PORTUGAL

MINISTÉRIO DA AGRICULTURA DO DESENVOLVIMENTO RURAL E DAS PESCAS
DIRECÇÃO-GERAL DE PROTECÇÃO DAS CULTURAS

# Report prepared in the context of the application for first inclusion of dodine in Annex I of the Council Directive 91/414/EEC

## DODINE

**Volume 3-1 rev.1**

**Annex B**

Sections B1-B5

**Summary, evaluation and assessments of the data.**

**List of tests and studies relied upon**

**2006**

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## B.1 Identity

### B.1.1 Identity of the active substance (Annex IIA 1 and 3.1)

All the points of Annex IIA, section 1 are addressed in the Report and Proposed Decision, Level 1.

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

Chimac-Agriphar S.A.
Rue de Renory, 26
B-4102 Ougré
Belgium

Telephone No: +32/4/385.97.11
Contact Person: [redacted]

### B.1.1.2 Common name and synonyms (Annex IIA 1.3)

Dodine (ISO common name).

### B.1.1.3 Chemical name (Annex IIA 1.4)

IUPAC: 1-dodecylguanidinium acetate

CA: Dodecylguanidine monoacetate

### B.1.1.4 Manufacturer's development code number (Annex IIA 1.5)

None – dodine.

### B.1.1.5 CAS, EEC and CIPAC numbers (Annex IIA 1.6)

CAS: 2439-10-3

EEC: 219-459-5

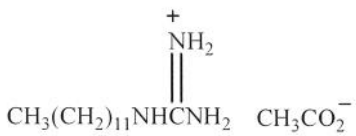
CIPAC: 101

### B.1.1.6 Molecular and structural formulae, molecular mass (Annex IIA 1.7)

Molecular formula: $C_{15}H_{33}N_3O_2$

Structural formula:

Dodine is a salt that can dissociate in a cation (dodecylguanidinium) and an anion (acetate) as follows:



Molecular mass: 287.4 g/mol

**B.1.1.7 Manufacturer or manufacturers of the active substance (Annex IIA 1.2)**

Confidential information included in Annex C.1.1.

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

Confidential information included in Annex C.1.1.

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

Not less than 950 g/kg.

Dodine minimum content does not comply with FAO specification CP/236 (1988) this is due to the fact that in this FAO specification the a.s. content is based on a titration method and as organic impurities also react with the colouring matter this leads to an artificial high purity. The new HPLC method only analyse dodine content thus leading to a lower purity. Chimac-Agriphar also informs that is working to update the FAO specification. The HPLC method was presented at the last annual CIPAC meeting. Once the method is accepted as a full CIPAC method, Chimac-Agriphar will apply for a new specification for dodine at FAO.

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

Confidential information included in Annex C.1.2.1.

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

Confidential information included in Annex C.1.2.2.

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

**B.1.2.1 Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)**

Trade name: SYLLIT 400 SC

Development code number: EXP10343A

**B.1.2.2 Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)**

Confidential information included in Annex C.1.3.

**B.1.2.3 Type of the preparation and code (Annex IIIA 1.5)**

Suspension concentrate – SC.

**B.1.2.4 Function (Annex IIA 3.1; Annex IIIA 1.6)**

Fungicide.

**B.1.2.5 Composition of the preparation (Annex III A 1.4)**

Content of pure active substance: 400 g/L or 40.1 % w/w

Identity and content of formulants: Confidential information included in Annex C.1.3.

## B.1.3 References relied on

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| **Annex IIA** | | | | | |
| IIA, 1.8/01 | Stephan, D. | 1998 | Dodine: Product identity and composition. Series 61.<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 98-03<br>GLP, Unpublished<br>CONFIDENTIAL INFORMATION | Y | CAG |
| IIA, 1.9/01 | Emeric, G.T. | 1999 | Technical dodine: Certification of Ingredient Limits.<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 99-08<br>GLP, Unpublished<br>CONFIDENTIAL INFORMATION | Y | CAG |
| IIA, 1.8 + 1.9/02 | Corman, C. | 2003 | Product identity, composition and certified limits.<br>Chimac-Agriphar, Report No. DOD 111203<br>GLP, Unpublished<br>CONFIDENTIAL INFORMATION | Y | CAG |
| IIA, 1.8 + 1.9/03 | Corman, C. | 2006 | History of dodine production: origin of batches used in the dossier.<br>Chimac-Agriphar<br>Unpublished<br>CONFIDENTIAL INFORMATION | Y | CAG |
| IIA, 1.10 + 1.11/01 | Cousin, J. | 1998 | Technical dodine: Analysis of product ingredients.<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 96-59<br>GLP, Unpublished<br>CONFIDENTIAL INFORMATION | Y | CAG |
| IIA, 1.10 + 1.11/02 | Fox, O. | 2003 | CONFIDENTIAL INFORMATION – see volume 4 | Y | CAG |
| IIA, 1.10 + 1.11/03 | Duff, S. | 2002 | Analytical profile of Technical Dodine<br>LIFESCIENTIFIC Laboratory, Ireland<br>Chimac-Agriphar, Report No. CHI-020709<br>GLP, Unpublished<br>CONFIDENTIAL INFORMATION | Y | CAG |
| IIA, 1.10 + 1.11/04 | O´Reilly, C. | 2006 | Analysis of Dodine technical [redacted]<br>LIFESCIENTIFIC Laboratory, Ireland<br>Chimac-Agriphar, Report No. CHI-020709<br>GLP, Unpublished<br>CONFIDENTIAL INFORMATION | Y | CAG |
| **Annex IIIA (SYLLIT 400 SC)** | | | | | |
| IIIA, 1.4 | Chimac-Agriphar | 2004 | Composition of formulation « SYLLIT 400 SC »<br>Chimac-Agriphar<br>Unpublished<br>CONFIDENTIAL INFORMATION | Y | CAG |

## B.2 Physical and chemical properties

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

**Table B.2.1 - Summary of the physical and chemical properties of dodine (studies were completed to an acceptable standard - GLP and results were considered to be valid unless specified otherwise)**

| Property/ Study | Method | Purity | Results | Comments | Reference |
|---|---|---|---|---|---|
| B.2.1.1 Melting point (Annex IIA 2.1.1) | EEC method A1 (DSC) | 1000 g/kg | 133.2 ºC | | 2.1.1/01 Bascou, J.P. (1998) R-97-57-part A |
| B.2.1.2 Boiling point (Annex IIA 2.1.2) | EEC method A2 (DSC) | 1000 g/kg | No boiling before the decomposition of the substance. | Decomposition occurs prior to boiling | 2.1.1/01 Bascou, J.P. (1998) R-97-57-part A |
| B.2.1.3 Temperature of decomposition or sublimation (Annex IIA 2.1.3) | EEC method A2 (DSC) | 1000 g/kg | 200.5ºC (at atmospheric pressure) | | 2.1.1/01 Bascou, J.P. (1998) R-97-57-part A |
| B.2.1.4 Relative density (Annex IIA 2.2) | EEC method A3 (Pycnometer method) | 1000 g/kg | 20 ºC<br>0.983 | | 2.1.1/01 Bascou, J.P. (1998) R-97-57-part A |
| B.2.1.5 Vapour pressure (Annex IIA 2.3.1) | EEC method A4 (Gas saturation method) | 1000 g/kg | $< 5.49 \times 10^{-6}$ Pa<br>Vapour pressure at 20 ºC could not be exactly determined from the preliminary test at 50ºC. | Low vapour pressure | 2.3.1/01 Bascou, J.P. (1999) R-97-57-part F |
| B.2.1.6 Volatility, Henry's law constant (Annex IIA 2.3.2) | Calculated | | At 20 ºC,<br>$<1.70 \times 10^{-3}$ Pa $m^3$ $mol^{-1}$ (estimated from vapour pressure < $5.49 \times 10^{-6}$ Pa at 20ºC, water solubility 0.93 g/L and dodine molecular weight 287.45 g/mol) | Medium volatility | 2.3.2/01 Bascou, J.P. (1999) R-R&D/CRLD/NA/99 16653 |

| Property/ Study | Method | Purity | Results | Comments | Reference |
|---|---|---|---|---|---|
| B.2.1.7 Physical state and colour (Annex IIA 2.4.1) | Visual assessment | 1000 g/kg<br><br>982 g/kg | Slightly yellow fine powder. | | 2.1.1/01<br>Bascou, J.P.<br>(1998)<br>R-97-57-part A |
| B.2.1.8 Odour (Annex IIA 2.4.2) | Organoleptic | 1000 g/kg<br><br>982 g/kg | Odourless | | 2.1.1/01<br>Bascou, J.P.<br>(1998)<br>R-97-57-part A |
| B.2.1.9 Spectra of active substance (Annex IIA 2.5.1) | In-house method | 1000 g/kg | UV/VIS<br>Acid medium (methanol soln.+ HCl – 1N) and neutral medium (methanol soln + deionised water): An absorption max. at 200 nm with $\varepsilon = 2600$ $Lmol^{-1}cm^{-1}$<br>at $\lambda \geq 290$ nm highest $\varepsilon < 1.5$ $Lmol^{-1}cm^{-1}$<br>Basic medium: Methanol soln + NaOH – 1N (possible interaction with the solvent and no absorption in range 200-210nm). | | 2.5.1/01<br>Jendrzejczak, N.<br>Maestracci, M.<br>(1994)<br>R-94-140 |
| | | 985 g/kg | IR<br>Spectrum is in agreement with proposed structure. | IR spectrum was not performed with pure dodine. | 2.5.1/02<br>Van Rijsbergen, L.<br>(2002)<br>R-343193 |
| | | 985 g/kg | $^{1}$H-NMR(methanol-$D_4$)<br>Spectrum is in agreement with proposed structure. | NMR spectrum was not performed with pure dodine. | 2.5.1/03<br>Van Rijsbergen, L.<br>(2002)<br>R-343204 |
| | | 985 g/kg | $^{13}$C-NMR(methanol-$D_4$)<br>Spectrum is in agreement with proposed structure. | NMR spectrum was not performed with pure dodine. | 2.5..1/05<br>Krips H..<br>(2002)<br>R-348874 |
| | | 985 g/kg | MS (electron impact)<br>Mass spectrum is in agreement with proposed structure. | MS spectrum was not performed with pure dodine. | 2.5.1/04<br>Brekelmans M.<br>(2002)<br>R-343215 |
| B.2.1.10 Spectra of tox., ecotox. or environmental impurities (Annex IIA 2.5.2) | | | None of the impurities present in the technical active substance are of toxicological, ecotoxicological or environmental significance | | |

| Property/ Study | Method | Purity | Results | Comments | Reference |
|---|---|---|---|---|---|
| B.2.1.11 Solubility in water including effect of pH (4 to 10) on solubility (Annex IIA 2.6) | EEC method A6 (Shake-flask method) | 1000 g/kg | 20 ºC<br>pH=4.9 0.87 g/L<br>pH=6.9 0.93 g/L<br>pH=9.1 0.79 g/L | Medium solubility without significative pH dependence | 2.6/01<br>Bascou, J.P.<br>(1999)<br>R-450045 |
| B.2.1.12 Solubility in organic solvents (technical active substance) (Annex IIA 2.7) | EEC method A6 (Shake-flask method) | 982 g/kg | At 20 ºC, in g/L<br><br>n-Heptane 0.018<br>Xylene <0.004<br>Acetone 0.048<br>Ethyl acetate 0.015<br>Dichloromethane 0.015<br>Ethanol 57.0<br>n-Octanol 16.54<br>Acetonitrile 0.044 | | 2.6/01<br>Bascou, J.P.<br>(1999)<br>R-450045 |
| B.2.1.13 Partition coefficient n-octanol/water (Annex IIA 2.8) | EEC method A8 (Shake-flask method) | 1000 g/kg<br>20-25 ºC | Log $P_{ow}$ = 0.96, independent of the pH | An estimative or calculation must be submitted as a.s. is tensioactive. | 2.8/01<br>Bascou, J.P.<br>(1999)<br>R-97-57-part D |
| | Estimation method | | Based on dodine solubilities at 20ºC in water an in n-octanol (see point B.2.1.11 and B.2.1.12):<br>pH (aqueous phase) / Log $P_{ow}$<br>4.9 / 1.28<br>6.9 / 1.25<br>9.1 / 1.32 | Estimation based on values from R-450045 (1999) Ref. 2.6/01 Bascou, J.P. | 2.8/02<br>Brekelmans, M.J.C.<br>(2006)<br>R-450045 |
| B.2.1.14 Stability in water Hydrolysis rate (Annex IIA 2.9.1) | EPA 40 CFR 158.130, N-161-1 | 975 g/kg | At 25ºC<br>pH 5: $DT_{50}$ = 576 days<br>pH 7: $DT_{50}$ = 914 days<br>pH 9: $DT_{50}$ = 1198 days<br>Dodine is hydrolytically stable in aqueous buffered solutions at pH 5, 7 and 9 at 25ºC. | Dodine does not hydrolyse in the pH range 5-9. | 2.9.1/01<br>Daly, D.;<br>Kabler, K.<br>Williamson, K.<br>(1991)<br>R-38680 |
| B.2.1.15 Stability in Water Photochemical degradation (Annex IIA 2.9.2) | | | Not required. No significative absorption (highest $\varepsilon < 1.5$ $Lmol^{-1}cm^{-1}$) at $\lambda \geq 290$ nm. | | |

| Property/ Study | Method | Purity | Results | Comments | Reference |
|---|---|---|---|---|---|
| B.2.1.16 Quantum yield of direct photodegradation in water (Annex IIA 2.9.3) | | | Not required. No significative absorption (highest $\varepsilon < 1.5$ $Lmol^{-1}cm^{-1}$) at $\lambda \geq 290$ nm. | | |
| B.2.1.17 Dissociation constant (pKa) (Annex IIA 2.9.4) | OECD 112 (potentiometric method) | 1000 g/kg<br>982 g/kg | No pKa value could be associated with dodine.[1] | | 2.9.4/01<br>Bascou, J.P.<br>(1999)<br>R-97-57-part B |
| B.2.1.18 Stability in air, photochemical degradation, identity of breakdown products (Annex IIA 2.10) | Atkinson method | | $\geq 2.47\times10^{-11}$ $cm^3molecule^{-1}s^{-1}$ | | 2.10/01 Slangen P.J.<br>(2001)<br>R-327072 |
| B.2.1.19 Flammability (technical active substance) (Annex IIA 2.11.1) | EEC method A10 | 983 g/kg<br><br><br>962 g/kg | Not highly flammable | | 2.11.1/01<br>Phong, J.T.T.<br>1998<br>R-98-131<br><br>2.11.1/02<br>Krips, H.J.<br>2001<br>R-327083 |
| B.2.1.20 Auto-flammability (technical active substance) (Annex IIA 2.11.2) | EEC method A16 | 983 g/kg | Not auto - flammable | | 2.11.1/01<br>Phong, J.T.T.<br>1998<br>R-98-131 |
| B.2.1.21 Flash point (Annex IIA 2.12) | | | Not required since dodine is not a liquid at temperature <40ºC | | |
| B.2.1.22 Explosive properties (technical active substance) (Annex IIA 2.13) | EEC method A14 | 983 g/kg | Shock sensitivity: not explosive<br>Attrition sensitivity: not explosive<br>Thermal sensitivity: not explosive | | 2.11.1/01<br>Phong, J.T.T.<br>1998<br>R-98-131 |

[1] By carrying out the acidic titration of dodine a pKa value was reached corresponding to acetic acid and of course not characteristic of dodine. In the basic titration of dodine no pKa of the test substance could be determined by this method.

| Property/ Study | Method | Purity | Results | Comments | Reference |
|---|---|---|---|---|---|
| B.2.1.23 Surface tension (technical active substance) (Annex IIA 2.14) | EEC method A5 (Ring method) | 982 g/kg | 20 ºC<br>27.87 mN/m (conc. 445.2 mg/L) | Surface active compound. A smaller value will be expected at 90% of dodine solubility in water 0.93 g/L | 2.1.1/01<br>Bascou, J.P.<br>1998<br>R-97-57-part A |
| B.2.1.24 Oxidising properties (technical active substance) (Annex IIA 2.15) | EEC method A17 | 982 g/kg | No oxidising properties | | 2.15/01<br>François, J.M.<br>2000<br>R-00-330-SEC |

### B.2.1.25 Evaluation and Assessment of physical and chemical properties of the active substance

Dodine is a slightly yellow fine powder with a melting point of 133.2ºC. The active substance starts decomposition at 200.5 ºC prior to boiling. It is a tensioactive substance (< 27.87 mN/m), it has a low volatility (vapour pressure < $5.49\times10^{-6}$ Pa at 20ºC) and a Henry's constant less than $1.7\times10^{-3}$ Pa x $m^3$ x $mol^{-1}$. It has a medium solubility in water (0.8-0.9 g/L), without significative pH dependence, and in most organic solvents. Dodine is hydrolytically stable at pH 5, 7 and 9 with half-lives superior to 1 year at 25°C. Photochemically dodine has a $DT_{50}$ of 38 days in natural water at 25ºC, pH 7. Its flammability, explosive and oxidising properties are not critical.

Data submitted are sufficient and acceptable, although IR, NMR and MS spectra should be submitted for pure dodine.

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

### Table B.2.2 - Summary of the physical and chemical properties of SYLLIT 400 SC

| Property/ Study | Method | Results | Comments | Reference |
|---|---|---|---|---|
| | | | | |
| B.2.2.1 Appearance (Annex IIIA 2.1) | Visual assessment Organoleptic | Physical state: liquid<br>Colour: medium cream opaque<br>Odour: without any detectable odour | | 2.1/01<br>Le Gren, I.<br>Uceda, L.<br>(1997)<br>R-97-99 |
| | Visual assessment Organoleptic | Physical state: liquid<br>Colour: opaque white<br>Odour: no characteristic odour | | 2.7.2/01<br>Ryckel, B. (2004)<br>CHIMAC<br>R-FO20722/CH.3014/2003/206 |
| B.2.2.2 Explosive properties (Annex IIIA 2.2.1) | CEE A14 | Not explosive<br>Mechanical (shock): negative<br>Mechanical (friction): not applicable<br>Thermal sensitivity: negative | ppp is not considered as explosive. | 2.2.1/01<br>Treand, G.<br>(1997)<br>R-97-166-SEC |
| B.2.2.3 Oxidising properties (Annex IIIA 2.2.2) | | SYLLIT 400 SC is a aqueous suspension concentrate of a non oxidising a.s., hense results are transferable. | ppp is not considered as oxidising. | 2.7.2/01<br>Ryckel, B<br>(2004)<br>CHIMAC<br>R-FO20722/CH.3014/2003/206 |
| B.2.2.4 Flammability/ Auto--flammability (Annex IIIA 2.3) | EEC A15 | SYLLIT 400 SC is not expected to show a flash point up to 85ºC as it does not contain any volatile flammable component (flash point > 85ºC)<br><br>Auto-ignition: 430 $^{O}$C | ppp is not to be classified as “flammable” | 2.2.1/01<br>Treand, G.<br>(1997)<br>R-97-166-SEC |
| B.2.2.5 Acidity/ alkalinity/ pH (Annex IIIA 2.4.1) | | Not relevant as SYLLIT 400 SC has a pH of 6.1 | | |

| Property/ Study | Method | Results | Comments | Reference |
|---|---|---|---|---|
| | | | | |
| B.2.2.6 pH (1% in water)<br>(Annex IIIA 2.4.2) | CIPAC MT 75.2 | At 23ºC<br>Initial: 6.1<br>After accelerate storage: 6.1 | | 2.1/01<br>Uceda, L.;<br>Le Gren, I.<br>(1997)<br>R-97-99 |
| B.2.2.7 Kinematic viscosity<br>(Annex IIIA 2.5.1) | | SYLLIT 400 SC is not for ultra low volume use. | | |
| B.2.2.8 Viscosity<br>(Annex IIIA 2.5.2) | Internal Method<br>(rotating rheometer) | At 23°C: 50 mPa.s | | 2.1/01<br>Le Gren, I.<br>Uceda, L.<br>(1997)<br>R-97-99 |
| B.2.2.9 Surface tension<br>(Annex IIIA 2.5.3) | EEC A5<br>(ring method) | At 20 ºC:<br>1% w/w: 27 mN/m | ppp considered as surface active. | 2.1/01<br>Le Gren, I.<br>Uceda, L.<br>(1997)<br>R-97-99 |
| B.2.2.10 Relative density<br>(Annex IIIA 2.6.1) | EEC A3<br>(mechanical oscillator) | At 20ºC:<br>1.015 g/cm$^3$ | | 2.1/01<br>Uceda, L.;<br>Le Gren, I.<br>(1997)<br>R-97-99 |
| | | At 20ºC:<br>1.0138 g/cm$^3$ | | 2.7.2/01<br>Ryckel, B<br>(2004)<br>CHIMAC<br>R-FO20722/CH.3014/2003/206 |
| B.2.2.11 Bulk (tap) density<br>(Annex IIIA 2.6.2) | | Not applicable as SYLLIT 400 SC is neither a powder or granular preparation | | |
| B.2.2.12 Stability after storage for 14 days at 54ºC<br>(Annex IIIA 2.7.1) | CIPAC MT 46.1 | Initial dodine content – 405 g/L decreases by 2.1 % after accelerated storage stability and changes in persistent foaming, suspensability, spontaneity of dispersion, pourability, wet sieve test and pH were not | | 2.1/01<br>Le Gren, I.<br>Uceda, L. |

<table>
<tr><th>Property/ Study</th><th>Method</th><th>Results</th><th>Comments</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td>significant.<br>SYLLIT 400 SC was considered to be stable over a 14-day period at 54°C.</td><td></td><td>(1997)<br>R-97-99</td></tr>
<tr><td>B.2.2.13 Low temperature stability (Annex IIIA 2.7.2)</td><td>CIPAC MT 39.3</td><td>Appearance, suspensablity and wet sieve test were confirmed.<br>SYLLIT 400 SC was considered to be stable over a 7-day period at 0°C.</td><td></td><td>2.7.2/01<br>Ryckel, B<br>(2004)<br>CHIMAC<br>R-FO20722/CH.3014/2003/206</td></tr>
<tr><td>B.2.2.14 Shelf life at ambient temperature<br>(Annex IIIA 2.7.3)</td><td>GIFAP Monograph and respective CIPAC methods</td><td>Initial values are those obtained during study 97-99 on the same SYLLIT 400 SC batch (Initial dodine content – 405 g/L).<br><u>After 2 years at ambient temperature</u>:<br>Dodine content: 398 g/L (decreases 1.7%)<br>Appearance: Medium cream opaque liquid<br>pH (22ºC): 6.1<br>Persistent foam (after 1 minute):
<table>
<tr><td>1.75g/L</td><td>2 g/L</td><td>3.75g/L</td></tr>
<tr><td>38 mL</td><td>45 mL</td><td>56 mL</td></tr>
</table>
Suspensibility:
<table>
<tr><td>1.75g/L</td><td>3.75 g/L</td><td>10g/L</td></tr>
<tr><td>100 (% w/w)</td><td>100 (% w/w)</td><td>100 (% w/w)</td></tr>
</table>
Spontaneity dispersion: 100 (% w/w)<br>Pourability: R [1] = 1.5 (% w/w); r [2] = 0.1 % w/w<br>Wet sieve test: 0.2 (% w/w)<br>Packaging: No changes in weight, no visible deformation, no changes in general appearance (coloration, cap, soldered joint) of HDPE bottle.<br>SYLLIT 400 SC was considered to be stable for 2 years at ambient temperature.</td><td></td><td>2.7.3/01<br>Le Gren, I.<br>Uceda, L.<br>(1999)<br>R-97-99/2A</td></tr>
<tr><td>B.2.2.15 Wettability<br>(Annex IIIA 2.8.1)</td><td></td><td>Not applicable as SYLLIT 400 SC is not a solid preparation</td><td></td><td></td></tr>
</table>

[1] R: residue
[2] r: rinse residue

| Property/ Study | Method | Results | Comments | Reference |
|---|---|---|---|---|
| | | | | |
| B.2.2.16 Persistent foaming<br>(Annex IIIA 2.8.2) | CIPAC MT 47.2 | At 2 g/L and 20ºC<br>Initial: 64 mL after 1 minute<br>After accelerated storage: 34 mL after 1 minute | | 2.1/01<br>Le Gren, I.<br>Uceda, L.<br>(1997)<br>R-97-99 |
| | | Initial: 10 mL after 1 minute at 30ºC and concentration of 1.8 g dodine/L water | | 2.7.2/01<br>Ryckel, B<br>(2004)<br>CHIMAC<br>R-FO20722/CH.3014/2003/206 |
| B.2.2.17 Suspensibility and suspension stability<br>(Annex IIIA 2.8.3.1) | CIPAC MT 161 | At 10 g/L and 20ºC<br>Initial: 99 % (w/w)<br>After accelerated storage: 100 % (w/w) | | 2.1/01<br>Le Gren, I.<br>Uceda, L.<br>(1997)<br>R-97-99 |
| B.2.2.18 Spontaneity of dispersion<br>(Annex IIIA 2.8.3.2) | CIPAC MT 160 | At 50 ml/L CIPAC water D and 20ºC<br>Initial: 100 % (w/w)<br>After accelerated storage: 100 % (w/w) | | 2.1/01<br>Le Gren, I.<br>Uceda, L.<br>(1997)<br>R-97-99 |
| B.2.2.19 Dilution stability<br>(Annex IIIA 2.8.4) | | Not applicable as SYLLIT 400 SC is a suspension concentrate preparation | | |
| B.2.2.20 Dry sieve test<br>(Annex IIIA 2.8.5) | | Not applicable as SYLLIT 400 SC is not a solid preparation | | |
| B.2.2.21 Wet sieve test<br>(Annex IIIA 2.8.5) | CIPAC MT 59.3 | Initial: 0.2 % (w/w) on a 40 µm sieve<br>After accelerated storage: 0.2 % (w/w) on a 40 µm sieve | | 2.1/01<br>Le Gren, I.<br>Uceda, L.<br>(1997)<br>R-97-99 |

| Property/ Study | Method | Results | Comments | Reference |
|---|---|---|---|---|
| | | | | |
| B.2.2.22 Particle size distribution (Annex IIIA 2.8.6.1) | light diffraction particle size analyser | At ambient temperature:<br>$D_{90\%}$: 16.4 µm<br>$D_{50\%}$: 4.6 µm | | 2.1/01<br>Le Gren, I.<br>Uceda, L.<br>(1997)<br>R-97-99 |
| B.2.2.23 Dust content (Annex IIIA 2.8.6.2) | | Not applicable as SYLLIT 400 SC is not a solid preparation | | |
| B.2.2.24 Friability (Annex IIIA 2.8.6.3) | | Not applicable as SYLLIT 400 SC is not a solid preparation | | |
| B.2.2.25 Emulsifiability, emulsion stability and re--emulsifiability (Annex IIIA 2.8.7.1) | | Not applicable as SYLLIT 400 SC is not a emulsionable preparation | | |
| B.2.2.26 Stability of dilute emulsions (Annex IIIA 2.8.7.2) | | Not applicable as SYLLIT 400 SC is not a emulsionable preparation | | |
| B.2.2.27 Flowability (Annex IIIA 2.8.8.1) | | Not applicable as SYLLIT 400 SC is not a solid preparation | | |
| B.2.2.28 Pourability (Annex IIIA 2.8.8.2) | CIPAC MT 148 | Initial: 1.6 % (w/w) of residue and<br>0.1% (w/w) of rinse residue<br>After accelerated storage: 1.8 % (w/w) of residue and 0.1 % (w/w) of rinse residue. | | 2.1/01<br>Le Gren, I.<br>Uceda, L.<br>(1997)<br>R-97-99 |
| B.2.2.29 Dustability (Annex IIIA 2.8.8.3) | | Not applicable as SYLLIT 400 SC is a suspension concentrate preparation | | |
| B.2.2.30 Physical compatibility of tank mixes (Annex IIIA 2.9.1) | | Compatible with most pesticide except for those containing sulfur. | No tank mixes are listed on the product label. | 2.9.1<br>Lamproye, J.L.<br>(2002)<br>R-2002-10-28 |
| B.2.2.31 Chemical compatibility of tank mixes (Annex IIIA 2.9.2) | | | No tank mixes are listed on the product label. | |

| Property/ Study | Method | Results | Comments | Reference |
|---|---|---|---|---|
| | | | | |
| B.2.2.32 Adherence and distribution to seeds (Annex IIIA 2.10) | | Not applicable (not for seed treatment). | | |

### B.2.2.33 Evaluation and Assessment of physical and chemical properties of the plant protection product

SYLLIT 400 SC is a suspension concentrate (SC) containing 400 g/L of dodine. It is a white to medium cream opaque liquid with no characteristic odour. Its pH is within the range that naturally occurs in the ambient. The preparation is not explosive and after 2 years storage at ambient temperature it was found stable in its packaging. SYLLIT 400 SC is not expected to have a flash point up to 85ºC. Its technical properties indicate no particular problems when used as recommended.

Data submitted are considered acceptable.

## B.2.3 References relied on

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| **Annex IIA** | | | | | |
| IIA, 2.1.1/01 | Bascou, J.P. | 1998 | Dodine: physical characteristics<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 97-57- part A<br>GLP, Unpublished | Y | CAG |
| IIA, 2.3.1/01 | Bascou, J.P. | 1999 | Dodine: vapour pressure<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 97-57- part F<br>GLP, Unpublished | Y | CAG |
| IIA, 2.3.2/01 | Bascou, J.P. | 1999 | Dodine: Henry´s law constant<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. R&D/CRLD/AN/9916653<br>GLP, Unpublished | Y | CAG |
| IIA, 2.5.1/01 | Maestracci, M.P. | 1994 | Dodine – UV-visible characteristics<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 94-140<br>GLP, Unpublished | Y | CAG |
| IIA, 2.6/01 | Bascou, J.P. | 1999 | Dodine: water and solvent solubility<br>Notox, NL<br>Chimac-Agriphar, Report No. 450045<br>GLP, Unpublished | Y | CAG |
| IIA, 2.8/02 | Brekelmans, M.J.C. | 2006 | Determination of the partition coefficient (n-octanol/water) of dodine<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 450045 (2006)<br>GLP, Unpublished | Y | CAG |
| IIA, 2.9.1/01 | Daly, D.;<br>Kabler, K.<br>Williamson, K. | 1991 | Dodine: Hydrolysis of dodecylguanidine HCl as function of pH at 25ºC<br>ABC Laboratories, USA<br>Chimac-Agriphar, Report No. 38680<br>GLP, Unpublished | Y | CAG |
| IIA, 2.9.2/01 | Slagen, P.J. | 2004 | Photodegradation of dodine in water<br>Notox, NL<br>Chimac-Agriphar, Report No. 327061<br>GLP, Unpublished | Y | CAG |
| IIA, 2.9.4/01 | Bascou, J.P. | 1999 | Dodine : pH and dissociation constant<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 97-57-part B<br>GLP, Unpublished | Y | CAG |
| IIA, 2.10/01 | Slagen, P.J. | 2001 | Estimation of the degradation rate in air of dodine (Atkinson calculation)<br>Notox, NL<br>Chimac-Agriphar, Report No. 327072<br>GLP, Unpublished | Y | CAG |
| IIA, 2.11.1/01 | Phong, J.T.T. | 1998 | Determination of the explosion properties, flammability, ability for self heating of technical dodine<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 98-131<br>GLP, Unpublished | Y | CAG |

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| IIA, 2.11.1/02 | Krips, H.J. | 2001 | Determination of the flammability of technical dodine<br>Notox, NL<br>Chimac-Agriphar, Report No. 327083<br>GLP, Unpublished | Y | CAG |
| IIA, 2.15/01 | François, J.M. | 2000 | Dodine: determination of the oxidising properties<br>Rhône-Poulenc, France<br>Chimac-Agriphar, Report No. 00-330-SEC<br>GLP, Unpublished | Y | CAG |
| **Annex IIIA (SYLLIT 400 SC)** | | | | | |
| IIIA, 2.1/01 | Le Gren, I.<br>Uceda, L. | 1997 | EXP 10343A: Determination of physical-chemical characteristics and storage stability<br>Rhône-Poulenc Agro, France<br>Chimac-Agriphar, Report No. 97-99<br>GLP, Unpublished. | Y | CAG |
| IIIA, 2.2.1/01 | Treand, G. | 1997 | Determination of the flash point, the autoflamability and the explosion properties of EXP10343A<br>Rhône-Poulenc Industrie, France<br>Chimac-Agriphar, Report No. 97-166-SEC<br>GLP, Unpublished. | Y | CAG |
| IIIA, 2.7.2/01 | Ryckel de, B. | 2004 | Chemical and physico-chemical properties of Dodine 400 SC<br>Agricultural Research Center, Belgium<br>Chimac-Agriphar, Report No. FO20722/3014/2003/206<br>GLP, Unpublished. | Y | CAG |
| IIIA, 2.7.3/01 | Le Gren, I.<br>Uceda, L. | 1999 | EXP 10343A: Stability after 2 years storage at ambient temperature<br>Rhône-Poulenc Agro, France<br>Chimac-Agriphar, Report No. 97-99/2A<br>GLP, Unpublished. | Y | CAG |
| IIIA, 2.9.1 | Lamproye, J.L. | 2002 | Evaluation of physical compatability of tank-mixes with Syllit 400 SC<br>Chimac-Agriphar, Report No. 2002-10-28<br>No GLP, Unpublished. | Y | CAG |

## B.3 Data on application and further information

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

#### B.3.1.1 Function (Annex IIA 3.1)

Dodine is a fungicide.

#### B.3.1.2 Effects on harmful organisms systemic or not in plants (Annex IIA 3.2)

#### B.3.1.2.1 Effect (Annex IIA 3.2.1)

Foliar fungicide with protective and some curative action (Pesticide Manual, 11th ed., 1999).

Multisite inhibitor acting mainly on the fungus membranes.

#### B.3.1.2.2 Translocation in plants (Annex IIA 3.2.2)

Not systemic but translaminar action. Dodine penetrates partially in the leaves and stops the disease.

#### B.3.1.3 Field of use (Annex IIA 3.3)

Orchards

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

**Existing and intended uses**

Foliar spray in early or late season applications depending on crops. Mainly spring applications. In Europe, mainly used as a fruit fungicide against scab on apples and pears, leaf spots diseases on cherries, leaf curl on peaches. Also used on pecans (USA), ornamentals (poplar trees), vegetables (celery). Secondary bactericidal action. Also used in the EU and US as a biocide under its hydrochloride salt form (Dodine HCl).

**Details of harmful organisms against which protection is afforded**

Specifically effective on *Taphrina deformans*, *Venturia inaequalis* and *V. pyrina*, *Blumeriella jaapii*, *Xanthomonas* sp.

**Main crop/pest usages for dodine**

| Crops | Pest(s) |
|---|---|
| Apple trees | Scab (*Venturia inaequalis*) |
| Pear trees | Scab (*Venturia pyrina*) |
| Peach trees | Peach Leaf curl (*Taphrina deformans*) |
| Cherry trees | Leaf spot (*Blumeriella jaapii = Coccomyces hiemalis*) |

## Table B.3-1 – Authorized uses of the active substance Dodine in EU member states (Source: notifier)

| COUNTRY | Authorized uses (crops, harmful organisms, rates and number of application, timings, growth stage) |
|---|---|
| Austria | Tradename : Syllit 450 SC (Dodine **450 g/l** SC, Reg.nr : 971)<br>**Apple/Pear** : Scab (Venturia sp.), 0.14% before flowering (140 ml/hl) and 0.1% after flowering (100 ml/hl) in multiple applications from the bud opening till 14 days before harvest.<br>**Cherry** : Leaf spot (Blumeriella jaapii), 0.1% (100 ml/hl) in multiple applications from petal fall til 2 weeks before harvest. Post-harvest applications possible on infected trees. |
| Belgium | Tradename : Syllit 400 SC (Dodine **400 g/l** SC, Reg.nr : 8418/B)<br>**Apple/Pear** : Scab (Venturia sp.), 0.15% before or after flowering (150 ml/hl or 2.25L/ha soil or 1.32 L/ha foliage hedge) in multiple applications from the bud opening till 28 days before harvest.<br>**Sweet or sour cherry** : Leaf spot (Blumeriella jaapii – Cylindrosporium padi), 0.1% (100 ml/hl) in multiple applications (2 to 4 with 10 days interval) from petal fall til 4 weeks before harvest. 1-2 post-harvest applications possible on infected trees. |
| Czech Republik | Tradename: Syllit 65% WP (Dodine **65%** WP, reg.nr: 3221-6)<br>**Apple**: Scab (Venturia sp.), 0.75-1.5 kg/ha from bud burst until 21 days pre-harvest with 7-10 days intervals.<br>**Peach**: against leaf curl (*Taphrina deformans*) at 1.5-3.0 kg/ha.<br>**Cherry and sour cherry**: Leaf spot (Blumeriella jaapii) at 0.75-1.5 kg/ha. PHI: 21 days.<br>**Apricots:** against leaf browning at 1.0-1.5 kg/ha. PHI: 21 days<br>**Roses:** against black spot: 1.0-1.5 kg/ha. |
| Denmark | not registered |
| Finland | not registered |
| France | Tradename : Syllit 400 SC (Dodine **400 g/l** SC, Reg.nr : 9800392)<br>**Apple** : Scab (Venturia sp.), 0.17 % (170 ml/hl) in multiple applications from the bud opening till 28 days before harvest.<br>**Peach** : Leaf curl (Taphrina deformans), 0.225% (225 ml/hl) in multiple applications from bud opening til petal fall at the latest 75 days before harvest. |
| Germany | not registered (previously registered before 1990 against Apple/pear scab). New application for registration sent in 2003. Registration expected in 2005. |
| Greece | Tradename : Syllit 65 WP (Dodine **65%** WP, Reg.nr : 6328)<br>**Apple :** Scab (Venturia sp.), 60 g/hl (preventive) or 100 g/hl (curative). 2 applications maximum from the bud opening. PHI: 15 days<br>**Pears / Medlars :** Scab (Venturia sp.), 90 g/hl (preventive) or 120 g/hl (curative). 2 app. max from the bud opening. PHI: 15 days<br>**Cherry and sour cherry** : Leaf spot (Blumeriella jaapii – Cylindrosporium padi), Gnomonia and Erythrostoma diseases, 80-100 g/hl). One spraying at appearance of symptoms. PHI: 15 days<br>**Olives** : a) against *Spitocata oleagina* at 100 g/hl. 1 application before start of autumn rains and the second by the end of winter before trimming. B) against *Gleosporium olivarum* at 100 g/hl, max. 2 sprays just before the change of color of olives |
| Hungary | Tradename: Efuzin 500 FW (Dodine **500 g/l** SC, reg.nr: 25226)<br>**Apple/Pear**: Scab (Venturia sp.), 0.8-1.3L/ha from bud burst until 10 days pre-harvest with 10-14 days intervals.<br>**Peach** : against leaf curl (*Taphrina deformans*) at 2-2.6 l/ha until 10 days pre-harvets with 10-14 days intervals. One autumn application (post harvest) permitted.<br>**Cherry and sour cherry**: Leaf spot (Blumeriella jaapii) at 0.8-1.0 L/ha. PHI: 10 days. 1-2 treatment after harvest also possible. |

| COUNTRY | Authorized uses (crops, harmful organisms, rates and number of application, timings, growth stage) |
|---|---|
| Ireland | Tradename : Syllit **400g/l** SC (Dodine **400 g/l** SC, Reg.nr: PM01797)<br>**Apple/Pear**: Scab (Venturia sp.), 1.7-2.5L/ha from bud burst until 28 days pre-harvest. 5 applications with 7-10 days intervals.<br>**Blackcurrant, gooseberries, roses:** Leaf spot: 75 ml/hl in multiple applications from early grape stage at 2-3 weeks interval. 1 post-harvest application after picking. |
| Italy | Tradename : Syllit Flo (Dodine **400 g/l** SC, Reg.nr : 7369)<br>**Apple/Pear / Medlars :** Scab (*Venturia sp.*), 80-100 ml/hl (preventive) or 120-150 ml/hl (curative). Multiple applications from the bud opening til 10 days before harvest.<br>**Cherry** : Leaf spot (*Blumeriella jaapii – Cylindrosporium padi*), 100 ml/hl). Multiple applications til 10 days before harvest.<br>**Apricots** : against *Corineum* and *Monilia sp.* : 150-200 ml/hl (preventive). Multiple applications til 10 days before harvest.<br>**Peach** : against *Corineum* and leaf curl (*Taphrina deformans*) at 150-200 ml/hl in autumn/winter and 100 ml/hl in spring/summer, against *Monilia* during flowering till petal fall at 100-150 ml/hl and before harvest at 150-200 ml/hl (PHI 10 days), against bacterial leaf spot (*Xanthomonas campestris pv. Pruni*) at 200 ml/hl.<br>**Olives** : 100-180 ml/hl<br>**Poplars** : against *Marssonina brunea* at 80-100 ml/hl (preventive) or 120-150 ml/hl (curative)<br>**Onions, celery, Spinach, carrot, tomato, cucurbits** : against *Peronospora sp.*, *Septoria sp.*, *Ramularia* and *Cercospora* at 100 (preventive) or 150-200 (curative) |
| Luxemburg | Tradename: Syllit (Dodine **400 g/l** SC, reg. nr : L01568-062)<br>Uses: see Belgium, same uses. |
| Netherlands | Tradename : Syllit Flow 450 SC (Dodine **450 g/l** SC, Reg.nr : 11647)<br>**Apple/Pear** : Scab (Venturia sp.), 0.13% (130 ml/hl, preventive at 5-7 days intervals or curative at 48h) before or after flowering in multiple applications from the bud opening till 28 days before harvest. Possible use in fruittree nurseries against scab.<br>**Cherry** : Leaf spot (Blumeriella jaapii – Cylindrosporium padi), 0.085% (85 ml/hl) in multiple applications after flowering (2 to 4 with 7-14 days interval) til 4 weeks before harvest.<br>**Ornementals** (Prunus) in nurseries : against leafspot (Bumeriella jaapii) at 0.13% (130 ml/hl) from end of may with 7 to 14 days interval. |
| Poland | Tradename: Syllit 65% WP (Dodine **65%** WP, reg.nr: 48/2002)<br>**Apple/Pear**: Scab (Venturia sp.), 1-2.25 kg/ha from bud burst with 7-10 days intervals.<br>**Peach**: against leaf curl (*Taphrina deformans*) at 7.5 kg/ha. Application at bud swelling.<br>**Cherry and sour cherry**: Leaf spot (Blumeriella jaapii) at 1.5 kg/ha directly after blooming. Repeat 2-3 times with 10-14 days intervals. Latest treatment one month after blooming.<br>**Plums:** at 7.5kg/ha before bud opening or 1.5kg/ha before blooming |
| Portugal | Tradename : Syllit 65 WP (reg nr 2232) : Dodine **65%** WP<br>**Apples/pear/Meddlars**: against Scab (*Venturia sp.*), 0.135% (135 g/hl, preventive at 10-12 days intervals) in multiple applications from the bud opening till 15 days before harvest.<br>**Cherry** : against Anthracnose, 0.08-0.1% (80-100 g/hl, preventive at 10-15 days intervals) in multiple applications<br>**Celery** : against *Septoria* diseases, 0.1 – 0.13% (100-130 g/hl) |
| Slovakia | Tradename: Syllit 65 WP (Dodine **65%** WP, reg.nr. 3221)<br>Uses: see Czech Republik. Same label. |

## Effects achieved

Disease suppression (Fungicide) by preventive and curative (up to 48h) action

The disease/ crop usage intended for dodine is described in Table B.3-2.

## Table B.3-2 – Summary of intended uses

| Crop and/ or situation | EU Area | Product name | F G or I[i] | Pests or group of pests controlled | Formulation | | Application | | | | Application rate per treatment | | | PHI[ii] (days) | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | type | conc. of a.s. | method kind | growth stage & season | number min max | min. interval between applications (days) | kg a.s./hl min max | Water L/ha min max | kg a.s./ha min max | | |
| Apple/pear | EU (North - South) | Syllit 400 SC | F | Scab (*Venturia inaequalis / Venturia piri*) | SC | 400 g/l | Foliar spray | from bud opening (BBCH 01) til 28 days before harvest (BBCH 74) | 5 max | repeat after 7-10 days | 0.045 - 0.18 | 500 - 1500L | 0.68-0.90 | 28 days | 1.7 – 2.25 L Syllit/ha |
| Peach | EU-South | Syllit 400 SC | F | Peach Leaf curl (*Taphrina deformans*) | SC | 400 g/l | Foliar spray | from bud swelling (BBCH 01) til petal fall (BBCH 69) | 5 max | repeat after 7-10 days | 0.06 - 0.18 | 500 - 1500L | 0.90 | 60 days | 2.25 L Syllit/ha |
| Cherry | EU (North - South) | Syllit 400 SC | F | Cherry leaf spot (*Blumeriella jaapii = Coccomyces hiemalis)* | SC | 400 g/l | Foliar spray | from flower opening (BBCH 60) til 2 weeks before harvest (BBCH 79) AND immediately after harvest | 3 max pre-harvest+ 2 post harvest | repeat after 7-10 days | 0.05 - 0.16 | 500 - 1500L | 0.8 | 14 days | 2 L Syllit/ha |

[i] Outdoor or field use (F), glasshouse application (G) or indoor application (I)

[ii] PHI – minimum pre-harvest interval

### B.3.1.5 Mode of action (Annex IIA 3.5)

Dodine is the only fungicide from the guanidine family with a unique mode of action. However, the mode of action is not very well understood. It seems that it is linked to the surfactant properties (soap) of the molecule dodine. Interactions with the carboxyle and phosphate groups from the fungus membrane are suspected. An intra-cellular action is also suspected but the site of action is unknown.

No active metabolites or degradation products have be found in the fruit metabolism studies.

### B.3.1.6 Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies (Annex IIA 3.6)

Dodine is an old active substance (1957). Exclusive uses of dodine (up to 15 applications/year) in some apple orchards in the USA in the 80's has proved to be a bad application strategy and high level of resistance appeared, especially with apple scab (*Venturia ineaqualis*). Many researches have been done afterwards and it seems irreversible.

Up to now, no sign of resistance of apple scab to dodine have been reported elsewhere in the world than in the USA. Some rumours have been heard in Poland or in Italy, where dodine is used abundantly, but this has not been confirmed.

Since dodine is used since many years now, we can conclude that resistance is possible (cf USA) but does not develop quickly (cf rest of the world). Chimac-Agriphar SA recommends strongly including dodine in a spraying program using different families of fungicides alternatively. This will preserve the best efficacy for dodine.

It should be noted that resistance to dodine has never been reported for any other diseases but only for apple scab.

## B.3.2 Data on application relevant to the plant protection product (Annex IIIA 3)

### B.3.2.1 Field of use envisaged e.g. field, protected crops, storage of plant products, home gardening (Annex IIIA 3.1)

Syllit$^{R}$ 400 SC is to be used in Agriculture: for the control of fungal diseases, especially in pome fruits and stone fruits like apple/pear, cherry, peach, plums.

### B.3.2.3 Details of intended use (Annex IIIA 3.3); Application rate (Annex IIIA 3.4); Concentration of active substance in diluted spray (Annex IIIA 3.5); Number and timing of applications and duration of protection (Annex IIIA 3.7)

**Details of intended use**

Syllit$^{R}$ 400 SC is intended for the crops and diseases referred in Table B.3-2, presented in B.3.1.4.

| Crop | Crop code | Disease | Disease code |
|---|---|---|---|
| Apple | MABSD | Apple Scab (*Venturia inaequalis*) | VENTIN |
| Pear | PYUCO | Pear Scab (*Venturia pyrina*) | VENPYR |
| Cherry | PRNKI | *Blumeriella jaapii = Coccomyces hiemalis* | BLUMJA |
| Peach | PRNPS | *Taphrina deformans* | TAPHDE |

**Rate of application per unit treated, in terms of g or kg of preparation and active substance**

Apple/Pear : 1.7 – 2.25 L Syllit 400 SC /ha = 680 - 900 g as/ha

Cherry : 2 L Syllit 400 SC /ha = 800 g as/ha

Peach : 2.25 L Syllit 400 SC /ha = 900 g as/ha

**Concentration of active substance in material used (diluted spray) in g/L**

0.5 g/L min (1.7 L Syllit 400 SC = 680 g as. in 1500 L water /ha)

1.8 g/L max (2.25 L Syllit 400 SC = 900 g as. in 500 L water /ha)

**Maximum number of applications and their timing**

| | Apples/Pear | Cherry | Peach |
|---|---|---|---|
| First application | Can be applied the whole season from very first stage in spring (BBCH 52-53) onwards | Petal fall | In autumn (80% leaf fall) |
| Additional applications | With 7-10 days intervals (max. 5 applications/year for apples and 4 for pear) | 2nd: 2 weeks after 1st application<br>3rd: 2 weeks before harvest<br>4rd: directly after harvest | 2nd, 3rd, 4th : in spring, from bud opening with 7-10 days intervals |
| Last applications | 28 days before harvest at the latest | 5th: end of summer (max. 5 applications /year) | 5th : petal fall<br>(max 5 applic. /year) |

**For each application, development stages of the harmful organism concerned**

As a preventive treatment before appearance of disease or as a curative treatment within 48h after infestation.

**Duration of protection given by each application**

7 – 10 days

**Duration of protection afforded by the maximum number of applications**

21 to 50 days depending on crops and disease pressure

### B.3.2.4 Method of application (Annex IIIA 3.6)

Spray application with standard fruit tree sprayers, water volume 500 L/ha up to 1500 L/ha.

### B.3.2.5 Necessary waiting periods or other precautions to avoid phytotoxic effects on succeeding crops (Annex IIIA 3.8)

No waiting periods and no limitations on succeeding crops.

### B.3.2.6 Proposed instructions for use (Annex IIIA 3.9)

See labels provided in document C of the dossier.

## B.3.3 Summary of data on application

Dodine is a foliar fungicide with protective and some curative action. Dodine is the only fungicide from the guanidine family with a unique mode of action. However, the mode of action is not very well understood. It seems that it is linked to the surfactant properties (soap) of the molecule dodine, being a multisite inhibitor acting mainly on the fungus membranes.Interactions with the carboxyle and phosphate groups from the fungus membrane are suspected. An intra-cellular action is also suspected but the site of action is unknown.

It is not systemic but has translaminar action and penetrates partially in the leaves and stops the disease.

It is applied by foliar spray in early or late season applications depending on crops, mainly in spring applications. In Europe, it is authorised mainly as a fruit fungicide against scab on apples and pears, leaf spots diseases on cherries, leaf curl on peaches. It is also used on pecans (USA), ornamentals (poplar trees), vegetables (celery). It is also used in the EU and US as a biocide under its hydrochloride salt form (Dodine HCl).

Dodine is specifically effective on *Taphrina deformans*, *Venturia inaequalis* and *V. pyrina*, *Blumeriella jaapii*, *Xanthomonas* sp.

Syllit$^{R}$ 400 SC is to be used in Agriculture: for the control of fungal diseases, especially in pome fruits and stone fruits like apple/pear, cherry, peach, plums and applied with standard fruit tree sprayers.

## B.3.4 Further information on the active substance (Annex IIA 3.7 to 3.9)

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

A Material Safety Data Sheet for the technical active substance was provided.

**Safe handling**

Do not get in eyes or on clothing. Avoid breathing vapour or mist. Wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet. Remove cloathing immediately if pesticide gets inside. Then wash thoroughly and put on clean cloathing. Do not apply directly to water, to areas where surface water is present, or to interstitial areas below the mean high water mark. Do not contaminate water when disposing of equipment wash waters. Do not contaminate water, foodstuffs, or feed by storage or disposal.

**Storage**

Keep locked up. Store in dry, cool, well-ventilated area. Keep container closed when not in use.

**Transport**

Ensure that vehicle´s driver is aware of the potential hazards of the load and knows what to do in the event of an accident or an emergency.

**Land**

| | |
|---|---|
| Shipping name: | Environmentally hazardous substance, solid, N.O.S. (dodine (ISO)), 9, III |
| UN No.: | 3077 |
| ADR/RID Class: | 9 |
| ADR/RID Packing group: | III |
| Hazard identification: | 90 |

**Sea**

| | |
|---|---|
| Proper shipping name: | Environmentally hazardous substance, solid, N.O.S. (dodine (ISO)), 9, III. Marine pollutant |
| UN No.: | 3077 |
| IMO-IMDG Class: | 9 |
| Packing group: | III |
| Emergency Schedules: | None |

**Air**

| | |
|---|---|
| Proper shipping name: | Environmentally hazardous substance, solid, N.O.S. (dodine (ISO)), 9, III |
| UN/ID Number: | 3077 |
| IATA Class: | 9 |
| IATA Packing group: | III |

**Fire**

Suitable extinguishing media:
Carbon dioxide, dry chemical powder, water spray or foam. A high pressure water jet is deemed not suitable.
Special procedures:
special air extraction essential; dike fire control water for later disposal, prevent all discharge into the environment.

Combustion gases:
Fire may produce irritating or toxic vapours, mists or products of combustion (CO, $CO_2$, $NO_x$, HCl, $Cl_2$, organochlorides).

Firefighters and others that may be exposed should wear full protective clothing and self-contained breathing apparatus.

### B.3.4.2 Procedures for destruction or decontamination (Annex IIA 3.8)

#### B.3.4.2.1 Controlled incineration (Annex IIA 3.8.1)

Dodine does not have a halogen content of more than 60%, a test of the pyrolytic behaviour is not required. The product and its container have to be disposed of at hazardous or special waste collection points / stations according to the local legislation.

#### B.3.4.2.2 Others (Annex IIA 3.8.2)

No other methods are proposed for the disposal of dodine.

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

**Personal precautions:**

Inhalation: Assure fresh air breathing. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. If you feel unwell, seek medical advice.

Skin contact: For even minor contact, immediately remove contaminated clothing/wash skin thoroughly with mild soap / water. Seek medical attention if ill effect or irritation develops. Wash clothing before re-using.

Eye contact: Rinse immediately with plenty of water. Retract eyelids often. Obtain medical attention if pain, blinking, tears or redness persists.

Ingestion: Rinse mouth. Do not induce vomiting. Seek medical advice (show the label where possible.

**Environmental precautions:**

Notify authorities if product enters sewers or public waters. Prevent entry to sewers and public waters. May contaminate water supplies.
Methods for cleaning up

Spill should be handled by trained cleaning personnel propely equipped with respiratory and eye protection. Use adequate ventilation to keep vapour concentration below applicable standard.
Contain and collect as any solid. Use appropriate container to avoid environmental contamination.

### B.3.5 Further information on the plant protection product (Annex IIIA 4)

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

#### B.3.5.1.1 Description of the packaging (Annex IIIA 4.1.1)

**Description and specification of the packaging and materials used in packaging, size, capacity, size of openings, types of closures and seals – 1L bottles; 5L containers**

Unspecified

CAG (2002)

(4.1.1/01; 4.1.2/02)

**Table B.3-3 - Description of the packaging of SYLLIT 400 SC**

| | | |
|---|---|---|
| 1 litre bottle | Material: | HDPE, code B110 1L container |
| | Shape/size: | Round bottle/241 mm height × 88 mm width |
| | Opening: | 39.5 mm diameter |
| | Closure: | Screw cap with additional induction sealing disk |
| 5 litre bottle | Material: | HDPE 5L container |
| | Shape/size: | Can/305 mm height × 193*142 mm width |
| | Opening: | 63 mm diameter |
| | Closure: | Screw cap with additional induction sealing disk. |

### B.3.5.1.2 Suitability (Annex IIIA 4.1.2)

These packagings were satisfactory tested (UN, IMDG, ICAO-TI, ADR, RID) for strength, leakproofness, resistance to normal transport and handling.

UN registration numbers: 1L bottle (12 × 1L): **u** 4G/Y19/S/--

**n** D/BAM 5391 – HOW

5L container (4 × 5L) **u** 4G/Y27/S/--

**n** B/AIRP-938506

### B.3.5.1.3 Resistance to its contents (Annex IIIA 4.1.3)

**CAG statement:**

The material proposed for use is known from experience to be very resistant to influence of chemicals. Moreover, SYLLIT 400 SC is a water based formulation and is not expected to react with the packaging material.

**Reference:**

EXP 10343A: Stability after 2 years storage at ambient temperature

Le Gren, I.; Uceda L. (1999)

Report no. 97-99/2A (2.7.3/01)

Findings: In a two-year storage stability study the packaging material was found unchanged and proved its appropriateness.

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

Rinsing with water and detergent.

The product can be removed from surfaces with water. The addition of detergent enhances the cleaning process.

### B.3.5.3 Re-entry periods, necessary waiting periods or other precautions to protect man, livestock and the environment (Annex IIIA 4.3)

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

A Material Safety Data Sheet for SYLLIT 400 SC was provided.

**Handling and storage**

Handling:

Ensure prompt removal from eyes, skin and clothing. Wash hands and other exposed areas with mild soap and water before eat, drink or smoke and when leaving work.

Storage:

Provide local exhaust or general room ventilation to minimize dust and/or vapour concentrations. Store in dry, cool area. Keep container closed when not in use. Keep container in a cool, well-ventilated area. Do not store below 0ºC. Do not contaminate water, foodstuffs, or feed by storage or

disposal. Keep away from food, drink and animal feeding stuffs. Keep away from heat. Keep away from sources of ignition.

**Transport**

| | |
|---|---|
| Land | |
| Shipping name : | UN 3082 ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (dodine (ISO)), 9, III |
| H.I. no.: | 90 |
| ADR/RID Class: | 9 |
| ADR/RID Packing group: | III |
| Sea | |
| Shipping name : | UN 3082 ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (dodine (ISO)), 9, III |
| IMO- IMDG Class: | 9 |
| IMO Packing group: | III |
| IMDG-Marine pollution: | No |
| Air | |
| Shipping name : | UN 3082 ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (dodine (ISO)), 9, III |
| IATA Class: | 9 |
| IATA Packing group: | III |

**Fire**

Suitable extinguishing media: In the case of a small fire extinguish using dry chemical powder.
In case of a large fire extinguish using water spray, fog or foam. Do not use water jet.
Fight fire in early stages if safe to do so. Wear respiratory protection. SYLLIT 400 SC is not subject to regulations on flammable liquids.
Vapours, mists or products like $CO_2$, CO, $NO_x$ may be produced upon combustion.

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

**Personal precautions**

Inhalation: Assure freash air breathing.

If breathing is difficult, give oxygen.

If not breathing, give artificial respiration.

Obtain medical attention if breathing difficulty persists.

Skin contact: Remove affected clothing and wash all exposed skin area with mild soap and water, followed by warm water rinse. Seek medical attention if irration develops.

Eye contact: Immediately rinse with clean water for 10-15 minutes. Retract eyelids often. Seek medical advice.

Ingestion: Do not induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. If swallowed, rinse mouth with water (only if person is conscious) and seek medical advice immediately and show the container or label of product.

**Environmental precautions**

Prevent entry to sewers and public waters. Notify Authorities if liquid enters sewers and public waters.

**Methods for cleaning up**

Clean up any spills as soon as possible, using an absorbent material to collect it. Use suitable disposable containers.

**Disposal**

Package product wastes. Close and label waste receptacles and, likewise any uncleaned empty containers. Dispose of them at a suitable waste incineration plant in accordance with the official regulations. Where large quantities are concerned, consult the supplier.

### B.3.5.6 Procedures for destruction or decontamination (Annex IIIA 4.6)

#### B.3.5.6.1 Possibility of neutralisation (Annex IIIA 4.6.1)

A neutralisation procedure cannot be proposed.

#### B.3.5.6.2 Controlled incineration (Annex IIIA 4.6.2)

Not applicable, as the product does not contain organic halogens.

Package product wastes. Close and label waste receptacles and, likewise any uncleaned empty containers. Dispose of them at a suitable waste incineration plant in accordance with the official regulations. Where large quantities are concerned, consult the supplier.

#### B.3.5.6.3 Others (Annex IIIA 4.6.3)

No other methods are currently available.

## B.3.6 References relied on

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| **Annex IIA** | | | | | |
| IIA, 3.7 | Unspecified | 2004 | Material safety data sheet: Dodine technical | N | CAG |
| **Annex IIIA (SYLLIT 400 SC)** | | | | | |
| IIIA, 4.1.1/01 | Unspecified | 2002 | Description and specification of the packaging and materials used in packaging, size, capacity, size of openings, types of closures and seals – 1L bottles<br>Chimac-Agriphar | N | CAG |
| IIIA, 4.1.1/02 | Unspecified | 2002 | Description and specification of the packaging and materials used in packaging, size, capacity, size of openings, types of closures and seals –5L containers<br>Chimac-Agriphar | N | CAG |
| IIIA, 4.1.3 (2.7.3/01) | Le Gren, I.; Uceda L. | 1999 | EXP 10343A: Stability after 2 years storage at ambient temperature<br>Chimac-Agriphar, Report no. 97-99/2A<br>GLP, Unpublished. | Y | CAG |
| IIIA, 4.4 | Unspecified | 2004 | Material safety data sheet: SYLLIT 400 SC | N | CAG |

## B.4 Proposals for classification and labelling

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

| | | |
|---|---|---|
| Hazard symbols: | T | Toxic |
| Risk phrases: | R22 | Harmful if swallowed. |
| | R23 | Toxic by inhalation. |
| | R38 | Irritating to skin. |
| | R41 | Risk of serious damage to eyes. |
| | R50/53 | Very toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment. |
| Safety phrases: | S1/2 | Keep locked up and out of the reach of children. |
| | S4 | Keep away from living quarters. |
| | S13 | Keep away from food, drink and animal feedingstuffs. |
| | S25 | Avoid contact with eyes. |
| | S26 | In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. |
| | S37/39 | Wear suitable gloves and eye/face protection. |
| | S38 | In case of insufficient ventilation, wear suitable respiratory equipment. |
| | S45 | In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). |
| | S60 | This material and its container must be disposed of as hazardous waste. |
| | S61 | Avoid release to the environment. Refer to special instructions/Safety Data Sheets. |
| | S63 | In case of accident by inhalation: remove casualty to fresh air and keep at rest. |
| | S64 | If swallowed, rinse mouth with water (only if the person is conscious). |

<u>Background for the proposed classification</u>

*R22:*

See point B.6.2.1: The oral $LD_{50}$ of dodine technical in rats was found to be 851 mg/kg bw with 95% confidence limits of 658 to 1100 mg/kg bw for males and females combined. There were no significant differences between male and female.

*R23:*

See point B.6.2.3: The estimated $LC_{50}$ (4-hour) for dodine technical administered nose-only as a particulate aerosol was 0.45 mg/l air with 95% confidence limits of 0.34 to 0.57 mg/l air.

*R38:*

See point B.6.2.4: Considering the average scores for the 24, 48 and 72 hours, obtained with dodine technical for each three rabbits in the study, 2/3 animals showed positive irritating effects (mean scores of 2/1.3/2 for erythema). Although erythema was not completely reversible at the end of the 14-day observation period, it could be observed that scores tended to decrease with time and it was found reasonable to expect that, at the end of a longer period of observation, irritation scores would be completely reversible.

*R41:*

See point B.6.2.5: only one animal was investigated. This screening rabbit did not vocalize upon instillation of dodine technical. The test material induced severe corneal (score 4), iridal (score 2) and conjunctival irritation (score 2.7 for redness and 4 for chemosis) that persisted through study termination, day 7. Other ocular findings were purulent discharge from the 24-hour observation onward, haemorrhage at the 4- and 7-day observations, and neovascularization at the 7-day observation. Observation with fluorescein at the 72-hour and 7-day showed a 25% of cornea retaining stain. Due to the severe ocular damage observed, the study was terminated on day 7 and no further animals were used to evaluate the ocular irritation potential of the test material.

## B.4.2 Proposals for the classification and labelling of preparations

| | | |
|---|---|---|
| Hazard symbol: | T | Toxic |
| Risk phrases: | R23 | Toxic by inhalation. |
| | R34 | Causes burns. |
| | R50/53 | Very toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment. |
| Safety phrases: | S1/2 | Keep locked up and out of the reach of children. |
| | S4 | Keep away from living quarters. |
| | S13 | Keep away from food, drink and animal feedingstuffs. |
| | S23 | Do not breathe spray. |
| | S25 | Avoid contact with eyes. |
| | S26 | In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. |
| | S28 | After contact with skin, wash immediately with plenty of … (*to be specified by the manufacturer*). |
| | S36/37/39 | Wear suitable protective clothing, gloves and eye/face protection. |
| | S38 | In case of insufficient ventilation, wear suitable respiratory equipment. |

| | |
|---|---|
| S45 | In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). |
| S60 | This material and its container must be disposed of as hazardous waste. |
| S61 | Avoid release to the environment. Refer to special instructions/Safety Data Sheets. |
| S63 | In case of accident by inhalation: remove casualty to fresh air and keep at rest. |
| S64 | If swallowed, rinse mouth with water (only if the person is conscious). |

Background for the proposed classification

*R23:*

See point B.6.11.3: The acute inhalation median lethal concentration ($LC_{50}$) and 95% confidence limits of the test material EXP 10343, administered nose-only for four hours to the Sprague-Dawley strain rat, was calculated to be 0.65 (0.57-0.75) mg/l air in males and females combined.

*R34:*

See point B.6.11.4: A 4-hour dermal exposure of 3 NZW rabbits resulted in well-defined erythema at all treated skin sites one hour after patch removal and at the 24, 48 and 72-hour observations. Loss of skin elasticity was also noted at one treated skin site at the 72-hour observation. Crust formation was noted at all treated skin sites seven days after treatment.

Moderate to severe oedema was noted at all treated skin sites one and 24 hours after patch removal, with slight to severe oedema at the 48-hour observation and very slight to moderate oedema at the 72-hour observation.

EXP 10343 (Syllit R) was shown to be also with risk of serious damage to the eyes (R41) in one animal as described in point B.6.11.5.

## B.4.3 References relied on

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| **Annex IIA** | | | | | |
| IIA, 5.2.1/01 | Kern T.G. | 1999 | Acute oral toxicity study of dodine technical material in albino rats<br>WIL Research Laboratories, USA<br>Report no. WIL-21130<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.2.2 | Kern T.G. | 1999 | Acute dermal toxicity study of dodine technical material in albino rats<br>WIL Research Laboratories, USA<br>Report no. WIL-21131<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.2.3 | Kenny T., Fensome Z. | 1999 | Dodine technical : acute (four hour) inhalation study in rats<br>Huntingdon Life Sciences, UK<br>Report no. RNP 605/992051<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.2.4 | Kern T.G. | 1999 | Acute dermal irritation study of dodine technical material in albino rabbits<br>WIL Research Laboratories, USA<br>Report no. WIL-21132<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.2.5 | Kern T.G. | 1999 | Acute eye irritation study of dodine technical material in Albino rabbits<br>WIL Research Laboratories, USA<br>Report no. WIL-21133<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.2.6 | Manciaux X. | 1999 | Dodine technical : skin sensitization test in guinea-pigs (Maximization method of Magnusson, B. and Kligman, A.M.)<br>Centre International de Toxicologie, France<br>Report no. 17473 TSG<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.3.1/01 | Batham P. | 1994a | A 4 week oral (gavage) toxicity study of dodecylguanidine acetate (dodine) in the albino rat<br>Bio-Research Laboratories, Canada<br>Report no. 84568<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.3.1/02 | Batham P. | 1994b | A 4 week oral (diet) toxicity study of dodecylguanidine acetate (dodine) in the albino rat<br>Bio-Research Laboratories, Canada<br>Report no. 84569<br>GLP<br>Unpublished | Yes | CAG |

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| IIA, 5.3.1/03 | Dange M. | 1997 | Dodecylguanidine acetate (dodine) - 28-day toxicity study in the rat by dietary administration<br>Rhône-Poulenc Agrochimie, France<br>Report no. SA94448<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.3.1/04 | Dange M. | 1996 | Dodecylguanidine acetate (dodine) - Assessment of gut motility following dietary administration of dodine in the rat<br>Rhône-Poulenc Agrochimie, France<br>Report no. SA94453<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.3.2/01 | Lina B.A.R., Til H.P., *et al.* | 1984 | Sub-chronic (90-day) oral toxicity study with dodine in rats<br>TNO, Netherlands<br>Report no. V83.130/220623<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.3.2/02 | Kangas L. | 1994 | A 13-week dietary toxicity study of Dodecylguanidine acetate (dodine) in the albino mouse<br>Bio-Research Laboratories, Canada<br>Report no. 84582<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.3.2/03 | Trutter J.A. | 1996 | 52-Week toxicity study in dogs with dodine<br>Corning Hazleton, USA<br>Report no. CHV 656-192<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.3.3/01 | Kern T.G. | 1999 | A 28-day dermal toxicity study of dodine technical material in rats<br>WIL Research Laboratories, USA<br>Report no. WIL-21140<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.4.1/01 | Willems M.I. | 1981 | Evaluation of dodine tech 95% for mutagenic activity in the Ames test<br>TNO, Netherlands<br>Report no. V81.102/210064-7<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.4.1/02 | Verspeek-Rip C.M. | 2003 | Evaluation of the mutagenic activity of dodine technical in the *Escherichia Coli* reverse mutation assay (with independent repeat)<br>Notox, Netherlands<br>Report no. 394482<br>GLP<br>Unpublished | Yes | CAG |

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| IIA, 5.4.1/03 | Wilmer J.W.G.M. | 1985 | Chromosome analysis of cultured human lymphocytes treated *in vitro* with dodine<br>TNO, Netherlands<br>Report no. V85.164/250209<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.4.1/04 | Davis P.B. | 1985 | An investigation into the possible induction of point mutation at the HGPRT locus of Chinese hamster ovary cells by dodine<br>TNO, Netherlands<br>Report no. R85/105<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.4.2/02 | Hemalatha Murli | 1992 | Mutagenicity test on dodecylguanidine acetate technical *in vivo* mammalian micronucleus assay<br>Hazleton Washington, USA<br>Report no. 14710-0-455<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.5/01 | Dange M. | 1998 | Chronic toxicity and carcinogenicity study of dodecylguanidine acetate (dodine) in the Sprague-Dawley rat by dietary administration<br>Rhône-Poulenc Agro, France<br>Report no. SA95083<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.5/01 *bis* | Semino G. | 2000 | Dodine : Evaluation of clinical signs in the rat chronic study<br>Aventis CropScience, France<br>Unpublished Statement | Yes | CAG |
| IIA, 5.5/02 | Williams K.D. | 1998 | 78-week dietary oncogenicity study with dodine in mice<br>Covance Laboratories, USA<br>Report no. 6224-220<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.6.1/01 | Henwood S.M. | 1996 | Two-generation reproduction study with dodine in rats<br>Corning Hazleton, USA<br>Report no. HWI 6224-218<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.6.2/01 | Hazelden K.P., Wilson J.A. | 1989a | Dose range finding study in rats preliminary to teratogenicity study<br>Inveresk Research International, Scotland<br>Report no. 5596<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.6.2/02 | Hazelden K.P., Wilson J.A. | 1989b | Dodine : teratogenicity study in rats<br>Inveresk Research International, Scotland<br>Report no. 5965<br>GLP<br>Unpublished | Yes | CAG |

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| IIA, 5.6.2/03 | Mc Cay C., Hazelden K.P. | 1989a | Dodine : dose range finding study in rabbits preliminary to teratogenicity study<br>Inveresk Research International, Scotland<br>Report no. 5687<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.6.2/04 | Mc Cay C., Hazelden K.P. | 1989b | Dodine : teratogenicity study in rabbits<br>Inveresk Research International, Scotland<br>Report no. 5861<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 5.9.1 | Chimac-Agriphar | 2002 | Report on medical surveillance of manufacturing plant personnel<br>Chimac-Agriphar<br>Unpublished Statement | Yes | CAG |
| IIA, 7.2.1.3.1/01 | Desmares-Koopmans M.J.E | 2002 | Determination of 'ready' biodegradability: carbon dioxide ($CO_2$) evolution test (modified sturm test) with dodine technical.<br>Notox, NL, report # 327105,<br>GLP<br>Unpublished | Yes | CAG |
| IIA, 8.2.1/02 | Caley, C. Y.<br>Cameron, B. D.<br>Chapleo, S.<br>Knight, B. | 1990b | Dodine: determination of acute toxicity (LC50) to bluegill sunfish (96h, semi-static) (EPA);<br>Inveresk Research report # 7071,<br>GLP,<br>Unpublished. | Yes | CAG |
| IIA, 8.2.4.1/01 | Putt A.E. | 1992 | Dodine technical: acute toxicity to daphnids (*Daphnia magna*) under flow-through conditions;<br>Springborn Laboratories SLI report # 92-4-4245,<br>GLP,<br>Unpublished. | Yes | CAG |
| IIA, 8.2.6/01 | Hoberg J.R. | 1993 | Dodine : toxicity to the freshwater green alga, *Selenastrum capricornutum*;<br>Springborn Laboratories,<br>SLI report # 92-12-4550,<br>GLP,<br>Unpublished. | Yes | CAG |
| **Annex IIIA** | | | | | |
| IIIA, 7.1.1 | Dreher D.M. | 1991 | EXP 10343: Acute oral toxicity (limit test) in the rat<br>Safepharm Laboratories, UK<br>Report no. 282/141<br>GLP<br>Unpublished | Yes | CAG |
| IIIA, 7.1.2 | Dreher D.M. | 1991 | EXP 10343: Acute dermal toxicity (limit test) in the rat<br>Safepharm Laboratories, UK<br>Report no. 282/142<br>GLP<br>Unpublished | Yes | CAG |

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| IIIA, 7.1.3 | Blagden S.M. | 1992 | EXP 10343: Acute inhalation toxicity study four-hour exposure (nose only) in the rat<br>Safepharm Laboratories, UK<br>Report no. 282/146<br>GLP<br>Unpublished | Yes | CAG |
| IIIA, 7.1.4/01 | Dreher D.M. | 1991 | EXP 10343: Acute dermal irritation test in the rabbit<br>Safepharm Laboratories, UK<br>Report no. 282/143<br>GLP<br>Unpublished | Yes | CAG |
| IIIA, 7.1.4/02 | Manciaux X. | 1999 | Acute dermal irritation in rabbits<br>Centre International de toxicologie, France<br>Report no. 18689TAL<br>GLP<br>Unpublished | Yes | CAG |
| IIIA, 7.1.5/01 | Dreher D.M. | 1991 | EXP 10343: Acute eye irritation test in the rabbit<br>Safepharm Laboratories, UK<br>Report no. 282/144<br>GLP<br>Unpublished | Yes | CAG |
| IIIA, 7.1.5/02 | Manciaux X. | 1999 | Acute eye irritation in rabbits<br>Centre International de toxicologie, France<br>Report no. 18690TAL<br>GLP<br>Unpublished | Yes | CAG |
| IIIA, 7.1.6 | Dreher D.M. | 1992 | EXP 10343: Buehler delayed contact hypersensitivity study in the guinea pig<br>Safepharm Laboratories, UK<br>Report no. 282/145<br>GLP<br>Unpublished | Yes | CAG |
| IIIA, 10.2.1/01 | Migchielsen M. | 2004 | Acute toxicity study in daphnia magna with Dodine 400 SC (Semi-static).<br>Notox/NL; report # 413213<br>GLP<br>Unpublished, | Yes | CAG |
| IIIA, 10.2.1/02 | Migchielsen M. | 2004 | Fresh water algal growth inhibition test with Dodine 400 SC.<br>Notox/NL; report # 413224,<br>GLP<br>Unpublished | Yes | CAG |

# 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 Methods for the analysis of the active substance as manufactured (Annex IIA 4.1)

#### B.5.1.1.1 Analytical method for determination of the pure active substance (Annex IIA 4.1.1 and 4.1.3)

**Technical dodine: HPLC determination of active ingredient**

Reynaud R. (1997a)

Rhône-Poulenc Agro, Study no. 96-59; Method D-867-06-96 (E) (4.1.1/01)

GLP: yes.

Principle of the method:

Sample is dissolved in dilution solvent (1000ml ethanol + 5ml acetic acid + 1.8g 1-octane sulfonic acid, sodium salt). Dodine content is determined by HPLC with refractometry detection, using a Suplex PKB-100, 5 µm, at 40ºC and mobile phase: 600ml acetonitrile + 400ml water + 5ml acetic acid + 1.8g 1-octane sulfonic acid, sodium salt, monohydrate.

Findings:

**Table B.5.1.1.1: Summary of validation data for determination of dodine in technical material**

| Compound / method | Selectivity Interferences | Linearity | | Accuracy Recovery% | Repeatability RSD% |
|---|---|---|---|---|---|
| | | Range / calibration line | $r^2$ | | |
| Dodine / HPLC – refractive index | no interferences | 0.8 - 1.2 g/L (a) $y = 1.978\times10^{6}x - 7.703\times10^{4}$ | 0.996 | 99 - 101.5 100.2 (mean) (b) | 0.3 (c) |

(a) 5 concentration levels, double injection
(b) 14 injections of 2 independent samples at 1 g/L level
(c) 6 independent samples at the same level

Conclusions:

Method is validated for all parameters except specificity which was only based on retention times. A recent study on specificity for dodine and impurities on technical active substance was submitted by Chimac-Agriphar (see 4.1.1/03 and 4.1.2/04). Representative chromatograms are available.

A CIPAC method is available but it is still based on a titration (non-specific), which is considered not suitable for the correct determination of the a.s. in the technical material, see next sub-point (4.1.1/02).

**Applicability of existing CIPAC methods**

CIPAC Handbook 1B, Method MT 101: Dodine; p. 1802-1804 (4.1.1/02)

CAG Statement:

"The method was developed in the past using titration by perchloric acid after dodine has been dissolved in acetic acid.

Titration does not correspond to modern standard and CIPAC method is therefore not applicable any more. Moreover, it artificially increases the purity of the active substance since all impurities containing the amine group also react with the perchloric acid."

**Validation of specificity of HPLC method of determination of impurities in Dodine technical (quality analysis by LC/MS/MS)**

Ryckel, de B. (2006)

Chimac-Agriphar, Report no. FO 21257/Ch.3196/2006A (4.1.1/03) (cross reference 1.10+1.11/05)

GLP: no.

Principle of the method:

Sample is dissolved in methanol. Dodine and impurities (see volume 4 for the name of impurities) are determined by LC-MS/MS with positive electrospray ionisation (using at least the molecular ion and two fragment ions for identification of each analyte), using a Zorbax Eclipse XDB-C18, 250 x 4.6 mm x 5 µm, at 40ºC and mobile phase: 0.4% formic acid aqueous solution / methanol (10 / 90 v/v). Representative chromatograms were presented.

Findings:

The MS/MS spectra after fragmentation of the molecular ion of dodine and of each impurity, obtained from the injections of reference and sample solutions are similar with the same characteristic fragment ions.

Conclusions:

The structure of dodine and each impurity is now confirmed.

### B.5.1.1.2 Analytical method for determination of impurities (Annex IIA 4.1.2 and 4.1.3)

**Significant impurities**

CONFIDENTIAL INFORMATION

Reynaud, R. (1997b)

Chimac-Agriphar, Report no. part of study # 96-59 (4.1.2/01)

GLP: yes.

CONFIDENTIAL INFORMATION

Reynaud, R. (1997c)

Chimac-Agriphar, Study no. Method D-869-06-96 (E) as part of study 96-59 (4.1.2/02)

GLP: yes.

CONFIDENTIAL INFORMATION

Duff S. (2002)

Chimac-Agriphar, as part of Report no. CHI-020709 (4.1.2/03)

GLP: yes.

**Analytical profile of technical dodine**

Duff S. (2002)

Chimac-Agriphar, Report no. CHI-030407 (1.10 + 1.11/03)

GLP: yes.

Principle of the method:

HPLC-refractive index method and Official CIPAC methods MT 17.2 and MT 30.1 are used for determination of impurities in technical dodine.

Findings:

Detailed data on validation submitted for impurities are presented in annex C.1.2.4.

Conclusions:

HPLC-refractive index method is not fully validated for all parameters, as specificity was only based on retention times. Representative chromatograms are available including the blank.

**Validation of specificity of HPLC method of determination of impurities in Dodine technical (quality analysis by LC/MS/MS)**

Ryckel, de B. (2006)

Chimac-Agriphar, Report no. FO 21257/Ch.3196/2006A (4.1.2/04) (cross reference 1.10+1.11/05)

GLP: no.

Principle of the method:

Sample is dissolved in methanol. Dodine and impurities (see volume 4 for the name of impurities) are determined by LC-MS/MS with positive electrospray ionisation (using at least the molecular ion and two fragment ions for identification of each analyte), using a Zorbax Eclipse XDB-C18, 250 x 4.6 mm x 5 µm, at 40ºC and mobile phase: 0.4% formic acid aqueous solution / methanol (10 / 90 v/v). Representative chromatograms were presented.

Findings:

The MS/MS spectra after fragmentation of the molecular ion of dodine and of each impurity, obtained from the injections of reference and sample solutions are similar with the same characteristic fragment ions.

Conclusions:

The structure of dodine and each impurity is now confirmed. Data on specificity validation submitted for impurities are presented in annex C.1.2.4.

## B.5.1.2 Methods for the analysis of the preparation (Annex IIIA 5.1)

### B.5.1.2.1 Analytical method for determination of the active substances (Annex III A 5.1.1)

**Dodine: Determination by HPLC analysis in formulation EXP10343A (SC)**

Le Gren I. (1997)

Chimac-Agriphar, Report no. D-930-11-97 (5.1.1a/01)

GLP: yes.

Principle of the method:

Sample is dissolved in (1.8g 1-octane sulfonic acid sodium salt monohydrate + 5ml acetic acid + 1000ml ethanol). The active substance content is determined by reverse phase liquid chromatography using Suplex PKB-100/5 µm column, with refractometer detection, column and refractometer at a temperature of 40ºC and an isocratic mobile phase (1.8g 1-octane sulfonic acid sodium salt monohydrate + 5ml acetic acid + 400 ml water + 600 ml acetonitrile).

Findings:

**Table B.5.1.2 - Data on validation of dodine in SYLLIT 400 SC**

| Compound / Method | Specificity Interferences | Linearity | | Accuracy Recovery % | Repeatability RSD % |
|---|---|---|---|---|---|
| | | Range / Calibration line | $r^2$ | | |
| Dodine / HPLC-refractive index | No interferences | 0.2 - 2 g/L (a) / $y = 1.071 \times 10^5 x + 5.463 \times 10^2$ | 1.000 | 99.19-100.70 (n=6) | 0.5 (n=6) |

(a) 5 concentrations; double injection

Conclusions:

The submitted method is acceptable validated for determination of dodine in SYLLIT 400 SC. Representative chromatograms are available including the blank.

A CIPAC method is not available for SYLLIT 400 SC formulation type (suspension concentrate).

## B.5.2 Analytical methods (residue) for plants, plant products, foodstuffs (of plant and animal origin), feedingstuffs (Annex IIA 4.2.1; Annex IIIA 5.2.1)

**Dodine: Validation of Method of Analysis for Dodine in fruit**

Pittman, J. (1996)

Chimac-Agriphar, Report no. part of study # 96-59 (4.2.1/01)

GLP: yes.

**Independent Laboratory Confirmation of the Tolerance Enforcement Method by EPA PR Notice 88-5 for Dodine: Method of Analysis for Dodine in fruit**

Herzig R. (1996)

Chimac-Agriphar, Report no.: #RES9608 (4.2.1/02)

GLP: yes.

**Materials and Methods:**

**Test material:** Apples, plums and apple wet pomace

**Fortified analyte(s):** Dodine.

**Analyte(s) determined as:** Derivatised dodine (converted to dodine by molecular weight quotient).

Principle of the method:

Dodine was extracted from test material with methanol, followed by cleaned-up with liquid-liquid partition with dichloromethane after addition of sodium chloride and water. The extract was then reconstituted in 1-chlorobutane. Dodine was converted to Derivatised dodine: 2-dodecyl-4,6-

bis(trifluoromethyl)pyrimidine[1] during reflux with hexafluoroacetylacetone[2] and methanol. The solvent was evaporated and the samples were reconstituted in cyclohexane for analysis of derivatized dodine by GC-MSD (method 45137).

Findings:

The derivatisation reaction is considered to remain specific (derivatised dodine is considered specific to dodine – see figure B.5.2). GC-MSD analysis of derivatised dodine is accomplished using the respective analytical standard and then converted to dodine using the molecular weight conversion factor.

This method is fully validated for determination of dodine in apples, plums and apple wet pomace (see Table B.5.2.1). No additional confirmatory method is required, the method is considered highly specific as three fragment-ion were used in a specific ratio for identification (m/z = 244, 245 and 399). At least two blank (untreated control) samples are reported for each matrix demonstrating that interferences are below 30% of LOQ. Validation included the testing of linearity for derivatized dodine in the range 20 – 150 ng/ml (five concentrations, single injection) and typical chromatograms including those for untreated control samples.

Independent Laboratory Validation - ILV was submitted with only one matrix type chosen for evaluation: apple wet pomace, which was considered the most difficult matrix to work with and only two recoveries at each level were performed in this study. Data on validation are shown in Table B.5.2.

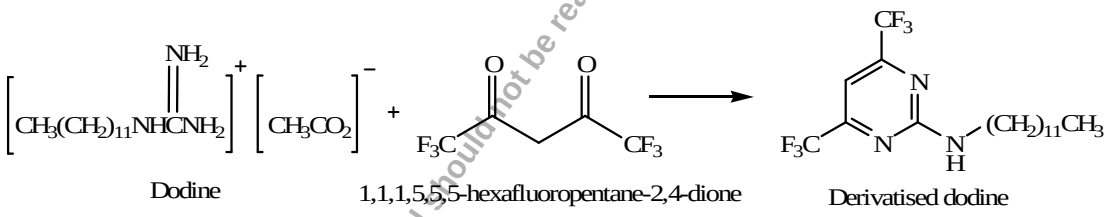



Figure B.5.2: Derivatisation reaction for dodine

**Analytical Method validation of Dodine Residues in peach, pear, apple, cherry and plum samples.**

Goller, G.; Duchene, P. (1998)

Chimac-Agriphar, Report no. RPA/DOD/97112 code 97-176/AR 156-97 (4.2.1/03)

GLP: yes.

**Materials and Methods:**

**Test material:** Peach, pear, apple, cherry and plum.

**Fortified analyte(s):** Dodine.

**Analyte(s) determined as:** Derivatised dodine (converted to dodine by molecular weight quotient).

Principle of the method:

Method of Analysis for Dodine in fruit (described above) it's amended at ADME BIOANALYSIS laboratory on several fruit substrates: peach, pear, apple, cherry and plum.

[1] CA name: N-dodecyl-4,6-bis(trifluoromethyl)pyrimidin-2-amine

[2] CA name: 1,1,1,5,5,5-hexafluoropentane-2,4-dione

Findings:

The derivatisation reaction is considered to remain specific. GC-MSD analysis of derivatized dodine is accomplished using the dodine analytical standard which is derivatized as the samples. The efficiency and precision of the derivatisation step should have been demonstrated in order for the purity of the derivatized standard to be known. Although as demonstrated in study reference Chimac-Agriphar, Report no. part of study # 96-59 (4.2.1/01), in which the same analytical method is validated with the derivatised dodine analytical and acceptable recoveries and RSD are obtained, this information is not considered relevant. At least two blank (untreated control) samples are reported for each matrix demonstrating that interferences are below 30% of LOQ and typical chromatograms including those for untreated control samples were submitted. This ILV study can also be considered sufficiently validated for determination of dodine residues in high water content commodities.

The submitted data on validation are shown in Table B.5.2.1.

Conclusions:

GC-MSD method with derivatisation is successfully validated and it is acceptable as an enforcement method for commodities with high water content with a LOQ of 0.05 mg/kg.

**Chimac-Agriphar statement concerning the applicability of a multi-residue method for dodine:**

"The DFG Multiresidue Method S 19 (Gas-chromatographic determination after cleanup by gel permeation chromatography and silica gel minicolumn chromatography for Organochloride, Organophosphorus, Nitrogen-Containing and Other Pesticides) is not applicable for the determination of dodine residues.

Dodine cannot be analysed directly by gas chromatography due to the fact that the molecule is not volatile (without derivatisation). Therefore the method S 19 is not applicable."

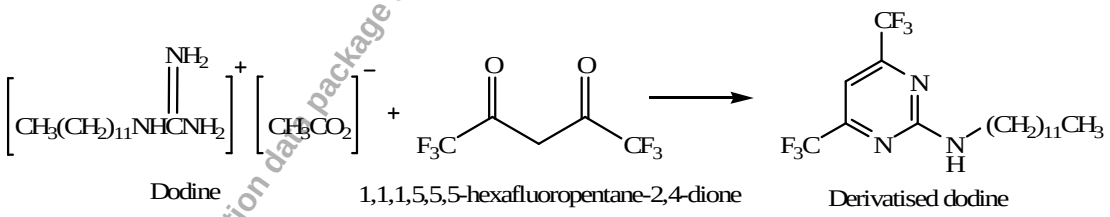



Figure B.5.2: Derivatisation reaction for dodine

**Table B.5.2.1: Summary of validation data for determination of residues of dodine in food of plant origin**

| Reference | Matrix | Method | Analyte | Fortification level (mg/kg) | n | Recoveries (%) | | LOQ (mg/kg) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Mean | RSD | |
| Pittman, J. (1996) (4.2.1/01) | Apple | GC-MSD | Dodine | 0.05 | 5 | 87.80 | 12.5 | 0.05[a] |
| | | | | 0.25 | 5 | 79.92 | 11.0 | |
| | | | | 5.0 | 5 | 76.78 | 7.2 | |
| | Plum | GC-MSD | Dodine | 0.05 | 5 | 76.03 | 10.05 | 0.05[b] |
| | | | | 0.25 | 5 | 71.63 | 6.49 | |
| | | | | 5.0 | 5 | 79.03 | 7.95 | |
| | Apple wet pomace | GC-MSD | Dodine | 0.10 | 5 | 92.18 | 13.19 | 0.1[c] |
| | | | | 0.50 | 5 | 92.54 | 14.16 | |
| | | | | 5.0 | 5 | 96.76 | 6.28 | |
| Herzig R. (1996) (4.2.1/02) | Apple wet pomace | GC-MSD | Dodine | 1.0 | 2 | 96 | 13.3 | - |
| | | | | 5.0 | 2 | 91.5 | 7.0 | |
| | | | | 25.0 | 2 | 102 | 16.6 | |
| Goller, G.; Duchene, P. (1998) (4.2.1/03) | Peach | GC-MSD | Dodine | 0.05 | 2 | 84 | 16.8 | 0.05 |
| | | | | 0.063 | 2 | 106.5 | 2.0 | |
| | | | | 0.315 | 2 | 91.5 | 13.1 | |
| | Pear | GC-MSD | Dodine | 0.050 | 2 | 86 | 16.4 | |
| | | | | 0.063 | 2 | 102.5 | 0.7 | |
| | | | | 0.315 | 2 | 81.5 | 9.5 | |
| | Apple | GC-MSD | Dodine | 0.050 | 2 | 96 | 2.9 | |
| | | | | 0.063 | 2 | 93.5 | 6.8 | |
| | | | | 0.315 | 2 | 82 | 15.5 | |
| | Cherry | GC-MSD | Dodine | 0.050 | 2 | 94 | 9 | |
| | | | | 0.063 | 2 | 108 | 0 | |
| | | | | 0.315 | 2 | 106 | 0 | |
| | Plum | GC-MSD | Dodine | 0.050 | 2 | 93 | 7.6 | |
| | | | | 0.063 | 2 | 102.5 | 3.4 | |
| | | | | 0.315 | 2 | 110 | 0 | |

[a] 63 ppb, calculated as 10×SD; [b] 31 ppb, calculated as 10×SD; [c] 122 ppb, calculated as 10×SD

Equation of the calibration line: $y = 2.84\times10^{3}x - 1.58\times10^{4}$; $r^2 = 0.997$

## B.5.3 Analytical methods (residues) for soil, water and air (Annex IIA 4.2.2 to 4.2.4; Annex IIIA 5.2.2 to 5.2.4)

### B.5.3.1 Analytical methods (residues) for soil (Annex IIA 4.2.2; Annex IIIA 5.2.2)

**Dodine: Validation of Method of Analysis for dodine in Soil using GC-MSD**

Yang, Yu (1998)

Chimac-Agriphar, Report no. EC-97-384 (4.2.2/01)

GLP: yes.

**Materials and Methods:**

**Test material:** According to this study: "Soil samples were obtained from untreated areas adjacent to the plots established for the Rhône-Poulenc Ag Company Study US96X10342, a field dissipation study conducted in California, Washington, Georgia and New Jersey.". See Table B.5.3.1 (cross-reference 7.1.1.2.2/01).

**Fortified analyte(s):** Dodine.

**Analyte(s) determined as:** Derivatised dodine (converted to dodine by molecular weight quotient).

Principle of the method:

Dodine was extracted from soil twice using KOH in methanol/water and once using 1% HCl in methanol, followed by cleaned-up with liquid-liquid partition with dichloromethane after addition of sodium chloride and water. The extract was then reconstituted in 1-chlorobutane. Dodine was converted to derivatized dodine: 2-dodecyl-4,6-bis(trifluoromethyl)pyrimidine during reflux with hexafluoroacetylacetone and methanol. The solvent was evaporated and the samples were reconstituted in methanol (MeOH) for analysis of derivatized dodine by GC-MSD.

Findings:

The derivatisation reaction is considered to remain specific. GC-MSD analysis of derivatised dodine is accomplished using the respective analytical standard and then converted to dodine using the molecular weight conversion factor.

This method is fully validated for determination of dodine in soil (see Table B.5.3.1). No additional confirmatory method is required, the method is considered highly specific as three fragment-ion were used in a specific ratio for identification (m/z = 244, 245 and 399). Validation included the testing of linearity for derivatised dodine in the range 20 – 150 ng/ml (five concentrations, single injection) in two different days and typical chromatograms. At least two blank (untreated control) samples are reported for each matrix demonstrating that no interferences were detected and typical chromatograms including those for untreated control samples were submitted.The LOQ in soil is 0.01 mg/kg.

**Table B.5.3.1: Summary of validation data for determination of residues of dodine in soil**

| Reference | Matrix [a] | Method | Analyte | Fortification level (mg/kg) | n | Recoveries (%) | | LOQ (mg/kg) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Mean | RSD | |
| Yang, Yu (1998) 4.2.2/01 | California soil (loamy sand) | GC-MSD | Dodine | 0.05<br>0.5 | 5<br>5 | 96.8<br>77.7 | 13.7<br>16.2 | 0.05 |
| | Washington (loamy fine sand), Georgia (loamy sand), New Jersey (loam) soils | GC-MSD | Dodine | 0.01<br>0.50<br>5 | 6 [b]<br>6 [b]<br>6 [b] | 81.7<br>72.2<br>63.3 | 17.4<br>11.9<br>8.1 | 0.01 |

[a] Location and composition of the soils:
Madera, Madera, California, USA: sand 85%; silt 10%; clay 5%; organic matter 0.5%; pH 7.1
Ephrata, Grant,Washington, USA: sand 89%; silt 8%; clay 3%; organic matter 1.2%; pH 6.7
Hawkinsville, Palaski, Georgia, USA: sand 87%; silt 10%; clay 3%; organic matter 1.2%; pH 7.3
Kingwood, Hunterton, New Jersey, USA: sand 33%; silt 47%; clay 20%; organic matter 2.3%; pH 6.0

[b] 2 samples from each of the 3 soils
Equation of the calibration line: $y = 3.25\times10^{3}x - 1.46\times10^{3}$; $r^2 = 0.9942$ in day 1 and
$y = 2.21\times10^{2}x - 9.05\times10^{1}$; $r^2 = 0.9976$ in day 2

## B.5.3.2 Analytical methods (residues) for water (Annex IIA 4.2.3; Annex IIIA 5.2.3)

## B.5.3.2 Analytical methods (residues) for water (Annex IIA 4.2.3; Annex IIIA 5.2.3)

**Validation of an analytical method for the determination of dodine residues in water**

Schoutsen, T.P. (2001)

Chimac-Agriphar, Report no. 335058 (4.2.3/01)

GLP: yes.

**Materials and Methods:**

**Test material:** Surface water.

**Fortified analyte(s):** Dodine.

**Analyte(s) determined as:** Dodine.

Principle of the method:

Dodine residues in water samples are extracted onto a Waters Oasis HLB 6cc (200 mg) solid phase extraction column, and eluted with 49 ml acetonitrile (ACN) + 21 ml MeOH mixed with 30 ml of a 2% acetic acid solution. After evaporation of solvent the residue was reconstituted in acetonitrile /water + 0.1% heptafluorbutyric acid (HFBA) (45/55, % v/v) for analysis by LC-MS/MS.

Findings:

The method is highly specific and was fully validated for the determination of dodine residues in surface water (see Table B.5.3.2). At least two blank (untreated control) samples are reported for each matrix demonstrating that no interferences were detected and typical chromatograms including those for untreated control samples were submitted.

Validation also included the testing of linearity in the range 0.005 – 0.1 µg/L (six concentrations, single injection) and typical chromatograms including the blank. The LOQ = 0.008 µg/L in surface water (lower than the criteria – 0.1 µg/L as set for tap water and ground water) and considered also applicable for the analysis of dodine residues in tap water and ground water (in these untreated control samples it was not detected any interference). The laboratory responsible for the study used its tap water as the source for drinking water; ground water was taken from a groundwater well (Loosbroek, The Netherlands).

**Table B.5.3.2: Summary of validation data for dodine in water**

| Reference | Matrix | Method | Analyte | Fortification level (µg/L) | n | Recoveries (%) | | LOQ (µg/L) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Mean | RSD | |
| Schoutsen, T.P. (2001) (4.2.3/01) | Surface water (a) | LC-MS/MS | Dodine | 0.008<br>0.080 | 6<br>6 | 84.4<br>78 | 5.5<br>4.9 | 0.008 |

(a) Source of surface water: river Waal (Loenen, The Netherlands)
Details about the surface water: pH 7.97; total hardness 14 German degrees, medium-hard; DOC 7.0 mg/L; suspended solids 26.4 mg/L

Equation of the calibration line: $y = 1.5\times10^5 x + 80.6$; $r^2 = 0.9973$ and $y = 1.6\times10^5 x + 78.1$; $r^2 = 0.9987$ for two sets of independent calibration standards.

## B.5.3.3 Analytical methods (residues) in air (Annex IIA 4.2.4; Annex IIIA 5.2.4)

**Validation of an analytical method for the determination of dodine residues in air.**

Schoutsen, T.P (2002)

Chimac-Agriphar, Report no.: 335069 (4.2.4/01)

GLP: yes.

**Materials and Methods:**

**Test material:** Air (conditioned at least 35ºC with relative humidity of at least 80%)

**Fortified analyte(s):** Dodine.

**Analyte(s) determined as:** Dodine.

Principle of the method:

Dodine residues in air were absorbed onto an ORBO$^{TM}$-402 Tenax® tube (2 ml/min for 6 hours) and extracted with ACN/MeOH (70/30, % v/v). Samples extracts were further diluted with ACN/water + 0.1% HFBA (45/55, %v/v) for analysis by LC-MS/MS. A preliminary test was performed to estimate desorption efficiency and the trapping efficiency of absorber tube.

Findings:

The test concentration value, a C-value, calculated as C = $AOEL_{systemic}$ × safety factor × body weight (kg) / air intake ($m^3$): C = 0.045 × 0.1 × 60 / 20 = 0.0135 mg dodine / $m^3$ air and considering an airflow of 2 L/ min and a flow time of 6 hours (0.72 $m^3$), the C-value is therefore equivalent to 0.01 mg dodine on the absorber.

The method is highly specific and was fully validated for the determination of dodine residues in air (see Table B.5.3.3) with a LOQ of 0.0085 mg/absorber in air.

Validation also included the testing of linearity in the range 20 – 400 µg/L (six concentrations, single injection) and typical chromatograms.

Absorber tubes were spiked at 0.901 mg/absorber, dried and direct eluted showed a desorption efficiency of 101.3% and 101.6% (duplicate test). Two absorber tubes spiked at 0.901 mg/absorber, dried and exposed to unconditioned air (2 L/min) for two hours, showed a trapping efficiency from 92% and 94%, respectively. A blank absorber tube yield a response of about 4% of lowest standard indicating that no breakthrough was seen.

**Table B.5.3.3 Summary of validation data for determination of residues of dodine in air**

| Reference | Matrix | Method | Analyte | Fortification level[1] (mg/absorber) | n | Recoveries (%) | | LOQ (mg/absorber) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Mean | RSD | |
| Schoutsen, T.P (2002) (4.2.4/01) | Air (36ºC, 82% RH) | LC-MS/MS | Dodine | 0.0085<br>0.8990 | 6<br>6 | 91.9<br>90.7 | 5.2<br>11.3 | 0.0085<br>(a) |

[1] According to Chimac-Agriphar: The test concentrations were based on a C-value calculated as C = $AOEL_{systemic}$ × safety factor × body weight (kg) / air intake ($m^3$). C = 0.4 × 0.1 × 60 / 20 = 0.12 mg dodine / $m^3$ air

Considering an airflow of 2 L/ min and a flow time of 6 hours (0.72 $m^3$), the C-value is therefore equivalent to 0.0864 mg dodine on the absorber, which results in the test concentrations of LOQ: ± 0.1C = ± 0.0085 mg/ absorber and ± 10C = 0.9 mg/ absorber.

**(a) equivalent to a LOQ of 11.8 µg/$m^3$ (conversion performed by RMS)**

Equation of the calibration line: $y = 5.4\times10^2 x + 3.75\times10^3$; $r^2 = 0.9921$ and

$y = 4.7\times10^2 x + 3.92\times10^3$; $r^2 = 0.9938$ for two set of independent calibration standards.

## B.5.4 Analytical methods (residues) in body fluids and tissues (Annex IIA 4.2.5; Annex IIIA 5.2.5)

**Development and Validation of an Analytical Method for the Determination of Dodine and Its Metabolite in Body Fluids and Tissue.**

Bacher, R. (2004)

Chimac-Agriphar, Report no.: P/B 603 G (4.2.5/01)

GLP: yes.

**Materials and Methods:**

**Test material:** Human urine and blood and bovine liver.

**Fortified analyte(s):** Dodine and 12-hydroxydodecylguanidine metabolite.

**Analyte(s) determined as:** Dodine and 12-hydroxydodecylguanidine metabolite.

Principle of the method:

Human urine sample is diluted with 1% formic acid and acetonitrile. The diluted extracts are directly analysed for dodine and 12-hydroxydodecylguanidine metabolite by LC-MS/MS.

Human blood sample is centrifuged to separate plasma from cellular precipitate. Plasma is acidified with 1% formic acid. The aqueous solution is applied to a HLB solid phase extraction cartridge, after washing of the SPE material first with a slightly basic, then with a slightly acidic wash solution, dodine and 12-hydroxydodecylguanidine metabolite are eluted from the cartridge with ACN/MeOH/2 % acetic acid (49/21/30, % v/v/v). After concentrating, the final extract is diluted with 1% formic acid and residues of dodine are analysed by LC-MS/MS.

Bovine liver sample is extracted with methanol followed by liquid partition with n-hexane for fat clean-up. For analysis of 12-hydroxydodecylguanidine metabolite residues the methanol phase is diluted with 1% formic acid and subsequently purified on a HLB SPE cartridge for LC-MS/MS analysis. For the analysis of dodine the methanol phase is concentrated, potassium hydroxide and sodium chloride are added followed by liquid: liquid partition clean-up with MeOH/1% formic acid (2/8, %v/v) for LC-MS/MS analysis.

Findings:

The LC-MS/MS method is highly specific and fully validated for determination of dodine and 12-hydroxydodecylguanidine metabolite in body fluids (human urine and human blood) with a LOQ of 2 µg/L and in bovine liver the method was only successfully validate for 12-hydroxydodecylguanidine metabolite residues with a LOQ of 5 µg/kg; for dodine residues analysis in bovine liver the method is not acceptable, because of low recoveries (see Table B.5.4).

For bovine liver, a different method approach based on alkaline partion of dodine for clean-up was tried and resulted in an improved average recovery but still lower than 70%. These low recoveries for dodine, according to Applicant, may be caused either by the high enzymatic activity of liver extracts possibly leading to the formation of dodine conjugates, or by loss of dodine on active sites of surfaces on the equipment used for extraction, clean-up and concentration. Several variations to the analytical method were also investigated in trying to optimise dodine recoveries but none result in satisfactory results. However the LC-MS/MS is highly specific and capable of detecting dodine residues in bovine liver in the desired concentration range (note: 0.1 mg/kg is the LOQ in general accepted for toxic active substances in tissues).

At least two blank (untreated control) samples are reported for each matrix demonstrating that no interferences were detected and typical chromatograms including those for untreated control samples were submitted. Validation also included the testing of linearity.

**Table B.5.4: Summary of validation data for determination of residues of dodine and 12-hydroxydodecylguanidine metabolite in human urine, human blood and bovine liver**

| Reference | Matrix | Method | Analyte | Fortification level (µg/L) | n | Recoveries (%) | | LOQ (µg/L) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Mean | RSD | |
| Bacher, R. (2004) (4.2.5/01) | Human urine | LC-MS/MS | Dodine[(a)] | 2<br>10 | 5<br>5 | 109<br>104 | 8<br>11 | 2 |
| | | | 12-hydroxy dodecylguanidine[(b)] | 2<br>10 | 5<br>5 | 100<br>98 | 12<br>4 | 2 |
| | Human blood | LC-MS/MS | dodine[(c)] | 2 | 5 | 73 | 15 | 2 |
| | | | 12-hydroxy dodecylguanidine[(d)] | 2 | 5 | 99 | 6 | 2 |
| | Bovine liver | LC-MS/MS | dodine[(e)] | 5 µg/kg<br>10 µg/kg[1] | 7<br>5[1] | 25<br>55[1] | 20<br>20[1] | - |
| | | | 12-hydroxy dodecylguanidine[(f)] | 5 µg/kg | 7 | 70 | 13 | 5 µg/kg |

[1] Different method approach based on alkaline partition clean-up
Equation of the calibration lines:
[(a)] $y = 796x + 147$; $r^2 = 0.9953$ in the range 0.08 – 4 µg/L (6 levels)
[(b)] $y = 3x + 1.73$; $r^2 > 0.99$ in the range 0.08 – 4 µg/L (6 levels)
[(c)] $y = 420x$; $r^2 = 0.9888$ in the range 0.4 – 4 µg/L (3 levels with at least double injection)
[(d)] $y = 3x + 1.8$; $r^2 = 0.9965$ in the range 0.4 – 4 µg/L (3 levels with at least double injection)
[(e)] $y = 3x + 1.01$; $r^2 = 0.9885$ in the range 1 – 10 µg/L (4 levels with at least double injection)
[(f)] $y = 3x + 2.16$; $r^2 = 0.9920$ in the range 1 – 5 µg/L (3 levels with at least double injection)

## B.5.5 Evaluation and assessment

### B.5.5.1 Analytical methods for plant protection products

The submitted analytical methods allow the determination of dodine and impurities in technical material. The LC-MS/MS confirmatory technique allows the identification of dodine and impurities in technical material. No further validation is required.

The submitted analytical method allows the determination of dodine in the SYLLIT 400 SC preparation and is fully validated.

**Table B.5.5.1: Summary of analytical methods for technical active substance and formulation analysis**

| Matrix | Analyte | Method | Validation | References |
|---|---|---|---|---|
| Technical active substance | Dodine | HPLC-refractive index<br>LC-MS/MS | Full | Reynaud, R. (1997a)<br>Ryckel, de B. (2006) |
| | Impurities | HPLC-refractive index, Karl Fisher titration and LC-MS/MS | Full | Duff, S. (2002)<br>Reynaud, R. (1997b and c)<br>Ryckel, de B. (2006) |
| SYLLIT 400 SC | Dodine | HPLC-refractive index | Full | Le Gren, I. (1997) |

The existing CIPAC method (by titration) is obsolete and not suitable for a correct determination of dodine in technical material. A CIPAC method is not available for SYLLIT 400 SC formulation type (a suspension concentrate).

### B.5.5.2 Analytical methods for residues analysis

The submitted analytical methods enable the enforcement of the following relevant residue definitions and limits (at the time of evaluation) are listed bellow:

**Table B.5.5.2-1: Summary of relevant residues definitions and limits**

| Matrix | Residue defination | Residue limit |
|---|---|---|
| Food of plant origin:<br>Apple<br>Pear<br>Cherry<br>Peach | dodine | <br>1 mg/kg<br>1 mg/kg<br>1 mg/kg<br>0.1 mg/kg |
| Food of animal origin: | Not required / no MRL is proposed | |
| Soil | dodine | 0.05 mg/kg general limit |
| Surface water<br>Drinking water | dodine | 0.08 µg/L NOEC<br>0.1 µg/L EU drinking water limit |
| Air | dodine | 0.0135 mg dodine / $m^3$ air based on a $AOEL_{systemic}$ of 0.045 mg/kg bw/day |
| Blood<br>Tissues - liver | dodine | Toxic<br>(ADI = 0.1 mg/kg bw/day; $AOEL_{systemic}$ of 0.045 mg/kg bw/day) |

In the following table, an overview of the accepted enforcement methods is given. Subsequently, parameters of the enforcement methods are summarised.

**Table B.5.5.2-2: Overview of accepted residue analytical methods**

| Matrix | Primary method | Confirmatory method | ILV |
|---|---|---|---|
| Food of plant origin:<br>Commodities with high water content | Pittman, J. (1996) | Primary method is highly specific | Herzig R. (1996)<br>Goller, G.; Duchene, P. (1998) |
| Food of animal origin | No method necessary | | |
| Soil | Yang, Yu (1998) | Primary method is highly specific | - |
| Surface water<br>Drinking water | Schoutsen, T.P. (2001) | Primary method is highly specific | - |
| Air | Schoutsen, T.P (2002) | Primary method is highly specific | - |
| Blood<br>Tissues - liver | Bacher, R. (2004)<br>A successful validation was not accomplished for tissues. | Primary method is highly specific | - |

**Table B.5.5.2-3: Analytical methods for the determination of residues**

| Matrix | Analyte | Method | LOQ | References |
|---|---|---|---|---|
| Food of plant origin:<br>Apple<br>Pear<br>Cherry<br>Peach | Dodine | GC-MSD | 0.05 mg/kg | Pittman, J. (1996)<br>Goller, G.; Duchene, P. (1998) |
| Soil | Dodine | GC-MSD | 0.01 mg/kg | Yang, Yu (1998) |
| Surface water<br>Drinking water | Dodine | LC-MS/MS | 0.008 µg/L | Schoutsen, T.P. (2001) |
| Air (at 36ºC and 82% RH) | Dodine | LC-MS/MS | 0.0085 mg/ absorber (equivalent to 11.8 µg/$m^3$ of air) | Schoutsen, T.P (2002) |
| Human blood and urine<br>Tissues: bovine liver | Dodine | LC-MS/MS | 2 µg/L<br>- | Bacher, R. (2004) |

Fully validated GC-MSD methods (with derivatisation) are available for determination of dodine residues in high water content fruit, with a LOQ = 0.05 mg/kg and in soil with a LOQ = 0.01 mg/kg.

Methods for food of animal origin are not relevant as no LMR will be proposed or likely to be proposed.

Fully validated LC-MS/MS methods are available for determination of dodine residues in water, with a LOQ of 0.008 µg/L and in air (at 36ºC and 82% RH) with a LOQ of 0.0085 mg/absorber (equivalent to 11.8 µg/$m^3$ air).

Fully validated LC-MS/MS methods are available for determination of dodine residues in body fluids (human blood and urine) with a LOQ = 2 µg/L, however for bovine liver the method is not acceptable for dodine residues analysis at the tested LOQ (10 µg/kg). The method needs to be validated for dodine residues in bovine liver at a LOQ of 0.1 mg/kg, according to "Guidance document on residue analytical methods" SANCO/825/00 rev. 7 (17/03/2004).

**Table B.5.5.2-4 - Summary of analytical methods (residue) for plants and foodstuffs of animal origin**

| Matrix | Analyte | Method | Method range (mg/kg commodity) | Validation | References |
|---|---|---|---|---|---|
| Apple<br>Plum<br>Apple wet pomace | dodine | GC-MSD | 0.05* – 5.0<br>0.05* – 5.0<br>0.10* – 5.0 | Full | Pittman, J. (1996)<br>(4.2.1/01) |
| Apple wet pomace | dodine | GC-MSD | 1 – 25.0 | Scarce data | Herzig, R. (1996)<br>(4.2.1/02) |
| Peach<br>Pear<br>Apple<br>Cherry<br>Plum | dodine | GC-MSD | 0.05* – 0.315 | Full | Goller, G.; Duchene, P. (1998)<br>(4.2.1/03) |
| Food of animal origin | Not relevant, no LMR will be proposed | | | | |

* LOQ

### Table B.5.5.2-5 - Summary of analytical methods (residue) for soil

| Matrix | Analyte | Method | Method range (mg/kg commodity) | Validation | References |
|---|---|---|---|---|---|
| Loamy sand | dodine | GC-MSD | 0.05* – 0.5 | Full | Yang, Yu (1998) (4.2.2/01) |
| Loamy fine sand<br>Loamy sand<br>Loam soils | dodine | GC-MSD | 0.01* – 0.5 | Full | |

* LOQ

### Table B.5.5.2-6 - Summary of analytical methods (residue) for water

| Matrix | Analyte | Method | Method range (µg/L) | Validation | References |
|---|---|---|---|---|---|
| Surface water (ground water and drinking water) | dodine | LC-MS/MS | 0.008* – 0.080 | Full | Schoutsen, T.P. (2001) (4.2.3/01) |

* LOQ

### Table B.5.5.2-7 - Summary of analytical methods (residue) in air

| Matrix | Analyte | Type of method | Method range (µg/m$^3$) | Validation | References |
|---|---|---|---|---|---|
| Air | dodine | LC-MS/MS | 11.8* – 1248<br>(given data of 0.0085 – 0.8990 mg/absorber) | Full | Schoutsen, T.P. (2002) (4.2.4/01) |

* LOQ

### Table B.5.5.2-8 - Summary of analytical methods (residue) in body fluids and tissues

| Matrix | Analyte | Type of method | Method range (µg/L) | Validation | References |
|---|---|---|---|---|---|
| Human urine | dodine | LC-MS/MS | 2* – 10 | Full | Bacher, R. (2004) (4.2.5/01) |
| | 12-hydroxy dodecylguanidine | | | | |
| Human blood | dodine | LC-MS/MS | 2* | Full | |
| | 12-hydroxy dodecylguanidine | | | | |
| Bovine liver | dodine | LC-MS/MS | 5 – 10 µg/kg | Not acceptable, low recoveries | |
| | 12-hydroxy dodecylguanidine | | 5* µg/kg | Full | |

* LOQ

## B.5.6 References relied on

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| **Annex IIA** | | | | | |
| IIA, 4.1<br><br>(1.10 + 1.11/03) | Duff S. | 2002 | CONFIDENTIAL INFORMATION – See volume 4<br>Analytical profile of technical dodine<br>Chimac-Agriphar, Report no. CHI-030407<br>GLP, unpublished | Y | CAG |
| IIA, 4.1.1/01 | Reynaud, R. | 1997a | Technical dodine HPLC determination of active ingredient, Method D-867-06-96 {E}<br>Rhône-Poulenc Agro, France<br>Chimac-Agriphar, Report no. part of study # 96-59<br>GLP, unpublished | Y | CAG |
| IIA, 4.1.1/02 | Unspecified | 1983 | Analysis of technical and formulated pesticides, method MT 101: Dodine; p. 1802-1804<br>No GLP, published CIPAC Handbook 1B | N | - |
| IIA, 4.1.1/03<br>IIA, 4.1.2/04<br><br>(1.10 + 1.11/05) | Ryckel, de B. | 2006 | Validation of specificity of HPLC method of determination of impurities in Dodine technical (quality analysis by LC/MS/MS)<br>Walloon Agricultural Research Centre, Belgium<br>Chimac-Agriphar, Report no. FO 21257/Ch.3196/2006A<br>Not GLP, unpublished<br>CONFIDENTIAL INFORMATION – See also volume 4 | Y | CAG |
| IIA, 4.1.2/01 | Reynaud, R. | 1997b | CONFIDENTIAL INFORMATION – See volume 4<br>Rhône-Poulenc Agro, France<br>Chimac-Agriphar, Report no. part of study # 96-59<br>GLP, unpublished | Y | CAG |
| IIA, 4.1.2/02 | Reynaud, R. | 1997c | CONFIDENTIAL INFORMATION – See volume 4<br>Rhône-Poulenc Agro, France<br>Chimac-Agriphar, Report no. part of study # 96-59<br>GLP, unpublished | Y | CAG |
| IIA, 4.1.2/03 | Duff, S. | 2002 | CONFIDENTIAL INFORMATION – See volume 4<br>Chimac-Agriphar, Report no. part of study report no. CHI-020709<br>GLP, unpublished | Y | CAG |
| IIA, 4.2.1/01 | Pittman, J.H. | 1996 | Dodine – Validation of method of analysis for dodine in fruit. Method 45137.<br>Rhône-Poulenc Ag, USA<br>Chimac-Agriphar, Report no. EC-96-342<br>GLP, unpublished | Y | CAG |

| Annex point / reference number | Author(s) | Year | Title<br>Source (where different from company)<br>Company, Report No<br>GLP or GEP status (where relevant),<br>Published or not | Data Protection claimed<br><br>Y/N | Owner |
|---|---|---|---|---|---|
| IIA, 4.2.1/02 | Herzig, R. | 1996 | Independent Laboratory Confirmation of the Tolerance Enforcement Method by EPA PR Notice 88-5 for "Dodine – Validation of method of analysis for dodine in fruit. Method 45137".<br>Agvise Lab, USA<br>Chimac-Agriphar, Report no. RES9608<br>GLP, unpublished | Y | CAG |
| IIA, 4.2.1/03 | Duchene, P.; Goller, G. | 1998 | Analytical method validation of dodine residues in Peach, Pear, Aplle, Cherry and plum samples.<br>ADME Bioanalyses, France<br>Chimac-Agriphar, Report no. RPA/DOD/97112 code 97-176/AR 156-97<br>GLP, unpublished | Y | CAG |
| IIA, 4.2.1/04 | Unspecified | 2003 | Chimac-Agriphar statement concerning the applicability of a multi-residue method for dodine | N | CAG |
| IIA, 4.2.2/01 | Yang, Ju | 1998 | Validation of Method of analysis for dodine in soil using GC-MSD.<br>Rhône-Poulenc Ag, USA<br>Chimac-Agriphar, Report no. EC-97-384<br>GLP, unpublished | Y | CAG |
| IIA, 4.2.3/01 | Schoutsen, T.P.; Wierda, F. | 2001 | Validation of an analytical method for the determination of dodine residues in water.<br>Notox, NL<br>Chimac-Agriphar, Report no. 335058<br>GLP, unpublished | Y | CAG |
| IIA, 4.2.4/01 | Loeffen, H.; Schoutsen, T.P. | 2002 | Validation of an analytical method for the determination of dodine residues in air.<br>Notox, NL<br>Chimac-Agriphar, Report no. 335069<br>GLP, unpublished | Y | CAG |
| IIA, 4.2.5/01 | Bacher, R. | 2004 | Dodine: Development and Validation of an Analytical method for the determination of dodine and its metabolite in body fluids and tissues.<br>PTRL Europe / Germany.<br>Chimac-Agriphar, Report no. P/B603G<br>GLP, unpublished | Y | CAG |
| **Annex IIIA (SYLLIT 400 SC)** | | | | | |
| IIIA, 5.1.1a/01 | Le Gren, I. | 1997 | Dodine: Determination by HPLC analysis in formulation EXP10343A (SC). Method reference D-930-11-97.<br>Rhône-Poulenc Agro, France.<br>Chimac-Agriphar, Report no. R&D/CRLD/AN /9716711<br>GLP, Unpublished | Y | CAG |