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 1 rev.1

Report and proposed decision

2006

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DODINE

LEVEL 1

Statement of subject matter and purpose for which the monograph was prepared

2006

1 Statement of subject matter and purpose for which the monograph was prepared

1.1 Purpose for which the monograph was prepared (Dossier Document A)

This monograph was prepared to support the request for the first inclusion of the existing active substance dodine, made by Chimac-Agriphar, S.A., in Annex I of the Council Directive 91/414/EEC, in the scope of Commission Regulation EC/1490/2002 dated 14 August 2002, list 3B, laying down the detailed rules for implementation of the third stage of the work programme referred to in Article 8(2) of council directive 91/414/EC.

1.2 Summary and assessment of information relating to the collective provision of dossiers (Dossier Document B)

Two companies notified to defend the active substance dodine, Chimac-Agriphar, S.A. and Oxon-Sipcam.

According to Chimac-Agriphar, S.A., meetings were held between both companies. It became rapidly clear that the main data holder was Chimac-Agriphar, Oxon-Sipcam not having a complete dossier. [redacted]

Only one dossier was submitted on behalf of Chimac-Agriphar, S.A.

1.3 Identity of the active substance (Annex IIA 1)

1.3.1 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]

1.3.2 Common name and synonyms (Annex IIA 1.3)

Dodine (ISO common name).

1.3.3 Chemical name (Annex IIA 1.4)

IUPAC: 1-dodecylguanidinium acetate

CA: Dodecylguanidine monoacetate

1.3.4 Manufacturer's development code number (Annex IIA 1.5)

None – dodine.

1.3.5 CAS, EEC and CIPAC numbers (Annex IIA 1.6)

CAS: 2439-10-3

EEC: 219-459-5

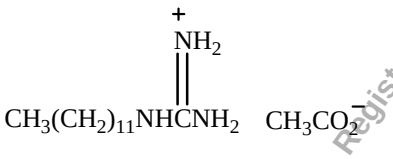
CIPAC: 101

1.3.6 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

1.3.7 Manufacturer or manufacturers of the active substance (Annex IIA 1.2)

Confidential information included in Annex C.1.1.

1.3.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information included in Annex C.1.1.

1.3.9 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 dodine 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 analyses dodine content thus leading to a lower purity.

1.3.10 Identity of isomers, impurities and additives (Annex IIA 1.10)

Confidential information included in Annex C.1.2.1.

1.3.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information included in Annex C.1.2.2.

1.4 Identity of the plant protection product (Annex IIA 3.1; Annex IIIA 1)

1.4.1 Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Trade name: SYLLIT 400 SC

Development code number: EXP10343A

1.4.2 Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

Confidential information included in Annex C.1.3.

1.4.3 Type of the preparation and code (Annex IIIA 1.5)

Suspension concentrate – SC.

1.4.4 Function (Annex IIA 3.1; Annex IIIA 1.6)

Fungicide.

1.4.5 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.

1.5 Uses of the plant protection product (Annex IIA 3.2 to 3.4; Annex IIIA 3.1 to 3.7 and 12.1)

1.5.1 Field of use (Annex IIA 3.3; Annex IIIA 3.1)

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

1.5.2 Effects on harmful organisms (Annex IIA 3.2; Annex IIIA 3.2)

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

Multisite inhibitor acting mainly on the fungus membranes.

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

1.5.3 Summary of intended uses (Annex IIA 3.4; Annex IIIA 3.3 to 3.7, 3.9)

The intended uses are summarised in Table 1.5-1.

Dodine is intended to be used as a foliar spray in early or late season applications depending on crops. Mainly spring applications. In Europe it is mainly used as a fruit fungicide against scab on apples and pears, leaf spots diseases on cherries, leaf curl on peaches.

Table 1.5-1 – Summary of intended uses

Crop and/ or situation	EU Area	Product name	F G or I[1]	Pests or group of pests controlled	Formulation		Application				Application rate per treatment			PHI[2] (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

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

[2] PHI – minimum pre-harvest interval

1.5.4 Information on authorisations in EU Member States (Annex IIIA 12.1)

The summary of authorisations in the EU Member States of Dodine under different formulations is summarised in Table 1.5-2 (according to the information provided by the notifier).

Table 1.5-2 – 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) **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. **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) **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. **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) **Apple**: Scab (Venturia sp.), 0.75-1.5 kg/ha from bud burst until 21 days pre-harvest with 7-10 days intervals. **Peach**: against leaf curl (*Taphrina deformans*) at 1.5-3.0 kg/ha. **Cherry and sour cherry:** Leaf spot (Blumeriella jaapii) at 0.75-1.5 kg/ha. PHI: 21 days. **Apricots:** against leaf browning at 1.0-1.5 kg/ha. PHI: 21 days **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) **Apple** : Scab (Venturia sp.), 0.17 % (170 ml/hl) in multiple applications from the bud opening till 28 days before harvest. **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.

COUNTRY	Authorized uses (crops, harmful organisms, rates and number of application, timings, growth stage)
Greece	Tradename : Syllit 65 WP (Dodine **65%** WP, Reg.nr : 6328) **Apple :** Scab (Venturia sp.), 60 g/hl (preventive) or 100 g/hl (curative). 2 applications maximum from the bud opening. PHI: 15 days **Pears / Medlars :** Scab (Venturia sp.), 90 g/hl (preventive) or 120 g/hl (curative). 2 app. max from the bud opening. PHI: 15 days **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 **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) **Apple/Pear**: Scab (Venturia sp.), 0.8-1.3L/ha from bud burst until 10 days pre-harvest with 10-14 days intervals. **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. **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.
Ireland	Tradename : Syllit **400g/l** SC (Dodine **400 g/l** SC, Reg.nr: PM01797) **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. **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) **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. **Cherry** : Leaf spot (*Blumeriella jaapii – Cylindrosporium padi*), 100 ml/hl). Multiple applications til 10 days before harvest. **Apricots** : against *Corineum* and *Monilia sp.* : 150-200 ml/hl (preventive). Multiple applications til 10 days before harvest. **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. **Olives** : 100-180 ml/hl **Poplars** : against *Marssonina brunea* at 80-100 ml/hl (preventive) or 120-150 ml/hl (curative) **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) Uses: see Belgium, same uses.

COUNTRY	Authorized uses (crops, harmful organisms, rates and number of application, timings, growth stage)
Netherlands	Tradename : Syllit Flow 450 SC (Dodine **450 g/l** SC, Reg.nr : 11647) **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. **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. **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) **Apple/Pear**: Scab (Venturia sp.), 1-2.25 kg/ha from bud burst with 7-10 days intervals. **Peach**: against leaf curl (*Taphrina deformans*) at 7.5 kg/ha. Application at bud swelling. **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. **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 **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. **Cherry** : against Anthracnose, 0.08-0.1% (80-100 g/hl, preventive at 10-15 days intervals) in multiple applications **Celery** : against *Septoria* diseases, 0.1 – 0.13% (100-130 g/hl)
Slovakia	Tradename: Syllit 65 WP (Dodine **65%** WP, reg.nr. 3221) Uses: see Czech Republik. Same label.

DODINE

LEVEL 2

Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

2006

2 Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

2.1.1 Identity

Dodine is a fungicide that has been used in a large number of applications worldwide for many years.

A fully acceptable technical specification based on representative batches of the industrial scale was submitted.

FAO specification CP/236 (1988) is obsolete and considered not applicable.

All points of Annex III A (SYLLIT 400 SC) relating to Identity have been addressed.

2.1.2 Physical and chemical properties

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 < 5.49×10^{-6} Pa at 20ºC) and a Henry's constant less than 1.7×10^{-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-lifes greater than 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.

The representative formulation 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.

2.1.3 Details of uses and further information

2.1.3.1 Details of uses

The intended uses of dodine are summarised in Level 1 – point 1.5.3. The summary of authorisations in the EU Member States of dodine in different formulations is in Level 1 – point 1.5.4.

Dodine (SYLLIT 400 SC) is intended to be used as a foliar spray in early or late season applications depending on crops. Mainly spring applications. In the EU it is mainly used as a fruit fungicide against scab on apples and pears, leaf spots diseases on cherries, leaf curl on peaches.

2.1.3.2 Further information

Information supplied is adequately addressed concerning Annex II and Annex III (SYLLIT 400 SC).

MSDS were submitted for technical dodine and SYLLIT 400 SC.

2.1.4 Classification and labelling

2.1.4.1 Proposals for the classification and labelling of the active substance

Hazard symbols:	T	Toxic
	N	Dangerous to the environment
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.

R50/53:

See point B.8.4.3: Considering the absence of toxic effects on biodegradation and since more than 25% of degradation occurred within 14 days (based on $ThCO_2$), therefore the test substance has no inhibitory effects on microbial activity. However, the percentage of degradation was less than 28% under the test conditions; due to this fact dodine was shown to be not readily biodegradable.

Regarding the aquatic toxicity dodine shows to be very toxic to all aquatic taxa – fish, aquatic invertebrates and algae – with LC50 values less than 0.1 µg/L (see point B.9.2; Table B.2.6.2.3)

2.1.4.2 Proposals for the classification and labelling of preparations

Hazard symbol:	T	Toxic
	N	Dangerous to the environment
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.

R50/53:

See point B.8.4.3: Considering the absence of toxic effects on biodegradation and since more than 25% of degradation occurred within 14 days (based on $ThCO_2$), therefore the test substance has no inhibitory effects on microbial activity. However, the percentage of degradation was less than 28% under the test conditions; due to this fact dodine was shown to be not readily biodegradable.

Regarding the aquatic toxicity dodine shows to be very toxic to all aquatic taxa – fish, aquatic invertebrates and algae – with LC50 values less than 0.1 µg/L (see point B.9.2; Table B.2.6.2.3)

2.2 Methods of analysis

2.2.1 Analytical methods for analysis of the active substance as manufactured

Acceptable analytical methods were submitted for determination of dodine and impurities in technical material. CIPAC titration method is obsolete and not suitable for the correct determination of dodine in technical material.

2.2.2 Analytical methods for formulation analysis

Fully validated analytical method was submitted for determination of dodine in the SYLLIT 400 SC preparation and accepted.

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

2.2.3 Analytical methods for residues analysis

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 of 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), due to low recoveries. 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).

2.3. Impact on human and animal health

2.3.1. Effects having relevance to human and animal health arising from exposure to dodine or to impurities contained in the active substance or to their transformation products

Kinetics and metabolism:

Absorption, distribution, metabolism and excretion of dodine were tested in 2 studies in Sprague-Dawley rats using a single dose (low), a second single dose (high) and a repeated dose (low) by the oral route.

The first study from 1985 used also a single intravenous administration at the low dose level of 5 mg/kg bw. Plasma levels of radioactivity after single oral administration were low reaching a maximum at 4 h post dosing and decreasing rapidly during the following 8 hours. When administered intravenously, the elimination from plasma was rapid, 1% of the administered dose was recorded 5 minutes post dosing. Repeated oral administration of dodine for 7 days indicated that the peak plasma levels (4 hours post dosing) increased slightly until the day 6, after the 5th dose however, the peak plasma levels remained approximately constant and the overall profile of plasma radioactivity after the 7th dose was similar to that observed after a single oral dose. Oral administration of a high dose (50 mg/kg bw) resulted also to a maximum level of radioactivity 4 hours post dosing, the peak plasma level of radioactivity was maintained from 4 h until 12 hours decreasing thereafter slowly to 24 hours.

Following oral administration, dodine was eliminated almost equally via the urine and faeces (approx 45% each), whereas the majority of radioactivity was eliminated in the urine (approx 70%) in the case of intravenous administration. This indicates either low absorption of the compound or increased biliary elimination following oral administration. Expired $^{14}CO_2$ was a minor route of elimination (ca. 0.5% on both types of administration), suggesting that complete degradation is limited. Radioactivity remaining in the residual carcass was higher by intravenous injection (8%) compared to oral administration (0.6%), in both cases excretion was rapid; urine and faeces accounted for more than 80% of radioactivity eliminated in 96 hours.

Following single oral administration of ^{14}C-dodine, radioactivity was distributed unevenly to the tissues; whilst radioactivity in most tissues rapidly declined over 96 h post dose, the levels of fat tissues declined only slowly. The ovaries, thyroid and skin showed some degree of retention similar to that of the fat tissue. Multiple dose administration resulted in a slower decrease of radioactivity than after single dosing, showing the same pattern of elimination.

The plasma protein binding study indicates that dodine is rapidly metabolised to more water soluble metabolites with less affinity to plasma proteins. Analysis of the metabolites indicates that ^{14}C-dodine was rapidly metabolised to a number of unidentified polar components, which were chromatographically dissimilar to dodine dodecylamine and dodecylurea.

The second study (1992), guideline compliant, was conducted with oral dose levels of 40 (single and multiple administration) and 400 mg/kg bw (single administration). The major portion (>90% of the total urinary dose) of the low (single or multiple) oral dose was eliminated by 48 hours in urine and faeces of both sexes, but in the high dose group, elimination took 120 h to be complete (only c.a. 50% of the total urinary dose was excreted in 48 h). The study author presumed that inhibition of GI tract motility (peristaltic movements) may have resulted in the prolonged excretion of dodine in the high dose group following first-order absorption process.

In this study, faecal elimination (47.6-59.7%) was higher than urine excretion (40.5-45.3%) in all dose groups. Very low amounts of radioactivity were recovered from tissues and carcass at the 120 h post dosing (all together ranged from 0.62 to 3.34% of the administered dose), the overall distribution pattern was similar in all dose groups and in both sexes. Analysis of the ^{14}C-content of expired air during the preliminary study indicated that less than 1% of the initial dose was recovered as either $^{14}CO_2$ or volatiles throughout the 72-hours period. There was no evidence of accumulation of dodine or its metabolites in tissues after single or multiple exposures.

Analysis of the faecal extracts using mass spectrometry indicated that dodine-derived radioactivity excreted in faeces was mainly the parent compound (M1), representing 42-63% of the dose, but most of the dodine-derived radioactivity in urine was eliminated as metabolites; no significant amounts of the parent compound were detected. Urine analysis using HPLC indicated 4 major peaks: M2, M3, M4 and M5, which together accounted for 33 to 48% of the dose.

M2 was identified as an alcohol of dodine, dodecylanolguanidine (DOLG), an omega-oxidation product; this was the major peak in urine samples, accounting for 11-23% of the cumulative percent of dose excreted in urine up to 120 hours post dosing. M5 was identified as urea and accounted for 3-5% of the cumulative percent of dose excreted in the urine samples. The second and third major peaks in the chromatogram (M3 and M4) were not identified; these 2 regions typically comprised 4-13% of the cumulative percent of dose excreted in urine sample. M4 was however tentatively identified as a mixture of acidic products produced by beta-oxidation of the alkane side chain of dodine. Overall, the 4 major urine peaks typically accounted for 33-48% of the dose. No glucuronide or sulphate conjugates were found.

Because of the presence of the hydroxy dodecylguanidine (M2) and the other tentatively identified acids in the M4 peak, the author of the study postulated that, the metabolism of dodine follows a beta oxidation pathway similar to that of medium- or long-chain fatty acids. Upon entering the liver cell, dodine may be activated by formation of a CoA derivative. With the help of a carrier (similar

to carnitine) it may be entering the mitochondrial matrix, and being oxidized by a sequence of reactions in which the alkyl chain of dodine is shortened by two carbon atoms at a time (beta oxidation). This series of reactions may also be catalyzed by a monooxygenase that requires NADPH, O_2, and cytochrome P450.

The absorbed dodine probably enters the liver through the portal circulation and is metabolized to hydroxydodecylguanidine and other intermediate products with shorter chain lengths which are then eliminated through the urine. Urea may also be formed in the liver as a result of the action of arginase on dodine and/or one or more of its metabolites and eliminated through the urine.

A Summary of kinetics and metabolism studies is presented in Table 2.3-1.

Table 2.3-1 – Summary of kinetics and metabolism of dodine

Study type	Species / strain	Vehicle	Results	Comments	Reference
Single dose (p.o. & i.v.), second single dose and repeated dose, oral route	Sprague Dawley CD rat (3 rats/sex/ group)	Oral: 0.5% CMC aqueous sol. i.v: ethanol	After oral dosing, ~45% of ^{14}C-dodine was eliminated via urine and ~45% via faeces; after i.v. dosing, elimination via urine was more important: up to 70% in 96h; Expired $^{14}CO_2$ was a minor route of elimination; Residual radioactivity in carcass was higher after i.v. dosing (8%) than after oral dosing (0.6%)	Oral absorption was considered to be about 45%; No potential for bioaccumulation was observed, although higher levels of radioactivity remained in fat (mainly), ovaries, thyroid and skin; Multiple dosing caused a slower elimination than single dosing	Cameron, B.D., Milner, N.P. & Dunsire., J.P., 1985
Single dose, second single dose and repeated dose, oral route	Sprague Dawley Crl: CD (BR) rat (5 rats/sex/ group)	Corn oil	Major portion of low dose (single or multiple was eliminated in 48h. in urine & faeces; elimination of high dose was complete only after 120h. Elimination via urine was between 40 and 45% of dose. Recovery of radioactivity was low in all tissues (0.62 to 3.34% of dose. In urine, no significant amount of parent compound was found and metabolites M2, M3, M4 and M5; in faeces, major compound (M1) was the parent compound	M1: parent compound 40-55% of dose in faeces M2: hydroxy dodecylguanidine 11-23% (major) in urine M3 unidentified metabolite, 7-11% in urine M4: tentatively identified as a mixture of acidic products of β-oxidation, 8-13% of dose in urine M5: urea, 3-5% of dose in urine	Reddy, V., Litle, L. and Murrill, E., 1992

Mammalian toxicity:

Acute toxicity

Dodine technical is harmful by ingestion with a LD_{50} oral of 851 mg/kg bw in rat, both sexes combined. Most frequent observations were abnormal defecation, various discoloured areas due to discharges/excretions and hypoactivity; with exception of discoloured areas and hair loss, all surviving animals appeared normal by day 12. Necropsy findings on animals which died prematurely, showed gastrointestinal abnormalities, emaciated abdominal cavity with thick white material in it, which were correlated to the severely irritating properties of test material. In mice, dodine tested orally at the limit dose of 500 mg/kg bw did not show any signs of toxicity.

By the dermal route, dodine presented low systemic toxicity in rats (LD_{50} dermal > 5000 mg/kg bw), showing, however, sign of severe erythema and slight oedema on the site of application.

If inhaled as an aerosol (nose only during 4 hours), dodine was found to be toxic in rats (LC_{50} = 0.45 mg/l air, both sexes combined). Abnormal breathing, swollen abdomen, pilo-erection, and/or staining around snout and/or jaws, and wet, matted fur were observed during the post exposure period. Macroscopical findings included severe congestion of the lungs and intestines, and distension of the gastro intestinal tract, mainly at the doses causing death.

In rabbits, dodine was found to be irritating to the skin and to cause serious damage to the eye. In a guinea pigs Magnussen & Kligman test, test material did not show sensitizing potential.

Table 2.3-2 summarises the results of acute toxicity testing conducted with dodine. It was concluded that dodine has to be classified as toxic by inhalation, harmful if swallowed, irritating to skin and with risk of serious damage to eyes derived from the acute toxicity studies.

Table 2.3-2 - Summary of acute toxicity of dodine including irritancy and skin sensitization

Test/Species (purity of a.s.)	Dose levels / vehicle	Results	Comments / Classification	References
Acute oral, rat (96.7%)	450, 761 and 1285 mg/kg bw in 0.5% methylcellulose	LD_{50} = 851 mg/kg bw	R22 – harmful if swallowed	Kern, T.G., 1999
Acute oral, mouse (98%)	250 and 500 mg/kg bw 10% in propylene glycol	LD_{50} > 500 mg/kg bw	No death and no signs of intoxication were observed in either dose levels. **Additional information**	Spanjers, M.Th.; Til, H.P., 1985
Acute dermal, rat (96.7%)	5000 mg/kg bw in deionised water	LD_{50} > 5000 mg/kg bw	No classification is required	Kern, T.G., 1999
Acute inhalation, rat (96.7%)	0, 0.25, 0.34 and 0.51 mg/l air/4h Nose only, aerosol	LC_{50} = 0.45 mg/l air	R23 – toxic by inhalation	Kenny, T., 1999
Skin irritation, rabbit (96.7%)	3 rabbits, 0.5 g in deionised water	erythema: 2/1.3/2 oedema: 0/0/0.3 almost completely reversible in days 14	R38 – Irritating to skin	Kern, T.G., 1999
Eye irritation, rabbit (96.7%)	1 animal 47 mg/0.1 ml termination at day 7	Cornea: 4; iris: 2; redness conj: 2.7; chemosis: 4; not reversible at day 7	R41 – Risk of serious damage to eyes	Kern, T.G., 1999
Skin sensitization – M&K, guinea pig (96.7%)	40% in corn oil (challenge)	All scores were 0 after challenge	No classification is required	Manciaux, X., 1999

Short-term toxicity

The short-term oral toxicity of dodine was investigated through 6 subacute/dose range-finding studies and 3 subchronic studies in rat, mouse and dog. Two dermal 21-28-day studies in rat were also presented.

Oral route

Dose range-finding studies in rats were conducted by gavage and by dietary administration. 28-day gavage administration of doses from 75 to 200 mg/kg bw/day resulted in excessive toxicity as demonstrated by a dose related increased incidence of mortality at all dose levels. Treatment-related increases incidences of deterioration of health status (reduced activity, hunched posture, partly closed eyes, blue skin tone, decreased body temperature), of respiratory distress, firm abdomens and abnormal faeces were observed at 100 mg/kg bw/day and higher dose levels. Body weight, body

weight gain and food consumption were decreased at all dose levels, and microscopical examination of gastrointestinal tract showed oedema, cell infiltration, hyperplasia of the squamous mucosa of the stomach also in all groups.

Dietary administration of dodine for the same period of time in the same strain of rats at dose levels of 0, 500, 750 and 1000 ppm [corresponding to 0, 47, 71 and 87 mg/kg bw/day in males and 0, 50, 72 and 92 mg/kg bw/day in females] resulted also in decreased body weight/body weight gain and food consumption at all dose levels.

A subsequent 28-day dietary toxicity study tested only dose levels of 0, 200 and 800 ppm [corresponding to 0, 17.7 and 67.7 mg/kg bw/day in males and 0, 19.2 and 76.7 mg/kg bw/day in females] and reached the same kind of effects at the 800 ppm dose level as the ones referred in the previous study, as well as a statistically significantly decrease in absolute and relative to body weight liver weight without correlated histopathological findings. The NOAEL was the dose level of 200 ppm corresponding to 17.7 and 19.2 mg/kg bw/day in males and females respectively.

A further dietary study in rats conducted at the same dose levels of 0, 200 and 800 ppm (conducted in parallel with the previous study) revealed no abnormal gut motility neither after a 7-day nor 28-day treatment period with dodine.

Another range-finding study in mouse was conducted at dose levels of 0, 100/1250, 250 and 650 ppm [corresponding to 0, 30.3/232.2, 49.4 and 109.4 mg/kg bw/day in males and 0, 34/323.6, 61.3 and 150.4 mg/kg bw/day in females] for a period of 8 weeks. After 3 weeks dosing, the low concentration of 100 ppm was increased to 1250 ppm due to no obvious toxic effects being observed. Toxic effects were limited to this latter higher dose level (decreased body weight/body weight gain and mild eosinophilia in the liver), however no haematological or biochemical exams were performed. The NOAEL was considered to be the 625 ppm dose level corresponding to 109.4 to 150.4 mg/kg bw/day only as additional information.

Dose-range finding study in dogs was carried out for a period of up to 6 weeks, 2 low dose levels were increased after 1 week (12.5 mg/kg bw/day → 50 mg/kg bw/day) and 3 weeks (6.25 mg/kg bw/day → 60 mg/kg bw/day) of dosing, using 2 dogs/group according to the following dosing schedule:

Table 2.3-3 – Dosing schedule

Dose Level (mg/kg bw/day)	Duration (Weeks)	Study Week	Group No.
1.25	5	1 to 5	4
6.25	3	1 to 3	3
12.5	1	1	1
25	6	1 to 6	2
50	5	2 to 6	1
60	2	4 to 5	3

Vomiting (at 12.5 mg/kg bw/day during 1 week and up) and excessive salivation were observed in most dogs treated with dodine at levels of 25 mg/kg bw/day and higher. Weight losses along with decreased food consumption were observed in all 3 highest doses tested and it was necessary to sacrifice prematurely 1 male at 50 mg/kg bw/day due to its poor health condition. Undigested food in the stomach was noted at necropsy in the same 3 highest dose animals and abnormal clearance time of contrast material from the stomach of the one dog tested at 50 mg/kg bw/day, while the low dose (1.25 mg/kg bw/day) animal showed a normal emptying time. Although no consistent adverse effects were observed at 12.5 mg/kg bw/day, no conclusion could be derived on this dose level (if it can be considered as a NOAEL or not) because treatment at this dose level lasted only for 7 days,

females had episodes of vomiting and decreased food consumption, one animal presented soft faeces and no information is available at necropsy due to change in dose level.

Oral subchronic toxicity was investigated in rat, mouse and dog; in dog, no 90-day toxicity study is available, but a 1-year toxicity study with observations at 6 months treatment was consider adequate to assess this end-point (which is in line with the revised version of Annex II to Council Directive 91/414/EEC), although an important deviation in this study was that no determination on haematological and urinalysis parameters were performed after 3 months treatment with dodine as recommended by guideline (B.30 of EU).

In a 1984 dietary study in rats, dose levels of 0, 50, 200 and 400 ppm were used initially, after the first week of treatment (day 7), dose level of 400 ppm was increased to 800 ppm because no growth depression was observed at 400 ppm. Achieved dosages were (0), 3.6, 14.1 and 55.8 mg/kg bw/day in males and (0), 3.9, 14.9 and 60.4 mg/kg bw/day in females for the 0, 50, 200 and 800 ppm dose levels respectively for the 90-day treatment period. Body weights and food consumption were decreased in both sexes of the top dose group throughout the study. In the top dose group, increased number of neutrophils in males, and a decreased plasma alanine aminotransferase activity in females were the only findings in clinical pathology and the NOAEL was the dose level of 200 ppm corresponding to 14.1 and 14.9 mg/kg bw/day in males and females respectively.

A 90-day dietary toxicity study in mouse was conducted in 1994, dose levels used were 0, 150, 300, 600, 1250 and 2500 ppm corresponding to 0, 24, 48, 94, 181 and 350 mg/kg bw/day in males and 0, 31, 60, 116, 223 and 305 mg/kg bw/day in females. Deaths (4/10 females), apparent stiffening of the tail in females were observed at the top dose level of 2500 ppm; reduced growth accompanied with lower food consumption was observed at dose levels of 2500 ppm and 1250 ppm. Significant increase in mean segmented neutrophil and decrease in mean eosinophils values were noted in 2500 ppm males group; increased levels of BUN, bilirubin and aspartate aminotransferase (AST) values at the same dose level were considered related to nutritional status of the animals, AST was also increased at lower dose levels in females, but without association with histopathological changes in the liver or kidneys. Some difference in organ weights relative to control animals at 1250 and 2500 ppm were not considered biologically significant as no histopathological changes were noted in any of the organs considered. The NOAEL was the dose level of 600 ppm corresponding to 94 and 116 mg/kg bw/day in males and females respectively, based on the reduced body weight gain at the higher level of 1250 ppm.

Oral 1-year toxicity in dogs (1996) was performed at dose levels of 0, 2, 10 and 20 mg/kg bw/day administered in gelatine capsules. Three animals (one 10 mg/kg bw/day female, one 20 mg/kg bw/day male, and one 20 mg/kg bw/day female) exhibited notably marked body weight losses and low feed intake during the first few weeks of compound administration, indicating adaptation problems to dosing. Supplemental feeding regimens were instituted for the three dogs to preclude mortality; two of the three dogs were successfully returned to basal diet by Week 8 or 15 and the third (the 20 mg/kg bw/day female) was maintained on supplemental feeding throughout the majority of the study, continuing through study termination. These findings indicate that the maximum tolerated dose in dogs was closely approximated in this evaluation. No definitive evidence of toxicity was seen in any of the other parameters evaluated in this study: The only clear pattern indicative of a treatment-related difference was the occurrence of dose-related salivation, which was most frequently noted in anticipation of dosing in the 10 and 20 mg/kg bw/day dogs. This finding was considered most likely to be a conditioned reflex or secondary effect, rather than a direct treatment-related effect. The NOAEL was the dose level of 10 mg/kg bw/day.

Dermal route

A 28-day dermal toxicity study of dodine was conducted in rats in 1999. Dose levels of 0, 50, 125 and 200 mg/kg bw/day were applied on the shave skin and occluded 6 hours/day, 5 days/week for 4 weeks resulted in a dose related local dermal irritation at all dose level. Decreased body weight gain

was observed in male rats at the 2 highest dose levels. Although the study author considered this finding as not related to dodine administration because, the gains in these males after the initial week of dosing were comparable to the control group gains, there was no trend present in the females, in the 200 mg/kg bw/day group females there was a significantly decreased mean weight gain for week 2 to 3 followed by a significantly increased gain for week 3 to 4. The overall decrease in bodyweight was 13% and 22% at 125 and 200 mg/kg bw/day respectively, RMS agreed with Applicant that severe dermal irritation may have contributed to these findings, but systemic toxicity could not be ruled out and the NOAEL was considered to be the 50 mg/kg bw/day dose level; no NOAEL could be established for local dermal irritation effects.

A 21-day dermal study was conducted with a 35% SL formulation of dodine hydrochloride salt, which produced the same kind of effects as the previous study performed with dodine (acetate form) technical. Dose levels of 12.5, 25 and 50 mg/kg bw/day presented dose-related dermal irritation, but no clear, consistent systemic effects. The systemic NOAEL was considered to be the highest dose level used of 50 mg/kg bw/day and no NOAEL could be established for dermal irritation effects.

Conclusion

It was concluded from the short-term toxicity studies in rat, mouse and dog, that the most consistently observed effects were decreased body weight and body-weight gain, which were frequently accompanied by decreased food consumption. The NOAELs for these parameters were relatively similar in the short- and longer term studies and between species. Mice showed to be less sensitive by a factor of 10 than rats or dogs. Other toxic effects were reported only rarely in these studies. Delayed gastric emptying, as measured by barium contrast radiography, was observed in one dog at 50 mg/kg bw/day.

In a mechanistic study, rats administered up to 800 ppm of dodine in the diet for 7 or 28 days and then a charcoal suspension had no evidence of altered gastrointestinal motility.

The short-term dermal studies of 21 of 28 days in duration demonstrated that dodine is a severe irritant at doses as low as 12.5 mg/kg bw/day. There was some evidence that systemic toxicity resulted from dermal application at a dose as low as 50 mg/kg bw/day, however the contribution of the severe dermal irritation could not be dismissed.

Lowest NOAEL from in the oral studies were found in the 90-day oral toxicity study in rat (14.1 mg/kg bw/day) and in the 1-year toxicity in dog (10 mg/kg bw/day); **the overall short-term NOAEL was the dose level of 10 mg/kg bw/day from the 1-year toxicity study in dog.**

Table 2.3-4 summarises the results of short-term toxicity studies conducted with dodine.

Table 2.3-4 - Summary of short term-toxicity of dodine

Test / Species (purity of test substance)	Dose levels	Results			References
		NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	Critical endpoints	
Oral, 28-day / rat (94.07%), range-finding by gavage	0, 75, 100 and 200 mg/kg bw/d	-	MTD < 75 mg/kg bw	75 mg/kg: 1/10 rat died, respiratory distress, salivation and/or staining of the fur; ↓ body weight, changes in clinical pathology, and histopathology	Batham, P., 1994a

Dodine – Level 2 – Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

Test / Species (purity of test substance)	Dose levels	Results			References
		NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	Critical endpoints	
Oral, 28-day / rat (94.07%), range-finding dietary	0, 500, 750 and 1000 ppm <> 0, 47, 71 and 87 (M) and 0, 50, 72 and 92 (F) mg/kg bw/d	< 500 ppm <> 47 -50 mg/kg bw/d	500 ppm <> 47 – 50 mg/kg bw/d	500 ppm: ↓ body weight gain (M + F)	Batham, P., 1994b
Oral, 28-day / rat (98.6%), range-finding dietary	0, 200 and 800 ppm <> 0, 17.7 and 67.7 (M) and 0, 19.2 and 76.7 (F) mg/kg bw/d	200 ppm <> 17.7 – 19.2 mg/kg bw/d	800 ppm <> 67.7 – 76.7 mg/kg bw/d	800 ppm: ↓ body weight /bw gain and food consumption (M); ↓ absolute and relative liver weight (F)	Dange, M., 1997
Assessment of gut motility / rat (98.6%), dietary for 7 – 28 days	0, 200 and 800 ppm			Normal gut motility was seen after administration of dodine for 7 and 28 days at both dose levels	Dange, M., 1996
Oral, 8-weeks / mice (95%), range-finding dietary	0, 100/1250, 250 and 625 ppm <> 0, 30.3/232.2, 49.4 and 109.4 (M) and 0, 34/323.6, 61.3 and 150.4 (F) mg/kg bw/d	625 ppm <> 109.4-150.4 mg/kg bw/d	1250 ppm <> 232.2-323.6 mg/kg bw/d	Group 2: 100 ppm: week 1-3; 1250 ppm: week 4-8 (dose level was increased due to no obvious toxic effects observed; 1250 ppm: ↓ body weight gain and mild eosinophilia in the liver. **Additional information**	Mulhern, M., Perry C.J., Snodgrass E., 1988
Oral, 6-week / dog (94.07%), range-finding by capsules	1.25, 6.25/60, 12.5/50 and 25 mg/kg bw/d only 2 dogs/group	Due to varying doses/time of dosing, it was not possible to determine NOAEL/LOAEL		Undigested food in the stomach at necropsy and abnormal clearance time of contrast material from the stomach of 1 dog (50 mg/kg bw/d) suggest an effect of a.i. on gastric emptying**.** **Additional information**	Smith, S.Y., 1994
Oral, 90-day / rat (95%), dietary	0, 50, 200 and 800 ppm <> 0, 3.6, 14.1 and 55.8 (M) and 0, 3.9, 14.9 and 60.4 (F) mg/kg bw/d	200 ppm <> 14.1-14.9 mg/kg bw/d	800 ppm <> 55.8-60.4 mg/kg bw/d	800 ppm: ↓ body weight gain (M + F), ↑ heart & kidney weights without histopathological correlates, ↓ Ca, ALT	Lina, B.A.R, Til, H.P. *et al.*, 1984
Oral, 90-day / mice (94.07%), dietary	0, 150, 300, 600, 1250 and 2500 ppm <> 0, 24, 48, 94, 181 and 350 (M) and 0, 31, 60, 116, 223 and 305 (F) mg/kg bw/d	600 ppm <> 94-116 mg/kg bw/d	1250 ppm <> 181-223 mg/kg bw/d	1250 ppm: ↓ body weight gain and food intake	Kangas, L., 1994
Oral, 1-year / dog (98.6%), by capsules	0, 2, 10 and 20 mg/kg bw/d	10 mg/kg bw/d	20 mg/kg bw/d	20 mg/kg bw/d: a supplemental feeding regimen was considered necessary (in 1 female) to prevent mortality	Trutter, J.A., 1996
Dermal, 28-day / rat (98%)	0, 50, 125 and 200 mg/kg bw/d	Systemic: 50 mg/kg bw/d No dermal NOAEL	Systemic: 125 mg/kg bw/d Dermal: 50 mg/kg bw/d	Dermal irritation at all dose levels; 125 mg/kg bw/d: ↓ body weight /bw gain (M)	Kern, T.G., 1999

Test / Species (purity of test substance)	Dose levels	Results			References
		NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	Critical endpoints	
Dermal, 21-day / rat (35% SL formulation)	0, 12.5, 25 and 50 mg/kg bw/d	Systemic: 50 mg/kg bw/d No dermal NOAEL		Dermal irritation at all dose levels; no consistent systemic effects **Additional information**	Auletta, C.S., 1989

(M): males; (F): females; bw: body weight

Genotoxicity

No potential for mutagenicity was observed with dodine tested *in vitro* in bacteria (Ames test in *Salmonella typhimurium* and *Escherichia coli*), and in mammalian cells (test for clastogenicity in cultured human lymphocytes and gene mutation at the HGPRT locus of Chinese hamster ovary cells). Two *in vivo* micronucleus tests in mice confirmed the negative results obtained *in vitro*. Table 6.80 summarises the results of genotoxicity studies.

Table 2.3-5 – Summary of genotoxicity studies.

Test / Species	Purity (%)	Conditions	Results	Comments	References
***In vitro* genotoxicity testing**					
Reverse mutation assay in bacteria / *S. typhimurium* (TA 98, 100, 1535, 1537, and 1538)	95	Concentrations of 0.06-5.0 µg/plate, vehicle: methanol + and – S9-mix	Negative	Cytotoxicity was noted at 10 µg/plate; no growth inhibition at 1 µg/plate no confirmatory experiment	Willems M.I., 1981
Reverse mutation assay in bacteria / *E. coli* (strain WP_2uvrA	98.5	1st experiment: 0.3-100 µg/plate +S9-mix 0.1-33 µg/plate –S9-mix 2nd experiment: 1-200 µg/plate +S9-mix 0.3-66 µg/plate –S9-mix vehicle: ethanol	Negative	Some toxicity was observed at 24 µg/plate and up without S9-mix, and at 66 µg/plate and up with S9-mix	Verspeek-Rip C.M., 2003
In vitro mammalian chromosome aberration test / Cultured human lymphocytes	98	+S9-mix: 0.56-15.0 µg/ml, exposure period of 2h – S9-mix: 0.37-10.0 µg/ml, exposure period of 24h vehicle: ethanol	Negative	One sampling time used for all doses, 2 highest dose showed ↓ mitotic index of 50% or more	Wilmer J.W.G.M., 1985
In vitro mammalian cell gene mutation test / Chinese hamster ovary fibroblast cells (at HGPRT locus)	98	+ S9-mix: 5.0-35.0 µg/ml - S9-mix: 2.5-20.0 µg/ml vehicle: ethanol	Negative	No independent experiment was performed	Davis P.B., 1985
***In vivo* genotoxicity testing in somatic cells**					
Micronucleus test / Swiss mouse	98	5 mice/sex/group: 0 and 500 mg/kg bw by gavage; 2 mice/sex/positive control group, i.p. sacrifice at 24, 48 and 72h vehicle: propylene glycol	Negative	No signs of toxicity were evident **Additional information**	Willems M.I., 1985
Micronucleus test / ICR mouse	94	5 mice/sex/group treated by gavage at dose levels of 100, 200 and 400 mg/kg bw; sampling time: 24, 48 and 72h (dodine); positive and negative controls: 24h vehicle: corn oil	Negative	Signs of toxicity noted at 200 and 400 mg/kg bw	Hemalatha Murli, 1992

Long-term toxicity and carcinogenicity

In the mouse chronic toxicity/carcinogenicity study, the only evidence of chronic toxicity was decreased body weight gain and food consumption at 750 ppm, the mid dose. At the high dose, there was increased severity of the same effects. There was a positive trend for hepatocellular adenomas and combined adenomas/carcinomas. There was also a statistically significant pair wise increase in combined hepatocellular adenomas/carcinomas in females. The incidence of hepatocellular adenomas and combined adenomas/carcinomas in females also exceeded the historical control values for these tumors in 1500 ppm. The high dose was considered adequate for testing the carcinogenic potential of dodine in mice.

In the chronic toxicity/carcinogenicity study in rats, the only evidence of chronic toxicity was decreased body weight, body weight gain and food consumption at 800 ppm. There was a dose-dependent increase in the incidence of combined thyroid C-cell adenomas/carcinomas in the treated males. The incidence in all treated males exceeded the mean and upper limit of the historical control range. However, the incidence in the concurrent control group also exceeded the mean of the historical control data.

Table 2.3-6 - Summary of long-term toxicity and carcinogenicity of dodine

Test / Specie (purity of test substance)	Dose levels	Results			References
		NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints	
2-years, rat (98.6%)	0, 200, 400, 800 ppm (equivalent to 0, 10, 20 or 40 mg/kg bw/day for males and 0, 13, 26.5 or 53.5 mg/kg bw/day for females)	400 ppm (equivalent to 20 – 26.5 mg/kg bw/day)	800 ppm (equivalent to 40 – 53.5 mg/kg bw/day)	800 ppm body weights: ↓ up to 10% males and ↓ 15% in female; mean total white blood cell count: ↓ 24% in males dose dependent increase in the combined thyroid adenomas/carcinomas: 23/66 (35%), 21/52 (40%), 27/60 (45%) and 33/62 (53%) in the control, low –mid and – high dose males respectively **but statistically with no significance**.	Dange, 1998
78 week, mice (98.6%)	0, 200, 750 , 1500 ppm (equivalent to 0, 29, 110 or 225 mg/kg bw/day in males and 0, 36, 136 or 277 mg/kg bw/day in females	200 ppm (equivalent to 29 – 36 mg/kg bw/day)	750 ppm (equivalent to 110 – 136 mg/kg bw/day)	1500 ppm mean body weight gains: ↓ 25.1% males and ↓ 34.6% in females. females: mean food consumption ↓ significantly. Incidence of combined hepatocellular adenomas and carcinomas significantly increased in the high-dose females (5/60, 8.3% in treated vs. 0/60 in controls) 750 ppm overall mean body weight gain for females was ↓ when compared to controls (20.1% lower); mean food consumption ↓ significantly **positive trend (no statistically significant) in the incidence of hepatocellular adenomas in females**	Williams, 1998

Reproductive toxicity

There was no evidence that dodine is a reproductive or developmental toxicant. In the multigeneration reproduction study in the rat, decreased body weight, body weight gain and food consumption were observed in both the P and F1 generations at 400 ppm and 800 ppm.There was no evidence of a treatment-related effect on reproduction parameters. Offspring of both the F1 and F2 generations had decreased mean body weights at postnatal day (PND) 4 and through PND 21 at 400 and 800 ppm.

In the rat developmental study, decreased body weight gain and food consumption was observed in maternal animals at 45 mg/kg bw per day, the mid dose. At the high dose of 90 mg/kg bw per day, the same effects, with increased severity, were observed. There was no evidence of developmental toxicity at 90 mg/kg bw per day.

In the rabbit developmental study, the evidence of maternal toxicity was decreased food consumption at 80 mg/kg bw per day, the highest dose tested. There was no evidence of developmental toxicity at 80 mg/kg bw per day.

Table 2.3-7 - Summary of reproductive toxicity of dodine

Type of test Test species Test substance purity	Dose levels	Results			References
		NOAEL (mg/kg b w/ day)	LOAEL (mg/kg bw /day)	Critical endpoints	
rat, 2 generation study 98.6%	0, 200, 400, 800 ppm (equiv. to 0, 13.14, 26.20 and 52.61 mg/kg bw/day for F0 males and 0,18, 35.34 and 67.58 mg/kg bw/day for F0 females; 0, 14.91, 30.20 and 63.03 mg/kg bw/day for F1 males and 0, 19.18, 38.77 and 76.03 mg/kg bw/day for F1 females	200 ppm for maternal toxicity (equivalent to 13.14 mg/kg bw/day) 800 ppm for reproductive performance (equivalent to 52.61 mg/kg bw/day) 200 ppm for pup development (equivalent to 13.14 mg/kg bw/day)	400 ppm for maternal toxicity (equivalent to 35.34 mg/kg bw/day) 400 ppm for pup development (equivalent to 30.20 – 38.77 mg/kg bw/day)	800 ppm: ↓ body weight gain, body weight and food consumption for F0 and F1 males and females. 400 ppm: ↓ body weight gain in F1 females Offspring: 800 and 400 ppm ↓ body weight No effects in reproductive parameters	Henwood, 1996
rat, developmental 95%	0, 10, 45 and 90 mg/kg bw/day	10 mg/kg bw/day for maternal toxicity 90 mg/kg bw/day for developmental toxicity	45 mg/kg bw/day for maternal toxicity	↓ body weight gain and food consumption at 45 and 90 mg/kg bw/day No developmental toxicity – no teratogenic effects	Hazelden, Wilson, 1989
Rabbit, developmental 95%	0, 10, 40 and 80 mg/kg bw/day	40 mg/kg bw/day for maternal toxicity 80 mg/kg bw/day for developmental toxicity	80 mg/kg bw/day for maternal toxicity	↓ food consumption at 80 mg/kg bw/day No developmental toxicity – no teratogenic effects	Hazelden, Mc Cay, 1989

Dermal absorption

Following topical administration of [^{14}C]-Dodine at 0.6 g/1 to the shaved dorsal area of male rats, the absorption was minimal. The majority of the applied radiolabel was removed by washing at 8 hours, most of the remaining residue was associated with the stratum corneum.

At the end of the application period approximately 90% of the applied radiolabel was removed by rinsing the application site. Following application less than 2% of the applied radiolabel was absorbed. At 3 to 5 days after application, approximately 7% of the applied radiolabel had been lost from the skin surface by desquamation, at 10 days this amount increased to almost 13% (skin lost by desquamation was collected in dressings placed on the animals daily, some of this will have spread under the dressing to the fur away from the treated site, both the dressings and the fur & skin were included in the estimate of total desquamation). The applied radiolabel associated with the

skin at the treated site was mainly found in the stratum corneum, at 3 to 5 days approximately 4% of the applied radiolabel was within this layer but by Day 10 the level had fallen to about 0.7% (these values were extrapolated from disc 2 where the radiolabel in the various skin compartments were measured).

The changes in distribution of the applied radiolabel over the duration of the study demonstrated that the [^{14}C]-Dodine was poorly absorbed through the skin (<2%) and that the residue within the skin was mainly associated with the stratum corneum. The data show that during the post application period, there were increasing amounts recovered from skin dressings (i.e. skin lost by desquamation) and decreasing amounts remaining in the stratum corneum, but there was no increase in the total amounts found in the urine, faeces, blood or carcass.

For risk assessment was considered that dermal absorption was 2.75% (considering the amount in the stratum corneum at 10 days) for both concentrate and the dilution.

2.3.2. ADI

The calculation of an acceptable daily intake (ADI) is established on the basis of the highest dose at which no adverse effect is observed in the most appropriate study in the most sensitive species.

With a conclusive data package dodine was found to cause no specific concern after repeated exposure: main critical effects were reduced body weight gain, eventually associated with decreased food consumption.

The most critical effects were observed in the combined chronic/carcinogenicity study in rats, where a non-statistically significant dose dependent increase in combined thyroid adenomas/carcinomas was observed in males [23/66 (35%), 21/52 (40%), 27/60 (45%) and 33/62 (53%) in the control, low –mid and –high dose males respectively] and in the carcinogenicity study in mice, where a positive trend (also not statistically significant) in the incidence of hepatocellular adenomas was observed in females. These observations were not considered to reflect a carcinogenic potential of dodine.

Dodine is unlikely to be genotoxic, no effects on reproductive or developmental parameters were observed and no concern on neurotoxicity was raised.

The more relevant NOAEL for this purpose is considered to be the dose level of 10 mg/kg bw/day derived from the 1-year, dog study. A safety factor of 100 is proposed on the basis of the low concern on the toxicological endpoints, resulting in an ADI of 0.1 mg/kg bw/day.

$$\textbf{ADI dodine} = \frac{\textbf{NOAEL}}{\textbf{S.F.}} = \frac{\textbf{10}}{\textbf{100}}\ \textbf{mg/kg bw/day} = \textbf{0.1 mg/kg bw/day}$$

2.3.3 ARfD

Dodine was found to be harmful if swallowed and toxic by inhalation in the acute toxicity studies; it was also irritating to skin and with risk of serious damage to eyes. As referred before, a low degree of concern was raised from the whole toxicological data package submitted.

As the main concern from the acute toxicity studies refers to the inhalative route, no acute reference dose is proposed for dodine.

2.3.4. AOEL

According to the principles of Annex VI to Directive 91/414 EEC, the proposed AOEL should be established on the basis of the highest dose at which no adverse effect is observed in relevant studies in the most sensitive species.

Considering that short-term and long-term studies gave similar results, as shown in the following table, the same NOAEL was considered appropriate for the AOEL as the one used for the ADI:

Study type	Species	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)
28-day oral	rat	17.7	67.7
90-day oral	rat	14.1	55.8
90-day oral	mice	94	181
1-year oral	dog	10	20
2-year	rat	20	40
78-week	mice	29	136
2 generations reproduction	rat	13.1	30.2
teratogenicity oral	rat	10	45
teratogenicity oral	rabbit	40	80

Considering the NOAEL of 10 mg/kg bw/day from the 1-year dog study, which is the same as the NOAEL obtained for maternal toxicity in the rat teratogenicity study, a safety factor of 100 as no specific concern on toxicological endpoints was raised, and an oral absorption of 45% based on urinary excretion within 24 h (see B.6.1.5.), the following systemic AOEL is proposed:

$$\text{AOEL}_{\text{systemic}}\ \text{dodine} = \frac{\text{NOAEL}}{\text{S.F.}} \times \text{oral abs.} = \frac{10}{100} \times 0.45 \ \text{mg/kg bw/day} = 0.045 \ \text{mg/kg bw/day}$$

2.3.5 Drinking water limit

Assuming average consumption of 2 litres of water per person per day and body weight of 70 Kg and one tenth of the ADI allocated to drinking water, according to the WHO approach, the maximum allowable concentration (MAC) in water results:

$$\text{MAC} = \frac{0.1 \times 70 \times 0.1}{2} = 0.35 \ \text{mg/l}$$

2.3.6 Impact on human or animal health arising from exposure to dodine or to impurities contained in it

Operator exposure according to UK POEM model

It was concluded that, using the UK POEM, exposure is acceptable when PPE [like gloves during mixing/loading and application, but based on the corrosivity potential of the formulation, R 34 "Causes burns" PPE are already recommended (safety phrases S36/37/39: Wear suitable protective clothing, gloves and eye/face protection, see B.6.4.2)] are used during mixing and loading and

application of 1500 l of spray, therefore **the intended uses are acceptable.** With the application of 500 l of spray the exposure even when PPE are used is always higher than the AOEL.

Operator exposure according to German model

Based upon the worst case estimates produced by the German operator model, when Syllit SC 400 is applied in accordance with label instructions and operator wearing gloves during mixing/loading and application [based on the corrosivity potential of the formulation, R 34 "Causes burns" PPE are already recommended (safety phrases S36/37/39: Wear suitable protective clothing, gloves and eye/face protection, see B.6.4.2)], estimated systemic exposure to dodine is a maximum of 72.3% of the proposed Acceptable Operator Exposure Level (0.045 mg/kg bw/day).

Bystander exposure

Predicted systemic exposure for a bystander (assuming a 70 kg body weight and 2.75 % dermal absorption) from a treatment in high crops (orchards) is **0.0000589 mg/kg bw/day** which is equivalent to 0.131 % of the systemic AOEL.

So we can conclude that the calculated amount of dodine which might reach a bystander has no toxicological relevance, and for the proposed uses is acceptable taking into account the proposed AOEL

Worker exposure

Re-entry exposure as soon as spray was dried and during 35 days after the last of 4 applications in high crops, treated with Syllit 400SC represents an acceptable level of risk for workers when PPE like gloves, long sleeved shirt and long trousers are worn.

2.4 Residues

2.4.1 Definition of the residues relevant to MRL's

The proposed plant and animal residue definition for monitoring and risk assessment is the parent dodine.

2.4.2 Residues relevant to consumer safety

Metabolism in plants

In plants (apples, strawberries and pecans) dodine is the residue of concern and it is degraded to terminal residues of guanidine or urea. Dodine accounted for 79% TRR in apples; about 80% of the residues were associated with apple peels. In strawberries dodine represented 85-89% TRR. In pecans the major metabolite was guanidine (36% TRR); dodine represents 13.2% TRR and urea 4.4% TRR.

The terminal carbon of the dodecyl chain of dodine is oxidized to a carboxyl group and then the chain is degraded, apparently two carbon atoms at a time, consistent with β-oxidation, until all that remains are the terminal metabolites: guanidine and urea.

Metabolism in livestock

In goats dodine was extensively metabolized. After dosing 13 ppm in the diet, 68% TRR was excreted in urine and faeces and 0.05% in milk (0.014 ppm), while less than 1% remained in the edible tissues (0.020 ppm in muscle, 0.11 ppm in kidney and 0.17 ppm in liver). In these tissues dodine was present in small percentages ($\leq$ 5.2%; $\leq$ 0.004 ppm). No dodine was detected in milk. Urea was present in all the edible tissues. Alkyl guanidine carboxylic acids (dodecylguanidine carboxylic acid, octylguanidine carboxylic acid and hexylguanidine carboxylic acid) were the largest portion of the residue in the edible tissues (52% TRR - $\leq$0.01 ppm in muscle, 41% TRR -

≤0.07 ppm in liver and 50% TRR - ≤0.05 ppm in kidney). The presence of the carboxylic acid group on the chain distal to the guanidine group should prevent these metabolites from having the same toxicity as dodine being so less toxic than dodine.

Residue trials and LMR proposals

The intended GAP for apples and pears for the North and South of E.U. is: max. 5x0.045-0.18kg a.s./hl; PHI of 28 days.

For apples, there are 16 acceptable residue trials, located in France (in 1998 e 1999). Eight are from the North and eight from the South. The residues found in the whole fruit in the North are: 0.088, 0.114, 0.121, 0.160, 0.180, 0.263, 0.277, 0.383 mg/kg; in the South are: 0.126, 0.267, 0.303, 0.310, 0.357, 0.440, 0.727, 0.930 mg/kg. Considering together the North and South, the Rmax is 0.89mg/kg, the R(ber) is 0.74mg/kg, the STMR: 0.27mg/kg and the HR:0.93mg/kg. The MRL proposal is:1 mg/kg.

There are also 16 acceptable residue trials in pears, located in France (in 1998, 1999 and 2001). Eight are from the North and eight from the South. The residues in the whole fruit in the North are: 0.180, 2x0.370, 0.450, 0.480, 0.540, 0.610, 1.300 mg/kg; in the South are: 0.160, 0.250, 0.260, 0.290, 0.310, 0.400, 0.540, 0.600 mg/kg. Considering the North and South, the Rmax is 1.12, the R(ber) is 1.08, the STMR is 0.39mg/kg and the HR is 1.3 mg/kg. The MRL proposal is:1 mg/kg.

For cherries the intended GAP for the North and South of E.U. is: max. 3x0.05-0.16kg a.s./hl; PHI of 14 days.

The acceptable data base contains eight residue trials located in France (in 1997, 1998, 1999 and 2001). Four are from the North and four from the South. The residues in the whole fruit in the North/South are: 2x0.14, 0.27, 0.46, 0.56, 2x0.70, 0.77 mg/kg. The Rmax is 1.29mg/kg, the R(ber) is 1.4mg/kg, the STMR is 0.51mg/kg and the HR is 0.77mg/kg. The MRL proposal is 1 mg/kg.

For peaches the intended GAP is for the South of E.U. is: max. 5x0.06-0.18kg a.s./hl; PHI of 60 days.

The acceptable data base contains two residue trials located in the South of France (in 1997 and 1998). The residues in the whole fruit are: 0.053 and 0.063 mg/kg. For this PHI we have only two more trials, but with a higher concentration of application (>than 25%), giving residues < 0.05 mg/kg. For a PHI of 75 days and considering also the higher concentrations (>25%), we have seven residue trials (94-272 g a.s./hl, PHI of 71-93 days), located in France (1997 and 1998). Residue values: 6x<0.05, 0.073mg/kg. The R(ber) is 0.12mg/kg the STMR:0.05mg/kg and the HR:0.073 mg/kg. The MRL proposal is 0.1 mg/kg (for a 75 days PHI).

Stability of the residues

The storage stability of the residue of dodine was evaluated in two studies. The residue was stable in apple, apple juice; apple wet pomace, peaches and cherries when stored at -18 or -20ºC, during 18 months.

Derivatized dodine showed to be stable in the pear and cherry extracts for at least 5 days at ambient temperature.

Livestock feeding studies

Fruit pomace can represent 10 or 30% in the feed intake of dairy cattle and beef cattle, respectively. If we consider the residue in pomace of 4,65mg/kg obtained with the highest residue in apples - 0.93 mg/kg and the concentration factor (from apple into pomace) of 5, the intake calculation gives 20 mg/kg diet/day on a dry weight basis. Total radioactive residues in the goat tissues from the goat metabolism study, were 0.17 ppm in the liver and 0.11 ppm in kidney, with an intake of 13 ppm in the diet during 5 days.

According to this a livestock feeding study seamed to be necessary to determine the residue in products of animal origin. However it seams unessential if we consider the following:

- the metabolism study in lactating goat, using 13 ppm in the diet indicated that dodine was a minor component in all edible tissues (0.001 mg/kg in the muscle, 0.004 mg/kg in the liver and 0.003 mg/kg in kidney) and was not present in milk;
- even if the dose fed to the goats in the metabolism study was double (2x13 ppm), considering the calculated intake of pomace of 20 mg/kg diet/day, the dodine residue values in edible tissues and milk would be below 0.01 mg/kg;
- the other metabolites found in the metabolism of the goat are three alkyl guanidine carboxylic acids (dodecyl guanidine carboxylic acid, octylguanidine carboxylic acid and hexylguanidine carboxylic acid, representing 52% TRR - $\leq$0.01 ppm in muscle, 41% TRR - $\leq$0.07 ppm in liver and 50% TRR - $\leq$0.05 ppm in kidney), however, the presence in those metabolites of the carboxylic acid groups at the distal end of the alkyl group, besides the quaternary amine, makes them unlikely to share any of the biological effects of dodine and are not expected to have dodine toxicity.

So, we can conclude that the residues resulting from the livestock feeding study should not be of concern and there is no need to make a livestock feeding study.

Effects of industrial processing

Treated apple processed fraction samples showed a mean residue value of 1.67 ppm in the whole apples, 0.13 ppm in the juice (reduction factor of 12) and 7.77 ppm in the wet pomace (concentration factor of 5).

Risk assessment

Considering the Acceptable Daily Intake of 0.1 mg/kg bw/day and the chronic risk assessment estimate, it can be concluded that only a small percentage (0.3-7%) of the ADI is reached with the proposed uses.

2.4.3 Residues relevant to worker safety

The residues relevant to worker safety are the a.s.

2.4.4 Proposed EU MRLs and compliance with existing MRLs

Apples and pears: 1 mg/kg

Cherries: 1 mg/kg

Peaches: 0.1 mg/kg

2.4.5 Proposed EU import tolerances and compliance with existing MRLs

No import tolerances were requested.

2.4.6 Basis for differences if any, in conclusions reached having regard to established or proposed CAC MRLs

The CAC MRLs are listed bellow:

pome fruit:	5 mg/kg
Peaches:	5 mg/kg
Nectarines:	5 mg/kg
Cherries:	3 mg/kg

The CAC MRL of 5 mg/kg for pome fruit was established considering the GAP from USA (6x0,75-2,2 kg as/ha; 0.07-0.43 g as/hl; 7 days PHI), more critical than the EU GAP.

The CAC MRL of 5 mg/kg for peaches was established considering the GAP from USA (5x1,5-3 kg as/ha; 0.07-0.31 kg as/hl; 15 days PHI), more critical than the EU GAP.

The CAC MRL of 3 mg/kg for cherries was based on a GAP from Canada (6x1,5 kg as/ha; 0.07-0.22 kg as/hl; 7 days PHI), more critical than the EU GAP.

2.5 Fate and behaviour in the environment

2.5.1 Definition of the residues relevant to the environment

Definition of the residue in soil

Dodine was shown to be extensively degraded in all aerobic laboratory and field studies. The major degradation product was CO_2. Bound residues remain at low levels .No major metabolites were identified, only minor metabolites accounting for a very low percentage of applied radioactivity. These compounds have no toxicological or environmental significance. Thus the relevant residue in soil is dodine.

Definition of the residue in water

The water sediment study conducted with dodine showed that the a.s. dissipates rapidly from the water phase, by mineralisation and dissipation into the sediment. In sediment dodine dissipates rapidly by mineralisation or by formation of bound residues strongly adsorbed to the sediment. No major metabolites were detected in water/sediment systems. These compounds have no toxicological or environmental significance. Thus the relevant residue in water is dodine.

2.5.2 Fate and behaviour in soil

The degradation of dodine was studied in aerobic and anaerobic conditions, in laboratory studies. The influence of irradiation in the degradation process of dodine was also investigated. Dodine was rapidly degradated under aerobic conditions, with DT_{50} (1^{st} order)values between 3 and 6 days. Under anaerobic conditions the degradation was significantly slow, with an estimated DT_{50} far greater than 1 year. Considering the results of dodine photodegradation, it can be considered that photolysis does not play a significant role for dodine degradation, since a DT_{50} of 96 days was estimated in the irradiated sample and a DT_{50} of 103 days was determined in the dark soil sample. These results are consistent with the conclusion that dodine degrades in the environment by microbial degradation.

The rate of dodine degradation in soil is slightly dependent on pH and moisture content on degradation is not influenced by the soil type or tested concentration.

Under field conditions a DT_{50} (1^{st} order) between 7 and 19 days and a DT_{90} lower than 90 days were estimated, with expception of the DT_{90} estimated in soil 8. Dodine was found to be not persistent in soil. Degradation of dodine should occur via microbial activity, mediated by oxidation to CO_2, with formation of multiple and smaller minor metabolites. No major metabolite was found in the laboratory or field studies. Indeed no metabolites reached more than 6% of RA. The major degradation product was CO_2, with a maximum of 95.4% for guanidine labelled dodine at the end

of the study and 81.4 for labelled chain dodine. The bound residues remained at low levels with a maximum of 11.4% of AR during the first 10 days and values lower than 4.2% were registred at the end of the study, for all soils and for guanidine labelled dodine. Higher values of bound residues were registred in chain labelled dodine, the maximum value was 27% of AR at day 5, decreasing to 17.2% at the end of the study.

For the purpose of estimating the PEC in soil the following proposed uses (Table 2.5-1) were forwarded by the notifier:

Dodine formulated as a 400g/l SC formulation (A.S. 400SC) will be applied five times, spaced by 7 days, at maximum rate of 0.9 kg dodine/ha. Since there were no major metabolites formed in soil, predicted environmental concentrations (PEC) were calculated for dodine only. The initial predicted environmental concentration in soil (PECs) is a worst case estimation based on the maximum rate being applied with canopy interceptions of 20%. For calculation purposes, it is assumed that the residues of dodine are uniformly distributed in the soil to a depth of 5 cm (bulk density 1.5 g/cm3).

Using the realistic worst-case DT_{50} of 18.6 days from field studies, the actual and TWA PEC_S values have been calculated for dodine. The calculated actual and TWA PECs values are presented in Table X

Table 2.5-1 - Actual PECs values and time-weighted average concentrations for dodine calculated using the first-order DT_{50} value of 18.6 days

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.96		3.04	
Short term 24h	0.940	0.923	2.98	2.928
2d	0.921	0.889	2.928	2.821
4d	0.889	0.825	2.823	2.618
Long term 7d	0.8429	0.738	2.675	2.341
28d	0.5945	0.337	1.887	1.070
50d	0.4342	0.149	1.378	0.472
100d	0.2508	1.19E-06	0.796	7.32E-02

2.5.2.1 Adsorption/desorption and mobility in soil

The adsoption/desorption characteristics of dodine were studied using a batch equilibrium method. Adsorption coefficients ranging between $5.51x10^5$ and $1.29x10^7$ were determined for tested soils. Dodine was classified as immobile in soil. This result is supported by a dodine column leaching study with aged residues, where dodine showed low potential to leach (see Table B.8 24).

The leaching potential of dodine has been determined using FOCUS PELMO model version 3.3.2, all nine scenarios have been considered, Châteaudun, Hamburg, Jokioinen, Kremsmünster, Okehampton, Piacenza, Porto, Sevilla and Thiva. The model simulations were carried out using realistic worst-case input parameters (see Table B.8 43) and one realistic application scenario was taken in account. Five applications at the highest dose, 900 g a.s./ha, with 7 to 10 application interval in apple were assumed.

Dodine is a fungicide for apple/pear, cherry and peach, the “apple scenario” is the only available in the different models and can be considered representative for intended uses. Since the application

on apples is made from the bud opening (BBCH 01) until 28 days before harvest (BBCH 69), early application will be considered for modelisation. Regarding the FOCUSgw guidance (2000) recommendations, the applications were simulated to be carried out on the soil surface and the application rates were manually corrected for interception accordingly. The interception varies according to the time of application, 50% without leaves, 65% flowering, 70% foliage development and 80% full foliage.

For PELMO and PEARL models early applications were considered, ranging from March to May. For PRZM model, the application is relative to the emergence. For all models the relation between range between 50% for the first two applications, 65% for the third and fourth applications and 70% of interceptions for the last application. This can be considered a conservative approach because the foliage development is reduced and the interception is therefore smaller.

For the model MACRO, only one scenario (Chateaudun) is taken into account. The application range between April and May, and the same scheme of interception was considered.

Table 2.5-2 - Predicted concentrations of dodine at 1 meter soil depth following the use of dodine 400 SC in apples using the FOCUS gw Models

Scenario	80th percentile annual average concentration at 1m			
	PELMO	PEARL	PRZM	MACRO
Chateaudun	0.000	0.000	0.000	0.000
Hamburg	0.000	0.000	0.000	-
Jokioinen	0.000	0.000	0.000	-
Kremsmunster	0.000	0.000	0.000	-
Okehampton	0.000	0.000	0.000	-
Piacenza	0.000	0.000	0.000	-
Porto	0.000	0.000	0.000	-
Sevilla	0.000	0.000	0.000	-
Thiva	0.000	0.000	0.000	-

The model predicted that dodine would not be found at annual average concentrations as defined by FOCUS at concentrations greater than 0.001 µg/L, at 1 m depth, in any Châteaudun, Hamburg, Jokioinen, Kremsmünster, Okehampton, Piacenza, Porto, Sevilla and Thiva scenarios.

2.5.3 Fate and behaviour in water

Dodine was hydrolytically stable at pH7 and 25ºC with DT_{50} of 914 days. Under alkaline conditions dodine showed more stability and at acidic conditions dodine was less stable. Hydrolysis is not likely to be a significant route of dissipation of dodine in water. Photolysis may not play a important role for dodine degradation in water, since a DT_{50} of 174 days in buffer pH 7 was estimated, however in natural water conditions the DT_{50} was sigificatly lower (12days). Under dark conditions no degradation occurred (DT_{50} of 450 days), but in natural water the degradation occurred with a DT_{50} of 30 days, indicating that the degradation conditions are more related with water conditions than with light radiation.

Dodine is not readly biodegradable.

The water sediment study conducted with dodine showed that the a.s. dissipates rapidly from the water phase, by mineralisation and dissipation into sediment, with a DT_{50} < 1 day in the water phase. In sediment dodine dissipates rapidly from the sediment by mineralisation or by formation of bound residues strongly adsorbed to the sediment. In the whole system a DT_{50} also lower than 1 day was estimated.

The Predicted concentration of dodine in surface water and in sediment was estimated regarding the worst case application scenario, i.e. 5 early applications of 900 g a.s/ha in orchards, with 7 days interval and interception of 40% (average crop cover).The assessment of PECsw and PECsed followed the STEP 1, STEP 2, STEP 3 and STEP 4 (for buffer zones). For STEP 1 and STEP 2 was used an FOCUS model version 1.1, for pome/stone fruit, for North and South of Europe, regarding early applications and crop interception of 40%.The STEP 3 simulation was conducted with SWASH version 2.1 and drift calculator 1.1, MACRO version 4.3b or PRZM version 3.21β models to simulate potential surface water exposure and TOXSWA version 2.2.1 to simulate the fate and behaviour of the compound in the water body. As in the guideline 7193/VI/99 rev0 (Guidance document of calculation PEC values of plant protection products for soil, ground water, surface water and sediment) the route of contamination via drains in only possible when Koc < 500. In case of dodine, which has a Koc ranging from 5.51 x 105 to 1.27 x 107, there is no need to consider this source of loading. So, the TXSWA calculations were only performed on scenarios where the product enter the compartment surface water by spray drift and run off, i.e. R1 pond, R1 stream, R2 stream, R3 stream and R4 stream. Five applications by air blast with an interval of 7 days between each application were considered.

Note that only the initial PEC (global maximum) and the 21 day values were presented since they are the representative input paramenter for aquatic risc assessment.

Table 2.5-3 - FOCUS Step 1 PECsw and PEDsed for dodine application to pome/stone fruit

FOCUS STEP1 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0	**87.644**		**2.25E^{+03}**	
	1	0.032	43.838	1.37E^{+03}	1.81E^{+03}
	2	0.015	21.930	644.090	1.39E^{+03}
	4	0.003	**10.969**	142.736	858.861
	7	0.000	6.269	14.891	515.019
	14	0.000	3.134	0.076	258.914
	21	0.000	**2.090**	0.000	**172.614**
	28	0.000	1.567	0.000	129.461
	42	0.000	1.045	0.000	86.307
	50	0.000	0.878	0.000	72.498
	100	0.000	0.439	0.000	36.249

Table 2.5-4 - FOCUS Step 2 PECsw and PEDsed for dodine application to pome/stone fruit

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU	0	**69.348**		**618.900**	
	4	0.015	**9.606**	30.384	204.420
	21	0.000	**1.830**	0.000	**40.947**
Southern EU	0	**69.348**		1220.000	
	4	0.034	**10.969**	142.736	858.862
	21	0.000	**1.831**	0.000	**60.469**

Table 2.5-5 - FOCUS Step 3 PECsw and PEDsed for dodine application to pome/stone fruit

FOCUS STEP 3 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	3.063		1.658	
		4	0.053	0.930	0.665	1.433
		21	0.004	0.454	0.798	0.812
R1	Stream	0	41.862		4.786	
		4	0.000	1.682	1.398	2.919
		21	0.000	0.813	1.722	1.456
R2	Stream	0	55.589		5.345	
		4	0.000	1.140	0.873	2.893
		21	0.000	0.434	0.446	1.347
R3	Stream	0	**59.298**		**12.710**	
		4	0.001	**4.146**	6.177	7.505
		21	0.000	**2.255**	1.930	**4.750**
R4	Stream	0	42.110		10.977	
		4	0.000	1.927	1.763	6.067
		21	0.000	0.968	0.000	2.226

Table 2.5-6 - FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (10 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	1.915		1.037	
		4	0.033	0.581	0.416	0.499
		21	0.003	0.284	0.499	0.508
R1	Stream	0	17.042		2.310	
		4	0.000	0.685	0.295	1.266
		21	0.000	0.331	0.779	0.594
R2	Stream	0	22.633		5.232	
		4	0.000	0.464	0.855	2.822
		21	0.000	0.179	0.182	0.910
R3	Stream	0	**24.149**		6.215	
		4	0.000	**1.754**	1.444	3.784
		21	0.000	**0.960**	0.805	2.126
R4	Stream	0	17.143		**10.977**	
		4	0.431	0.797	1.763	6.067
		21	0.000	0.394	0.000	**1.527**

Table 2.5-7 - FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (20 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	0.554		0.300	
		4	0.003	0.168	0.119	0.260
		2	0.000	0.0821	0.136	0.147
R1	Stream	0	4.149		1.235	
		4	0.000	0.167	0.270	0.803
		21	0.000	0.0806	0.000	0.266
R2	Stream	0	5.511		5.174	
		4	0.000	0.113	0.846	2.786
		21	0.000	0.0470	0.045	0.688
R3	Stream	0	**5.887**		2.859	
		4	0.000	**0.511**	0.666	2.021
		21	0.000	**0.250**	0.201	0.760
R4	Stream	0	4.174		**10.976**	
		4	0.431	0.210	1.763	6.067
		21	0.000	0.096	0.000	**1.527**

Table 2.5-8 - FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (30 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	0.240		0.130	
		4	0.001	0.072	0.052	0.112
		21	0.001	0.036	0.062	0.064
R1	Stream	0	1.392		1.234	
		4	0.000	0.078	0.215	0.705
		21	0.000	0.270	0.000	0.210
R2	Stream	0	1.849		5.161	
		4	0.000	0.038	0.844	2.778
		21	0.000	0.019	0.015	0.664
R3	Stream	0	**1.981**		2.477	
		4	0.000	**0.245**	0.705	1.656
		21	0.000	**0.097**	0.111	0.497
R4	Stream	0	1.400		**10.976**	
		4	0.431	0.202	1.763	6.067
		21	0.000	0.051	0.000	**1.527**

Table 2.5-9 - FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (35 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	0.173		0.094	
		4	0.001	0.052	0.037	0.080
		21	0.001	0.255	0.045	0.046
R1	Stream	0	0.917		1.234	
		4	0.000	0.064	0.206	0.688
		21	0.000	0.021	0.000	0.201
R2	Stream	0	1.218		5.159	
		4	0.000	0.025	0.843	2.777
		21	0.000	0.014	0.010	0.660
R3	Stream	0	**1.309**		2.472	
		4	0.000	**0.200**	0.662	1.592
		21	0.000	**0.072**	0.073	0.442
R4	Stream	0	0.922		**10.976**	
		4	0.431	0.202	4.404	6.067
		21	0.000	0.540	0.001	**1.527**

Table B.2.5-10 - FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (40 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	0.129		0.070	
		4	0.001	0.039	0.277	0.060
		21	0.001	0.019	0.033	0.034
R1	Stream	0	0.638		1.234	
		4	0.000	0.055	0.200	0.678
		21	0.000	0.018	0.000	0.195
R2	Stream	0	0.848		5.157	
		4	0.000	0.024	0.843	2.776
		21	0.000	0.011	0.007	0.657
R3	Stream	0	**0.914**		2.470	
		4	0.000	**0.173**	0.637	1.556
		21	0.000	**0.056**	0.051	0.421
R4	Stream	0	0.642		**10.976**	
		4	0.431	0.202	1.763	6.067
		21	0.000	0.051	0.000	**1.527**

The scenario R3 was identified as the representative worst case scenario, for surface water, as result of application of dodine to pomme/stone fruits. The worst case scenario identified for sediment was the R4.

2.5.4 Fate and behaviour in air

Regarding the physical-chemical properties of dodine, in particular the vapour pressure of 5.49 x 10^{-6} Pa at 50ºC and the Henry's law constant < 1.7 x 10^{-3} Pa m^3/mol at 20ºC, it is possible to expect a very little potential of dodine to volatilise.

The predicted environmental concentrations in air (PEC_A) are expected to be negligible for dodine, since was estimated a vapour pressure, at 50ºC, lower than 5.49 x 10^{-6} Pa and a Henry's law constant < 1.7 x 10^{-3} Pa m^3/mol at 20ºC.

2.6 Effects on non-target species

2.6.1 Effects on terrestrial vertebrates

2.6.1.1 Birds

The acute LD_{50} values for species tested were between 857 and 981 mg/kg. The lowest value was 857 mg/kg obtained for Mallard duck (Hakin, 1990b) and the highest being 981 mg/kg obtained for bobwhite quail (Hakin, 1990a).

Two dietary LC_{50} studies have been reported. Those studies were conducted with mallard duck and bobwhite quail and indicated LC_{50} values of 2263 and 5200 ppm respectively.

The lowest NOEL values for reproduction studies conducted with mallard duck and bobwhite quail were 200 and 300 ppm respectively.

Table 2.6-1 - Summary of toxicological endpoints on birds dosed with dodine technical

Species	Study type	Findings	GLP status	Reference
Bobwhite quail	Acute oral LD_{50}	21-day LD_{50} 981 mg/kg	GLP	Hakin, 1990a
Mallard duck	Acute oral LD_{50}	21-day LD_{50} 857 mg/kg	GLP	Hakin, 1990b
Bobwhite quail	Sub-chronic LC_{50}	8 day LC_{50} > 5200 ppm (976 mg as/kg/day)	GLP	Hakin, 1990a
Mallard duck	Sub-chronic LC_{50}	8 day LC_{50} 2263 ppm (280 mg as/kg/day)	GLP	Hakin, 1990b
Bobwhite quail	Sub-chronic (Range finding)	6-week NOEL 1500 ppm (135 mg as/kg/day)	GLP	Peterson & Mumper, 1993a
Bobwhite quail	Reproduction	24-week NOEL reproduction 1000 ppm (95 mg as/kg/day)	GLP	Peterson, 1994a
Bobwhite quail	Reproduction	21-week NOEL reproduction 300 ppm (27 mg as/kg/day)	GLP	Peterson, 1999
Mallard duck	Sub-chronic (Range finding)	6-week NOEL 750 ppm (50 mg as/kg/day)	GLP	Peterson & Mumper, 1993b
Mallard duck	Reproduction	20-week NOEL reproduction 200 ppm (20 mg as/kg/day)	GLP	Peterson, 1994b

Reproduction studies were conducted on the Bobwhite quail and Mallard duck. Before the definitive studies two range finding studies were developed. The bobwhite quail was less susceptible tested species and a NOEC of 300 ppm was established. The mallard duck showed more susceptibility to dodine with statistically significant effects on eggs laid per hen per laid, on % of viable embryos, on % 14-day-old survivors and on mean body weight of 14-day-old survivors at concentrations of 600 and 1000 ppm. A NOEC (20 weeks) was established as 200 ppm (20 mg as/kg/day).

No studies were conducted with the formulation, Syllit 400 SC for assessing acute or cronic toxicity. However, in principle it is not expected that the formulation will pose a significantly higher risk to non target birds than the active substance alone. On this basis, the risk assessment is based only on the predicted dodine exposure from the use of the product and no additional testing is required.

For the refinement of the risk assessment for birds a residue study of dodine in insects -*Tenebrio molitor* L. has been presented.

Based on the data of the analytical part the 1st order kinetic Model DT_{50} and DT_{90} of dodine could be determined to be 2.6 and 8.64 days for larvae and 1.55 and 5.14 days for beetles, respectively. The coefficient of variance was $r^2 = 0.809$ for larvae and $r^2 = 0.819$ for beetle which are higher than 0.7. The initial concentration C_0 for larvae and beetles, when applied directly on quartz sand was 23 mg/kg.

Exposure via Contaminated Food

Avian risk assessment is a sequential process, initially the acute short- and long-term toxicity/exposure ratios (TER_a TER_{st} and TER_{lt}) have been calculated using a worst case scenario.

Toxicity Exposure Ratio (TER) and Estimated Theoretical Exposure (ETE) were calculated based on the methods, i.e. equations and tabulated values described in the "Guidance Document on Risk Assessment for Birds and Mammals Under Council Directive 91/414/EEC" (Sanco/4145/2000 of 25 September 2002).

A realistic approach will take into account real food ingestion of birds in orchards and for this scenario an insectivorous bird (a 10g wren) will be considered as the standard species. Exposure of birds to dodine contained in the plant protection product SYLLIT 400 SC is considered to arise mainly from feeding dodine-contaminated insects present in treated orchards.

The scenarios considered for the Risk Assessment included the consumption of contaminated food (insects) and the uptake of contaminated water. The risk assessments were conducted in a stepwise approach in accordance with the model proposed in the document "Guidance document on risk assessment for birds and mammals[1]".

The key toxicological endpoints used for the Risk Assessment Calculation are the following:

Table 2.6-2 - Key toxicological endpoints

More sensitive specie	Endpoint	Reference
Mallard duck	21-day LD50 = 857 mg as/kg	Hakin, 1990b
Mallard duck	8-day LC50 = 2263 ppm corresponding to 280 mg as/kg bw/day	Hakin, 1990b
Mallard duck	20-week NOEL = 200 ppm corresponding to 20 mg as/kg bw	Peterson, 1994

The worst-case scenario is as follows: peach, 5 x 900 g as/ha with 7 days interval between applications.

1 SANCO/4145/2000 "Guidance document on risk assessment for birds and mammals under Council Directive 91/414/EEC", Draft Working Document, September 25th 2002.

Table 2.6-3 - Calculated 1st Tier TER values for acute, short-term, subchronic and reproductive risk for birds.

Type	Indicator Specie	Scenario	FIR/bw	RUD	Ftwa	AR	PT	C	ETE	Toxicity	TER
Tier 1											
Acute	Insectivorous bird (passerines)	Small insects	1.04	52	1	0.9	1	46.8	48.7	857	17.6
Short-term			1.04	29	1	0.9	1	26.1	27.1	280	10.3
Long-term			1.04	29	1	0.9	1	26.1	27.1	20	**0.7**

FIR = Food intake rate; bw = Bodyweight; RUD = Residue per unit dose; Ftwa = Time weighted average factor; AR = Application rate; PT = Fraction of diet obtained in treated area; C = Concentration in diet = RUD * AR; ETE = Estimated theoretical exposure = C*FIR/bw*Ftwa*PT; TER = Toxicity exposure ratio.

The resulting TER values for acute, short- and long-term sub-chronic exposures were respectively 17.6, 10.3 and **0.7**. The TER_{lt} are below the trigger value of 5 for long-term toxicity. In conclusion, the 1st risk assessment indicates an unacceptable risk to birds from long-term exposure.

Refinement of the long-term exposure is possible by using a lower PT value. On a long-term basis, a PT value of 1 is not realistic since birds will gather their food also in untreated areas. With reference to Crocker et al. (1998) with a PT value of 0.61 for small insectivorous bird (blue tits) which spends less than 61 % of their foraging time among orchards. With a more realistic PT = 0.61, the TER_{lt} = **1.2** (ETE = 27.1 * 0.61 = 16.5) which is however still below the trigger value of 5.

Further refinement is needed. According to SANCO/4145/2000 (25/09/2006), the long-term exposure assessment employs time-weighted-average residues rather than initial residues and if data show that the DT50 is shorter than 10 days which is used as a default value in tier 1 then f_{twa} should be recalculated.

Taking into account the degradation of dodine in insects described in the residue study (Hirth, N., 2005), the a DT50 of 2.6 days for larvae of *T. molitor* sprayed on sand at the normal field application rate without plant cover could be considered to refine f_{twa} factor.

Based on these results, the twa factor could be refined as follows:

$f_{twa} = (1-e^{-kt})/kt$

$k = \ln 2/DT50$

t = average time

With a DT50 in insects of 2.6 days and a default averaging time of 21 days for long term exposure, the refined twa factor is 0.178.

Considering PT and f_{twa} refinement the ETElt will be 2.95 (= 1.04 x 26.1 x 0.178 x 1 x 0.61 = 2.95) and the consequent TERlt = 6.78 which is higher than the trigger value of 5.

Based on the assessment described above, it can therefore be concluded that the **risk to insectivorous birds from the use of dodine is acceptable**.

Exposure via Drinking Water

Birds that frequent open water bodies can also be exposed to dodine via drinking water, if they ingest residues of a.s. that reach water for example via spray drift from treated fields. The exposure concentration in this case is equal to PECsw, obtained from the environmental fate section (B.8.6.1), regarding the worst case application scenario, i.e. 5 early applications of 900 g a.s/ha in orchards, with 7 days interval and interception of 40% (average crop cover).

For the estimation of exposure via drinking water (SANCO/4145/2000) it was considered that birds obtain all their water demand directly from puddles with contaminated water. Table 2.6.1.1.4 summarises the evaluation of exposure via drinking water.

Table 2.6-4 – Daily Water Intake by different types of birds as a function of their body weight and TERa for different types of birds consuming contaminated water.

Bird Type	Approx. body weight (kg)	Total water ingestion rate (l/day)	PECsw (µg/l)	DWI (dm^3/day)	TERa
			orchards	orchards	orchards
large bird (e.g. goose)	3.0	0.123	87.64	$3.6x10^{-3}$	$>10x10^4$
medium bird (e.g. duck)	1.0	0.059		$5.2x10^{-3}$	
medium bird (e.g. pigeon)	0.30	0.026		$7.8x10^{-3}$	
small bird (e.g. wren, tit)	0.010	0.003		$23.6x10^{-3}$	

The resulting TER values for acute exposures were for all bird types greater than 10^4. These TERs are all higher the trigger value of 10 for acute toxicity. The conclusion is that all results indicate an acceptable risk to birds expose to contaminate water via drinking water.

In conclusion, the risk to birds from exposure to dodine, *via* consumption of contaminated food or *via* consumption of contaminated water is low.

2.6.1.2 Vertebrates other than birds

Mammals may be exposed to dodine mainly through the consumption of contaminated food following application of Syllit 400 SC to orchards.

For this evaluation the data from the following mammalian toxicity studies have been used:

Risk evaluation	Toxicity study endpoint	Result	Reference
Acute	Acute rat oral toxicity (LD_{50})	851 mg as/kg bw/d	Kern, T. G., 1999
Long-term	Rat, 2-Generations (NOAEL)	13.14 mg as/kg bw/d	Henwood, S. M., 1996
	Rat, Teratogenicity (NOAEL)	45 mg as/kg bw/d	Hazelden, K.P. *et al*, 1989b

Toxicity Exposure Ratio (TER) and Estimated Theoretical Exposure (ETE) were calculated based on the methods, i.e. equations and tabulated values described in the "Guidance Document on Risk Assessment for Birds and Mammals Under Council Directive 91/414/EEC" (Sanco/4145/2000 of 25 September 2002).

A realistic approach will take into account real food ingestion of small mammals in orchards. Exposure of small mammals to dodine contained in the plant protection product Syllit 400 SC is considered to arise mainly from feeding on contaminated short grasses present in treated orchards. One small herbivorous mammal (a 25g vole) will be considered as the standard species.

The worst-case scenario is as follows apples/pears/peach, 5 x 900 g as/ha with 7 days application interval.

Estim. Theor Exposure (ETEa) = (FIR/BW) * C * AV * PT * PD

(mg/kg bw/d)

In the 1st Tier calculations, the AV (Avoidance factor), PT (fraction of diet obtained in treated area) and PD (fraction of food in diet) factors were considered to be 1 (worst case) both for acute and for long term risk assessment.

The Table below summarises the acute risk assessment.

Table 2.6-5 - Calculated 1st and 2nd Tier TER values for acute risk for mammals.

Type	Indicator Species	Scenario	FIR/bw	RUD	MAF	AR	C	ETE	Toxicity	TER
Orchards										
Acute 1st Tier	Small herbivorous mammal	Short grass	1.39	85	1.9	0.9	145.4	202	851	**4.2**
			1.39	42.5	1.9	0.9	38.25	101		**8.4**
Acute 2nd Tier	Small herbivorous mammal	Residue data	1.39	-			4.50	6.25		136

FIR = Food intake rate; bw = Bodyweight; RUD = Residue per unit dose; Ftwa = Time weighted average factor; AR = Application rate; PT = Fraction of diet obtained in treated area; C = Concentration in diet = RUD* AR; ETE = Estimated theoretical exposure = C*FIR/bw*Ftwa*PT; TER = Toxicity exposure ratio.

From the Table above it's possible to conclude that an insufficient margin of safety exists in the worst case scenario.

The C value used was estimated based on the standard RUD value for orchard given in the guidance document SANCO/4145 (25/9/2002) based on generic data obtained from Fletcher et al. 1994 and Fisher and Bowers 1997. It may be used for a first Tier assessment but refinement is possible regarding that the application of the active substance dodine will occur in later stages were deposition will be lower (30%), considering that the RUD value will be 42.5. Using this refinement TERa value will be 8.4 which is still below the trigger value.

For 2nd Tier risk assessment calculations the data obtained from residue trials which already include a sum up of residue after multiple applications at exaggerated rates (no MAF factor required in this case) could be used.

On apple, the highest residue level found 2 hours after the 12th application (exaggerated number of application) was 3.4 mg/kg (see B.7.). On pear, the highest residue level found 2 hours after the 4th application was 3.5 mg/kg (see B.7). On cherry, the highest residue level found 2 hours after the 3rd application was 4.5 mg/kg (see B.7).

Based on these results, it sounds reasonable to use a revised máx. C value of 4.5 mg/kg from residue trials on cherry, no deposition factor will be used to convert residue from foliage to short grass.

With a more realistic exposure value the acute TER value was 136, which is higher than the trigger value of 10, safe uses could be identified to small herbivorous mammals following applications of dodine in orchards.

For the long-term toxicity exposure ratio (TERlt) to small mammals, the worst-case scenario was the use in peach, 5 x 900 g as/ha spaced 7 days.

Table below summarises the long term risk assessment.

Table 2.6-6 - Calculated 1st Tier TER values for long term risk for mammals.

Type	Indicator Species	Scenario	FIR/bw	RUD	MAF	AR	C	Ftwa	ETE	Toxicity	TER
Orchards											
Long-term 1st Tier	Small herbivorous mammal	Short grass	1.39	46	2.4	0.9	99.4	0.53	73.2	13.14	**0.2**
										45	**0.6**

FIR = Food intake rate; bw = Bodyweight; RUD = Residue per unit dose; Ftwa = Time weighted average factor; AR = Application rate; PT = Fraction of diet obtained in treated area; C = Concentration in diet = RUD* AR; ETE = Estimated theoretical exposure = C*FIR/bw*Ftwa*PT; TER = Toxicity exposure ratio.

Insufficient margin of safety is concluded for mammals for the first Tier long term risk assessment. Therefore a refined long-term risk assessment is needed.

A refined long-term mammalian risk assessment has been conduced according to SANCO/4145/2000.

It is unlikely that mammal species would be feeding exclusively on treated grass. The high food intake rate (FIR) of 1.39 employed in the 1st Tier SANCO/4145/2000 is representative of small herbivorous mammals but most species, such as the wood mouse (*Apodemus sylvaticus*), harvest mouse (*Micromys minitus*), common dormouse (*Muscardinus avellanarius*) and bank vole (C*lethrionomys glareolus*) are largely omnivorous, taking a range of food items including insects, fruit and seeds plus mixed vegetation.

Regarding the fact that wood mice are found in hedgerows in cultivated land all year round and further enhanced by the fact that wood mice are found almost everywhere in central Europe, the refined long-term risk assessment for mammals will consider the wood mice as a relevant species.

For assessing the exposure of wood mice feeding on a mixed diet, the calculation of food intake rates was performed according to SANCO/4145/2000 using information indicated by Croker *et al*. (2002) on Daily Energy Expenditure (DEE), energy and moisture contents of different food types and on assimilation efficiencies for mammals. A mean body weight of 18 g was assumed for the wood mouse (Guerney, *et al*., 1998).

The log (DEE) was estimated according to the following equation using values for other eutherians as indicated by Croker *et al*. (2002):

$$\text{Log (DEE)} = 0.8459 + 0.7050 * (\log \text{bw (g)}) = 0.8459 + 0.7050 * \log 18 = 1.731$$

$$\text{DEE} = 53.8 \text{ kJ/d}$$

In accordance with Croker *et al*. (2002) the average daily food intake was then estimated according to the following equation for four food types: short grass, small seeds, large insects and earthworms:

$$\text{Daily Food Intake (FIR) (wet weight)} = \frac{\text{Daily Energy Expenditure (DEE) (kJ)}}{\text{Energy in Food (kJ/g) * (1- Moisture)* Assimilation Efficiency}}$$

Values for energy and moisture content as well as for assimilation efficiency of the separate food items were drawn from SANCO/4145/2000 as indicated in Table below. The resulting food intake rates were related to the average body weight of wood mice (18 g) to estimate FIR/g bw values. As these values are based on the assumption that wood mice feed exclusively on the separate food items, they are weighted for ETE calculation by PD values.

Table 2.6-7 – Daily energy expenditure (DEE), energy and moisture content, assimilation efficiencies and resulting food intake rates (FIR and FIR/g bw) for different food types for a small mammal weighing 18 g.

Food type	DEE (kJ/g)	Energy content (kJ/g)	Moisture content	Assimilation efficiency	FIR (g/d)	FIR/g bw
Short grass	53.8	18.0	0.764	0.46	27.5	1.53
Small seeds	53.8	21.0	0.119	0.83	3.2	0.19
Large insects	53.8	21.9	0.705	0.88	9.5	0.53
Earthworms	53.8	19.3	0.846	0.88	20.6	1.14

For estimating the residues in different food types, for the long-term exposure, the default values (SANCO/4145/2000) for residues in short grass of 76 mg as/kg and for small seeds of 40.2 mg as/kg were considered. However, a deposition factor of 0.3 was applied, considering that by the time of application orchards foliage were at development foliage phase. The resulting RUD values will be 22.8 mg as/kg for short grass and 12.1 mg as/kg for small seeds.

For insects, the default residue value of 5.1 mg as/kg for long-term exposure will be used in the risk assessment.

Regarding earthworms the residue of dodine in those organisms are based on the consideration that dodine is not expected to accumulate in earthworms due to the low log Pow of 0.96 and accordingly, the PEC for soil represents the worst case for residues. The PEcsoil for an application rate of 1 kg as/ha, 30% deposition and a soil layer of 5 cm depth with a soil bulk density of 1.5 g/cm^3 is 0.4 mg as/kg, representing the worst case RUD value for earthworms.

For estimating residue decline in insects the DT_{50} of 2.6 day from the laboratory study with *T. molitor* (Hirth, 2005) was used and the resulting f_{twa} will be 0.2 . Regarding earthworms, f_{twa} was determined based on the mean $DT_{50field}$ in soil of 13 days (mean value of all soil degradation studies under field conditions) and the resulting f_{twa} will be 0.83.

F_{twa} values calculated above were based on a minimum interval between applications of 7 days and the correspondent DT_{50} values for insects and earthworms.

For short grass and small seeds the default DT_{50} value of 10 days was considered and consequently the f_{twa} long-term used for risk assessment will be 0.53.

Considering the different food types the MAF factor will be the following:

Table 2.6-8 - Calculated MAF values for long term risk for mammals.

Food type	Interval between applications	DT50	MAF
Short grass	7 days	10	2.4
Small seeds		10	2.4
Large insects		2.6	1.2
Earthworms		13	2.7

In addition and according to radio-tracking data obtained by the Central Science Laboratory[1] (2003), it may be expected that wood mice do not satisfy their entire food demand in the treated area. Accordingly, a refined PT value can be used in the risk assessment. Observations by the Central Science Laboratory (2003) were based on 58 wood mice that were caught and radio-tagged in cereal fields in autumn and winter and in potato fields in summer (median contact of 6 hours 50 min). According to these observations, the average value for the proportion of active time that was spent in cultivated areas is 26%, corresponding to a PT value of 0.26 for long-term exposure.

In refining PD, data from stomach contents, faecal analysis, and pellet analysis can be used to determine likely food consumption. Therefor the following considerations will be used for the refinement of PD.

Data on the different food types in the diet of wood mice was collected by Pelz (1989, as cited by Guerney *et al*., 1998) on arable farms in the Rhineland, Germany. Data (volume percent of stomach contents) were collected from 346 individuals trapped over a seven year period on a monthly base. In view of the expected time of application of dodine, diet composition data for the months of March to July were taken into consideration for the mammalian risk assessment (based on a total of 146 individuals). The different food types encountered by Pelz (1989, as cited by Guerney *et al*., 1998) were: cereal grain (ranging from 5 to 48% of stomach contents over the period in question), vegetative plant material (8 to 24%), dicotyledonous seeds (0-25%), insect larvae (10 to 45%) and earthworms (9 to 40%). Although proportions are indicated as volume percent, it is evident from this data that all food items indicated above contribute to a large but varying extent of the diet of wood mice.

Depending upon availability, the diet of the wood mouse representative for a 3-week period considered in the long-term risk assessment may thus be expected to be composed of all of the food items indicated above. As wood mice are not expected to find cereal seeds within pome fruit orchards, cereals are not included in the risk assessment calculations. Approximate PD values of 0.25 are thus assigned to the different food type categories.

Calculation of the refined ETE value for long-term exposure is summarised below.

[1] Central Science Laboratory (2003): Improving estimates of wildlife exposure to pesticides in arable crops. Final report, DEFRA project code PN0915 (available via the DEFRA website www.defra.gov.uk as at December 2005)

Table 2.6-9 - Calculated 1st Tier TER values for long term risk for mammals.

Indicator Species	FIR/ g bw	Food type	RUD	AR	MAF	PT	PD	Ftwa	ETE
Wood mouse	1.53	Short grass	22.8	0.9	2.4	0.26	0.25	0.53	2.60
	0.19	Small seeds	12.1		2.4	0.26	0.25	0.53	0.171
	0.53	Insects	5.1		1.2	0.26	0.25	0.20	0.038
	1.14	Earthworms	0.4		2.7	0.26	0.25	0.83	0.060
								Overall (Sum):	**2.869**

FIR = Food intake rate; bw = Bodyweight; RUD = Residue per unit dose; Ftwa = Time weighted average factor; AR = Application rate; PT = Fraction of diet obtained in treated area; ETE = Estimated theoretical exposure = FIR/bw*RUD*AR*MAF*PT*PD*Ftwa.

The long-term TER was calculated by relating the mammalian toxicity endpoints to the overall theoretical exposure value as summarised below:

Table 2.6-10 - Calculated Refined TER values for long term risk for mammals.

Risk evaluation	Toxicity study endpoint	Endpoint	Overall ETE	TERlt
Long-term	Rat, 2-Generations (NOAEL)	13.14 mg as/kg bw/d	2.869	4.6
	Rat, Teratogenicity, (NOAEL)	45 mg as/kg bw/d		15.7

Based on the assessment described above and considering both long-term studies the overall risk for **mammals from the use of dodine is acceptable.** However for safety precautions the use of dodine during breeding season should be restricted.

2.6.2 Effects on aquatic species

Acute and chronic toxicity studies with dodine technical showed that this active substance is very toxic to fish, aquatic invertebrates and algae.

According to the available toxicity data, dodine will be classified with the R-phrases **R50/R53 – "Very toxic to aquatic organisms/may cause long term adverse effects in the aquatic environment** on account of its toxicity to *D. magna* and *S. subspicatus* and also because dodine is non readily biodegradable. Studies with the preparation Syllit 400 SC with *D. magna* and *S. subspicatus* also indicate that the preparation is very toxic to those aquatic organisms.

Aquatic organisms may be exposed to dodine as a reslut of water systems being contaminated by emissions from treated fields.

The proposed uses for dodine are presented on Table below:

Table 2.6-11 - Proposed use pattern for dodine.

Crop	Application (maximum frequency)	Max. application rate per season (kg as/ha)
Orchards/peach	5	5 x 0.900 = 4.5
cherry	3	3 x 0.800 = 2.4

Regarding exposure for aquatic organisms the PEC_{SW} and PECsed values for dodine were calculated using the FOCUS scenarios and the four-steps approach as recommended in the European Guidance doc. on Focus surface water scenarios (SANCO/4802/2001-rev.2 final May 2003) as described on section B.8.6.1. These PEC values will be used for the risk assessment. Table 2.6.2.2 summarised the worst case PECsw and PECsed values.

Table 2.6-12 - PECsw and PECsed values calculated using the FOCUS scenarios

Step		PECsw initial (µg/L)	PECsw TWA 4d (µg/L)	PECsw TWA 21d (µg/L)	PECsed initial (µg/kg)	PECsed TWA 21d (µg/kg)
Step 1		87.64	10.97	2.09	0.225	172.61
Step 2	North./EU	69.35	9.61	1.83	618.9	40.95
	South EU	69.35	9.61	1.83	1220.0	60.47
Step 3 (R3 Stream)		59.30	4.15	2.255	12.71	4.75
Step 4 - 10m		24.149 (R3 Stream)	1.75 (R3 Stream)	0.960 (R3 Stream)	10.977 (R4 Stream)	1.527 (R4 Stream)
Step 4 - 20m		5.887 (R3 Stream)	0.511 (R3 Stream)	0.250 (R3 Stream)	10.976 (R4 Stream)	1.527 (R4 Stream)
Step 4- 30m		1.981 (R3 Stream)	0.245 (R3 Stream)	0.097 (R3 Stream)	10.976 (R4 Stream)	1.527 (R4 Stream)
Step 4- 35m		1.309 (R3 Stream)	0.200 (R3 Stream)	0.072 (R3 Stream)	10.976 (R4 Stream)	1.527 (R4 Stream)
Step 4- 40m		0.914 (R3 Stream)	0.173 (R3 Stream)	0.056 (R3 Stream)	10.976 (R4 Stream)	1.527 (R4 Stream)

The endpoints from selected studies to the aquatic organisms were summarised in the Table below.

Table 2.6-13 - Toxicity endpoints used in the risk assessment.

Time -scale	Species	Toxicity test	Endpoint (mg as/L)	Reference
Acute	Fish (Bluegill sunfish)	LC50 96h (daily renewal)	0.7	Caley *et al*, 1991
	Daphnia	EC50 48h (flow through)	0.018	Putt, 1992
	Daphnia	EC50 48h (static + sediment)	0.146	Migchielsen, 2002
	S. capricornutum	EbC50 120h ErC50 120h (static)	0.00095 0.011	Hoger, 1993
Chronic	Fish (Fathead minnow)	NOEC 30d (flow through; Early Life Stage)	0.099	Sousa, 1995
	Daphnia	NOEC 21d (flow through)	0.0044	Putt, 1992
	S. capricornutum	NOEb,rC 15d (semi-static)	0.00015	Hoger, 1995

The acute toxicity end point for bluegill sunfish and for Daphnia was taken as a worst case. For Daphnia, the result of the higher tier static + sediment study was also used. This more realistic approach was necessary because of the high sensitivity of daphnia to dodine.

Acute risk

In order to calculate TER values for acute risk, the initial PECSW of dodine were used.

The following TER for fish, daphnia and algae were obtained:

Table 2.6-14 - Acute risk assessment to aquatic organisms.

Species	End point (mg/l)	PEC initial (mg/L)		TER	Trigger value
Bluegill sunfish	0.7	Step 1	0.08764	**7.99**	100
		Step 2	0.06935	**10.09**	
		Step 3	0.05993	**11.80**	
		Step 4 – 10m	0.02415	**28,99**	
		Step 4 – 20m	0.00588	119,05	
		Step 4 – 30m	0.00198	353,54	
		Step 4 – 35m	0.00131	534,35	
		Step 4 – 40m	0.00091	769,23	
Daphnia	0.018 (0.146)	Step 1	0.08764	**0,21 (1.67)**	100
		Step 2	0.06935	**0,26 (2.11)**	
		Step 3	0.05993	**0,30 (2.46)**	
		Step 4 – 10m	0.02415	**0,75 (6.05)**	
		Step 4 – 20m	0.00588	**3,06 (24.83)**	
		Step 4 – 30m	0.00198	**9,09 (73.74)**	
		Step 4 – 35m	0.00131	**13,74** (111.45)	
		Step 4 – 40m	0.00091	**19,78** (160.44)	
S. capricornutum	0.00095	Step 1	0.08764	**0,01084**	10
		Step 2	0.06935	**0,013699**	
		Step 3	0.05993	**0,01602**	
		Step 4 – 10m	0.02415	**0,039337**	
		Step 4 – 20m	0.00588	**0,161565**	
		Step 4 – 30m	0.00198	**0,479798**	
		Step 4 – 35m	0.00131	**0,725191**	
		Step 4 – 40m	0.00091	**1,043956**	

For **fish** a safe TER is reached with a buffer zone of **20 meters**.

Since dodine has a high adsorption potential with a mean Koc > 423.6 x 10^4, the toxicity study performed with sediment reflects a more realistic exposure.

For **Dapnhia** values in brackets correspond to the study performed with sediment and it can be concluded that for a **35m buffer zone** safe use was identified.

Regarding algae no safe use could be derived, if we consider PECinitial. Since dodine has a DT50water value < 1 day, it will be more realistic to compare the toxicity value (EbC50 120h) with TWA PEC values, as recommended on Higher-tier Aquatic Risk Assessment Guidance Doc.[1]. The following table summarises the 4 days TER values to algae.

[1] Campbell PJ, Arnold DJS, Brock TCM, Grandy NJ, Heger W, Heimbach F, Maund SJ, Streloke M (1999) Guidance document on higher-tier aquatic risk assessment for pesticides (HARAP). Lacanau Ocean, France: Setac-Europe Publication. 178 pp.

Table 2.6-15 - Refined acute risk assessment to algae.

Species	End point (µg/l)	PEC TWA 4 days (µg/L)		TER	Trigger value
S. capricornutum	0.95	Step 1	10.97	**0.086**	10
		Step 2	9.61	**0.099**	
		Step 3	4.15	**0.229**	
		Step 4 – 10m	1.75	**0.543**	
		Step 4 – 20m	0.511	**1.859**	
		Step 4 – 30m	0.245	**3.877**	
		Step 4 – 35m	0.200	**4.75**	
		Step 4 – 40m	0.173	**5.491**	

It is evident that a safety margin of 10 is not granted. However, one higher Tier study for 15 days has been submitted (Hoger, 1995).

However risk assessment for algae will be further discussed under the chronic risk assessment.

Chronic risk

The first stage chronic risk assessment was based on the initial PEC values as a worst case. This first approach leads to TERlt below the relevant triggers. In a second step, the risk assessment was refined as suggested in the guidance document on aquatic ecotoxicology (Sanco/3268/2001 rev.4). Indeed, it is appropriate to refine the risk assessment using PECtwa values if an unrealistic exposure regime prevailed in the relevant toxicity test. This is the case for dodine: chronic toxicity studies on fish and daphnia were performed using a flow-through system which maintained the level of concentration of dodine constant during all the study. This type of studies are quite unrealistic and represent a worst case knowing the very rapid dissipation of dodine from the water phase (DT50 water=0.37).

Table 2.6-16 – Long-term risk assessment to aquatic organisms (1st Tier).

Species	End point (mg/l)	PEC initial (mg/L)		TERlt	Trigger value
Fathead minnow	0.099	Step 1	0.08764	**1.13**	10
		Step 2	0.06935	**1.43**	
		Step 3	0.05993	**1.67**	
		Step 4 – 10m	0.02415	**4.10**	
		Step 4 – 20m	0.00588	16.84	
		Step 4 – 30m	0.00198	50.00	
		Step 4 – 35m	0.00131	75.57	
		Step 4 – 40m	0.00091	108.79	
Daphnia	0.0044	Step 1	0.08764	**0.05**	10
		Step 2	0.06935	**0.06**	
		Step 3	0.05993	**0.07**	
		Step 4 – 10m	0.02415	**0.18**	
		Step 4 – 20m	0.00588	**0.75**	
		Step 4 – 30m	0.00198	**2.22**	
		Step 4 – 35m	0.00131	**3.36**	
		Step 4 – 40m	0.00091	**4.84**	
S. capricornutum	0.00015	Step 1	0.08764	**0.002**	10
		Step 2	0.06935	**0.002**	
		Step 3	0.05993	**0.003**	
		Step 4 – 10m	0.02415	**0.006**	
		Step 4 – 20m	0.00588	**0.026**	
		Step 4 – 30m	0.00198	**0.076**	
		Step 4 – 35m	0.00131	**0.115**	
		Step 4 – 40m	0.00091	**0.165**	

Table 2.6-17 - Long-term risk assessment to aquatic organisms (2nd Tier).

Species	End point (mg/l)	PEC TWA 21d (mg/L)		TER	Trigger value
Fathead minnow	0.099	Step 1	0.00209	47.37	10
		Step 2	0.00183	54.10	
		Step 3	0.00233	43.81	
		Step 4 – 10m	0.00096	103.13	
		Step 4 – 20m	0.00025	396	
		Step 4 – 30m	0.000097	1020.62	
		Step 4 – 35m	0.000072	1375	
		Step 4 – 40m	0.000056	1767.86	
Daphnia	0.0044	Step 1	0.00209	**2.12**	10
		Step 2	0.00183	**2.40**	
		Step 3	0.00226	**1.95**	
		Step 4 – 10m	0.00096	**4.58**	
		Step 4 – 20m	0.00025	17.60	
		Step 4 – 30m	0.000097	45.36	
		Step 4 – 35m	0.000072	61.11	
		Step 4 – 40m	0.000056	78.57	
S. capricornutum	0.00015	Step 1	0.00209	0.072	10
		Step 2	0.00183	0.082	
		Step 3	0.00233	0.067	
		Step 4 – 10m	0.00096	0.156	
		Step 4 – 20m	0.00025	0.6	
		Step 4 – 30m	0.000097	1.546	
		Step 4 – 35m	0.000072	2.083	
		Step 4 – 40m	0.000056	2.679	

Regarding the long-term risk assessed using PEC_{twa} (more realistic approach), no buffer zone is necessary for fish whereas a buffer zone of 20 meters is necessary for daphnia.

For algae no safe use could be identified; however in the 15 day study it is observed that:

- multiple dodine treatments (resulting in initial exposure levels of 20 to 45 µg as/L) did not demonstrate a cumulative effect on cell growth

- based on the results of the recovery phase conducted subsequent to the 15-day exposure phase, it was concluded that *Selenastrum capricornutum* has the ability to recover from exposure to dodine concentrations as high as 45 µg as/L (leading to 99% reduction of cell density), when sufficient nutrients are available. Dodine proved to be algistatic rather than algicidal.

In conclusion, a sufficient margin of security is obtained for fish and daphnia using a buffer zone of 35 meter.

Since dodine partitions into the sediment, a particular concern can be raised regarding exposure of sediment dwelling organisms. In order to assess exposure of midges, TER was calculated using (1) toxicity end point obtained in the water spiked 28 days test on *Chironomus riparius* and (2) initial Step4 PECsw value calculated considering 10m buffer zone.

Table 2.6-18 - Risk assessment to sediment dwelling organisms.

Species	Test type	Endpoint (µg as/l)	PECsw initial 10m (µg/l)	TER	Trigger value
Chironomus riparius	Acute, 28-day, water spiked (static)	EC50 > 3200	24.149	132	100

For **sediment dwelling** organisms a safety margin of **10 meters** is sufficient for safe uses.

2.6.3 Effects on bees and other arthropod species

The acute toxicity of dodine technical and Syllit 400 SC was been evaluated (Servajean, 2004a and b). With Syllit 400 SC the 48 hr oral and contact LD_{50} expressed as dodine was 61.2 µg as/bee > 40 µg as/bee, respectively. It seems that Syllit was more toxic to bees than the active. The LD_{50} values obtained with the a.s. were higher than the ones obtained from the study with the preparation (48 hr oral LD_{50} > 200 µg/bee, contact LD_{50} > 100 µg/bee). Since mortality didn't stabilise during the 48 hr observation period the two oral acute studies were prolonged till 96 hr, however the oral LD_{50} was still > 200 µg/bee. These values are summarised in the Table below.

Table 2.6-19 - Honeybees toxicity studies

Test species	Test material	Results	References
Honeybee *(Apis mellifera* L*)*	a.s.	LD_{50} (48h) contact > 100 µg a.s./bee LD_{50} (48h) oral > 200 µg a.s./bee	Servajean, 2004a
Honeybee *(Apis mellifera* L*)*	Syllit 400 SC	LD_{50} (48h) contact > 40 µg a.s./bee LD_{50} (48h) oral = 61.2 µg a.s./bee	Servajean, 2004b

Bees may be exposed to dodine while foraging on treated crops or when flowering weeds are present in the field or in its vicinity. The maximum application rate for dodine spray applications is of 0.900 kg as/ha as a result of treatments with Syllit 400 SC.

For bees, TER values are superseded by the expression of the hazard quotient (HQ) which is defined as the ratio of application rate and LD_{50} oral and contact with the LD_{50} in µg a.s./bee and the application rate in g a.s./ha eventually corrected by a multiple application factor (MAF).

The following hazard quotients were obtained with the maximum application rate of dodine and a MAF factor of 1.9 (DT50 7 days: spray interval 7 days; ESCORT 2) for 5 applications.

Table 2.6-20 - Risk to bees from exposure to dodine

Test substance	LD50 (µg/bee)	Application rate (g as/ha)	Hazard quotient	Trigger
dodine	Contact > 100	1.9 x 900 = 1710	17.1	< 50
	Oral > 200		8.55	
Syllit 400 SC	Contact = 40		42.75	
	Oral = 61.2		27.9	

Both the hazard quotients are less than 50, indicating that dodine poses a negligible acute risk to adult bees.

The results of studies conducted with **non-target arthropod** species are summarised in Table 2.6.3.3.

Regarding the two standard non-target arthropod species, *Typhlodromus pyri* was the most sensitive with a reduction of beneficial capacity of 73.5%. For *Aphidius rhopalosiphi* the toxicity was considerably lower with a reduction of beneficial capacity of 30.3%. In laboratory conditions but with natural substrate (bean leaves), *Typhlodromus pyri*, exhibit a LR50 > 4000 g/ha (maximum application rate) and can be concluded that dodine was harmless for *T. pyri*.

Regarding the other species tested, *C. carnea*, *C. septempunctata* and *O. insidiosus* in the laboratory, the results obtain for all of them indicate that dodine could be classified as harmless when applied at the maximum application rate of 1800 g as/ha.

Table 2.6-21 - Results of Tier I LR50 studies with Diazol 60EC

Species	Test material	Conditions and Results	Reference
T.pyri	Syllit 400 SC	**Laboratory study** **Artificial substrate** (glass plates) Max. applic. rate: 900 g as/ha **Reduction of beneficial capacity of 73.5%** Harmful = Class 4	Kühner, 1997a
T.pyri	Syllit 400 SC	**Laboratory study** **Natural substrate** (bean leaves) Max. applic. rate: 4000 g as/ha **LR50 > 4000 g as/ha** Harmless = Class 1	Jansen, 2001a
A. rhopalosiphi	Syllit 400 SC	**Laboratory study** **Artificial substrate** (glass plates) Max. applic. rate: 1800 g as/ha **Reduction of beneficial capacity of 30.3%** Slightly Harmful = Class 2	Kühner, 1997b
C. carnea	Syllit 400 SC	**Laboratory study** **Natural substrate** (bean leaves) Max. applic. rate: 1800 g as/ha **Reduction of beneficial capacity of 15.3%** Harmless = Class 1	Jansen, 2001b
C. septempunctata	Syllit 400 SC	**Laboratory study** **Natural substrate** (bean leaves) Max. applic. rate: 1800 g as/ha **Reduction of beneficial capacity of 18.2%** Harmless = Class 1	Jansen, 2001c
O. insidiosus	Syllit 400 SC	**Laboratory study** **Natural substrate** (bean leaves) Max. applic. rate: 1800 g as/ha **Reduction of beneficial capacity of 21.3%** Harmless = Class 1	Jansen, 2002

In conclusion, on artificial substrate, *Typhlodromus pyri* was shown to be severely affected following exposure to dodine. Therefore, the test was repeated on natural substrate resulting in a reduced effect of the preparation. Syllit 400 SC was shown to be of low toxicity to non-target arthropods.

Terrestrial non-target arthropods will be exposed to residues of Syllit 400 SC both in-field, and in off-field environments as a result of spray drift. In evaluating the effects of the preparation Syllit 400 SC to non-target arthropod species, a tiered testing approach was adopted as recommended in the ESCORT 2 workshop (Candolfi *et al.* 2001)

Initial evaluations of the toxicity of Syllit 400 SC were conducted under worst case laboratory conditions to determine LR_{50} values with the most sensitive indicator species *Typhlodromus pyri*. The result of this study is summarised in the Table below.

Table 2.6-22 - Results of Tier I LR50 study with Syllit 400 SC

Species	Test material	Result	Reference
T.pyri	Syllit 400 SC	**Laboratory study** LR_{50} > 4000 g as/ha.	Jansen, 2001a

The following hazard quotients are obtained with maximum application rate of 900 g dodine/ha and a MAF factor of 1.9 (DT50 7 days: spray interval 7 days and 5 applications; ESCORT 2).

The drift factor used, was based on the overall 72nd percentile for 5 late season applications of the product in orchard crops, when there will be maximal intercept (6.59%drift/100 = 0.0659)

Both vegetation distribution factor and correction factor are set at 10. Hence, these parameters cancel each other out.

Table 2.6-23 - Hazard quotients for Syllit 400 SC

Species	LR50 (g as/ha)	Application rate (g as/ha)	MAF	HQ Orchard use (5 late season applications)	
				HQ in-field	HQ off-field
T.pyri	4000	900	1.9	0.43	0.028

Hazard quotient is less than 2, indicating that dodine poses a negligible risk to terrestrial non-target arthropods both in field and off field.

2.6.4 Effects on earthworms and other soil macro-organisms

Dodine is slightly toxic to earthworms with a LC_{50} (14 days) of 547 mg/kg. No major soil metabolites were identified on soil degradation studies of dodine.

Therefore, dodine is considered to be of no ecotoxicologically of concern in the soil environment to earthworms.

Table 2.6-24 - Summary of effects on soil non-target organisms with dodine.

Test conditions	Findings	References
Earthworm – acute	LC_{50} = 547 mg/kg (14 day) NOEC = 171 mg/kg	Suteau, 1995

The predicted maximum point soil PECs for the proposed uses of Syllit 400 SC, assuming 80% is deposited on soil in orchard are presented in Table B.8.25 (see point B.8.3). From the acute earthworm toxicity study with dodine technical a 14 day LC_{50} value was determined to be 547 mg/kg soil (Suteau, 1995). Using this data the TERa value has been calculated and are summarised in Table 2.6.4.2.

Table 2.6-25 - Acute TER values based on worst case maximum point soil concentrations

Species & Test type	PECinitial[a)]	Ecotox. Endpoint[b)]	TERa	Trigger value
Earthworm 14 days acute Test	3.04 mg/kg	LC50 = 316.18 mg/kg	104.0	10
		NOEC = 98.84 mg/kg	32.5	

a) Multiple application actual PECinitial. Allowance has been made for the degradation of diazinon between successive applications, the DT_{50} used for PEC calculations were 18.6 days.
b) Toxicity values were corrected for organic matter content of the soil (1.73)

This assessment indicates that dodine is of low risk to earthworms for all the proposed uses, with TER values well in excess of the Annex VI trigger of 10.

No data submitted. However laboratory soil degradation studies with dodine showed that the geometric mean DT_{90} was 60.08 days, accordingly, no further testing is required. Studies conducted with earthworms and soil micro-organisms (see point B.9.6 and B.9.8) show low risk to soil organisms following exposure to dodine. Effects on organic matter breakdown were not investigated, as the DT_{90} in soil was less than 1 year.

2.6.5 Effects on soil micro-organisms

The effects of dodine on soil microbial activity were investigated on respiration and soil nitrification in a loamy sand and a silt soil at test concentrations of 900 and 9000 g a.s./ha.

It was concluded that dodine had no adverse effects on soil microflora at 12 mg/kg (equivalent to 9 kg/ha) in a 28-day study.

2.6.6 Effects on other non-target organisms (flora and fauna)

No significant differences were detected in dry weight. None of the ten species tested yielded evidence of a reduction in plant weight any greater than 21%

Dodine was shown to be phytotoxic on certain species. It appears that only radish, cucumber and cabbage yielded an effect greater than 25% in any of the test parameters evaluated in this study. These effects were evident in regards to plant phytotoxicity as evaluated on the 21 DAT evaluations only.

Dodine was shown to affect mainly cabbage which yielded evidence of a reduction of plant height by 22% and dry weight by 25%. When dodine-treated cabbage plants were compared with the ethyl alcohol-treated plants, reductions of only 6% and 9% were noted in the later case for the mean plant dry weight and mean plant height evaluations respectively.

Only in two of the ten species tested, there was a notable reduction in germination, 2.5% for ryegrass and 7.5% for tomato without being statistically significant.

2.6.7 Effects on biological methods of sewage treatment

Under the conditions of this test, Dodine was toxic to waste water (activated sludge) bacteria at and above 18 mg/L, the lowest concentration tested. **The EC_{50} was found to be 52 mg as/L** with a 95% confidence interval ranging from 14 to 197 mg/L.

DODINE

LEVEL 2

Appendix 1: Standard terms and abbreviations

2006

Appendix 1 Standard terms and abbreviations

Part 1 Technical terms

A	ampere
ACh	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADP	adenosine diphosphate
AE	acid equivalente
AFID	alkali flame-ionization detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD50	approximate median lethal dose, 50%
ALT	alanine aminotransferase (SGPT)
AOEL	acceptable operator exposure level
AMD	automatic multiple development
ANOVA	analysis of variance
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathie
BSP	bromosulfophthalein
Bt	bacillus thuringiensis
Bti	bacillus thuringiensis israelensis
Btk	bacillus thuringiensis kurstaki
Btt	bacillus thuringiensis tenebrionis
BUN	blood urea nitrogen
bw	body weight
c	centi- ($\times 10^{-2}$)
ºC	degree Celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application
cDNA	complementary DNA
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
cv	coefficient of varation
CXL	Codex Maximum Residue Limit (Codex MRL)

d	day
DES	diethylstilboestrol
DFR	dislodgeable foliar residue
DMSO	dimethylsulphoxide
DNA	deoxyribonucleic Acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days pot inoculation
DRES	dietary risk evaluation system
DT50	period required for 50 percent dissipation (define method estimation)
DT90	period required for 90 percent dissipation (define method estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ξ	decadic molar extinction coefficient
EC50	median effective concentration
ECD	electron capture detector
ECU	European currency unit
ED50	median effective dose
EDI	estimated daily intake
ELISA	enzyme linked immonosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EPMA	electron probe micro analysis
ERC	environmentally relevant concentration
ERL	extraneous residue limit
F	field
F0	parental generation
F1	filial generation, first
F2	filial generation, second
FIA	fluorescence immuno assay
FID	flame ionization detector
FOB	functional observation battery
fp	freezig point
FPD	fame photometric detector
FPLC	fast protein liquid chromatography
g	gram
G	glasshouse
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionization detector
GC-MS	gas chromatography-mass spectrometry
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro.intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPPP	good plant protection practice
GPS	global positioning system
GSH	glutathion

GV	granulosevirus
h	hour(s)
H	Henry´s Law constant (calculated as a unitless value) (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionization detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HS	Shannon-Weaver index
Ht	haemotocrit
I	indoor
I50	inhibitory dose, 50%
IC50	median immobilization concentration or median inhibitory concentration[1]
ICM	integrated crop management
ID	ionization detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
iv	intravenous
IVF	in vitro fertilisation
k	kilo
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H)[1]
Kads	adsorption constant
Kdes	apparent desorption coefficient
Koc	organic carbon adsorption coefficient
Kom	organic matter adsorption coefficient
kg	kilogram
L	litre
LAN	local area network
LASER	light amplification by stimulated emission of radiation
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography – mass spectrometry
LC50	lethal concentration, median
LCA	life cycle analysis
LCLO	lethal concentration low
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD50	lethal dose, median; dosis letalis media
LDLO	lethal dose low
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration

[1] The first time the abbreviation is used in a document, it should be defined (using a footnote to do so)

LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintilation spectometry
LT	lethal threshold
m	meter
M	molar
µm	micrometer (micron)
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram
MHC	moisture holding capacity
min	minute(s)
mL	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
mo	month(s)
mol	Mole(s)
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
MRL	maximum residue level or limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
n	normal (defining isomeric configuration) or number of observations[1]
NAEL	no adverse effect level
nd	not detected
NEDI	national estimated daily intake
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometer
NMR	nuclear magnetic resonance
no	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase

[1] The first time the abbreviation is used in a document, it should be defined (using a footnote to do so)

OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OM	organic matter content
op	organophosphorus pesticide
Pa	Pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidixime
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PECA	predicted environmental concentration in air
PECS	predicted environmental concentration in soil
PECSW	predicted environmental concentration in surface water
PECGW	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler´s exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the dissociation constant
PNEC	predicted no effect concentration
po	by mouth
POW	partition coefficient between n-octanol and water
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion (10^{-12})
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r	correlation coefficient
r2	coefficient of determination
RBC	red blood cell
REI	restricted entry interval
Rf	retardation factor
RfD	reference dose
RH	relative humidity
RL50	median residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	rotations per minute
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RSD	relative standard deviation
s	second

SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SD	standard deviation
se	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
sq	square
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STMR	supervised trials median residue
t	tonne (metric ton)
t1/2	half-life (define method of estimation)
T3	tri-iodothyroxine
T4	thyroxine
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TCLO	toxic concentration, low
TID	themionic detector, alkali flame detector
TDLO	toxic dose low
TDR	time domain reflectrometry
TER	toxicity exposure ration
TERI	toxicity exposure ration for initial exposure
TERST	toxicity exposure ration following repeated exposure
TERLT	toxicity exposure ration following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
TIm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	theoretical maximum residue limit
TOC	total organic carbon
Tremcard	Transport emergency card
tRNA	transfer ribonucleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)

WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
ww	wet weight
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Part 2 Organisations and publications

ACPA	American Crop Protection Association
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
CA	Chemical Abstracts
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CIPAC	Collaborative International Pesticides Analytical Council Ltd
COREPER	Comite des Representants Permanents
EC	European Commission
ECB	European Chemical Bureau
ECCA	European Crop Care Association
ECDIN	Environmental Chemicals Data and Information Network of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECLO	Emergency Centre for Locust Operations
ECMWF	European Centre for Medium Range Weather Forecasting
ECPA	European Crop Protection Association
EDEXIM	European Database on Export and Import of Dangerous Chemicals
EHC (number)	Environmental Health Criteria (number)
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organization
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques (now known as GCPF)
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GIEWS	Global Information and Early Warning System for Food and Agriculture
GRIN	Germplasm Resources Information Network
HRAC	Herbicide Resistance Action Committee

IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
IBT	Industrial Bio-Test Laboratories
ICBB	International Commission of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commission for Plant-Bee Relationships
ILO	International Labour Organization
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Organization
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JFCNT	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
NATO	North Atlantic Treaty Organisation
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Centre for Toxicological Research (USA)
NGO	non-governmental organization
NTP	National Toxicology Programme (USA)
OECD	Organization for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
PAN	Pesticide Action Network
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCPH	Standing Committee on Plant Health
SETAC	Society of Environmental Toxicology and Chemistry
SI	Systeme International d'Unites
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UN	United Nations
UNEP	United Nations Environment Programme
WCDP	World Climate Data Programme
WCP	World Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organization
WTO	World Trade Organization
WWF	World Wildlife Fund

Part 3 International codes for technical & formulated pesticides*

Code	Term	Definition
AB	Grain bait	Special form of bait.
AE	Aerosol dispenser	A container-held formulation which is dispersed generally by a propellant as fine droplets or particles upon the actuation of a valve.
AL	Any other liquid	A liquid not yet designated by a specific code, to be applied undiluted.
AP	Any other powder	A powder not yet designated by a specific code, to be applied undiluted.
BB	Block bait	Special form of bait.
BR	Briquette	Solid block designed for controlled release of active ingredient into water.
CB	Bait concentrate	A solid or liquid intended for dilution before use as a bait.
CF	Capsule Suspension for Seed Treatment	A stable suspension of capsules in a fluid to be applied to the seed, either directly or after dilution.
CG	Encapsulated granule	A granule with a protective or granule release-controlling coating.
CL	Contact liquid or gel	Rodenticidal or insecticidal formulation in the form of a liquid/gel for direct application, or after dilution in the case of gels.
CP	Contact powder	Rodenticidal or insecticidal formulation in powder form for direct application. Formerly known as tracking powder (TP).
CS	Capsule suspension	A stable suspension of capsules in a fluid, normally intended for dilution with water before use.
DC	Dispersible concentrate	A liquid homogeneous formulation to be applied as a solid dispersion after dilution in water. (Note: there are some formulations which have characteristics intermediate between DC and EC).
DP	Dustable powder	A free-flowing powder suitable for dusting.
DS	Powder for dry seed treatment	A powder for application in the dry state directly to the seed.
DT	Tablet for direct application	Formulation in the form of tablets to be applied individually and directly in the field, and/or bodies of water, without preparation of a spraying solution or dispersion.
EC	Emulsifiable concentrate	A liquid, homogeneous formulation to be applied as an emulsion after dilution in water.
ED	Electrochargeable liquid	Special liquid formulation for electrostatic (electrodynamic) spraying.
EG	Emulsifiable Granule	A granular formulation to be applied as an oil-in-water emulsion of the active ingredient after disintegration in water, which may contain water insoluble formulants.
EO	Emulsion, water in oil	A fluid, heterogeneous formulation consisting of a solution of pesticide in water dispersed as fine globules in a continuous organic liquid phase.
ES	Emulsion for seed treatment	A stable emulsion for application to the seed either directly or after dilution.
EW	Emulsion, oil in water	A fluid, heterogeneous formulation consisting of a solution of pesticide in an organic liquid dispersed as fine globules in a continuous water phase.
FD	Smoke tin	Special form of smoke generator.
FG	Fine granule	A granule in the particle size range from 300 to 2500 µm.
FK	Smoke candle	Special form of smoke generator.
FP	Smoke cartridge	Special form of smoke generator.
FR	Smoke rodlet	Special form of smoke generator.
FS	Flowable concentrate for seed treatment	A stable suspension for application to the seed either directly or after dilution.
FT	Smoke tablet	Special form of smoke generator.
FU	Smoke generator	A combustible formulation, generally solid, which upon ignition releases the active ingredient(s) in the form of smoke.
	Special forms of smoke generators	
	Smoke candle	(FK)
	Smoke cartridge	(FP)
	Smoke pellet	(FW)
	Smoke rodlet	(FR)
	Smoke tablet	(FT)
	Smoke tin	(FD)
FW	Smoke pellet	Special form of smoke generator.
GA	Gas	A gas packed in pressure bottle or pressure tank.
GB	Granular bait	Special form of bait.

* Note: based on *Catalogue of Pesticide Formulation Types and International Coding System*. Technical Monograph No.2, GIFAP, Brussels. Revised February 1989.

GE	Gas generating product	A formulation which generates a gas by chemical reaction.
GF	Gel for Seed Treatment	A homogeneous gelatinous formulation to be applied directly to the seed.
GG	Macrogranule	A granule in the particle size range from 2000 to 6000 µm.
GL	Emulsifiable gel	A gelatinized formulation to be applied as an emulsion in water.
GP	Flo-dust	Very fine dustable powder for pneumatic application in greenhouses.
GR	Granule	A free-flowing solid formulation of a defined granule size range ready for use.
	Special forms of granules:	
	Encapsulated granule (CG)	A granule with a protective or release-controlling coating.
	Fine granule (FG)	Particle size range from 300 to 2500 µm.
	Macrogranule (GG)	Particle size range from 2000 to 6000 µm.
	Microgranule (MG)	Particle size range from 100 to 600 µm.
GS	Grease	Very viscous formulation based on oil or fat.
GW	Water soluble gel	A gelatinized formulation to be applied as an aqueous solution.
HN	Hot fogging concentrate	A formulation suitable for application by hot fogging equipment, either directly or after dilution.
KK	Combi-pack solid/liquid	A solid and a liquid formulation, separately contained within one outer pack, intended for simultaneous application in a tank mix.
KL	Combi-pack liquid/liquid	Two liquid formulations, separately contained within one outer pack, intended for simultaneous application in a tank mix.
KN	Cold fogging concentrate	A formulation suitable for application by cold fogging equipment, either directly or after dilution.
KP	Combi-pack solid/solid	Two solid formulations, separately contained within one outer pack, intended for simultaneous application in a tank mix.
LA	Lacquer	Solvent-based, film-forming composition.
LS	Solution for seed treatment	A clear to opalescent liquid to be applied to the seed either directly or as a solution of the active ingredient after dilution in water. The liquid may contain water insoluble formulants.
ME	Micro-emulsion	A clear to opalescent, oil and water containing liquid, to be applied directly or after dilution in water, when it may form a diluted micro-emulsion or a conventional emulsion.
MG	Microgranule	A granule in the particle size range from 100 to 600 µm.
OF	Oil miscible flowable concentrate (oil miscible suspension)	A stable suspension of active ingredient(s) in a fluid intended for dilution in an organic liquid before use.
OL	Oil miscible liquid	A liquid, homogeneous formulation to be applied as a homogeneous liquid after dilution in an organic liquid.
OP	Oil dispersible powder	A powder formulation to be applied as a suspension after dispersion in an organic liquid.
PA	Paste	Water-based, film-forming composition.
PB	Plate bait	Special form of bait.
PC	Gel or paste concentrate	A solid formulation to be applied as a gel or paste after dilution with water.
PO	Pour-on	Solution for pouring on the skin of animals in a high volume (normally more than 100 ml per animal).
PR	Plant rodlet	A small rodlet, usually a few centimetres in length and a few millimetres in diameter, containing an active ingredient.
PS	Seed coated with a pesticide	Self defining.
RB	Bait (ready for use)	A formulation designed to attract and be eaten by the target pests.
	Special forms of baits:	
	Block bait (BB)	
	Grain bait (AB)	
	Granular bait (GB)	
	Plate bait (PB)	
	Scrap bait (SB)	
SA	Spot-on	Solution for spot application on the skin of animals in a low volume (normally less than 100 ml per animal).
SB	Scrap bait	Special form of bait.
SC	Suspension concentrate (= flowable concentrate)	A stable suspension of active ingredient(s) in a fluid, which may contain other dissolved active ingredient(s), intended for dilution with water before use.
SE	Suspo-emulsion	A fluid, heterogeneous formulation consisting of a stable dispersion of active ingredients in the form of solid particles and fine globules in a continuous water phase.
SG	Water soluble granule	A formulation consisting of granules to be applied as a true solution of the active ingredient after dissolution in water, but which may contain insoluble inert ingredients.
SL	Soluble concentrate	A clear to opalescent liquid to be applied as a solution of the active ingredient after dilution in water. The liquid may contain water insoluble formulants.
SO	Spreading oil	Formulation designed to form a surface layer on application to water.

SP	Water soluble powder	A powder formulation to be applied as a true solution of the active ingredient after dissolution in water, but which may contain insoluble inert ingredients.
SS	Water soluble powder for seed treatment	A powder to be dissolved in water before application to the seed.
ST	Water soluble tablet	Formulation in form of tablets to be used individually, to form a solution of the active ingredient after disintegration in water. The formulation may contain water insoluble formulants.
SU	Ultra-low volume (ULV) suspension	A suspension ready for use through ULV equipment.
TB	Tablet	Pre-formed solids of uniform shape and dimensions, usually circular, with either flat or convex faces, the distance between faces being less than the diameter.
	Special forms of tablets: DT - tablets for direct application ST - tablets for dissolution in water WT - tablets for dispersion in water	
TC	Technical material	A material resulting from a manufacturing process comprising the active ingredient, together with associated impurities. This may contain small amounts of necessary additives.
TK	Technical concentrate	A material resulting from a manufacturing process comprising the active ingredient, together with associated impurities. This may contain small amounts of necessary additives and appropriate diluents. For use only in the preparation of formulations.
(TP)	(Tracking powder)	(Discontinued terms. Refer to CP)
UL	Ultra-low volume (ULV) liquid	A homogeneous liquid ready for use through ULV equipment.
VP	Vapour releasing product	A formulation containing one or more volatile active ingredients, the vapours of which are released into the air. Evaporation rate is normally controlled by using suitable formulations and/or dispensers.
WG	Water dispersible granules	A formulation consisting of granules to be applied after disintegration and dispersion in water.
WP	Wettable powder	A powder formulation to be applied as a suspension after dispersion in water.
WS	Water dispersible powder for slurry seed treatment	A powder to be dispersed at high concentration in water before application as a slurry to the seed.
WT	Water dispersible tablet	Formulation in the form of tablets to be used individually, to form a dispersion of the active ingredient after disintegration in water.
XX	Others	Temporary categorization of all other formulations not listed above.

DODINE

LEVEL 2

Appendix 2: Specific terms and abbreviations

2006

Appendix 2 Specific terms and abbreviations

Part 1 Technical terms

2AA	2-aminoanthracene
Abs	Absolute
A/G ratio	Albumin/globulin ratio
Alb	Albumin
ALT	Alanine aminotransferase (= glutamic pyruvic transaminase - GPT)
AP	Alkaline phosphatase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (= glutamic oxaloacetic transaminase – GOT)
c	Completely reversible
Ca^{++}	Calcium
CECD	Coulson electrolytic detector
CHO	Chinese hamster ovary
Cl^-	Chloride
CMC	Carboxymethyl cellulose
CP	cyclophosphamide
d	Desquamation
DMN	dimethylnitrosamine
DNCB	2,4-dinitrochlorobenzene
EMS	ethylmethane sulphonate
Excl.	Excluding
F	Female
FCA	Freund's complete adjuvant
σg	Standard geometric deviation
GGT	γ-glutamyl transpeptidase
GI	Gastro-intestinal
Glob	Globulin
Hb	Haemoglobin
HECD	Hall electrolytic detector
HGPRT	Hyproxanthine-guanine phosphoribosyl transferase
Ht	Haematocrit
ILV	Independent laboratory validation
incl.	Including
i.v.	Intravenous
K^+	Potassium
LDH	Lactate dehydrogenase
Lymph	Lymphocytes
M	Male
M&K	maximization test of Magnusson and Kligman
MMAD	Mass median aerodynamic diameter
MMC	mitomycin C
MMS	Methyl methane sulphonate
MNC	Micronucleated cells
MPV	Mean platelet volume
n	Not reversible
N.	Necrosis
Na^+	Sodium

NaCl	Sodium chloride
nc	Not completely reversible
NCE	Normochromatic erythrocyte
Neut seg	Neutrophils segmented
NG	Normal background lawn of bacterial growth
4-NQO	4-nitroquinolina N-oxide
PCE	Polychromatic erythrocyte
Plt	Platelet count
p.o.	*Per os*
POEM	predictive operator exposure model
pp	post-partum
QA	quality assurance
RBC	Erythrocyte count
RDW	Red cell distribution width
Rel	Relative
RMS	Rapporteur Member State
S9	liver homogenate fraction
S9 Mix	metabolic activation mixture
sd	Standard deviation
SD	Standard deviation
SE	Standard error
Soln.	solution
6TG	6-thioguanidine
TG	Triglyceride
TP	Total protein
Trp+	Tryptophan independent
TSD	Thermionic specific detector
UA	Uric acid

Part 2 Organisations and publications

CAG	Chimac-Agriphar
DFG	Deutsche Forschungsgemeinschaft
DGPC	Direcção-Geral de Protecção das Culturas

DODINE

LEVEL 2

Appendix 3: Listing of end points

2006

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

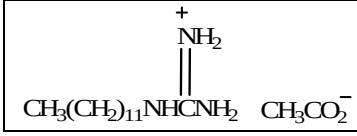
Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

Appendix 3 Listing of end points

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Dodine
Function (*e.g.* fungicide)	Fungicide
Rapporteur Member State	Portugal
Co-rapporteur Member State	

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	1-dodecylguanidinium acetate
Chemical name (CA) ‡	Dodecylguanidine monoacetate
CIPAC No ‡	101
CAS No ‡	2439-10-3
EC No (EINECS or ELINCS) ‡	219-459-5
FAO Specification (including year of publication) ‡	AGP: CP/236 (1988) Dodine: min. 970 g/kg (titration method) Water: max. 10 g/kg
Minimum purity of the active substance as manufactured ‡	950 g/kg (HPLC method)
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	-
Molecular formula ‡	$C_{15}H_{33}N_3O_2$
Molecular mass ‡	287.4 g/mol
Structural formula ‡	

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Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	133.2 ºC (1000 g/kg)
Boiling point (state purity) ‡	No boiling before decomposition.
Temperature of decomposition (state purity)	200.5 ºC (1000 g/kg)
Appearance (state purity) ‡	Odourless slightly yellow fine powder (1000 g/kg and 982 g/kg)
Vapour pressure (state temperature, state purity) ‡	$<5.49 \times 10^{-6}$ Pa (20ºC)
Henry's law constant ‡	$<1.70 \times 10^{-3}$ Pa m^3 mol^{-1} (20 ºC)
Solubility in water (state temperature, state purity and pH) ‡	pH 4.9: 0.87 g/L (20 ºC) pH 6.9: 0.93 g/L (20 ºC) pH 9.1: 0.79 g/L (20 ºC)
Solubility in organic solvents ‡ (state temperature, state purity)	n-heptane: 0.018 g/L (20ºC) xylene: <0.004 g/L (20ºC) acetone: 0.048 g/L (20ºC) ethyl acetate / dichloromethane: 0.015 g/L (20ºC) ethanol: 57 g/L (20ºC) n-octanol: 16.54 g/L (20ºC) acetonitrile: 0.044 g/L (20ºC)
Surface tension ‡ (state concentration and temperature, state purity)	27.87 mN/m (conc. 445.2 mg/L) at 20 ºC
Partition co-efficient ‡ (state temperature, pH and purity)	At 20ºC pH (aqueous phase) / Log Pow 4.9 / 1.28 6.9 / 1.25 9.1 / 1.32
Dissociation constant (state purity) ‡	No pKa could be associated with dodine
UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	ε max = 2600 $Lmol^{-1}cm^{-1}$ at λ = 200 nm ε < 1.5 $Lmol^{-1}cm^{-1}$ at λ ≥ 290 nm
Flammability ‡ (state purity)	Not highly flammable (983 g/kg and 962 g/kg)
Explosive properties ‡ (state purity)	Not explosive (983 g/kg)
Oxidising properties ‡ (state purity)	No oxidising properties (982 g/kg)

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Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

Summary of representative uses evaluated (*name of active substance or the respective variant*)*

Crop and/ or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Preparation** Type (d-f)	Conc. of as (i)	**Application** method kind (f-h)	growth stage & season (j)	number min/ max (k)	interval between applications (min)	**Application rate per treatment** (for explanation see the text in front of this section) kg as/hL min – max (l)	water L/ha min – max	kg as/ha min – max (l)	**PHI (days)** (m)	**Remarks**
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

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Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

* For uses where the column "Remarks" is marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s). (a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure) (b) Outdoor or field use (F), greenhouse application (G) or indoor application (I) (c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds (d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR) (e) GCPF Codes - GIFAP Technical Monograph No 2, 1989 (f) All abbreviations used must be explained (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench (h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated	(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).** (j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application (k) Indicate the minimum and maximum number of application possible under practical conditions of use (l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha (m) PHI - minimum pre-harvest interval

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Rapporteur Member State	Month and year	Active Substance (Name)
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Methods of Analysis

Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (analytical technique)	HPLC-refractive index LC-MS/MS
Impurities in technical as (analytical technique)	HPLC-refractive index and CIPAC MT 17 and 30. LC-MS/MS
Plant protection product (analytical technique)	HPLC-refractive index

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		dodine
Food of animal origin		Not required / no MRL is proposed
Soil		dodine
Water	surface	dodine
	drinking/ground	dodine
Air		dodine
Body tissues and fluids		dodine

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	GC-MSD (with derivatisation) - LOQ 0.05 mg/kg (high water content fruit)
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Not relevant. No LMR will be proposed.
Soil (analytical technique and LOQ)	GC-MSD (with derivatisation) – LOQ 0.01 mg/kg
Water (analytical technique and LOQ)	LC-MS/MS – LOQ 0.008 µg/L
Air (analytical technique and LOQ)	LC-MS/MS – LOQ 0.0085 mg/absorber in air (36°C, 82% RH) (equivalent to 11.8 µg/m^3 air)
Body fluids and tissues (analytical technique and LOQ)	LC-MS/MS: LOQ 2 µg/L (human urine and blood) for dodine The method for dodine residues in bovine liver is not acceptable (low recoveries at tested LOQ 10 µg/kg).

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Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Methods of Analysis

Classification and proposed labelling with regard to physical and chemical data (Annex IIA, point 10)

	RMS/peer review proposal
Active substance	Not classified

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Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Mammalian toxicology

Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA, point 5.1)

Rate and extent of oral absorption ‡	About 45%, based on urinary excretion within 24 h. Maximum concentration in plasma within 4 h after administration.
Distribution ‡	Initially widely distributed; highest residues in fat (mainly), ovaries, thyroid and skin at 96 h.
Potential for accumulation ‡	No evidence of accumulation.
Rate and extent of excretion ‡	>90 % after 48 h (at 40 mg/kg bw) or after 120 h (at 400 mg/kg bw); about 45% via urine and 45% via faeces.
Metabolism in animals ‡	Extensive metabolism of dose excreted in urine: Beta-oxidation pathway to hydroxydodecylguanidine (M2, 11-23% major metabolite in urine) and mixture of acidic products of beta-oxidation (M4, 8-13% in urine); other metabolites in urine: M3 (7-11%, unidentified) and M5 (urea, 3-5%). Up to 55% of dose excreted as parent in faeces (M1).
Toxicologically relevant compounds ‡ (animals and plants)	Parent compound
Toxicologically relevant compounds ‡ (environment)	Parent compound

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	851 mg/kg bw	Xn, R22
Rat LD_{50} dermal ‡	> 5000 mg/kg bw	
Rat LC_{50} inhalation ‡	> 0.45 mg/L 4h, nose only, particulate aerosol	T; R23
Skin irritation ‡	Irritant	Xi; R38
Eye irritation ‡	Risk of serious damage to eyes	Xi; R41
Skin sensitisation ‡	Non-sensitiser (Magnusson & Kligman)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Decreased body weight gain and food intake	
Relevant oral NOAEL ‡	1y dog: 10 mg/kg bw/d	
Relevant dermal NOAEL ‡	28d rat: 50 mg/kg bw/d (systemic); no dermal NOAEL	
Relevant inhalation NOAEL ‡	No data available – not required.	

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Portugal	**August 2006**	**Dodine**

Mammalian toxicology

Genotoxicity ‡ (Annex IIA, point 5.4)

	Dodine is unlikely to be genotoxic.	

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect ‡	Decreased body weight, body weight gain and food consumption in rats and mice. Statistically non-significant increase in the incidence of thyroid C-cell adenomas and carcinomas in males rats; positive trend in the incidence of hepatocellular adenomas combined with carcinomas in mice females.	
Relevant NOAEL ‡	20 mg/kg bw/day; 2-year rat 29 mg/kg bw/day; 18-month mice	
Carcinogenicity ‡	Dodine is unlikely to pose a risk to humans	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	Decreased pup weights at parental toxic levels.	
Relevant parental NOAEL ‡	13.14 mg/kg bw/day	
Relevant reproductive NOAEL ‡	52.61 mg/kg bw/day	
Relevant offspring NOAEL ‡	13.14 mg/kg bw/day	

Developmental toxicity

Developmental target / critical effect ‡	No developmental effects at maternally toxic levels in rats and rabbits.	
Relevant maternal NOAEL ‡	Rat: 10 mg/kg bw/day Rabbit: 40 mg/kg bw/day	
Relevant developmental NOAEL ‡	Rat: 90 mg/kg bw/day Rabbit: 80 mg/kg bw/day	

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No data-not required	
Repeated neurotoxicity ‡	No data-not required	
Delayed neurotoxicity ‡	No data-not required	

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Mammalian toxicology

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	Not applicable
Studies performed on metabolites or impurities ‡	Not applicable

Medical data ‡ (Annex IIA, point 5.9)

No detrimental effects on health in manufacturing personnel. Actual cases of intoxication with dodine are not well documented. The long existence of this product (over 50 years) without major known intoxication events rather suggests accidental or occupational poisoning to be hardly possible.

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI ‡	0.1 mg/kg bw/d	Dog, 1y study	100
AOEL ‡	0.045 mg/kg bw/d	Dog, 1y study	100
ARfD ‡	Not allocated – not necessary		

Dermal absorption ‡ (Annex IIIA, point 7.3)

Formulation (e.g. name 50 % EC)	2.75% concentrate and spray dilution Rat *in vivo.*

Exposure scenarios (Annex IIIA, point 7.2)

Operator	The estimated exposure for (formulation) according the UK POEM (application rate 0.9 kg as/ha) was bellow AOEL, only if PPE are worn. <u>Tractor mounted equipment</u> • (1.7 L product/ha, 0.9 kg as/ha in an application volume of 500 l/ha) Without PPE: 244% of AOEL With PPE (gloves mixing/loading and application): 137.7% AOEL • (2.25 L product/ha, 0.9 kg as/ha in an application volume of 1500 l)

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Portugal	**August 2006**	**Dodine**

Mammalian toxicology

Workers	Without PPE. 162.2% of AOEL With PPE (gloves mixing/loading and application): 63% of AOEL The estimated exposure for (formulation) according the GERMAN MODEL (application rate 0.9 kg as/ha) was bellow AOEL, for tractor mounted equipment even when no PPE are worn; for handheld equipment PPE are needed. <u>Tractor mounted equipment</u> Without PPE. 91.6% of AOEL With PPE (gloves mixing/loading and application): 72.3% of AOEL <u>Handheld equipment</u> Without PPE. 102.4% of AOEL With PPE (gloves mixing/loading and application): 55.3% of AOEL
	PPE worn (gloves, long sleeved shirt and long trousers): 83.53% of AOEL, after the spray was dried and during 35 days after the last of 4 applications.
Bystanders	0.13% of AOEL

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

Substance classified (name)	RMS/peer review proposal	
	T	Toxic
	R22	Harmful if swallowed
	R23	Toxic by inhalation
	R38	Irritating to skin
	R41	Risk of serious damage to eyes

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Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Fruits (apples, strawberries, pecans)-Foliar treatment
Rotational crops	Not applicable
Metabolism in rotational crops similar to metabolism in primary crops?	Not applicable
Processed commodities	Pasteurisation, sterilisation, baking/brewing/boiling
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Dodine is hydrolytically stable at elevated temperatures and pH 4, 5 or 6.
Plant residue definition for monitoring	dodine
Plant residue definition for risk assessment	dodine
Conversion factor (monitoring to risk assessment)	Not applicable

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Goats
Time needed to reach a plateau concentration in milk and eggs	3-5 days in milk
Animal residue definition for monitoring	dodine
Animal residue definition for risk assessment	dodine
Conversion factor (monitoring to risk assessment)	none
Metabolism in rat and ruminant similar (yes/no)	yes
Fat soluble residue: (yes/no)	no

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

Not applicable

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

Residues of dodine were stable in apple, apple juice, apple wet pomace, peaches and cherries when stored at -18/-20ºC during 18 months.

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Residues

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	Yes (dairy cattle and beef cattle: 20 mg/kg diet)	no	no
Potential for accumulation (yes/no):	no	-	-
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	no	-	-
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices : Mean (max) mg/kg		
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-		
Eggs		-	

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Residues

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Apples	N	0.088, 0.114, 0.121, 0.160, 0.180, 0.236, 0.277, 0.383.		1		0.17
	S	0.126, 0.267, 0.303, 0.310, 0.357, 0.440, 0.727, 0.930.		1		0.33
	N/S	0.088, 0.114, 0.121, 0.126, 0.160, 0.180, 0.263, 0.267, 0.277, 0.303, 0.310, 0.357, 0.383, 0.440, 0.727, 0.930.		1	0.93	0.27
Pears	N	0.18, 2x0.37, 0.45, 0.48, 0.54, 0.61, 1.3		1		0.47
	S	0.16, 0.25, 0.26, 0.29, 0.31, 0.4, 0.54, 0.6.		1		0.30
	N/S	0.16, 0.18, 0.25, 0.26, 0.29, 0.31, 2x 0.37, 0.40, 0.45, 0.48, 2x0.54, 0.6, 0.61, 1.3.		1	1.3	0.39
Cherries	N/S	2x0.14, 0.27, 0.46, 0.54, 2x0.7, 0.77		1	0.77	0.51

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Residues

Peaches	S	6x<0.05 mg/kg, 0.073		0.1	0.073	0.05

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use
(c) Highest residue

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Portugal	**August 2006**	**Dodine**

Residues

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.1 mg/kg b.w./day
TMDI (% ADI) according to WHO European diet	1 %
TMDI (% ADI) according to national (to be specified) diets	1.5 % (Portuguese diet)
IEDI (WHO European Diet) (% ADI)	0.3 %
NEDI (specify diet) (% ADI)	0.45 % (Portuguese diet); <1%-7% (UK diet)
Factors included in IEDI and NEDI	STMR, no processing factors
ARfD	Not established
IESTI (% ARfD)	-
NESTI (% ARfD) according to national (to be specified) large portion consumption data	-
Factors included in IESTI and NESTI	-

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor	Yield factor	
Apple/fresh juice	1	0.09	-	Not calculated
Apple/wet pomace	1	5	-	Not calculated

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Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Residues

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Apples and pears	1 mg/kg
Cherries	1mg/kg
Peaches	0.1 mg/kg

When the MRL is proposed at the LOQ, this should be annotated by an asterisk after the figure.

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	91.2-95.4 % after 100 d, [^{14}C-guanidine]-label (n[6]= 5) 81.4 % after 120 d, [^{14}C-chain]-label (n= 1)
Non-extractable residues after 100 days ‡	1.9-1.4 % after 100 d, [^{14}C-guanidine]-label (n= 5) 17.2 % after 120 d, [^{14}C-chain]-label (n= 1)
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	None

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡

Mineralization after 100 days	0.08 % after 360 d, [^{14}C-guanidine]-label (n= 1) Sterile conditions: not estimated
Non-extractable residues after 100 days	11.7% after 360 d, [^{14}C-guanidine]-label (n= 1)
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	None

Soil photolysis ‡

Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	None

[6] n corresponds to the number of soils.

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Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies ‡

Parent	Aerobic conditions						
Soil type	X[7]	pH	t. °C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam		5.3	25ºC/16%	6.2/28.0	6.0	0.988	1st order
Sandy loam		5.9	25ºC/17%	5.6/22.6	5.7	0.972	1st order
Sandy silt loam		6.6	20ºC/pF 2.5	4.3/13.1	4.3	0.987	1st order
Clay loam		7.4	20ºC/pF 2.5	2.7/9.9	2.7	0.990	1st order
Sand		6.7	20ºC/pF 2.5	4.4/12.9	4.4	0.985	1st order
Geometric mean/median				4.6/17.3	4.3	0.985	

Field studies ‡

Parent	Aerobic conditions								
Soil type (indicate if bare or cropped soil was used).	Location (country or USA state).	X[1]	pH	Depth (cm)	DT_{50} (d) actual	DT_{90}(d) actual	St. (r^2)	DT_{50} (d) Norm.	Method of calculation
Sand	Washington/USA		6.7	15 cm	13.0	108.3	0.81	13.0	1st order
Loam	New Jersy/USA		6.0	15 cm	6.7	22.1	0.75	6.7	1st order
Sandy loam	Georgia/USA		7.1-7.4	15 cm	18.6	61.2	0.81	18.6	1st order
Sandy loam	California/USA		7.1	15 cm	14.7	14.7	0.91	14.7	1st order
Geometric mean/median					13.25	60.08			

pH dependence ‡ (yes / no) (if yes type of dependence)	No
Soil accumulation and plateau concentration ‡	Not relevant

[7] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

Laboratory studies ‡

Parent	Anaerobic conditions						
Soil type	X[8]	pH	t. °C / % MWHC	DT_{50} / DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam		6.8	25ºC/11.6	2492/ -	2553	0.3	1st order
Geometric mean/median				2553			

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Sand	0.05	7.6	6440	$1.29x10^7$	nd	nd	0.877
Sandy loam	0.40	6.5	2202	$5.51x10^5$	nd	nd	0.974
Clay loam	0.65	6.4	18019	$2.77x10^6$	nd	nd	0.996
Silt loam	2.10	7.4	15228	$7.15x10^5$	nd	nd	0.996
Arithmetic mean/median			10472	$423.65x10^4$	nd	nd	0.967
pH dependence, Yes or No			No				

nd- not determined

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	No data submitted
Aged residues leaching ‡	Aged for (d): 3.25 d Time period (d): 2.7 d Elution (mm): 273 mm
	Analysis of soil residues post ageing (soil residues pre-leaching): 99.6 % active substance, < 0.1 % Met
	Leachate: < 2 % total residues/radioactivity in leachate >88 % total residues/radioactivity retained in top

[8] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

Lysimeter/ field leaching studies ‡	No data submitted

PEC (soil) (Annex IIIA, point 9.1.3)

Parent	DT_{50} (d): 18 days
Method of calculation	Kinetics: 1st order
	Field: representative worst case from field studies.
Application data	Crop: Orchards
	Depth of soil layer: 5cm or 20cm
	Soil bulk density: 1.5g/cm^3
	% plant interception: 20
	Number of applications: 5
	Interval (d): 7
	Application rate(s): 900 g as/ha

$PEC_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.96		3.04	
Initial		0.940	0.923	2.98	2.928
Short term	24h	**0.921**	0.889	2.928	2.821
	2d	**0.889**	0.825	2.823	2.618
	4d	0.8429	0.738	2.675	2.341
Long term	7d	0.5945	0.337	1.887	1.070
	28d	0.4342	0.149	1.378	0.472
	50d	0.2508	1.19x10-06	0.796	$7.32x10^{-02}$

Plateau concentration	not relevant

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	pH 5: 576 d at 25 °C (1st order, r^2=x) Metabolites detected at levels below 10%
	pH 7: 914 d at 25 °C (1st order, r^2=x) Metabolites detected at levels below 10%
	pH 9: 1198 d at 25 °C (1st order, r^2=x) Metabolites detected at levels below 10%
Photolytic degradation of active substance and metabolites above 10 % ‡	DT_{50} : 12,6 d Natural light, 40°N; DT_{50} 28 days Met I: 42 % AR guanidine DT_{50} of guanidine not estimated
Quantum yield of direct phototransformation in water at Σ > 290 nm	Not required. No significative adsorption (highest ε < 1.5 lmol-1 cm-1 at λ > 290 nm
Readily biodegradable ‡ (yes/no)	Not ready biodegradable.

Degradation in water / sediment

Parent	Distribution (eg max in water x% after *n* d. Max. sed x % after *n* d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} water	St. (r^2)	DT_{50}-DT_{90} sed	St. (r^2)	Method of calculation
Lake	7.6	8.4	20ºC	0.51/1.7	0.98	0.37/1.2	0.98	nd	-	1st order
Pool	7.3	8.1	20ºC	0.92/3.1	0.95	0.12/0.4	0.98	nd	-	1st order
Geometric mean/median				0.71/2.4		0.25/0.8				

nd- not determined

PEC (surface water) and PEC sediment (Annex IIIA, point 9.2.3)

Parent Parameters used in FOCUSsw step 1 and 2	Version control no. of FOCUS calculator: Version 1.1 Molecular weight (g/mol): 287.4 Water solubility (mg/L): 930 at 20ºC K_{OC} (L/kg): 423.65x10^4 (geometric mean from 4 soils) DT_{50} soil (d): 13.25 days (field) DT_{50} water/sediment system (d): 0.92 d (representative worst case from sediment water studies)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

	DT_{50} water (d): 0.37 d DT_{50} sediment (d): 0.92 d Crop interception (%): 40% (average crop cover)
Parameters used in FOCUSsw step 3 (if performed)	Version control no.'s of FOCUS software: Vapour pressure: 5.49x10-6 at 50°C Kom/Koc: 30000 (pragmatic value to run the program properly) 1/n: 0.9 (default)
Application rate	Crop: Pome/stone fruit Crop interception: 40% average crop cover for Step 1 and Step 2 and default values for Step 3 and Step 4 Number of applications: 5 Interval (d): 7 Application rate(s): 900 g as/ha Application window: 58 days (March to May)

FOCUS Step 1 PECsw and PEDsed for dodine application to pome/stone fruit

FOCUS STEP1 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0	**87.644**		**2.25E^{+03}**	
	1	0.032	43.838	1.37E^{+03}	1.81E^{+03}
	2	0.015	21.930	644.090	1.39E^{+03}
	4	0.003	**10.969**	142.736	858.861
	7	0.000	6.269	14.891	515.019
	14	0.000	3.134	0.076	258.914
	21	0.000	**2.090**	0.000	**172.614**
	28	0.000	1.567	0.000	129.461
	42	0.000	1.045	0.000	86.307

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

FOCUS Step 2 PECsw and PEDsed for dodine application to pome/stone fruit

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU	0	**69.348**		**618.900**	
	4	0.015	**9.606**	30.384	204.420
	21	0.000	**1.830**	0.000	**40.947**
Southern EU	0	**69.348**		1220.000	
	4	0.034	**10.969**	142.736	858.862
	21	0.000	**1.831**	0.000	**60.469**

FOCUS Step 3 PECsw and PEDsed for dodine application to pome/stone fruit

FOCUS STEP 3 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	3.063		1.658	
		4	0.053	0.930	0.665	1.433
		21	0.004	0.454	0.798	0.812
R1	Stream	0	41.862		4.786	
		4	0.000	1.682	1.398	2.919
		21	0.000	0.813	1.722	1.456
R2	Stream	0	55.589		5.345	
		4	0.000	1.140	0.873	2.893
		21	0.000	0.434	0.446	1.347
R3	Stream	0	**59.298**		**12.710**	
		4	0.001	**4.146**	6.177	7.505
		21	0.000	**2.255**	1.930	**4.750**
R4	Stream	0	42.110		10.977	
		4	0.000	1.927	1.763	6.067
		21	0.000	0.968	0.000	2.226

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (10 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	1.915		1.037	
		4	0.033	0.581	0.416	0.499
		21	0.003	0.284	0.499	0.508
R1	Stream	0	17.042		2.310	
		4	0.000	0.685	0.295	1.266
		21	0.000	0.331	0.779	0.594
R2	Stream	0	22.633		5.232	
		4	0.000	0.464	0.855	2.822
		21	0.000	0.179	0.182	0.910
R3	Stream	0	**24.149**		6.215	
		4	0.000	**1.754**	1.444	3.784
		21	0.000	**0.960**	0.805	2.126
R4	Stream	0	17.143		**10.977**	
		4	0.431	0.797	1.763	6.067
		21	0.000	0.394	0.000	**1.527**

FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (20 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	0.554		0.300	
		4	0.003	0.168	0.119	0.260
		2	0.000	0.0821	0.136	0.147
R1	Stream	0	4.149		1.235	
		4	0.000	0.167	0.270	0.803
		21	0.000	0.0806	0.000	0.266
R2	Stream	0	5.511		5.174	
		4	0.000	0.113	0.846	2.786
		21	0.000	0.0470	0.045	0.688
R3	Stream	0	**5.887**		2.859	
		4	0.000	**0.511**	0.666	2.021
		21	0.000	**0.250**	0.201	0.760
R4	Stream	0	4.174		**10.976**	
		4	0.431	0.210	1.763	6.067
		21	0.000	0.096	0.000	**1.527**

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (30 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	0.240		0.130	
		4	0.001	0.072	0.052	0.112
		21	0.001	0.036	0.062	0.064
R1	Stream	0	1.392		1.234	
		4	0.000	0.078	0.215	0.705
		21	0.000	0.270	0.000	0.210
R2	Stream	0	1.849		5.161	
		4	0.000	0.038	0.844	2.778
		21	0.000	0.019	0.015	0.664
R3	Stream	0	**1.981**		2.477	
		4	0.000	**0.245**	0.705	1.656
		21	0.000	**0.097**	0.111	0.497
R4	Stream	0	1.400		**10.976**	
		4	0.431	0.202	1.763	6.067
		21	0.000	0.051	0.000	**1.527**

FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (35 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	0.173		0.094	
		4	0.001	0.052	0.037	0.080
		21	0.001	0.255	0.045	0.046
R1	Stream	0	0.917		1.234	
		4	0.000	0.064	0.206	0.688
		21	0.000	0.021	0.000	0.201
R2	Stream	0	1.218		5.159	
		4	0.000	0.025	0.843	2.777
		21	0.000	0.014	0.010	0.660
R3	Stream	0	**1.309**		2.472	
		4	0.000	**0.200**	0.662	1.592
		21	0.000	**0.072**	0.073	0.442
R4	Stream	0	0.922		**10.976**	
		4	0.431	0.202	4.404	6.067
		21	0.000	0.540	0.001	**1.527**

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

FOCUS Step 4 PECsw and PEDsed for dodine application to pome/stone fruit (40 m buffer)

FOCUS STEP 4 Scenario	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
R1	Pond	0	0.129		0.070	
		4	0.001	0.039	0.277	0.060
		21	0.001	0.019	0.033	0.034
R1	Stream	0	0.638		1.234	
		4	0.000	0.055	0.200	0.678
		21	0.000	0.018	0.000	0.195
R2	Stream	0	0.848		5.157	
		4	0.000	0.024	0.843	2.776
		21	0.000	0.011	0.007	0.657
R3	Stream	0	**0.914**		2.470	
		4	0.000	**0.173**	0.637	1.556
		21	0.000	**0.056**	0.051	0.421
R4	Stream	0	0.642		**10.976**	
		4	0.431	0.202	1.763	6.067
		21	0.000	0.051	0.000	**1.527**

Metabolite X	Not applicable
Parameters used in FOCUSsw step 1 and 2	
Parameters used in FOCUSsw step 3 (if performed)	Not applicable
Application rate	Not applicable
Main routes of entry	Not applicable

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	For FOCUS gw modelling, values used – Modelling using FOCUS model(s), with appropriate FOCUSgw scenarios, according to FOCUS guidance. Model(s) used: FOCUS Models: Pelmo 3.3.2, Pearl 2.2.2, PRZM 2.4.1and MACRO Scenarios: Chateaudun, Hamburg; Jokioinen, Kremsmunster, Okehampton, Piacenza, Porto, Sevilla and Thiva Crop: apples Geometric mean or median parent $DT_{50field:}$ 13.25 d (normalisation to 10kPa or pF2, 20 °C with Q10 of 2.2). K_{OC}: dodine 423.65x10^4, arithmetic mean, $^1/_n$= 0.9. Metabolites: no relevant
Application rate	Application rate: 900 g/ha. No. of applications: 5 Time of application: March to May

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m)

	Scenario	Parent (µg/L)	Metabolite (µg/L)
Pelmo and Pearl /Apples	Chateaudun	0.000	na
	Hamburg	0.000	na
	Jokioinen	0.000	na
	Kremsmunster	0.000	na
	Okehampton	0.000	na
	Piacenza	0.000	na
	Porto	0.000	na
	Sevilla	0.000	na
	Thiva	0.000	na

na- not applicable

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	Not studied - no data requested

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

Quantum yield of direct phototransformation	Not required
Photochemical oxidative degradation in air ‡	Not studied
Volatilisation ‡	Not studied
	Not studied
Metabolites	Not studied

PEC (air)

Method of calculation	Expert judgement, based on vapour pressure, dimensionless Henry's Law Constant

$PEC_{(a)}$

Maximum concentration	negligible

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).	Soil:	dodine
	Surface Water:	dodine
	Sediment:	dodine
	Ground water:	dodine
	Air:	dodine

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	No data submitted – not requested
Surface water (indicate location and type of study)	No data submitted – not requested
Ground water (indicate location and type of study)	No data submitted – not requested
Air (indicate location and type of study)	No data submitted – not requested

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Fate and behaviour in the environment

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

R53 – not ready biodegradable

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Species	Test substance	Time scale	End point (mg/kg bw/day)	End point (mg/kg feed)
Birds ‡				
Anas platyrhynchos.	a.s.	Acute	-	857
	Preparation	Acute	-	-
	Metabolite 1	Acute	-	-
	a.s.	Short-term	280	2263
	a.s.	Long-term	20	200
Mammals ‡				
Rat	a.s.	Acute	851	-
	Preparation	Acute	-	-
	Metabolite 1	Acute	-	-
	a.s. (2-Generations)	Long-term	13.14	-
	a.s. (Teratogenicity)	Long-term	45	
Additional higher tier studies ‡				
Not submitted				

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Crop and application rate

Indicator species/Category[2]	Time scale	ETE	TER[1]	Annex VI Trigger[3]
Tier 1 (Birds)				
	Acute	48.7	17.6	10
	Short-term	27.1	10.3	10
	Long-term	27.1	**0.7**	5
Higher tier refinement (Birds)				
	Acute			10
	Short-term			10
PT=0.61; f_{twa} (DT_{50} = 2.6) = 0.178	Long-term	2.95	6.8	5
Tier 1 (Mammals)				
	Acute	202	**4.2**	10

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Indicator species/Category[2]	Time scale	ETE	TER[1]		Annex VI Trigger[3]
	Long-term	73.2	**0.2**		5
Higher tier refinement (Mammals)					
C=4.5 mg/kg (highest residue levels on cherry)	Acute	6.25	136		10
				TER	
Refinements for long-term see below	Long-term	**2.869**	13.14	4.6	5
			45	15.7	

[1] in higher tier refinement provide brief details of any refinements used (e.g., residues, PT, PD or AV)
[2] for cereals indicate if it is early or late crop stage
[3] If the Annex VI Trigger value has been adjusted during the risk assessment of the active substance (e.g. many single species data), it should appear in this column.

Table - Calculated 2nd Tier TER values for long term risk for mammals.

Indicator Species	FIR/ g bw	Food type	RUD	AR	MAF	PT	PD	Ftwa	ETE
Wood mouse	1.53	Short grass	22.8	0.9	2.4	0.26	0.25	0.53	2.60
	0.19	Small seeds	12.1		2.4	0.26	0.25	0.53	0.171
	0.53	Insects	5.1		1.2	0.26	0.25	0.20	0.038
	1.14	Earthworms	0.4		2.7	0.26	0.25	0.83	0.060
								Overall (Sum):	**2.869**

FIR = Food intake rate; bw = Bodyweight; RUD = Residue per unit dose; Ftwa = Time weighted average factor; AR = Application rate; PT = Fraction of diet obtained in treated area; ETE = Estimated theoretical exposure = FIR/bw*RUD*AR*MAF*PT*PD*Ftwa.

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
Laboratory tests ‡				
Fish				
Lepomis macrochirus	a.s.	96 hr (daily renewal)	Mortality, EC_{50}	0.7(mm)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
Pimephales promelas	a.s.	30 d (flow-through)	Growth NOEC	0.099(mm)
	Preparation	96 hr (flow-through)	Mortality, EC_{50}	
	Preparation	28 d(flow-through)	Growth NOEC	
	Metabolite 1	96 hr (flow-through)	Mortality, EC_{50}	
Aquatic invertebrate				
D. magna.	a.s.	48 h (flow-through)	Mortality, EC_{50}	0.018(mm)
D. magna	a.s. + sediment	48 h (static)	Mortality, EC_{50}	0.146(mm)
D. magna	a.s.	21 d (flow-through)	Reproduction, NOEC	0.0044(mm)
D. magna	Syllit 400 SC	48 h (semi-static)	Mortality, EC_{50}	0.123 mg form./L (0.049 mg as/L) (mm)
	Preparation	21 d (static)	Reproduction, NOEC	
	Metabolite 1	48 h (static)	Mortality, EC_{50}	
Sediment dwelling organisms				
C. riparius.	a.s.	28 d (static)	NOEC	3.2(mm)
	Metabolite 2	28 d (static)	NOEC	
Algae				
S. capricornutum.	a.s.	120 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.00095(mm) 0.011(mm)
S. capricornutum.	Dodine 400 SC	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.0056 (as) 0.0088 (as) (mm)
	Metabolite 1	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	
Higher plant				
Indicate species.	a.s.	14 d (static)	Fronds, EC_{50}	
	Preparation	14 d (static)	Fronds, EC_{50}	

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
	Metabolite 1	14 d (static)	Fronds, EC_{50}	
Microcosm or mesocosm tests				
Not submitted				

[1] indicate whether based on nominal ($_{nom}$) or mean measured concentrations ($_{mm}$). In the case of preparations indicate whether end points are presented as units of preparation or a.s.

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

FOCUS Step1

Crop and application rate

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC_i	PEC_{twa}	TER	Annex VI Trigger[1]
a.s.	Fish	0.7	Acute	0.087	-	**7.99**	100
a.s.	Fish	0.099	Chronic		-	**1.13**	10
a.s.	Aquatic invertebrates	0.018	Acute		-	**0.21**	100
a.s. + sediment	Aquatic invertebrates	0.146	Acute		-	**1.67**	100
a.s.	Aquatic invertebrates	0.044	Chronic		-	**0.05**	10
a.s.	Algae	0.00015	Chronic		-	**0.0017**	10
a.s.	Higher plants[2]		Chronic				10
a.s.	Sediment-dwelling[3] organisms	3.2	Chronic	0.087	-	37	10
Metabolites	Relevant organisms						
Product	Relevant organisms						

[1] If the Annex VI Trigger value has been adjusted during the risk assessment of the active substance, it should appear in this column. E.g. if it is agreed during the risk assessment of mesocosm, that a trigger value of 5 is required, it should appear as a minimum requirement to MS in relation to product approval.
[2] only required for herbicides
[3] consider the need for PEC_{sw} and PEC_{sed} and indicate which has been used

FOCUS Step 2

State crop, application rate and growth stage, Northern Europe or Southern Europe

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Test substance	N/S[1]	Organism[2]	Toxicity end point (mg/L)	Time scale	PEC[3] (máx.)	TER	Annex VI Trigger[4]
a.s.	N/S	Fish	0.7	Acute	0.069	**10.09**	100
a.s.	N/S	Fish	0.099	Chronic		**1.43**	10
a.s.	N/S	Aquatic invertebrates	0.018	Acute		**0.26**	100
a.s. + sediment	N/S	Aquatic invertebrates	0.146	Acute		**2.11**	100
a.s.	N/S	Aquatic invertebrates	0.044	Chronic		**0.06**	10
a.s.	N/S	Algae	0.00015	Chronic		**0.0022**	10
a.s.		Higher plants[5]	-	Chronic		-	10
a.s.	N/S	Sediment-dwelling organisms[6]	3.2	Chronic		46	10
Metabolites		Relevant organisms					
Product		Relevant organisms					

[1] indicate whether Northern of Southern
[2] include critical groups which fail at Step 1.
[3] indicate whether maximum or twa values have been used.
[4] If the Annex VI Trigger value has been adjusted during the risk assessment of the active substance, it should appear in this column. E.g. if it is agreed during the risk assessment of mesocosm, that a trigger value of 5 is required, it should appear as a minimum requirement to MS in relation to product approval.
[5] only required for herbicides
[6] consider the need for PEC_{sw} and PEC_{sed} and indicate which has been used

Refined aquatic risk assessment using higher tier FOCUS modelling.

FOCUS Step 3

State crop and application rate

Test substance	Scenario[1]	Water body type[2]	Test organism[3]	Time scale	Toxicity end point (mg/L)	PEC[4] (máx.)	TER	Annex VI trigger[5]
a.s.	R3	Stream	Fish	acute	0.7	0.069	**11.8**	100
a.s.			Fish	chronic	0.099		**1.43**	10
a.s.			D. magna	acute	0.018		**0.3**	100
a.s. + sediment			D. magna	acute	0.146		**2.46**	100
a.s.			D. magna	chronic	0.044		**0.64**	10
a.s.			algae	chronic	0.00015		**0.003**	10

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Test substance	Scenario[1]	Water body type[2]	Test organism[3]	Time scale	Toxicity end point (mg/L)	PEC[4] (máx.)	TER	Annex VI trigger[5]
Metabolites								
Product								

[1] drainage (D1-D6) and run-off (R1-R4)
[2] ditch/stream/pond
[3] include critical groups which fail at Step 2.
[4] indicate whether PEC_{sw}, or PEC_{sed} and whether maximum or twa values used
[5] If the Annex VI Trigger value has been adjusted during the risk assessment of the active substance, it should appear in this column. E.g. if it is agreed during the risk assessment of mesocosm, that a Trigger value of 5 is required, it should appear as a minimum requirement to MS in relation to product approval.

FOCUS Step 4

Crop and application rate

Scenario[1]	Water body type[2]	Test organism[3]	Time scale	Toxicity end point	Buffer zone distance	PEC[4]	TER	Annex VI trigger[5]
R3	Stream	Fish	acute	0.7	20	0.0058	119	100
		Fish	chronic	0.099	20		16.84	10
		D. magna	acute	0.018	35	0.00131	**13.74**	100
		D. magna (as + sediment)	acute	0.146	35		111.45	100
		D. magna	chronic	0.044	40	0.00091	**4.84**	10
		algae	chronic	0.00015	40	0.00091	**0.165**	10

[1] drainage (D1-D6) and run-off (R1-R4)
[2] ditch/stream/pond
[3] include critical groups which fail at Step 3.
[4] indicate whether PEC_{sw}, or PEC_{sed} and whether maximum or twa values used
[5] If the Annex VI Trigger value has been adjusted during the risk assessment of the active substance, it should appear in this column. E.g. if it is agreed during the risk assessment of mesocosm, that a Trigger value of 5 is required, it should appear as a minimum requirement to MS in relation to product approval.

Bioconcentration				
	Active substance	Metabolite1	Metabolite2	Metabolite3

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Bioconcentration				
$logP_{O/W}$	0.9	-	-	-
Bioconcentration factor (BCF)[1] ‡	X*	-	-	-
Annex VI Trigger for the bioconcentration factor	-	-	-	-
Clearance time (days) (CT_{50})	-	-	-	-
(CT_{90})	-	-	-	-
Level and nature of residues (%) in organisms after the 14 day depuration phase	-	-	-	-

[1] only required if log $P_{O/W}$ >3.
* based on total ^{14}C or on specific compounds

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Test substance	Acute oral toxicity (LD_{50} µg/bee)	Acute contact toxicity (LD_{50} µg/bee)
a.s. ‡	> 200	> 100
Preparation[1]	61.2 µg as/bee	40.0 µg as/bee
Metabolite 1		
Field or semi-field tests	Not submitted	
Indicate if not required	Not required	

[1] for preparations indicate whether end point is expressed in units of a.s. or preparation

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Crop and application rate

Test substance	Route	Hazard quotient	Annex VI Trigger
a.s.	Contact	17.1	50
a.s.	oral	8.55	50
Preparation	Contact	42.75	50
Preparation	oral	27.9	50

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Laboratory tests with standard sensitive species

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Species	Test Substance	End point	Effect (LR_{50} g/ha[1])
Typhlodromus pyri ‡	Syllit 400 SC	Mortality	> 4000 g as/ha (Natural substrate; bean leaves)
Aphidius rhopalosiphi ‡	Syllit 400 SC	Mortality	> 1800 g as/ha

[1] for preparations indicate whether end point is expressed in units of a.s. or preparation

Crop and application rate

Test substance	Species	Effect (LR_{50} g/ha)	HQ in-field	HQ off-field[1]	Trigger
Syllit 400 SC	*Typhlodromus pyri*	4000	0.43	0.028	2
Syllit 400 SC	*Aphidius rhopalosiphi*	1800	0.96	0.062	2

[1] indicate distance assumed to calculate the drift rate

Further laboratory and extended laboratory studies ‡

Species	Life stage	Test substance, substrate and duration	Dose (g/ha)[1,2]	End point	% effect[3]	Trigger value
C. carnea	Larvae 2-3 days old	Syllit 400 SC 19 days exp. + 4 weeks rep. phase	1800 g as/ha	Red. of beneficial capacity	15.3%	50 %
C. septempunctata	Larvae 2-3 days old	Syllit 400 SC 21 days exp. + 4 weeks rep. phase	1800 g as/ha	Red. of beneficial capacity	18.2%	50 %
O. insidiosus	protonymphs 5 days old	Syllit 400 SC 10 days exp. + 10 days rep. phase	1800 g as/ha	Red. of beneficial capacity	21.3%	50 %

[1] indicate whether initial or aged residues
[2] for preparations indicate whether dose is expressed in units of a.s. or preparation
[3] indicate if positive percentages relate to adverse effects or not

Field or semi-field tests	Not submitted
Indicate if not required	Not required

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	End point[1]
Earthworms			
	a.s. ‡	Acute 14 days	LC_{50} = 547 mg a.s./kg d.w.soil NOEC = 171 mg a.s./kg d.w.soil
	a.s. ‡	Chronic 8 weeks	NOEC mg a.s./kg d.w.soil (mg a.s/ha)
	Preparation	Acute	Indicate whether toxicity is expressed in terms of form or a.s.
	Preparation	Chronic	
	Metabolite 1	Acute	
	Metabolite 1	Chronic	
Other soil macro-organisms			
Soil mite	a.s. ‡	-	
	Preparation	-	
	Metabolite 1	-	
Collembola	No data submitted		
	a.s. ‡	Chronic	NOEC mg a.s./kg d.w.soil (mg a.s/ha)
	Preparation	-	
	Metabolite 1	-	
Soil micro-organisms			
Nitrogen mineralisation	a.s. ‡	28 days	< 25% effect at day 28 at 900 and 9000 g a.s/ha
	Metabolite 1		
Carbon mineralisation	a.s. ‡	42 days	< 25% effect at day 28 at 900 and 9000 g a.s/ha
	Metabolite 1		
Field studies[2]	No data submitted		
Indicate if not required	Not required		

[1] indicate where end point has been corrected due to log Pow >2.0 (e.g. LC_{50corr})
[2] litter bag, field arthropod studies not included at 8.3.2/10.5 above, and earthworm field studies

Toxicity/exposure ratios for soil organisms

Crop and application rate

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Test organism	Test substance	Time scale	Soil PEC[2]	TER**	Trigger
Earthworms					
	a.s. ‡	Acute	3.04*	104	10
	a.s. ‡	Chronic	3.04*	32.5	5
	Preparation	Acute			10
	Preparation	Chronic			5
* Multiple application actual PECinitial ** Toxicity values were corrected for organic matter content of the soil (1.73)					
Other soil macro-organisms					
Soil mite	a.s. ‡				
	Preparation				
	Metabolite 1				
Collembola	a.s. ‡				
	Preparation				
	Metabolite 1				

[1] to be completed where first Tier triggers are breached
[2] indicate which PEC soil was used (e.g. plateau PEC)

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Preliminary screening data

Not required for herbicides as ER_{50} tests should be provided

Laboratory dose response tests

Most sensitive species	Test substance	ER_{50} (g/ha)[2] vegetative vigour	ER_{50} (g/ha)[2] emergence	Exposure[1] (g/ha)[2]	TER	Trigger

[1] explanation of how exposure has been estimated should be provided (e.g. based on Ganzelmeier drift data)
[2] for preparations indicate whether dose is expressed in units of a.s. or preparation

Additional studies (e.g. semi-field or field studies)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Effects on biological methods for sewage treatment (Annex IIA 8.7)

Test type/organism	end point
Activated sludge	EC50 = 52 mg as/L
Pseudomonas sp	

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

Compartment	
soil	Parent (dodine)
water	Parent (dodine)
sediment	
groundwater	

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

	RMS/peer review proposal
Active substance	R50

	RMS/peer review proposal
Preparation	R50

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rapporteur Member State	Month and year	Active Substance (Name)
Portugal	**August 2006**	**Dodine**

Ecotoxicology

Code/Trivial name	Chemical name	Structural formula

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

DODINE

LEVEL 3

Proposed decision with respect to the application for inclusion of the active substance in Annex I

2006

3 Proposed decision with respect to the application for inclusion of the active substance in Annex I

3.1 Background to the proposed decision

Dodine is the ISO common name for 1-dodecylguanidinium acetate. It is a fungicide that has been used in a large number of applications worldwide for many years. The representative formulation SYLLIT 400 SC is a suspension concentrate to be used on apple, pear, cherry and peach.

Taking in account the proposed residue definition, fully validated analytical methods are available for dodine residues analysis in food of plant origin, environmental matrices and in human blood (and human urine). A validated method is not available for the determination of dodine residues in bovine liver, however the submitted LC-MS/MS method is highly specific and capable of detect dodine residues in bovine liver in the desired concentration range (i.e. below the LOQ of 0.1 mg/kg in general accepted for toxic active substances in tissues).

Taking into consideration all toxicological and metabolism studies it is proposed an ADI of 0.1 mg/kg bw/day and an AOEL of 0.045 mg/kg bw/day. ARfD establishment was not considered necessary.

Concerning the risk assessment to operator of SYLLIT 400 SC, it was verified that for the intended uses exposure is acceptable when gloves during mixing/loading and application are used. Exposure of bystanders was considered to have no toxicological relevance. Re-entry exposure in high crops treated with SYLLIT 400 SC represents an acceptable level of risk for workers when PPE like gloves, long-sleeved shirts and long trousers are worn.

Harmful effects on human or animal health are not expected from residues that occur in plant or animal tissues as a consequence of the use of dodine in accordance with the principle of Good Agricultural Practice.

On the basis of the data provided to assess the fate and behaviour of dodine in the environment it can be concluded that dodine is a non persistent compound with expected soil DT50 and DT90 values lower than 3 months and 1 year, respectively and a DT50 in water systems below one month. Dodine can be considered immobile in soil and there are no degradation products of concern regarding the contamination of ground waters. In fact, the results from modelling studies performed for scenarios and leaching studies with aged residues identify a safe use of dodine application regarding ground water contamination. In one water sediment study dodine showed rapid dissipation into sediment, where dodine dissipates rapidly by mineralisation or by formation of bound residues strongly adsorbed to the sediment. Dodine is not readily biodegradable.

The ecotoxicological data submitted indicate that dodine is relatively toxic to terrestrial vertebrates (birds and mammals) and aquatic organisms and has negligible risk to bees, other non-target arthropods, earthworms and other soil micro and macro-organisms.

Regarding risk assessment to the organisms mentioned above acceptable risk was identified for all species. However refinement of the risk for aquatic organisms was needed. Security is obtained for those organisms with mitigation measures, e.g. a buffer zone (35 meters).

3.2 Proposed decision concerning inclusion in Annex I

[redacted]

3.3 Rational for the postponement of the decision [redacted]

The information in sections 3.2 and 3.3 has been removed upon request by the European Commission as it relates to risk management recommendations or proposals.

DODINE

LEVEL 4

Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex I

2006

4 Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex I

4.1 Identity of the active substance

No further data required.

4.2 Physical and chemical properties of the active substance

Annex IIA

IIA 2.5.1 - Spectra of active substance:
IR, NMR and MS spectra of the purified active substance need to be submitted.

(May be required at MS Level)

4.3 Data on application and further information

No further data required.

4.4. Classification, packaging and labelling

No further data required.

4.5 Methods of analysis

Annex IIA

IIA 4.2.5 - Analytical methods (residues) in body fluids and tissues:
Proposed method must be validated for dodine residues in bovine liver at a LOQ of 0.1 mg/kg.

4.6. Toxicology and metabolism

No further data required.

4.7 Residue data

No further data required.

4.8 Environmental fate and behaviour

No further data required.

4.9 Ecotoxicology

No further data required.