-ECD). Confirmatory analysis was performed by gas chromatography with mass specific detection (GC-MS). The sample of surface water used for the validation was characterised for the parameters requested in the EU guideline, including pH, DOC, alkalinity and hardness.

Recovery findings

Samples of ground, surface and drinking water were fortified with 0.1 and 1.0 µg/L Chloropicrin. Mean recovery was determined at each fortification level. Mean recoveries were within the required range (70 to 110%), with values between 77 and 100%.

The results are presented in Tables B.5.4-01 and Table B.5.4-02

Table B.5.4-01 Recovery results from method validation of a method for the determination of Chloropicrin residues in water using GC-ECD (reference IIA, 4.5/01, Todd, 2007c)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Ground water	0.1	86	82 – 90	3.5	5
		1.0	82	78 – 84	3.0	5
	Surface water	0.1	87	78 – 93	7.1	5
		1.0	85	77 – 93	7.3	5
	Drinking water	0.1	92	80 – 96	7.6	5
		1.0	94	84 - 100	7.6	5

Table B.5.4-02 Recovery results from method validation of a method for the determination of Chloropicrin residues in water using confirmatory GC-MS (reference IIA, 4.5/01, Todd, 2007c)

Reference (analyte)	Matrix	Fortification level [mg/kg]	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Ground water	0.1	94	92 – 95	1.2	5
		1.0	85	81 – 86	3.1	5
	Surface water	0.1	83	75 – 89	7.5	5
		1.0	80	76 – 87	5.4	5
	Drinking water	0.1	80	76 – 89	6.4	5
		1.0	80	75 - 83	4.3	5

Linearity

The GC-ECD system showed a linear response to Chloropicrin for ten concentrations in the range 0.5 to 100 ng/mL. The response of the GC-MS system was shown to be linear in the range 0.5 to 80 ng/mL. The coefficient of determination (r^2) was 0.999, with the equation $y = 339.7x + 8.294$, using GC-ECD and 0.999, with the equation $y = 707700x - 262400$, using confirmatory GC-MS.

Specificity

Control samples determined according to the method showed that there was no apparent response >30% of the LOQ in the region corresponding to the retention time of Chloropicrin using either GC-ECD or GC-MS.

Limit of determination

The limit of detection (LOD) was determined to be 0.5 ng/mL for Chloropicrin, equivalent to 0.05 µg/L in all three water types. The limit of quantification (LOQ) was determined to be 0.1 µg/L for Chloropicrin in all three water types.

Repeatability

The accuracy of the method was determined by the recoveries compared to the controls. The precision of the method was determined from the relative standard deviation (RSD) of the recovery results. The overall precision (RSD) was 4.1% in ground water, 6.9% in surface

water and 7.2% in drinking water. Precision was within the required specified limit, i.e. RSD $\leq 20\%$.

Stability

The final extract stability samples indicated that Chloropicrin was stable in the final extract for a period of three days when stored at -18°C . Day 0 stability samples indicated that there were no significant enhancement or suppression effects for Chloropicrin in any of the water types.

Conclusions:

The analytical method for the determination of Chloropicrin in three water types (ground, surface and drinking) was validated and found to be acceptable, with an LOQ of $0.1 \mu\text{g/L}$.

B 5.5 Analytical methods (residue) air (Annex II A 4.7 (EU 4.2.4))

Single residue method

Todd, M., Chloropicrin: Validation of Methodology for the Determination of Residues of Chloropicrin in Air. Huntingdon Life Sciences, Ltd., UK. Unpublished report No. SXC/0005/072973. Owner European Chloropicrin Group, 2007d. (IIA 4.7/01)

GLP: Yes

Principle of the method

Four scenarios were assessed in order to find appropriate conditions for the study. The scenarios are summarised in Table B.5.5-01.

For all scenarios air under the specified conditions was passed through tubes containing the appropriate sorbent material, which were fortified with Chloropicrin at two levels. Residual Chloropicrin was extracted from the sorbent material with hexane. Quantitation was performed by gas chromatography with electron capture detection (GC-ECD). Confirmatory analysis was performed by gas chromatography with mass spectrometric detection (GC-MS). For details of the evaluated scenarios see Table B.5.5-01

Table 5.5-01 Scenarios evaluated for a method for the determination of Chloropicrin residues in air (reference IIA 4.7/01, Todd, 2007d)

Scenario	Sorbent material	Air temperature ($^{\circ}\text{C}$)	Relative humidity (%)	Air flow rate (L/min)	Sampling time (hr)
A	Tenax	35	80	1	6
B	XAD-4	35	80	1	6
C	XAD-4	20	30	1	6
D	XAD-4	20	30	1	2

Recovery findings

Scenario A gave recoveries of between 0 and 2%, scenario B gave recoveries between 20 and 40%, scenario C gave recoveries between 50 and 70% and scenario D gave recoveries between 70 and 91% which are within the required range (70 to 110%) and therefore this scenario was the one selected for reporting of validation results.

The results are presented in Table B.5.5-02 and Table B.5.5-03.

Table B.5.5-02 Recovery results from method validation of a method for the determination of Chloropicrin residues in water using GC-ECD (reference IIA, 4.5/01, Todd, 2007c)

Reference (analyte)	Matrix	Amount on sorbent (µg)	Equivalent fortification level (µg/m ³)	Recovery rate [%]		CV (%)	n
				Mean	Range		
Chloropicrin	Air	0.1	0.83	82	70 – 91	11.9	5
		1.0	8.3	84	75 – 88	6.0	5
	Breakthrough test	1.0	8.3	5.0	5.0 – 5.0	-	2

Table B.5.5-03 Recovery results from method validation of a method for the determination of Chloropicrin residues in water using confirmatory GC-MS (reference IIA, 4.5/01, Todd, 2007c)

Reference (analyte)	Matrix	Amount on sorbent (µg)	Equivalent fortification level (µg/m ³)	Recovery rate [%]		CV (%)	n
				Mean	Range		
Chloropicrin	Air	0.1	0.83	98	93 – 105	5.2	5
		1.0	8.3	82	76 - 88	5.5	5

Linearity

The GC-ECD system showed a linear response in the range 1.0 to 100 ng/mL. The GC-MS system showed a linear response in the range 1 to 80 ng/mL. The coefficient of determination (r^2) was 0.998, with the equation $y = 41.80x - 22.07$, using GC-ECD and 0.995, with the equation $y = 58435.3x - 79765.9$, using confirmatory GC MS.

Specificity

Control samples determined according to the method showed that there was no apparent response >30% of the LOQ in the region corresponding to the retention time of Chloropicrin using either GC-ECD or GC-MS.

Limit of determination

The limit of detection (LOD) was 1 ng/mL, equivalent to 0.05 µg on a cartridge and 0.42 µg/m³ in air. The limit of quantitation (LOQ) was 0.1 µg on a cartridge, equivalent to 0.83 µg/m³ in air.

Repeatability

The accuracy of the method was determined by the recoveries compared to the controls. The precision of the method was determined from the relative standard deviation (RSD) of the recovery results. The overall precision (RSD) in air was 8.9%. Precision was within the required specified limit, i.e. $RSD \leq 20\%$.

Breakthrough

Breakthrough of Chloropicrin from the front air sampling cartridge to the rear section was shown to be $<10\%$ of the fortified amount, tested at the upper fortification level.

Stability

The final extract stability samples indicated that Chloropicrin was stable in the final extract for a period of three days when stored at -18°C . Day 0 stability samples indicated that there were no significant enhancement or suppression effects for Chloropicrin in air.

Conclusions

The analytical method for the determination of Chloropicrin in air was validated and found to be acceptable, with an LOQ of $0.1 \mu\text{g}$ on a cartridge (equivalent to $0.83 \mu\text{g}/\text{m}^3$ in air). This LOQ is well within the EU requirements for the method to be capable of determining concentrations below the AOEL ($200 \mu\text{g}/\text{m}^3$ in air).

B.5.6 Analytical methods (residue) for body fluids and tissues (Annex II A 4.8 (EU 4.2.5))

Single residue method

Airs, D., Chloropicrin: Validation of Methodology for the Determination of Residues of Chloropicrin in Human Blood, Porcine Muscle and Liver. Huntingdon Life Sciences, Ltd., UK. Unpublished report No. SXC/0026. Owner European Chloropicrin Group. 2009. (IIA 4.8/02)

GLP: Yes

Principle of the method

Samples were extracted with acetone: phosphoric acid mixture followed by a partition into 2,2,4-trimethylpentane prior to determination by gas chromatography using electron capture detection (GC-ECD). Confirmatory analysis was performed by gas chromatography with mass specific detection (GC-MS).

Recovery findings

Porcine muscle and liver samples were fortified at 0.01 and 0.1 mg/kg and human blood samples were fortified at 0.05 and 0.5 mg/L. Mean recovery was determined at each fortification level. Mean recoveries were within the required range (70 to 110%), with values between 70 and 109%.

The results are presented in Table B.5.6-01 and Table B.5.6-02.

Table B.5.6-01 Recovery results from method validation of a method for the determination of Chloropicrin residues in porcine muscle and liver and in human blood using GC-ECD (reference IIA 4.8/02, Airs, 2009)

Reference (analyte)	Matrix	Fortification level (mg/kg or mg/L)	Recovery rate [%]		RSD (%)	n
			Mean	Range		
Chloropicrin	Porcine muscle	0.01	95	89 – 98	3.8	5
		0.1	95	93 – 97	1.7	5
	Porcine liver	0.01	97	88 – 109	11.2	5
		0.1	107	101 – 109	3.3	5
	Human blood	0.05	78	70 – 82	5.9	5
		0.5	77	74 – 82	4.2	5

Table B.5.6-02 Recovery results from method validation of a method for the determination of Chloropicrin residues in porcine muscle and liver and in human blood using confirmatory GC-MS (reference IIA 4.8/02, Airs, 2009)

Reference (analyte)	Matrix	Fortification level (mg/kg or mg/L)	Recovery rate [%]		CV (RSD) (%)	n
			Mean	Range		
Chloropicrin	Porcine muscle	0.01	92	84 – 105	10.1	5
		0.1	102	93 – 108	6.4	5
	Porcine liver	0.01	103	96 – 108	4.5	5
		0.1	102	93 – 110	7.5	5
	Human blood	0.05	81	74 – 85	5.6	5
		0.5	89	75 – 101	11.3	5

Linearity

The GC-ECD system showed a linear response to Chloropicrin when log peak area was plotted against log concentration for nine concentrations in the range 0.5 to 50 ng/mL. The GC-MS system showed a linear response for eight concentrations over the range 0.5 to 50 ng/mL. The coefficient of determination (r^2) was 0.9998, with the equation $y = 1.09224x + 3.09412$, using GC-ECD and 0.9990, with the equation $y = 721.254x - 317.496$, using confirmatory GC-MS.

Specificity

Control samples determined according to the method showed that there was no significant response >30% of the LOQ in the region corresponding to the retention time of Chloropicrin using either GC-ECD or GC-MS.

Limit of determination

The limit of detection (LOD) was 0.5 ng/mL, equivalent to 0.005 mg/kg in porcine muscle and liver and 0.01 mg/L in human blood. The limit of quantification (LOQ) was 0.01 mg/kg in porcine muscle and liver and 0.05 mg/L in human blood.

Repeatability

The accuracy of the method was determined by the recoveries compared to the controls. The precision of the method was determined from the relative standard deviation (RSD) of the recovery results. The overall precision (RSD) was 2.8% in porcine muscle, 9.2% in porcine liver and 4.7% in human blood. Precision was within the required specified limit, i.e. RSD $\leq 20\%$.

Stability

The final extract stability samples performed at 20 ng/mL indicated that Chloropicrin was stable in the final extract for a period of six days when stored at approximately -20°C.

Conclusions

The analytical method for the determination of Chloropicrin in porcine muscle and liver and in human blood was validated and found to be acceptable, with an LOQ of 0.01 mg/kg in porcine muscle and liver and 0.05 mg/L in human blood. This method in conjunction with the procedure used for fresh urine (reference IIA 4.8/01, Wimbush 2004) provides suitable enforcement methodology for Chloropicrin if needed, which is an EU requirement for compounds of this nature.

B.5.7 Analytical methods (residue) for wildlife

No data is submitted as it is proposed that Chloropicrin does not endanger wildlife when used as recommended.

Table B.5.1: Summary of method validation (treated plants, environment and human biofluids).

Substrate and reference	Overall Mean % recovery	Overall Precision - repeatability (% RSD)	Limit of determination (mg/kg, unless stated)
Plant material			
Tomatoes (Gatti, 2001a)	80	4	0.01
Melons (Gatti, 2001b)	87	4	0.01
Tomatoes (Todd, 2007a)	74	3.6	0.01
Tomatoes (Gandhi, 2009)	92	5.9	0.005
Tomatoes (Zoboli, 2009a)	75	3.7	0.005
DCNM in Tomatoes (Zoboli, 2009b)	84	12.7	0.005
Environment			
Soil –Clayey (Todd, 2007b)	85	3.5	0.05
Soil – Sandy (Todd, 2007b)	89	2.9	0.05
Ground water (Todd, 2007c)	84	4.1	0.1 µg/L
Surface water (Todd, 2007c)	86	6.9	0.1 µg/L
Drinking water (Todd, 2007c)	93	7.2	0.1 µg/L
Air (Todd, 2007d)	83	8.9	0.1 µg/tube = 0.83 µg/m ³
Human and animal tissues and fluids			
Urine (Wimbush, 2004)	79	3.0	0.05 mg/L
Muscle (Airs, 2009)	95	2.8	0.01 mg/kg
Liver (Airs, 2009)	102	9.2	0.01 mg/kg
Blood (Airs, 2009)	78	4.7	0.05 mg/L

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B.5.8 References relied on

Active substance

Annex point / reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Data Protection claimed Y/N	Owner
IIA 4.2.1/02 ⇒ IIA 1.11/01 Document J	Arndt, T	2009	Analysis and Certification of Product Ingredients in Five batches of Chloropicrin PTRL West, Inc Report No. 1801W GLP, Unpublished	Y	Chloropicrin Manufacturers Task Force
IIA 4.3/03	Todd, M.	2007a	Chloropicrin: Independent Laboratory Validation of Methodology for the Determination of Residues of Chloropicrin in Tomatoes Huntingdon Life Sciences, Ltd Report No. SXC 0006/072457 GLP, Unpublished	Y	Chloropicrin Manufacturers Task Force
IIA 4.3/04 ⇒ IIA 6.3.1/05	Zoboli, G.	2009a	Residue Determinations of Chloropicrin in Tomatoes According to the OECD Principles of GLP (Good Laboratory Practice) NEOTRON, S.r.l. Report No. LN93-08 GLP, Unpublished	Y	Chloropicrin Manufacturers Task Force
IIA 4.3/05 ⇒ IIA 6.3.1/04	Gandhi, J	2009	Gandhi, J. Analysis of Residues of Chloropicrin in Outdoor Grown Tomatoes with Associated Validation in Compliance with Good Laboratory Practice Oxford Analytical Ltd Report No. OA01626 GLP, Unpublished	Y	Chloropicrin Manufacturers Task Force
IIA 4.3/06	Zoboli, G.	2009b	Determination of Residues of Dichloronitromethane In Tomato. Validation of the Analytical Method NEOTRON, S.r.l. Report No. LN95 (validation) GLP, Unpublished	Y	Chloropicrin Manufacturers Task Force
IIA 4.4/01	Todd, M.	2007b	Chloropicrin: Validation of Methodology for the Determination of Residues of Chloropicrin in Two Soil Types Huntingdon Life Sciences, Ltd Report No. SXC0004/072450 GLP, Unpublished	Y	Chloropicrin Manufacturers Task Force
IIA 4.5/01	Todd, M.	2007c	Chloropicrin: Validation of Methodology for the Determination of Residues of Chloropicrin in Ground, Drinking and Surface Water) Huntingdon Life Sciences, Ltd Report No. SCX0007/072387 GLP, Unpublished	Y	Chloropicrin Manufacturers Task Force

IIA 4.7/01	Todd, M.	2007d	Chloropicrin: Validation of Methodology for the Determination of Residues of Chloropicrin in Air Huntingdon Life Sciences, Ltd Report No. SXC0005/072973 GLP, Unpublished	Y	Chloropicrin Manufacture rs Task Force
IIA 4.8/02	Airs, D.	2009	Chloropicrin: Validation of Methodology for the Determination of Residues of Chloropicrin in Human Blood, Porcine Muscle and Liver) Huntingdon Life Sciences, Ltd Report No. SXC0026 GLP, Unpublished	Y	Chloropicrin Manufacture rs Task Force

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