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## CONCLUSION ON PESTICIDE PEER REVIEW

# Conclusion on the peer review of the pesticide risk assessment of the active substance flurprimidol[1]

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**SUMMARY**

Flurprimidol is one of the 84 substances of the third stage Part B of the review programme covered by Commission Regulation (EC) No 1490/2002[3], as amended by Commission Regulation (EC) No 1095/2007[4]. 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 set out in the EFSA Conclusion finalised on 31 July 2008 (EFSA Scientific Report (2008) 151).

Following the Commission Decision of 13 January 2009 (2009/28/EC)[5] concerning the non-inclusion of flurprimidol in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant SePRO Europe Limited made a resubmission application for the inclusion of flurprimidol in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008[6]. The resubmission dossier included further data in response to the issues and concerns identified in the conclusions leading to the Decision on non-inclusion, as set out in the Review Report (SANCO/173/08) as follows:

- The risk to operators and workers

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[1] On request from the European Commission, Question No EFSA-Q-2010-00856, issued on 16 December 2010.

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[3] 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)

[4] OJ L 246, 21.9.2007, p. 19

[5] OJ L 10, 15.1.2009, p.25

[6] OJ L 15, 18.01.2008, p.5

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- The exceedence of the AOEL (acceptable operator exposure level) for operators and workers in all evaluated scenarios and conditions of use;
- The lack of information on impurities present in the batches used in the toxicological studies.

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, Finland, being the designated RMS, submitted an evaluation of the additional data in the format of an Additional Report. The Additional Report was received by the EFSA on 10 March 2010.

In accordance with Article 19 of Commission Regulation (EC) No. 33/2008, the EFSA distributed the Additional Report to Member States and the applicant for comments on 11 March 2010. The EFSA collated and forwarded all comments received to the Commission on 26 April 2010.

In accordance with Article 20, following consideration of the Additional Report and the comments received, the Commission requested the EFSA to conduct a focussed peer review in the area of mammalian toxicology and deliver its conclusions on flurprimidol.

The conclusion of the resubmission 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 Appendix A.

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

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.

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 end points 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. Dermal absorption was 6 % for the concentrate formulation and 15 % for the in-use spray dilution based on an *in vitro* study performed on human skin. The estimated level of operator exposure calculated for glasshouses' uses on ornamentals with the representative formulation 'Topflor'

according to the EUROPOEM II and the Dutch model is below the AOEL when the use of personal protective equipment (PPE, i.e. gloves and protective clothing) is considered. Estimated exposure of workers is below the AOEL after one application of 'Topflor' when the use of gloves and coverall is considered. After 2 applications (assuming that there is no decay in the residues during the 14-days interval between applications), estimated worker exposure exceeds the AOEL (103 %) even when PPE are worn and a critical area of concern was identified. Furthermore, flurprimidol is a racemate and there is no information on the relative toxicity of each isomer or whether there is a shift in the isomer ratio workers are exposed to. A data gap is identified to address this. Bystander's exposure is not relevant for the representative use.

No data were submitted to study and assess the residue behaviour of flurprimidol in plants and livestock in order to define the relevant residues for dietary consumer risk assessment. The representative use of flurprimidol in containerised ornamentals, pot and bedding plants are normally not expected to result in any dietary exposure to consumers or livestock. Potted herbs or any other edible container plants are not meant to be included in the representative use. A potential transfer of residues from recycled soil and/or compost to crops intended for human or animal consumption should be avoided, by taking 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 representative use.

All available fate and behaviour into the environment studies 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 are very limited. Information on the fate of the individual enantiomers is not available. Data on the route of degradation in soil are insufficient to assess any use for which exposure could not be completely excluded. The data available show that flurprimidol exhibits medium to high persistence 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 the aquatic environment in the situation that exposure could not be completely excluded from the representative use. No water sediment study is available in the dossier. Potential groundwater contamination was precluded from the representative use 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 can be effectively restricted / managed in order to avoid exposure to the environment, including the potential exposure arising from disposal of used soil and residues of plants. Note the PPR panel of EFSA, has questioned the effectiveness of risk management measures such as those proposed here, to limit environmental exposure from uses in glasshouses.

The environmental risk assessment covers only the use in glasshouses 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 glasshouses. 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 representative use if the use is restricted to high technology glasshouse 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 glasshouse 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 glasshouse 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 glasshouses 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

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## 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 1490/2002, and 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 (RMS). 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 (Finland, 2007), hereafter referred to as the draft assessment report (DAR), received by EFSA on 20 April 2007. The DAR 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 DAR 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 set out in the EFSA Conclusion finalised on 31 July 2008 (EFSA, 2008).

Following the Commission Decision of 13 January 2009 (2009/28/EC)[7] concerning the non-inclusion of flurprimidol in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant SePRO Europe Limited made a resubmission application for the inclusion of flurprimidol in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008[8]. The resubmission dossier included further data in response to the issues and concerns identified in the conclusions leading to the Decision on non-inclusion, as set out in the Review Report (SANCO/173/08) as follows:

- The risk to operators and workers
- The exceedence of the AOEL (acceptable operator exposure level) for operators and workers in all evaluated scenarios and conditions of use;
- The lack of information on impurities present in the batches used in the toxicological studies.

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, Finland, being the designated RMS, submitted an evaluation of the additional data in the format of an Additional Report (Finland, 2010a). The Additional Report was received by the EFSA on 10 March 2010.

In accordance with Article 19 of Commission Regulation (EC) No. 33/2008, the EFSA distributed the Additional Report to Member States and the applicant for comments on 11 March 2010. The EFSA collated and forwarded all comments received to the Commission on 26 April 2010.

[7] OJ L 10, 15.1.2009, p.25
[8] OJ L 15, 18.01.2008, p.5

The collated comments were also forwarded to the RMS for compilation in the format of a Reporting Table. The applicant was invited to respond to the comments in column 3 of the Reporting Table. The comments and the applicant's response were evaluated by the RMS in column 3.

In accordance with Article 20, following consideration of the Additional Report and the comments received, the Commission decided to further consult the EFSA. By written request, received by the EFSA on 25 May 2010, the Commission requested the EFSA to arrange a consultation with Member State experts as appropriate and deliver its conclusions on flurprimidol within 6 months of the date of receipt of the request, subject to an extension of a maximum of 90 days where further information were required to be submitted by the applicant in accordance with Article 20(2).

The scope of the peer review and the necessity for additional information, not concerning new studies, to be submitted by the applicant in accordance with Article 20(2), was considered in a telephone conference between the EFSA, the RMS, and the Commission on 27 May 2010; the applicant was also invited to give its view on the need for additional information. On the basis of the comments received, the applicant's response to the comments, and the RMS' subsequent evaluation thereof, it was concluded that the EFSA should organise a consultation with Member State experts in the area of mammalian toxicology and that further information should be requested from the applicant in the area of identity, physical/chemical/technical properties.

The outcome of the telephone conference, together with EFSA's further consideration of the comments is reflected in the conclusions set out in column 4 of the Reporting Table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration were compiled by the EFSA in the format of an Evaluation Table.

The conclusions arising from the consideration by the EFSA, and as appropriate by the RMS, of the points identified in the Evaluation Table were reported in the final column of the Evaluation Table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in November - December 2010.

The conclusion from the original review was reached on the basis of the evaluation of the representative uses as presented in the DAR. The conclusion of the peer review of the resubmission was reached on the basis of the evaluation of the same representative uses but with a lower application rate and longer application interval. A list of the relevant end points for the active substance as well as the formulation is provided in Appendix A.

The documentation developed during the resubmission peer review was compiled as a Peer Review Report (EFSA, 2010a) comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's Additional Report:

- the comments received,
- the reporting table (rev.1-1 of 31 May 2010)
- the evaluation table (9 December 2010)

Given the importance of the Additional Report including its addendum (compiled version of November 2010 containing all individually submitted addenda) (Finland, 2010b) and the Peer Review Report, both documents are considered respectively as background documents A and B to this conclusion. The documents of the Peer Review Report and the final addendum developed and prepared during the course of the initial review process are made publicly available as part of the background documentation to the original conclusion, finalised on 31 July 2008 (EFSA, 2008).

## 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 of 2 applications at a maximum individual application rate per spray of 22.5 g a.s./ha, with an interval of 14 days between applications. This is a lower application rate and longer application interval than that considered in the previous EFSA conclusion (EFSA, 2008).

## CONCLUSIONS OF THE EVALUATION

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

The following guidance documents were followed for drafting this conclusion SANCO/3030/99 rev. 4 (European Commission, 2000), SANCO/10597/2003 rev. 8.1 (European Commission, 2009) and SANCO/825/00 rev. 7 (European Commission, 2004a).

The minimum purity of flurprimidol technical material is 983 g/kg. Flurprimidol is a racemate. No FAO specification exists.

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 A.

Acceptable analytical methods are available for the determination of flurprimidol in the technical material (GC-FID) and in the representative formulation (HPLC-UV). 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 determine 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 were identified as data gaps, with appropriate confirmatory methods.

As the 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 in body fluids and tissues was identified as a data gap.

### 2. Mammalian toxicity

Flurprimidol was discussed at the PRAPeR Experts' Meeting on mammalian toxicology (PRAPeR 44) in April 2008. It was re-discussed at the PRAPeR 83 in October 2010.

There is no information on the impurity profile of the batches used in the toxicological studies. However, as no impurity is present in the technical specification above the trigger level of 1 g/kg, as agreed by section 1 on identity, no further information is required from the toxicological point of view.

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

Flurprimidol was rapidly absorbed with a mean peak plasma concentration 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 and 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 carbine-carbon atom and dehydration between the carbinol-carbon atom and the isopropyl group.

### 2.2. Acute toxicity

Acute oral toxicity of flurprimidol was moderate with an oral $LD_{50}$ of 709 mg/kg bw in rat and 602 mg/kg bw in mouse. Dermal and inhalation toxicity were low. Slight and transient skin and eye irritation were observed. According to a Magnusson & Kligman and a modified Buehler test, no sensitisation potential was found.

Therefore, classification as **Xn, harmful**, and the risk phrase **R22 "harmful if swallowed"** are 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. During the PRAPeR 44 meeting, the experts considered **1.96 mg/kg bw/day** as the relevant intake for this dose level as critical effects were observed in 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 the 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 test *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, during the PRAPeR 44 meeting, 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 doses 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. During PRAPeR 44, the experts discussed the 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 none of the species 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 the structurally related active substance fenarimol. However, no mechanistic study was provided on flurprimidol. Moreover, the experts at PRAPeR 44 noted that end points considered sensitive to aromatase inhibition (as oestrous cyclicity or anogenital distance) were not measured with flurprimidol.

Reproduction toxicity

Reproduction toxicity was indicated by increased precoital period, dystocia and progeny mortality in the $F_0$ animals and by reduced mating performance and fertility in $F_1$ 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".**

During PRAPeR 44, the experts discussed the need to require further studies on sensitive end points. 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 set at 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 is 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 effects on health were reported. Searches in 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 (Finland, 2007), 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 during the PRAPeR 44 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 because the data package failed to investigate parameters related to aromatase inhibition. After an intensive discussion on the value to be used (with opinions varying between 200 and 1000), the majority of 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 (Finland, 2007) 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.

During the PRAPeR 44 meeting, 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 is 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 (Finland, 2007), based on the NOAEL of 9 mg/kg bw/day from the developmental toxicity study in rabbit and a safety factor of 200.

During the PRAPeR 44 meeting, 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 is 0.09 mg/kg bw.**

### 2.11. Dermal absorption

The guidance document SANCO/22/200 rev. 7 (European Commission, 2004b) was followed in this chapter. Two *in vivo* studies in monkeys performed with the active substance were not considered appropriate to derive the dermal absorption value of flurprimidol as the recoveries were low. An *in vitro* study, performed with a more concentrated formulation than 'Topflor', on human skin was presented during the resubmission (Finland, 2010a). Although drawbacks were identified due to the high variability observed in the results, a dermal absorption value of **6 %** was considered appropriate **for the concentrate formulation** and **15 % for the spray 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 2 to volume 3 of November 2010 (Finland, 2010b) based on the parameters agreed at the PRAPeR 83 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 maximum applied dose is 0.0225 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 14 days.

Operator exposure

New calculations for the operator exposure risk assessment were presented in the addendum 2 to volume 3 of the Additional Report of November 2010 (Finland, 2010b) considering the parameters agreed at the PRAPeR Expert Meeting 83. A transfer coefficient (TC) of 5000 $cm^2$/person x h for bare The exposure of operators was calculated by the rapporteur Member State using the EUROPOEM II model (75$^{th}$ percentile) and a modified Dutch model (90$^{th}$ percentile) for glasshouse applications (Van Goldstein, Brouwers, 1996).

According to the EUROPOEM II model for ornamentals, treatment of 1 ha/day is assumed. In the Dutch model 0.3 ha is assumed for carnations and roses, while 0.8 ha is used for chrysanthemums. The operator is assumed to weight 70 kg.

Estimated operator exposure presented as % of AOEL (0.003 mg/kg bw/day)

| Model/Scenario | No PPE | With PPE [(a)] |
|---|---|---|
| EUROPOEM II (hand-held downwards, ornamentals) | 710 | 73 |
| Dutch model (hand-held indoors, roses and carnations) | 190 | 28 |
| Dutch model (hand-held indoors, chrysanthemums) | 170 | 2 |

[(a)] PPE: gloves during mixing/loading and gloves & protective clothing during application; default of 10 % was used as penetration factor through PPE.

For all scenarios considered, estimated operator exposure is below the AOEL when personal protective equipment (PPE) is worn.

The rapporteur Member State was asked by the experts at PRAPeR 44 meeting to assess in more detail a field study that was briefly summarised in the DAR (Finland, 2007). This assessment was presented in the addendum 3 to volume 3 of May 2008 (Finland, 2008). In a field study using a surrogate active substance for the treatment of ornamentals in glasshouses, a similar type of application was used to the one described in the flurprimidol DAR (Finland, 2007), however the formulation type, active ingredient, product concentration and dilution concentrations differed significantly from the flurprimidol representative formulation, 'Topflor'. Therefore, the usefulness of these field data in characterizing exposures from flurprimidol in glasshouse applications is limited and is not considered further in the risk assessment.

Worker exposure

New calculations for the worker exposure risk assessment were presented in the addendum 2 to volume 3 of the Additional Report of November 2010 (Finland, 2010b) considering the parameters agreed at the PRAPeR Expert Meeting 83. A transfer coefficient (TC) of 5000 $cm^2$/person x h for bare hands and coverall is used and of 1400 $cm^2$/person x h for gloves and coverall. Since no specific dislodgeable foliar residue (DFR) value is available, a conservative default value of 0.003 mg/$cm^2$ is used.

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

| Scenario | With PPE[(a)] | With PPE [(b)] |
|---|---|---|
| Ornamentals (1 application) | 180 | 53 |
| Ornamentals (2 applications) | 340 | 103 |

[(a)] Long sleeved shirt and long trousers.
[(b)] Gloves & coverall; default of 10 % was used as penetration factor through PPE.

According to the representative uses, the maximum amount of treatments with flurprimidol is two, with a 14-day interval. There are no residue decline rate data available for flurprimidol. Therefore, as a worst case scenario, the dislodgeable amount after two treatments is assumed. After one application of 'Topflor', the estimated worker exposure is below the AOEL when the use of gloves and coverall is considered. After 2 applications (summing up two consecutive applications), worker exposure exceeds the AOEL even when PPE are worn and a critical area of concern is identified. Furthermore, flurprimidol is a racemate and there is no information on the relative toxicity of the respective isomers or whether the isomer ratio is maintained in the residues workers are exposed to. A data gap is identified to address this.

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 (PRAPeR 45). The resubmission application for flurprimidol did not necessitate an amendment of the conclusion previously reached in this section.

### 3.1. Nature and magnitude of residues in plant

#### 3.1.1. Primary crops

No data were submitted to investigate the nature and magnitude of residues in plants. As dietary exposure of consumers to flurprimidol residues is normally not expected from the representative use in container grown ornamentals, pot and bedding plants, no such data were 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 were 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

No data were 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 consumer risk assessment is only based on the premise of a 'no dietary exposure situation' for humans and livestock from the representative use.

The representative use 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 the representative use.

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 representative use.

### 3.4. Proposed MRLs

The representative use does not concern food or feed items. Under the provision set out above the representative use does 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.

All available fate and behaviour into the environment studies 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 by the experts attending PRAPeR 42 to be non essential for the assessment of the representative use, if this is restricted in order to avoid / minimise exposure to the environment, including the potential exposure arising from disposal of soil used in pots and any plant residues when the ornamental production is not sold. However, it should be noted that subsequent to the advice of PRAPeR 42 experts and the Member State comments on the Additional Report (Finland, 2010a), the PPR panel of EFSA published an Opinion (EFSA, 2010b) that questions the effectiveness of risk management measures, such as those proposed here, to limit environmental exposure from uses in glasshouses.

Fluprimidol is a racemate and none of the fate and behaviour studies have utilised methods of analysis that would quantify the individual enantiomers. Further information would be needed to address the risk consequent from exposure to potentially varying isomer composition. As with appropriate restrictions, it was proposed significant environmental exposure might be precluded and further information may not be necessary on this. However, this would require that the restrictions were strictly adhered to and that they were effective.

The resubmission application for flurprimidol did not necessitate any expert consultation in this section. Whilst the resubmission application was made on the basis of a revised lower application rate and longer application interval, no amendments to the environmental exposure estimates were made by the applicant or RMS. It should be noted that the predicted environmental exposure (PEC) estimates in Appendix A of this conclusion have not been updated and represent the higher dose rate of 30 g a.s./ha and shorter application interval of 7 days considered in EFSA (2008). Therefore the PEC values in Appendix A overestimate environmental exposure, compared to what was requested by the applicant in their resubmission application.

### 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 $^{14}C$ labelled at the phenyl ring. In the first study, four metabolites were found. Two

of the metabolites (M1 and M2)[9] 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 section 4.1.1. Flurprimidol is medium to high persistent in soil ($DT_{50}$ = 98 – 183 d) under dark aerobic conditions at 20 °C. The laboratory data trigger field studies. The 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 $DT_{90}$ 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 (Koc = 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 only be considered as providing supplementary information. Components of the radioactivity found in the leachate or in the soil column was not characterised in any of these studies. There was also a North American field leaching study available that was assessed by the RMS as only sufficient to be considered as providing supplementary information for the EU assessment.

### 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** (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** (max. 9.2% AR after 5 d, end of the study). An additional aqueous photolysis study was performed under glasshouse 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.

[9] No chemical identification of metabolites M1 and M2 is available.

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 to 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 were 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 the representative use proposed if it is restricted to high technology glasshouse production systems with irrigation / excess water management systems that guarantee no release of contaminated water to the environment.

#### 4.2.2. Potential for groundwater contamination of the active substance their metabolites, degradation or reaction products

Potential contamination of groundwater of flurprimidol and its soil metabolites has been excluded on the basis of the proposed representative use (application in ornamentals in pots in glasshouses 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 groundwater. 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 form plant surfaces. The tropospherical half-life of flurprimidol was 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

The risk assessment was based on the following documents: European Commission (2002a, 2002b, 2002c), SETAC (2001).
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 glasshouses that are permanent structures. The risk assessment does not cover situations where the treated soil or plants are disposed of in the environment.

The resubmission application for flurprimidol did not necessitate any expert consultation in this section. Whilst the resubmission application was made on the basis of a revised lower application rate and longer application interval, no amendments to the toxicity exposure ratio (TER) estimates were made by the applicant or RMS. It should be noted that the TER estimates in Appendix A of this conclusion have not been updated and represent the slightly higher dose rate of 30 g a.s./ha and shorter application interval of 7 days considered in EFSA (2008). Therefore the risk characterisation discussed below and included in Appendix A is more conservative than is necessary for the use pattern requested in the resubmission application.

### 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- and fish-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 representative use if the use is restricted to high technology glasshouse production systems with irrigation/excess water management systems.

### 5.2. Risk to aquatic organisms

The acute end points for fish, daphnids and algae were 17.2, 11.8 and 1.05 mg a.s./L. Flurprimidol is very toxic for the aquatic organisms. The toxicity of flurprimidol was increased in the tested formulation. The $LC/EC_{50}$ for fish and daphnids tested with the formulation were 0.422 and 0.688 mg a.s./L and the 72-h $EbC_{50}$ 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 representative 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 µg a.s./bee for technical flurprimidol and >1.31 and >1.99 µg formulation/bee for the formulation 'Topflor'. 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* ($LR_{50}$ = 89.2 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 g a.s. x 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*, *Phytoseiulus persimilis*, *Chrysoperla carnea*, *Orius insidiosus* and *Poecilus cupreus* were submitted. All tests were limited 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 higher application rates 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 14 d $LC_{50}$ (corrected by 2) value for earthworms was 164 mg a.s./kg dry soil. Based on a PECsoil 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 and therefore a data gap was identified. However, a long-term (reproduction) study is considered not necessary to finalise the EU risk assessment 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 and a data gap was identified. However, 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 and a data gap was identified. However, 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 higher 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

### 6.1. 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 it will be used only in high technology glasshouses with management measures to prevent environmental exposure).

### 6.2. Water

#### 6.2.1. 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 it will be used only in high technology glasshouses with management measures to prevent environmental exposure).

### 6.2.2. 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 it will be used only in high technology glasshouses with management measures to prevent environmental exposure).

### 6.3. Air

Definition for risk assessment: flurprimidol

Definitions for monitoring: flurprimidol

### 6.4. 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

### 6.5. 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

## 7. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments

### 7.1. 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. However, this data gap is considered not essential if the representative use is restricted as proposed. |
| 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

## 7.2. 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 | Very toxic to aquatic organisms, end point driving the aquatic risk assessment: algae $E_bC_{50}$ = 0.624 mg a.s./L (regulatory concentration including a safety factor of 10 = 0.0624 mg a.s./L). A low risk to the aquatic environment was indicated in the surface water risk assessment. |
| Soil metabolite M1 | No data available* | No data available* | No data available* | No data available* | No data 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

### 7.3. Surface water and sediment

| Compound (name and/or code) | Ecotoxicology |
|---|---|
| flurprimidol | Very toxic to aquatic organisms, end point driving the aquatic risk assessment: algae $E_bC_{50}$ = 0.624 mg a.s./L (regulatory concentration including a safety factor of 10 = 0.0624 mg a.s./L). A low risk to the aquatic environment was indicated in the surface water risk assessment. A data gap was identified for a study with higher aquatic plants since flurprimidol is a plant growth regulator. However, this data gap is considered not essential if the representative use is restricted as proposed. |
| Photolysis metabolite D | No data available* |
| Photolysis metabolite E | No data available* |
| Soil metabolite M1 | No data available* |
| Soil metabolite M2 | No data available* |
| Potential metabolites from the pyrimidine ring | No data available* |
| 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

### 7.4. Air

| Compound (name and/or code) | Toxicology |
|---|---|
| flurprimidol | Rat $LC_{50}$ inhalation > 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

- 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).

- Applicant 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 applicant; refer to chapter 1, proposal for classification of flurprimidol as toxic, R60).

- Flurprimidol is a racemate. The preferential metabolism/degradation of each isomer and the possible impact on the toxicity of residues to which workers are exposed, needs to be addressed (relevant for all representative uses evaluated; data gap identified by EFSA during drafting of the conclusion; submission date proposed by the applicant: unknown; refer to chapter 2.12).

- Data gap identified for a full data package of fate and behaviour into the environment studies with pyrimidine labelled flurprimidol (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 4).

- Data gap identified for the risk to non target wild organisms consequent from exposure to potentially varying isomer composition of fluprimidol to be addressed (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 4).

- Data gap identified for a route of degradation in soil study under aerobic conditions and depending on results an update of the risk assessment to non-target wildlife from exposure to metabolites (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 4.1).

- Data gap identified for field dissipation studies in soil as triggered by the available laboratory data (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 4.1).

- Data gap identified to address potential accumulation in soil (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 4.1).

- Data gap identified to further assess exposure to aqueous photolysis metabolites and completion of consequent aquatic organisms risk assessment (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 4.2.1).

- Data gap identified for water / sediment studies in at least two systems (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 4.2.1).

- A risk assessment for earthworm- and fish-eating birds and mammals (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 5.1).

- A study and a risk assessment for higher aquatic plants (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 5.2).

- A long-term (reproduction) study with earthworms (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapter 5.5).

- The risk to soil non-target macro- and micro-organisms needs to be addressed. (not essential if the representative use can be effectively restricted as proposed; no submission date proposed by the applicant; refer to chapters 5.6 and 5.7).

## CONCLUSIONS AND RECOMMENDATIONS

### OVERALL CONCLUSIONS

The conclusion of the resubmission was reached on the basis of the evaluation of the representative use 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 of 2 applications at a maximum individual application rate per spray of 22.5 g a.s./ha, with an interval of 14 days between applications. Note that for the environmental risk assessment the assessment available is for the previous representative use considered in the review, i.e. for 2 applications at a maximum individual application rate per spray of 30 g a.s./ha, 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.

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 an 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 end points 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 estimated level of operator exposure calculated for glasshouse uses on ornamentals according to the EUROPOEM II and the Dutch model is below the AOEL when the use of PPE (gloves and protective clothing) is considered. Estimated exposure of workers is below the AOEL after one application of 'Topflor' when the use of gloves and coverall is considered. After 2 applications (assuming that there is no decay in the residues during the 14-days interval between applications), estimated worker exposure exceeds the AOEL (103 %) even when PPE are worn and a critical area of concern is identified. Furthermore, flurprimidol is a racemate, there is no information on the relative toxicity of each isomer or whether there is a shift in the isomer ratio workers are exposed to. A data gap is identified to address this. Bystander's exposure is not relevant for the representative use.

No data were submitted to study and assess the residue behaviour of flurprimidol in plants and livestock in order to define the relevant residues for dietary consumer risk assessment. The representative use of flurprimidol in containerised ornamentals, pot and bedding plants are normally not expected to result in any dietary exposure to consumers or livestock. Potted herbs or any other edible container plants are not meant to be included in the representative use. A potential transfer of residues from recycled soil and/or compost to crops intended for human or animal consumption should be avoided, by taking 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 representative use.

All available fate and behaviour into the environment studies 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 are very limited. Information on the fate of the individual enantiomers was not available. 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 show that flurprimidol exhibits medium to high persistence in soil ($DT_{50}$ = 98 – 183 d) under laboratory aerobic conditions (no field studies 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 the aquatic environment in the situation that exposure could not be completely excluded from the representative use. No water sediment study is available in the dossier. Potential groundwater contamination was precluded from the representative use 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 can be effectively restricted / managed in order to avoid exposure to the environment, including the potential exposure arising from disposal of used soil and residues of plants. Note the PPR panel of EFSA published an Opinion (EFSA, 2010b) that questions the effectiveness of risk management measures, such as those proposed here, to limit environmental exposure from uses in glasshouses.

The environmental risk assessment covers only the use in glasshouses 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 glasshouses. 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 representative use if the use is restricted to high technology glasshouse 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 glasshouse 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 glasshouse 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 glasshouses 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**

- Operators have to use PPE (gloves during mixing and loading, gloves and protective clothing during application) to obtain a level of exposure below the AOEL.
- Workers have to use PPE (gloves and coverall) to obtain a level of exposure below the AOEL when considering only one application of 'Topflor'.
- 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:

    - avoid the use of recycled/composted material to grow edible crops
    - preclude disposal of contaminated soil and plant material (including recycled/ composted material) in the environment
- The environmental risk assessment may be concluded for the representative use proposed if it is restricted to high technology glasshouse production systems with irrigation / excess water management systems that guarantee no release of contaminated water to the environment. This may be difficult to achieve in practice (EFSA 2010b).

**CRITICAL AREAS OF CONCERN**

- Estimated worker exposure exceeds the AOEL when the two proposed applications are summed up even when PPE are worn. Furthermore, the isomer ratio identification/relative toxicity to which workers are exposed is not finalised.

- Environmental data package clearly insufficient to perform the environmental risk assessment for any use with fewer restrictions than the ones proposed to be applied to the representative use[10].

[10] Note the opinion (EFSA, 2010b) questions the effectiveness of risk management measures, such as those proposed here, to limit environmental exposure from uses in greenhouses.

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# APPENDICES

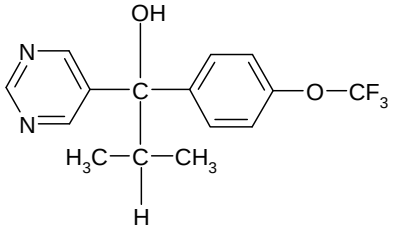
## APPENDIX A – LIST OF END POINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

### 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) ‡** | (*RS*)-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 ‡ | 983 g/kg (racemate) |
| Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured | none |
| **Molecular formula ‡** | $C_{15}H_{15}F_3N_2O_2$ |
| **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 x $10^{-4}$ Pa at 25 °C (99.4 %) |
| Henry's law constant ‡ | 2.74 x $10^{-4}$ 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) | **Solvent:** **Solubility:**<br>acetone 1530 g/l at 20 °C (99.4 %)<br>dichloromethane 1810 g/l at 20 °C (99.4 %)<br>ethyl acetate 1200 g/l at 20 °C (99.4 %)<br>methanol 1990 g/l at 20 °C (99.4 %)<br>toluene 144 g/l at 20 °C (99.4 %)<br>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 %)<br>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 %)<br>Maximum absorption at<br>neutral:<br>$\lambda_{max}$ = 204.8 nm ε = 19100 l $mol^{-1}$ $cm^{-1}$<br>acid:<br>$\lambda_{max}$ = 203.8 nm ε = 18000 l $mol^{-1}$ $cm^{-1}$<br>basic:<br>$\lambda_{max}$ = 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 %) |

**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 | | | 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 | '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 | 14 days | 1.125-2.25 | 1000-2000 | 22.5 | 14 | Total rate/season 45.0 g as/ha [1], [2] |
| | S | 'Topflor' | G | Growth regulator | ME | 3.8 g/L | | | 2 | 14 days | 1.5 -4.5 | 500-1500 | 22.5 | 14 | Total rate/season 45.0 g as/ha [1], [2] |

[1] Environmental data package clearly insufficient to perform the environmental risk assessment for any use with fewer restrictions than the ones proposed to be applied to the representative use.

[2] Estimated worker exposure exceeds the AOEL after 2 applications, even when the use of PPE is considered. Furthermore, the isomer ratio identification/relative toxicity workers are exposed to is not finalised.

* For uses where the column "Remarks" is marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).

(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)

(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)

(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds

(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989

(f) All abbreviations used must be explained

(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench

(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated

(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. 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).**

(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(k) Indicate the minimum and maximum number of application possible under practical conditions of use

(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha

(m) PHI - minimum pre-harvest interval

## 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) | None |
| 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.<br>Residue definition is not relevant. |
| Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes) | No analytical method is required.<br>Residue definition is not relevant. |
| Soil (analytical technique and LOQ) | Open, method required |
| Water (analytical technique and LOQ) | Open, method required |
| Air (analytical technique and LOQ) | Open, method required |
| 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 |

## 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, bile 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 |
| Toxicologically relevant compounds ‡ (environment) | Flurprimidol |

### Acute toxicity (Annex IIA, point 5.2)

| | | |
|---|---|---|
| Rat $LD_{50}$ oral ‡ | 709 mg/kg bw (rat)<br>602 mg/kg bw (mouse) | **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 and modified Buehler tests) | |

### 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)<br>1.96 mg/kg bw/day (90-day, rat)<br>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 according to the studies submitted; genotoxicity data of the material of the new source not available | |

### 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)<br>**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 ‡ | Parental: Decreased body weight and liver effects<br>Reproduction: Dystocia, increased progeny mortality in $F_0$ animals, decreased mating index, increased precoital period and decreased mean litter/pup weight.<br>Offspring: Reduced pup survival and body weight gain | **Repr. Cat. 2; R60** |
| Relevant parental NOAEL ‡ | 7.3 mg/kg bw/day | |
| Relevant reproduction NOAEL ‡ | 1.8 mg/kg bw/day | |
| Relevant offspring NOAEL ‡ | 7.3 mg/kg bw/day | |

### Developmental toxicity

| | | |
|---|---|---|
| Developmental target / critical effect ‡ | Rat: | **Repr.** |

| | | |
|---|---|---|
| | *Maternal*: Reduced food consumption and body weight gain<br>*Foetal*: Malformations (microphthalmia), increased incidence of variants and abnormal foetuses<br>Rabbit:<br>*Maternal*: decreased bodyweight<br>*Foetal*: increased incidence of variants and abnormal foetuses | **Cat. 3; R63** |
| Relevant maternal NOAEL ‡ | Rat: 10 mg/kg bw/day<br>Rabbit: 9.0 mg/kg bw/day | |
| Relevant developmental NOAEL ‡ | Rat: 10 mg/kg bw/day<br>Rabbit: 9.0 mg/kg bw/day | |

**Neurotoxicity (Annex IIA, point 5.7)**

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

**Other toxicological studies (Annex IIA, point 5.8)**

| | |
|---|---|
| Mechanism studies ‡ | No data - not required |
| Studies performed on metabolites or impurities ‡ | 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 missing investigation of sensitive parameters;

** Higher SF based on 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) | 6 % for the concentrate<br>15 % for the spray dilution<br>based on an *in vitro* study with human skin performed with Topflor 15 g flurprimidol/L ME |

**Exposure scenarios (Annex IIIA, point 7.2)**

| | |
|---|---|
| Operator | Estimated exposure for Topflor according to the EUROPOEM II and Dutch –model (application rate 0.0225 kg flurprimidol/ha)<br><br>Handheld equipment, indoors, ornamentals (EUROPOEM II) % of AOEL<br>without PPE: 710 %<br>with PPE (gloves during M/L, gloves and protective clothing during application): 73 %<br><br>Handheld equipment, indoors, roses, carnations and chrysanthemums (Dutch-model) % of AOEL<br>without PPE: 170 – 190 %<br>with PPE (gloves during M/L, gloves and protective clothing during application): 2 – 28 % |
| Workers | Estimated exposure for Topflor (EUROPOEM II). % of AOEL<br>After 1 application:<br>with PPE (long sleeved shirt and long trousers): 180 %<br>with PPE (gloves and coverall): 53 %<br><br>After 2 applications:<br>with PPE (long sleeved shirt and long trousers): 340 %<br>with PPE (gloves and coverall): 103 % |
| Bystanders | Not relevant for the representative use |

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

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

## Residues

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

| | |
|---|---|
| Plant groups covered | No representative use on edible crops or animal feed; any studies have been neither 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: |
|---|---|---|---|
| | Conditions of requirement of feeding studies | | |
| Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level) | 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)<br>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.

**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<br><br>(a) | Recommendation/comments | MRL estimated from trials according to the representative use | HR<br><br>(c) | STMR<br><br>(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 | 0.003 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 | 0.09 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 |

## 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 20ºC and 40 % MWHC, (n=3)<br>4.6 % AR after 102 d at 20ºC and 80 % MWHC, (n=1) |
| Non-extractable residues after 100 days ‡ | 15.1-18.9% AR after 102 d at 20ºC and 40 % MWHC, (n=3)<br>29.6 % AR after 102 d at 20ºC and 80 % MWHC, (n=1) |
| Metabolites requiring further consideration for risk assessment ‡ | No major metabolites exceeding 10 % AR is formed in soil<br>Metab. M1: 5.0-9.2% AR on ≥ 2 consecutive time points.<br>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 / % MWHC | $DT_{50}$ /$DT_{90}$ (d) | $DT_{50}$ (d) 20°C pF2/10kPa | St. ($r^2$) | Method of calculation |
| Loamy sand | 6.1 | 20 °C/40 %<br>10 °C<br>30 °C | 118 / 393<br>260 / 865<br>54 / 179 | not available | 0.87 | SFO<br>Arrhenius eq.<br>Arrhenius eq. |
| Sandy loam | 8.1 | 20 °C/40 %<br>10 °C<br>30 °C | 98 / 326<br>216 / 717<br>45 / 148 | not available | 0.95 | SFO<br>Arrhenius eq.<br>Arrhenius eq. |
| Sandy clay | 8.3 | 20 °C/40 %<br>10 °C<br>30 °C | 157 / 522<br>345 / 1148<br>71 / 237 | Not available | 0.99 | SFO<br>Arrhenius eq.<br>Arrhenius eq. |
| Peat | 4.3 | 20 °C/80 %<br>10 °C<br>30 °C | < 183 / < 608<br>< 403 / < 1338<br>< 83 / < 276 | Not available | 0.89 | SFO<br>Arrhenius eq.<br>Arrhenius eq. |
| Geometric mean DT50 | | 20 °C | 178 | Not available | | |

| | |
|---|---|
| Field studies ‡ | No reliable field dissipation data available, data gap.<br>Not required for the representative use according to GAP if restricted as proposed by the meeting of experts. |
| 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 | Kd | Koc | Kf | Kfoc | 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 | Eluation (mm): 200 mm<br>Time period (d): 2 days |
| | Leachate: 0.29 % of applied radioactivity in leachate,<br>53 % of applied radioactivity retained in top 5 cm (n=1) |
| Column leaching ‡ / 02 | Eluation (mm): 508 mm<br>Time period (d): 5 × □≤ 2 days |
| | Leachate: 0.74 - 1.07 % of applied radioactivity in leachate,<br>22.6–94.1 % of applied radioactivity retained in top 6 cm (n=4) |
| Aged residues leaching ‡ / 01 | Aged for (d): 98 days<br>Eluation (mm): 200 mm<br>Time period (d): 2 days |
| | Analysis of soil residues post ageing: 81.2 % active substance,<br>3.8 % Met I, 2.4 % Met II (not identified further) |
| | Leachate: 1.2 % of applied radioactivity in leachate,<br>62.0 % of applied radioactivity retained in top 5 cm (n=1) |
| Aged residues leaching ‡ / 02 | Aged for (d): 30 days<br>Eluation (mm): 508 mm<br>Time period (d): 5 × ≤ 2 days |
| | Analysis of soil residues post ageing: Not analyzed |
| | Leachate: 1.58-2.34 % of applied radioactivity in leachate,<br>20.0 – 35.8 % of applied radioactivity retained in top 6 cm (n=4) |

| | |
|---|---|
| Aged residues leaching ‡ / 03 | Aged for (d): 30 days<br>Eluation (mm): 563 mm<br>Time period (d): 45 days |
| | Analysis of soil residues post ageing: Recovery 92.9 %, metabolites not determined. |
| | Leachate: 7.3 % of applied radioactivity in leachate,<br>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 PECsoil has been calculated for a soil outside the glasshouse.

The PECsoil given in the DAR represents a concentration in the pot only.

| | |
|---|---|
| Method of calculation | Initial (single application)<br>$\text{Initial PEC}_{soil} = \frac{A \times (1 - f_{int})}{100 \times \text{soil depth} \times \text{soil density}}$<br>Where:<br>A = application rate (g as/ha)<br>$f_{int}$ = fraction intercepted by crop (assumed to be zero)<br>Soil depth = 5 cm<br>Soil density = 1.5 g/cm$^3$<br><br>To calculate the actual and time weighed PEC values following treatment, a worst case $DT_{50}$ of 183 days was used. |
| Application data | A maximum of two applications at a rate of 30 g as/ha at minimum interval of 7 days apart. (Note this is not the representative use. The representative use is 22.5 g as/ha at minimum interval of 14 days).<br>Single: 30 g as/ha<br>Multiple: 60 g as/ha (assuming no degradation between applications) |

| Time interval | Predicted Environmental Concentration in soil[1] | | | |
|---|---|---|---|---|
| | Single application<br>Actual **PEC**$_{soil}$ | Single application<br>Time weighted | Multiple application | Multiple application |

| | | (mg/kg) | average **PEC**$_{twa}$ (mg/kg) | Actual **PEC**$_{soil}$ (mg/kg) | Time weighted 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 PECsoil 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<br>pH 4: > 1 year at 25°C |
| | pH 7: > 1 year at 50°C<br>pH 7: > 1 year at 25°C |
| | pH 9: > 1 year at 50°C<br>pH 9: > 1 year at 25°C |
| Photolytic degradation of active substance ‡ / 01 | $DT_{50}$ : 1.4 days<br>Natural light, 39.8°N<br>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.<br>Photo-product D: max. 16.1% AR at day 5<br>Photo-product E: max. 9.2 % AR at day 5 |
| Photolytic degradation of active substance ‡ / 02 | $DT_{50}$ : 1.4 days<br>Natural light under outdoor conditions, 50°N<br>$DT_{50}$ : 29.0 days<br>Natural light under glasshouse conditions, 50°N |
| Photolytic degradation of active substance ‡ / 03 | $DT_{50}$ : 7.9 hours<br>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 | The initial concentration in surface water is calculated using the following equation:<br>$\frac{A \times dep.rate}{V_{sw} \times 100}$<br>Where:<br>A = application rate: 60 g as/ha<br>dep.rate = deposition rate: 0.1 %<br>$V_{sw}$ = water volume: 300 L/m$^2$ |
| Application data | A maximum of two applications at a rate of 30 g as/ha at minimum interval of 7 days apart.<br>Single: 30 g as/ha<br>Multiple: 60 g as/ha (assuming no degradation between applications)<br>(Note this is not the representative use. The representative use is 22.5 g as/ha at minimum interval of 14 days). |
| Main routes of entry | 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.<br>However, a simplistic Tier 1 scenario of a conservative amount of 0.1 % loading to an adjacent water body is considered. |
| 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 PECsw value would only ever cover high technology glasshouse production systems with irrigation/excess water management systems

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

| | |
|---|---|
| PEC groundwater<br>Not calculated – not required | 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. |

### 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 $34.15\times10^{-12}$ $cm^{-3}$ $molec^{-1}$ $sec^{-1}$ for the hydroxyl reaction and the assumptions of OH radical concentration of $1.5\times10^{6}$ 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<br>No significant atmospheric exposure is expected based on the indoor use, low application rate and low vapour pressure. |

**Residues requiring further assessment**

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

## 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<br>(bodyweight gain, food consumption, erythrocyte counts and packed cell volumes, decreased MCH and MCHC, increased AP, weight and enzymatic induction in liver) |
| Rat | Flurprimidol | Reproductive toxicity (two generation study) | NOEL 1.8 mg/kg bw/day<br>(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. Note this is not the representative use. The representative use is 22.5 g as/ha at minimum interval of 14 days

| Indicator species/Category | Time scale | ETE | TER | Annex VI Trigger |
|---|---|---|---|---|
| Tier 1 (Birds) | | | | |
| No data submitted – justification accepted.<br>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. | | | | |
| Tier 1 (Mammals) | | | | |
| No data submitted – justification accepted.<br>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 | | | | |
| *Oncorhynchus mykiss* | Flurprimidol | 96 hr (static) | Mortality, $LC_{50}$ | 18.3 (nom.) |
| *Lepomis macrochirus* | Flurprimidol | 96 hr (static) | Mortality, $LC_{50}$ | 17.2 (nom.) |
| *Lepomis macrochirus* | Flurprimidol | 28 d (flow-through) | NOEC (based on weight gain) | 0.42 (nom.) |
| *Oncorhynchus mykiss* | Flurprimidol | 21 d (semi-static) | NOEC (based on mean length and wet weight) | 1.63 (m.m.) |
| *Oncorhynchus mykiss* | "Topflor" (3.74 g as/L) | 96 hr (flow-through) | Mortality, $LC_{50}$ | 112.8 (prep.)<br>0.422 (flurprimidol) |
| Aquatic invertebrates | | | | |
| *Daphnia magna* | Flurprimidol | 48 h (static) | Mortality, $EC_{50}$ | 11.8 (nom.) |
| *Daphnia magna* | Flurprimidol | 21 d (semi-static) | NOEC (based on reproduction) | 1.7 (m.m.) |
| *Daphnia magna* | "Topflor" (3.74 g as/L) | 48 h (static) | Mortality, $EC_{50}$ | 233.7 (prep.)<br>0.688 (flurprimidol) |
| Sediment dwelling organisms | | | | |
| No data available – not required. | | | | |
| Algae | | | | |
| *Pseudokirch. subcapitata* | Flurprimidol | 120 h (static)<br>72 h (static) | Biomass: $E_bC_{50}$ | 0.84 (m.m.)<br>1.05 (m.m.) |
| *Pseudokirch. subcapitata* | "Topflor" (3.74 g as/L) | 72 h (static) | Biomass: $E_bC_{50}$<br>Growth rate: $E_rC_{50}$ | 166.8 (prep.)<br>0.624 (flurprimidol)<br>496.8 (prep.)<br>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 end points 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)**

**Step 1**

Ornamentals under glasshouse conditions, 2 × 30 g as/ha at 7 days interval. Note this is not the representative use. The representative use is 22.5 g as/ha at minimum interval of 14 days

| Test substance | Organism | Toxicity endpoint (mg as/L) | Time scale of endpoint | $PEC_i^*$ (µg/L) | TER | Annex VI Trigger |
|---|---|---|---|---|---|---|
| Flurprimidol | *L. macrochirus* | 17.2 | Acute 96-h $LC_{50}$ | 0.02* | 860000 | 100 |
| Flurprimidol | *L. macrochirus* | 0.42 | Chronic 28-d NOEC | 0.02 | 21000 | 10 |
| Flurprimidol | *D. magna* | 11.8 | Acute 48-h $EC_{50}$ | 0.02 | 590000 | 100 |
| Flurprimidol | *D. magna* | 1.7 | Chronic 21-d NOEC | 0.02 | 85000 | 10 |
| Flurprimidol | *P. subcapitata* | 0.84 | Acute 120-h $E_bC_{50}$ | 0.02 | 42000 | 10 |
| "Topflor" | *O. mykiss* | 0.422 | Acute 96-h $LC_{50}$ | 0.02 | 21100 | 100 |
| "Topflor" | *D. magna* | 0.688 | Acute 48-h $EC_{50}$ | 0.02 | 34400 | 100 |
| "Topflor" | *P. subcapitata* | 0.624<br>1.858 | Acute 72-h $E_bC_{50}$<br>Acute 72-h $E_rC_{50}$ | 0.02 | 31200<br>92900 | 10 |

*PECsw were calculated based on the former application rate "maximum of two applications at a rate of 30 g as/ha at minimum interval of 7 days" (Note this is not the representative use. The representative use is 22.5 g as/ha at minimum interval of 14 days). The PECsw represent a worst case situation, and the outcome of the risk assessment would not change.

### Bioconcentration

| | |
|---|---|
| Log Pow | 3.34 |
| Bioconcentration factor (BCF)* ‡ | 19.3, 52.8 and 35.1 for fillet, viscera and whole fish, respectively, for *L. macrochirus* following 21-28 d exposure (based on $^{14}C$) |
| 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 µg formulation/bee | > 1.99 µg 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. Note this is not the representative use. The representative use is 22.5 g as/ha at minimum interval of 14 days

| Test substance | Route | Hazard quotient | Annex VI Trigger |
|---|---|---|---|
| Flurprimidol | Contact | < 0.3 | 50 |

| Test substance | Route | Hazard quotient | Annex VI Trigger |
|---|---|---|---|
| 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) |
|---|---|---|---|
| *Typhlodromus pyri* ‡ | "Topflor" (EF-1195, 14.8 g as/L) | Mortality | > 29.6 g as/ha |
| *Aphidius rhopalosiphi* ‡ | "Topflor" (0.38 % w/w) | Mortality | 89.2 g as/ha |

Hazard quotients for two sensitive standard species
Ornamentals under glasshouse conditions, 2 × 30 g as/ha at 7 days interval. Note this is not the representative use. The representative use is 22.5 g as/ha at minimum interval of 14 days

| Species | Effect ($LR_{50}$ g/ha) | MAF (multiple application factor) | HQ in-field | HQ off-field | Trigger |
|---|---|---|---|---|---|
| *Typhlodromus pyri* | > 29.6 g as/ha | 2.0 | < 2.03 | Not applicable | 2 |
| *Aphidius rhopalosiphi* | 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 |
|---|---|---|---|---|---|
| *C. carnea* | 2-3 days old larvae | "EF-1195" (14.8 g as/L) on glass plate, 19 days exposure | 14.8<br>29.6 | 3.4 % mortality, no significant effects on reproduction<br>7.0 % mortality, no significant effects on reproduction | 50 % |
| *O. insidiosus* | Second instar nyphs | "EF-1195" on glass plate, 10 days exposure | 17.8 | 15.2 % mortality, no significant effects on reproduction | 50 % |
| *E. formosa* | 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 % |
| *P. persimilis* | Phytoseiid mites | Residues on bean leaves | 18.0 | 40 % mortality, no effects on reproduction | 50% |
| *P. cupreus* | 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 |

**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 | | | |
| *Eisenia foetida* | Flurprimidol ‡ | Acute 14 days<br>Acute 14 days | $LC_{50corr}$ 164 mg as/kg dry soil<br>$NOEC_{corr}$ 31.3 mg as/kg dry soil |
| *Eisenia foetida* | "Topflor"<br>(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.<br>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 $PEC_i$ * (mg/kg)[1] | TER | Trigger |
|---|---|---|---|---|---|
| Earthworms | | | | | |
| *Eisenia foetida* | Flurprimidol | Acute 14 days ($LC_{50}$) | 0.08 | 2050 | 10 |
| *Eisenia foetida* | Flurprimidol | Acute 14 days (NOEC) | 0.08 | 391 | 5 |

* PECs were calculated based on the former application rate "maximum of two applications at a rate of 30 g as/ha at minimum interval of 7 days" (Note this is not the representative use. The representative use is 22.5 g as/ha at minimum interval of 14 days). The PECs would represent a worst case situation, and the outcome of the risk assessment would not change.

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

Preliminary screening data

| |
|---|
| No data available – not required.<br>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/$L_{(nom)}$ |

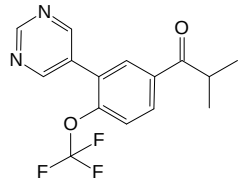
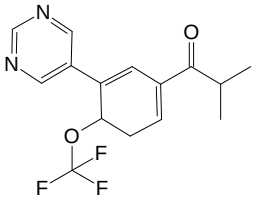
**Ecotoxicologically relevant compounds**

| 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)**

| | RMS proposal |
|---|---|
| Flurprimidol | R51/53 |

## APPENDIX B – 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-(5-pyrimidinyl)-4-(trifluoromethoxy)-1,5-cyclohexadien-1-yl]-1-propanone |  |

* ACD/ChemSketch, Advanced Chemistry Development, Inc., ACD/Labs Release: 12.00 Product version: 12.00 (Build 29305, 25 Nov 2008)

## ABBREVIATIONS

| | |
|---|---|
| λ | wavelength |
| ADI | acceptable daily intake |
| AOEL | acceptable operator exposure level |
| AP | alkaline phosphatase |
| AR | applied radioactivity |
| ARfD | acute reference dose |
| a.s. | active substance |
| bw | body weight |
| °C | degree Celsius (centigrade) |
| CA | Chemical Abstract |
| CAS | Chemical Abstract Service |
| CIPAC | Collaborative International Pesticides Analytical Council Limited |
| cm | centimetre |
| d | day |
| DAR | draft assessment report |
| DFR | dislodgeable foliar residue |
| DM | dry matter |
| DNA | deoxyribonucleic acid |
| DT50 | period required for 50 percent dissipation (define method of estimation) |
| DT90 | period required for 90 percent dissipation (define method of estimation) |
| ε | decadic molar extinction coefficient |
| EC50 | 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 |
| ETE | estimated theoretical exposure |
| EU | European Union |
| EUROPOEM | European Predictive Operator Exposure Model |
| F0 | parental generation |
| F1 | filial generation (first) |
| FAO | Food and Agriculture Organisation of the United Nations |
| FID | flame ionisation detector |
| FOCUS | Forum for the Co-ordination of Pesticide Fate Models and their Use |
| g | gram |
| GAP | good agricultural practice |
| GC-FID | gas chromatography with flame ionisation detector |
| 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 |
| HPLC-UV | high performance liquid chromatography with ultra violet detector |
| HQ | hazard quotient |
| ISO | International Organisation for Standardisation |
| IUPAC | International Union of Pure and Applied Chemistry |
| Koc | organic carbon adsorption coefficient |
| kg | kilogram |
| L | litre |
| LC | liquid chromatography |
| LC50 | lethal concentration, median |
| LD50 | 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 |
| MCH | mean corpuscular haemoglobin |
| MCHC | mean corpuscular haemoglobin concentration |
| ME | micro-emulsion |
| mg | milligram |
| MRL | maximum residue limit or level |
| MS | mass spectrometry |
| MWHC | maximum water holding capacity |
| 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 |
| Pa | pascal |
| PEC | predicted environmental concentration |
| PECA | predicted environmental concentration in air |
| PECS | predicted environmental concentration in soil |
| PECSW | predicted environmental concentration in surface water |
| PECGW | predicted environmental concentration in ground water |
| PHI | pre-harvest interval |
| pKa | negative logarithm (to the base 10) of the dissociation constant |
| PPE | personal protective equipment |
| ppm | parts per million (10-6) |
| ppp | plant protection product |
| r2 | coefficient of determination |
| RMS | rapporteur member state |
| RPE | respiratory protective equipment |
| SF | safety factor |
| SFO | single first-order |
| STMR | supervised trials median residue |
| T | time |
| TC | transfer coefficient |
| TER | toxicity exposure ratio |
| TMDI | theoretical maximum daily intake |
| TSF | task specific factor |
| UV | ultraviolet |
| VIS | visible |
| WHO | World Health Organisation |
| yr | year |