

Conclusion regarding the peer review of the pesticide risk assessment of the active substance

Flurprimidol

Finalised: 31 July 2008

SUMMARY

Flurprimidol is one of the 84 substances of the third stage Part B of the review programme covered by Commission Regulation (EC) No 1490/2002¹. 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.

Finland being the designated rapporteur Member State submitted the DAR on flurprimidol in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 20 April 2007. The peer review was initiated on 17 September 2007 by dispatching the DAR for consultation of the Member States and the sole applicant SePRO Europe Limited. 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 March-April 2008.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in July 2008 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as a plant growth regulator in ornamentals as proposed by the applicant. Full details of the GAP can be found in the attached end points.

The representative formulated product for the evaluation was “Topflor”, a micro-emulsion (ME) containing 3.8 g/l flurprimidol.

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)

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection products are possible. There are no adequate methods available to monitor flurprimidol in the environmental matrices and in body fluids and tissues. There is no agreed specification.

A critical area of concern was raised by the experts in mammalian toxicology on the lack of information on impurities present in the batches used in the toxicological studies.

In mammalian metabolism studies, flurprimidol was rapidly but not completely absorbed after oral administration; it was extensively metabolised and distributed through the body; excretion was rapid, mainly via urine although some excretion was observed via bile and faeces. Moderate acute oral toxicity was found in rat and mouse, requiring classification with Xn, R22 “harmful if swallowed”, but no classification was needed related to acute dermal or inhalation toxicity. Flurprimidol was not a skin or eye irritant and no sensitisation potential was found. Main effects observed in short term and long term toxicity studies were liver toxicity including enzyme induction and histopathological findings, and uterine and ovary weight changes down to the lowest dose tested, indicative of endocrine disruption effects at low doses. Genotoxicity studies covering all required endpoints (*in vitro* bacterial and mammalian gene mutation, chromosomal aberration and *in vivo* micronucleus test) were negative and no carcinogenic potential was observed in either rats or mice upon 2-year oral exposure.

Flurprimidol was thought to inhibit aromatase activity because the observed effects were similar to those observed with structurally related active substance fenarimol. However, no mechanistic study was performed with flurprimidol and sensitive endpoints for aromatase inhibition were not measured in studies conducted with flurprimidol. Reproductive toxicity was indicated by increased precoat period, dystocia, progeny mortality, reduced mating performance and fertility which were not considered secondary to parental systemic toxicity; accordingly, classification as toxic, reproduction toxicity category 2 for fertility, R60 “may impair fertility”, was proposed. In the rat developmental toxicity study, the proportion of fetuses with developmental variations and abnormalities was increased and could not be explained by maternal toxicity alone; accordingly classification as harmful, reproduction toxicity category 3 for development, R63 “possible risk of harm to the unborn child” was proposed. The Acceptable Daily Intake (ADI) was 0.003 mg/kg bw/day, the Acceptable Operator Exposure (AOEL) was 0.003 mg/kg bw/day and the Acute Reference Dose (ARfD) was 0.09 mg/kg bw. Dermal absorption was 10 % for the concentrate formulation (default value, taking into account that measurements were available in an *in vivo* monkey study with the active substance) and 100 % for the in-use spray dilution (default value for no data). The level of operator exposure calculated for glasshouses’ uses on ornamentals with the representative formulation Topflor exceeded the AOEL, even when the use of protective clothing was considered, according to the EUROPOEM II and the Dutch model. Estimated exposure of workers entering crops treated with flurprimidol exceeded also the AOEL, even after only one application and when the use of gloves was considered. Bystander’s exposure was not relevant for this type of use.

No data was submitted to study and assess the residue behaviour of flurprimidol in plants and livestock animals in order to define the relevant residues for dietary consumer risk assessment. The representative uses of flurprimidol in containerized ornamentals, pot and bedding plants are normally not expected to result in any dietary exposure to consumers or livestock animals. Potted herbs or any other edible container plants are not meant to be included in these notified uses. A potential transfer of residues from recycled soil and/or compost to crops intended for human or animal consumption should be avoided, possibly by appropriate restriction measures. Under conditions excluding any potential consumer exposure to flurprimidol residues through food, there will be no dietary consumer risk related to the notified representative uses.

All fate and behaviour into the environment studies available have been performed with flurprimidol labelled exclusively at the phenyl ring and / or at the carbinol bridge. The meeting of experts identified a data gap for a full fate and behaviour data package of studies performed with flurprimidol labelled at the pyrimidine ring.

The data available for fate and behaviour of flurprimidol into the environment is very limited. Data on the route of degradation in soil is insufficient to assess any use for which exposure could not be completely excluded. The data available shows that flurprimidol is medium to high persistent in soil ($DT_{50} = 98 - 183$ d) under laboratory aerobic conditions (no field study available) and that it is not hydrolysed in buffered water in the range of environmental pHs. Photolysis of flurprimidol in water was relatively rapid ($DT_{50} = 1.4$ d) and results in the formation of two photolysis metabolites that would need to be further assessed for aquatic environment in case exposure could not be completely excluded from the use proposed. No water sediment study is available in the dossier. Potential ground water contamination was precluded from the representative use proposed if it is restricted as proposed by the meeting of experts. In general a number of data gaps for fate and behaviour into the environment were identified during the peer review; however, they were considered not to be essential for the assessment of the representative use if this is restricted / managed in order to avoid exposure to the environment, including the potential exposure arising from disposal of soil used and residues of plants.

The environmental risk assessment covers only the use in greenhouses that are permanent structures. No risk assessment was conducted for birds and mammals. Direct exposure of birds and mammals is expected to be negligible for the representative use in greenhouse. The $\log P_{ow}$ of flurprimidol is >3 and therefore a risk assessment should be conducted for secondary poisoning of earthworm and fish-eating birds and mammals if treated substrate and plants are disposed of in the environment. The risk to fish, aquatic invertebrates and algae was assessed as low. A study with higher aquatic plants is needed since flurprimidol is a plant growth regulator. However the study is not required to finalise the EU risk assessment for the proposed use if the use is restricted to high technology greenhouse production systems with irrigation/excess water management systems. Effects of $>50\%$ on mortality and reproduction were observed in sensitive groups of non-target arthropods at concentrations below the suggested application rate of 60 g a.s./ha. Arthropods used in glasshouses for biological plant protection purpose are likely to be severely impacted by the use of flurprimidol. The risk to non-

target arthropods in the environment surrounding the greenhouse was considered to be low due to negligible exposure. The acute risk to earthworms was assessed as low. No study was submitted to investigate long-term (reproductive) effects on earthworms. Such a study was considered not necessary provided that treated soil and plants are not disposed of in the environment. No risk assessment was conducted for other soil non-target organisms and non-target micro-organisms. However the risk to soil dwelling organisms is assumed to be low for the use in high technology greenhouse production systems with irrigation/excess water management systems and provided that treated substrate and plants are not disposed of in the environment. The risk to non-target plants in the vicinity of greenhouses was considered to be low.

The risk to bees and biological methods of sewage treatment was assessed as low.

Key words: flurprimidol, peer review, risk assessment, pesticide, plant growth regulator

TABLE OF CONTENTS

Summary	1
Table of Contents	5
Background	6
The Active Substance and the Formulated Product	7
Specific Conclusions of the Evaluation	7
1. Identity, physical/chemical/technical properties and methods of analysis	7
2. Mammalian toxicology	8
2.1. Absorption, Distribution, Excretion and Metabolism (Toxicokinetics)	8
2.2. Acute toxicity	9
2.3. Short term toxicity	9
2.4. Genotoxicity	10
2.5. Long term toxicity	10
2.6. Reproductive toxicity	10
2.7. Neurotoxicity	11
2.8. Further studies	11
2.9. Medical data	12
2.10. Acceptable daily intake (ADI), acceptable operator exposure level (AOEL) and acute reference dose (ARfD)	12
2.11. Dermal absorption	13
2.12. Exposure to operators, workers and bystanders	13
3. Residues	15
3.1. Nature and magnitude of residues in plant	15
3.1.1. Primary crops	15
3.1.2. Succeeding and rotational crops	15
3.2. Nature and magnitude of residues in livestock	16
3.3. Consumer risk assessment	16
3.4. Proposed MRLs	16
4. Environmental fate and behaviour	16
4.1. Fate and behaviour in soil	17
4.1.1. Route of degradation in soil	17
4.1.2. Persistence of the active substance and their metabolites, degradation or reaction products	17
4.1.3. Mobility in soil of the active substance and their metabolites, degradation or reaction	17
4.2. Fate and behaviour in water	18
4.2.1. Surface water and sediment	18
4.2.2. Potential for ground water contamination of the active substance their metabolites, degradation or reaction products	18
4.3. Fate and behaviour in air	18
5. Ecotoxicology	19
5.1. Risk to terrestrial vertebrates	19
5.2. Risk to aquatic organisms	19
5.3. Risk to bees	20
5.4. Risk to other arthropod species	20
5.5. Risk to earthworms	20
5.6. Risk to other soil non-target macro-organisms	20
5.7. Risk to soil non-target micro-organisms	21
5.8. Risk to other non-target-organisms (flora and fauna)	21
5.9. Risk to biological methods of sewage treatment	21
6. Residue definitions	21
List of studies to be generated, still ongoing or available but not peer reviewed	26
Conclusions and Recommendations	27
Critical areas of concern	30
Appendix 1 – List of endpoints for the active substance and the representative formulation	31
Appendix 2 – Abbreviations used in the list of endpoints	60
Appendix 3 – used compound code(s)	62

BACKGROUND

Commission Regulation (EC) No 1490/2002 laying down the detailed rules for the implementation of the third stage 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. Flurprimidol is one of the 84 substances of the third stage, part B, covered by the Regulation (EC) No 1490/2002 designating Finland as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, Finland submitted the report of its initial evaluation of the dossier on flurprimidol, hereafter referred to as the draft assessment report, received by EFSA on 20 April 2007. The draft assessment report was distributed for consultation in accordance with Article 11(2) of the Regulation (EC) No 1490/2002 on 17 September 2007 to the Member States and the main applicant SePRO Europe Limited 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 applicant as well as issues for further detailed discussion at expert level.

Taking into account the requested information received from the applicant, a scientific discussion took place in expert meetings in March - April 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 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 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 end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial

evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received,
- the resulting reporting table (rev.1-2 of 28 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 (rev.2-1 of 30 July 2008)

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

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Flurprimidol is the ISO common name for (*RS*)-2-methyl-1-pyrimidin-5-yl-1-(4-trifluoromethoxyphenyl)propan-1-ol (IUPAC).

Flurprimidol is a pyrimidinyl carbinol type plant growth retardant. Flurprimidol acts by reducing the biosynthesis of gibberellins. The translocation in plants is apoplastic. Flurprimidol is used on container grown ornamentals, pot plants and bedding plants to reduce internode length.

The representative formulated product for the evaluation was "Topflor", a micro-emulsion (ME) containing 3.8 g/l flurprimidol, registered in several EU member states.

The representative uses evaluated comprise foliar spraying with conventional spraying devices on container grown ornamentals, pot plants and bedding plants, from when young shoots are 1 to 2 cm to before flowering, in northern and southern EU countries, up to a maximum 2 applications at a maximum individual application rate per spray of 30 g a.s./ha in north EU and respectively 22.5 g a.s./ha in south, with an interval of 7 days between applications.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

Flurprimidol is a racemate, the minimum purity is still open. No FAO specification exists.

PRAPeR 41 meeting could not agree on the acceptability of the technical specification for the technical material of the source mentioned in the DAR because the acceptability of the method used for impurity determination could not be concluded on. It should be noted that the production has been moved to a new site, the new data have been evaluated by the RMS, however according to Regulation

(EC) No 1095/2007 these data cannot be taken into consideration in the peer review. The meeting identified a new data gap for new five batch analysis data, representative of current production.

Besides 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 flurprimidol or the respective formulation.

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

Acceptable analytical methods are available for the determination of flurprimidol in the technical material (GC-FID) and in the representative formulation (HPLC). PRAPeR 41 meeting could not conclude on the acceptability of the method used for impurity determination in the technical material. Sufficient test methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

The applicability of the multi-residue methods to determining residues of flurprimidol was assessed, but was found to be unacceptable.

No residue definitions are proposed in food/feed of plant and animal origin, and as a consequence, no analytical methods are required in these matrices.

For the monitoring of residues of flurprimidol in soil, surface, drinking and ground water and air fully validated methods of analysis are required, with appropriate confirmatory methods.

As PRAPeR 44 meeting proposed flurprimidol to be classified as toxic, Reproduction (fertility) Category 2, R60, an analytical method for the determination of residues of a biological marker, to be proposed by the applicant, in body fluids and tissues is required.

2. Mammalian toxicology

Flurprimidol was discussed at the PRAPeR Expert's Meeting on mammalian toxicology (PRAPeR 44) in April 2008.

The meeting discussed the confidential information provided in volume 4 and the information from Section 1 (PRAPeR 41) that there was no agreed technical specification. Considering the total lack of information on impurities present in the batches used in the toxicological studies, the experts considered this issue as a critical area of concern for flurprimidol.

Toluene is toxicologically relevant; however at the concentration stated in the current technical specification (below 0.1 %), no concern is raised.

2.1. ABSORPTION, DISTRIBUTION, EXCRETION AND METABOLISM (TOXICOKINETICS)

Flurprimidol was rapidly absorbed with a mean peak plasma at 5 hours after oral administration. Based on urinary excretion (> 60 % after 72 hours), the extent of oral absorption was considered to be 60 % of the administered dose. Excretion through the bile was about 25 % after 24 hours; however,

this finding could not be used for the assessment of oral absorption as no determination of the urinary excretion was conducted in the same study.

Distribution of flurprimidol was uniform, higher concentrations were found in liver, kidneys, adrenals, blood/plasma, and to a lower extent in fat. Elimination occurred predominantly via urine (61.6 – 74.7 % after 7 days) and to a lesser extent via faeces (25.1 – 33.9 %), but most of the radioactivity had been eliminated already after 48 hours (89.9 – 96.1 % of the administered dose) via urine and faeces.

Flurprimidol was extensively metabolised; twelve primary metabolites were identified in urine, bile and faeces; less than 2.5 % of the dose was recovered as parent. Major metabolic pathways included oxidation of the isopropyl group, the pyrimidine ring and the carbene-carbon atom and dehydration between the carbinol-carbon atom and isopropyl group.

2.2. ACUTE TOXICITY

Acute oral toxicity of flurprimidol was moderate with oral LD₅₀ of 700 - 900 mg/kg bw in rat and 600 - 700 mg/kg bw in mouse. Dermal and inhalation toxicity were low; only slight and transient skin and eye irritation were observed; according to a Magnusson & Kligman and a modified Buehler tests, no sensitisation potential was found.

Therefore, classification as **Xn, harmful**, and risk phrase **R22 “harmful if swallowed”** was proposed.

2.3. SHORT TERM TOXICITY

The short term effects of flurprimidol were investigated in a 14-day dog study, four 90-day studies in rat, mouse and dog by dietary administration, and one 1-year dog study by capsule. A 21-day dermal toxicity study in rabbit was also presented.

In rat, decreased body weight gain and food consumption were noted with changes in haematological parameters; liver effects included increased liver weight, enzymatic induction and centrilobular hepatocyte hypertrophy. Dose-related reduction of uterine weight was also observed down to the lowest dose level; the experts agreed with the rapporteur Member State to set the NOAEL at this low dose corresponding to 1.62 and 1.96 mg/kg bw/day in males and females respectively, based on reduced uterus weight, increased ovary and liver weights, and p-nitroanisole-O-demethylase activity induction at the next dose level of 5.8 mg/kg bw/day. The experts considered the **1.96 mg/kg bw/day** the relevant intake for this dose level as critical effects were observed on females.

Mice were less sensitive to flurprimidol administration, main effects included increased liver weight, enzymatic induction and centrilobular hepatocyte hypertrophy at the highest dose of 300 mg/kg bw/day; the NOAEL was set at the next lower dose of 67.5 mg/kg bw/day.

In dogs, reduced body weight and hepatic enzyme induction were also observed; additionally, adrenal changes, including functional, organ weight and histopathological changes were observed, beginning at the dose level of 2 mg/kg bw/day. The overall NOAEL for dogs' studies was set at **1.5 mg/kg bw/day**.

When administered dermally for 21 days, flurprimidol did not cause adverse effect up to the limit dose of 1000 mg/kg bw/day.

2.4. GENOTOXICITY

A comprehensive data package of genotoxicity studies was submitted, including bacterial gene mutation assays, chromosomal aberration, mammalian cell gene mutation and unscheduled DNA synthesis *in vitro*, and a mouse micronucleus and a sister chromatid exchange tests *in vivo*.

All studies gave negative results with flurprimidol. The rapporteur Member State proposed in the draft assessment report to require a new *in vivo* study as none of the submitted ones had been conducted according to up-to-date guidelines. However the experts considered that the database available was complete and that there was no need for a further study. Flurprimidol is unlikely to be genotoxic.

2.5. LONG TERM TOXICITY

Four long term studies were conducted with flurprimidol, two 2-year studies in rat and in mouse and two 18-month studies in both species that included a 6-month recovery period.

In rats, treatment with 12 mg/kg bw/day flurprimidol and higher resulted in induction of hepatic microsomal enzyme activity, increased liver weight and histopathological liver changes; in females ovary weights were increased and uterus weights decreased, while in males, increased thyroid, parathyroid and testes weights were observed. Based on these effects, the rapporteur Member State proposed a NOAEL of 3.6 mg/kg bw/day. The experts discussed endocrine effects observed from the lowest dose tested on, as indicated by changes in organ weights (mainly ovary and uterus) and concluded that no NOAEL could be derived from this study, the **LOAEL was the low dose level of 1.0 mg/kg bw/day**.

Mice treated with flurprimidol for two years presented organ weight changes from 9.8 mg/kg bw/day on (increased liver, decreased uterus and kidney weights); reversible hepatocellular focal atypia was also observed in males. The NOAEL was the dose level of 1.3 mg/kg bw/day.

In either species no evidence of carcinogenicity was observed.

2.6. REPRODUCTIVE TOXICITY

Reproductive toxicity of flurprimidol was tested in a two-generation reproduction toxicity study in rat and a developmental toxicity study in rat and in rabbit.

Flurprimidol was stated to inhibit aromatase activity because the observed effects were similar to those observed with structurally related active substance fenarimol. However no mechanistic study was provided on flurprimidol. Moreover, the experts noted that endpoints considered sensitive to aromatase inhibition (as oestrous cyclicity or anogenital distance) were not measured with flurprimidol.

Reproductive toxicity

Reproductive toxicity was indicated by increased precoital period, dystocia and progeny mortality in the F₀ animals and by reduced mating performance and fertility in F₁ animals, which was not considered secondary to parental systemic toxicity.

The NOAEL for reproduction was set at **1.8 mg/kg bw/day based** on increased precoital period at the next dose of 7.3 mg/kg bw/day. The NOAEL for parental toxicity was set at the dose level of 7.3

mg/kg bw/day based on consistent liver effects, decreased body weight and food consumption, and female mortality at parturition at the highest dose of 74 mg/kg bw/day. The same NOAEL of 7.3 mg/kg bw/day was attributed for offspring's toxicity due to decreased survival, reduced body weight and histopathological changes in the liver at the highest dose level.

Considering the reproductive effects observed without parental toxicity, the experts proposed a classification with **T, toxic, reproduction toxicity category 2, R60 "may impair fertility"**.

The experts discussed the need to require further studies on sensitive endpoints. Although it was acknowledged that the mechanism of action should have been investigated and that the two-generation reproduction toxicity study presented some weaknesses, reference values could be set with the available data package. Therefore the meeting agreed that no further study was required.

Developmental toxicity

In the rat developmental toxicity study, the proportion of foetuses with developmental variations (extra vertebrae, extra ribs, rudimentary ribs, cervical ribs, hydronephrosis, hydroureter, and incomplete ossification of the calvaria, sternebrae, vertebrae, and pelvis) or foetal growth retardation was increased from the dose of 45 mg/kg bw/day on. The incidence of abnormal foetuses (microphthalmia) and foetal runts was increased at 200 mg/kg bw/day together with marked maternal toxicity (uterine haemorrhage, stained stout, chromodacryorrhea, alopecia decreased muscle tone, hyperactivity and death). Maternal toxicity at 45 mg/kg bw/day consisted of decreased body weight gain and food consumption, which was not considered sufficient to explain the effects on the foetuses at this dose level. Both maternal and developmental NOAELs were the dose level of 10 mg/kg bw/day. The experts proposed a classification with **Xn, harmful, reproduction toxicity category 3, R63 "possible risk of harm to the unborn child"**.

In the rabbit developmental toxicity study, maternal toxicity at the highest dose level of 45 mg/kg bw/day included decreased body weight gain and food consumption. The same high dose produced an increased incidence of foetuses with abnormalities and skeletal variations, which were generally minor and unspecific. The experts considered that the increased incidence of resorptions at 9.0 mg/kg bw/day was low and set this dose level as both maternal and developmental NOAELs.

2.7. NEUROTOXICITY

No study was conducted. Flurprimidol does not belong to a chemical group known to induce neurotoxicity, no concern was raised from the other general studies, and therefore no study was required.

2.8. FURTHER STUDIES

Metabolism studies showed that flurprimidol is metabolised to a large number of metabolites and all of them can contribute to the toxicity of the active substance. This is not relevant for the representative uses of flurprimidol under consideration. No study is available, and no study is required.

2.9. MEDICAL DATA

In routine medical examinations on plant personnel involved in flurprimidol production, no ill effects were reported. Searches on open literature in the internet did not reveal any data on human poisoning or incidents related to flurprimidol use.

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

ADI

Initially in the draft assessment report, the rapporteur Member State proposed an ADI of 0.007 mg/kg bw/day based on the mouse long term study presenting a NOAEL of 1.3 mg/kg bw/day and a safety factor of 200 – an extra factor of 2 considering that indirect indications of aromatase inhibition was observed in many repeated dose studies, but no measurement of relevant indicators for aromatase activity was available.

As the long term NOAEL was lowered for the long term rat study by the meeting, the basis for the ADI became a LOAEL of 1.0 mg/kg bw/day. The safety factor was increased based on this fact and also on the fact that the data package failed to investigate parameters related to aromatase inhibition. So after an intensive discussion on the value to be used (with opinions varying between 200 and 1000), the experts agreed with a safety factor of 300 and the **ADI for flurprimidol was established at 0.003 mg/kg bw/day.**

AOEL

The rapporteur Member State proposed in the draft assessment report an AOEL of 0.008 mg/kg bw/day based on the NOAEL of 1.62 mg/kg bw/day from the 90-day, rat study and a safety factor of 200.

The experts proposed to base the AOEL on the 90-day dog study with a NOAEL of 1.5 mg/kg bw/day, which is supported by the 90-day rat and the 2-generation rat studies, and a safety factor of 300 due to the uncertainties and missing information referred above. A correction factor of 60 % is added to account for the apparent limited oral absorption. **The AOEL was set at 0.003 mg/kg bw/day.**

ARfD

The rapporteur Member State proposed an ARfD of 0.045 mg/kg bw in the draft assessment report, based on the NOAEL of 9 mg/kg bw/day from the developmental toxicity study in rabbit and a safety factor of 200.

The experts agreed that the NOAEL is relevant to set the ARfD, which is supported by the rat developmental toxicity study. However it was considered that the standard safety factor of 100 was more appropriate since the critical effects for setting the ARfD were not the endocrine effects.

The ARfD was set at 0.09 mg/kg bw.

2.11. DERMAL ABSORPTION

Two *in vivo* studies in monkeys performed with the active substance were submitted to address the dermal absorption of flurprimidol. As recovery of radioactivity was low in the first study, it could not be used to assess dermal absorption. The second study presented higher levels of recovery (84-91 %) and indicated that dermal absorption was below 10 % - about 2.5-3.8 % - depending on the calculation.

The experts considered that these measured data were indicative that the default value of **10 %** was appropriate for the dermal absorption of **the concentrate formulation**; however, as no data was provided with the formulation Topflor, the **100 %** default value has to be used **for the in-use field dilution**.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The representative plant protection product Topflor is a micro emulsion (ME) formulation containing 3.8 g flurprimidol/L.

Estimation of operator exposure was recalculated in the addendum 3 to volume 3 of May 2008 based on the parameters agreed at the PRAPeR expert meeting.

Topflor is a systemic growth regulator, which controls the vegetative growth of plants by inhibiting the gibberellin hormone. It is intended to control the height growth of several glasshouse ornamentals, including pot and bedding plants in order to produce lower and denser plants. The plants may be treated both with hand-held equipment, i.e. hand-held knapsack or hand-gun, and with an automatic boom sprayer.

According to the representative uses, the applied dose varies between 0.0225 and 0.03 kg flurprimidol/ha; application volume varies between 500 and 2000 L spray/ha; the maximum number of applications per season is two, with a minimum interval between applications of seven days.

Operator exposure

The exposure of operators was calculated by the rapporteur Member State using the EUROPOEM II database (EUROPOEM 2002) and a modified Dutch model for glasshouse applications (van Goldstein Brouwers, Y.G.C. *et. al.* 1996).

Since more than 99 % of the dermal exposure comes from the application phase in glasshouses, the exposure from mixing and loading phase was also calculated using 100 % dermal absorption, which would not cause a significant error in the calculations. The rapporteur Member State made the calculations separately for realistic worst case scenarios (RWC), considering that 1 ha is treated per day, and realistic case (RC) scenarios, where 0.3 to 0.8 ha are treated per day pending on the type of crop considered. The operator is assumed to weight 70 kg.

Estimated operator exposure presented as % of AOEL (0.003 mg/kg bw/day) according to the EUROPOEM II (ornamentals)

Scenario	No PPE	With PPE ^(a)
RWC	6200	1200
RC	3100	590

^(a) PPE: gloves during mixing/loading and gloves & protective clothing during application; default of 10 % was used as penetration factor for gloves and 20 % for other clothing.

Estimated operator exposure presented as % of AOEL (0.003 mg/kg bw/day) according to the Dutch model (hand-held indoors)

Scenario	No PPE	With PPE ^(b)
Roses and carnations RWC	4300	450
Roses and carnations RC	1300	135
Chrysanthemums RWC	1400	150
Chrysanthemums RC	1100	120

^(b) Penetration through protective garment is 10 %

For all scenarios considered, operator exposure exceeds the AOEL even when protective equipment is worn.

The rapporteur Member State was asked by the experts at PRAPeR meeting to assess in more details a field study that was briefly summarised in the draft assessment report. This assessment was presented in the addendum 3 to volume 3 of May 2008; however this information was not peer-reviewed:

In a field study using a surrogate active substance for the treatment of ornamentals in greenhouses, a similar type of application was used to the one described in the flurprimidol draft assessment report, however the formulation type, active ingredient, product concentration and dilution concentrations differed significantly from the flurprimidol representative formulation, Topflor. Therefore, the usefulness of this field data in characterizing exposures from flurprimidol in greenhouse applications is limited. For a comparison to the model calculations, the result of the field study is given below. Dermal absorption rate of 100 %, treatment period of 1 hour and operator body weight of 70 kg were used.

Estimated operator exposure presented as % of AOEL (0.003 mg/kg bw/day) according to a field study using the fungicide aluminium tris-*o*-ethyl phosphonate - **not peer-reviewed**

Scenario	With PPE
Ornamentals hand-held indoors	470

Worker exposure

New calculations for the worker exposure risk assessment were presented in the addendum 3 to volume 3 of May 2008 considering the parameters agreed at the expert meeting. Transfer coefficient

of 5000 cm²/person x h for bare hands and coverall was used and of 1400 cm²/person x h for gloves and coverall. Since no specific dislodgeable foliar residue data was available, a conservative default value of 0.003 mg/cm² was used.

Estimated worker exposure presented as % of AOEL (0.003 mg/kg bw/day) according to the EUROPOEM II (2002) after one application

Scenario	No PPE ^(a)	With PPE ^(b)
Ornamentals (1 application)	1503	420

^(a) Bare hands & coverall

^(b) Gloves & coverall; default of 10 % was used as penetration factor through gloves.

According to the representative uses, the maximum amount of treatments with flurprimidol is two, with a seven day interval. There is no available decline rate data available for flurprimidol. Therefore, as a worst case scenario, the dislodgeable amount after two treatments must be assumed to be double the amount after a single treatment.

Taking the second treatment into account does not change the conclusion on worker exposure, which is higher than the AOEL already after the first treatment.

Bystander exposure

According to the indoor uses of flurprimidol, the presence of bystanders is not allowed during applications; therefore bystander exposure is not relevant.

3. Residues

Flurprimidol was discussed by the experts in residues in the PRAPeR meeting in April 2008 in Parma (PRAPeR 45, Round 9).

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

No data was submitted to investigate the nature and magnitude of residues in plants. As dietary exposure of consumers to flurprimidol residues is normally not expected from the notified representative use in container grown ornamentals, pot and bedding plants, no such data was required. A plant residue definition for flurprimidol cannot be proposed.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

The meeting of experts considered the possibility that recycled plant matter and soil, previously treated with flurprimidol, could be used to grow edible crops. Flurprimidol is medium to high persistent in soil (refer to point 4.1.2).

It was noted by the meeting that a potential transfer of residues from recycled soil and/or compost to rotational crops cannot be assessed due to lack of data. Therefore it was proposed to consider a

restriction not to recycle treated soil or plant material in the environment, and in addition not to use recycled materials to grow crops intended for human or animal consumption.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

No livestock exposure resulting from the representative uses in container grown ornamentals, pot and bedding plants is expected. These crops are usually not part of livestock diet.

Therefore, data on the nature and magnitude of residues in livestock was neither evaluated nor provided. A potential transfer of residues from recycled soil and/or compost to crops intended for animal consumption should be avoided since this situation has not been assessed.

3.3. CONSUMER RISK ASSESSMENT

It is noted that no data was submitted to study and assess the residue behaviour of flurprimidol in plants and livestock animals in order to define the relevant residues for dietary consumer risk assessment.

However, the representative uses of flurprimidol in containerized ornamentals, pot and bedding plants are normally not expected to result in any dietary exposure to consumers.

The applicant has clarified that potted herbs or any other edible container plants are not meant to be included in these notified uses. Moreover, a potential transfer of residues from recycled soil and/or compost to crops intended for human or animal consumption should be avoided (see point 3.1.2 above).

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

3.4. PROPOSED MRLS

The notified representative use does not concern food or feed items. Under the provision set out above the notified representative uses do not require MRL setting.

4. Environmental fate and behaviour

The fate and behaviour of flurprimidol in the environment was discussed in the meeting of experts PRAPeR 42 on basis of the DAR (March 2007) and the updated list of end points (March 2008).

All fate and behaviour into the environment studies available have been performed with flurprimidol labelled exclusively at the phenyl ring and / or at the carbinol bridge. The meeting of experts identified a data gap for a full fate and behaviour data package of studies performed with flurprimidol labelled at the pyrimidine ring.

In general the data gaps identified for fate and behaviour into the environment were considered not to be essential for the assessment of the representative use if this is restricted in order to avoid exposure

to the environment, including the potential exposure arising from disposal of soil used in pots and plants residues or not sold.

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

The route of degradation of flurprimidol in soil was investigated at 20 °C under dark aerobic conditions in two studies with a total of seven soils (pH 6.0 – 8.3; OC 0.9 – 41.9 %; clay 7 – 38.4 %) with flurprimidol ¹⁴C labelled at the phenyl ring. In the first study, four metabolites were found. Two of the metabolites (M1 and M2)² exceeded 5 % AR in two consecutive data points and would require further assessment for potential ground water contamination. These metabolites were not adequately characterized and the meeting of experts identified a data gap for an adequate route of degradation study. The data gap may be considered not essential to finalise the risk assessment of the representative use if it is restricted as suggested by the experts in the meeting to avoid any environmental exposure.

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

Rate of degradation of flurprimidol in soil was investigated in the same study reported in the route section. Flurprimidol is medium to high persistent in soil (DT₅₀ = 98 – 183 d) under dark aerobic conditions at 20 °C. The laboratory data triggers field studies. Meeting of experts identified a data gap for field dissipation studies in soil. Additionally, the meeting of experts identified a data gap for PEC soil accumulation calculation since DT₉₀ is expected to exceed one year. The data gaps may be considered not essential to finalise the risk assessment of the representative use if it is restricted as suggested by the experts in the meeting to avoid any environmental exposure.

PECs soil calculated in the DAR were considered not appropriate for risk assessment by experts in the meeting since they represent the concentration in the soil of the pots where the product is applied. A data gap to address potential accumulation in soil was identified by the meeting of experts. However, no PEC soil calculation is necessary if the use is restricted as proposed by the experts meeting to avoid any environmental exposure.

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

An acceptable batch adsorption / desorption study is available in the dossier. Flurprimidol may be considered medium to high mobile in soil (K_{oc} = 132 – 238 mL / g).

A number of column and aged column leaching studies are available in the dossier. Some deficiencies in these studies were identified by the RMS who considered that they may be considered as additional information. Components of the radioactivity found in the leachate or in the soil column is not characterised in any of these studies. There is also a field leaching study available considered as additional information by the RMS.

² No chemical identification of metabolites M1 and M2 is available.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Hydrolysis of flurprimidol was investigated in two studies in buffered aqueous solutions (pH 4, 7, 9) at 25°C and 50 °C. Flurprimidol is stable under these conditions.

An aqueous photolysis degradation study provided in the dossier was considered acceptable by the RMS. The study was performed for 5 d under natural light in Indiana (USA) (39.8 °N) at 25 °C. Photolysis of flurprimidol in water was relatively rapid ($DT_{50} = 1.4$ d). A major photolysis metabolite was identified **metabolite D**³ (max. 16.1 % AR after 5 d, end of the study). Another photolysis metabolite reached a maximum at the end of the study, **metabolite E**⁴ (max. 9.2 % AR after 5 d, end of the study). An additional aqueous photolysis study was performed under greenhouse and outdoors conditions. This study had a number of deficiencies and temperature was not recorded. A third study is available in accordance with current guidance, however non labelled material was used and no attempt to identify degradation products was done. A photolytic half life of 7.9 h was calculated in this study. The meeting of experts identified a data gap to further assess the aqueous photolysis metabolites in the context of the aquatic risk assessment.

Flurprimidol is not readily biodegradable according the available biodegradability study.

No information on the degradation of flurprimidol in water/sediment is available. A data gap for water / sediment studies in at least two systems was identified by the meeting of experts. The data gaps was considered not essential to finalize the risk assessment if the representative use is restricted as proposed by the meeting to avoid any environmental exposure.

PEC_{SW} were calculated assuming a loading of 0.1 % of applied dose to a water body 30 cm depth. Based on the low concentration calculated for surface water no PEC sed was calculated. However, with the current data available, the risk assessment can only be concluded for those situations where management of excess glasshouse water to avoid any contamination of natural surface waters is in place.

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

Potential contamination of ground water of flurprimidol and its soil metabolites has been excluded on basis of the proposed representative use (application in ornamentals in pots in greenhouses at low application rate). The meeting of experts agreed that this is only acceptable if it is assumed that in high technology glasshouses management may be set to avoid any environmental exposure of natural ground water. Therefore, potential routes of exposure (i.e. waste water, soil and plant residues) should be properly considered in establishing specific conditions of use.

4.3. FATE AND BEHAVIOUR IN AIR

Flurprimidol is only very slightly volatile. Volatilization from soil is negligible but significant volatilization is observed from plant surfaces. The tropospheric half life of flurprimidol was

³ **metabolite D**: 2-Methyl-1-(3-pyrimidin-5-yl-4-trifluoromethoxy-phenyl)-propan-1-one

⁴ **metabolite E**: 2-Methyl-1-(5-pyrimidin-5-yl-4-trifluoromethoxy-cyclohexa-1,5-dienyl)-propan-1-one

calculated to be 3.8 h based on the reaction with OH radical. Flurprimidol is not considered prone to the long term transport through the atmosphere.

5. Ecotoxicology

Flurprimidol was discussed by the experts in ecotoxicology in the PRAPeR meeting in April 2008 (PRAPeR 43). The environmental risk assessment for the representative use of flurprimidol covers only the use in greenhouses that are permanent structures. The risk assessment does not cover situations where the treated soil or plants are disposed of in the environment.

5.1. RISK TO TERRESTRIAL VERTEBRATES

No direct exposure of birds and mammals from the representative use in glasshouse is expected and therefore no risk assessment for birds and mammals was conducted. However flurprimidol is persistent in soil and degradation in water was not fully investigated (no water-sediment study). The log-Pow of flurprimidol is >3 and hence the potential risk to earthworm-eating birds and mammals should be assessed if treated substrate and plants are disposed of in the environment. A data gap was identified in the meeting of experts for the applicant to address the risk to earthworm- and fish-eating birds and mammals. The data are not considered essential to finalise the EU risk assessment of the proposed use if the use is restricted to high technology greenhouse production systems with irrigation/excess water management systems.

5.2. RISK TO AQUATIC ORGANISMS

The acute endpoints for fish, daphnids and algae were 17.2, 11.8 and 1.05 mg a.s./L. The toxicity of flurprimidol was increased in the tested formulation. The LC/EC₅₀ for fish and daphnids were 0.422 and 0.688 mg a.s./L and the 72-h EbC₅₀ for algae was 0.624 mg a.s./L. In the risk assessment it was assumed that 0.1% of the applied rate would reach surface water. The resulting TERs are significantly above the trigger for all tested aquatic organisms indicating a low risk for the evaluated glasshouse use.

The bioconcentration study with bluegill-sunfish (*Lepomis macrochirus*) was conducted with only one test concentration and is therefore not fully in accordance with the OECD test guideline. However the results give some indication that the risk of bioconcentration and bioaccumulation is low. The experts agreed that the study is valid and the test results are sufficient to demonstrate a low potential for bioconcentration.

A study with higher aquatic plants is a core data requirement for plant growth regulators. Therefore a data gap was identified by the experts. However the experts agreed that no data are necessary to finalise the EU risk assessment for the proposed use if the use is restricted to avoid contamination of surface water and soil.

5.3. RISK TO BEES

The acute oral and contact toxicity to bees was $>100 \mu\text{g a.s./bee}$ for technical flurprimidol) and >1.31 and $>1.99 \mu\text{g formulation/bee}$. The corresponding HQ values of <0.3 , <15 and <23 are below the trigger of 50 indicating a low risk to bees for the representative use.

5.4. RISK TO OTHER ARTHROPOD SPECIES

A standard dose-response study was conducted with *Aphidius rhopalosiphi* ($\text{LR}_{50} = 89.2 \text{ g a.s./ha}$). The resulting HQ of 0.67 is below the trigger of 2. The second indicator species *Typhlodromus pyri* was tested on glass plates with two concentrations only. The observed effects were 17% mortality at 14.8 g a.s./ha and 47.9% mortality and a significant reduction in reproduction at 29.6 g a.s./ha . Since only two concentrations were tested it is questionable if a reliable LR_{50} can be calculated from this study. The trigger of 30% effect is already exceeded at a concentration of 29.6 g a.s./ha . For risk assessment a rate of 60 g a.s./ha ($30 \text{ g a.s.} \times \text{MAF of } 2$) needs to be covered. It is expected that at 60 g a.s./ha mortality would have been even significantly higher than 50%.

Additional studies with *Encarsia formosa*, *Phytoseilus persimilis*, *Chrysoperla carnea*, *Orius insidiosus* and *Poecilus cupreus* were submitted. All tests were limit tests conducted under standard laboratory conditions except the study with *P. persimilis* where the animals were exposed to residues on bean leaves (extended laboratory study). The tested rates were too low to cover the rate of 60 g a.s./ha . 40% and 83 % mortality were observed in the tests with *P. persimilis* and *E. formosa* at an application rate of 18 g a.s./ha . No mortality and no effects were observed in the test with *P. cupreus* at a rate of 600 g a.s./ha . It is therefore concluded that severe impacts on sensitive non-target arthropod species are to be expected at the application rates proposed in the GAP.

No new studies at application rates high enough are considered necessary for the glasshouse use since exposure of non-target species in the surrounding environment is considered negligible. However it should be noted that arthropods used in glasshouses for biological plant protection purpose are likely to be severely impacted by the use of flurprimidol.

5.5. RISK TO EARTHWORMS

The acute 14d LC_{50} (corrected by 2) value for earthworms was $164 \text{ mg a.s./kg soil}$. Based on a PEC_{soil} of 0.08 mg a.s./kg the resulting TER is 2050 indicating a low acute risk to earthworms. No long-term study investigating effects on earthworm reproduction was submitted. Such a study is required since the $\text{DT}_{90}(\text{f})$ is between 100 and 365 days. However a long-term (reproduction) study is considered not necessary for the use in glasshouse assuming that earthworms are not exposed to flurprimidol provided that treated soil and plants are not disposed of in the environment (see proposed restriction).

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

No risk assessment was conducted for other soil dwelling non-target macro-organisms. It is assumed that exposure of naturally occurring soil dwelling macro-organisms from the representative use in

glasshouse is negligible provided that treated substrate and plants are not disposed of in the environment (see proposed restriction).

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

No risk assessment was conducted for soil micro-organisms. It is assumed that exposure of naturally occurring communities of soil micro-organisms is negligible provided that treated substrate and plants are not disposed of in the environment (see proposed restriction).

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

Studies were conducted to screen for insecticidal, fungicidal and herbicidal activity of flurprimidol. The study was considered as not acceptable for risk assessment purpose. However exposure of non-target plants is considered negligible for the representative use in glasshouse and therefore no further study is considered necessary.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

The inhibition of respiration of activated sludge was investigated with technical flurprimidol. The observed EC_{50} was >1000 mg a.s./L. It is not likely that flurprimidol reaches sewage treatment plants in amounts greater than 1000 mg a.s./L if it is applied according to the GAP. Therefore the risk to biological sewage treatment plants is considered to be low.

6. Residue definitions

Soil

Definition for risk assessment: flurprimidol and potential soil metabolites from the pyrimidine ring

Definition for monitoring: flurprimidol (for misuse since it is assumed that will be only used in high technology greenhouses with management measures to prevent environmental exposure).

Water

Ground water

Definition for exposure assessment: flurprimidol, uncharacterized soil metabolite M1, uncharacterized soil metabolite M2 and potential soil metabolites from the pyrimidine ring.

Definition for monitoring: flurprimidol (for misuse since it is assumed that only will be only used in high technology greenhouses with management measures to prevent environmental exposure).

Surface water

Definition for risk assessment: flurprimidol, aqueous photolysis metabolite D and aqueous photolysis metabolite E, soil metabolite M1, soil metabolite M2 and potential soil metabolites from the pyrimidine ring and potential metabolites formed in water sediment systems (originated from either ring).

Definition for monitoring: flurprimidol (for misuse since it is assumed that only will be only used in high technology greenhouses with management measures to prevent environmental exposure).

Air

Definition for risk assessment: flurprimidol

Definitions for monitoring: flurprimidol

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

Compound (name and/or code)	Persistence	Ecotoxicology
flurprimidol	Medium to high persistent in soil (DT ₅₀ = 98 – 183 d)	The acute risk to earthworms is low. A data gap was identified to address the long-term risk to earthworms and the risk to other non-target soil macro- and micro-organisms.
Potential soil metabolites from the pyrimidine ring	No data available*	No data available

* data gap not essential if the representative use is restricted as proposed by experts meeting PRAPeR 42

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
flurprimidol	Medium to high mobile in soil (Koc = 132 – 238 mL /g)	Not assessed*	Yes	Yes	Yes
Soil metabolite M1	No data	No data available*	No data available*	No data available*	No data available*

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
	available*				
Soil metabolite M2	No data available*	No data available*	No data available*	No data available*	No data available*
Potential soil metabolites from the pyrimidine ring	No data available*	No data available*	No data available*	No data available*	No data available*

* data not essential if the representative use is restricted as proposed by experts meeting PRAPeR 42

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
flurprimidol	The risk to fish, aquatic invertebrates and algae was assessed as low. A data gap was identified for a study with higher aquatic plants since flurprimidol is a plant growth regulator.
Photolysis metabolite D*	No data available*
Photolysis metabolite E*	No data available*
Soil metabolite M1*	No data available*
Soil metabolite M1*	No data available*
Potential metabolites	No data available*

from the pyrimidine ring*	
Potential metabolites formed in water / sediment systems (originated from either ring).*	No data available*

* data not essential if the representative use is restricted as proposed by experts meeting PRAPeR 42

Air

Compound (name and/or code)	Toxicology
flurprimidol	Inhalation rat LC ₅₀ > 5.231 mg/L air/4 h no classification is required

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

- Five batch data representative to the current production (relevant for all representative uses evaluated, already submitted and evaluated in an addendum in October 2007, however not peer-reviewed; refer to chapter 1)
- Fully validated analytical methods for the monitoring of residues of flurprimidol in soil, surface, drinking and ground water and air (relevant for all representative uses evaluated, date of submission unknown, data gap identified by experts of PRAPeR 41 meeting, April 2008; refer to chapter 1)
- Analytical methods for the determination of residues of a biological marker representative of flurprimidol exposure in body fluids and tissues is required. (relevant for all representative uses evaluated, date of submission unknown, data gap identified by experts of PRAPeR 44 meeting, April 2008; refer to chapter 1 and 2.6)
- Notifier to propose a biological marker representative of flurprimidol exposure to be detected by a suitable analytical method (relevant for all representative uses evaluated; no submission date proposed by the Notifier; refer to point 2.6, proposal for classification of flurprimidol as toxic, R60)
- Data gap identified for a route of degradation in soil study under aerobic conditions (not essential if the representative use is restricted as proposed; no submission date proposed by the notifier; refer to the point 4.1)
- Data gap identified for field dissipation in soil studies as triggered by the available laboratory data (not essential if the representative use is restricted as proposed; no submission date proposed by the notifier; refer to the point 4.1)
- Data gap identified to address potential accumulation in soil (not essential if the representative use is restricted as proposed; no submission date proposed by the applicant; refer to the point 4.1)
- Data gap identified to further assess aqueous photolysis metabolites in the context of the aquatic risk assessment (not essential if the representative use is restricted as proposed; no submission date proposed by the applicant; refer to the point 4.1)
- Data gap identified for water / sediment studies in at least two systems (not essential if the representative use is restricted as proposed; no submission date proposed by the applicant; refer to the point 4.2.1)
- Data gap identified for a full data package of fate and behaviour into the environment studies with with pyrimidine labelled flurprimidol (not essential if the representative use is restricted as proposed; no submission date proposed by the applicant; refer to chapter 4)
- A risk assessment for earthworm- and fish-eating birds and mammals (not essential if the representative use is restricted as proposed; no submission date proposed by the applicant; refer to point 5.1)
- A study and a risk assessment for higher aquatic plants (not essential if the representative use is restricted as proposed; no submission date proposed by the applicant; refer to point 5.2)

- The risk to aquatic organisms from photolysis and soil metabolites needs to be addressed (not essential if the representative use is restricted as proposed; no submission date proposed by the applicant; refer to chapter 4)
- A long-term (reproduction) study with earthworms (not essential if the representative use is restricted as proposed; no submission date proposed by the applicant; refer to point 5.5)
- The risk to soil non-target macro- and micro-organisms needs to be addressed. (not essential if the representative use is restricted as proposed; no submission date proposed by the applicant; refer to points 5.6 and 5.7)

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as proposed by the applicant, which comprise foliar spraying with conventional spraying devices, for reducing internode length, on container grown ornamentals, pot plants and bedding plants, from when young shoots are 1 to 2 cm to before flowering, in northern and southern EU countries, up to a maximum 2 applications at a maximum individual application rate per spray of 30 g a.s./ha in north EU and respectively 22.5 g a.s./ha in south, with an interval of 7 days between applications.

The representative formulated product for the evaluation was “Topflor”, a micro-emulsion (ME) containing 3.8 g/l flurprimidol, registered in several EU member states.

There are no adequate methods available to monitor flurprimidol in the environmental matrices and in body fluids and tissues.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection products are possible. There is no agreed specification.

A critical area of concern was raised by the experts in mammalian toxicology on the lack of information on impurities present in the batches used in the toxicological studies.

In mammalian toxicity studies, moderate acute oral toxicity was found in rat and mouse, requiring classification with Xn, R22 “harmful if swallowed”, but no classification was needed related to acute dermal or inhalation toxicity. Flurprimidol was not a skin or eye irritant and no sensitisation potential was found. Main effects observed in short term and long term toxicity studies were liver toxicity including enzyme induction and histopathological findings, and uterine and ovary weight changes down to the lowest dose tested, indicative of endocrine disruption effects at low doses. No genotoxic or carcinogenic potential was observed in either the rat or the mouse upon 2-year oral exposure.

Flurprimidol was thought to inhibit aromatase activity because the observed effects were similar to those observed with structurally related active substance fenarimol. However, no mechanistic study was performed with flurprimidol and sensitive endpoints for aromatase inhibition were not measured in studies conducted with flurprimidol. Reproductive toxicity was indicated by increased precoital

period, dystocia, progeny mortality, reduced mating performance and fertility which were not considered secondary to parental systemic toxicity; accordingly, classification as toxic, reproduction toxicity category 2 for fertility, R60 “may impair fertility”, was proposed. In the rat developmental toxicity study, the proportion of foetuses with developmental variations and abnormalities was increased and could not be explained by maternal toxicity alone; accordingly classification as harmful, reproduction toxicity category 3 for development, R63 “possible risk of harm to the unborn child” was proposed. The Acceptable Daily Intake (ADI) was 0.003 mg/kg bw/day, the Acceptable Operator Exposure (AOEL) was 0.003 mg/kg bw/day and the Acute Reference Dose (ARfD) was 0.09 mg/kg bw. The level of operator exposure calculated for glasshouses’ uses on ornamentals with the representative formulation Topflor exceeded the AOEL, even when the use of protective clothing was considered. Estimated exposure of workers entering crops treated with flurprimidol exceeded also the AOEL, even after only one application and when the use of gloves was considered. Bystander’s exposure was not relevant for this type of use.

No data was submitted to study and assess the residue behaviour of flurprimidol in plants and livestock animals in order to define the relevant residues for dietary consumer risk assessment. The representative uses of flurprimidol in containerized ornamentals, pot and bedding plants are normally not expected to result in any dietary exposure to consumers or livestock animals. Potted herbs or any other edible container plants are not meant to be included in these notified uses. A potential transfer of residues from recycled soil and/or compost to crops intended for human or animal consumption should be avoided, possibly by appropriate restriction measures. Under conditions excluding any potential consumer exposure to flurprimidol residues through food, there will be no dietary consumer risk related to the notified representative uses.

All fate and behaviour into the environment studies available have been performed with flurprimidol labelled exclusively at the phenyl ring and / or at the carbinol bridge. The meeting of experts identified a data gap for a full fate and behaviour data package of studies performed with flurprimidol labelled at the pyrimidine ring.

The data available for fate and behaviour of flurprimidol into the environment is very limited. Data on the route of degradation in soil is insufficient to assess any use for which exposure could not be completely excluded. The data available shows that flurprimidol is medium to high persistent in soil ($DT_{50} = 98 - 183$ d) under laboratory aerobic conditions (no field study available) and that it is not hydrolysed in buffered water in the range of environmental pHs. Photolysis of flurprimidol in water was relatively rapid ($DT_{50} = 1.4$ d) and results in the formation of two photolysis metabolites that would need to be further assessed for aquatic environment in case exposure could not be completely excluded from the use conditions proposed. No water sediment study is available in the dossier. Potential ground water contamination was precluded from the representative use proposed if it is restricted as proposed by the meeting of experts. In general a number of data gaps for fate and behaviour into the environment were identified during the peer review; however, they were considered not to be essential for the assessment of the representative use if this is restricted /

managed in order to avoid exposure to the environment, including the potential exposure arising from disposal of soil used and residues of plants.

The environmental risk assessment covers only the use in greenhouses that are permanent structures. No risk assessment was conducted for birds and mammals. Direct exposure of birds and mammals is expected to be negligible for the representative use in greenhouse. The log P_{ow} of flurprimidol is >3 and therefore a risk assessment should be conducted for secondary poisoning of earthworm and fish-eating birds and mammals if treated substrate and plants are disposed of in the environment. The risk to fish, aquatic invertebrates and algae was assessed as low. A study with higher aquatic plants is needed since flurprimidol is a plant growth regulator. However the study is not required to finalise the EU risk assessment for the proposed use if the use is restricted to high technology greenhouse production systems with irrigation/excess water management systems. Effects of $>50\%$ on mortality and reproduction were observed in sensitive groups of non-target arthropods at concentrations below the suggested application rate of 60 g a.s./ha. Arthropods used in glasshouses for biological plant protection purpose are likely to be severely impacted by the use of flurprimidol. The risk to non-target arthropods in the environment surrounding the greenhouse was considered to be low due to negligible exposure. The acute risk to earthworms was assessed as low. No study was submitted to investigate long-term (reproductive) effects on earthworms. Such a study was considered not necessary provided that treated soil and plants are not disposed of in the environment. No risk assessment was conducted for other soil non-target organisms and non-target micro-organisms. However the risk to soil dwelling organisms is assumed to be low for the use in high technology greenhouse production systems with irrigation/excess water management systems and provided that treated substrate and plants are not disposed of in the environment. The risk to non-target plants in the vicinity of greenhouses was considered to be low.

The risk to bees and biological methods of sewage treatment was assessed as low.

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

- Management measures should establish conditions of use to avoid exposure to residues of flurprimidol with respect to:
 - crops for human and animal consumption (refer to chapter 3)
 - natural soils and non-target organisms (refer to chapter 4 and 5)Such measures would need to
 - preclude disposal of contaminated soil and plant material (including recycled/composted material) in the environment;
 - avoid the use of recycled/composted material to grow edible crops.
- The environmental risk assessment may be concluded for the representative use proposed if it is restricted to high technology greenhouse production systems with irrigation / excess water management systems that guarantee no release of contaminated water to the environment.

Critical areas of concern

- There is no agreed specification.
- Lack of adequate enforcement methods for the environmental matrices and for body fluids and tissues.
- No information is available on the impurity profile of batches used in the toxicological studies.
- Operator exposure exceeds the AOEL even considering the use of PPE.
- Worker exposure exceeds the AOEL even considering the use of PPE.
- 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 uses. No data was submitted to study and assess the residue behaviour of flurprimidol in plants and livestock animals in order to define the relevant residues in dietary consumer risk assessment.
- Environmental data package clearly insufficient to perform the environmental risk assessment for any use with fewer restrictions than the ones proposed for the representative use.

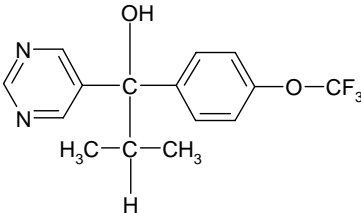
APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(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) ‡	Flurprimidol
Function (e.g. fungicide)	Plant growth regulator
Rapporteur Member State	Finland
Co-rapporteur Member State	-

Identity (Annex IIA, point 1)

CHEMICAL NAME (IUPAC) ‡	(<i>RS</i>)-2-methyl-1-pyrimidin-5-yl-1-(4-trifluoromethoxyphenyl)propan-1-ol
CHEMICAL NAME (CA) ‡	α -(1 methylethyl)- α -[4-(trifluoromethoxy)phenyl]-5-pyrimidinemethanol
CIPAC NO ‡	696
CAS NO ‡	56425-91-3
EC NO (EINECS OR ELINCS) ‡	Not allocated
FAO SPECIFICATION (INCLUDING YEAR OF PUBLICATION) ‡	Not established
Minimum purity of the active substance as manufactured ‡	(racemate), open
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	toluene
MOLECULAR FORMULA ‡	C ₁₅ H ₁₅ F ₃ N ₂ O ₂
Molecular mass ‡	312.3
Structural formula ‡	

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	93.5 – 97.0 °C (99.4 %)														
Boiling point (state purity) ‡	Substance decomposes before boiling. (99.4 %)														
Temperature of decomposition (state purity)	Signs of decomposition noted from 200 °C upwards.														
Appearance (state purity) ‡	White to pale yellow crystalline solid. (≥ 98 %)														
Vapour pressure (state temperature, state purity) ‡	1.0×10^{-4} Pa at 25 °C (99.4 %)														
Henry's law constant ‡	2.74×10^{-4} Pa m ³ mol ⁻¹ at 25 °C														
Solubility in water (state temperature, state purity and pH) ‡	114 mg/l at 20 °C, pH 7.00 (99.4 %)														
Solubility in organic solvents ‡ (state temperature, state purity)	<table> <tr> <th>Solvent:</th><th>Solubility:</th></tr> <tr> <td>acetone</td><td>1530 g/l at 20 °C (99.4 %)</td></tr> <tr> <td>dichloromethane</td><td>1810 g/l at 20 °C (99.4 %)</td></tr> <tr> <td>ethyl acetate</td><td>1200 g/l at 20 °C (99.4 %)</td></tr> <tr> <td>methanol</td><td>1990 g/l at 20 °C (99.4 %)</td></tr> <tr> <td>toluene</td><td>144 g/l at 20 °C (99.4 %)</td></tr> <tr> <td>hexane</td><td>1.26 g/l at 20 °C (99.4 %)</td></tr> </table>	Solvent:	Solubility:	acetone	1530 g/l at 20 °C (99.4 %)	dichloromethane	1810 g/l at 20 °C (99.4 %)	ethyl acetate	1200 g/l at 20 °C (99.4 %)	methanol	1990 g/l at 20 °C (99.4 %)	toluene	144 g/l at 20 °C (99.4 %)	hexane	1.26 g/l at 20 °C (99.4 %)
Solvent:	Solubility:														
acetone	1530 g/l at 20 °C (99.4 %)														
dichloromethane	1810 g/l at 20 °C (99.4 %)														
ethyl acetate	1200 g/l at 20 °C (99.4 %)														
methanol	1990 g/l at 20 °C (99.4 %)														
toluene	144 g/l at 20 °C (99.4 %)														
hexane	1.26 g/l at 20 °C (99.4 %)														
Surface tension ‡ (state concentration and temperature, state purity)	51.9 mN/m at 24 °C, 108 mg/l aq. solution (99.4 %)														
Partition co-efficient ‡ (state temperature, pH and purity)	log P _{ow} = 3.34 at 20°C (99.4 %) log P _{ow} = 2.66 ± 0.12 (Leo and Hansch estimation method)														
Dissociation constant (state purity) ‡	Flurprimidol does not dissociate.														
UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	UV/VIS measured in neutral (pH 7.48), acidic (pH 0.68) and basic (pH 12.92) methanolic solutions. (99.4 %) Maximum absorption at <u>neutral:</u> λ _{max} = 204.8 nm ε = 19100 l · mol ⁻¹ · cm ⁻¹ <u>acid:</u> λ _{max} = 203.8 nm ε = 18000 l · mol ⁻¹ · cm ⁻¹ <u>basic:</u> λ _{max} = 218.6 nm ε = 9140 l · mol ⁻¹ · cm ⁻¹														
Flammability ‡ (state purity)	Not flammable. (99.4 %)														
Explosive properties ‡ (state purity)	Not explosive. (99.4 %)														
Oxidising properties ‡ (state purity)	Not oxidizing. (99.4 %)														

Appendix 1 – list of endpoints

Summary of representative uses evaluated (flurprimidol)*

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		Application				Application rate per treatment (for explanation see the text in front of this section)			PHI (days) (m)	Remarks
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min/max (k)	interval between applications (min)	g as/hL min – max (l)	water L/ha min – max	g as/ha min – max (l)		
Container grown ornamentals, pot plants, bedding plants	N (Germany)	'Topflor'	G	Growth regulator	ME	3.8 g/L	High volume spray. Knapsack sprayer, automatic boom sprayer or hand-gun	Apply from when young shoots are 1-2 cm to before flowering.	2	7 days	1.5 - 3	1000-2000	30	NA	Total rate/season 60.0 g as/ha [1], [2] Environmental risk assessment may only be concluded for uses restricted to high technology glasshouses managed to avoid any environmental exposure.
	S (Italy)	'Topflor'	G	Growth regulator	ME	3.8 g/L			2	7 days	1.5 -4.5	500-1500	22.5	NA	Total rate/season 45.0 g as/ha [1], [2] Environmental risk assessment may only be concluded for uses restricted to high technology glasshouses managed to avoid any environmental exposure.

[1] Operator exposure exceeds the AOEL even when the use of PPE is considered.

[2] Worker exposure exceeds the AOEL even when the use of PPE is considered.

<p>* 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).</p> <p>(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)</p>	<p>(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. fluroxypyr). In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).</p>
--	---

Appendix 1 – list of endpoints

<p>(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)</p> <p>(c) <i>e.g.</i> biting and suckling insects, soil born insects, foliar fungi, weeds</p> <p>(d) <i>e.g.</i> wettable powder (WP), emulsifiable concentrate (EC), granule (GR)</p> <p>(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989</p> <p>(f) All abbreviations used must be explained</p> <p>(g) Method, <i>e.g.</i> high volume spraying, low volume spraying, spreading, dusting, drench</p> <p>(h) Kind, <i>e.g.</i> overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated</p>	<p>(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</p> <p>(k) Indicate the minimum and maximum number of application possible under practical conditions of use</p> <p>(l) The values should be given in g or kg whatever gives the more manageable number (<i>e.g.</i> 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha)</p> <p>(m) PHI - minimum pre-harvest interval</p>
--	---

Chapter 2.2 Methods of Analysis

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

Technical as (analytical technique)	Capillary gas chromatography with FID
Impurities in technical as (analytical technique)	Open.
Plant protection product (analytical technique)	Reversed phase column HPLC-UV at 250 nm

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin	Residue definition is not relevant.
Food of animal origin	Residue definition is not relevant.
Soil	flurprimidol
Water surface	flurprimidol
drinking/ground	flurprimidol
Air	flurprimidol
Body fluids and tissues	open

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	No analytical method is required. Residue definition is not relevant.
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	No analytical method is required. Residue definition is not relevant.
Soil (analytical technique and LOQ)	Open
Water (analytical technique and LOQ)	Open
Air (analytical technique and LOQ)	Open
Body fluids and tissues (analytical technique and LOQ)	open, method required

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

	RMS/peer review proposal
Active substance flurprimidol	None

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 ‡	> 60 % based on urinary excretion within 72 hours and > 25 % based on biliary excretion within 24 hours, in separate studies
Distribution ‡	Uniformly distributed
Potential for accumulation ‡	No evidence for accumulation
Rate and extent of excretion ‡	Urinary and faecal excretion accounted for 95.5 - 99.8 % of administered dose within 7 days; 61.6-74.7 % appeared in urine.
Metabolism in animals ‡	Extensively metabolized. Less than 2.5 % of radioactivity appeared in the urine and faeces as unchanged parent. Twelve primary metabolites were identified, the most abundant accounting for 10-20 % of administered dose and appearing primarily as a urinary metabolite. Other metabolites individually accounted for less than 6 % of the radioactivity. Oxidation and dehydration reactions.
Toxicologically relevant compounds ‡ (animals and plants)	Flurprimidol and metabolites
Toxicologically relevant compounds ‡ (environment)	Flurprimidol and metabolites

Acute toxicity (Annex IIA, point 5.2)

Rat LD ₅₀ oral ‡	709 mg/kg bw	R22
Rabbit LD ₅₀ dermal ‡	> 5000 mg/kg bw	
Rat LC ₅₀ inhalation ‡	> 5.231 mg/L air/4 h (nose-only, air-milled sample)	
Skin irritation ‡	Slightly irritating	
Eye irritation ‡	Slightly irritating	
Skin sensitisation ‡	Non-sensitiser (M&K)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Decreased bodyweight gain, increased liver weight and liver enzyme induction in rodents. Reduced uterine weight and increased ovary weight in rats and adrenocortical vacuolation in dogs	
Relevant oral NOAEL ‡	1.5 mg/kg bw/day (90-day, dog) 1.96 mg/kg bw/day (90-day, rat) 67.5 mg/kg bw/day (90-day mouse)	
Relevant dermal NOAEL ‡	> 1000 mg/kg bw/day (21-day, rabbit)	
Relevant inhalation NOAEL ‡	No data - not required	

Genotoxicity ‡ (Annex IIA, point 5.4)

No genotoxic potential	
------------------------	--

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

Target/critical effect ‡	Increased liver weight, induction of liver enzymes and liver histopathology; decrease in uterus weight, and increased ovary and testes weight in rat; liver, uterus and kidney weight changes in mouse.	
Relevant NOAEL ‡	1.3 mg/kg bw/day (2-year, mouse) LOAEL: 1.0 mg/kg bw/day (2-year, rat)	
Carcinogenicity ‡	No carcinogenic potential.	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	<u>Parental:</u> Decreased body weight and liver effects <u>Reproduction:</u> Dystocia, increased progeny mortality in F ₀ animals, decreased mating index, increased precoat period and decreased mean litter/pup weight. <u>Offspring:</u> Reduced pup survival and body weight gain	Repr · Cat. 2; R60
Relevant parental NOAEL ‡	7.3 mg/kg bw/day	
Relevant reproductive NOAEL ‡	1.8 mg/kg bw/day	
Relevant offspring NOAEL ‡	7.3 mg/kg bw/day	

Developmental toxicity

Developmental target / critical effect ‡

<u>Rat:</u> <i>Maternal:</i> Reduced food consumption and body weight gain <i>Foetal:</i> Malformations (microphthalmia), increased incidence of variants and abnormal fetuses <u>Rabbit:</u> <i>Maternal:</i> decreased bodyweight <i>Foetal:</i> increased incidence of variants and abnormal fetuses	Repr • Cat. 3; R63
Rat: 10 mg/kg bw/day Rabbit: 9.0 mg/kg bw/day	
Rat: 10 mg/kg bw/day Rabbit: 9.0 mg/kg bw/day	

Relevant maternal NOAEL ‡

Relevant developmental NOAEL ‡

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡

Repeated neurotoxicity ‡

Delayed neurotoxicity ‡

No data - not required	
No data - not required	
No data - not required	

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡

Studies performed on metabolites or impurities ‡

No data - not required
No data - not required

Medical data ‡ (Annex IIA, point 5.9)

No detrimental effects on health in manufacturing personnel and no reports in open literature about adverse health effects in humans.

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI ‡	0.003 mg/kg bw/day	2-year, rat	300*
AOEL ‡	0.003 mg/kg bw/day	90-day dog, supported by 90-day rat and multigeneration rat studies	Overall: 500 (300/60%)*
ARfD ‡	0.09 mg/kg bw	Developmental, rabbit supported by developmental, rat study	100

*Higher SF based on LOAEL and severity of the effects;

** Higher SF based on severity of effects, sensitive endpoints in multigeneration study not investigated, corrected for 60 % oral absorption

Dermal absorption ‡ (Annex IIIA, point 7.3)

Formulation: Topflor (3.8 g flurprimidol/L ME)

10% for the concentrate (default value)
 100% for the dilution (default value)
 Concentrate value based on *in vivo* study conducted with flurprimidol in monkeys (No study with the preparation available)
 Dilution based on default assumption – no data

Exposure scenarios (Annex IIIA, point 7.2)

Operator	<p>The estimated exposure for Topflor according to the EUROPOEM II and Dutch –model (application rate 0.03 kg flurprimidol/ha) showed that exposure is higher than the AOEL, even when PPE are used.</p> <p><u>Handheld equipment (EUROPOEM II) % of AOEL</u></p> <p>Without PPE: 3100-6200 %</p> <p>PPE (gloves during Mix/Load. & application and protective clothing during application): 590-1200 %</p> <p><u>Handheld equipment (Dutch-model) % of AOEL</u></p> <p>Without PPE: 1100-4300 %</p> <p>PPE (gloves): 120-450 %</p>
Workers	<p>The estimated exposure for Topflor exceeds the AOEL, even if PPE is used, and even considering only one application (EUROPOEM II). % of AOEL</p> <p>Without PPE: 1053 %</p> <p>PPE (gloves and coverall): 420 %</p>
Bystanders	Not relevant for the intended use

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

Substance classified (flurprimidol)	<p>RMS/peer review proposal</p> <p>T, Toxic</p> <p>Xn; R22 "Harmful if swallowed"</p> <p>T; Repr. Cat 2; R60 "May impair fertility"</p> <p>Xn; Repr. Cat 3; R63 "Possible risk of harm to the unborn child"</p>
-------------------------------------	---

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	No intended use on edible crops or animal feed; any studies has neither been submitted nor requested.
Rotational crops	Residue is persistent in soil. Recycling of the soil or plant material should be restricted.
Metabolism in rotational crops similar to metabolism in primary crops?	Not relevant.
Processed commodities	Not relevant.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not relevant.
Plant residue definition for monitoring	Not relevant.
Plant residue definition for risk assessment	Not relevant.
Conversion factor (monitoring to risk assessment)	Not relevant.

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

Animals covered	No studies submitted.
Time needed to reach a plateau concentration in milk and eggs	Not relevant.
Animal residue definition for monitoring	Not relevant.
Animal residue definition for risk assessment	Not relevant.
Conversion factor (monitoring to risk assessment)	Not relevant.
Metabolism in rat and ruminant similar (yes/no)	Not relevant.
Fat soluble residue: (yes/no)	Not relevant.

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

Not relevant.

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

Not relevant.

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

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

¹ State whether intake by specified animals is ≥ 0.1 mg/kg diet/day or not, based on a dry weight basis as given in table 1 of Guidance Document Appendix G

² Fill in results from appropriate feeding studies at appropriate dose rates according to Guidance Document Appendix G. State 'not required' when the conditions of requirement of feeding studies according to directive 91/414/EEC are not met.

Appendix 1 – list of endpoints

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

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)

(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

³ MRL proposal derived from supervised residue trials according to Guidance Document Appendix I. When the MRL is estimated at the LOQ, this should be annotated by an asterisk after the figure.

⁴ STMR value from results of supervised residue trials.

⁵ If several representative uses or European regions are foreseen for one crop, one row must be used for each specific situation

⁶ For some crop/pesticide combinations, the residue definition for monitoring and RA may differ. If trials are reported in this table with analysis of the residues accordingly to both definitions, the results are reported in the format x(y), x being the result according to the definition for monitoring and y the result according to the definition for RA. The same applies for the HR and the STMR

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)⁷

ADI	0.007 mg/kg
TMDI (% ADI) according to WHO European diet	No dietary exposure expected.
TMDI (% ADI) according to national (to be specified) diets	No dietary exposure expected.
IEDI (WHO European Diet) (% ADI)	No dietary exposure expected.
NEDI (specify diet) (% ADI)	No dietary exposure expected.
Factors included in IEDI and NEDI	None.
ARfD	0.045 mg/kg/day
IESTI (% ARfD)	Not relevant.
NESTI (% ARfD) according to national (to be specified) large portion consumption data	Not relevant.
Factors included in IESTI and NESTI	Not relevant.

⁷ To be done on the basis of WHO guidelines and recommendations with the deviations within the EU so far accepted (especially diets).

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 ⁸	Yield factor ⁸	
Not relevant.				

⁸ See separate examples at the beginning of the section

⁹ Mention whether case B1 or case B2

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

None proposed

An asterisk after a figure annotates that MRL is at the LOQ.

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 ‡	5.9-26.8% AR after 102 d at 20°C and 40 % MWCH, (n=3) 4.6 % AR after 102 d at 20°C and 80 % MWCH, (n=1)
Non-extractable residues after 100 days ‡	15.1-18.9% AR after 102 d at 20°C and 40 % MWCH, (n=3) 29.6 % AR after 102 d at 20°C and 80 % MWCH, (n=1)
Metabolites requiring further consideration for risk assessment ‡	No major metabolites exceeding 10 % AR is formed in soil Metab. M1: 5.0-9.2% AR on ≥ 2 consecutive time points. Metab. M2: 6.9-8.4% AR on 2 consecutive time points

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

Anaerobic degradation ‡	No reliable anaerobic degradation data available, not required for the indoor use according to GAP.
Soil photolysis ‡	No significant photolysis under glasshouse conditions

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

Laboratory studies ‡

Parent under aerobic conditions						
Soil type	pH	t. °C / % MWCH	DT ₅₀ /DT ₉₀ (d)	DT ₅₀ (d) 20°C pF2/10kPa	St. (r ²)	Method of calculation
Loamy sand	6.1	20 °C/40 % 10 °C 30 °C	118 / 393 260 / 865 54 / 179	not available	0.87	SFO Arrhenius eq. Arrhenius eq.

Sandy loam	8.1	20 °C/40 % 10 °C 30 °C	98 / 326 216 / 717 45 / 148	not available	0.95	SFO Arrhenius eq. Arrhenius eq.
Sandy clay	8.3	20 °C/40 % 10 °C 30 °C	157 / 522 345 / 1148 71 / 237	Not available	0.99	SFO Arrhenius eq. Arrhenius eq.
Peat	4.3	20 °C/80 % 10 °C 30 °C	< 183 / < 608 < 403 / < 1338 < 83 / < 276	Not available	0.89	SFO Arrhenius eq. Arrhenius eq.
Geometric mean DT50		20 °C	178	Not available		

Field studies ‡ No reliable field dissipation data available, data gap.
 Not required for the representative use according to GAP if restricted as proposed by the meeting of experts.

Parent under aerobic conditions						
Soil type	Location	pH	Depth (cm)	DisT _{50f} (days)	DisT _{90f} (days)	Method of calculation

Soil accumulation and plateau concentration ‡ Not applicable for the representative use assessed if restricted as proposed by the meeting of experts.

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent ‡							
Soil Type	OC %	Soil pH	K _d	K _{oc}	K _f	K _{foc}	1/n
Clay loam	2.4	8.1	2.6-4.6	141	3.4	142	0.87
Clay	1.3	8.4	1.3-2.2	132	1.7	131	0.89
Loamy sand	1.4	6.1	2.3-5.1	238	3.3	236	0.83
Peat	45.6	5.7	94.3-174	228	104	228	0.88

Geometric mean				
Arithmetic mean			184	0.87
pH dependence	No pH dependence			

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

No studies required. The following supportive data was provided:

Column leaching ‡ / 01	<p>Elution (mm): 200 mm Time period (d): 2 days</p> <p>Leachate: 0.29 % of applied radioactivity in leachate, 53 % of applied radioactivity retained in top 5 cm (n=1)</p>
Column leaching ‡ / 02	<p>Elution (mm): 508 mm Time period (d): 5 × ≤ 2 days</p> <p>Leachate: 0.74 - 1.07 % of applied radioactivity in leachate, 22.6–94.1 % of applied radioactivity retained in top 6 cm (n=4)</p>
Aged residues leaching ‡ / 01	<p>Aged for (d): 98 days Elution (mm): 200 mm Time period (d): 2 days</p> <p>Analysis of soil residues post ageing: 81.2 % active substance, 3.8 % Met I, 2.4 % Met II (not identified further)</p> <p>Leachate: 1.2 % of applied radioactivity in leachate, 62.0 % of applied radioactivity retained in top 5 cm (n=1)</p>
Aged residues leaching ‡ / 02	<p>Aged for (d): 30 days Elution (mm): 508 mm Time period (d): 5 × ≤ 2 days</p> <p>Analysis of soil residues post ageing: Not analyzed</p> <p>Leachate: 1.58-2.34 % of applied radioactivity in leachate, 20.0 – 35.8 % of applied radioactivity retained in top 6 cm (n=4)</p>
Aged residues leaching ‡ / 03	<p>Aged for (d): 30 days Elution (mm): 563 mm Time period (d): 45 days</p> <p>Analysis of soil residues post ageing: Recovery 92.9 %, metabolites not determined.</p>

	Leachate: 7.3 % of applied radioactivity in leachate, 15.6 % of applied radioactivity retained in top 5 cm (n=1)
Field leaching studies ‡	Not applicable for the representative use assessed

PEC (soil) (Annex IIIA, point 9.1.3)

No PEC_{soil} has been calculated for a soil outside the glasshouse.

The PEC_{soil} given in the DAR represents a concentration in the pot only.

Method of calculation	<p>Initial (single application)</p> $\text{Initial PEC}_{\text{soil}} = \frac{A \times (1 - f_{\text{int}})}{100 \times \text{soil depth} \times \text{soil density}}$ <p>Where: A = application rate (g as/ha) f_{int} = fraction intercepted by crop (assumed to be zero) Soil depth = 5 cm Soil density = 1.5 g/cm³</p> <p>To calculate the actual and time weighed PEC values following treatment, a worst case DT₅₀ of 183 days was used.</p>
Application data	<p>A maximum of two applications at a rate of 30 g as/ha at minimum interval of 7 days apart.</p> <p>Single: 30 g as/ha Multiple: 60 g as/ha (assuming no degradation between applications)</p>

Time interval	Predicted Environmental Concentration in soil ¹			
	Single application Actual PEC _{soil} (mg/kg)	Single application Time weighed average PEC _{twa} (mg/kg)	Multiple application Actual PEC _{soil} (mg/kg)	Multiple application Time weighed average PEC _{twa} (mg/kg)
Initial	0.040	--	0.080	--
Short term 24 hours	0.040	0.040	0.080	0.080
2 days	0.040	0.040	0.079	0.080
4 days	0.039	0.040	0.079	0.079
Long term 7 days	0.039	0.040	0.078	0.079

28 days	0.036	0.038	0.072	0.076
50 days	0.033	0.036	0.066	0.073
100 days	0.027	0.033	0.055	0.067

¹ The PEC_{soil} represents a concentration in the pot only and are not considered relevant for the risk assessment.

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

Hydrolytic degradation of the active substance (DT ₅₀) ‡	pH 4: >1 year at 50°C pH 5: > 1 year at 25°C
	pH 7: > 1 year at 50°C pH 7: > 1 year at 25°C
	pH 9: > 1 year at 50°C pH 9: > 1 year at 25°C
Photolytic degradation of active substance ‡ / 01	DT ₅₀ : 1.4 days Natural light, 39.8°N Two significant degradation products were observed, named photo-products D and E. Formation was via oxidation of the hydroxyl group and rearrangement of the pyrimidine ring. Photo-product D: max. 16.1% AR at day 5 Photo-product E: max. 11.6% AR at day 5
Photolytic degradation of active substance ‡ / 02	DT ₅₀ : 1.4 days Natural light under outdoor conditions, 50°N DT ₅₀ : 29.0 days Natural light under glasshouse conditions, 50°N
Photolytic degradation of active substance ‡ / 03	DT ₅₀ : 7.9 hours Artificial (xenon) light source
Quantum yield of direct phototransformation in water	0.362
Readily biodegradable ‡	Not readily biodegradable
Degradation in water / sediment	
No data available – not required	No data required for the use under glasshouse conditions

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

Method of calculation	<p>The initial concentration in surface water is calculated using the following equation:</p> $\frac{A \times \text{dep.rate}}{V_{\text{sw}} \times 100}$ <p>Where: A = application rate: 60 g as/ha dep.rate = deposition rate: 0.1 % V_{sw} = water volume: 300 L/m²</p>
Application data	<p>A maximum of two applications at a rate of 30 g as/ha at minimum interval of 7 days apart. Single: 30 g as/ha Multiple: 60 g as/ha (assuming no degradation between applications)</p>
Main routes of entry	<p>Typical use of "Topflor" involves direct application to container grown ornamentals under glasshouse conditions. Therefore, direct loading to adjacent water bodies is unlikely and any runoff/drainage following a rainfall event will be minimal. However, a simplistic Tier 1 scenario of a conservative amount of 0.1 % loading to an adjacent water body is considered.</p>
Initial PEC in surface water ¹	
Single application ¹	0.01 µg/L
Multiple applications ¹	0.02 µg/L
PEC sediment	Not calculated, not required

¹ The PEC_{sw} value only covers the high technology greenhouse production systems with irrigation/excess water management systems

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

PEC groundwater	
Not calculated – not required	<p>Typical use of "Topflor" involves direct application to container grown ornamentals under glasshouse conditions. The application rates are low. It is therefore considered that exposure to soil outdoors will be minimal if uses are restricted as proposed by the expert meeting. Under this assumption, it is considered that the likelihood of flurprimidol exceeding the threshold of 0.1 µg/L in groundwater is very low.</p>

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

Direct photolysis in air ‡	No data available – not required. Due to usage pattern, the concentrations in air are assumed to be negligible.
Quantum yield of direct phototransformation	Not applicable.
Photochemical oxidative degradation in air ‡	DT ₅₀ of 3.758 hours derived by the Atkinson method of calculation (based on the overall rate constant of $34.15 \times 10^{-12} \text{ cm}^3 \text{ molec}^{-1} \text{ sec}^{-1}$ for the hydroxyl reaction and the assumptions of OH radical concentration of $1.5 \times 10^6 \text{ molecule cm}^3$ and 12 h irradiation per day).
Volatilisation ‡	From plant surfaces: 24.2 % after 24 hours
	From soil surfaces: 6.6 % after 24 hours

PEC (air)

PEC _{air}	Not calculated – not required No significant atmospheric exposure is expected based on the indoor use, low application rate and low vapor pressure.
--------------------	--

Residues requiring further assessment

Relevant to the environment:	<p>Soil</p> <p>Definition for risk assessment: flurprimidol and potential soil metabolites from the pyrimidine ring</p> <p>Definition for monitoring: flurprimidol (for misuse since it is assumed that only will be only used in high technology greenhouses with management measures to prevent environmental exposure).</p> <p>Water</p> <p>Ground water</p> <p>Definition for exposure assessment: flurprimidol, uncharacterized soil metabolite M1, uncharacterized soil metabolite M2 and potential soil metabolites from the pyrimidine ring.</p> <p>Definition for monitoring: flurprimidol (for misuse since it is assumed that only will be only used in high technology greenhouses with management measures to prevent environmental exposure).</p>
------------------------------	---

Surface water

Definition for risk assessment: flurprimidol, aqueous photolysis metabolite D and aqueous photolysis metabolite E, soil metabolite M1, soil metabolite M2 and potential soil metabolites from the pyrimidine ring and potential metabolites formed in water sediment systems (originated from either ring).

Definition for monitoring: flurprimidol (for misuse since it is assumed that only will be only used in high technology greenhouses with management measures to prevent environmental exposure).

Air

Definition for risk assessment: flurprimidol

Definitions for monitoring: flurprimidol

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

Soil:

No data provided - none requested

Surface water:

No data provided - none requested

Ground water:

No data provided - none requested

Air:

No data provided - none requested

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

Not readily biodegradable, candidate for R 53.

Chapter 2.6 Ecotoxicology

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

Species	Test substance	Time scale	Endpoint
Birds ‡			
Bobwhite quail and mallards	Flurprimidol	Acute	LD ₅₀ >2000 mg/kg bw
	Preparation	Acute	Not relevant
Bobwhite quail and mallards	Flurprimidol	Short-term	LD ₅₀ >5000 mg/kg diet
	Flurprimidol	Long-term	Not required for a product used indoor
Mammals ‡			
Mouse	Flurprimidol	Acute oral	LD ₅₀ 602 mg/kg bw
Rat	Flurprimidol	Short term (90 day) dietary	NOEL 1.62 mg/kg bw/day (bodyweight gain, food consumption, erythrocyte counts and packed cell volumes, decreased MHC and MCHC, increased AP, weight and enzymatic induction in liver)
Rat	Flurprimidol	Reproductive toxicity (two generation study)	NOEL 1.8 mg/kg bw/day (parental toxicity and effects on reproductive performance)
Additional higher tier studies ‡ Not relevant			

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

Ornamentals under glasshouse conditions, 2 × 30 g as/ha at 7 days interval.

Indicator species/Category	Time scale	ETE	TER	Annex VI Trigger
Tier 1 (Birds)				
No data submitted – justification accepted. The acute oral and short-term dietary toxicity for birds is very low and a significant exposure of birds to flurprimidol is unlikely due to usage pattern of "Topflor" (indoor use with low application rates). Consequently, the risk to birds is considered low and no TERs have been determined.				

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

Indicator species/Category	Time scale	ETE	TER	Annex VI Trigger
Tier 1 (Mammals)				
No data submitted – justification accepted. A significant exposure of wild mammals to flurprimidol is unlikely due to usage pattern of "Topflor" (indoor use with low application rates). Consequently, the risk to wild mammals outside glasshouses is considered low and no TERs have been determined.				

Toxicity data for aquatic species (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale (Test type)	Endpoint	Toxicity ¹ (mg/L)
Laboratory tests ‡				
Fish				
<i>Oncorhynchus mykiss</i>	Flurprimidol	96 hr (static)	Mortality, LC ₅₀	18.3 (nom.)
<i>Lepomis macrochirus</i>	Flurprimidol	96 hr (static)	Mortality, LC ₅₀	17.2 (nom.)
<i>Lepomis macrochirus</i>	Flurprimidol	28 d (flow-through)	NOEC (based on weight gain)	0.42 (nom.)
<i>Oncorhynchus mykiss</i>	Flurprimidol	21 d (semi-static)	NOEC (based on mean length and wet weight)	1.63 (m.m.)
<i>Oncorhynchus mykiss</i>	"Topflor" (3.74 g as/L)	96 hr (flow-through)	Mortality, LC ₅₀	112.8 (prep.) 0.422 (flurprimidol)
Aquatic invertebrates				
<i>Daphnia magna</i>	Flurprimidol	48 h (static)	Mortality, EC ₅₀	11.8 (nom.)
<i>Daphnia magna</i>	Flurprimidol	21 d (semi-static)	NOEC (based on reproduction)	1.7 (m.m.)
<i>Daphnia magna</i>	"Topflor" (3.74 g as/L)	48 h (static)	Mortality, EC ₅₀	233.7 (prep.) 0.688 (flurprimidol)
Sediment dwelling organisms				
No data available – not required.				
Algae				
<i>Pseudokirch. subcapitata</i>	Flurprimidol	120 h (static) 72 h (static)	Biomass: E _b C ₅₀	0.84 (m.m.) 1.05 (m.m.)

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

Group	Test substance	Time-scale (Test type)	Endpoint	Toxicity ¹ (mg/L)
<i>Pseudokirch. subcapitata</i>	"Topflor" (3.74 g as/L)	72 h (static)	Biomass: E _b C ₅₀ Growth rate: E _r C ₅₀	166.8 _(prep.) 0.624 (flurprimidol) 496.8 _(prep.) 1.858 (flurprimidol)
Higher plant				
No data available – justification accepted.				
Microcosm or mesocosm tests				
No data available – not required.				

¹ based on nominal (nom.) or mean measured concentrations (m.m.). In the case of preparations endpoints are presented as units of preparation (prep.) or a.s. (flurprimidol)

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

Step1

Ornamentals under glasshouse conditions, 2 × 30 g as/ha at 7 days interval.

Test substance	Organism	Toxicity endpoint (mg as/L)	Time scale of endpoint	PEC _i (µg/L)	TER	Annex VI Trigger
Flurprimidol	<i>L. macrochirus</i>	17.2	Acute 96-h LC ₅₀	0.02	860000	100
Flurprimidol	<i>L. macrochirus</i>	0.42	Chronic 28-d NOEC	0.02	21000	10
Flurprimidol	<i>D. magna</i>	11.8	Acute 48-h EC ₅₀	0.02	590000	100
Flurprimidol	<i>D. magna</i>	1.7	Chronic 21-d NOEC	0.02	85000	10
Flurprimidol	<i>P. subcapitata</i>	0.84	Acute 120-h E _b C ₅₀	0.02	42000	10
"Topflor"	<i>O. mykiss</i>	0.422	Acute 96-h LC ₅₀	0.02	21100	100
"Topflor"	<i>D. magna</i>	0.688	Acute 48-h EC ₅₀	0.02	34400	100
"Topflor"	<i>P. subcapitata</i>	0.624 1.858	Acute 72-h E _b C ₅₀ Acute 72-h E _r C ₅₀	0.02	31200 92900	10

Bioconcentration

logPow	2.97 – 3.34
Bioconcentration factor (BCF)* ‡	19.3, 52.8 and 35.1 for fillet, viscera and whole fish, respectively, for <i>L. macrochirus</i> following 21-28 d exposure (based on ¹⁴ C)

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

Annex VI trigger for the bioconcentration factor	1000
Clearance time (days) (CT ₅₀)	0.58, 0.58 and 0.53 days for fillet, viscera and whole fish, respectively.
(CT ₉₀)	Not measured.
Level of residues (%) in organisms after the 14 day depuration phase	< 1 %

* Bioconcentration factor is based on only one test concentration.

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

Test substance	Acute oral toxicity (LD ₅₀ µg/bee)	Acute contact toxicity (LD ₅₀ µg/bee)
Flurprimidol ‡	> 100 µg/bee	> 100 µg/bee
"Topflor" (0.38 % as (w/w))	> 1.31 µL formulation/bee	> 1.99 µL formulation/bee
Field or semi-field tests not required		

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

Ornamentals under glasshouse conditions, 2 × 30 g as/ha at 7 days interval.

Test substance	Route	Hazard quotient	Annex VI Trigger
Flurprimidol	Contact	< 0.3	50
Flurprimidol	Oral	< 0.3	50
"Topflor"	Contact	< 15	50
Preparation	Oral	< 23	50

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

Laboratory tests with two sensitive standard species

Species	Test Substance	Endpoint	Effect (LR ₅₀ g/ha)
<i>Typhlodromus pyri</i> ‡	"Topflor" (EF-1195, 14.8 as g/L)	Mortality	> 29.6 g as/ha
<i>Aphidius rhopalosiphii</i> ‡	"Topflor" (0.38 % w/w)	Mortality	89.2 g as/ha

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

Hazard quotients for two sensitive standard species
 Ornamentals under glasshouse conditions, 2 × 30 g as/ha at 7 days interval.

Species	Effect (LR ₅₀ g/ha)	MAF (multiple application factor)	HQ in-field	HQ off-field	Trigger
<i>Typhlodromus pyri</i>	> 29.6 g as/ha	2.0	< 2.03	Not applicable	2
<i>Aphidius rhopalosiphi</i>	89.2 g as/ha	2.0	0.67	Not applicable	2

Further laboratory and extended laboratory studies ‡

Species	Life stage	Test substance, substrate and duration	Dose ¹ (g as/ha)	Endpoint and effect	Trigger value
<i>C. carnea</i>	2-3 days old larvae	"EF-1195" (14.8 g as/L) on glass plate, 19 days exposure	14.8 29.6	3.4 % mortality, no significant effects on reproduction 7.0 % mortality, no significant effects on reproduction	50 %
<i>O. insidiosus</i>	Second instar nymphs	"EF-1195" on glass plate, 10 days exposure	17.8	15.2 % mortality, no significant effects on reproduction	50 %
<i>E. formosa</i>	Wasps up to 24 hours old	"EF-1195" on glass plate, 6 days exposure	18.0	83.0 % mortality**, no significant effects on reproduction of survivals	50 %
<i>P. cupreus</i>	27-31 days old beetles	"Topflor" (0.38 % as (w/w)) on quartz sand, 14 days exposure	600	No mortality, no effects on feeding rate	50 %

** High risk for *Encarsia formosa*.

¹ dried residues

Field or semi-field tests not required

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

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	Endpoint ¹
Earthworms			
<i>Eisenia foetida</i>	Flurprimidol ‡	Acute 14 days Acute 14 days	LC _{50corr} 164 mg as/kg dry soil NOEC _{corr} 31.3 mg as/kg dry soil
<i>Eisenia foetida</i>	"Topflor" (3.74 g as/L)	Acute 14 days	LC _{50corr} > 500 mg formulation/kg dry soil
Reproductive toxicity studies for earthworms ‡: No data available – not required.			
Studies for other soil macro-organisms ‡: No data available – not required.			
Soil micro-organisms ‡: No data submitted – justification accepted. Flurprimidol is used as foliar applications under glasshouse conditions. Therefore soil contamination in field and a significant exposure of soil micro-organisms is not expected to occur. Consequently, the studies on soil non-target micro-organisms are not required.			

Toxicity/exposure ratios for soil organisms

Ornamentals under glasshouse conditions, 2 × 30 g as/ha at 7 days interval.

Test organism	Test substance	Time scale	Soil PECi (mg/kg) ¹	TER	Trigger
Earthworms					
<i>Eisenia foetida</i>	Flurprimidol	Acute 14 days (LC ₅₀)	0.08	2050	10
<i>Eisenia foetida</i>	Flurprimidol	Acute 14 days (NOEC)	0.08	391	5

¹ The PEC_{soil} value represents a concentration in the pot only

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

Preliminary screening data

No data available – not required. Flurprimidol is used under glasshouse conditions. Therefore a significant exposure of non target plants outside glasshouses is not expected to occur. Consequently, the studies on non target plants are not required.

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

Test type/organism	Endpoint
Respiration inhibition test / activated sludge	Three-hour EC ₅₀ > 1000 mg as/L _(nom)

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

Ecotoxicologically relevant compounds

Compartment	
soil	Flurprimidol
water	Flurprimidol
sediment	Flurprimidol
groundwater	Flurprimidol

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

Flurprimidol

RMS proposal
R51/53

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

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

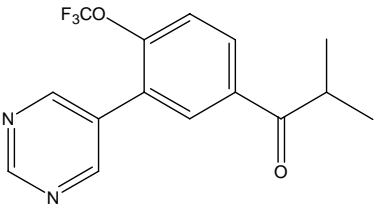
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT ₅₀	period required for 50 percent dissipation (define method of estimation)
DT ₉₀	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC ₅₀	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
F ₀	parental generation
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K _{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography

flurprimidol

Appendix 2 – abbreviations used in the list of endpoints

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
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
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PEC	predicted environmental concentration
PEC _A	predicted environmental concentration in air
PEC _S	predicted environmental concentration in soil
PEC _{SW}	predicted environmental concentration in surface water
PEC _{GW}	predicted environmental concentration in ground water
PHI	pre-harvest interval
pK _a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10 ⁻⁶)
ppp	plant protection product
r ²	coefficient of determination
RPE	respiratory protective equipment
SF	safety factor
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year

APPENDIX 3 – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
Aqueous photolysis metabolite D	2-Methyl-1-(3-pyrimidin-5-yl-4-trifluoromethoxy-phenyl)-propan-1-one	
Aqueous photolysis metabolite E	2-Methyl-1-(5-pyrimidin-5-yl-4-trifluoromethoxy-cyclohexa-1,5-dienyl)-propan-1-one	