CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion regarding the peer review of the pesticide risk assessment of the active substance dodemorph (considered variant dodemorph acetate)

Issued on 17 September 2008

SUMMARY

Dodemorph is one of the 84 substances of the third stage Part B of the review programme covered by Commission Regulation (EC) No 1490/2002[1]. This Regulation requires the European Food Safety Authority (EFSA) to organise upon request of the EU-Commission 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 six months a conclusion on the risk assessment to the EU-Commission.

The Netherlands being the designated rapporteur Member State submitted the DAR on dodemorph in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 9 February 2007. The peer review was initiated on 4 May 2007 by dispatching the DAR for consultation of the Member States and the sole applicant BASF AG. Subsequently, the comments received on the DAR were examined and responded by the rapporteur Member State in the reporting table. This table was evaluated by EFSA to identify the remaining issues. The identified issues as well as further information made available by the applicant upon request were evaluated in a series of scientific meetings with Member State experts in May – June 2008.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in July – August 2008 leading to the conclusions as laid down in this report. This conclusion was reached on the basis of the evaluation of the representative use as a fungicide on roses under permanent protection. Full details of the GAP can be found in the attached list of end points.

[1] OJ No L 224, 21.08.2002, p. 25, as amended by Regulation (EC) No 1095/2007 (OJ L 246, 21.9.2007, p. 19)

The representative formulated product for the evaluation was "Mehltaumittel", an emulsifiable concentrate (EC). In the formulation the active substance is present as the acetate variant.

Methods of analysis for products of plant and animal origin are not required for the representative use on roses. Adequate methods are available to monitor the sum of *cis* and *trans* dodemorph in soil and air. Methods of analysis for water have been identified as a data gap.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that at least some of the quality control measurements of the plant protection product are possible. Several data gaps have been identified. Namely new 5 batch data, water solubility, vapour pressure, Henry's law constant and surface tension.

Mammalian toxicology was assessed in a series of tests. Dodemorph is absorbed rapidly to an extent of at least 40%. It is distributed widely and uniformly. It has no potential for accumulation. It is excreted rapidly and practically completely and is extensively metabolised. It is of low acute toxicity by the oral and dermal route. Based on its irritant, corrosive and sensitising properties a classification as **Xi; R37 "Irritant to the respiratory system", C; R34 "Corrosive; Causes burns"** (Xi; R41 "Irritant; Risk of serious damage to eyes" is implicit) and **Xi; R43 "Irritant; May cause skin sensitisation"** was proposed. Short term studies were carried out with rats, dogs and rabbits. The liver was the main target of toxicity. The lowest NOAEL of 8.2 mg/kg bw/d was based on vomiting, salivation, changes in faecal excretion and liver effects seen in dogs. Dodemorph is not genotoxic. A 2-year rat and an 18-month mouse study have been reported. Critical effects observed were decreased bodyweight gain (both species) and liver effects (rat) while no increased tumour incidences could be observed in these investigations. Dodemorph did not cause effects on reproduction but induced developmental effects in rabbits (open eye, irregularly shapen sternebrae) based on which a classification as **Xn; Repr. Cat. 3 R63 "Harmful; Possible risk of harm to the unborn child"** was proposed. The acceptable daily intake (ADI) was set at 0.082 mg/kg bw/d, the acceptable operator exposure level (AOEL) and the acute reference dose (ARfD) were set at 0.033 mg/kg bw/d and at 0.33 mg/kg bw respectively. Operator exposure amounts to 88% of the AOEL when personal protective equipment (PPE) in the form of gloves, coverall and gas mask is worn. Worker exposure when PPE (gloves, coverall and gas mask) is used amounts to 45% of the systemic AOEL of 0.033 mg/kg bw/d. Bystander exposure is not anticipated based on the use of dodemorph in greenhouses.

No data were submitted to study and assess the residue behaviour of dodemorph in plants and livestock animals in order to define the relevant residues for dietary consumer risk assessment. The representative use of dodemorph on roses is normally not expected to result in any dietary exposure to humans or livestock animals. A situation where treated rose petals are used for human consumption was neither assessed nor considered. Under conditions excluding any potential consumer exposure to dodemorph residues, there will be no dietary consumer risk related to the notified representative use.

In soil under aerobic conditions dodemorph acetate exhibits moderate to high persistence forming no major metabolite (> 10% applied radioactivity (AR)), but forming an unknown minor non-transient metabolite. Mineralisation to carbon dioxide accounted for 17.1-35.9% AR after 93-125 days. The formation of unextractable residues was a sink accounting for 21.9% to 43.4% of the applied radioactivity after 93-125 days. Dodemorph is immobile in soil and there was no indication that adsorption was pH dependant.

In dark natural sediment water systems dodemorph degraded exhibiting fast disappearance from the water column, but high persistence in sediment. No major metabolites were found. The terminal metabolite, carbon dioxide, accounted for 15.4-23.2% AR by 103 days (study end). Unextracted sediment residues were a significant sink representing 27-28% AR at study end. The necessary surface water and sediment exposure assessments were carried out assuming 0.1% emission from glasshouse (Dutch approach). These values are the basis for the risk assessment discussed in this conclusion.

The potential for groundwater exposure from the applied for intended uses by dodemorph above the parametric drinking water limit of 0.1 µg/L, was concluded to be low in geoclimatic situations that are represented by all 9 FOCUS groundwater scenarios. However no calculation for the unknown minor non-transient metabolite was available.

Although it is expected that dodemorph does not reach the surrounding environment in significant amounts, emission to surface water is considered possible. A risk assessment for birds and mammals was provided for exposure from contaminated drinking water and for consumption of contaminated fish. A PECsw value was based on the Dutch model. A long-term reproductive endpoint for birds was estimated by using the lower endpoint from reproductive effect studies on birds for related substances (Structure Activity Relationship). The risk assessment indicated a low risk to birds and mammals exposed to dodemorph through drinking water and fish. In the aquatic environment dodemorph was most toxic to fish and daphnia. It was considered to be toxic to aquatic organisms on an acute scale and very toxic on a chronic scale. Dodemorph is lipophilic (logPow = 4.6) and the bioaccumulation factor was estimated in the range of 583-746 based on whole fish. Given a TER >> 10 based on the fish early life stage endpoint the risk from bioaccumulation was considered to be low. Whereas the risk to bees was considered to be low, assessment of non-target arthropods (NTA) indicated a risk. This is of particular importance as various non-target arthropods may be used in integrated pest management in greenhouses. The risk to earthworms was considered to be low as was the risk to non-target soil micro-organisms and micro-organisms in sewage treatment plant. No data were submitted nor required for non-target macro soil organisms. Risk to non-target plants was considered to be negligible for glass house use and no data were submitted by the applicant.

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

TABLE OF CONTENTS

BACKGROUND

Commission Regulation (EC) No 1490/2002 laying down the detailed rules for the implementation of the third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000 as amended by Commission Regulation (EC) No 1095/2007, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Dodemorph is one of the 84 substances of the third stage, part B, covered by the Regulation (EC) No 1490/2002 designating the Netherlands as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, the Netherlands submitted the report of its initial evaluation of the dossier on dodemorph, hereafter referred to as the draft assessment report, received by the EFSA on 9 February 2007. Following an administrative evaluation, the draft assessment report was distributed for consultation in accordance with Article 11(2) of the Regulation (EC) No 1490/2002 on 4 May 2007 to the Member States and the main applicant BASF AG 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, EFSA identified and agreed on lacking information to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the requested information received from the notifier, a scientific discussion took place in expert meetings in May – June 2008. 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 during a written procedure with the Member States in July – August 2008 leading to the conclusions as 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 Protection Products and their Residues (PPR).

In accordance with Article 11c(1) of the amended Regulation (EC) No 1490/2002, 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 endpoints 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 (revision 1-1, 14 February 2008)

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 (revision 2-1, 28 August 2008).

Given the importance of the draft assessment report including its addendum (compiled version of July 2008 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.

By the time of the presentation of this conclusion to the EU-Commission, the rapporteur Member State has made available amended parts of the draft assessment report which take into account mostly editorial changes. Since these revised documents still contain confidential information, the documents cannot be made publicly available. However, the information given can be found in the original draft assessment report together with the peer review report, both of which are publicly available.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Dodemorph is the ISO common name for *cis/trans*-[4-cyclododecyl]-2,6-dimethylmorpholine (IUPAC). Due to the fact that the dodemorph acetate, a variant of dodemorph, is used in the formulated product, it should be noted that the evaluated data belong to the variant dodemorph acetate, unless otherwise specified. Dodemorph belongs to the class of morpholine fungicides. Dodemorph is a systemic fungicide with protective, curative and eradicative effect. It inhibits the formation of appressoria and haustoria and controls mycelial growth and sporulation. Dodemorph is used in roses for the control of powdery mildew. The representative formulated product for the evaluation was "Mehltaumittel", an emulsifiable concentrate (EC). The evaluated representative uses are as a fungicide on roses. Full details of the GAP can be found in the attached list of endpoints.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

The minimum purity of dodemorph acetate as manufactured should not be less than 950 g/kg on a dry weight basis, for the wet cake TK the purity range is from 544 g/kg to 594 g/kg. At the moment no FAO specification exists. However, new batch data are required because closure on the current batches was not by analysis because the content of xylene was derived by calculation. Therefore, the specification for the technical material as a whole should be regarded as provisional. No relevant impurities have been identified.

The content of dodemorph acetate in the representative formulation is 385 g/L (pure). It should be noted that the formulation is classified as flammable.

Beside the specification, the assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of dodemorph acetate or the respective formulation. However, the following data gaps were identified:

- Water solubility at pH 5 and 7
- Vapour pressure
- Henry's law constant
- Surface tension at 25ºC of the neat formulation

The main data regarding the identity of dodemorph 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 dodemorph in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material. The meeting of experts PRAPeR 46 considered if it was necessary to be able to identify the variant in the formulation. The current method only analyses for dodemorph. The meeting of experts was unable to conclude on this point.
However, sufficient test methods and data relating to physical, chemical and technical properties and analytical methods are available to ensure that at least some quality control measurements of the plant protection product are possible.

Methods of analysis for products of plant and animal origin are not required because the representative use is on roses which are not used as food or feed. Adequate methods are available for soil and air for the residue definition of sum of *cis* and *trans* dodemorph. Soil is analysed by LC-

MS/MS with an LOQ of 0.1 mg/kg for the sum of the two isomers. There is also a second method for soil GC-NPD with an LOQ of 0.04 mg/kg for the sum of the two isomers. Air is analysed by GC-NPD with an LOQ of 0.15 µg/m3. The soil method can be used as a confirmatory method for air. For surface water it was considered that the LOQ of the currently available method was not low enough and a data gap was identified for a new surface water method. It was considered in the DAR that the method for ground/drinking water was not sufficiently validated. Therefore the peer review process identified a data gap for a new method for drinking water/ground water. It is noted that some new validation data are available but were considered a new study. In view of the restrictions concerning the acceptance of new studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review.

2. Mammalian toxicology

EFSA Note: Although the subject of the evaluation is dodemorph, all toxicological studies have been performed with the variant dodemorph acetate which readily dissociates in dodemorph and acetate in laboratory animals (and humans). At the meeting of experts (PRAPeR 49, June 2008) it was agreed that the observed effects can all be attributed to the dodemorph moiety of dodemorph acetate. The values obtained in the different investigations are presented in the conclusion already corrected for dodemorph content. In the list of endpoints the respective values for dodemorph acetate are given in addition for any possible future assessment.

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

When given orally, dodemorph is absorbed rapidly (within 24 hours after application) and to an extent of at least 40% based on urinary excretion (~ 25%), exhaled air (~ 10%) and carcass residue (~ 4%) of morpholine ring labelled radioactivity. It is uniformly distributed. Slightly increased residue levels were found in the liver. There is no evidence for accumulation. Metabolites of dodemorph are rapidly and extensively excreted at low dose to an extent of more than 90% within 24 hours, via the urine (~ 40%) and the faeces (~ 60%). Although none of the metabolites have been identified, extensive metabolism of the substance is obvious as dodemorph acetate could not be detected in urine and only in very small amounts in faeces. The experts discussed the lack of metabolism studies in the DAR, but considered that not to be of concern taking into account also the fact that the substance was used only on ornamentals.

2.2. Acute toxicity

Dodemorph is of low toxicity by the oral (LD_{50} > 4100 mg/kg bw) and the dermal route (LD_{50} > 1640 mg/kg bw). An acute inhalation study was not presented in the DAR. The experts agreed that such a study was not necessary since it was technically not feasible to produce an adequate aerosol and also because the substance was corrosive, based on which they proposed also a classification as **Xi; R37**

"Irritant to the respiratory system". Dodemorph caused very severe effects in skin and eye irritation tests with rabbits and skin sensitisation in a Magnusson & Kligman test with guinea pigs. Consequently also classification as **C; R34 "Corrosive; Causes burns"** (Xi; R41 "Irritant; Risk of serious damage to eyes" is implicit) and **Xi; R43 "Irritant; May cause skin sensitisation"** was proposed.

2.3. SHORT TERM TOXICITY

With rats two 90-day dietary studies, with dogs a 28-day, a 90-day and a 1-year oral study and with rabbits a 21-day dermal study are reported. Overall, the liver was the main target of toxicity. The NOAELs of 66 mg/kg bw/d and 65 mg/kg bw/d respectively set in the two rat studies are based on essentially similar findings of reduced body weight gain, increased liver weight and liver histopathology. The lowest oral NOAEL in dogs (8.2 mg/kg bw/d) was obtained in the 1-year study and was based on vomiting, increased salivation, changes in faecal excretion, gastric erosion and changes in the liver (bile duct hyperplasia, peribiliary fibrosis). The systemic NOAEL in rabbits was set at 49 mg/kg bw/d (the highest dose tested) since no systemic effects were observed while a NOAEL of 10 mg/kg bw/d was set for local effects based on erythema and oedema occurring at the application site.

2.4. GENOTOXICITY

The experts agreed, based on the information available, that dodemorph is not genotoxic.

2.5. LONG TERM TOXICITY

In this section of the DAR a 2-year rat study and an 18-month mouse study are presented. In the rat study a systemic NOAEL of 45 mg/kg bw/d was set at based on reduced body weight gain and food consumption and histopathological findings in the liver. In an addendum to the DAR (April 2008) further information on neoplastic lesions in several organs that were observed in this study was provided (i.e. historical controls for liver, thyroid, adrenals, brain, kidneys, pancreas, uterus and ovaries) and the experts agreed that there was no indication that dodemorph induces tumours.

In the 18-month mouse study the systemic NOAEL of 37 mg/kg bw/d was derived from observations of reduced bodyweight gain. The preneoplastic lesions seen were considered as spontaneous and not treatment related.

2.6. REPRODUCTIVE TOXICITY

A two-generation study, a developmental study with rats and one with rabbits have been presented in the DAR. In the two-generation study the parental and the developmental NOAEL were fixed at 52 mg/kg bw/d (600 ppm) based on reduced body weight gain, decreased cholesterol levels and slight hepatocyte hypertrophy in parental animals and on reduced body weight gain and effects on

development in pups (reduced viability and delayed pinna unfolding, auditory canal opening and eye opening) at the highest dose (1800 ppm). No effects on reproduction could be detected.

In the rat developmental study based on reduced food consumption, changes in haematological and clinical parameters a maternal NOAEL of 25 mg/kg bw/d was derived while that for developmental effects was set at 82 mg/kg bw/d based on reduced foetal body weight and increased skeletal variations (delayed ossification, misshapen sternebrae).

In rabbits maternal toxicity was not observed up to the top dose of 98 mg/kg bw/d while at that dose specific malformations (open eye) occurred together with irregularly shapen sternebrae resulting in a developmental NOAEL of 33 mg/kg bw/d and a classification proposal for dodemorph as **Xn; Repr. Cat. 3 R63 "Harmful; Possible risk of harm to the unborn child".**

2.7. NEUROTOXICITY

No specific neurotoxicity studies are available. Neither in the 90-day rat study where motor activity tests were carried out nor in any other investigation have indications of a neurotoxic potential been observed.

2.8. FURTHER STUDIES

No studies have been reported in this section.

2.9. MEDICAL DATA

Medical surveillance of manufacturing plant personnel did not indicate a causal association between dodemorph exposure and any medical effect.

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

The experts agreed to set the **ADI was set at 0.082 mg/kg bw/d** on the NOAEL of 8.2 mg/kg bw/d obtained in the 1-year dog study, applying a safety factor of 100.

The AOEL was set at 0.033 mg/kg bw/d based on the NOAEL of 8.2 mg/kg bw/d obtained in the 1-year dog study corrected for gastrointestinal absorption of 40% and applying a safety factor of 100.

The experts agreed to set an **ARfD of 0.33 mg/kg bw** based on the NOAEL of 33 mg/kg bw/d for developmental effects seen in the rabbit teratogenicity study applying a safety factor of 100.

2.11. DERMAL ABSORPTION

In the original DAR the values for dermal absorption of "Mehltaumittel" were based on an *in vivo* dermal penetration study with rats combined with an *in vitro* dermal absorption study with human and rat skin. Because of shortcomings in the *in vivo* study the experts agreed to derive the values solely from the *in vitro* study resulting in values of 2.7% for the concentrate and 20% for the dilution.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The representative plant protection product "Mehltaumittel" is formulated as an emulsifiable concentrate containing 385 g/L dodemorph. It is used as a fungicide for the control of powdery mildew on roses in greenhouses. The maximum applied dose is 2.0 kg (dodemorph) in 2000 L water/ha. It is applied 1-10 times by hand-held spraying. With an addendum to the DAR (April, 2008) revised operator and worker exposure calculations (using the revised values for dermal absorption) have been provided and have been agreed upon also at a meeting of experts.

Operator exposure

The exposures have been estimated using the Dutch model[2] with the outcome of an experimental study as supplementary information to support the model calculations. The estimated exposures were 879% and 88% without and with personal protective equipment (gloves, coverall and gas mask) respectively of the systemic AOEL of 0.033 mg/kg bw/d.

Worker exposure

Worker exposure in greenhouses was estimated using the EUROPOEM II[3]/Dutch model. For the refinement of the model estimate the results from a field study (presented in detail in the addendum to the DAR) were employed. The exposures in the model calculations (combining input parameters from EUROPOEM II & the Dutch model) amounted to 1309% and 131% of the AOEL without and with the use of PPE (gloves, coverall and gas mask). A refinement of the assessment has been carried out using a field study and the values obtained there, namely 452% and 45% without and with PPE (gloves, coverall and gas mask) respectively, have been used for the final assessment for re-entry worker exposure.

Bystander exposure

No exposure is anticipated due to the application of "Mehltaumittel" in greenhouses.

[2] Van Golstein Brouwers Y.G.C., Marquart J., Van Hemmen J.J. (1996) Assessment of occupational exposure to pesticides in agriculture. Part IV. Protocol for the use of generic exposure data. TNO Nutrition and Food Research Institute, The Netherlands. TNO Report V 96.120

[3] EUROPOEM II (2003) The development, maintenance and dissemination of a European Predictive Operator Exposure Model (EUROPOEM II) database. A EUROPEAN II Database and Harmonised Model, FAIR-3CT96-1406, TNO-BIBRA International, Carshalton.

3. Residues

Dodemorph was not discussed by the experts in residues in a PRAPeR meeting. Dietary human and livestock exposure to dodemorph residues is normally not expected from the notified representative use on roses and therefore no data were submitted on residue behaviour of this active substance.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

No data were submitted to investigate the nature and magnitude of residues in plants. A situation where treated rose petals are used for human consumption was neither assessed nor considered by the peer review.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

No data were submitted or required to support the notified representative use.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

No data were submitted or required to support the notified representative use. Significant livestock exposure to roses is not expected to occur.

3.3. CONSUMER RISK ASSESSMENT

It is noted that no data were submitted to study and assess the residue behaviour of dodemorph in plants and livestock animals in order to define the relevant residues for dietary consumer risk assessment. However, the notified representative use of dodemorph in roses is normally not expected to result in any dietary exposure to consumers. A situation where treated rose petals are used for human consumption was neither assessed nor considered by the peer review.

It was concluded that, under conditions excluding any potential consumer exposure to dodemorph residues through food, there will be no dietary consumer risk from the notified representative use.

3.4. PROPOSED MRLS

The notified representative use does not concern food or feed items. The notified representative use does not require MRL setting.

4. Environmental fate and behaviour

Dodemorph was discussed at the PRAPeR experts' meeting for environmental fate and behaviour PRAPeR 47 in May 2008. It should be noted that the methods of analysis used in some fate and

behaviour studies were not able to discriminate between the *cis* and *trans* isomers. Where information on the behaviour of each individual dodemorph isomer in the environment was available it is reported in this conclusion.

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

Soil experiment (sandy loam soil) was carried out under aerobic conditions in the laboratory (24-26°C, 75% maximum field capacity) in the dark. Information regarding the route of degradation in soil from a rate of degradation study performed on two soils (sandy loam and silt loam, 20-22°C, pF 2.5) was also available. The formations of residues not extracted by acetonitrile/acetic acid or methanol/chloroform/HCl were a sink for the applied ^{14}C-dodemorph acetate or a mixture of *cis/trans* isomers of ^{14}C-dodemorph (in the range of 21.9% to 43.4% of the applied radioactivity (AR) after 93-125 days). Mineralisation to carbon dioxide accounted for 17.1-35.9% AR after 93-125 days. The only extractable breakdown product for further consideration was the unknown metabolite 1 (peak 5) reaching 6.5% after 369 days, but still increasing at study termination. There was some indication from comparison of results of different studies that this product was 2,6-dimethylmorpholine. However, in line with the opinion of experts from Member States, the available experimental evidence was not sufficient to support the identity of metabolite 1 as 2,6-dimethylmorpholine. Therefore a data gap was agreed by the experts for identification and for further assessment of this unknown metabolite 1 (peak 5).

The degradation of ^{14}C-dodemorph acetate under anaerobic conditions was investigated on the same sandy loam soil used also for determination of the route of degradation under aerobic conditions (24-26°C). From the anaerobic part of this study no reliable conclusion could be drawn as the soil samples were kept under aerobic conditions for 32 days before the anaerobic condition had started and too few samples were taken after the onset of the anaerobic condition to estimate a degradation rate. The formations of not extracted residues were 7.8% and the mineralisation to carbon dioxide accounted for 1.5% during the 61 days anaerobic period. No metabolites were found under these conditions. More reliable data however are not necessary to complete an assessment for the applied for representative use in this case, which is only glasshouse application to roses. A laboratory soil photolysis study (sandy loam) revealed a relatively fast degradation of dodemorph acetate (DT_{50} 2.4 days at 43°N). However the study was not in line with the recent requirements of relevant guidelines (too short study duration) moreover at least one photoproduct could be considered as major, the experts agreed that in relation to this use, further consideration of the photodegradation was not required (glasshouse can filter the irradiation and change the nature of the light irradiation energy).

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

The rate of degradation of dodemorph was estimated from the results of the study described in 4.1.1 above (test substance: dodemorph acetate) and two additional studies on three soils, sandy loam, silt loam and loamy sand. The test substance in the second study with sandy loam and silt loam was a mixture of *cis*-*trans* isomers, while in the third study on loamy sand soil dodemorph acetate was applied. DT_{50} values were: 24-83 days (single first-order (SFO) non linear regression, pF 2.5 soil moisture content, 20-26 °C, 4 different soils). After normalisation to 20°C this range of single first order DT_{50} became 24-125 days (pF 2.5 soil moisture content). The geometric mean that is appropriate for use in FOCUS modelling, based on the opinion of the experts was 41 days (see addendum 2 to the DAR). Information from 3 soils revealed that *cis*-isomer of dodemorph is more persistent (DT_{50} 49-237) than the *trans*-isomer (DT_{50} 11-34) (SFO, 20°C, pF 2.5). The mean (n=3) *cis*:*trans* ratio was 58:42 at the beginning of the studies. The longest available laboratory un-normalized dodemorph single first order soil DT_{50} of 83 days (24-26 °C) was agreed by the experts from the Member States for use in PEC soil calculations for this glasshouse use. All the input parameters of the calculation and the resulting soil PECs can be found in addendum 2 to the DAR.

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

The adsorption / desorption of dodemorph acetate was investigated in 5 USA soils in satisfactory batch adsorption experiment, from which 4 reliable data were available. Calculated adsorption K_foc values based on these 4 soils varied from 5300 to 49000 mL/g (mean 25200 mL/g) (1/n 0.74 – 0.95, mean 0.855). There was no evidence of a correlation of adsorption with pH. The meeting of experts agreed with the RMS that Koc 1450 mL/g (estimated Koc for the acidic sand soil) could be used for worst case FOCUS PECgw calculations. The low mobility of dodemorph was confirmed by the results of laboratory unaged (3 soils) and aged (1 soil) column leaching studies.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Dodemorph acetate was essentially stable under sterile hydrolysis conditions at 24-25°C at pH 5, pH 7 and pH 9.

The aqueous photolysis of dodemorph acetate was investigated under sterile conditions in the laboratory at pH 5, 7 and 9. The rate of degradation (linear first order DT_{50}) of 3.6 and 1.6 days equated to continuous summer sunlight at 43°N was determined for pH 7 and pH 9, respectively. At pH 5 dodemorph acetate was stable. Products found above 10% of applied radioactivity were *cis* and *trans* isomers, free base isomers of dodemorph and an initially unidentified product (Area 2,

molecular weight 282) (30.5 % at pH 7, 33.1% at pH 9 at the study end) which was subsequently attributed to be protonised dodemorph.

Dodemorph can not be considered as readily biodegradable as a biodegradability test was not submitted.

In water-sediment studies (2 systems studied at 20°C in the laboratory, water pH 8.25, sediment pH 7.4 and 8.1) dodemorph dissipated rapidly from the water partitioning to sediment in both systems (SFO DT_{50} 0.5 and 1.5 days) than a slow degradation in the sediment was observed (SFO DT_{50} 126 and 281 days). Only one whole system degradation value (SFO DT_{50} 53 days, silt loam system) was considered reliable by the meeting of experts from the member states. The expert's meeting also discussed the validity of the study as the sediment of both systems had higher organic matter content (organic carbon content (OC) 4.3 and 7.4%) than recommended by the relevant guideline. It was agreed that notwithstanding these shortcomings no new water-sediment study is required and considering the intended use, the surface water PEC calculation based on one water-sediment system data is accepted for this case. Further details of this discussion can be found in the discussion table of the peer review report. Major metabolites were not found in this study. The terminal metabolite, carbon dioxide, accounted for 15.4-23.2% AR by 103 days. Residues not extracted from sediment by a mix of methanol:chloroform:hydrochloric acid and hexane were a significant sink representing 27-28% AR at study end (103 days). The experts agreed that for dodemorph water and sediment DT_{50} of 53 days (whole system values) were acceptable for use as PECsw calculation input.

PECsw and PECsed values were calculated assuming 0.1% of the dose was emitted from glasshouse and transferred to surface water using FOCUS calculator 1.1 and appropriately factoring the application rate. The peer review agreed these PEC surface water and sediment as presented in Appendix 1 were appropriate for use in risk assessment.

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

No specific scenarios are available for glasshouse uses for the EU level registration. Therefore winter cereals (10 applications start 25th May, N & S Europe) was simulated by FOCUS PEARL 2.2.2 using the following input parameters, which was discussed and agreed by the experts: SFO DT_{50} 41 days, K_{foc} 1450 mL/g (K_{fom} 841 mL/g), 1/n=0.855 (for more details see addendum 2 to the DAR). The physical-chemical expert meeting PRAPeR 46 identified some data gaps for some substance properties needed as input parameters for FOCUS groundwater modelling (vapour pressure, Henry's law constant, water solubility). Consequently, in the modelling the following non-reliable data were used: vapour pressure 0.48 mPa (20°C), water solubility 100 mg/L. No calculation for the unknown

metabolite 1 (peak 5) was available for the peer review. A data gap was therefore agreed by the Member State experts.

Parent dodemorph was calculated to be present in leachate leaving the top 1m soil layer at 80th percentile annual average concentrations of <0.0001µg/L.

4.3. FATE AND BEHAVIOUR IN AIR

No reliable vapour pressure or water solubility data for dodemorph were available. Based on the results of a laboratory closed chamber experiment where a dodemorph acetate EC formulation was applied to bare soil it was measured that 2.94% of the applied dodemorph acetate was lost to the air compartment in 24 hours. However, this value was considered as an underestimation of the possible total volatilisation as the rate of the volatilisation at the end of the study (24 hours) was still as high as at the start of the experiment. Calculations using the method of Atkinson (using the software APOWIN vs.1.90) for indirect photo oxidation in the atmosphere through reaction with hydroxyl radicals resulted in an atmospheric half life estimated at about 1.6 hours (assuming an atmospheric hydroxyl radical concentration of $1.5x10^6$ radicals cm^{-3}) indicating that the dodemorph that will volatilise would be unlikely to be subject to long range atmospheric transport.

5. Ecotoxicology

Dodemorph was discussed at the PRAPeR experts' meeting for ecotoxicology (PRAPeR 48 subgroup 1) during May 2008.

The formulation "Mehltaumittel", with dodemorph acetate as active substance, is applied for use in roses in glasshouses in Northern and Southern Europe as a fungicide against powdery mildew. It is sprayed with a dose of 2 kg a.s./ha and a maximum frequency of 10 (interval 7 – 10 days).

The risk assessment was conducted for the use in a permanent glasshouse where exposure of wildlife is considered negligible. Member states where non-permanent structures are used should take this into consideration in their national registration.

The subject for the present evaluation is dodemorph. However, all toxicity tests have been performed with dodemorph acetate. In the aquatic and terrestrial test organisms dodemorph acetate may readily dissociate into dodemorph and acetate. Experts from the meeting on mammalian toxicology and experts from PRAPeR 48 agreed that the data obtained with dodemorph acetate could be used for the assessment of dodemorph.

The two isomer forms of dodemorph were considered to have different degradation profiles and hence different exposure profiles in the environment (see section 4.1). No ecotoxicological data were provided by the applicant to address the potential different risk of the two isomers. At PRAPeR 48 a data gap was agreed for the applicant to address the influence of the two isomers on the risk assessment of dodemorph.

5.1. RISK TO TERRESTRIAL VERTEBRATES

Whereas there are no studies available on the acute, short-term and chronic toxicity of dodemorph to birds, the toxicity to mammals is considered low (LD50 = 4510 mg dodemorph/kg, NOEC = 21 mg dodemorph/kg bw/day). Although it is expected that dodemorph does not reach the surrounding environment in significant amounts, emission to surface water is considered possible. Birds and mammals may therefore be exposed by drinking surface water or by consuming fish. A risk assessment was conducted by the RMS for drinking water exposure and fish-eating birds and mammals based on the PECsw of the Dutch model and the long-term endpoint from the reproductive studies. To have an estimation of long-term toxicity associated with dodemorph acetate the reproductive toxicity to birds of several substances with the same mode of action as dodemorph acetate was compiled by the applicant. The meeting of experts (PRAPeR 48 subgroup 1) agreed to the approach, but for indoor use only. In case of outdoor use, data on reproductive effect to birds should be required for dodemorph. The resulting TERs of 87 and 313 respectively for birds and mammals indicate a low risk from secondary poisoning. In addition, the risk was considered to be low from drinking water exposure to birds and mammals (TER > 1000), based on the worst case long-term reproductive NOEC endpoints.

5.2. RISK TO AQUATIC ORGANISMS

Based on the data available dodemorph was considered to be toxic to aquatic organisms in acute studies and very toxic in the chronic studies. The lowest endpoint was observed for fish (acute LC_{50} = 1.23 mg dodemorph/L). The chronic toxicity to fish was a 28 days juvenile growth test. The observed overall NOEC was 0.1 mg dodemorph/L. The 21-d NOEC for daphnids was 0.08 mg dodemorph/L. The risk assessment was based on the Dutch model for glasshouse uses (0.1% entry into surface water). Exposure was based on FOCUSsw calculations. The acute TERs were well above the trigger of 100 indicating a low acute risk to aquatic organisms. The long-term TER for fish was calculated as 145. The TER for daphnids was 116.

Given a $logP_{ow}$ of 4.6 at standard conditions, the BCF of dodemorph was found to be in the range of 583-746 based on whole fish in a fish bio-concentration study. Concentration during the depuration phase was not determined. The risk from bioaccumulation was considered to be addressed with the fish early life stage study, where a TER value >> 10 indicated a low risk. This was in line with the risk assessment of secondary poisoning of birds and mammals (see above).

No major metabolites were detected in the water/sediment system.

5.3. RISK TO BEES

The lowest acute oral LD_{50} of 73.4 µg dodemorph/bee was for the formulation whereas the lowest contact LD_{50} of >76.6 µg dodemorph/bee was for the active substance. The hazard quotient was <21.5 and 22.5 for the contact and oral toxicity respectively, which indicated that a high risk to bees is not expected.

5.4. RISK TO OTHER ARTHROPOD SPECIES

LR_{50} values of 204.8 and 291 g dodemorph/ha were derived in laboratory dose-response studies with *Aphidius rhopalosiphi* and *Typhlodromus pyri* respectively. The default MAF was extrapolated from 3.5 for eight applications to 3.6 for ten applications. In-field hazard quotients of 29 and 20.4 for *A. rhopalosiphi* and *T. pyri* respectively, indicated a risk to non-target arthropods. This is of particular importance as various non-target arthropods may be used in integrated pest management in greenhouses. This issue should be dealt with by the Member States. Refined risk assessment may be required. However, there are no data submitted to perform such refined risk assessment.

Off-field assessment is not required as dodemorph is only to be used in greenhouses.

5.5. RISK TO EARTHWORMS

The toxicity of technical and formulated dodemorph acetate was tested with earthworms. The acute LC_{50} was >330 mg dodemorph/kg soil (corrected for logPow >2: $LC_{50\ corr}$ = >165 mg dodemorph/kg soil). The chronic NOEC based on reproductive effects was at the concentrations of 103 mg dodemorph/kg soil (corrected for logPow >2: $NOEC_{corr}$ = 51.5 mg dodemorph/kg soil). Although soil exposure from the proposed glasshouse use is expected to be negligible, a risk assessment for earthworms has been conducted for completeness. The risk assessment for earthworms was recalculated by EFSA after the peer-review, based on the highest initial PECsoil form multiple application of 8.57 mg dodemorph/kg resulting from application to roses and agreed by the meeting of fate experts. The TER values for the acute and long-term risk assessment were >19.3 and 6 respectively, indicating a low risk for earthworms.

5.6. RISK TO OTHER SOIL NON-TARGET MACRO-ORGANISMS

No risk assessment was conducted since exposure of naturally occurring populations of soil non-target macro-organisms is considered negligible.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

No effects of >25% on soil respiration and nitrification were observed at rates of 5 and 50 mg dodemorph/kg dw soil respectively. Based on the expected low levels of soil exposure, the risk to soil non-target micro-organism was considered to be low.

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

No studies have been submitted addressing the potential effects to non-target organisms (flora and fauna). Exposure of non-target plants in the vicinity of glasshouses is considered to be low and hence the risk is assumed to be low for the representative uses.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

An EC50 of 74.5 mg dodemorph/L was derived from an activated sludge respiration study. If remaining spray solution is discharged to a STP, it is expected that the maximum concentration of dodemorph in the spray solution of 824 mg dodemorph/L will be diluted due to mixing with other wastewater sources. Therefore, a risk to micro-organisms in the STP is not expected.

6. Residue definitions

Soil

Definition for risk assessment: dodemorph

Definition for monitoring: dodemorph

Water

Ground water

Definition for exposure assessment: dodemorph, unknown minor non-transient metabolite

Definition for monitoring: dodemorph (provisional), pending on the final assessment for the unknown minor non-transient metabolite

Surface water

Definition for risk assessment:

surface water: dodemorph

sediment: dodemorph

Definition for monitoring: dodemorph

Air

Definition for risk assessment: dodemorph

Definitions for monitoring: dodemorph

Food of plant origin

Definition for risk assessment: none proposed; no representative use on crops intended for consumption

Definition for monitoring: none proposed; no representative use on crops intended for consumption

Food of animal origin

Definition for risk assessment: none proposed; no representative use on crops intended for consumption

Definition for monitoring: none proposed; no representative use on crops intended for consumption

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

Soil

Compounds (name and/or code)	Persistence	Ecotoxicology
Dodemorph	Moderate to high persistence Single first order DT_{50} 24-125 days (20°C, pF 2.5 soil moisture)	Low risk to earthworms and non-target soil micro-organisms. Risk to non-target soil macro-organisms considered negligible for glass house use.

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 relevance	Ecotoxicological activity
Dodemorph	Immobile $K_{f}oc$ 5300-49000 mL/g	No	Yes	Yes	Yes
Unknown minor non-transient metabolite	No information	No information	No information	No information	No information

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Dodemorph	Low risk to aquatic organisms

Air

Compound (name and/or code)	Toxicology
Dodemorph	**Dodemorph is proposed to be classified as Xi; R37 "Irritant to the respiratory system" based on its corrosive properties**

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

- New 5 batch data with supporting methods and validation (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- Water solubility at pH 5 and 7 (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- Vapour pressure (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- Henry's law constant (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- Surface tension at 25ºC of the neat formulation (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- Surface water method with an LOQ of 40 µg/L for each isomer (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- Ground and drinking water method with an LOQ of 0.05 µg/L for each isomer (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts May 2008, data have already been submitted and are evaluated in addendum 1 to Vol. 3 but they have not been peer reviewed, refer to chapter 1)
- Identification of unknown minor non-transient soil metabolite (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts May 2008, date of submission unknown, refer to chapter 4.1.1)
- An assessment of the potential contamination of groundwater by unknown minor non-transient soil metabolite (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts May 2008, date of submission unknown, refer to chapter 4.2.2)
- An assessment of the effects of the different exposure profile of the *cis*- and *trans*-isomer forms of dodemorph is required (relevant for all uses evaluated, data gap identified by PRAPeR 48 subgroup 1, date of submission unknown, refer to chapter 5).

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

This conclusion was reached on the basis of the evaluation of the representative uses as a fungicide on roses under permanent protection. Full details of the GAP can be found in the attached list of end points.

The representative formulated product for the evaluation was "Mehltaumittel", an emulsifiable concentrate (EC). In the formulation the active substance is present as the acetate variant.

Methods for products of plant and animal origin are not required for the representative use on roses. Adequate methods are available to monitor the sum of *cis* and *trans* dodemorph in soil and air. Methods for water have been identified as a data gap.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that at least some of the quality control measurements of the plant protection product are possible. Several data gaps have been identified. Namely new 5 batch data, water solubility, vapour pressure, Henry's law constant and surface tension.

Dodemorph is absorbed rapidly to an extent of at least 40%. It is distributed widely and uniformly. It has no potential for accumulation. It is excreted rapidly and practically completely and is extensively metabolised. It is of low acute toxicity by the oral and dermal route. Based on its irritant, corrosive and sensitising properties a classification as **Xi; R37 "Irritant to the respiratory system", C; R34 "Corrosive; Causes burns"** (Xi; R41 "Irritant; Risk of serious damage to eyes" is implicit) and **Xi; R43 "Irritant; May cause skin sensitisation"** was proposed. Short term studies were carried out with rats, dogs and rabbits. The liver was the main target of toxicity. The lowest NOAEL of 8.2 mg/kg bw/d was based on vomiting, salivation, changes in faecal excretion and liver effects. Dodemorph is not genotoxic. A 2-year rat and an 18-month mouse study have been reported. Critical effects observed were decreased bodyweight gain (both species) and liver effects (rat) while no increased tumour incidences could be observed in these investigations. Dodemorph did not cause effects on reproduction but induced developmental effects in rabbits (open eye, irregularly shapen sternebrae) based on which a classification as **Xn; Repr. Cat. 3 R63 "Harmful; Possible risk of harm to the unborn child"** was proposed. The acceptable daily intake (ADI) was set at 0.082 mg/kg bw/d, the acceptable operator exposure level (AOEL) and the acute reference dose (ARfD) were set at 0.033 mg/kg bw/d and at 0.33 mg/kg bw respectively. Operator exposure amounts to 88% of the AOEL when personal protective equipment (gloves, coverall, gas mask) is worn. Worker exposure when PPE (gloves, coverall, gas mask) is used amounts to 45% of the systemic AOEL of 0.033 mg/kg bw/d. Bystander exposure is not anticipated based on the use of dodemorph in greenhouses.

No data were submitted to study and assess the residue behaviour of dodemorph in plants and livestock animals in order to define the relevant residues for dietary consumer risk assessment. The representative use of dodemorph on roses is normally not expected to result in any dietary exposure to humans or livestock animals. A situation where treated rose petals are used for human consumption was neither assessed nor considered. Under conditions excluding any potential consumer exposure to dodemorph residues, there will be no dietary consumer risk related to the notified representative use.

The information available on the fate and behaviour in the environment is sufficient to carry out an appropriate environmental exposure assessment for the parent dodemorph acetate at the EU level. For the applied for intended uses, the potential for groundwater exposure by dodemorph above the parametric drinking water limit of 0.1 µg/L, is low. However no calculation for the unknown minor non-transient metabolite was available for peer review.

Although it is expected that dodemorph does not reach the surrounding environment in significant amounts, emission to surface water is considered possible. A risk assessment to birds and mammals was provided for exposure from contaminated drinking water and for consumption of contaminated fish. A PECsw value was based on the Dutch model. A long-term reproductive endpoint for birds was estimated by using the lower endpoint from reproductive effect studies on birds for related substances (structure activity relationship). The risk assessment indicated a low risk to birds and mammals exposed to dodemorph through drinking water and fish. In the aquatic environment dodemorph was most toxic to fish and daphnia. It was considered to be toxic to aquatic organisms on an acute scale and very toxic on a chronic scale. Dodemorph is lipophilic (logPow = 4.6) and the bioaccumulation factor was estimated in the range of 583-746 based on whole fish. Given a TER >> 10 based on the fish early life stage endpoint the risk from bioaccumulation was considered to be low. Whereas the risk to bees was considered to be low, assessment of non-target arthropods (NTA) indicated a risk. This is of particular importance as various non-target arthropods may be used in integrated pest management in greenhouses. The risk to earthworms was considered to be low as was the risk to non-target soil micro-organisms and micro-organisms in sewage treatment plant. No data were submitted or required for non-target macro soil organisms. Risk to non-target plants was considered to be negligible for glass house use and no data were submitted by the applicant.

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

- Personal protective equipment (gloves, coverall and gas mask) is needed for operators and re-entry workers.

CRITICAL AREAS OF CONCERN

- The specification can not be finalised.
- Method of analysis for drinking water is not validated.
- The consumer risk assessment is only based on the premise of a ‘no dietary exposure situation’ for humans and livestock animals from the notified representative use. No data were submitted to study and assess the residue behaviour of dodemorph in plants and livestock animals in order to define the relevant residues in dietary consumer risk assessment.
- The potential groundwater contamination by the unknown minor non-transient metabolite in soil can not be finalised.

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

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

Chapter 2.1 Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Dodemorph (ISO published) Unless stated otherwise, the following data relate to the variant dodemorph acetate
Function (e.g. fungicide)	Fungicide

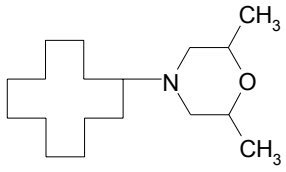
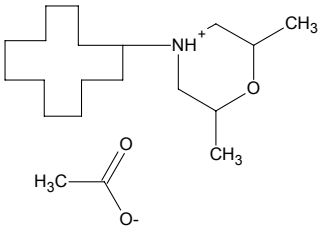
Rapporteur Member State	The Netherlands
Co-rapporteur Member State	-

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	Dodemorph: cis/trans-[4-cyclododecyl]-2,6-dimethylmorpholine Dodemorph acetate: cis/trans-4-[cyclododecyl]-2,6-dimethylmorpholine actate
Chemical name (CA) ‡	Dodemorph: 4-cyclododecyl-2,6-dimethylmorpholine Dodemorph acetate: 4-cyclododecyl-2,6-dimethylmorpholine acetate
CIPAC No ‡	Dodemorph: 300 Dodemorph acetate: 300.401
CAS No ‡	Dodemorph: 1593-77-7 Dodemorph acetate: 31717-87-0
EC No (EINECS or ELINCS) ‡	Dodemorph: 216-474-9 Dodemorph acetate: 250-778-2
FAO Specification (including year of publication) ‡	None
Minimum purity of the active substance as manufactured ‡	950 g/kg for the variant dodemorph acetate as technical solid and 544 - 594 g/kg for the technical concentrate (TK) The active substance is a mixture of cis and trans isomers ranging from a ratio of minimally 50:50 cis:trans and maximally 60:40 cis:trans

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

Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	No relevant impurities
Molecular formula ‡	Dodemorph: $C_{18}H_{35}NO$ Dodemorph acetate: $C_{18}H_{35}NO.C_2H_4O_2$ or $C_{20}H_{39}NO_3$

Molecular mass ‡	Dodemorph: 281.5 Dodemorph acetate: 341.5
Structural formula ‡	Dodemorph:  Dodemorph acetate: 

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	35-48 ºC (98.2%)
Boiling point (state purity) ‡	Determination not possible due to decomposition before boiling
Temperature of decomposition (state purity)	158 °C (loss of acetic acid; 98.2%)
Appearance (state purity) ‡	Pure: non-homogeneous solid at 5 ºC and a viscous liquid at 40 ºC, yellow with an acid aromatic or lemon piquant odour. At ambient temperature the pure active substance is a yellow biphasic liquid/solid compound. (98.2%) Technical: Technical concentrate: yellow to orange, paste-like, non-homogeneous suspension or viscous liquid with aromatic odour (ca 92%) Technical concentrate: clear homogeneous liquid with aromatic odour
Vapour pressure (state temperature, state purity) ‡	OPEN

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

Henry's law constant ‡	OPEN
Solubility in water (state temperature, state purity and pH) ‡	OPEN for measurement at pH 5 and 7. 2.29 mg/L at 25°C (pH 9) (99.6%)
Solubility in organic solvents ‡ (state temperature, state purity)	Solubility at 25 °C in g/L (98.2%) n-heptane: >1000 g/L toluene: >1000 g/L dichloromethane: >1000 g/L methanol: >1000 g/L acetone: >1000 g/L ethyl acetate: >1000 g/L acetonitrile 66.07 g/L
Surface tension ‡ (state concentration and temperature, state purity)	55.1 mN/m at 20 °C (90 % saturated solution)(98.2%)
Partition co-efficient ‡ (state temperature, pH and purity)	The logK_{ow} of the un-protonated dodemorph is 4.6. (98.2%)
Dissociation constant (state purity) ‡	pK_a = 8.5 (98.2%)
UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	Ambient temperature, 9.55 mg/L in methanol, cell path 1 cm pH of the solution not stated (pure, 99.0% w/w, enriched in cis-isomer, ratio 8.2:1 for cis:trans). **Acidic** No data submitted, not required. **Neutral (methanol)** λ(max) = 206 nm (ε = 1008 L.mol.cm) no absorbance expected in the range 400-750 nm. No absorbance expected for trans isomer. **Alkaline** No data submitted, not required.
Flammability ‡ (state purity)	Auto-ignition temperature 264 °C (98.2%) Flashpoint 73.8 °C (98.2%)
Explosive properties ‡ (state purity)	No explosive properties (98.2%)
Oxidising properties ‡ (state purity)	No oxidising properties (98.2%)

Classification and proposed labelling (Annex IIA, point 10)

	RMS/peer review proposal
Active substance	None

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

Summary of representative uses evaluated (dodemorph acetate)*

Crop and/or situation (a)	Member State or Country	Product name	F, G or I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application per treatment			PHI (days)	Remarks (m)
					type (d-f)	conc of as (i)	method kind (f-h)	growth stage & season (j)	number min-max (k)	interval between applications (min-max)	kg as/hL; min-max	water L/ha; min-max	kg as/ha; min-max		
roses	Northern and Southern Europe	Mehltaumittel®	G	powdery mildew, *Sphaerotheca pannosa*	EC	385 g/L	spray (n)	not stated	1-10	7-10	0.1	2000	2	-	

* For uses where the column "Remarks" is marked in grey further consideration is necessary.
Uses should be crossed out when the notifier no longer supports this use(s).
(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval
n. Roses are mostly sprayed manually using handheld knapsack equipment and spray lances.
o. The number of applications should not exceed 2 x 5 sprays per season (total of 10 sprays).

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

Chapter 2.2: Methods of Analysis

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

Technical as (analytical technique)	GC-FID (method A). GC-FID method CP 142/1
Impurities in technical as (analytical technique)	GC-FID (**additional validation required**)
Plant protection product (analytical technique)	GC-FID (GF-A594)

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin	Not applicable. Dodemorph acetate is not intended for use on food or feed crops.
Food of animal origin	Not applicable. Dodemorph acetate is not intended for use on feed crops.
Soil	Sum of cis- and trans-dodemorph
Water surface, drinking/ground	Sum of cis- and trans-dodemorph
Air	Sum of cis- and trans-dodemorph

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	Not applicable. Dodemorph acetate is not intended for use on edible or feedible crops.
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Not applicable. Dodemorph acetate is not intended for use on feedible crops.
Soil (analytical technique and LOQ)	**Cis- and trans-dodemorph** LC-MS/MS. LOQ 0.05 mg/kg for each isomer. **Cis- and trans-dodemorph** GC-NPD LOQ 0.04 mg/kg for sum of isomers.

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

Water (analytical technique and LOQ)	**Cis- and trans-dodemorph** **OPEN**
Air (analytical technique and LOQ)	**Cis- and trans-dodemorph** GC-NPD. LOQ 0.15 µg/m^3.
Body fluids and tissues (analytical technique and LOQ)	Not applicable (not toxic)

Classification and proposed labelling (Annex IIA, point 10)

	RMS/peer review proposal
Active substance	none

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

Chapter 2.3: Impact on Human and Animal Health

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

Rate and extent of oral absorption ‡	Extent of absorption: ca 40% based on urine (ca 25%), exhaled air (ca 10%) and body (ca 4%) within 24h at 10 mg/kg bw. Plasma peak concentration after 6-8h at 10 mg/kg bw
Distribution ‡	Uniformly distributed, slightly increased levels in the liver
Potential for accumulation ‡	No evidence for accumulation
Rate and extent of excretion ‡	Rapid and extensive (>90 % within 24 h, at low dose (10 mg/kg bw). Slower at high dose (1000 mg/kg bw). Excretion in urine (40%) and in feces (60%, possibly partly via bile).
Metabolism in animals ‡	Extensively metabolised. No dodemorph acetate is excreted in urine, low percentage of dodemorph acetate excreted in feces. Metabolites are very polar. No metabolites have been identified.
Toxicologically relevant compounds ‡ (animals and plants)	Dodemorph
Toxicologically relevant compounds ‡ (environment)	Dodemorph

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	>4100 mg/kg bw (dodemorph acetate >4920 mg/kg bw)	
Rat LD_{50} dermal ‡	>1640 mg/kg bw (dodemorph acetate > 2000 mg/kg bw)	
Rat LC_{50} inhalation ‡	No data, not necessary. Corrosive compound	**R37**
Skin irritation ‡	Corrosive	**C, R34**
Eye irritation ‡	Corrosive	**C, R34**
Skin sensitisation ‡	Sensitizing (GPMT)	**R43**

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

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Body weight, decreased body weight gain, liver (bile duct) toxicity	
Relevant oral NOAEL ‡	1-year, dog: 8.2 mg/kg bw/day (dodemorph acetate 10 mg/kg bw/day 90-day, rat: 65 mg/kg bw/day (dodemorph acetate 80 mg/kg bw/day	
Relevant dermal NOAEL ‡	21-day, rabbit: 49 mg/kg bw/day (dodemorph acetate 60 mg/kg bw/day, highest dose tested)	
Relevant inhalation NOAEL ‡	No data - not required	

Genotoxicity ‡ (Annex IIA, point 5.4)

Not genotoxic	

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

Target/critical effect ‡	Decreased body weight gain (rat and mouse), liver changes (rat)	
Relevant NOAEL ‡	18-month, mouse: 37 mg/kg bw/day (dodemorph acetate 45 mg/kg bw/day) 2-year, rat: 45 mg/kg bw/day (dodemorph acetate 55 mg/kg bw/day)	
Carcinogenicity ‡	Not carcinogenic	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	No reproduction toxicity. Decreased pup weight, viability and retarded physical development at parentally toxic doses (reduced body weight gain, food consumption, liver toxicity)	
Relevant parental NOAEL ‡	52 mg/kg bw/day (dodemorph acetate 64 mg/kg bw/day)	

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

Relevant reproductive NOAEL ‡	159 mg/kg bw/day (dodemorph acetate 194 mg/kg bw/day), highest dose tested	
Relevant offspring NOAEL ‡	52 mg/kg bw/day (dodemorph acetate 64 mg/kg bw/day)	

Developmental toxicity

Developmental target / critical effect ‡	Rabbit: Malformations (open eye; variation (irregularly shaped sternebra), at maternal NOAEL Rat: decreased body weight; skeletal variations at maternal toxic dose	**R63**
Relevant maternal NOAEL ‡	Rabbit: 98 mg/kg bw/day (dodemorph acetate 120 mg/kg bw/day), highest dose tested Rat: 25 mg/kg bw/day (dodemorph acetate 30 mg/kg bw/day)	
Relevant developmental NOAEL ‡	Rabbit: 33 mg/kg bw/day (dodemorph acetate 40 mg/kg bw/day) Rat: 82 mg/kg bw/day (dodemorph acetate 100 mg/kg bw/day)	

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No evidence for neurotoxicity	
Repeated neurotoxicity ‡	No evidence for neurotoxicity	
Delayed neurotoxicity ‡		

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	-
Studies performed on metabolites or impurities ‡	Studies on impurities revealed no evidence for genotoxic potential

Medical data ‡ (Annex IIA, point 5.9)

No indication of adverse effects in plant production personnel

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

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.082 mg/kg bw/day (dodemorph acetate: 0.1 mg/kg bw/day)	1 year dog	100
AOEL ‡	0.033 mg/kg bw/day (dodemorph acetate: 0.04 mg/kg bw/day)	1 year dog	100 and 40% oral absorption
ARfD ‡	0.33 mg/kg bw (dodemorph acetate: 0.4 mg/kg bw)	developmental study rabbit	100

Dermal absorption ‡ (Annex IIIA, point 7.3)

Formulation EC BAS 238 14 F	Concentrate: 2.7% Spray dilution: 20% *In vivo* rat and *in vitro* rat/human skin study with Mehltaumittel (BAS 238 13F and BAS 238 14F, EC 385 g/L)

Exposure scenarios (Annex IIIA, point 7.2)

Operator	Greenhouse: Manual spraying on roses (Dutch 90th model) Without PPE: 879% of AOEL PPE: 88% of AOEL
Workers	Greenhouse: Re-entry in roses (Dutch field study) Without PPE: ≤452% of AOEL PPE: ≤45% of AOEL
Bystanders	Exposure considered to be negligible

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

	RMS/peer review proposal
Substance classified (dodemorph)	**C** "Corrosive" **R34** "Causes burns" **R37** "Irritating to respiratory system" **R43** "May cause sensitization by skin contact" **R63** "Possible risk of harm to the unborn child"

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

Chapter 2.4: Residues

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

Plant groups covered	Not applicable. Dodemorph is not intended for use on edible or feedible crops.
Rotational crops	Not applicable. Dodemorph is not intended for use on edible or feedible crops.
Metabolism in rotational crops similar to metabolism in primary crops?	-
Processed commodities	Not applicable. Dodemorph is not intended for use on edible or feedible crops.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	-
Plant residue definition for monitoring	-
Plant residue definition for risk assessment	-
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	Not applicable. Dodemorph is not intended for use on edible or feedible crops.
Time needed to reach a plateau concentration in milk and eggs	-
Animal residue definition for monitoring	-
Animal residue definition for risk assessment	-
Conversion factor (monitoring to risk assessment)	-
Metabolism in rat and ruminant similar (yes/no)	-
Fat soluble residue: (yes/no)	-

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

Not applicable. Dodemorph is not intended for use on edible or feedible crops.

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

Not applicable. Dodemorph is not intended for use on edible or feedible crops.

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

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)	Not applicable	Not applicable	Not applicable
Potential for accumulation (yes/no):	Not applicable	Not applicable	Not applicable
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	Not applicable	Not applicable	Not applicable
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices: Mean (max) mg/kg		
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-		
Eggs		-	

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

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

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Not applicable. Dodemorph acetate is not intended for use on edible or feedible crops						

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

Appendix 1 – list of endpoints

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

ADI	-
TMDI (% ADI) according to WHO European diet	-
TMDI (% ADI) according to national (to be specified) diets	-
IEDI (WHO European Diet) (% ADI)	-
NEDI (specify diet) (% ADI)	-
Factors included in IEDI and NEDI	-
ARfD	-
IESTI (% ARfD)	-
NESTI (% ARfD) according to national (to be specified) large portion consumption data	-
Factors included in IESTI and NESTI	-

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

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor	Yield factor	
-	-	-	-	-
-	-	-	-	-
-	-	-	-	-

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

None	

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

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

Appendix 1 – list of endpoints

Chapter 2.5: Fate and Behaviour in the Environment

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

Mineralization after 100 days	17.1 and 22.7% after 93 and 125 days [4-cyclododecyl-2,6-dimethyl (3,5-^{14}C) morpholine acetate] (n = 1) 29.7% AR for sandy loam and 35.9% AR for silt loam after 102 days [4-cyclododecyl-2,6-dimethylmorpholine-(morpholine-2,6-^{14}C-) (mixture of cis/trans isomers)] (n = 2) Anaerobic conditions: 1.5% after 61 days (n = 1)
Non-extractable residues after 100 days	21.9 % after 93 and 125 d, [4-cyclododecyl-2,6-dimethyl (3,5-^{14}C) morpholine acetate] (n = 1) 43.4% AR and 42.9% AR for sandy loam and silt loam, respectively, after 102 days [4-cyclododecyl-2,6-dimethylmorpholine-(morpholine-2,6-^{14}C-) (mixture of cis/trans isomers)] (n = 2) Anaerobic conditions: 7.8 % after 61 d (n = 1)
Metabolites requiring further consideration - name and/or code, % of applied (range and maximum)	Unknown Metabolite 1 (peak 5): 6.5% after 369 d (increasing at study termination)

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

Anaerobic degradation	No fully anaerobic studies submitted; too few data points for reliable conclusions on this point. Bound residues:7.8% during the anaerobic incubation (61 days) Mineralization: 1.5% during the anaerobic incubation (61 days)
Photolysis	DT_{50}: 2.6 days, equivalent to 2.4 summer sunlight days at 43 °N No identification for isomer 1 and isomer 2 could be obtained from the original study report.

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

Appendix 1 – list of endpoints

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

Laboratory studies

Dodemorph	Aerobic conditions								
Soil type	X	pH	T (°C)	pF	DT_{50} (d)	DT_{90} (d)[1]	DT_{50} (d) 20°C	St. (r^2)	Method of calculation
Sandy loam		8	24-26	2.5	83	274	125[2]	0.93	SFO
Sandy loam		6.9	20-22	2.5	27	89	29[3]	0.92	SFO
Silt loam		6.4	20-22	2.5	30	99	32[3]	0.93	SFO
Loamy sand		5.6	20	2.5	24	79	24	0.84	SFO
Geometric mean/median					36/28.5	118/94	41/30.5		

1: calculated as 3.3 x DT_{50}
2: calculated with Arrhenius equation using 25 °C
3: calculated with Arrhenius equation using 21 °C

Field studies‡

No field studies submitted

pH dependence ‡ (yes / no) (if yes type of dependence)	No
Soil accumulation and plateau concentration ‡	No data submitted, no data required

Soil adsorption/desorption (Annex IIA, point 7.1.2)

dodemorph acetate							
Soil Type	OC (%)	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Sandy loam	1.0	8.0			54	5500	0.7416
Clay loam	2.9	7.0			155	5300	0.8394
Silt loam	0.6	7.0			312	49000	0.9452
Silty clay loam	0.8	7.8			336	41000	0.8937
Arithmetic mean/median					214-234	25200/23250	0.8550
pH dependence, Yes or No			No				

Remark: for FOCUS PECgw calculations Koc 1450 mL/g (estimated Koc for the acidic sand soil) was used as worst case

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

Column leaching ‡	Dodemorph Elution (mm): 200 mm

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

Appendix 1 – list of endpoints

	Time period (d): 2 d
	Leachate: < LOQ (0.02 mg/L) dodemorph in leachate
Aged residues leaching ‡	Dodemorph Aged for (d): 30 d Time period (d): 32 d Elution (mm): 327 and 383 mm
	Analysis of soil residues post ageing (soil residues pre-leaching): 82 and 84.0% of total radioactivity retained in top 6 cm
	Leachate: 0.34 % total radioactivity in leachate
Lysimeter/field leaching studies ‡	No studies submitted

PEC (soil) (Annex IIIA, point 9.1.3)

Application data	Crop: roses, glasshouse applications Depth of soil layer: 5 cm Soil bulk density: 1500 kg/m^3 % plant interception: 50 % Number of applications: 10 Interval (d): 7 d Application rate(s): 2 kg dodemorph acetate/ha equivalent to 1.649 kg dodemorph/ha
Dodemorph Method of calculation	DT50 (d): 83 days Kinetics: SFO

PEC$_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		1.0991		8.570	
Short term	24h			8.499	8.534
	2d			8.428	8.499
	4d			8.289	8.429
Long term	7d			8.084	8.324
	28d			6.783	7.642
	50d			5.645	7.006
	100d			3.718	5.810
Plateau concentration		x mg/kg after n yr			

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

Appendix 1 – list of endpoints

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

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	dodemorph acetate pH 5, 7 and 9: > 45 d at 20 °C
Photolytic degradation of active substance and metabolites above 10 % ‡	DT_{50} : 3.6 and 1.6 summer sunlight days at 43 °N at pH 7 and 9, respectively dodemorph acetate: 96.1 % AR (455 h at pH 5), 45.2 % AR (99 h at pH 7), 24.0 % AR (72 h at pH 9) *Cis* -isomer: 68.8, 42.5 and 24.0 % AR (455, 99 and 72 h at pH 5, 7 and 9, respectively) *Trans*-isomer: 27.3 % AR (455 h at pH 5) Free base isomers: 17.4 % and 11.8 % (72 h at pH 9) Protonised dodemorph 30.5 % and 33.1 % AR (72 h at pH 7 and 9, respectively)
Quantum yield of direct phototransformation in water at Σ > 290 nm	Not assessed
Readily biodegradable ‡ (yes/no)	No study submitted

Degradation in water / sediment

Dodemorph	Distribution: max. in water 67.4 - 74.5% after 0 d. Max. in sediment 43.1 - 56.1% after 14 d												
Water/ sediment system	pH water	pH sed	T (°C)	DT_{50}	DT_{90} [1]	St. (r^2)	DT_{50}-	DT_{90} [1]	St. (r^2)	DT_{50}	DT_{90} [1]	St. (r^2)	Method of calculation
				whole sys			water			sediment			
silty clay loam	8.25	8.1	20 ± 2	-[3]	-	-	0.5[2]	1.65	0.99	281	927	0.75	SFO
silt loam	8.25	7.4	20 ± 2	53	175	0.70	1.5[2]	4.95	0.98	126	416	0.80	SFO
median				53	175		1.0	3.3		204	672		

1: calculated as 3.3 x DT_{50}
2: dissipation including sorption
3: no reliable whole system DT_{50} could be estimated for the silty clay loam system with the kinetic evaluation tools available at the time the dossier was composed

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

Appendix 1 – list of endpoints

Mineralization and non extractable residues					
Water / sediment system	pH water phase	pH sed	Mineralization x % after n d. (end of the study).	Non-extractable residues in sed. Max x % after n d	Non-extractable residues in sed. Max x % after n d (end of the study)
silty clay loam	8.25	8.1	15.4 (103 d)	30.4 (28 d)	27.5 (103 d)
silt loam	8.25	7.4	23.2 (103 d)	39.6 (68 d)	27.3 (103 d)

Metabolites	No major metabolites

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

dodemorph Parameters used in FOCUSsw step 2	Version control no. of FOCUS calculator: 1.1 Molecular weight (g/mol): 281.5 Water solubility (mg/L): 100 K_{OC}(L/kg): 25200 DT_{50} soil (d): 41 days (Lab SFO) DT_{50} water/sediment system (d): 53[1] DT_{50} water (d): 53[1] DT_{50} sediment (d): 53[1] Crop interception (%): no interception
Parameters used in FOCUSsw step 3 (if performed)	

[1] the DT50 (whole system) used for both water and sediment phase is based on one W/S system only

Application data		Crop: roses, glasshouse applications Crop interception: 0 % Number of applications: 10 Interval (d): 7 Application rate(s): 26.71 g dodemorph/ha (rate corrected to obtain total emission to water body of 0.1 % of original application rate 1649 g dodemorph/ha) Application window: March-May			
FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern and Northern EU	0 h	0.69		25.95	
	24 h	0.33	0.51	25.88	25.91
	2 d	0.21	0.39	25.63	25.83
	4 d	0.16	0.28	25.00	25.58
	7 d	0.15	0.23	24.04	25.12

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

Appendix 1 – list of endpoints

Application data		Crop: roses, glasshouse applications Crop interception: 0 % Number of applications: 10 Interval (d): 7 Application rate(s): 26.71 g dodemorph/ha (rate corrected to obtain total emission to water body of 0.1 % of original application rate 1649 g dodemorph/ha) Application window: March-May			
FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	14 d	0.13	0.18	21.94	24.05
	21 d	0.12	0.17	20.02	23.02
	28 d	0.11	0.15	18.27	22.05
	42 d	0.09	0.14	15.21	20.27

PEC (groundwater) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	Modelling using FOCUS model(s), with appropriate FOCUSgw scenarios, according to FOCUS guidance. Model(s) used: PEARL 2.2.2 (release November 2002)
Application data	dodemorph Mean DT_{50lab} 41 d (normalisation to 20 °C with Q10 of 2.2). K_{OC}:1450 mL/g, 1/n: 0.855
Application rate	Roses, glasshouse application, Northern Europe Scenarios (list of names) Chateaudun, Hamburg, Kremsmünster, Jokioinen, Okehampton Crop: winter wheat Application rate: 1649 g/ha. No. of applications: 10 Interval: 7 d Time of application (month or season): start 25/5 Roses, glasshouse application, Southern Europe Scenarios (list of names): Piacenza, Porto, Sevilla, Thiva Crop: winter wheat Application rate: 1649 g/ha. No. of applications: 10 Interval: 7 d Time of application (month or season): start 25/5

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

Appendix 1 – list of endpoints

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

	Scenario	Parent (µg/L)	Metabolite (µg/L)		
Roses, Glass, Northern and Southern Europe	Piacenza	0.0001			
	Porto	0.0001			
	Sevilla	0.0001			
	Thiva	0.0001			
	Chateaudun	0.0001			
	Hamburg	0.0001			
	Kremsmünster	0.0001			
	Jokioinen	0.0001			
	Okehampton	0.0001			

$PEC_{(gw)}$ From lysimeter / field studies

Parent	1st year	2nd year	3rd year
Annual average (µg/L)			

Metabolite X	1st year	2nd year	3rd year
Annual average (µg/L)			

Repeat for as many metabolites as necessary

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

Application rate	Application rate: 1649 g dodemorph/ha. No. of applications: 10 Time of application (month or season):
Direct photolysis in air	No significant photolysis
Quantum yield of direct phototransformation	Not studied
Photochemical oxidative degradation in air	Not studied
Volatilisation	2.94% volatilisation from soil after 1 day
Metabolites	No

PEC_A (air)

Method of calculation	Based on the vapour pressure of 0.48 mPa (20°C), it is considered that volatilisation of dodemorph may occur, but concentrations will generally be low.

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

Appendix 1 – list of endpoints

PEC_A

Maximum concentration	

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).	Soil: dodemorph Surface Water: dodemorph Sediment: dodemorph Groundwater: dodemorph, unknown minor non-transient metabolite Air: dodemorph

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

Soil (indicate location and type of study)	No data provided - none requested
Surface water (indicate location and type of study)	No data provided - none requested
Groundwater (indicate location and type of study)	No data provided - none requested
Air (indicate location and type of study)	No data provided - none requested

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

No readily biodegradable test submitted. Potential candidate to R53

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

Appendix 1 – list of endpoints

Chapter 2.6: Effects on Non-target Species

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

Species	Test substance	Time scale	End point (mg/kg bw/day)	End point (mg/kg feed)
Birds				
	dodemorph	chronic	9.4 (extrapolated from related substances)*	
Mammals				
rat	dodemorph	acute	4100 mg/kg bw	
rabbit	dodemorph	chronic	21	
Additional higher tier studies				

*The extrapolation is agreed on for indoor use only.

Exposure of birds to surface water used as drinking water; Crop and application rate**: roses in glasshouses, Northern and Southern Europe, 10 x 1.649 kg dodemorph/ha**

Crop	Category (e.g. insectivorous bird)	Time-scale	NOEL	PECsurface water (initial) (mg/L)	TER	Annex VI trigger
roses (glasshouses)	small insectivorous birds	acute	9.4	0.00069	>1000	10

Food chain from fish to fish-eating birds

Crop and application rate**: roses in glasshouses, Northern and Southern Europe, 10 x 1.649 kg dodemorph/ha**

Application	NOEL	PECsurface water (initial) (mg/L)	PECfish (mg/kg)	Daily dose birds (mg/kg bw/d)	TER birds
roses (glasshouses)	9.4	0.00069	0.515	0.108	87

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

Appendix 1 – list of endpoints

Exposure of mammals to surface water used as drinking water; Crop and application rate**: roses in glasshouses, Northern and Southern Europe, 10 x 1.649 kg dodemorph/ha**

Crop	Category (e.g. insectivorous bird)	Time-scale	NOEL	PECsurface water (initial) (mg/L)	TER	Annex VI trigger
roses (glasshouses)	small insectivorous mammal	acute	21	0.00069	>1000	10

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

Appendix 1 – list of endpoints

Food chain from fish to fish-eating mammals

Crop and application rate**: roses in glasshouses, Northern and Southern Europe, 10 x 1.649 kg dodemorph/ha**

Application	NOEL	PECsurface water (initial) (mg/L)	PECfish (mg/kg)	Daily dose mammals (mg/kg bw/d)	TER mammals
roses (glasshouses)	21	0.00069	0.515	0.067	313

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

Crop and application rate: **roses in glasshouses, Northern and Southern Europe, 1 x 1.649 kg dodemorph/ha**

FOCUS Step 2

Test substance	Organism	Toxicity end point (µg dodemorph/L)	Time scale	PECi (µg dodemorph/L)	PECtwa	TER	Annex VI Trigger
dodemorph acetate	Fish	1230	Acute	0.55		2236	100
BAS 238 07 F	Fish	2410	Acute	0.55		4382	100
dodemorph acetate	Fish	100	Chronic	0.55		182	10
dodemorph acetate	Aquatic invertebrates	1480	Acute	0.55		2691	100
BAS 238 07 F	Aquatic invertebrates	3120	Acute	0.55		5691	100
dodemorph acetate	Aquatic invertebrates	80	Chronic	0.55		145	10
dodemorph acetate	Algae	250	Chronic	0.55		455	10
BAS 238 07 F	Algae	1550	Chronic	0.55		2818	10

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

Appendix 1 – list of endpoints

Crop and application rate**: roses in glasshouses, Northern and Southern Europe, 10 x 1.649 kg dodemorph/ha**

FOCUS Step 2

Test substance	Organism	Toxicity end point (µg dodemorph/L)	Time scale	PECi (µg dodemorph/L)	PECtwa	TER	Annex VI Trigger
dodemorph acetate	Fish	1230	Acute	0.69		1783	100
BAS 238 07 F	Fish	2410	Acute	0.69		3493	100
dodemorph acetate	Fish	100	Chronic	0.69		145	10
dodemorph acetate	Aquatic invertebrates	1480	Acute	0.69		2145	100
BAS 238 07 F	Aquatic invertebrates	3120	Acute	0.69		4536	100
dodemorph acetate	Aquatic invertebrates	80	Chronic	0.69		116	10
dodemorph acetate	Algae	250	Chronic	0.69		362	10
BAS 238 07 F	Algae	1550	Chronic	0.69		2246	10

Bioconcentration

	Active substance	Metabolite 1	Metabolite 2	Metabolite 3
$logP_{O/W}$	2.5 – 4.6[1]			
Bioconcentration factor (BCF)[2]‡	583 - 746 L/kg[3]			
Annex VI Trigger for the bioconcentration factor	100			
Clearance time (days) (CT_{50})				
(CT_{90})				
Level and nature of residues (%) in organisms after the 14 day depuration phase				

[1] pH 5 - 9
[2] only required if log $P_{O/W}$ >3
[3] based on whole fish

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

Appendix 1 – list of endpoints

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

Test substance	Acute oral toxicity (LD_{50} µg dodemorph/bee)	Acute contact toxicity (LD_{50} µg dodemorph/bee)
dodemorph acetate	>106.3	> 76.6
BAS 238 07 F	73.4	144
Field or semi-field tests: not required		

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

Crop and application rate: **roses, glasshouse 1649 g as/ha**

Test substance	Route	Hazard quotient	Annex VI Trigger
dodemorph acetate	Contact	<21.5	50
BAS 238 07 F	Oral	22.5	50

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

Laboratory tests on inert substrates

Species	Test Substance	Dose (kg dodemorph /ha)	End point	Adverse Effect (%)	Annex VI Trigger
T. pyri	BAS 238 07 F	0.0165	mortality fecundity	16.4 +21.6[1]	2
		0.0415	mortality fecundity	21.8 +23.0[1]	2
		0.1039	mortality fecundity	16.4 +35.1[1]	2
		0.2621	mortality fecundity	47.3 33.8	2
		0.6594	mortality fecundity	87.2 n.r.	2
A. rhopalosiphi	BAS 238 07 F	0.0938	mortality parasitisation	2.6 19.6	2
		0.1595	mortality parasitisation	30.8 16.5	2

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

Appendix 1 – list of endpoints

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

Laboratory tests on inert substrates

Species	Test Substance	Dose (kg dodemorph /ha)	End point	Adverse Effect (%)	Annex VI Trigger
		0.2709	mortality parasitisation	71.8 n.r.	2
		0.4600	mortality parasitisation	97.4 n.r.	2
		0.7818			

[1] positive values for fecundity indicate an increase as compared to the controls.

Crop and application rate

Test substance	Species	Effect (LR_{50} g dodemorph/ha)	HQ in-field	HQ off-field[1]	Trigger
BAS 238 07 F	*Typhlodromus pyri*	291	20.4	not required	2
	Aphidius rhopalosiphi	204.8	29.0	not required	2

Calculated In-field (1st tier)

Crop	F/G	Max. single dose (g dodemorph/ha)	Number of applications	MAF
Roses (N-EU)	G	1649	10	3.6

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

Appendix 1 – list of endpoints

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

Test organism	Test substance	Time scale	End point[1]
Earthworms			
Eisenia fetida	dodemorph acetate	Acute 14 days	LC_{50} > 824 mg dodemorph/kg d.w.soil ($LC_{50,corr}$ > 412 mg dodemorph/kg d.w. soil)
Eisenia fetida	BAS 238 07 F	Acute 14 days	LC_{50} 330 mg dodemorph/kg d.w.soil ($LC_{50,corr}$ 165 g dodemorph/kg d.w. soil)
Eisenia fetida	BAS 238 07 F	Sub-lethal 56 days	NOEC 103 mg dodemorph/kg d.w.soil ($NOEC_{,corr}$ 51.5 mg dodemorph/kg d.w. soil)
Other soil macro-organisms: no data available, additional information required.			
Soil micro-organisms			
Nitrogen mineralisation			soil 1: 10.8% effect at day 7 at 5 and 50 mg dodemorph/kg d.w.soil; effects < 25 % after 28 d soil 2: 36% effect at day 7 at 5 mg dodemorph/kg d.w.soil and 44% effect at day 7 at 50 mg dodemorph/kg d.w.soil (both not significant); effects < 25 % after 28 d
Carbon mineralization			1% effect at 0.63 and 3.13 mg dodemorph/kg d.w. soil
Field studies			
Field studies are not required			

[1] indicate where end point has been corrected due to log Pow >2.0 (e.g. LC_{50corr})

Toxicity/exposure ratios for soil organisms

Crop and application rate

Test organism	Test substance	Time scale	Soil PEC	TER*	Trigger
Earthworms					
Eisenia fetida		Acute	8.57	19.3	10

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

Appendix 1 – list of endpoints

Toxicity/exposure ratios for soil organisms

Crop and application rate

Test organism	Test substance	Time scale	Soil PEC	TER*	Trigger
		Long-term	8.57	6	5
Other soil macro-organisms: no data available, additional information required.					

* Calculated by EFSA after the peer-review process, based on revised initial PECsoil values for multiple application agreed in the meeting of fate experts.

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

Preliminary screening data

No data submitted, no additional information from screening studies required

Laboratory dose response tests

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

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

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

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

Test type/organism	end point
Activated sludge	EC_{50} 74.5 mg dodemorph/L

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

Compartment	
soil	
water	
sediment	
groundwater	

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

Appendix 1 – list of endpoints

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

	RMS/peer review proposal
Active substance	**R50/R53**

	RMS/peer review proposal
Preparation	**R51/R53**

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

Appendix 2 – abbreviations used in the list of endpoints

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
CAS	Chemical Abstract Service
d	day
DAR	draft assessment report
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
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)
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
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection

Appendix 2 – abbreviations used in the list of endpoints

LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OC	organic carbon content
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
SFO	single first-order
STMR	supervised trials median residue
TER	toxicity exposure ratio
TK	technical concentrate
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
yr	year

Appendix 3 – used compound code(s)

APPENDIX 3 – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
dimethylmorpholine	2,6-dimethylmorpholine