CONCLUSION ON PESTICIDE PEER REVIEW

Peer review of the pesticide risk assessment of the active substance folpet

(Question No EFSA-Q-2009-605)

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SUMMARY

Folpet is one of the 52 substances of the second stage of the review programme covered by Commission Regulation (EC) No 451/2000[1], as amended by Commission Regulation (EC) No 1490/2002[2]. This Regulation requires the European Food Safety Authority (EFSA) to organise a peer review of the initial evaluation, i.e. the draft assessment report (DAR), provided by the designated rapporteur Member State and to provide within one year a conclusion on the risk assessment to the EU-Commission.

Italy being the designated rapporteur Member State submitted the DAR on folpet in accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, which was received by the EFSA on 20 October 2003. Following a quality check on the DAR, the peer review was initiated on 6 July 2004 by dispatching the DAR for consultation of the Member States and the sole applicant Makhteshim Agan. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and the need for additional data was agreed in an evaluation meeting in 14 December 2004. Remaining issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in April and May 2005.

A final discussion of the outcome of the consultation of experts took place with representatives from the Member States on 6 April 2006 leading to the conclusions.

[1] OJ No L 53, 29.02.2000, p. 25
[2] OJ No L 224, 21.08.2002, p. 25

The outcome of experts' consultation was re-discussed within a series of scientific meetings in the section of mammalian toxicology and residues with Member States experts in November 2007 and April 2008. The conclusion has been amended accordingly and the changed reference values are laid down in this report. This updated conclusion replaces the previous version, which was finalised on 24 April 2006 (EFSA Scientific Report (2006) 70 refers).

The conclusion was reached on the basis of the evaluation of the representative uses as fungicide as proposed by the applicant which comprises foliar spraying to control various fungi in winter wheat, tomatoes and wine grapes at application rates of up to 750 g folpet per hectare in winter cereals, up to 1.6 kg in tomatoes and up to 1.5 kg in wine grapes. Folpet can be used only as fungicide.
The representative formulated product for the evaluation was "Folpan 80 WDG", a water dispersible granule (WG), registered in some EU Member States.

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. folpet in soil, water and air. It should be noted that for surface water no enforcement method is needed for the determination of folpet, due to the fact that the DT_{90} value is below 3 d (the trigger value given in SANCO/825/00). For food of plant origin no validated analytical methods for monitoring purposes are available.
Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. However, due to some outstanding data no final specification can be proposed for the technical material at the moment.

Folpet has a low acute oral and dermal toxicity but it is R20 'Harmful by Inhalation'. It is not irritating to the skin but it is severely irritating to eyes (proposal for classification as R41 "Risk of serious damage to eyes") and is a skin sensitiser (R43 'May cause sensitisation by skin contact' is proposed). Folpet does not show any genotoxic potential *in vivo* but it is carcinogenic in the mouse (category 3, R 40 proposed for the classification by the majority of the experts), with a clear threshold identified. Folpet did not cause adverse effects on adult fertility or reproduction in rats over two generations, but was shown to be teratogenic in rabbits (classification as R63 is still under discussion and is forwarded to ECB). The Acceptable Daily Intake (ADI) and the Acceptable Operator Exposure Level (AOEL) are 0.1 mg/kg bw/day, the Acute Reference Dose (ARfD) is 0.2 mg/kg bw. The operator estimated exposure accounts for 34 to 77% of the AOEL in outdoor scenarios (German model with PPE considered). Estimates provided for operator exposure in glass-houses ranged from 29% to 33% of the AOEL (PPE is worn). The exposure of bystanders is 1.6% of the AOEL. Worker exposure in harvesting grapes and tomatoes without protective gloves is 133% and 68% of the AOEL, with PPE such as gloves it is assumed that the exposure is below the AOEL. Worker exposure following applications of folpet to wheat can be expected to be lower than following applications to grapes or tomatoes.

The metabolism of folpet in plants has been adequately elucidated. The main degradation products after release of the trichloromethylthio-side chain are phthalimide and phthalic acid. As it is not possible at this stage to fully characterize the toxicological properties of phthalimide, this metabolite needs to be included in the residue definition for plant products for monitoring and risk assessment purposes. Supervised residue trials were carried out in most cases with analysis of folpet only and therefore it is not possible to establish MRLs and to conduct an exposure assessment covering the contribution of phthalimide to the residue. However, taking into account folpet only, an acute risk for toddlers consuming treated table grapes has been identified. Specific studies allowing a clear understanding of the behaviour of the compound during processing are not available. The drastic reduction of folpet level in processed commodities and the physico-chemical properties of the compound suggest that important amounts of phthalimide and/or phthalic acid could be produced during processing. No residue of folpet and related metabolites are expected in rotational crops and in animal commodities.

Folpet is very low or low persistent in soil. First degradation step involves the release of the highly reactive thiophosgene to yield the major soil metabolite phthalimide which is further degraded through phthalamic acid to phthalic acid. All major folpet metabolites are also very low or low persistent in soil under aerobic conditions at 20 °C. Mineralization is high and unextractable residues are formed in moderate amounts (max. 31.2 % AR at 14 d).

In relation to the thiophosgene moiety, further information was derived from captan. The experts' meeting agreed that it is not expected that free thiophosgene will reach significant levels due to the degradation of folpet in soil. Under anaerobic conditions folpet degraded slightly slower and no new metabolites were identified.

Photolysis does not contribute significantly to the environmental dissipation of folpet.

PEC soil presented in the DAR were based on worst case laboratory half life (DT_{50} = 4.3 d) with the critical GAP of ten applications of 1.5 kg a.s / ha at 7 days interval (grapes use). In the addendum March 2005 PEC soil are recalculated for all three uses taking into account crop interception given for FOCUS GW. However, EFSA considers that this calculation is not adequate for vines (were interception factor has been averaged) and needs to be further justified for tomatoes. New PEC soil values calculated by EFSA were used in the risk assessment for earthworms presented in the conclusion. Due to ambiguities with respect to the time of application interception for PEC soil, calculation cannot be established for wheat.

Folpet was estimated (based on physical chemical properties or theoretical calculations) to be medium mobile (K_{oc} = 304 mL / g), phtalamic acid very high mobile (K_{oc} = 10 mL / g) and phthalic acid high mobile (K_{oc} = 73 mL / g) in soil. Phthalimide was experimentally found to be medium to high mobile in soil (K_{foc} = 72 – 385 mL / g).

Hydrolysis of folpet is rapid at acidic and neutral pH (DT_{50} < 3 h) and very rapid at alkaline pH (DT_{50} < 3 min). Main hydrolysis metabolites were phathalimide and phthalic acid. Trichlomethylsulfenic acid and tricloromethylmercaptan are postulated to be the two major non characterized hydrolysis metabolites of folpet. These metabolites will degrade to thiophosgene, carbon oxysulfide and

ultimately to CO_2. Phthalimide was stable at 25 °C and pHs 4 and 7 and at pH 9 was hydrolysed with a half life of 2 h. Contribution of photolysis to the aqueous degradation of folpet was not significant. Folpet was shown to be readily biodegradable at concentrations of 1 mg C/L.

In the water sediment systems folpet degrades very rapidly and mineralization is relatively high. Folpet is not found in the sediment phase. Major metabolites in the water phase were phthalimide, phthalamic acid, phthalic acid, benzamide and 2-cyanobenzoic acid. No major metabolite was found in the sediment phase. All the metabolites degraded rapidly in both systems (DT_{50} < 7 d).

After the Experts' meeting new PECsw calculations have been presented based on FOCUS scheme. Whereas not peer reviewed, EFSA can confirm that the parameters already agreed by the experts' meeting have been used in this calculation. Values obtained for the different representative uses are lower than the worst case runoff estimation presented in the DAR (577 µg/L). This level could be of concern only for metabolite phthalimide. Therefore, FOCUS STEP 1 values have been used to complete the assessment of this metabolite (See 5.2.). FOCUS sw calculations for the parent up to STEP 4 are also summarized in the addendum of October 2005, these calculations have not been peer reviewed and have not been used for the EU risk assessment.

The acute risk to birds was assessed as low in a first tier risk assessment for all representative uses. The short-term and long-term TER values for herbivorous birds were below the Annex VI triggers of 10 and 5. But since the TER value of >8.9 is based on a NOEC from the highest tested dose and tomato foliage is considered not to be an attractive food source, the risk to herbivorous birds is assumed to be low for the representative use in tomatoes A high long term risk to insectivorous birds was identified in a first tier risk assessment for all representative uses. The refined risk assessment for birds was discussed in the EPCO expert meeting. It was agreed that the risk assessment should not be based on the highest observed NOEC of 769 mg a.s./kg/d and that the RUD refinement would not cover the risk from uptake of residues in small insects. On the basis of the peer reviewed data a high long-term risk to insectivorous birds cannot be excluded. The risk to mammals is low for the representative uses in winter wheat and tomatoes but a high acute and long term risk to small herbivorous mammals cannot be excluded for the representative use in grapes. The first tier risk assessment for the uptake of contaminated drinking water resulted in a high acute risk for birds and mammals if the solution is sprayed at the highest recommended concentration. The risk of secondary poisoning of birds and mammals from uptake of contaminated earthworms and fish is considered to be low for all representative uses. The intrinsic toxicity of folpet to fish and daphnids is high. Due to very rapid degradation the toxicity under static conditions is markedly lower. The acute risk to fish and daphnids is high and risk mitigation measures such as no spray buffer buffer zones of 5 m for the use in winter wheat and tomatoes and 10 m for the use in grapes are required. A long – term risk assessment for aquatic organisms is required since the representative uses cover multiple applications leading to repeated exposure. The long-term risk to fish is high and risk mitigation measures such as no spray buffer zones of 5 m and 15 m are required to for the representative uses in winter wheat, tomatoes and grapes, respectively. The available data do not allow drawing a conclusion on the long-term risk to aquatic invertebrates. The endpoints from a flow through study would lead to an overestimation of the long-term risk to daphnids. The risk of bioaccumulation and the risk from major metabolites posed to aquatic organisms are considered to be low. The risk to earthworms is low for

the use in tomatoes but a high risk to earthworms cannot be excluded for the uses in grapes. The risk to earthworms from the use in winter wheat cannot be concluded until a reliable PEC soil is established.
The risk to bees, other non-target arthropods, other soil non-target macro-organisms, soil non-target micro-organisms, other non-target organisms and biological methods of sewage treatment was assessed as low.

Key words: folpet, peer review, risk assessment, pesticide, fungicide

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BACKGROUND

Commission Regulation (EC) No 451/2000 laying down the detailed rules for the implementation of the second and third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC, as amended by Commission Regulation (EC) No 1490/2002, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Folpet is one of the 52 substances of the second stage covered by the amended Regulation (EC) No 451/2000 designating Italy as rapporteur Member State.

In accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, Italy submitted the report of its initial evaluation of the dossier on folpet, hereafter referred to as the draft assessment report, to the EFSA on 20 October 2003. Following an administrative evaluation, the EFSA communicated to the rapporteur Member State some comments regarding the format and/or recommendations for editorial revisions and the rapporteur Member State submitted a revised version of the draft assessment report. In accordance with Article 8(5) of the amended Regulation (EC) No 451/2000 the revised version of the draft assessment report was distributed for consultation on 6 July 2004 to the Member States and the main applicant Makhteshim Agan as identified by the rapporteur Member State.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, representatives from Member States identified and agreed in an evaluation meeting on 14 December 2004 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level. A representative of the notifier attended this meeting.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in expert meetings organised on behalf of the EFSA by the EPCO-Team at the Federal Office for Consumer Protection and Food Safety (BVL) in Braunschweig, Germany, in April and May 2005. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place with representatives from Member States on 6 April 2006 leading to the conclusions.

The outcome of experts' consultation was re-discussed within a series of scientific meetings in the section of mammalian toxicology and residues with Member States experts in November 2007 and April 2008. The conclusion has been amended accordingly and the changed reference values are laid down in this report.

During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR).

In accordance with Article 8(7) of the amended Regulation (EC) No 451/2000, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received
- the resulting reporting table (rev. 1-1 of 22 December 2004)
- the consultation report

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation
- the evaluation table (rev. 2-1 of 7 March 2006)

Given the importance of the draft assessment report including its addendum (compiled version of November 2005 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Folpet is the ISO common name for *N*-(trichloromethylthio)phthalimide or *N*-(trichloromethanesulfenyl)phthalimide (IUPAC, both).

Folpet belongs to the class of phthalimide fungicides such as captan or captafol. Folpet is a contact fungicide and inhibits many oxidative enzymes, carboxylases and enzymes involved with phosphate metabolism and citrate synthesis.

The representative formulated product for the evaluation was "Folpan 80 WDG", a water dispersible granule (WG), registered in some EU Member States.

The evaluated representative uses as fungicide comprise foliar spraying to control various fungi in winter wheat, tomatoes and wine grapes at application rates of up to 750 g folpet per hectare in winter cereals, up to 1.6 kg in tomatoes and up to 1.5 kg in wine grapes. Folpet can be used only as fungicide.

SPECIFIC CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

The minimum purity of folpet as manufactured should not be less than 940 g/kg, which is higher than the minimum purity given in the FAO specification 75/TC/S (1988) of 860 g/kg. The higher value relates to the submitted results of current batch analysis and not to any toxicological concern to increase the minimum purity.

The relevance of three impurities that are present in the technical material is under discussion. The rapporteur Member State has stated in an addendum to Volume 4 that one of these impurities does not need to be regarded as relevant. However, this assessment was neither peer reviewed by other MS nor discussed in a meeting of experts.

In addition to this, clarification is required with respect to certain impurities to confirm the proposed maximum levels in the technical material and analytical data for the confirmation of the identity of impurities, the specification for the technical material as a whole should be regarded as provisional at this stage.

Furthermore, there was some discussion on the data with respect to the flowability of the formulation after storage. The remaining residue was rather high, but the formed agglomerates could be broken by simple dropping or tapping. However, the data may need to reconsider for national authorisation in particular if new packing types are requested.

Besides this, the assessment of the data package revealed no particular area of concern with respect of the identity, physical, chemical and technical properties of folpet or the respective formulation.

The content of folpet in the representative formulation is 800 g/kg (pure).
At the moment no FAO specification exists for WG formulations.

The main data regarding the identity of folpet and its physical and chemical properties are given in appendix 1.

Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of folpet in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material.
Therefore, enough data are available to ensure that quality control measurements of the plant protection product are possible.

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. folpet in soil, water and air. It should be noted that for surface water no enforcement method is needed for the determination of folpet, due to the fact that the DT_{90} value is below the trigger value of 3 days as given in SANCO/825/00.
In case of food of plant origin the proposed residue definition was changed during the evaluation into folpet and phthalamide, expressed as folpet (see 3.1). As a consequence, a method is needed (incl. ILV and a confirmatory method, latter if appropriate). Moreover, a confirmatory method for the determination of residues of folpet in food of plant origin is needed.
An analytical method for food of animal origin is not required due to the fact that no MRLs are proposed (see 3.4).
The methodology used is GC with EC detection and HPLC with UV detection. A multi-residue method like the Dutch MM1 or the German S19 is not applicable to due the nature of the residues.

The discussion in the expert meeting (EPCO 25, May 2005) on identity, physical and chemical properties and analytical methods was limited to the specification of the technical material, certain physical, chemical and technical properties of folpet and the formulation and analytical methods. The missing clarification with respect to the modification indicated in the ILV is given in the evaluation table [17275/EPCO/BVL/04, rev. 2-1 (07.03.2006)].

2. Mammalian toxicology

Folpet was discussed at the EPCO experts' meeting for mammalian toxicology (EPCO 23) in May 2005, and at 2 PRAPeR expert meetings (PRAPeR 39 and 44) in 2007 and 2008.

2.1. Absorption, Distribution, Excretion and Metabolism (Toxicokinetics)

Folpet is rapidly absorbed, widely distributed and rapidly excreted after oral administration. The most toxicologically significant pathway is the potential to degrade to thiophosgene, which is highly reactive. Removal of the side-chain by hydrolysis or by detoxification mechanisms yields phthalimide, which is further metabolised to phthalamic acid, which may be converted to phthalic acid. Derivatives of phthalimide are excreted rapidly and extensively. Folpet does not show any potential for accumulation.

2.2. Acute toxicity

Folpet has a low acute toxicity (oral and dermal LD_{50} greater than 2000 mg/kg bw). The acute LC_{50} is 1.89 mg/L, therefore **R20 'Harmful by Inhalation'** is proposed. Folpet is not irritating to the skin but it is severely irritating to eyes (proposal for classification as **R41 "Risk of serious damage to eyes"**). Folpet caused positive delayed hypersensitivity and **R43 'May cause sensitisation by skin contact'** is proposed.

2.3. SHORT TERM TOXICITY

Folpet was tested in a number of short term studies in rats, mice and dogs. Main target effects in both rodents and dogs were decreased body weight and food consumption. Male dogs treated at high doses showed decreased size or weight of testes associated with microscopic testicular degeneration or with no spermatozoa in the epididymides.

A relevant short term NOAEL of 10 mg/kg bw/day from the 1-year dog study was agreed on by the experts.

2.4. GENOTOXICITY

The genotoxic potential of folpet was investigated in a battery of genotoxicity tests (with purities ranging from 85.6% to 98.99%). Folpet shows positive results in *in vitro* studies but there is no indication of DNA damage *in vivo* up to 2000 mg/kg bw/day. Therefore, the experts agreed that there is no genotoxic potential for folpet *in vivo*.

2.5. LONG TERM TOXICITY

Folpet has been tested in 3 long term studies in rats and 3 in mice.

The administration of folpet for 2 years to rats at dietary doses of 10 – 120 mg/kg bw/day produced decreased body weight and food consumption. Enzymatic activity and total protein levels were reduced at the higher dose levels. Hyperkeratosis of the non-glandular stomach and of the oesophagus were present in animals treated at levels of 50 mg/kg bw/day and above. Folpet was not carcinogenic in the rat.

Chronic dietary administration to mice produced treatment-related clinical signs of toxicity such as dry, flaking skin, skin encrustations, reduced body weights and food consumption, hyperkeratosis and acanthosis of the epidermis, hyperplasia of the duodenal mucosa and of the jejunum. Folpet was carcinogenic in mouse, duodenal carcinomas and adenomas were produced. Benign papillomas in the non-glandular region of the stomach were also observed. Therefore **category 3, R40** has been proposed by the majority of the experts. A clear threshold could be established; the NOAEL is 20 mg/kg bw/day. The relevant long term NOAEL is 10 mg/kg/day from the 1 year study in dogs supported by the two-year study in rats.

2.6. REPRODUCTIVE TOXICITY

Folpet did not cause adverse effects on adult fertility or reproduction in rats over two generations.

In two-generation studies in the rat, the NOAEL for parental toxicity and offspring is 14 mg/kg/day and the NOAEL for reproductive toxicity is greater than 180 mg/kg/day.

In teratogenicity studies, folpet caused embryotoxic effects (such as delayed ossification) at not frank maternotoxic dose levels in rabbit. The relevant NOAELs for maternal and developmental toxicity is 10 mg/kg/day (rabbit study). The effects observed on foetuses were hypothesised to be induced by the gastro-intestinal specific maternal toxicity, producing a severe unbalance on nutrients reaching the developing embryos and producing a general developmental impairment as a secondary effect. Teratogenic properties of folpet were discussed by the experts and the proposal to classify as R63 was

considered. A developmental study in rabbit is reported in the 2004 JMPR conclusion on folpet, but not evaluated: the rapporteur Member State was asked to submit the evaluation of the study. An agreement on this classification was not reached by the experts. The final decision is to be taken by ECB, Ispra. EFSA notes that "R63?" is highlighted in the list of end points.

2.7. NEUROTOXICITY

Folpet did not show any potential for delayed neurotoxicity in rodents.

2.8. FURTHER STUDIES

The toxicity of the metabolites phthalimide and phthalic acid was discussed during the meeting. No information was available in the DAR. A position paper (Seilfried, 2000) was presented in the addendum (March, 2005) to assess the toxicological profile of phthalic acid, phthalamic acid and phthalimide. According to this position paper phthalic acid which is not mutagenic in Ames or other bacterial assays, but does act synergistically with some heterocyclic amine mutagens. It is not carcinogenic based on negative rodent bioassays with phthalic anhydride (which converts to phthalic acid).

No specific toxicological studies meeting the criteria of the data requirements under Directive 91/414/EEC on phtalimide were available at the time of the experts´ meeting. According to the position paper by Seilfried, phtalimide would be negative in the Ames test. It should be noted that further studies were made available after the experts´ meeting which were partially evaluated by the RMS and presented in the final addendum; however, none of them were peer reviewed.

Although, it can be assumed that the reference values of the parent covers phtalimide as well, since folpet degrades very rapidly once absorbed and phtalimide is present in *in vivo* studies.

A final conclusion on their toxicological relevance for ground water cannot be made because of the lack of actual ground water concentrations. The experts concluded that the reference values for folpet cover the metabolites.

During PRAPeR 44 the toxicological profile of phthalimide was re-discussed, based on the availability of new toxicological studies. The experts agreed that the results of the existing studies demonstrate less toxicity of phthalimide compared with folpet. Also mechanistic data indicate that phthalimide does not have the potential to induce critical effects (carcinogenic, reproductive toxicity effects). As it was not possible to set specific reference values, the ones of folpet could be used for risk assessment, if needed.

2.9. MEDICAL DATA

A retrospective study of mortality was conducted in 134 manufacturing workers potentially exposed to folpet for three months. This indicated an apparent increase in the number of deaths in the workers compared with normal due primarily to circulatory disease and external causes unrelated to occupation. No duodenal cancers were observed. Other studies failed to produce any specific evidence that potential exposure to folpet could be a contributing factor related to illness or death.

2.10. ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) AND ACUTE REFERENCE DOSE (ARFD)

ADI

The ADI of 0.1 mg/kg bw/day has been proposed based on the NOAEL of 10 mg/kg/day from the 1-year dog study supported by the 2 year rat study, with safety factor of 100.

ARfD and AOEL

The ARfD and AOEL was discussed at the EPCO 25 and it was agreed to use the maternal NOAEL of 10 mg/kg bw/day based on reduced body weight gain in the developmental toxicity study in rabbit available in the dossier, resulting in 0.1 mg/kg bw as proposed also by the RMS in the DAR, the safety factor 100 is applied. The ARfD is applicable to the general population.

EFSA notes: The JMPR set an ARfD of 0.2 mg/kg bw on another reproduction study (developmental rabbit) not evaluated by the rapporteur Member State or discussed (not available in the final addendum). In the evaluation meeting discussing the draft conclusion, the rapporteur Member State indicated to support the ARfD value agreed upon by JMPR.

During PRAPeR 39 the ARfD of folpet was re-discussed: the meeting established an ARfD of 0.2 mg/kg bw, based on a NOAEL of 20 mg/kg bw/day from developmental toxicity study (based on the occurrence of hydrocephalus at higher doses) and a safety factor of 100 (in accordance to JMPR).

2.11. DERMAL ABSORPTION

Dermal absorption of folpet was discussed during the meeting. In the DAR, 2 *in vitro* studies and one *in vivo* study were presented. Based on the available in vivo rat study a value of 10% for Folpan 80 WDG was agreed on by the experts.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The operator exposure estimates have been performed with the German model. No assessment was conducted with the UK POEM model.

The results of the German model calculations demonstrate that for the different spray application techniques and different crops, 148 to 236% of the AOEL is accounted for by exposure when spray operators wear no protective clothing. When protective equipment is worn (gloves during mixing/loading for applications to tomato using tractor-mounted sprayer; gloves during mixing/loading and application for applications to tomato by hand-held knapsack sprayer; gloves during mixing/loading and gloves and protective garment/sturdy footwear during application to grapes using tractor mounted airblast sprayer) estimated exposure accounts for 34 to 77% of the AOEL.

German Model	No PPE (% of the AOEL)	With PPE (% of the AOEL)
Tractor mounted sprayer, tomatoes (1.25 kg a.s./ha)	148	77
Tractor mounted/drawn airblast, grapes (1.5 kg a.s./ha)	236	34
Hand held knapsack sprayer, tomatoes (1.6 kg a.s./ha)	148	76

Estimates were provided for operator exposure in glass-houses, according to the IVA model (IVA, 1996). The estimated systemic exposure for mixing/loading plus application for protected operators wearing protective gloves, cotton overalls and impermeable coveralls ranged from 29% to 33% of the AOEL.

Worker

Calculations of worker exposure show that exposure of workers harvesting grapes and tomatoes without protective gloves is 133% and 68% of the AOEL, respectively. If PPE such as gloves are used it is assumed that the exposure is below the AOEL Worker exposure following applications of folpet to wheat can be expected to be lower than following applications to grapes or tomatoes.

Bystander

The exposure of bystanders is approximately 2% of the AOEL.

3. Residues

Folpet was discussed at EPCO experts' meeting for residues (EPCO 24) in May 2005 and at 2 PRAPeR expert meetings (PRAPeR 40 and 45) in 2007 and 2008.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

The metabolism of folpet in plants was investigated on winter wheat, grapes and avocadoes under conditions similar to the proposed modes of application (spray treatments) supported as representative uses by the applicant. In these studies most of the radioactivity on the edible plant parts was extractable. The metabolism of folpet was similar in the investigated crops. The compound is first degraded to phthalimide through release of the trichloromethylthio-side chain. The thiophogene produced through this cleavage is assumed to be rapidly transformed into CO_2 and incorporated in natural plant component, as demonstrated with metabolism studies on captan. Phthalimide is further hydrolysed to phthalamic acid, phthalic acid and related conjugates. Folpet, phthalimide and phthalic acid were the major compounds present in the plant for the relevant PHI and their amounts were in the same order of magnitude.

In addition, studies on tomatoes and potatoes were also submitted giving information on the nature of residues translocated from roots to foliar parts and from leaves to tubers. In these conditions phthalamic acid and phthalic acid were the most important components of the residues.

The residue definition was extensively discussed in particular during the expert meeting (EPCO 24), considering in particular the possible extensive formation of phthalimide and phthalic acid in processed commodities produced with a heating step (see below). It was the view of the expert meeting that phthalimide should be included in the residue definition for risk assessment and for monitoring, phthalimic acid being excluded from the definition given its lack of specificity due to its natural presence in the environment. This was opposed to the opinion of the Rapporteur Member State which considered that, despite the potential high level of phthalimide in processed commodities, the residue definition could be restricted to folpet only, given that in the view of the RMS arguments were available for considering phthalimide significantly less toxic than folpet.

This residue definition was discussed in an additional peer review exercise after the Annex I listing of folpet. The residue definition was confirmed by PRAPeR meetings 44 (mammalian toxicology,08-11/04/2008) and 45 (residues,10-11/04/2008).

Supervised residue trials have been submitted in accordance with the representative uses supported by the manufacturer. Generally only folpet had been analysed, but in some trials, its metabolite phthalimide was also analysed. In these few cases, the tendency observed in the metabolism study that the phthalimide levels are lower than the folpet levels was confirmed. However, the information related to the actual amounts of the metabolite phthalimide is not sufficient to conduct a robust risk assessment according to the residue definition proposed by the expert meeting. A full package of supervised residue trials with analysis of folpet and phtalimide should be submitted.

Therefore at this stage, reliable information on the actual residue levels in commodities is available for folpet only, despite the residue definition proposed by the expert meeting. In tomatoes the Highest Residues (HR) for indoor and outdoor productions were 2.0 and 0.96 mg/kg respectively. The weakness of the data base has been pointed out as only 6 valid trials have been identified for each representative use (indoor and outdoor productions). In grapes, a sufficient number of supervised trials are available, with HR found at 4.7 and 3.9 mg/kg for the Northern and Southern regions respectively. For both regions the Supervised Trials Median Residue (STMR) was similar (1.9 mg/kg). In wheat grown in Southern Europe, 7 trials are available with the HR at 0.02 mg/kg. One trial resulting in a residue of 0.13 mg/kg in grains was considered as an outlier and disregarded.

The results of these field trials can be considered as reliable on the basis of storage stability studies demonstrating that folpet is stable on entire commodities for at least 6 to 12 months when stored under deep freeze storage conditions at – 18 to – 20 °C. The information provided on the storage stability of residues of folpet in processed commodities is limited to 1 or 2 months storage and is therefore not conclusive. No data on the storage stability of phthalimide has been submitted or evaluated.

The effect of processing on the nature of residues was not investigated following the usually required hydrolysis studies at high temperature simulating pasteurisation, baking, brewing and sterilisation. The applicant argued that the available hydrolysis studies conducted at room temperature were sufficient to conclude to the transformation of folpet into phthalimide and phthalic acid under

processing conditions. However the expert meeting (EPCO 24) was of the opinion that the required hydrolysis studies conducted in extreme conditions should be carried out in order to identify eventual unpredictable breakdown or reaction products to enable a robust risk assessment for the safety of the consumer.

Studies have been submitted on the influence of industrial processing and household preparation on the residue level in processed commodities from grapes and tomatoes. In these studies only folpet was analysed. Residues of folpet in processed commodities for human consumption (grape wine and juice, tomato juice and puree, canned tomatoes) were below the Limit of Quantification (LOQ) and corresponding Transfer Factors (TF) were consequently below 0.1. Balance calculations carried out for tomato processing clearly suggest that folpet is degraded during process. Further data are necessary to determine the actual level of degradation products in processed commodities. Data on processing of wheat were also submitted, but were not evaluated given the low level of folpet expected on wheat grain.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

Studies on the nature and the levels of residues in succeeding and rotational crops were not carried out. This is acceptable given the low persistence of folpet and its main metabolites in soil.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

The metabolism of folpet has been investigated in lactating goats. The substance is extensively metabolised and excreted and was not found in any edible tissue. After oral administration for 6 days at dose rate of 14 mg/kg diet, residues in animal tissues were very low and no sign of accumulation is present. Only in liver and kidneys Total Radioactive Residues were above 0.01 mg eq folpet/kg (0.02 and 0.05 mg/kg respectively). The metabolism was found to be similar to that observed in rats with hydrolysis of the nitrogen-sulphur bond leading to thiophosgen and phthalimide which is further metabolised to phthalamic acid and phthalic acid. The residue definition for animal commodities was discussed during the expert meeting (EPCO 24) and it was concluded that phthalimide was the most appropriate indicator of the residue present. However, taking into account the results of the metabolism study, performed with an animal exposure one order of magnitude above the actual predictable exposure, no residue of phthalimide above the usual LOQ of method of analysis is expected. A feeding study in lactating ruminant and the establishment of MRLs for animal products are not necessary.

3.3. CONSUMER RISK ASSESSMENT

Assessments of the chronic and acute exposures of consumers could not be conducted on the basis of the residue definition proposed by the expert meeting (EPCO 24) and later confirmed in PRAPeR 45(residues, 10-11/2008) as data on the actual level of the metabolite phthalimide in plant commodities were not sufficient.

Only exposure assessments to folpet are at this stage possible and were performed by the rapporteur Member State.

The chronic dietary exposure assessment has been carried out according to the WHO guidelines for calculating Theoretical Maximum Daily Intakes (TMDI). Three consumption patterns were considered: the WHO European typical diet for adult consumers, the national diets of UK for infants, toddlers, child and adult populations, which take into consideration high individual consumption levels (at the 97.5th percentile of the distribution of consumptions in the respective populations) and the national diet of Germany for the 4 to 6 year old girl.
Residues in grapes, tomatoes and wheat were assumed to be at the level of the respective MRLs proposed on the basis of the supervised residue trials. No exposure resulting from the consumption of animal commodities was considered as it can be expected from the metabolism data that this exposure is very low.
All the TMDI calculations resulted in exposures well below the ADI. The highest TMDI value (28 % of the ADI) was obtained for the British toddlers.
The acute exposure to residues of folpet in table grapes and tomatoes has been assessed according to the WHO model for estimates of short term intakes. Large portion consumption data for adults and toddlers in UK were used. Calculations were carried out considering residues in composite samples of treated commodities at the level of the respective MRLs as well as high unit to unit variability (7 for tomatoes and 5 for table grapes). These calculations showed potential exposures in excess of the ARfD for toddlers in the case of table grapes and tomatoes grown under glass (270 and 120% of the ARfD, respectively). The residue situation of tomatoes grown outdoor is slightly less critical, and would require a MRL of 2 mg/kg, with resulting potential acute intakes close to but below the ARfD.

The acute reference dose was discussed in an additional peer review exercise after the Annex I listing. In PRAPeR meeting 39 (mammalian toxicology,08-11/4/2008) the ARfD was changed from 0.1 mg/kg bw to 0.2 mg/kg bw. So this changes the percentage of the ARfD as follows. For table grapes 135 % and for tomatoes 60 % of the ARfD for the critical population subgroup toddlers.

It must be kept in mind that the exposure assessments summarised here above represent an underestimation of the actual toxicological burden as the phthalimide metabolite was not included in the calculations. Nevertheless, based on the currently available information restricted to the folpet residue levels, a potential for acute risk for the health of consumer has been demonstrated for table grapes.

3.4. PROPOSED MRLS

MRL proposals can be made only on a provisional basis as residue data in accordance with the residue definition proposed by the expert meeting are not available. Taking into account folpet only, and based on the results of supervised residue trials, MRLs of 5, 3 and 0.05 mg/kg would be needed for grapes, tomatoes and wheat respectively. These proposals may not be sufficient, depending on the contribution of phthalimide to the total residues.
No MRL is needed for animal commodities.

4. Environmental fate and behaviour

Fate and behaviour in the environment of folpet was discussed in experts' meeting EPCO 21 (April 2005) on basis of the DAR and the addendum of March 2005. Additional information has been summarized by the rapporteur Member State in the addendum of October 2005.

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

Folpet metabolism in soil under dark aerobic conditions at 25 °C and 75 – 80 % MHC was investigated in one study with a sandy loam soil (pH = 5.4, 17 % clay, 1.16 % OC) at an application rate of 11.9 mg a.s. / kg soil (equivalent to a rate of 8.9 kg a.s. / ha) with the substance ^{14}C labelled at the phenyl ring of the molecule. A second study to address the route of degradation of [carbonyl-^{14}C] folpet is available in the dossier (Pack, D.E. 1976**)**, however the lack of essential methodological information prevents to use it for the EU assessment. An additional study with three soils that cover a range of pH (pH = 4.8 – 7.5), organic carbon (OC = 0.9 – 3.9 %) and soil textures investigates the rate of degradation of folpet in soil under aerobic conditions at 20 °C but main metabolites are also quantified and provides useful soil metabolism information of folpet.

First degradation step involves the release of the highly reactive **thiophosgene** (not labelled and therefore no measured in the study) to yield the major soil metabolite **phthalimide** (1H-isoindole-1,3, (2H)-dione; max 65 % AR after 5 d). Phthalimide is further degraded through **phthalamic acid** (max. 16.7 % AR at 1d) to **phthalic acid** (max 16.6 % AR at 1 d). Mineralization was high (60 % AR as CO_2 after 90 d, 69.8 % AR as CO_2 at the end of the route study after 1 yr). Unextractable residues were formed in moderate amounts (max. 31.2 % AR at 14 d).[3]

With respect to the thiophosgene moiety further information may be derived from the closely related compound captan. Degradation of this compound in soil was investigated with trichloromethyl-^{14}C labelled compound in three different viable sandy loam soils (25 °C and 75-80 % of 1/3 bar soil moisture content for 2 of the soils, conditions not reported for the third soil). CO_2 formed reached levels corresponding to 80-91 % AR and unextractable residues amounted to 13.3-14.3 % AR at the end of the studies at 28-30 d. In captan no thiophosgene was detected but the **thiocarbonic acid** that may result from its rapid hydrolysis was detected at low levels in the soil extracts between days 7 and 28 (0.6 – 1.1 %). The volatiles trap in this study contained only low levels of radioactivity (max. 0.21 % AR) that was proposed to be also thiocarbonic acid by the notifier. The experts' meeting considered this was likely, but noted it could not be excluded that thiophosgene was present at trace levels in the volatile traps. Therefore, it is not expected that free thiophosgene reach significant levels as a consequence of the degradation of folpet in soil.

Dark anaerobic metabolism in soil at 25 °C was also investigated in the same soil used for the aerobic study. The study consisted in four days aerobic phase followed by 60 days anaerobic one. Degradation under anaerobic conditions followed that same general route found under aerobic conditions. Both phthalimide (max. 50.6 % AR at the start of the anaerobic phase) and phthalic acid

[3] Clarification on the amount of bounded residues reported in the route study was given in the addendum of March 2005.

(max. 13.3 % AR after 60 d of the anaerobic phase) were found as major metabolites under anaerobic conditions. During the anaerobic phase of the study CO_2 continued to increase from 6.14 % AR at 0 d to 26.3 % AR at 60 d.

A second dark anaerobic metabolism study of folpet in a loamy sand soil at 20 °C is available (Pack, D.E. 1980). This study was considered not reliable for the EU risk assessment (see addendum March 2005).

A photolysis study is available. Photolysis under natural sunlight does not contribute significantly to the environmental dissipation of folpet.

Three field studies carried out in the USA were submitted in the dossier. Only folpet and phthalimide were found in these studies.

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The rate of degradation of folpet in soil under aerobic conditions at 20 °C or 25 °C was investigated in the same studies used to establish the route of degradation in soil. Folpet is very low or low persistent in soil ($DT_{50\ lab\ 20\ °C}$ = 0.2 -3.8 d; $DT_{50\ lab\ 25\ °C}$ = 4.3 d; a maximum half life of 16.2 d was considered in the assessment based on a different fitting procedure). Half lives for the metabolites were derived from the study performed with the parent. All major folpet metabolites also exhibited very low or low persistent in soil under aerobic conditions at 20 °C. However, in the study performed at 25 °C a longer half life was determined for phthalimide ($DT_{50\ lab\ 25\ °C}$ = 28.2 d). In one of the experiments the degradation was investigated at 10 °C. The metabolites still exhibited low persistence, but degradation was about four times slower than at 20 °C in the same soil. Further information on the fitting procedures and normalised half lives were provided in the addendum of March 2005.

Under anaerobic conditions folpet degraded slightly slower that under aerobic ones. No anaerobic half life was determined for the metabolites.

Under field conditions folpet half lives was always below 3 d. It was not possible to determine any field half lives for the metabolites.

PEC soil presented in the DAR were based on worst case laboratory half life (DT_{50} = 4.3 d) with the critical GAP of ten applications of 1.5 kg a.s/ha at 7 days interval (grapes use) and 50 % interception. In the addendum March 2005 PEC soil are recalculated for all three uses taking into account crop interception given for FOCUS GW. These PEC soil were not explicitly considered in the expert' meeting and were not incorporated in the list of end points by the RMS. In fact the calculation provided cannot be considered acceptable since average interception (66.3 % for the 10 applications period) has been used for vines. Due to the fact that folpet is low persistent in soil the maximum PEC is driven by the interception at the time of individual applications. Representative uses table indicate that for vines applications program may start at shoot emergence (corresponding to grow stage 07-08). At this stage interception will be only 40 % and higher PEC soils are expected. Provisional risk assessment has been therefore based on the PEC soil provided in the original dossier (50 %

interception assumed for vines).[4] Due to ambiguities with respect to the time of application interception for PEC soil calculation cannot be defined for wheat. PEC soil values provided in the addendum need to be clarified for tomatoes since they were not confirmed by the EPCO experts' meeting and differ from the values calculated by EFSA.[5] A risk assessment for earthworms based on the PEC soil values calculated by EFSA is presented in the conclusion.

4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

A batch adsorption / desorption study in four soils is available for folpet. However, no adsorption parameters were derived from this study due to the high instability of folpet. Therefore, K_{oc} was estimated based on K_{ow}. Six different methods found in the scientific literature were used and the most conservative value (K_{oc} = 304 mL / g) was selected for the assessment.

A batch adsorption / desorption study in five soils is available for phthalimide. Due to the high instability of this compound under neutral and alkaline conditions all soils investigated were acidic (pH < 6). This metabolite was found to be medium to high mobile in soil (K_{foc} = 72 – 385 mL / g). Experts' meeting agreed to only consider the values obtained in this study for the EURO soils and disregard the values from the LUFA soils.

Mobility of the metabolites phtalamic acid and phthalic acid was estimated with the PCKOC program of the EPIWIN packadge (EPA). According this model phtalamic acid is very high mobile in soil (K_{oc} = 10 mL / g) and phthalic acid is high mobile in soil (K_{oc} = 73 mL / g). The experts' meeting agreed to accept the estimation in this case due to the fast degradation of these metabolites.

An aged soil column leaching study was performed with folpet. The majority of the radioactivity was found in the top 2 cm soil layer as unextractable material. The leachate contained up to 2.6 % AR. Phtalic acid was found as the major component identified in the leachate. Folpet, phthalimide and phthalamic acid were not detected in the leachate.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Hydrolysis of folpet in buffer solutions at environmental relevant pHs (4, 5, 7, 9) and temperature (25 °C) was investigated in three separated studies with carbonyl-^{14}C and trichloromethyl-^{14}C labelled folpet. Hydrolysis is rapid at acidic and neutral pH (DT_{50} < 3 h) and very rapid at alkaline pH (DT_{50} < 3 min).

Main hydrolysis metabolites were phathalimide (max. 91 % AR at pH 5 after 24 h) and phthalic acid (max. 78.4 % AR at pH 9 after 10 min). Two major uncharacterized (**unknown 1**; max. 36 % AR at pH 9 after 24 h and **unknown 2**: max. 51.8 % at pH 9 after 1h) metabolites were found in the

[4] Assuming an application with 40 % interception (shoot emergence) followed by an application with 50 % interception (first leaves) a maximum PEC soil of 1.39 mg /kg is obtained.

[5] Two options with three or four applications are proposed for tomatoes in the table of representative uses. EFSA calculated PEC soil = 0.69 to 0.82 mg /kg assuming 80 % interception. The value given in the addendum was significantly lower (0.49 mg /kg). However, the risk assessment shows no risk for earthworms for the more conservative of these values (see point 5.5).

hydrolysis study performed with the trichloromethyl-^{14}C labelled folpet. No definitive characterization of these metabolites was accomplished but it was postulated that unknown 1 will be the trichlomethylsulfenic acid salt and that unknown 2 will be tricloromethylmercaptan that will degrade to thiophosgene, carbon oxysulfide and ultimately to CO_2.

Hydrolysis of phthalimide in buffer solutions (pH 4, 7 and 9) was investigated in a separated study at 25, 40 and 100 °C. At 25 °C and pH 4 and 7 phthalimide was stable. At 25 °C and pH 9 phthalimide was hydrolysed with a half life of 2 h. Hydrolysis of phthalic acid was not investigated further but according to its structure this compound is not prone to suffer hydrolysis and no further investigation was required.

An aqueous photolysis study is available. Contribution of photolysis to the aqueous degradation of folpet was not significant.

Folpet was shown to be readily biodegradable in one of the ready biodegradability studies available (1 mg C /L). At higher concentrations (10 mg C/L) it did not fulfil the criteria to be considered readily biodegradable but could be considered inherently biodegradable. No significant inhibition of the degradation of reference material (sodium benzoate) was observed at the higher concentration and the slower degradation was attributed to the low solubility in water (0.8 mg/L). Fate and behaviour experts' meeting agreed not to propose R53 for this compound.

A water sediment study investigates the degradation of folpet in the aquatic environment with two different water sediment systems at 20 °C in the dark. Very low recoveries were obtained for some data points and the experiments were repeated with 21 d experiments. This second experiments showed that the most likely reason for the low recoveries on some of the data points of the first experiment was the partly loss of CO_2 loss during sampling processing. Mineralization at the end of the study (100 d) was relatively high in both systems (51-54 % AR). Folpet degrades very rapidly in both systems (DT_{50} < 1h; DT_{90} < 5 h). Folpet is not found in the sediment phase. Major metabolites in the water phase were phthalimide (max. 20.4-26.0 % AR at 4 h), phthalamic acid (max. 13.3 % AR at 1h), phthalic acid (max. 26.3 -37.5 % AR at 1d), benzamide (max. 10.2 % AR at 1 d) and **2-cyanobenzoic acid** (max. 39.7 % AR at 1d). No major metabolite was found in the sediment phase. The main metabolites encountered in the sediment were phthalimide (max. 5.9 %) and phthalic acid (max. 3.8 %). Half lives were calculated by fitting to a multicompartmental model. All the metabolites degraded rapidly in both systems. The longest half lives are determined for phthalamic and phthalic acid (phthalamic acid: $DT_{50\ whole\ system}$ = 6.1 d; phthalic acid: $DT_{50\ whole\ system}$ = 6.4 d).

Considerable amounts of bound residues were found in the sediment 7 d and 14 d after application. Due to the fact that uses include 10 repeated applications at weekly intervals, the applicant was required to address the potential for accumulation of bounded residues in the sediment (Evaluation meeting, December 2004). Notifier presented the case that sediment was exhaustively extracted and that the remaining non extracted radioactivity was mostly associated to the humin fraction. It was possible to postulate that this residue was covalently bounded to organic matter of the sediment and formed by the phthalic acid type of moieties that would be further degraded and release as CO_2 and CH_4 (actually not trapped) (see addendum March 2005). The rapporteur Member State and experts' meeting agreed that bound residues were not likely to be bioavailable and will not constitute a risk for sediment dwelling organisms.

PECsw presented in the DAR for folpet considered spray drift route as the main route of surface water contamination due to the fast degradation in soil. Calculations only cover use in vines because it was considered the critical GAP in terms of application rate. Potential contribution to surface water contamination by run off under worst case assumptions and 0.5 % run off of applied dose are also presented in the DAR. Maximum PECsw for metabolites were presented in the addendum of March 2005 based on spray drift. PECsed were also provided for the main sediment metabolites phthalimide and phthalic acid. Taking into consideration the proposed representative use on winter cereals in northern Europe and the high number of applications the experts' meeting agreed that potential contamination through drainage needed to be addressed. FOCUS STEP 1 PEC sw calculations for metabolites phthalimide, phthalamic acid and phthalic acid have been presented by the notifier and summarized by the rapporteur Member State in the addendum of October 2005. Whereas not peer reviewed EFSA can confirm that the parameters already agreed by the experts' meeting have been used in this calculation. Values obtained for the different representative uses are lower than the worst case runoff estimation presented in the DAR (577 μg/L). This level could be of concern only for metabolite phthalimide. Therefore, FOCUS STEP 1 value has been used to complete the assessment of this metabolite (see point 5.2). FOCUSsw for the parent calculations up to STEP 4 are also summarized in the addendum of October 2005, these calculations have not been peer reviewed and have not been used on the EU risk assessment.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

PECgw of folpet and aerobic soil metabolites phthalimide, phthalamic acid, and phthalic acid were estimated using FOCUS PELMO 1.1.1. Two critical uses were selected: grapes (7 x 1.5 kg a.s./ha and 7 d interval) and wheat (2 x 0.75 kg a.s./ha and 14 d interval)**.** Detailed description of the parameters selection was presented in the addendum of March 2005 and discussed by the experts' meeting. Experts did not agreed on the use of median DT_{50}s and the K_{oc} value for the phthalimide metabolite. Therefore, a new data gap was identified. New calculations using FOCUS PELMO 3.3.2 have been presented by the applicant on September 2005 and summarized by the rapporteur Member State in a new addendum of October 2005. The addendum has not been Peer Reviewed but EFSA may confirm that the parameters have changed according experts' meeting recommendations. The same uses have been modelled except use in winter wheat in the Northern EU, which is not longer supported by the notifier The calculated PECgw values demonstrated that the predicted 80th percentile concentrations for folpet, phthalimide, phthalamic acid and phthalic acid were all 0.001 μg/L at 1 m depth in all scenarios simulated (seven grape scenarios in Northern and Southern EU and for winter wheat scenarios in Southern EU). According the table of representative uses interval between applications of 7 d is also possible in wheat. However, the modelling of vines can be regarded as a worst case with respect to the tomatoes and wheat uses and therefore no further modelling would probably not be necessary to complete the EU risk assessment with respect to potential for ground water contamination.

4.3. FATE AND BEHAVIOUR IN AIR

Concentrations of folpet in the air are expected to be negligible, due to low volatility and short persistence in the atmosphere. Potential release of thiophosgene due to soil degradation of folpet was addressed by the notifier with captan soil degradations studies. Based on these studies, the experts' meeting concluded that it could not be excluded that thiophosgene might be released to the air as a result of the soil metabolism of folpet, but that if this occurs; it would only be present in trace amounts.

5. Ecotoxicology

Folpet was discussed at the EPCO Experts` meeting for ecotoxicology (EPCO 22) in April 2005.

5.1. RISK TO TERRESTRIAL VERTEBRATES

The risk assessment for birds and mammals presented in the DAR was done according to EPPO 1992 (Hoerger and Kenaga, 1982). The relevant trigger values were not breached for birds and mammals. The rapporteur Member State asked the applicant to submit a risk assessment according to SANCO/4145/2000. The new risk assessment was summarized in an addendum from March 2005 and discussed at the EPCO experts` meeting.

The acute risk to birds was assessed as low in a first tier risk assessment for all representative uses. The short-term TER values were above the Annex VI trigger except for medium herbivorous birds in tomatoes (TER >8.9). Since the TER is based on a NOEC at the highest tested dose and taking into account that tomato foliage is considered to be not an attractive food source, the risk to medium herbivorous birds is considered to be low. A high long-term risk was identified in a first tier risk assessment to insectivorous birds for all representative uses and to medium herbivorous birds for the use in tomatoes. The refined risk assessment was based on a refinement of the endpoint for long-term toxicity (769 mg a.s./kg/d), RUD (residue per unit dose) value of 5.1 for insects and a PT (Proportion of diet obtained in the treated area) value of 0.61 (based on blue tits, *Parus caeruleus* in orchards). The expert meeting agreed to the use of the PT value of 0.61 for grapevine but rejected the suggested endpoint of 769 mg a.s./kg bw/d. The use of a RUD value of 5.1 was not accepted by the meeting since this value relates to residues in large insects and would not cover the risk from uptake of residues in small insects. A new long-term risk assessment was submitted by the applicant and evaluated by the rapporteur Member State in an addendum from October 2005. The new refined risk assessment was not peer reviewed. Yellow wagtail (*Motacilla flava*), yellowhammer (*Emberiza citronella*) and cirl bunting (*Emberiza cirlus*) were chosen as focal species in tomato fields and vineyards in central and southern Europe. Refinements of FIR (Food intake rate), PD (Proportion of food type in the diet), PT and the use of a deposition factor were suggested to refine the long-term risk for the focal species. The resulting long term TER values for the representative uses in tomatoes and grapes were in the range of 11.3 to 13.27. Some of the refinement steps are questionable. A deposition factor for residues in insects is not applicable since interception is already taken into account in the RUD values for insects. Yellowhammer and cirl bunting search for food mainly on the

ground, therefore it is not clear whether the risk to small insectivorous birds feeding on insects in the foliage of grapes is covered by yellowhammer and cirl bunting. The use of a MAF of 1 for weed seeds potentially underestimate the residue level in weed seeds since folpet is a systemic fungicide and the GAP suggests 10 applications with an interval of 7 – 28 days. The PT value of 0.61 for insectivorous birds was accepted by the experts' meeting for vineyards but it was not supported by data for the use in cereals. The refined risk assessment presented in the addendum of October 2005 is not peer reviewed. Based on the peer reviewed data it is not possible to exclude a high long-term risk to small insectivorous birds for the representative uses in cereals, tomatoes and vineyards. The long-term risk to herbivorous birds in tomatoes is considered to be low because tomato foliage is not attractive as a food source and the product is applied at a growth stage of tomatoes where a high level of solanin reduces the palatability of the tomato plants. A statement was delivered by the applicant that the product is applied only in late spring early summer to a late growth stage of winter wheat. At this growth stages the plants are not attractive as a food source for grazing birds and therefore the risk to herbivorous birds is considered to be low.

The revised risk assessment for mammals according to SANCO/4145/2000 resulted in a low acute risk for insectivorous mammals in winter wheat and for herbivorous mammals in tomato fields. The first tier acute TER value of > 6.8 was below the Annex VI trigger value of 10 for the use in grapes. The long-term TER values for mammals exceeded the Annex VI trigger for all representative uses. The highest tested dose from a two generation reproduction study with rats was considered as a NOEC and used for the risk assessment although a reduction in food consumption and bodyweight were observed at the highest tested dose in the parent generation and in the F1 generation. The applicant explained the reduced food intake and bodyweight by reduced palatability of the food and irritation of the mucal membranes of the intestinal tract due to the high concentration of folpet. An open point was set at the expert meeting for the rapporteur Member State to revise the long-term NOEC used for the risk assessment and to conduct a new risk assessment based on the revised long-term NOEC if necessary. The rapporteur Member State considered the endpoint of 5000 ppm as appropriate for the risk assessment arguing that no effects were observed on reproductive success (litter size) in the laboratory. The EFSA is of the opinion that it is not clear whether a reduction in bodyweight of up to 10% in the F0 and F1 generation is an effect which does not lead to adverse reproductive effects in wild populations of mammals when animals are exposed to additional stressors in their natural environment (e.g. periods of low food availability). No data were presented to support the assumption that the reduced body weight would not lead to any adverse effects in natural populations. The applicant stated that the exposure of animals in the field would be lower compared to the exposure in the laboratory tests. However, 10 applications with a minimum interval of 7-28 days are recommended for the representative use in grapes. Therefore it cannot be excluded that at least two generations of small herbivorous mammals (voles) are potentially repeatedly exposed to high levels of folpet residues. The opinion of the PPR panel[6] (Panel on Plant Health, Plant

[6] Opinion of the Scientific Panel on Plant health, Plant protection products and their Residues on a request from EFSA related to the choice of endpoints to assess the long term risk to mammals. The EFSA Journal (2006) 344, 1-22; http://www.efsa.europa.eu/science/ppr/ppr_opinions/1437/ppr_op_ej344_noec_mammals_en1.pdf

Protection Products and their Residues) on the ecotoxicological relevance of effects observed in toxicological tests could be taken into account at Member State level to evaluate the endpoint used for the risk assessment.

Since the endpoint (NOEC of 5000 ppm) used for the risk assessment is not scientifically fully justified EFSA suggests to use the next lower NOEC of 1500 ppm for the long-term risk assessment for mammals. This would result in a long term risk to small mammals in grapes. The applicant stated that tomato foliage is not an attractive food source for mammals and that folpet is applied only to late growth stages of winter wheat which is assumed to be not an attractive food source. Overall it is concluded that the risk to mammals is low from the representative uses in winter wheat and tomatoes but a high acute and long term risk to small herbivorous mammals cannot be excluded for the representative use in grapes.

No risk assessment for the uptake of contaminated drinking water was available. It is not clear whether exposure to contaminated drinking water can be excluded for the representative uses of folpet. Therefore the EFSA calculated in an addendum the TER values according to Sanco/4115/2000. The acute TER values for birds and mammals exceeded the relevant Annex VI trigger values except for the use in grapes if the solution is sprayed at the highest recommended concentration. The short-term and long-term TER values for birds and the long-term TER values for mammals were below the Annex VI trigger values for the representative uses in winter wheat and grapes. For the representative use in tomatoes only a high long-term risk for birds was indicated.
A refined risk assessment or risk mitigation measures (e.g. restriction to the lowest recommended spray concentration) are required to address the high acute risk to birds and mammals from the use in grapes at the highest recommended concentration of folpet in the sprayed solution. A refined risk assessment for the uptake of contaminated drinking water is required for the intended uses in winter wheat and grapes to address the short-term and long term risk to birds and the long-term risk to mammals and for the intended use in tomatoes a refined risk assessment is required to address the long-term risk to birds.
It is likely that the rapid degradation of folpet via hydrolysis reduces the risk to birds. However the degree is uncertain and depends on the behaviour of birds (e.g. motivation to drink from fresh puddles) and if repeated single exposure peaks could lead to long-term effects.

A high risk from contaminated drinking water was shown from a first tier risk assessment based on worst case assumptions (e.g. the total daily water demand is taken from leaf axils or puddles which are contaminated by the sprayed solutions). Some MSs are of the opinion that long-term exposure to contaminated drinking water can be excluded and hence regard the long-term risk from uptake of contaminated drinking water as low. However, no common agreement among MSs exists yet on the potential long-term risk from contaminated drinking water. It is planned to discuss the risk to birds and mammals from uptake of contaminated drinking water as a general point in an EPCO expert meeting.

The risk from secondary poisoning for fish eating birds was assessed in the DAR and is considered to be low. In the addendum of March 2005 a revised risk assessment for secondary poisoning via uptake of contaminated earthworms was presented. The calculation was based on a BCF of 1.8 and the 14 d twa PEC following the final of 10 applications in grapevines and applying an interception factor of 70 %. The resulting TER of 130 indicates a low risk from uptake of contaminated earthworms.

5.2. RISK TO AQUATIC ORGANISMS

Folpet is inherently very toxic to fish and aquatic invertebrates. Flow through tests with fish and daphnids gave acute LC_{50}/EC_{50} values of 15 – 65.5 µg/L fish and 20 µg/L for daphnids. Due to rapid hydrolysis and degradation to much less toxic metabolites the acute toxicity observed under static test conditions was markedly lower. In the expert meeting it was pointed out that the acute risk assessment should be based on the acute endpoint of 98 µg/L for brown trout (*Salmo trutta*) instead of 233 µg/L for rainbow trout (*Oncorhynchis mykiss*) since brown trout was the most sensitive species out of six different fish species tested under static conditions for 96 hours. Because of the additional acute toxicity data on six different fish species the Annex VI trigger was lowered from 100 to 10. If the acute endpoint of 98 µg/L is compared to the initial PECsw as calculated in the DAR, the revised Annex VI trigger of 10 is met for winter wheat but a no spray buffer zone of 10 m and 5 m is needed to achieve TER values above 10 for the representative uses in grapes and tomatoes. The opinion of the PPR panel[7] on the possibility of lowering the uncertainty factor if additional species were tested should be taken into account at Member State level.

Two early life stage studies with fathead minnow (*Pimephales promelas*) under flow through conditions and a prolonged toxicity study with rainbow trout under semi-static test conditions were available. The rapporteur Member State considered these studies as not relevant for the long-term risk assessment since the degradation of folpet in the water/sediment system is very fast with DT_{50} values of < 1h. However, the representative uses include repeated applications of the product of up to 10 times for orchards. The expert meeting decided that the long-term risk assessment for fish should be based on the prolonged toxicity study with rainbow trout because the static renewal test system reflects the repeated exposure in the water body next to a field. The rapporteur Member State concludes, based on a statement of the applicant, that the results of the study should not be used in the risk assessment since the exposure regime in the study was worst case compared to the expected exposure in the field (the interval of renewal of test media 2-3 days is shorter than the minimum spray interval of 7 days). It is also stated that the study does not show build up of sub-lethal effects and that reversibility of non-lethal effects (hyperventiliation) were observed in the static acute tests within 48 to 72 hours which was considered to be a sufficient short time to recover in between the spray intervals of 7 days. The EFSA agrees that the dosing interval in the test is shorter and hence worst case compared to the interval suggested in the GAP. Nevertheless it reflects the expected repeated

[7] Opinion of the Scientific Panel on Plant health, Plant protection products and their Residues on a request from EFSA related to the assessment of the acute and chronic risk to aquatic organisms with regard to the possibility of lowering the uncertainty factor if additional species were tested. The EFSA Journal (2005), 301, 1-45. http://www.efsa.europa.eu/science/ppr/ppr_opinions/1332/ppr_op_ej301_aquatic_ecotox_en1.pdf

exposure of fish in a water body adjacent to the treated area better than exposure to a single dose. The argument of the applicant that it is unlikely that an individual fish is repeatedly exposed to the same high dose is not scientifically justified and certainly not valid for fish inhabiting a pond. Sub-lethal effects like hyperventilation and darkened pigmentation were observed during the whole study period of 28 days for the test concentration of 39 µg a.s./L and higher. It is difficult to quantify the sublethal effects in terms of adverse effects in the natural environment but hyperventilation or darkening of the pigmentation could increase the mortality rate during periods of oxygen depletion or high pressure from predators. Since no effects on growth were observed (except for the highest tested dose) and the exposure in the study is worst case compared to the field exposure it is considered appropriate to use the observed mortality instead of the sublethal effects as a relevant parameter for deriving an endpoint for the long-term risk assessment. No mortality was observed at a dose of 39 µg a.s./L. If this value is compared to the PECsw values which have been calculated on the basis of spray drift in the DAR, the chronic TER values are below the Annex VI trigger of 10. Risk mitigation measures such as no spray buffer zones of 15 m for grapes (TER = 12) and 5 m for winter wheat and tomatoes (TER = 27 and 16.8) are required for the long-term risk to fish from the representative uses of folpet. It was noted in the expert meeting that rainbow trout reacted less sensitive compared to brown trout. This could have resulted in a potential underestimation of the long-term risk to fish but the exposure regime in the test was worst case compared to the GAP and could have counterbalanced a potential underestimation of the long-term risk to fish.

The intrinsic toxicity to daphnids (48 h EC_{50} = 20 µg/L) is similar to fish. Compared to the endpoints from flow through studies the acute toxicity observed under static conditions was markedly less by more than one order of magnitude. The 24h EC_{50} (680 µg a.s./L) from a study with the formulation "Folpan 80 WDG" under semi static test conditions with renewal of the test medium after 24 hours was used for the risk assessment. The 48 h EC_{50} (110 µg a.s./L) from the same study was not taken into account. The results from the acute studies with daphnids suggest that a single exposure to folpet is less severe than exposure to a second peak after 24 hours. The EC_{50} after 48 hours (= 24 hours after the first renewal of test medium = 2^{nd} peak of exposure) is about 6 times lower than after 24 h (= 1^{st} peak of exposure). The EFSA is of the opinion that the use of the 24 h EC_{50} may be appropriate to assess the acute effects of a single exposure peak because the 48 h EC_{50} includes a second exposure peak within a period of time much shorter than expected from the representative uses. Based on 680 µg a.s./L the acute TER values would exceed the Annex VI trigger of 100 if a no spray buffer zone of 5 m for the use in winter wheat and tomatoes and a no spray buffer zone of 10 m is applied for the use in grapes.

Since the representative uses include multiple applications of up to 10 times for grapes a long-term risk assessment for aquatic invertebrates is considered necessary. Based on the NOEC of 2.1 µg a.s./L from the available 21-d reproduction study with *D. magna* and initial PECsw the resulting TERs for the use in winter wheat, tomatoes and grapes are 0.17 (2.1/6.93), 0.18 (2.1/11.54) and 0.05 (2.1/40.1). Risk mitigation measures such as buffer zones of up to 40 m for winter wheat and > 50 m for tomatoes and grapes would be required. The 21 d reproduction study with daphnids was conducted under flow through conditions which would lead to an overestimation of the risk. The expert meeting

identified the need for a new long-term study with daphnids under semi-static test conditions. The new 21 d study with *D. magna* under semi-static test conditions is essential to finalise the long-term risk assessment for daphnids since exposure to a single peak does not adequately address the long-term risk from repeated exposure and the available 21 d reproduction study conducted under flow through conditions would lead to an overestimation of the risk to daphnids.
It is concluded that the acute risk to daphnids from a single exposure is high and risk mitigation measures such as no spray buffer zones of 5m for the representative uses in winter wheat and tomatoes and 10 m for the representative use in grapes are needed. However, a final conclusion on the long-term risk to daphnids from the representative uses cannot be drawn based on the available data.

The algae growth inhibition test was conducted under static conditions for 72-hours and resulted in an E_bC_{50} value of > 10 mg/L. The resulting TER values for all representative uses exceeded the Annex VI trigger value indicating a low risk to algae.

The risk of bioconcentration and of bioaccumulation of folpet is considered to be low although the product is repeatedly applied because of the low BCF value for fish (whole fish BCF = 56) and the very fast degradation in the water phase. Although no assessment of the potential risk of bioconcentration and of bioaccumulation of the major metabolites was conducted, the risk is assumed to be low because of the relative rapid degradation in the water phase (DT_{50} values ranging from 0.334 to 6.35 days) and taking into consideration that the metabolites are usually more polar than the parent for which the BCF was determined to be very low (BCF value of 56).

The major metabolites in the water phase phthalimide, phthalamic acid, phthalic acid, benzamide and 2-cyanobenzoic acid are of low toxicity to aquatic organisms with acute $LC_{50}/EC_{50}/E_bC_{50}$ values of >100 mg/L except for phathalimide for which LC_{50}/EC_{50} values for fish and daphnids of 38 and 39 mg phtalimide/L were observed. The TER values based on peak PECsw values from spray drift were in the range of 7350 to >61078 indicating a low risk to aquatic organisms from the major metabolites. Based on worst case assumptions for entry via run-off the maximum concentration for each of the metabolites was calculated in the DAR as 577 µg/L. Only for the metabolite phthalimide the acute TER trigger of 100 is breached by applying the PECsw of 577 µg phthalimide/L. The TER value is above the Annex VI trigger if the maximum PECsw of 132.26 µg phthalimide/L (grapes, late) from FOCUS step1 is used. The FOCUS step 1 calculation is not peer reviewed but the input parameter for the FOCUS calculations were agreed in the experts' meeting on fate and behaviour and thus the PECsw from FOCUS step 1 is considered reliable. Overall it is concluded that the risk of the major metabolites to aquatic organisms is low.

5.3. RISK TO BEES

Data on the acute contact and oral toxicity of folpet technical and on the acute inhalation, contact and oral toxicity to honeybees (*Apis mellifera*) is available. The formulated product (Folpan 80 WDG) is-more toxic than technical folpet. The acute risk to bees from the representative uses is considered to

be low since the HQ values calculated for the highest application rate for outdoor uses (1500 g a.s./ha) are below the Annex VI trigger of 50 (< 8.9 for oral toxicity and < 9.4 for contact toxicity).

5.4. RISK TO OTHER ARTHROPOD SPECIES

The applicant submitted new studies and a new risk assessment for non target arthropods since the studies used for the original risk assessment were conducted at too low application rates. The new extended laboratory studies with *Typhlodromus pyri*, *Aphidius rhopalosiphi*, *Coccinella septempunctata* and *Chrysoperla carnea* and the new risk assessment were summarized in the addendum from March 2005. No effect on mortality and reproduction of > 50 % was observed for *T. pyri*, *C. septempunctata* and *C. carnea* up to a dose of 5.25 kg a.s./ha which corresponds to the use in grapes by applying the default MAF of 3.5 for 8 applications. A high mortality of 75.7 % was observed for *A. rhopalosiphi* at a dose of 5.25 kg a.s./ha indicating a high in field risk for *A. rhopalosiphi* from the representative use us in grapes. Exposure to 14 day aged residues did not result in effects on *A. rhopalosiphi* showing that recolonisation after a non-spray period of 14 days is possible. No new off-field risk assessment according to ESCORT 2 was provided in the addendum. However, the off-field HQ in the original off-field risk assessment in the DAR were markedly below 2 and since the observed effects in the new studies were less than 50 % at dose rates equivalent to/or higher than the highest single application rate of the representative uses, it is assumed that the off-field risk to non-target arthropods is low. Overall it is concluded that the risk to non-target arthropods is low for the representative uses of folpet.

5.5. RISK TO EARTHWORMS

The acute risk to earthworms was assessed as low. The appropriate endpoint for the long-term risk assessment was discussed in the expert meeting. In the original risk assessment no correction factor of 2 was applied to the endpoints of the toxicity tests although the $\log P_{OW}$ for folpet is >2 and the peat moss content was 10% in the artificial substrate. The applicant submitted a new reproduction study where the peat moss content was only 5 % instead of 10 %. The observed NOEC of 8.53 mg a.s./kg was higher than the NOEC of 5.18 mg a.s./kg from the original study. The applicant argued that this is an indication that the peat moss content has no influence on the test results and suggested to use the new endpoint without a correction factor. The expert meeting concluded that the two tests are not directly comparable because of different feeding regimes but that an indication was provided that the organic matter content did not influence the toxicity of folpet. The meeting concluded that the lowest endpoint from the two studies (NOEC = 5.18 mg a.s./kg) should be used for the risk assessment without applying a correction factor of 2. The PECsoil values used by the rapporteur Member State in the addendum of March 2005 were assessed as either not correct or needed further clarification (see point 4.1.2.). The EFSA recalculated the maximum PEC soil values as 1.39 mg a.s./kg for the use in grapes and 0.69 - 0.82 mg a.s./kg for the use in tomatoes. The resulting TERs are 3.7 and 6.3 for the grape and tomato use, respectively. If the maximum PEC soil of 1.478 mg a.s./kg is used the resulting TER would be 3.5 for the use in grapes. Therefore, it is concluded that the risk to earthworms is low for the use in tomatoes but a high risk to earthworms cannot be excluded for the uses in grapes. Further data are required to address the long-term risk to earthworms for the representative use in

grapes. The risk to earthworms from the use in winter wheat cannot be concluded until a reliable PECsoil is established (see point 4.1.2.).

The toxicity of the major soil metabolites phtalimide, phthalic acid and phthalamic acid was not tested with earthworms but since they are formed rapidly by hydrolysis it is assumed that the metabolites were present in the tests with folpet and hence the risk is covered by the risk assessment for folpet.

5.6. RISK TO OTHER SOIL NON-TARGET ORGANISMS

No studies are triggered to address the risk to other soil non-target organisms for the representative uses in winter wheat and tomatoes and grapes. The risk to other soil non-target organisms from the representative uses is considered to be low.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

The effects of folpet formulated as Folpan 500 SC on soil nitrification and dehydrogenase activity were measured to assess the impact on the soil microbial activity. No effects of > 25 % were observed at a dose of 21.4 mg a.s./kg soil. No soil respiration or carbon mineralization test was carried out and Folpan 500 SC is not the lead formulation. The tested formulation Folpan 500 SC is a different type of formulation with different co-formulants compared to the lead formulation Folpan 80 WG.

The rapporteur Member State considers the water based suspension Folpan 500 SC as an acceptable means of presenting the active substance for testing with soil micro-organisms. The rapporteur Member State argues that the relationship between the active substance and its coformulants are unlikely to persist in a soil matrix.

The EFSA agrees to the provided argumentation. Taking into account that no effects > 25% were observed on dehydrogenase activity and nitrification at a dose rate which is more than 10 times higher than the estimated maximum PECsoil the risk to soil non-target mirco-organisms is considered to be low for all representative uses.

The effects of the major soil metabolites phtalimide, phthalic acid and phthalamic acid on soil nitrification and respiration were not tested with but since they are formed rapidly by hydrolysis it is assumed that the metabolites were present in the tests with folpet and hence the risk is covered by the risk assessment for folpet.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

Folpan 80 WDG and Merpan 80 WDG were tested with a range of crop species to identify phytotoxic effects. The rapporteur Member State concluded in the DAR that no phytotoxic effects or reductions in crop vigour were observed up to an application rate of 6.4 kg a.s./ha under field conditions. Essential details were missing in the study summaries in the DAR. During the discussion in the expert meeting the rapporteur Member State presented further information on the studies with non-target plants. The meeting agreed that the presented information is sufficient to conclude on low risk for non-target plants from the representative uses.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

No studies on the effects of folpet on sewage sludge were presented. Folpet hydrolyses and degrades fast in the water sediment systems. If contamination of sewage treatment plants would occur from the representative uses it is expected that folpet would degrade very fast. Therefore it is assumed that the risk to biological methods of sewage treatment plants is low for all representative uses.

6. Residue definitions

Soil

Definitions for risk assessment: folpet, phthalimide, phthalamic acid and phthalic acid.
Definitions for monitoring: folpet

Water

Ground water

Definitions for exposure assessment: folpet (DT_{90} < 3d), phthalimide, phthalamic acid and phthalic acid.
Definitions for monitoring: folpet (DT_{90} < 3d) **EFSA note**: folpet is the only ecotoxicological relevant compound; folpet and phthalic acid are the only toxicological relevant compounds. Folpet has a DT_{90} well below 3d (maximum DT90 = 9h in buffered pH 5 or 7), phtalic acid is not expected to reach ground water at levels above 0.1 µg/L when used for the representative uses evaluated. Adequate marker may need to be identified to monitor folpet in ground / drinking water.

Surface water

Definitions for risk assessment: folpet (DT_{90} < 3d), phthalimide, phthalamic acid, phthalic acid, 2-cyanobenzoic acid
Definitions for monitoring: folpet is the only ecotoxicological relevant compound. Adequate marker may need to be identified to monitor folpet in surface water.

Air

Definitions for risk assessment: folpet
Definitions for monitoring: folpet

Food of plant origin

Definitions for risk assessment: sum of folpet and phthalimide expressed as folpet
Definitions for monitoring: sum of folpet and phthalimide expressed as folpet

Food of animal origin

Definitions for risk assessment: phthalimide expressed as folpet
Definitions for monitoring: phthalimide expressed as folpet

Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Folpet	Very low to low persistent ($DT_{50\ lab}$ = 0.2 -4.3 d)	The trigger values for the acute risk to earthworms are exceeded by more than one order of magnitude. The long-term Annex VI trigger value of 5 was met (TER = 5.18), indicating a low acute and long-term risk to earthworms from the representative uses of folpet. The risk of folpet to soil organisms is considered to be low.
Phthalimide	Very low to moderate persistent ($DT_{50\ lab}$ = 0.2 -4.3 d)	The toxicity of phthalimide was not tested with soil organisms but it is assumed that phthalimide was present in the tests with folpet. Therefore the risk to soil organism from the representative uses of folpet is considered to be low.
Phthalamic acid	Very low to low persistent ($DT_{50\ lab}$ = 0.35 -3.15 d)	The toxicity of phthalimic acid was not tested with soil organisms but it is assumed that phthalimic acid was present in the tests with folpet. Therefore the risk to soil organism from the representative uses of folpet is considered to be low.
Phthalic acid	Very low persistent ($DT_{50\ lab}$ = 0.22-0.23 d)	The toxicity of phthalic acid was not tested with soil organisms but it is assumed that phthalic acid was present in the tests with folpet. Therefore the risk to soil organism from the representative uses of folpet is considered to be low.

Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological activity	Ecotoxicological activity
Folpet	Estimated to be medium mobile (K_{oc}≈300 mL/g)	FOCUS-GW: trigger 0.1 µg/L not exceeded for any of the scenarios and uses simulated.	Yes	Yes	Yes
Phthalimide	Medium to high mobile in soil (K_{foc} = 72 – 385 mL/g)	FOCUS-GW: trigger 0.1 µg/L not exceeded for any of the scenarios and uses simulated.	No data available, No data required	Less toxic than folet; mechanistic data indicate that phthalimide does not have the potential to induce critical effects (carcinogenic, reprotoxic effects).	The toxicity to aquatic organisms is lower than that of folpet. The risk to aquatic organisms living in surface water was assessed as low.
Phthalamic acid	Estimated to be very high mobile (K_{oc}≈10 mL/g)	FOCUS-GW: trigger 0.1 µg/L not exceeded for any of the scenarios and uses simulated.	No data available, No data required	No toxicological data available.	The toxicity to aquatic organisms is lower than that of folpet. The risk to aquatic organisms living in surface water was assessed as low.
Phthalic acid	Estimated to be high mobile (K_{oc}≈73 mL/g)	FOCUS-GW: trigger 0.1 µg/L not exceeded for any of the scenarios and uses simulated.	No data available, No data required	Not mutagenic, but does act synergistically with some heterocyclic amine mutagens. It is not carcinogenic	The toxicity to aquatic organisms is lower than that of folpet. The risk to aquatic organisms living in surface water was assessed as low.

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Folpet (only water)	See point 5.2.
Phthalimide (only water)	Phthalimide has a much lower toxicity and poses a much lower risk to aquatic organisms compared to folpet.
Phthalamic acid (only water)	Phthalamic acid has a much lower toxicity and poses a much lower risk to aquatic organisms compared to folpet.
Phthalic acid (only water)	Phthalic acid has a much lower toxicity and poses a much lower risk to aquatic organisms compared to folpet.
2-cyanobenzoic acid (only water)	2-cyanobenzoic acid has a much lower toxicity and poses a much lower risk to aquatic organisms compared to folpet.

Air

Compound (name and/or code)	Toxicology
Folpet	Harmful by inhalation (acute LC_{50} 1.89 mg/L)

LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- Data to confirm the identity of the impurities revealed by chemical analysis must be provided to address the requirement of the Directive on the specificity of the method(s) (data gap identified at the evaluation meeting, December 2004 and confirmed by EPCO 25, May 2005; the rapporteur Member State has received a study, but did not evaluate it, March 2006;. refer to chapter 1)
- An analytical method for the determination of phthalimide (incl. ILV and a confirmatory method, latter if appropriate) in food of plant origin according to Directive 96/46/EC (date of submission unknown, data requirement identified at the expert meeting, May 2004; refer to chapter 1 and 3.1, applicant indicated that this will be addressed once the residue definition is finalised within the EU peer review process)
- A confirmatory method for the determination of residues of folpet in food of plant origin (method was submitted in September 2005, but not evaluated yet by the rapporteur Member State; refer to chapter 1)
- Supervised residue trials with analysis of the metabolite phthalimide (relevant for all representative uses evaluated; data gap identified after the EPCO 24 experts' meeting , under re-consideration of the adequacy of the available data for the residue definition adopted in expert meeting; date of submission unknown; refer to point 3.1.1).
- Storage stability studies for folpet (on processed commodities only) and for its metabolite phthalimide (all commodities) (relevant for all representative uses evaluated; data gap identified after the EPCO 24 experts' meeting , under re-consideration of the adequacy of the available data for the residue definition adopted in expert meeting; date of submission unknown; refer to point 3.1.1).
- Studies on the effect of processing on the nature of residues in representative hydrolytic conditions (simulating pasteurisation, baking, brewing, boiling and sterilisation) (relevant for all representative uses evaluated; date of submission unknown, but study ongoing; refer to point 3.1.1).
- Processing studies allowing quantifying the actual level of relevant degradation products in processed commodities (relevant for all representative uses evaluated; data gap identified after the EPCO 24 experts' meeting , under re-consideration of the adequacy of the available data for the residue definition adopted in expert meeting; date of submission unknown; refer to point 3.1.1).
- PECsoil need to be recalculated and justified in order to finalize the long term soil risk assessment (relevant for wheat; data gap identified by EFSA after the EPCO 21 experts' meeting, submission date unknown; refer to point 4.1.1).
- Calculation of PECsw with consideration of drainage (relevant for all representative uses evaluated; data gap identified by the EPCO 21 experts' meeting on fate and behaviour in the environment; submitted in September 2005 and summarized by the rapporteur Member State in the addendum of March 2005; refer to point 4.2.1).
- New FOCUSgw modelling with the mean DT_{50} (instead of the median) and with Koc value for phthalimide metabolite agreed by the EPCO 25 meeting (relevant for all representative uses

evaluated; data gap identified by the EPCO 21 experts' meeting on fate and behaviour in the environment; submitted in September 2005 and summarized by the rapporteur Member State in the addendum of October 2005; refer to point 4.2.2).

- A refined long-term risk assessment for birds (relevant for all representative uses; data gap identified by the EPCO 22 experts' meeting on ecotoxicology; a new refined risk assessment was submitted and summarized by the rapporteur Member State in the addendum of October 2005; refer to point 5.1.)
- A refined risk assessment is required to address the risk to small herbivorous mammals (relevant for the representative use in grapes, data gap identified by EFSA; date of submission unknown; refer to point 5.1).
- A refined risk assessment for birds and mammals is required to assess the risk from uptake of contaminated drinking water (relevant for all representative uses; data gap identified by EFSA; date of submission unknown; refer to point 5.1).
- A long-term (21 d) study with daphnids under semi-static test conditions (relevant for all representative uses; data gap identified by the EPCO 22 experts´ meeting; date of submission unknown; refer to point 5.2).
- Further data are required to address the long-term risk to earthworms for the representative use in grapes (relevant for the use in grapes; data gap identified by EFSA; date of submission unknown; refer to point 5.5).

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as fungicide as proposed by the applicant which comprises foliar spraying to control various fungi in winter wheat, tomatoes and wine grapes at application rates of up to 750 g folpet per hectare in winter cereals, up to 1.6 kg in tomatoes and up to 1.5 kg in wine grapes. Folpet can be used only as fungicide.

The representative formulated product for the evaluation was "Folpan 80 WDG", a water dispersible granule (WG), registered in some EU Member States.

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. folpet in soil, water and air. It should be noted that for surface water no enforcement method is needed due to the fact that the DT_{90} value is below 3 d (the trigger value given in SANCO/825/00).

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. folpet in soil, water and air. It should be noted that for surface water no enforcement method is needed for the determination of folpet, due to the fact that the DT_{90} value is below 3 d (the trigger value given in SANCO/825/00). For food of plant origin no validated analytical methods for monitoring purposes are available.

Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. However, due to some outstanding data no final specification can be proposed for the technical material at the moment.

Folpet has a low acute oral and dermal toxicity but it is R20 'Harmful by Inhalation'. It is not irritating to the skin but it is severely irritating to eyes (proposal for classification as R41 "Risk of serious damage to eyes") and is a skin sensitiser (R43 'May cause sensitisation by skin contact' is proposed). The relevant short and long term NOAELs are 10 mg/kg bw/day. Folpet does not show any genotoxic potential *in vivo* but it is carcinogenic in the mouse (category 3, R 40 proposed for the classification by the majority of the experts), with a clear threshold identified at 20 mg/kg bw/day. Folpet did not cause adverse effects on adult fertility or reproduction in rats over two generations, but was shown to be teratogenic in rabbits (classification as R63 is still under discussion and is forwarded to ECB). The Acceptable Daily Intake (ADI) and the Acceptable Operator Exposure Level (AOEL) are 0.1 mg/kg bw/day, the Acute Reference Dose (ARfD) is 0.2 mg/kg bw, with a safety factor of 100. The operator estimated exposure accounts for 34 to 77% of the AOEL in outdoor scenarios (German model with PPE considered). Estimates provided for operator exposure in glass-houses ranged from 29% to 33% of the AOEL (PPE is worn). The exposure of bystanders is 1.6% of the AOEL. Worker exposure in harvesting grapes and tomatoes without protective gloves is 133% and 68% of the AOEL, if PPE such as gloves are used it is assumed that the exposure is below the AOEL. Worker exposure following applications of folpet to wheat can be expected to be lower than following applications to grapes or tomatoes.

The metabolism of folpet in plants has been adequately elucidated. The main degradation products after release of the trichloromethylthio-side chain are phthalimide and phthalic acid. As it is not possible at this stage to fully characterize the toxicological properties of phthalimide, this metabolite needs to be included in the residue definition for plant products for monitoring and risk assessment purposes. Supervised residue trials were carried out in most cases with analysis of folpet only and therefore it is not possible to establish MRLs and to conduct an exposure assessment covering the contribution of phthalimide to the residue. However, taking into account folpet only, an acute risk for toddlers consuming treated table grapes has been identified. Specific studies allowing a clear understanding of the behaviour of the compound during processing are not available. The drastic reduction of folpet level in processed commodities and the physico-chemical properties of the compound suggest that important amounts of phthalimide and/or phthalic acid could be produced during processing. No residue of folpet and related metabolites are expected in rotational crops and in animal commodities.

Folpet is very low or low persistent in soil ($DT_{50\ lab\ 20\text{-}25\ °C}$ = 0.2 -4.3 d). First degradation step involves the release of the highly reactive thiophosgene to yield the major soil metabolite phtalimide. Phtalimide is further degraded through phthalamic acid to phthalic acid. All major folpet metabolites

are also very low or low persistent in soil under aerobic conditions at 20 °C. Mineralization is high and unextractable residues are formed in moderate amounts (max. 31.2 % AR at 14 d).

In relation to the thiophosgene moiety, further information may be derived from the closely related compound captan. Degradation of this compound in soil was investigated with trichloromethyl-^{14}C labelled substance. The experts' meeting noted that it could not be excluded that thiophosgene was present at trace levels in the volatile traps of the captan study. However, it is not expected that free thiophosgene reach significant levels as a consequence of the degradation of folpet in soil. Under anaerobic conditions folpet degraded slightly slower than under aerobic ones; no new metabolites were identified under these conditions.

Photolysis under natural sunlight does not contribute significantly to the environmental dissipation of folpet.

PEC soil presented in the DAR were based on worst case laboratory half life (DT_{50} = 4.3 d) with the critical GAP of ten applications of 1.5 kg a.s / ha at 7 days interval (grapes use). In the addendum March 2005 PEC soil are recalculated for all three uses taking into account crop interception given for FOCUS gw. However, EFSA considers that this calculation is not adequate for vines (were interception factor has been averaged) and needs to be further justified for tomatoes. New PEC soil values calculated by EFSA were used in the risk assessment for earthworms presented in the conclusion. Due to ambiguities with respect to the time of application interception for PEC soil, calculation cannot be established for wheat.

Due to the high instability of folpet and its metabolites phtalamic and phthalic acids, adsorption parameters were estimated based on K_{ow} (folpet) or PCKOC (EPIWIN) model (phtalamic and phthalic acids). Folpet was estimated to be medium mobile (K_{oc} = 304 mL / g), phtalamic acid very high mobile (K_{oc} = 10 mL / g) and phthalic acid high mobile (K_{oc} = 73 mL / g) in soil. Phthalimide was experimentally found to be medium to high mobile in soil (K_{foc} = 72 – 385 mL / g).

Hydrolysis of folpet is rapid at acidic and neutral pH (DT_{50} < 3 h) and very rapid at alkaline pH (DT_{50} < 3 min). Main hydrolysis metabolites were phatalimide and phtalic acid. Trichlomethylsulfenic acid and tricloromethylmercaptan are postulated to be the two major non characterized hydrolysis metabolites of folpet. These metabolites will degrade to thiophosgene, carbon oxysulfide and ultimately to CO_2. At 25 °C and pHs 4 and 7 phtalimide was stable and at pH 9 was hydrolysed with a half life of 2 h.

Contribution of photolysis to the aqueous degradation of folpet was not significant.

Folpet was shown to be readily biodegradable at concentrations of 1 mg C/L. Fate and behaviour experts' meeting agreed not to propose R53 for this compound.

In the two water sediment systems studied folpet degrades very rapidly (DT_{50} < 1h; DT_{90} < 5 h) and mineralization is relatively high (51-54 % AR at 100 d, end of the study). Folpet is not found in the sediment phase. Major metabolites in the water phase were phthalimide, phthalamic acid, phthalic acid, benzamide and 2-cyanobenzoic acid. No major metabolite (> 10 % AR) was found in the sediment phase. All the metabolites degraded rapidly in both systems (DT_{50} < 7 d).

PECsw presented in the DAR for folpet considered spray drift route and 0.5 % run off of the applied dose under worst case assumptions. Calculations only cover use in vines because it was considered the critical GAP in terms of application rate. Maximum PECsw for metabolites were presented in the

addendum of March 2005 based on spray drift. Taking into consideration the proposed representative use on winter cereals in northern Europe and the high number of applications the experts' meeting agreed that potential contamination through drainage needed to be addressed. FOCUS STEP 1 PEC sw calculations for metabolites phthalimide, phthalamic acid and phthalic acid have been presented by the notifier and summarized by the rapporteur Member State in the addendum of October 2005. Whereas not peer reviewed, EFSA can confirm that the parameters already agreed by the experts' meeting have been used in this calculation. Values obtained for the different representative uses are lower than the worst case runoff estimation presented in the DAR (577 μg/L). This level could be of concern only for metabolite phthalimide. Therefore, FOCUS STEP 1 values have been used to complete the assessment of this metabolite (see point 5.2.). FOCUS sw calculations for the parent up to STEP 4 are also summarized in the addendum of October 2005, these calculations have not been peer reviewed and have not been used on the EU risk assessment.

The calculated PECgw (FOCUS PELMO 3.3.2) demonstrated that the predicted 80th percentile concentrations for folpet, phthalimide, phthalamic acid and phthalic acid are equal or below 0.001 μg /L at 1 m depth in all the scenarios simulated (seven grape scenarios in Northern and Southern EU and four winter wheat scenarios in Southern EU).

Concentrations of folpet in the air are expected to be negligible. Potential release of thiophosgene due to soil degradation of folpet is considered possible only at trace amounts.

The short-term and long-term risk to herbivorous birds is considered to be low because the product is applied at growth stages which are not attractive as a food source. Some refinement steps in the long-term risk assessment for insectivorous birds were not accepted by the EPCO experts' meeting. A new refined risk assessment was presented in the addendum from October 2005 which was not peer reviewed. Some shortcomings and open questions were identified by EFSA. It was not sufficiently demonstrated that the representative uses do not pose a high long-term risk to insectivorous birds. The risk to mammals is low for the representative uses in winter wheat and tomatoes but a high acute and long term risk to small herbivorous mammals is indicated for the representative use in grapes. A refined risk assessment or risk mitigation measures are required to address the high acute risk for birds and mammals from uptake of contaminated drinking water if the solution is sprayed at the highest recommended concentration in grapes. The acute risk to fish and daphnids is high and risk mitigation measures such as no spray buffer buffer zones of 5 m for the use in winter wheat and tomatoes and 10 m for the use in grapes are required. A long-term risk assessment for aquatic organisms is required since the representative uses cover multiple applications leading to repeated exposure. The long-term risk to fish is high and risk mitigation measures such as no spray buffer zones of 5 m and 15 m are required to for the representative uses in winter wheat, tomatoes and grapes, respectively. A 21-d reproduction study with daphnids conducted under semi static conditions is required to conclude on the long-term risk to aquatic arthropods. The risk to earthworms is low for the use in tomatoes but a high risk to earthworms cannot be excluded for the uses in grapes. The risk to earthworms from the use in winter wheat cannot be concluded until a reliable PEC soil is established.

Particular conditions proposed to be taken into account to manage the risk(s) identified

- Data on flowability may need to be reconsidered for national authorisation in particular if new packing types are requested (refer to chapter 1).
- Personal protection equipment (PPE), i.e. gloves during mixing and loading, is considered in the estimation of operator exposure according to the German model (refer to point 2.12).
- The representative uses pose a high risk to aquatic organisms. Risk mitigation measures such as no spray buffer zones are required (refer to point 5.2.).

Critical areas of concern

- At the moment no final specification for the technical material can be proposed.
- Folpet is severely irritating to eyes, is a skin sensitizer and has carcinogenic properties (Cat 3 proposed). A classification for reproduction toxicity might be justified; the issue is forwarded to ECB (see chapter 2.6).
- For food of plant origin no validated analytical methods for monitoring purposes are available.
- An acute dietary risk for infants and toddlers has been identified in case of consumption of treated table grapes..
- The long term risk to insectivorous birds needs to be addressed.
- The acute and long-term risk to mammals for the representative use in grapes.
- A high acute risk to birds and mammals was identified from uptake of contaminated drinking water for the representative use in grapes.
- A high acute and long – term risk was identified for fish and a high acute risk was identified for daphnids which would require risk mitigations measures equivalent to a buffer zone of up to 15m. No final conclusion can be drawn on the long-term risk to aquatic arthropods.
- A high long-term risk to earthworms from the use in grapes.
- The risk to earthworms from the use in winter wheat cannot be concluded until a reliable PECsoil is established.
- The risk for birds and mammals for the use in winter wheat was assessed only for the use in late growth stages which are not attractive as a food source for herbivorous birds and mammals. For other uses in early growth stages a new risk assessment would be required.

Appendix 1: list of end points

APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

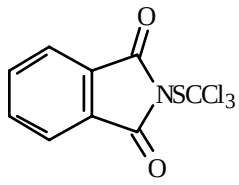
(Abbreviations used in this list are explained in appendix 2)

Appendix 1.1: Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Folpet
Function (e.g. fungicide)	Fungicide

Rapporteur Member State	Italy
Co-rapporteur Member State	--

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	*N*-(trichloromethylthio) phthalimide
Chemical name (CA) ‡	2-[(trichloromethyl)thio]-1*H*-isoindole-1,3(2H)-dione
CIPAC No ‡	75
CAS No ‡	133-07-3
EEC No (EINECS or ELINCS) ‡	205-088-6
FAO Specification ‡ (including year of publication)	880 g/kg ±20 g (FAO Specification 75/TC/S, 1988).
Minimum purity of the active substance as manufactured ‡ (g/kg)	940 g/kg
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	*Open*
Molecular formula ‡	$C_9H_4Cl_3NO_2S$
Molecular mass ‡	296.6
Structural formula ‡	

Appendix 1: list of end points

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	179 – 180 °C (99.6% purity)
Boiling point (state purity) ‡	Not determinable: the test substance decomposes below the boiling point
Temperature of decomposition	The test substance decomposes above its melting point starting at 184 °C (99.4% purity).
Appearance (state purity) ‡	White solid crystals (98.8% purity) Fine white powder (90.0% purity)
Relative density (state purity) ‡	1.72 kg/m³ (99.6% purity) – Density determined
Surface tension	Not required because the water solubility of the active substance is less than 1.0 mg/L.
Vapour pressure (in Pa, state temperature) ‡	2.1 x 10-5 Pa (25 °C) - purity not specified 9.7 x 10-5 Pa (35 °C) 4.5 x 10-4 Pa (45 °C)
Henry's law constant (Pa m^3 mol^{-1}) ‡	8 x 10^{-3} Pa.m^3.mol^{-1} at 25 °C
Solubility in water ‡ (g/L or mg/L, state temperature)	0.80 mg/L (max., 25 °C) – purity 98.8% 0.50 mg/L (mean, 15 °C) – purity 98.8%
Solubility in organic solvents ‡ (in g/L or mg/L, state temperature)	Acetone 34 g/L (25°C) *n*-octanol 1.4 g/L (25°C) methanol 3.1 g/L (25°C) toluene 26.3 g/L (25°C) carbon tetrachloride 6 g/L (25°C) acetonitrile 19 g/L (25°C) heptane 0.45 g/L (25°C)
Partition co-efficient (log POW) ‡ (state pH and temperature)	3.017 at 20°C (pH not reported) (purity 98.8%)
Hydrolytic stability (DT50) ‡ (state pH and temperature)	6.5 hours (pH 4; 25 °C) 1.06 hours (pH 4; 40 °C) 0.70 hours (pH 7; 25 °C) 0.178 hours (pH 7; 40 °C) too fast to measure (pH 9; 25 °C and 40 °C)
Dissociation constant ‡	Folpet does not dissociate at the pH ranges encountered in aqueous solution.

Appendix 1: list of end points

UV/VIS absorption (max.) ‡ (if absorption > 290 nm state ε at wavelength)	Molar extinction coefficients ε ($L.mol^{-1}.cm^{-1}$) 47100, 7900, 1780, 1720 at 223, 236, 295, 300 nm (purified water:methanol 1:9 v/v); 52600, 8410, 1770, 1720 at 223, 237, 296, 301 nm (aqueous hydrochloric acid: methanol 1:9 v/v); 19900, 11300, 7410, 1810, 1650, 1320 at 225, 238, 247, 280, 289, 301 nm (aqueous sodium hydroxide: methanol 24:1)
Photostability (DT_{50}) ‡ (aqueous, sunlight, state pH)	Photolysis either does not occur or is very slow relative to hydrolysis.
Quantum yield of direct phototransformation in water at λ > 290 nm ‡	Due to the rapid chemical hydrolysis of folpet the quantum yield is impossible to measure experimentally – No data submitted.
Flammability ‡	Not classified as flammable (purity 96%).
Explosive properties ‡	Non-explosive (purity 96%).

Summary of representative uses evaluated*

Crop and/or situation	Member State or Country	Product name	F G or I	Pests or Group of pests controlled	Formulation		Application				Application rate per treatment			PHI (days)	Remarks:
(a)			(b)	(c)	Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number[a] min max (k)	interval between applications (min)	kg as/hl min max	water L/ha min max	kg as/ha min max	(l)	(m)
Winter wheat	South EU	'Folpan' 80 WDG	F	Septoria, Brown rust	WG	800 g/kg	Foliar spray; down-ward	Up to Z65	2	7-28 d	0.375	200	0.75	42	[2]
Tomatoes	South EU	'Folpan' 80 WDG	F	various [a]	WG	800 g/kg	Foliar spray; down-ward	From beginning of fruit set	4	7-28 d	0.125	1000	1.25	7	[2]
	South EU	'Folpan' 80 WDG	G	various [a]	WG	800 g/kg	Foliar spray; down-ward	From beginning of fruit set	3	7-28 d	0.16	1000 - 1300	1.6	7	[1]
Wine Grapes	North and south EU	'Folpan' 80 WDG	F	various [b]	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	Shoot emergence to veraison	10	7-28 d	0.75	200 - 400	1.5	28	[2]
Table Grapes	North and south EU	'Folpan' 80 WDG	F	various [b]	WG	800 g/kg	Airblast foliar spray; upwards/ sideways	Shoot emergence to veraison	10	7-28 d	0.75	200 - 400	1.5	28	[1] [2]

[a] *Alternaria solanum, Cladospora, Colletotrichum, Septoria, Botrytis*
[b] Black rot, *Botrytis cinerea, Phomosis, Plasmopara viticola*.
[1] The risk assessment revelaed a risk in section 3 (acute dietary risk for toddlers).
[2] The risk assessment has revealed data gaps in section 4 as well as a risk/data gap in section 5.

Remarks:	*	Uses for which risk assessment could not been concluded due to lack of essential data are marked grey	(h)	Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
	(a)	For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)	(i)	g/kg or g/L
			(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
	(b)	Outdoor or field use (F), glasshouse 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)	(k)	The minimum and maximum number of application possible under practical conditions of use must be provided
	(e)	GCPF Codes - GIFAP Technical Monograph No 2, 1989		
	(f)	Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench	(l)	PHI - minimum pre-harvest interval
	(g)	All abbreviations used must be explained	(m)	Remarks may include: Extent of use/economic importance/restrictions

Appendix 1.2: Methods of Analysis

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

Technical as (principle of method)	Folpet technical material is dissolved in an acetonitrile solution containing the internal standard, propyl paraben. The sample is sonicated and filtered prior to determination by reverse-phase HPLC/UV. HPLC/UV determination is carried out at a wavelength of 254 nm using a C18 column and an acetonitrile/water/trifluoroacetic acid mobile phase. Peak purity test carried out using a DAD detector at 3 wavelenghts between 200 and 400 nm.
Impurities in technical as (principle of method)	Impurity No. 2 in table C.1.2.1.1. (confidential Annex C) capillary GC with flame photometric (FPD) detection Impurities no. 3 and 4 are determined simultaneously by GC with flame ionisation (FID) detection. Impurities no. 6, 7 e and 10 are determined simultaneously by reverse-phase HPLC/UV. Impurity No. 14 - Karl Fischer titration Impurity No. 16 - potentiometric titration.
Plant protection product (principle of method)	'Folpan' 80 WDG (0.1 g) is dissolved in dichloromethane and sonicated prior to filtering. Following further dilution with dichloromethane, determination is by capillary GC/FID using external reference standards. A confirmatory procedure is given based on GC with mass selective detection (MSD). A CIPAC method is not available for folpet formulated as a water dispersible granule. However, existing CIPAC methods for folpet technical, dustable powders and wettable powders are considered to be applicable.

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	1. Residues of folpet and phthalimide in non-oily crops: crop samples are extracted by blending with ethyl acetate and o-phosphoric acid. The extract is filtered and washed with phosphoric acid solution prior to evaporation and reconstitution in hexane. The extract is purified by florisil solid phase extraction cartridge prior to determination of folpet and phthalimide by capillary GC with electron capture detection (ECD). LOQs = 0.05 mg/kg for folpet and 0.20 mg/kg for phthalimide. 2. Residues of folpet in apples, melons, onions, lettuce, tomatoes and strawberries: crops are extracted by blending with ethyl acetate and o-phosphoric acid. The extract is filtered and washed with phosphoric acid solution prior to evaporation and reconstitution in hexane (for melons and strawberries) or aqueous acetonitrile (for apples, onions, lettuce and tomatoes). The extract is purified by soild phase extraction cartridge (florisil for melons and strawberries and C18 for apples, onions, lettuce and tomatoes) prior to determination of folpet by capillary GC/ECD. LOQ = 0.05 mg/kg. 3. Residues of folpet in avocados and other oily crops: crops are extracted by blending with ethyl acetate and o-phosphoric acid. The extract is filtered and washed with phosphoric acid solution prior to evaporation and reconstitution in hexane (for melons and strawberries) or aqueous acetonitrile (for apples, onions, lettuce and tomatoes). The extract is purified by soild phase extraction cartridge (florisil for melons and strawberries and C18 for apples, onions, lettuce and tomatoes) prior to determination of folpet by capillary GC/ECD. LOQ = 0.05 mg/kg.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	A method is provided for determination of folpet by capillary GC/ECD, although not needed, because no MRLs are proposed. Samples are extracted by blending with acetone and 0-phosphoric acid. Residues are partitioned into dichloromethane prior to clean-up by gel permeation chromatography (GPC). Fat samples are dissolved directly in the GPC mobile phase. Additional silica gel cleanup is required for liver

	and muscle. LOQs = 0.005 mg/kg (milk) 0.02 mg/kg (kidney, fat, eggs) 0.03 mg/kg (liver, muscle)
Soil (principle of method and LOQ)	Folpet and phthalimide are extracted by shaking with aqueous acetonitirile and residues are partitioned into dichloromethane. The extract is purified by C18 soild phase extraction cartridge prior to determination by capillary GC/ECD LOQ = 0.05 mg/kg for folpet and phthalimide. 2. A confirmatory procedure is presented for the determination of folpet residues in soil. Residues are extracted by shaking with aqueous acetonitrile. The extract is saturated with sodium chloride and the organic phase is evaporated to dryness prior to reconstitution in hexane/ethyl acetate. The extracts are purified by solid phase extraction on activated carbon. Determination of folpet is by capillary GC/MS with selected ion monitoring (five ions monitored). The limit of quantification is 0.05 mg folpet/kg
Water (principle of method and LOQ)	Drinking water: Folpet is extracted by shaking with dichloromethane. Determination is by reverse-phase HPLC/UV with a photodiode array detector. Additionally, a GC/ECD determination method is provided. The GC/ECD method was found not to be adequately repeatable but may be usefully employed for confirmatory purposes. LOQ = 0.02 μg/L Surface water: no method required DT_{90} <3 d
Air (principle of method and LOQ)	A measured volume of air is drawn through a filter paper and two activated silica gel tubes arranged in series by an air sampling pump. The filter paper and the front silica gel adsorbent are extracted by shaking with acetonitrile. The silica gel from the back tube is analysed separately to determine breakthrough. Determination of folpet is by reverse-phase HPLC/UV with a photodiode array detector. LOQ = 3.5 $\mu g/m^3$ (in 3 L of air) or 0.22 μg/m3 (in 480 L of air).
Body fluids and tissues (principle of method and LOQ)	An analytical method for body fluids (blood) is not required since folpet is not classified as toxic or highly toxic.

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	None

Appendix 1.3: Impact on Human and Animal Health

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

Rate and extent of absorption ‡	Absorbed rapidly in rats following oral administration (> 80%).
Distribution ‡	Widely distributed following initial absorption, but tissue residues negligible because of rapid excretion.
Potential for accumulation ‡	Very low.
Rate and extent of excretion ‡	Rapid excretion via urine and faeces.
Metabolism in animals ‡	Metabolic cleavage of the nitrogen-sulphur bond.
Toxicologically significant compounds ‡ (animals, plants and environment)	Folpet

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	> 2000 mg/kg bw	
Rat LD_{50} dermal ‡	> 2000 mg/kg bw	
Rat LC_{50} inhalation ‡	1.89 mg/L	**R20**
Skin irritation ‡	Not irritating.	
Eye irritation ‡	Severely irritating.	**R41**
Skin sensitization ‡ (test method used and result)	Sensitising (Magnusson and Kligman)	**R43**

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Minor effects in rat - reduced body weight and body weight gain. Higher doses associated with reversible hyperkeratosis of the non-glandular stomach. Skin irritation in dermal study. Decreases in body weight and food consumption in dogs plus poor general condition, vomiting, diarrhoea, salivation, reduction in testicular weight associated with microscopic testicular degeneration at high doses.
Lowest relevant oral NOAEL / NOEL ‡	10 mg/kg bw/day (1-year dog)
Lowest relevant dermal NOAEL / NOEL ‡	1 mg/kg bw/day (28-day male rat); > 30 mg/kg bw/day (28-day female rat).
Lowest relevant inhalation NOAEL / NOEL ‡	-

Genotoxicity ‡ (Annex IIA, point 5.4)

.....	Genotoxic *in vitro*, diminished/offset by metabolic activation, glutathione or cysteine. Not genotoxic *in vivo*.

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

Target/critical effect ‡	Reduced body weight and food consumption in rat and mouse. Reduction in enzymatic activity and total protein levels and hyperkeratosis of the non-glandular stomach and of the oesophagus at the higher dose levels in rat. Various clinical signs of toxicity in mouse.
Lowest relevant NOAEL / NOEL ‡	Rat: 10 mg/kg bw/day.
Carcinogenicity ‡	Not carcinogenic in rat. Carcinogenic (duodenal tumours) in mice, non-genotoxic mechanism, clear NOAEL established (about 20 mg/kg bw/day) **Cat 3, R40**

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	Reduced weight of offspring. No effect on fertility or general reproductive performance.
Lowest relevant reproductive NOAEL / NOEL ‡	180 mg/kg bw/day (reproductive effects) 14 mg/kg bw/day (parental toxicity) 14 mg/kg bw/day (offspring growth)
Developmental target / critical effect ‡	Embryotoxic.
Lowest relevant developmental NOAEL / NOEL ‡	Maternal and developmental: 10 mg/kg bw/day (rabbit). **R63?**

Neurotoxicity / Delayed neurotoxicity ‡ (Annex IIA, point 5.7)

.....	No studies conducted. Folpet is not a substance of similar or related structure to those capable of inducing delayed neurotoxicity.

Other toxicological studies ‡ (Annex IIA, point 5.8)

Metabolites	Phthalimide: less toxic than folpet. Mechanistic data indicate that phthalimide does not have the potential to induce critical effects (carcinogenic, reprotoxic effects).
Absorption	Percutaneous absorption through human skin was 1% for the concentrated and diluted product in an in vitro study measuring dermal absorption in human and rat skin.
Mechanistic studies	Studies were carried out to investigate the role of covalent binding of captan to DNA and the role of hyperplasia in the gastrointestinal tract in the mechanism of oncogenicity of captan in the mouse. Studies with captan are relevant for folpet since the side-chain is identical in both compounds. The results obtained are consistent with an irritant mode of action of folpet on the duodenal villus epithelium.

Medical data ‡ (Annex IIA, point 5.9)

.....	No evidence of carcinogenicity in humans in an epidemiology study.

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.1 mg/kg bw/day	52 wk, oral, dog	100
AOEL ‡	0.1 mg/kg bw/day	teratogenicity study in rabbits	100
ARfD ‡ (acute reference dose)	0.2 mg/kg bw/day	teratogenicity study in rabbits	100

Dermal absorption (Annex IIIA, point 7.3)

Folpan 80 WDG	10% for the concentrated and diluted product (based on *in vivo* rat and *in vitro* results from human/rat skin)

Acceptable exposure scenarios (including method of calculation)

Operator	Exposure below the AOEL when operators wear protective clothing (German model) for all proposed uses (%of AOEL). without PPE / with PPE Tractor mounted Drawn airblast 236% 34% Filed crop sprayer 148% 77% Hand held 148% 76%
Workers	Based on dislodgeable residue data (available for captan), exposure of workers harvesting grapes and tomatoes without protective clothing is respectively, 133% and 68% of the AOEL. It is necessary for workers to wear protective gloves for harvesting operations in treated grapes.
Bystanders	Exposure is negligible (approximately 2% of the AOEL).

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	Xn; Harmful R 20 Harmful by inhalation R 40 Limited evidence of carcinogenic effect R 41 Risk of serious damage to eyes R 43 May cause sensitisation by skin contact R 63? Possible risk of harm to the unborn child.

Appendix 1.4: Residues

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

Plant groups covered	Fruits; root vegetables; cereals
Rotational crops	-
Plant residue definition for monitoring	Sum of folpet and phthalimide expressed as folpet
Plant residue definition for risk assessment	Sum of folpet and phthalimide expressed as folpet
Conversion factor (monitoring to risk assessment)	-

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

Animals covered	Goat
Animal residue definition for monitoring	Phthalimide expressed as folpet
Animal residue definition for risk assessment	Phthalimide expressed as folpet
Conversion factor (monitoring to risk assessment)	-
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)

.....	The persistence of folpet and its metabolite phtalimide is low. Therefore, residues of folpet are not expected in crops grown in normal rotation after those treated with folpet. It is not necessary to propose MRLs for succeeding crops and no restriction on planting succeeding crops is necessary.

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

.....	Storage stability data were presented for grapes, grain and straw, whole tomato, tomato pure and paste, grape juice. Folpet is stable in grapes, grain and straw for periods longer than 1 year. Stability in whole tomato and in tomato pure and paste is limited (3 monts maximumin the whole fruit, 1 month in puree and paste). Folpet in grape juice is stable for 1 month. No data are available for phthalimide

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, the expected folpet intake is about 3 and 1 mg/kg diet (DM basis) for beef and dairy cattle resp.	No	No
Potential for accumulation (yes/no):	No	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	Study not required	Study not required	Study not required
Liver			
Kidney			
Fat			
Milk			
Eggs		Study not required	

Note: the exposure assessment of livestock was conducted considering the contribution of parent compound only to that exposure.

Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or southern European region	Trials results relevant to the critical GAP (mg folpet/kg)	Recommendation/comments	MRL	STMR (b)
Tomatoes	Greenhouse (Northern and Southern)	1 x 0.38; 1 x 0.53; 1 x 0.75; 1 x 0.83; 2 x 2.0	This table reports residue levels of folpet only as in most trials only the parent compound was analysed. Only provisional estimations of the MRLs and STMRs can be made as the contribution of phtalimide cannot be taken into account. A full package of supervised residue trials with analysis of folpet and phtalimide should be submitted. * considered as outlier	3 mg/kg (provisional)	0.83 (provisional)
	Outdoor (Southern)	1 x 0.31; 1 x 0.43; 1 x 0.55; 1 x 0.62; 1 x 0.83; 1 x 0.96			
Table and Wine Grapes	Northern	1 x 0.29; 1 x 0.42; 1 x 1.2; 1 x 1.7; 1 x 2.0; 1 x 3.3; 1 x 3.5; 1 x 4.7		5 mg/kg (provisional)	1.8 mg/kg (provisional)
	Southern	1 x 0.63; 1 x 1.1; 1 x 1.5; 1 x 1.6; 1 x 1.8; 1 x 1.9; 1 x 2.0; 1 x 2.8; 1 x 3.9			
Wheat	Southern	1 x 0.01; 2 x < 0.02; 4 x 0.02; 1 x 0.13*		0.05 (provisional)	0.02 (provisional)

(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 critical GAP

Appendix 1: list of end points

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

ADI	0.1 mg/kg bw/day	
TMDI (European Diet) (% ADI)	5 %	
TMDI (% ADI) according to national diet in UK	60 kg bw adult	18 %
	43.6 kg bw child	7 %
	14.5 kg bw toddler	28 %
	8.7 kg bw infant	5 %
TMDI (% ADI) according to national German diet	13.5 bw kg child	7 %
	60 kg bw woman	8 %
ARfD	0.1 mg/kg bw	
Acute exposure NESTI (% ARfD)	UK consumption data	
	Adult:	
	Tomatoes, raw	14 %
	Table grapes	34 %
	Toddler	
	Tomatoes, raw	60 %
	Table grapes	135 %
Factors included in NESTI calculations	Variability factors of 5 and 7 for grapes and tomatoes respectively; proposed MRLs instead of HRs	

Note: all these exposure assessments (acute and chronic) were made considering the contribution of the parent compound only. They may therefore underestimate the actual toxicological burden.

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

Crop/processed crop	Number of studies	Transfer factor	% Transference*
Tomato: fruit to puree	1	< 0.03	Not available
Tomato: fruit to canned	4	< 0.1	< 2
Tomato: fruit to juice (pasteurized)	4	< 0.1	< 2
Grapes: fruit to wine	16	<0.1	Not available
Grapes: fruit to juice	1	<0.03	Not available
Grapes: fruit to dry raisins	1	3.2	Not available

Note: these transfer factors were calculated for the parent compound only (not for the sum of folpet and phtalimide)

Appendix 1: list of end points

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

Tomatoes	3.0 mg/kg
Wine and table Grapes	5 mg/kg
Wheat	0.05 mg/kg
Milk, eggs and animal tissues	None

Note: these proposed MRLs must be considered as preliminary as they are based on residue trials where parent compound only was analysed.

Appendix 1: list of end points

Appendix 1.5: Fate and Behaviour in the Environment

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

Mineralization after 100 days ‡	60% after 90 days (U-phenyl label)
Non-extractable residues after 100 days ‡	16% after 90 days (U-phenyl label) 19.5% after 30 days for loamy sand soil at 20°C from 25 to 28% for silty loam (20°C and 10°C) and 23% for clay loam soil at 20°C after 30 days (U-phenyl label)
Major metabolites ‡	Phthalimide, phthalamic acid and phthalic acid. Phthalimide: max. 64.9% at day 5; 1.3% after 365 days. Phthalic acid: max. 16.6% at day 1, 0.3% after 30 days. Phthalamic acid: max. 16.7% at day 1, 0% after 30 days.

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

Anaerobic degradation ‡	4 days aerobic followed by 60 days anaerobic incubation: Anaerobic phase: Folpet DT_{50} (1^{st} order, r^2 0.98): 14.6 days Major metabolite phthalimide DT_{50}: 33.6 days
Soil photolysis ‡	Relatively minor route in the overall soil degradation process.

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

Method of calculation	Single first-order model
Laboratory studies ‡ (range or median, with n value, with r^2 value)	**Folpet:** DT_{50lab} (20°C, aerobic):): 0.2-3.8 days (r2 0.986-0.999, mean 1.6 days, n=3) DT_{50lab} (25°C, aerobic): 16.2 days (r2 0.8, n=1); (biphasic, expressed as SFO. During 1st 14 days DT_{50} was 4.3 days) DT_{50lab} (10°C): 3.8 days (r2 0.998, n=1) DT_{90lab} (20°C, aerobic): 0.7-12.8 days (mean 5.4 days, n=3) DT_{90lab} (25°C, aerobic): 53.8 days (n=1) (biphasic, expressed as SFO) DT_{90lab} (10°C): 12.6 days (n=1) FOCUS normalised DT50: 0.12-15.2 days (mean 4.68 days, n=4)

Appendix 1: list of end points

	degradation in the saturated zone ‡: Folpet not expected to leach to the saturated zone. **Phthalimide**: DT_{50lab} (20°C, aerobic): 0.5-4.8 days (r2 0.876-0.992, mean 2.3 days, n=3) DT_{50lab} (25°C, aerobic): 28.2 days (r2 0.83, n=1) (biphasic, expressed as SFO) DT_{50lab} (10°C): 3.2 days (r2 0.977, n=1) DT_{90lab} (20°C, aerobic): 1.7-16.1 days (mean 7.9 days, n=3) DT_{90lab} (25°C, aerobic): 93.7 days (n=1) (biphasic, expressed as SFO) DT_{90lab} (10°C): 10.6 days (n=1) FOCUS normalised DT_{50}: 0.29-26.5 days (mean 7.88 days, n=4) **Phthalic acid:** DT_{50lab} (20°C, aerobic): 0.6-4.1 days (r2 0.892-0.999, mean 1.9 days, n=3) DT_{50lab} (10°C): 1.8 days (r2 0.855, n=1) DT_{90lab} (20°C aerobic): 2.1-13.7 days (mean 6.1 days, n=3) DT_{90lab} (10°C): 5.9 days (n=1) FOCUS normalised: 0.35-3.15 days (mean 1.37 days, n=3) **Phthalamic acid:** DT_{50lab} (20°C, aerobic): 0.4 days (r2 0.999, n=1) DT_{50lab} (10°C): 0.8 days (r2 0.973, n=1) DT_{90lab} (20°C aerobic): 1.3 days (n=1) DT_{90lab} (10°C): 2.7 days (n=1) FOCUS normalised: 0.24 days (n=1)
Field studies ‡ (state location, range or median with n value)	DT_{50f}: < 3 days (folpet and phthalimide) DT_{90f}: -
Soil accumulation and plateau concentration ‡	Folpet and metabolites are not expected to accumulate in soil

Appendix 1: list of end points

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Kf /Koc ‡	K_{OC} Folpet: not measurable due to rapid hydrolysis. Worst-case estimate K_{OC}= 304 mL/g. Phthalimide: Kf_{OC} = 72 to 385 mL/g (mean 208.7, n=3) Phthalic acid: K_{OC} = 73.06 mL/g estimated using PCKOC within EPIWIN (US-EPA, v1.66, 2000) Phthalamic acid: K_{OC} = 10 mL/g estimated using PCKOC within EPIWIN (US-EPA, v1.66, 2000) K_F Folpet: K_F not estimated Phthalimide: K_F = 2.49 – 15.60 mL/g (n=3, 1/n = 0.84-0.89) Phthalic acid: K_F not estimated Phthalamic acid: K_F not estimated
Kd ‡	Folpet: K_d not estimated. Phthalimide: 1.92 - 12.98 mL/g (n=3) Phthalic acid: K_d not estimated Phthalamic acid: K_d not estimated
pH dependence ‡ (yes / no) (if yes type of dependence)	Phthalimide more readily adsorbed at lower pH.

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

Column leaching ‡	No data available
Aged residues leaching ‡	Folpet aged in soil and its degradates are unlikely to significantly leach through soil.
Lysimeter/ field leaching studies ‡	Field dissipation studies demonstrated folpet and phthalimide (its major soil degradate) do not leach below 15 cm under field conditions.

PEC (soil) (Annex IIIA, point 9.1.3)

Parent

Method of calculation	Folpet DT_{50} 4.3 days (highest relevant value from laboratory studies)
Application rate	Vines: 10 x 1.5 kg a.s./ha at 7 day intervals 50% crop interception applied in calculating PEC values (if refinement necessary in the risk assessment, more interception may be relevant).

Appendix 1: list of end points

PEC$_{(s)}$ Folpet (mg/kg)	Single application Actual	Multiple application Actual	Multiple application Time weighted average
Initial	1.000	1.478	
Short term 24 h		1.258	1.365
2 d		1.071	1.263
Long term 7 d		0.478	0.886
28 d		0.016	0.324
50 d		0.001	0.183
100 d		<0.001	0.092

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

Hydrolysis of active substance and relevant metabolites (DT_{50}) ‡ (state pH and temperature)	**Folpet** 2.6 hours (pH 5, 25ºC) 1.1 hours (pH 7, 25ºC) 67 seconds (pH 9, 25ºC) **Phthalimide** stable (pH 4, 25ºC) stable (pH 7, 25ºC) 1.99 hours (pH 9, 25ºC)
Photolytic degradation of active substance and relevant metabolites ‡	Minor route of degradation.
Readily biodegradable (yes/no)	Inherently degradable /Readily biodegradable.
Degradation in water/sediment	
folpet - DT_{50} whole system‡	0.014, 0.018 days (n=2)
folpet - DT_{50} aqueous phase ‡	0.014, 0.017 days (n=2)
folpet - DT_{90} whole system ‡	0.045, 0.058 days (n=2)
folpet - DT_{90} aqueous phase ‡	0.045, 0.058 days (n=2)
phthalimide - DT_{50} whole system‡	0.583, 0.645 days (n=2)
phthalimide - DT_{50} aqueous phase‡	0.543, 0.594 days (n=2)
phthalimide - DT_{90} whole system‡	1.550, 1.755 days (n=2)
phthalimide - DT_{90} aqueous phase‡	1.417, 1.585 days (n=2)
phthalamic acid - DT_{50} whole system	3.978, 6.087 days (n=2)
phthalamic acid - DT_{50} aqueous phase	3.546, 5.499 days (n=2)
phthalamic acid - DT_{90} whole system	10.893, 17.899 days (n=2)
phthalamic acid - DT_{90} aqueous phase	9.459, 15.945 days (n=2)

Appendix 1: list of end points

phthalic acid - DT_{50} whole system	1.409, 6.453 days (n=2)
phthalic acid - DT_{50} aqueous phase	1.381, 6.359 days (n=2)
phthalic acid - DT_{90} whole system	2.358, 19.113 days (n=2)
phthalic acid - DT_{90} aqueous phase	2.267, 18.803 days (n=2)
benzamide - DT_{50} whole system	1.625 days (n=1)
benzamide - DT_{50} aqueous phase	1.625 days (n=1)
benzamide - DT_{90} whole system	3.076 days (n=1)
benzamide - DT_{90} aqueous phase	3.076 days (n=1)
2-cyanobenzoic acid - DT_{50} whole system	0.357, 0.716 days (n=2)
2-cyanobenzoic acid - DT_{50} aqueous phase	0.334, 0.666 days (n=2)
2-cyanobenzoic acid - DT_{90} whole system	0.798, 1.992 days (n=2)
2-cyanobenzoic acid - DT_{90} aqueous phase	0.724, 1.827 days (n=2)
Mineralization	*ca* 50% after 62 days; in sterile systems negligible mineralization.
Non-extractable residues	Maximum of 26.3% after 14 days, subsequently declined to 12.5% after 100 days.
Distribution in water / sediment systems (active substance) ‡	Folpet declined rapidly from 79.7% AR at 5 minutes to 2.1% AR at 4 hours, all of which was present in the organo-soluble extract from the aqueous phase. No folpet was detected in the sediment phase at any time point.
Distribution in water / sediment systems (metabolites) ‡	Folpet was metabolised to carbon dioxide, phthalimide, phthalamic acid, phthalic acid, benzamide, 2-cyanobenzoic acid and low levels of polar materials and unknowns. No metabolite was detected in the sediment phase at levels approaching 10% of applied. Phthalimide reached a max. of 5.9% (at 4 hours, declining to 0.2% at end of study, 100 days) and Phthalic acid a max. of 3.8% (at 1 day, declining to 0.2% at end of study, 100 days). Major metabolites: Phthalimide up to 26.0% in water phase. Phthalic acid up to 37.5% in water. Phthalamic acid up to 13.3% in water. Benzamide up to 10.2% in water. 2-cyanobenzoic acid up to 39.7% in water. The majority of the radioactive residues present in the sediment phases on day 1 were unextractable and were shown to be mainly associated with the humin fraction, probably due to phthalate formation. The level of unextractable residue

Appendix 1: list of end points

	reached a maximum after 7 days and then declined, probably due to anaerobic degradation of the bound phthalates.

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

Parent

Method of calculation	Assuming spray drift to a water body of 30 cm depth. Spray drift values according to Rautmann (2001) drift from 3 m. PEC values for: single application 90th-percentile spray drift value; multiple applications 77th or 82nd-percentile spray drift values. Phthalimide formed to 26.0% of drifted folpet in water phase (DT_{50} 0.594 days). Phthalamic acid formed to 13.3% of drifted folpet in water phase (DT_{50} 5.499 days). Phthalic acid formed to 37.5% of drifted folpet in water phase (DT_{50} 6.359 days). Benzamide formed to 10.2% of drifted folpet in water phase (DT_{50} 1.625 days). 2-cyanobenzoic acid formed to 39.7% of drifted folpet in water phase (DT_{50} 0.666 days).
Application rate	Vines 10 x 1.5 kg a.s./ha; drift at 3 m.
Main routes of entry	Spray drift. Expert's meeting required to address drainage route of exposure due to high number of applications. Not Peer Reviewed FOCUS STEP 1 calculation is available in Addendum of October 2005. Risk assessment is covered with worst case run off value of 577 µg/L (see below). Maximum PEC_{SW} = 132.26 µ / L was calculated for phthalimide with FOCUS SW STEP1 and used in the risk assessment presented in the conclusion.

$PEC_{(sw)}$ Folpet (µg/L)	Single application Actual (8.09% drift)	Single application Time weighted average	Multiple applications Actual	Multiple applications Time weighted average
Initial	40.10			

Appendix 1: list of end points

Metabolites

PEC_{SW} phthalimide (µg/L)		Single application Actual (8.09% drift)	Single application Time weighted average	Multiple applications Actual (6.09% drift)	Multiple applications Time weighted average
Initial		5.17		4.45	
Short-term	24 h	1.61	3.39	1.39	2.92
	2 d	0.50	2.22	0.43	1.91
	4 d	0.05	1.22	0.04	1.05
Long-term	7 d	0.00	0.70	0.00	0.61
	14 d	0.00	0.35	0.00	0.61
	21 d	0.00	0.23	0.00	0.61
	28 d	0.00	0.18	0.00	0.61
	42 d	0.00	0.12	0.00	0.61

PEC_{SW} phthalamic acid (µg/L)		Single application Actual (8.09% drift)	Single application Time weighted average	Multiple applications Actual (6.09% drift)	Multiple applications Time weighted average
Initial		2.97		4.36	
Short-term	24 h	2.62	2.79	3.84	4.10
	2 d	2.31	2.63	3.39	3.86
	4 d	1.79	2.34	2.63	3.43
Long-term	7 d	1.23	1.98	1.80	2.90
	14 d	0.51	1.40	0.75	2.90
	21 d	0.21	1.04	0.31	2.90
	28 d	0.09	0.82	0.13	2.90
	42 d	0.01	0.56	0.02	2.89

Appendix 1: list of end points

PEC_{SW} phthalic acid (µg/L)		Single application Actual (8.09% drift)	Single application Time weighted average	Multiple applications Actual (6.09% drift)	Multiple applications Time weighted average
Initial		8.42		13.57	
Short-term	24 h	7.55	7.99	12.17	12.87
	2 d	6.77	7.58	10.91	12.21
	4 d	5.45	6.83	8.78	11.01
Long-term	7 d	3.93	5.90	6.33	9.50
	14 d	1.83	4.32	2.95	9.50
	21 d	0.85	3.31	1.38	9.50
	28 d	0.40	2.63	0.64	9.49
	42 d	0.09	1.82	0.14	9.44

PEC_{SW} benzamide (µg/L)		Single application Actual (8.09% drift)	Single application Time weighted average	Multiple applications Actual (6.09% drift)	Multiple applications Time weighted average
Initial		1.67		1.51	
Short-term	24 h	1.09	1.38	0.99	1.25
	2 d	0.71	1.14	0.65	1.03
	4 d	0.30	0.81	0.27	0.74
Long-term	7 d	0.08	0.54	0.08	0.49
	14 d	0.00	0.28	0.00	0.49
	21 d	0.00	0.19	0.00	0.49
	28 d	0.00	0.14	0.00	0.49
	42 d	0.00	0.09	0.00	0.49

PEC_{SW} 2-cyanobenzoic acid (µg/L)		Single application Actual (8.09% drift)	Single application Time weighted average	Multiple applications Actual (6.09% drift)	Multiple applications Time weighted average
Initial		7.90		6.80	
Short-term	24 h	2.79	5.34	2.40	4.60
	2 d	0.99	3.62	0.85	3.11
	4 d	0.12	2.03	0.11	1.75

Appendix 1: list of end points

PEC_{SW} 2-cyanobenzoic acid (µg/L)		Single application Actual (8.09% drift)	Single application Time weighted average	Multiple applications Actual (6.09% drift)	Multiple applications Time weighted average
Long-term	7 d	0.01	1.18	0.00	1.02
	14 d	0.00	0.59	0.00	1.02
	21 d	0.00	0.39	0.00	1.02
	28 d	0.00	0.30	0.00	1.02
	42 d	0.00	0.20	0.00	1.02

Method of calculation	Assuming run-off of soil metabolites from a 1 ha field following a 20 mm precipitation event, into a water body of 30 cm depth, 1 m width and 100 m length (total water 130,000 L). Run-off of equivalent to 0.5% of applied, assuming total season application in one application and complete conversion to metabolite (i.e. 100% of applied), no degradation in soil. PEC values for any folpet metabolite.
Application rate	Vines 10 x 1.5 kg a.s./ha:
Main routes of entry	Run-off.

$PEC_{(sw)}$ folpet metabolite (µg folpet equivalents/L)	Actual
Initial	557

PEC (sediment)

Parent

Method of calculation	Folpet was not detected in the sediment phase; therefore PECsed have not been calculated. Additionally, no folpet metabolite reached 10% of applied in the sediment phase.
Application rate	-
Route of entry	-

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

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	FOCUS PELMO (v3.3.2). New calculation based on Expert's meeting agreed parameters.
Application rate and modelling parameters used: [Key to scenarios: C: Châteaudun H: Hamburg J: Jokioinen K: Kremsmünster N: Okehampton O: Porto P: Piacenza S: Sevilla T: Thiva	Modelling based on the use of the 80 WDG formulation. Simulations were conducted with applications to vines, application rate of 10 x 1.5 kg a.s./ha in Northern and Southern EU (7 scenarios: C, O, P, H, K, S, T) and to winter wheat (4 scenarios: O, P, S, T) (EFSA note: interval between applications of 14 d instead of 7 d was used for wheat), application of 2 x 0.75 kg a.s./ha in Southern Europe. Crop interception was 50-85% for vines and 70% for winter wheat. Substance parameters: Folpet: K_{OC}: 304 mL/g (estimated), 1/n: 0.9 (FOCUS default), DT_{50}: 4.68 days (mean) Phthalimide: K_{fOC}: 208.7 mL/g (mean), 1/n: 0.87 (mean), DT_{50}: 7.88 days (mean) Phthalic acic: K_{OC}: 73.06 (EPIWIN estimate), 1/n: 0.9 (FOCUS default), DT_{50}: 3.15 days (worst case) Phthalamic aicd: K_{OC}: 10 (EPIWIN estimate), 1/n: 0.9 (FOCUS default), DT_{50}: 0.24 days (worst case).

$PEC_{(gw)}$

Maximum concentration	Not available, not required
Average annual concentration (Results quoted for modelling with FOCUS gw scenarios, according to FOCUS guidance)	For all scenarios and all substances, 80th-percentile annual average concentrations: <0.001 µg/L

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

Direct photolysis in air ‡	Non-volatile.
Quantum yield of direct phototransformation	Not available, not required.
Photochemical oxidative degradation in air ‡	Half-life for folpet due to reaction with hydroxyl radicals calculated to be 6.16 hours.
Volatilization ‡	Negligible.

PEC (air)

Method of calculation	Non-volatile.
Maximum concentration	Not relevant.

PEC(a)

Maximum concentration	Negligible

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Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	**Soil** Definitions for risk assessment: folpet, phthalimide, phthalamic acid and phthalic acid. Definitions for monitoring: folpet. **Water** **Ground water** Definitions for exposure assessment: folpet (DT_{90} < 3d), phthalimide, phthalamic acid and phthalic acid. Definitions for monitoring: folpet (DT_{90} < 3d) EFSA note: folpet is the only ecotoxicological relevant compound; folpet and phthalic acid are the only toxicological relevant compounds. Folpet has a DT_{90} well below 3d (maximum DT_{90} = 9h in buffered pH 5 or 7), phtalic acid is not expected to reach ground water at levels above 0.1 µg / L when used for the representative uses evaluated. **Surface water** Definitions for risk assessment: folpet (DT_{90} < 3d), phthalimide, phthalamic acid, phthalic acid, 2-cyanobenzoic acid. Definitions for monitoring: folpet is the only ecotoxicological relevant compound. **Air** Definitions for risk assessment: folpet. Definitions for monitoring: folpet.

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

Soil (indicate location and type of study)	No data available
Surface water (indicate location and type of study)	No data available
Ground water (indicate location and type of study)	No data available
Air (indicate location and type of study)	No data available

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	No labelling proposed

Appendix 1: list of end points

Appendix 1.6: Effects on non-target Species

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

Acute oral toxicity to mammals ‡	LD_{50} > 2,000 mg/kg bw (rat; folpet) LD_{50} > 2,000 mg/kg bw (rat; 'Folpan' 80 WDG)
Reproductive toxicity to mammals ‡	The EPCO meeting agreed on a NOEC of 1500 ppm
Acute oral toxicity to birds ‡	LD_{50} > 2,510 mg/kg bw (quail)
Dietary toxicity to birds ‡	LC_{50} > 5,000 ppm (quail, mallard) Calculated daily dose: quail: >1127 mg/kg bw/day mallard: >746 mg/kg bw/day
Reproductive toxicity to birds ‡	NOEC 1,000 ppm (quail, mallard) highest concentration tested). Calculated daily dose: quail: 78.3 mg/kg bw/day mallard: 90.0 mg/kg bw/day

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

Application rate (kg as/ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER[a]	Annex VI Trigger
1.5	grapes	small bird; consumption of insects	acute oral	Tier 1: >30.9	10
1.5	grapes	small bird; consumption of insects	short term dietary	Tier 1: >16.5	10
1.5	grapes	small bird; consumption of insects	long term dietary	Tier 1: 2.0	5
1.5	grapes	small mammal; consumption of grass	acute oral	Tier 1: >6.8b	10
0.75	winter wheat	insectivorous bird	acute oral	Tier 1: > 61.8	10
0.75	winter wheat	insectivorous bird	short term dietary	Tier 1: > 33	10
0.75	winter wheat	insectivorous bird	long term dietary	Tier 1: 4	5
0.75	winter wheat	insectivorous mammal	acute oral	Tier 1: > 303	10

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Application rate (kg as/ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER[a]	Annex VI Trigger
1.25	tomatoes	insectivorous bird	acute oral	Tier 1: > 37.1	10
1.25	tomatoes	insectivorous bird	short term dietary	Tier 1: > 19.8	10
1.25	tomatoes	insectivorous bird	long term dietary	Tier 1: 2.4	5
1.25	tomatoes	medium herbivorous bird	acute oral	Tier 1: > 16.9	10
1.25	tomatoes	medium herbivorous bird	short term dietary	Tier 1: > 8.9	10
1.25	tomatoes	medium herbivorous bird	long term dietary	Tier 1: 2	5
1.25	tomatoes	medium herbivorous mammal	acute oral	Tier 1: > 36.5	10

[a] The lowest TER values are shown based on the risk assessment.

Toxicity data for aquatic species - folpet and 'Folpan' 80 WDG (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/L)
Laboratory tests ‡				
Fish (rainbow trout)	Folpet	96-h (static)	96-h LC_{50}	233 µg/L
Fish (brown trout*)	Folpet	96-h (static)	96-h LC_{50}	98 µg/L
Fish (rainbow trout)	'Folpan' 500 SC	28-day (semi-static)	24-h LC_{50} 96-h LC_{50} 28-day LC_{50}	> 156 µg folpet/L 133 µg folpet/L 110 µg folpet/L
Invertebrates (*Daphnia magna*)	'Folpan' 80 WDG	48-h (semi-static)	24-h EC_{50}	680 µg folpet/L
Algae (*Scenedesmus subspicatus*)	folpet	72-h	E_rC_{50} E_bC_{50}	> 10000 µg folpet/L > 10000 µg folpet/L
* Six species of fish were tested. Brown trout (*Salmo trutta*) was the most sensitive species tested, and this LC50 should be used in the higher tier risk assessment. Uncertainty regarding interspecies variation in sensitivity has been reduced. Hence, a TER trigger of 10 should be used.				

Appendix 1: list of end points

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

Group	Test substance	Time-scale	Endpoint	Toxicity (µg/L)
Laboratory tests				
Fish (bluegill sunfish)	Phthalimide	96-h (semi-static)	96-hour LC_{50}	38000
Invertebrates (*Daphnia magna*)	Phthalimide	48-h (static)	48-hour EC_{50}	39000
Fish (rainbow trout)	Phthalic acid	96-h (static)	96-h LC_{50}	> 100000
Invertebrates (*Daphnia magna*)	Phthalic acid	48-h (static)	48-h EC_{50}	≥ 100000
Algae (*Selenastrum capricornutum*)	Phthalic acid	72 h (static)	72-h E_bC_{50}	> 100000
Fish (rainbow trout)	Phthalamic acid	96-h (static)	96-h LC_{50}	> 100000
Invertebrates (*Daphnia magna*)	Phthalamic acid	48-h (static)	48-h EC_{50}	≥ 100000
Algae (*Selenastrum capricornutum*)	Phthalamic acid	72 h (static)	72-h E_bC_{50}	> 100000
Fish (rainbow trout)	Benzamide	96-h (static)	96-h LC_{50}	> 100000
Invertebrates (*Daphnia magna*)	Benzamide	48-h (static)	48-h EC_{50}	≥ 102000
Algae (*Selenastrum capricornutum*)	Benzamide	72 h (static)	72-h E_bC_{50}	> 100000
Fish (rainbow trout)	2-cyanobenzoic acid	96-h (static)	96-h LC_{50}	> 100000
Invertebrates (*Daphnia magna*)	2-cyanobenzoic acid	48-h (static)	48-h EC_{50}	> 100000
Algae (*Selenastrum capricornutum*)	2-cyanobenzoic acid	72 h (static)	72-h E_bC_{50}	> 100000

Microcosm or mesocosm tests
No data submitted.

Appendix 1: list of end points

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

Application rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER*	Annex VI Trigger[a]
1.5	grapes	fish	acute	10	16	10
1.25	tomatoes	fish	acute	5	41	10

[a] Modified on the basis of a higher tier risk assessment (IIIA, 11.2).
* Based on LC_{50} for brown trout of 98 µg/L.

Bioconcentration

Bioconcentration factor (BCF) ‡	56 (whole fish).
Annex VI Trigger:for the bioconcentration factor	1,000 (for a readily degradable compound such as folpet)
Clearance time (CT_{50})	0.63 days (whole fish).
Level of residues (%) in organisms after the 14 day depuration phase	< 7% (edible tissue); < 2% (whole fish and non-edibles).

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

Acute oral toxicity ‡	LD_{50} > 236 µg folpet/bee LD_{50} > 179 µg folpet/bee (Folpan 80 WDG)
Acute contact toxicity ‡	LC_{50} > 200 µg folpet/bee LC_{50} > 160 µg folpet/bee (Folpan 80 WDG)

Hazard quotients for honey bees (Annex IIIA, point 10.4) based on endpoint for Folpan 80 WDG

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
1.5	grapes	oral	< 8.4	> 50
1.5	grapes	contact	< 9.4	> 50

Field or semi-field tests
Not required.

Appendix 1: list of end points

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

Species (exposed life stage)	Test and test Substance	Dose (kg as/ha)	Endpoint	Conclusion
Laboratory tests				
*Typhlodromus pyri** (protonymphs)	laboratory, residues on glass. 'Folpan' 500 SC	0.49	Mortality: control: 13%, 0.49 kg/ha: 14%. Reproduction: offspring/female control: 8.9 0.49 kg/ha: 9.3	No effects
*Coccinella septempunctata** (larvae)	laboratory, residues on glass 'Folpan' 500 SC	0.48	Mortality: control: 20%, 0.48 kg/ha: 13%. Reproduction, fertile eggs/female: control: 373 0.48 kg/ha: 206	No effect on survival. Effect (45%) on reproduction was less than ESCORT 2 trigger of 50%.
*Coccinella septempunctata** (larvae)	'Folpan' 80 WDG	0.53	Mortality: control: 22%, 0.53 kg/ha: 16%. Reproduction: fertile eggs/female: control: 419 0.53 kg/ha: 188	No effect on survival. Effect (55%) on reproduction was slightly higher than ESCORT 2 trigger of 50%.
*Chrysoperla carnea** (larvae)	laboratory, residues on glass 'Folpan' 500 SC	0.49	Mortality: control: 21.1%, 0.49 kg/ha:7.7%. Reproduction, fertile eggs/female: control: 610 0.49 kg/ha: 624	No effects.
Trichogramma cacoeciae (adult)	laboratory, residues on glass 'Folpan' 500 SC	0.53	Parasitised eggs/wasp: control: 7.7 0.53 kg/ha: 6.3 (18.5% reduction)	Effect on reproduction was lower than ESCORT 2 trigger of 50%.
Poecilus cupreus (adults)	laboratory, residues on sand. 'Folpan' 80 WDG	0.66	Mortality: 0% No effect on feeding.	No effect

Appendix 1: list of end points

Species (exposed life stage)	Test and test Substance	Dose (kg as/ha)	Endpoint	Conclusion
*Aleochara bilineata** (adults)	laboratory, residues on sand. 'Folpan' 500 SC	0.49	Parasitism: control: 36% 0.49kg/ha: 29% (19% reduction)	Effect lower than ESCORT 2 trigger of 50%.

*ESCORT 2 recommended test species

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

Species	Test and test substance	Dose (kg a.s./ha)	Endpoint	Conclusion
Extended laboratory tests				
Aphidius rhopalosiphi (adults)	Extended laboratory, residues on apple leaves. 'Folpan' 500 SC	0.1 - 2.0	Corrected mortality%: 0.1kg/ha:2.5 0.5kg/ha:10 1.2kg/ha:2.5 1.5kg/ha:7.5 2.0kg/ha:32.5 Reduction in parasitisation: 0.1kg/ha:32% 0.5kg/ha:33% 1.2kg/ha:23% 1.5kg/ha:68% 2.0kg/ha:75%	Effects on survival lower than ESCORT 2 trigger of 50%. Effects on reproduction lower than ESCORT 2 trigger of 50% at 1.2 kg/ha and below, and greater than 50% at 1.5 and 2.0 kg/ha.
*Typhlodromus pyri**	Extended laboratory, bean leaves, whole plants sprayed. 'Folpan' 80 WDG	1.64 3.38 5.25	*Corrected mortality:* 1.64kg/ha:0% 3.38kg/ha:0% 5.25kg/ha:0% *Eggs/female:* control:4.5 1.64kg/ha:8.1 3.38kg/ha:9.8 5.25kg/ha:9.2	No effects

Appendix 1: list of end points

Species	Test and test substance	Dose (kg a.s./ha)	Endpoint	Conclusion
*Aphidius rhopalosiphi**	Extended laboratory, bean leaves, whole plants sprayed. Fresh residues, and 14 day aged residues. 'Folpan' 80 WDG	1.64 3.38 5.25	<u>Fresh residues:</u> *Corrected mortality%:* 1.64kg/ha:2.7 3.38kg/ha:21.6 5.25kg/ha:75.7 *mummies/female:* control:38.0 1.64kg/ha:27.8 3.38kg/ha:25.6 <u>14 day aged residues:</u> *mortality%:* 1.64kg/ha:0 3.38kg/ha:0 5.25kg/ha:0 *mummies/female:* control:31.2 1.64kg/ha:24.6 3.38kg/ha:12.0 5.25kg/ha:28.8	Effects less than ESCORT 2 trigger of 50% for fresh residues for 3.38 kg/ha. Mortality >50% for fresh residues at 5.25 kg/ha. Effects less than ESCORT 2 trigger of 50% for 14 day aged residues for 5.25 kg/ha.
*Coccinella septempunctata**	Extended laboratory, bean leaves, whole plants sprayed. 'Folpan' 80 WDG	0.31 1.64 3.38 5.25	Corrected mortality%: 0.31kg/ha:0 1.64kg/ha:0 3.38kg/ha:0 5.25kg/ha:11.8 *Fertile eggs /female/day:* control:4.1 0.31kg/ha:6.8 1.64kg/ha:10.1 3.38kg/ha:8.2 5.25kg/ha:8.4	No statistically significant adverse effects

*ESCORT 2 recommended test species

Appendix 1: list of end points

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

Species	Test and test substance	Dose (kg a.s./ha)	Endpoint	Conclusion
Extended laboratory tests				
*Chrysoperla carnea**	Extended laboratory, bean leaves, whole plants sprayed. 'Folpan' 80 WDG	1.64 3.38 5.25	Corrected mortality%: 1.64kg/ha:20 3.38kg/ha:10 5.25kg/ha:17.5 *eggs/female/day* control:36.8 1.64kg/ha:31.8 3.38kg/ha:33.3 5.25kg/ha:34.1	No statistically significant effects.

*ESCORT 2 recommended test species
Low risk to non-target arthropods.

Field or semi-field tests
No significant population effects on *Typhlodromus pyri* under field conditions, applied at 0.3 to 2.1 kg a.s./ha.

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity ‡	14-day LC_{50} > 1,000 mg folpet/kg ($LC_{50\ corrected}$ > 500 mg folpet/kg*) 14-day LC_{50} >828 mg folpet/kg (Folpan 80 WDG) ($LC_{50\ corrected}$ > 414 mg folpet/kg*)
Reproductive toxicity ‡	NOEC = 5.18** mg folpet/kg soil

* 'Corrected' value derived by dividing endpoint by 2 (for substances with logPow >2) in accordance with EPPO earthworm scheme 2002.
** It was agreed in the EPCO 22 experts´ meeting on ecotoxicology that the lowest endpoint should be used without applying a correction factor.

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Application rate (kg as/ha)	Crop	Time-scale	TER	Annex VI Trigger
10 applications at 1.5 kg folpet/ha at 7 day intervals	grapes	acute	> 280*	10
10 applications at 1.5 kg folpet/ha at 7 day intervals	grapes	long-term	3.5 *	5.0

*TER based on the peer reviewed maximum PECsoil of 1.478 mg a.s./kg

Appendix 1: list of end points

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralization ‡	No significant effects of folpet (< 25% effect compared to untreated control) when tested at 1.593 and 15.93 kg folpet/ha.
Carbon mineralization ‡	Dehydrogenase activity affected by < 25% compared to untreated control when tested at 1.593 and 15.93 kgfolpet/ha.

Effects on other non-target organisms believed to be at risk (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Under field conditions, 'Folpan' 80 WDG was applied at 1.6, 4.8 and 8.0 kg product/ha to winter wheat, spring barley, winter oat, spring oat, winter rye, winter oilseed rape, linseed, peas, field beans and sugar beet. No phytoxicity observed. An additional field trial resulted in no phytotoxicity on a range of crops at 6.4 kg folpet/ha ('Folpan' 80 WDG).

Classification and proposed labelling (Annex IIA, point 10)

with regard to ecotoxicological data	N,	Dangerous for the environment
	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Appendix 2, List of abbreviations

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median

Appendix 2, List of abbreviations

LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
mo	month(s)
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
r^2	coefficient of determination
RPE	respiratory protective equipment
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year