European Food Safety Authority

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CONCLUSION ON PESTICIDE PEER REVIEW

Peer review of the pesticide risk assessment of the active substance cyflufenamid[1]

(Question No EFSA-Q-2009-313)

Issued on 8 April 2009

SUMMARY

Cyflufenamid is a new active substance for which in accordance with Article 6 (2) of Council Directive 91/414/EEC[2] the United Kingdom received an application from Nisso Chemical Europe GmbH for inclusion in Annex I to Directive 91/414/EEC. Complying with Article 6 of Directive 91/414/EEC, the completeness of the dossier was evaluated and confirmed by Commission Decision 2003/636/EC[3].

Following the agreement between the EU-Commission and the EFSA for the EFSA to organise a peer review of those new active substances for which the decision on the completeness of the dossier had been published after June 2002, the designated rapporteur Member State, the United Kingdom made the report of its initial evaluation of the dossier on cyflufenamid, hereafter referred to as the draft assessment report (DAR), available, which was received by EFSA on 30 January 2006.

The peer review was initiated on 10 May 2006 by dispatching the draft assessment report for consultation of the Member States and the notifier. Subsequently, the comments received on the DAR were examined by the rapporteur Member State in the reporting table. This table was evaluated by EFSA to identify the remaining issues which were agreed during a written procedure in May 2007. The identified issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in November-December 2007.

A final consultation on the outcome of the experts' discussion took place during a written procedure with Member States in February - March 2009 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as a fungicide as proposed by the notifier, which comprise foliar spraying to winter and spring cereals against powdery mildew. Full details of the GAPs can be found in the attached end points.

[1] For citation purposes: Conclusion on pesticide peer review regarding the risk assessment of the active substance cyflufenamid. *EFSA Scientific Report* (2009) 258, 1-99

[2] OJ No L 230, 19.8.1991, p. 1. Directive as last amended by L 20, 22.1.2005, p.19

[3] OJ No L 221, 4.9.2003, p.42

The representative formulated product for the evaluation was 'NF-149 EW', an oil-in-water emulsion (EW), containing 50 g/L cyflufenamid.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. Adequate methods are available to monitor all compounds given in the respective residue definition in food/feed of plant origin and environmental matrices, however a data requirement was identified in relation to the method for plants. A data requirement was identified for a monitoring method for the residues in food of animal origin.

In mammals, cyflufenamid is not acutely toxic via oral, dermal or inhalation routes; it is not a skin or eye irritant or skin sensitiser. In the short-term toxicity studies the dog was the most sensitive species showing alterations in the liver function and brain vacuolation. The relevant oral No Observed Adverse Effect Level (NOAEL) is 4.1 mg/kg bw/day (1-year dog study). Cyflufenamid did not show any genotoxic potential. Increased incidences of thyroid tumours and hepatocellular adenomas were observed in male rats and mice, respectively, however, these were not considered to be of relevance for the risk assessment. The relevant NOAEL from the long-term toxicity and carcinogenicity studies is 4.4 mg/kg bw/day (rat study). No specific effect on the reproductive parameters was found in multigeneration studies with rats: the relevant parental and offspring NOAEL is 18 mg/kg bw/day, whereas the reproductive NOAEL is 57 mg/kg bw/day. Tested in developmental toxicity studies, cyflufenamid did not cause malformations in the rat or rabbit: the relevant maternal NOAELs are 100 mg/kg bw/day and 5 mg/kg bw/day (rat and rabbit, respectively); the relevant developmental NOAELs are 1000 mg/kg bw/day (highest dose level tested) for rat, and 10 mg/kg bw/day for rabbit based on skeletal effects (enlarged anterior fontanels and retardation of ossification). The Acceptable Daily Intake (ADI) of 0.04 mg/kg bw/day was derived from the chronic rat study applying a safety factor (SF) of 100. The Acute Reference Dose (ARfD) is 0.05 mg/kg bw (NOAEL for maternal toxicity from the developmental rabbit studies, SF of 100). The Acceptable Operator Exposure Level (AOEL) of 0.03 mg/kg bw/day (rounded) is based on the 1-year dog study with a correction for oral absorption of 70% and a safety factor of 100. The operator, worker and bystander exposure was estimated to be below the AOEL even without the use of personal protective equipment.

The metabolism of cyflufenamid was investigated in wheat and rotational crops. The metabolism was found to be moderate. Besides cyflufenamid, its *E*-isomer 149-(*E*)-FB[4] and further metabolites (149-F-2-OH-B[5], 149-F-4-OH-B[6], 149-F-α-OH-B[7], 149-F[8] and 149-F4B-Glu[9]) were identified. The meeting of experts decided to include the *E*-isomer in the residue definition for plant matrices based on the assumption that the analytical methods used in the residue trials and for monitoring cannot separate the two isomers. The notifier was asked to confirm this assumption. Based on the results of a confined rotational crop study, no residues above the LOQ are expected in parts of rotational crops intended for human consumption.

[4]149-(E)-FB: *N*-{(*E*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-phenylacetamide
[5]149-F-2-OH-B:*N*-{(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-(2-hydroxyphenyl)acetamide
[6]149-F-4-OH-B:*N*-{(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-(4-hydroxyphenyl)acetamide
[7]149-F-α-OH-B:*N*-{(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-hydroxy-2-phenylacetamide
[8] 149-F:*N*'-(cyclopropylmethoxy)-2,3-difluoro-6-(trifluoromethyl)benzenecarboximidamide
[9] 149-F4B-Glu: *N*-{(*Z*)- [2,3-difluoro-6-trifluoromethy α-(β-glucopyranosylimino)benzyl]}-2-phenylacetamide

Dietary burden calculations showed a significant intake of cyflufenamid through cereal straw and grain for dairy and beef cattle only. A metabolism study on ruminants was submitted and showed low transfer of residues into milk and tissues. Cyflufenamid was the main radioactive component in fat. However, in other tissues and milk, the metabolite 149-F1[10] was the main radioactive component. The meeting of experts decided to include 149-(*E*)-FB and 149-F1 in the residue definitions for animal matrices. It was concluded that bioaccumulation of cyflufenamid is not expected, and that no significant residues are expected in food of animal origin after feeding with cereal grain and straw treated according to the notified cGAP.

MRLs for wheat, triticale, rye and barley were proposed provisionally on the basis of the residue trials on wheat and barley, pending confirmation that the analytical method used in the residue trials covers the residue definition for food in plant matrices. MRLs for animal matrices should be set at the LOQ when an analytical method for animal products is available.

A chronic and acute dietary intake estimate was carried out by the rapporteur Member State. The theoretical maximum daily intake (TMDI) was below 1% of the ADI and the national estimated short-term intake (NESTI) maximum 2% for all considered consumer groups.

In soil under aerobic conditions cyflufenamid exhibits low to high persistence forming the soil metabolites: 149-F (low to moderate persistence), 149-F11[11] (low persistence), 149-F1 (high to very high persistence), 149-F6[12] (very high persistence). Mineralisation to carbon dioxide represented less than 0.1% of the applied radioactivity (AR) in the fluorinated phenyl-labelled study, and represented 49.8% AR at 45 days in the cyclopropyl-labelled study. The formation of unextractable residues was a sink, accounting for 27.0-36.8% AR after 45-120 days. Cyflufenamid exhibits slight to low mobility in soil, with the four metabolites indicated above exhibiting very high mobility in soil. There was no indication that adsorption of any of these compounds was pH dependant.

In dark natural sediment-water systems cyflufenamid dissipated from the water phase with a first-order DT_{50} of 3.6-5.0 days. Cyflufenamid partitioned to the sediment with a peak concentration measured 14 days after dosing of 63.0-64.8% AR. The more prominent degradation products in both systems were 149-F11 (maximum 15.5% AR in water and maximum 6.8% AR in sediment) and 149-F (maximum 7.1% AR in water and maximum 8.6% AR in sediment). The terminal metabolite, CO_2, was a small sink in the material balance accounting for a maximum of 0.5-3.5% of the applied fluorinated phenyl-U-[^{14}C] cyflufenamid. Unextracted sediment residues were a sink representing 8.4-19.1% of this radiolabel at the study end. The available surface water exposure assessment for cyflufenamid and for the metabolites 149-F and 149-F11 only considered the spray drift route of entry to surface water bodies, as FOCUS SW was not available when the DAR of cyflufenamid was written.

The potential contamination of ground water by cyflufenamid and its soil metabolites 149-F, 149-F1, 149-F6 and 149-F11, when used according to the proposed representative uses, was assessed with FOCUS GW PELMO (v.3.3.2) model and the relevant scenarios. The results showed that for cyflufenamid and for the metabolites 149-F and 149-F11 no annual average concentration in the percolate at 1m soil depth exceeding 0.001 µg/L is to be expected. The concentrations for the metabolite 149-F1 are in the range of 0.011 – 0.546 µg/L. The concentration of 0.1 µg/L is exceeded in 7 out of 9 European FOCUS scenarios parameterised

[10] 149-F1: 2,3-difluoro-6-(trifluoromethyl)benzenecarboximidamide
[11] 149-F11:3-({(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}amino)-3-oxopropanoic acid
[12] 149-F6: 2,3-difluoro-6-(trifluoromethyl)benzamide

for winter cereals. For the metabolite 149-F6 the estimated PEC_{gw} are > 0.75 µg/L in all the simulated scenarios (80^{th} percentile annual average concentration at 1m ranged from 1.566 µg/L to 5.623 µg/L). The toxicological assessment was able to conclude that the metabolites 149-F1 and 149-F6 are not relevant concerning groundwater at the expected concentrations.

Cyflufenamid is not expected to be transferred to the atmospheric compartment and the potential for long-range transport may be considered negligible.

The acute, short-term and long-term risk to herbivorous and insectivorous birds and the acute and long-term risk for herbivorous and insectivorous mammals was low for the representative uses in cereals at an application rate of 25 g a.s./ha. The risk from secondary poisoning and from the uptake of contaminated drinking water to birds and mammals can be considered as low.

Aquatic organisms were more sensitive to the lead formulation 'NF-149 EW'. The potential exposure of surface water with the parent compound cyflufenamid and the soil major metabolites 149-F, 149-F1 and 149-F11 via the drainage and run-off routes of entry has not been assessed. The EFSA considers that the main route of exposure was via drift. Therefore, in case the new PECsw for the run-off and drainage are considered, it is expected that these would be lower than those obtained with the drift. The risk to aquatic organisms for the representative uses of cyflufenamid and its relevant metabolites can be regarded as low for exposure via drift. The resulting BCF (bioconcentration factor) exceeds the Annex VI trigger value of 100 for not readily biodegradable compounds. Nevertheless, the risk from bioconcentration in fish is considered to be low as more than 95% depuration was observed in 14 days.

Low acute and chronic risk to earthworms was assessed from the representative uses of cyflufenamid and its relevant metabolites.

The risk to bees, non-target arthropods, soil non-target macro-organisms, soil non-target micro-organisms, non-target terrestrial plants and biological methods for sewage treatment was assessed as low.

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

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BACKGROUND

In accordance with Article 6 (2) of Council Directive 91/414/EEC the United Kingdom received an application from Nisso Chemical Europe GmbH for inclusion of the active substance cyflufenamid in Annex I to Directive 91/414/EEC. Complying with Article 6 of Directive 91/414/EEC, the completeness of the dossier was evaluated and confirmed by Commission Decision 2003/636/EC.

Following the agreement between the EU-Commission and EFSA for EFSA to organise a peer review of those new active substances for which the completeness of the dossier had been officially confirmed after June 2002, the designated rapporteur Member State, the United Kingdom submitted the report of its initial evaluation of the dossier on cyflufenamid, hereafter referred to as the draft assessment report (DAR), which was received by EFSA on 30 January 2006. This draft assessment report was distributed for consultation to the Member States and the notifier on 10 May 2006.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State in the reporting table. Based on this evaluation, EFSA identified and agreed with Member States during a written procedure in May 2007 on lacking information to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in expert meetings organised on behalf of the EFSA in November – December 2007. The reports of these meetings have been made available to the Member States electronically.

A final consultation on the outcome of the experts' discussions took place during a written procedure with Member States in February - March 2009 leading to the conclusions as laid down in this report.

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

Following the agreement between the EU Commission and EFSA regarding the peer review of new active substances, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period. 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 peer review was compiled as a peer review report comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received,
- the resulting reporting table (revision 1-1; 22 June 2007),

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

- the reports of the scientific expert consultation,
- the evaluation table (revision 2-1; 2 April 2009).

Given the importance of the draft assessment report including its addendum (compiled version of January 2009 containing all individually submitted addenda) and the peer review report

with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Cyflufenamid is the ISO common name for *(Z)-N*-[α-(cyclopropylmethoxyimino)-2,3-difluoro-6-(trifluoromethyl)benzyl]-2-phenylacetamide (IUPAC).

Cyflufenamid belongs to the class of amide fungicides. It is fungitoxic to powdery mildew on cereals through translaminar and vapour activity, although the mode of action has not been established.

The representative formulated product for the evaluation was 'NF-149 EW', an oil-in-water emulsion (EW), containing 50 g/L cyflufenamid.

The representative uses evaluated comprise foliar spraying with conventional tractor-mounted devices against powdery mildew in winter and spring wheat, triticale, rye and barley, from growth stage of BBCH 30 up to growth stage of BBCH 59, in all EU countries, up to a maximum of two applications, at a maximum individual application rate per spray of 25 g a.s./ha, with an interval of 28 days between applications.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

The minimum purity of cyflufenamid is 980 g/kg. There is no FAO specification available.

The PRAPeR 36 meeting of experts (November 2007) agreed that the 5-batch data supported a minimum purity of 980 g/kg, and this agreed new minimum purity of the technical material was presented in an addendum to Volume 4 (February 2008).

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 cyflufenamid or the respective formulations.

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

Adequate analytical methods are available for the determination of cyflufenamid in the technical material (HPLC-UV, 210 nm) and in the representative formulation (HPLC-DAD, 254 nm), as well as for the determination of the respective impurities in the technical material (HPLC-UV, GC-FID).

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 residue definition for monitoring purposes for food/feed of plant origin was set to sum of cyflufenamid and its *E* isomer (cereals).

A GC-MS method is available to monitor cyflufenamid residues in food/feed of plant origin with a LOQ of 0.01 mg/kg (cereal grain), however a data requirement was set to amend the primary method regarding batch size and storage of extracts, and also to clarify whether the method is able to separate the *E* and *Z* isomers or not.

The PRAPeR 40 meeting of residues experts (December 2007) decided to set the residue definition for enforcement for food/feed of animal origin as the sum of the parent compound,

the *E*-isomer and metabolite 149-F1[13]. It was also decided that MRLs for animal commodities should be proposed at the LOQ of the analytical method for monitoring. Since no enforcement analytical method is available for the animal commodities, a data requirement was identified for the enforcement analytical method.

The residue definition for the environmental compartment is cyflufenamid.

GC-MS methods are available to monitor residues of cyflufenamid in soil with a LOQ of 0.03 mg/kg.

A GC-MS method is available to monitor residues of cyflufenamid in ground water, surface water and drinking water with a LOQ of 0.1 µg/l, however the confirmatory method was validated at this level only for one ion (m/z 412). However, the LC-MS method used to determine residues of cyflufenamid in leachate water at levels down to 0.05 µg/l, submitted in the original dossier to support pre-registration studies for the environmental fate and behaviour section, was deemed acceptable by the PRAPeR 36 meeting of experts (November 2007) as a confirmatory method.

Adequate GC-MS method is available to monitor residues of cyflufenamid in air with a LOQ of 1 µg/m^3.

Since cyflufenamid is not classified as acute toxic or very toxic, analytical methods for the determination of residues of cyflufenamid in body fluids and/or tissues are not required.

2. Mammalian toxicity

Cyflufenamid was discussed at the PRAPeR 39 meeting of experts held in Parma in December 2007.

The experts concluded that the proposed technical specification was covered by the batches used in the toxicity studies.

2.1. Absorption, distribution, excretion and metabolism (toxicokinetics)

Cyflufenamid oral absorption is rapid and estimated at 70%; most of the radioactivity following oral administration of radiolabelled cyflufenamid was eliminated via faeces (70%) and urine within 48 hours. Faeces were the major route of excretion for absorbed material. Some indication of potential bioaccumulation in the food chain was reached based on the ADME data. Metabolism of cyflufenamid in rats is extensive and proceeded mainly via reduction, hydroxylation and methoxylation.

2.2. Acute toxicity

Cyflufenamid is not acutely toxic to rats via the oral, dermal (LD_{50} > 5000 mg/kg bw and 2000 mg/kg bw, respectively) or inhalation (LC_{50} >4.76mg/l of air - nose only/4h) routes; it is not classified as a skin- or eye irritant, or skin sensitiser in the guinea pig maximization test.

[13] 149-F1: 2,3-difluoro-6-(trifluoromethyl)benzenecarboximidamide

2.3. Short-term toxicity

The short-term toxicity of cyflufenamid has been evaluated in rats, mice and dogs. The target organs were the liver (rats, mice, dogs); heart, testis (rats, mice); kidney (rats); uterus, ovaries, prostate and brain (dog). The dog was the most sensitive species. The relevant oral NOAEL was 4.1 mg/kg bw/day in the 1-year dog study based on alterations in liver function (increased serum alkaline phosphatase). In the 90-day dog study, dogs showed brain vacuolation of the white matter of cerebrum and thalamus at relatively high doses (76 mg/kg bw/day). The brain vacuolation did not disrupt neurologic functions and was reversible. The effect was treatment-related as well as duration- and dose dependant. Cyflufenamid did not cause signs of neurotoxicity in the 90-day rat neurotoxicity study, and vacuolation was absent from the 1- year dog study. During the meeting of experts the relevance of brain vacuolation was discussed. The finding was not observed in mice, rats and in the 1-year dog study (in this case the doses tested were lower than the ones tested in the 90-day study). No information was available on the first occurrence of brain vacuolation. In the absence of mechanistic studies, the finding was considered of relevance for human risk assessment. The relevant dermal NOAEL was 1000 mg/kg bw/day (the highest dose level tested) in a 28-day rat study.

2.4. Genotoxicity

In a set of adequately conducted *in vitro* and *in vivo* genotoxicity assays cyflufenamid was not genotoxic.

2.5. Long-term toxicity and carcinogenicity

A rat combined carcinogenicity/chronic toxicity study and a mouse carcinogenicity study were conducted. Data from mechanistic studies, using induction of hepatic enzyme and cellular proliferation, were also supplied.

Rats showed histopathological changes in the kidney (males) and liver (females). Mice showed reduced bodyweight gain, liver weight increase and histopathological changes in the liver, heart and lungs. Thyroid tumours (adenomas in particular) occurred in male rats, secondary to increased catabolism of the thyroid hormones consequent to the increased metabolic activity in the liver (enzyme induction). Mice showed an increased incidence of hepatocellular adenomas at high dose levels: they were considered to be a secondary response to continuous stimulation of hepatocytes by high concentrations of cyflufenamid and to reflect the progression of hypertrophy through hyperplasia to neoplasia. A threshold was determined for these tumours, which were considered as not relevant for humans.

The relevant NOAELs from the long-term toxicity and carcinogenicity studies are 4.4 mg/kg bw/day and 63 mg/kg bw/day for rats and mice, respectively.

2.6. Reproductive and developmental toxicity

In a two-generation study in rats, cyflufenamid did not affect the reproductive parameters; the relevant parental and offspring NOAEL is 18 mg/kg bw/day based on reduced bodyweight gain for offsprings and organ weight changes in the liver and thyroid of adults and offsprings, whereas the reproductive NOAEL is 57 mg/kg bw/day (highest dose tested). Tested in developmental toxicity studies, cyflufenamid did not cause malformations in rats or rabbits, even at doses where maternal toxicity was evident. The relevant maternal NOAELs are 100 mg/kg bw/day and 5 mg/kg bw/day (rat and rabbit, respectively), based on decreased food

consumption and bodyweight and increased liver weight. The relevant developmental NOAELs are 1000 mg/kg bw/day (highest dose level tested) for rat, and 10 mg/kg bw/day for rabbit based on skeletal effects (enlarged anterior fontanels and retardation of ossification).

2.7. Neurotoxicity

No neurotoxic effects were found in subchronic studies in rats, nor there was indication of any acute neurotoxic effect. In a 90-day study in dogs brain vacuolation occurred, its non-relevance to humans was not demonstrated (see point 2.3).

2.8. Further studies

Acute oral toxicity studies and Ames tests were performed with the metabolites 149-F[14], 149-F1, 149-F6[15], 149-F11[16], 149-(*E*)-FB[17], CPCA[18] and CPMOH[19]. The acute oral LD_{50} was 2697, 349, 686, 1123, higher than 5000, 743 and 391 mg/kg bw, respectively. Ames tests conducted with each of the above metabolites all gave negative results.

The experts discussed the relevance of metabolites 149-F1 and 149-F6, since they were found to exceed the threshold of 0.1 µg/L (see chapter 4). The metabolites were found in rats as well, where they are excreted rapidly and in significant amounts, indicating that they probably contribute to the toxicological profile of cyflufenamid. The genotoxicity studies available showed negative results, and the oral toxicity was higher than that of the parent compound. The meeting agreed with the rapporteur Member State's argumentation that these metabolites are not relevant for the ground water assessment.

EFSA note after the PRAPeR 39 meeting of experts: the toxicological potential of the stereoisomer of cyflufenamid, 149-(*E*)-FB, should be addressed for the consumers' risk assessment. The issue was not discussed during the meeting, however, according to the information summarised in the DAR, the stereoisomer 149-(*E*)-FB is not expected to be of any greater toxicity than the parent compound given the site of the steroisomerism. The stereoisomer was also tentatively identified in the rat faeces in trace amounts.

2.9. Medical data

Cyflufenamid has been manufactured in pilot plants using closed systems that would virtually preclude any possibility of exposure. Where worker exposure was possible, for example, during sampling or dryer filling, or emptying procedures, appropriate personnel protection measures were used to minimise exposure. Annual medical examinations of the workers were carried out as a routine procedure by the department of occupational medicine of the production plant. Since exposure to other active substances and co-formulants, including solvents, was possible, these workers were also examined in accordance with the requirements of the trade association of the Japanese chemical industry. This involved physical examination, blood chemistry, haematology and urinalysis. There were no reports of adverse effects on human health caused by cyflufenamid in the workplace.

[14] 149-F: *N*'-(cyclopropylmethoxy)-2,3-difluoro-6-(trifluoromethyl)benzenecarboximidamide
[15] 149-F6: 2,3-difluoro-6-(trifluoromethyl)benzamide
[16] 149-F11:3-({(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}amino)-3-oxopropanoic acid
[17] 149-(*E*)-FB:*N*-{(*E*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-phenylacetamide
[18] CPCA: cyclopropanecarboxylic acid
[19] CPMOH: cyclopropylmethanol

2.10. Acceptable daily intake (ADI), acceptable operator exposure level (AOEL) and acute reference dose (ARfD)

Acceptable Daily Intake (ADI):

In the DAR, considering the possible relevance to humans of brain vacuolation in dogs it was proposed to use the NOAEL for brain vacuolation from the 1-year dog study (17 mg/kg bw/day – top dose tested) with a 1000 fold safety factor to derive the ADI of 0.017 mg/kg bw/day. During the PRAPeR 39 meeting of experts the 2-year study in rat was also considered: the NOAEL was 4.4 mg/kg bw/day based on liver and kidneys changes. Applying a safety factor of 100, this would result in an **ADI of 0.04 mg/kg bw/day**. The margin of safety would be 575 with respect to the NOAEL for the brain vacuolation (23 mg/kg bw/day), and 1900 with respect to the LOAEL (76 mg/kg bw/day), and that was considered sufficiently protective to humans.

Acute Reference Dose (ARfD):

During the meeting, it was noted that no information is available on the first occurrence of brain vacuolation. The NOAEL of the oral 28-day dog study is 93 mg/kg bw/day with regard to neurotoxic effects. Vacuolation was observed at the highest dose level.

The maternal toxicity NOAEL of 5 mg/kg bw/day from the developmental rabbit studies is based on the decreased bodyweight over the first few days. With a safety factor of 100 the resulting **ARfD** would be **0.05 mg/kg bw**. A margin of safety of 460 is provided with regard to the brain effects observed in the 90-day dog study.

Acceptable Operator Exposure Level (AOEL):

The meeting of experts discussed whether to base the AOEL on the NOAEL of 6.5 mg/kg bw/day for the liver effects from the 90-day dog study, with a safety factor of 100 and a correction for the oral absorption. For consistency reasons the meeting agreed to base the AOEL on the 1-year dog study (NOAEL 4.1 mg/kg bw/day) with a correction for oral absorption of 70% and a safety factor of 100, resulting in an **AOEL of 0.03 mg/kg bw/day** (rounded).

2.11. Dermal absorption

The proportions of dose absorbed for the spray dilution were 45.32% (rat) and 29.52% (human), meaning that the rat skin was 1.54 times more permeable to diluted material. The proportions of dose absorbed for the undiluted material were 19.35% (rat) and 3.87% (human), meaning that the rat skin was 5 times more permeable to undiluted material.

Applying correction factors of 1.54 and 5 to the results of the rat *in vivo* penetration study, this would lead to dermal absorption of cyflufenamid of about 8% from the in-use dilution of an EW (oil-in-water emulsion) formulation, and 1% for the undiluted formulation.

2.12. Exposure to operators, workers and bystanders

Based on *in vivo* rat and *in vitro* rat/human studies performed with the representative formulation 'NF-149 EW', the dermal absorption values were considered 8% and 1% for the dilution and concentrate formulation, respectively.

Operator

Estimated systemic exposures (mg/kg bw/day) were performed according to calculations with the German and UK POEM model. The default for bodyweight of operator is 70 kg in the German model and 60 kg in the UK-POEM model. The treated area is 20 ha/day for the German model and 50 ha/day for the UK POEM.

The available model calculations were re-considered taking into account the new dermal absorption values agreed during the written procedure.

	Crop	**Systemic exposure (mg/kg bw/day)**	**% of systemic AOEL**
German model	Cereals	0.0013	4
UK POEM	Cereals	0.009	30

The operator exposure estimates were below the AOEL of 0.03 mg/kg bw/day for both the German and the UK POEM model, assuming no use of personal protective equipment (PPE).

Worker

The harvesting of cereals is a predominantly mechanised process; however, some manual operations will result in direct contact with treated foliage. To assess the re-entry exposure, the German generic re-entry exposure model[20] has been used, resulting in 0.0024 mg/kg bw/day, which is 8% of the AOEL (8-hour daily exposure).

Bystander

Based on actual measurements of bystander exposure in the United Kingdom for boom spray applications (Lloyd and Bell, 1983[21]), the total systemic exposure of bystanders is estimated to be 0.00002 mg/kg bw/day, which is <1% of the AOEL.

3. Residues

3.1. Nature and magnitude of residues in plant

Cyflufenamid was discussed at the PRAPeR 40 meeting of experts on residues in December 2007.

It is noted that cyflufenamid is *(Z)-N*-[[(cyclopropylmethoxy)amino][2,3-difluoro-6-(trifluoromethyl)phenyl]methylene]benzeneacetamide. The technical material contains low concentrations of the *E*-isomer. The studies were carried out with the *Z*-isomer. However, it is assumed that the analytical methods used in the residue studies cannot separate the two isomers and therefore the results cover both isomers. A data requirement has been formulated

[20] Hoernicke, E., Nolting H. G., Westphal, D., Anwenderschutz, F., 1998. Hinweise in der Gebrauchsanleitung zum Schutz von Personen ben Nachfolgearbeiten in mit Pflanzenschutzmitteln behandelten Kulturen. Nachrichtenbl. Deut. Pflanzenschtzd. 50 (10) p. 267

[21] Lloyd G.A., Bell G.J., 1983. Hydraulic nozzles: a comparative spray drift study.

concerning the analytical method. The notifier should clarify whether the method is able to separate cyflufenamid and its *E*-isomer.

3.1.1. Primary crops

To support the notified uses on cereals (winter and spring wheat, triticale, rye and barley), three metabolism studies on wheat were submitted. Cyflufenamid radiolabelled either in the 2,3-difluoro-6-(trifluoromethyl) phenyl (in the following text referred to as fluorinated phenyl) or the cyclopropyl ring was applied two times at 25 g a.s./ha (representing the dose rate of the notified cGAP), and two times at 100 g a.s./ha, respectively (4N rate). The growth stages at the time of applications were in line with the notified GAPs.

The major component of radioactive residues in all crop samples was cyflufenamid at levels of up to 99% of the TRR in forage, 37% of the TRR in straw and 7% in grain. 149-(*E*)-FB, the *E*-isomer of cyflufenamid, was found in forage and parts of mature crops at levels of up to 4% of the TRR (up to approximately 10% of the level of cyflufenamid). In samples from mature plants also low concentrations (all < 5%) of the following metabolites were identified: 149-F-2-OH-B[22], 149-F-4-OH-B[23], 149-F-α-OH-B[24], 149-F and 149-F4B-Glu[25].

The PRAPeR 40 meeting of experts noted that the *E*-isomer of cyflufenamid was quantified in samples at levels up to approximately 10% of the level of cyflufenamid, which is significantly higher than the content of the *E*-isomer in the technical material of cyflufenamid. It was concluded that these findings indicate a shift of isomer ratio of the *Z*-isomer to the *E*-isomer.

The PRAPeR 40 meeting of experts decided to propose the following residue definition for monitoring and risk assessment: **sum of cyflufenamid (*Z*-isomer) plus its *E*-isomer**. The EFSA notes that it is restricted to cereal crops as no metabolism studies for other crops were submitted.

A total of 10 residue trials carried out in Northern Europe in the years 1998 and 1999, and 10 trials carried out in Southern Europe in the years 1998, 1999 and 2001 were submitted on wheat. On the basis of the trials on wheat extrapolation to rye is possible. A total of 10 residue trials carried out in Northern Europe in the years 1998 and 1999, and 10 trials carried out in Southern Europe in the years 1998, 1999 and 2001 were submitted on barley. All submitted trials were performed in line with the notified GAPs (as clarified in the reporting table, rev1-1, 22 June 2007).

Submitted data on freezer storage stability showed that cyflufenamid is stable in barley straw and shoots for at least 25 months, and in barley grain for at least 22 months.

No data on the effects of processing on the nature of the residues or on residue levels were submitted, nor are they required for the notified intended uses.

[22]149-F-2-OH-B:*N*-{(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-(3-hydroxyphenyl)acetamide

[23]149-F-4-OH-B:*N*-{(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-(4-hydroxyphenyl)acetamide

[24]149-F-α-OH-B:*N*-{(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-hydroxy-2-phenylacetamide

[25]149-F4B-Glu:*N*-{(*Z*)- [2,3-difluoro-6-trifluoromethy α-(β-glucopyranosylimino)benzyl]}-2-phenylacetamide

3.1.2. Succeeding and rotational crops

Confined rotational crop studies are available. [^{14}C]-fluorinated phenyl ring labelled cyflufenamid was applied to soil at a rate of 50 g a.s./ha (notified seasonal application rate for cereals). Spring wheat was sown after 30, 120 and 270 days of ageing, carrots after 30 and 120 days, and lettuce after 30 days. Translocation of radioactive residues was low. TRR found in crop parts intended for human consumption were maximum 0.006 mg/kg. Highest levels of TRR were found in wheat straw (maximum 0.09 mg/kg).

Cyflufenamid is extensively metabolised in soil to 149-F11, 149-F, 149-F1 and 149-F6. Metabolites in rotational crops were not identified apart from a single compound in carrot foliage identified as 149-F6.

In the DAR the rapporteur Member State raised the question whether the metabolism in soil (and eventually in rotational crops) was sufficiently addressed, as only studies with [^{14}C]-fluorinated phenyl ring label were submitted. The issue was discussed at the PRAPeR 37 meeting of experts on environmental fate and behaviour. It was concluded that the probable formation of phenyl acetic acid during metabolism of cyflufenamid gives no cause for concern. Therefore, the studies with [^{14}C]-fluorinated phenyl ring label were sufficient to characterise the environmental fate of cyflufenamid in soil (see section 4.1.1.). In line with this decision, no metabolism study is necessary on rotational crops with radiolabelling in the phenyl acetic acid moiety.

Field studies on rotational crops are not necessary, as based on the results of the submitted metabolism study, residues of cyflufenamid in parts of rotational crops intended for human consumption are expected below the LOQ.

3.2. Nature and magnitude of residues in livestock

For goats dosed with [^{14}C]-fluorinated phenyl ring labelled cyflufenamid at 1.2 mg/kg feed (representing approximately 7 and 3 times the residue intake calculated for dairy and beef cattle, respectively) and 13.3 mg/kg feed for five consecutive days, the majority of the applied radioactivity was excreted. Transfer of radioactivity into milk and tissues was low. A residue plateau in milk of 0.3 mg/kg was reached after 2-3 days in the high dose group. In the low dose group residues in milk were maximum 0.008 mg/kg, in muscle 0.003 mg/kg, in kidney 0.015 mg/kg, in liver 0.113 mg/kg and in fat 0.014 mg/kg.

The major radioactive component in fat (80% of TRR) was identified as cyflufenamid besides low levels (<2% of TRR) of 149-F, 149-F-4-OH-B, 149-(*E*)-FB and 149-F-α-OH-B. In the other tissue samples and milk, the main radioactive compound was 149-F1 (31-62% of TRR), besides lower levels of 149-F6 (3-30% of TRR). Cyflufenamid (22% of TRR) and 149-F (15% of TRR) were additionally found in muscle and liver, respectively.

The rapporteur Member State noted in the DAR that only a metabolism study with [^{14}C]-fluorinated phenyl ring labelled cyflufenamid was available. In line with the decision concerning metabolism studies on rotational crops (see section 3.1.2) and in soil (see section 4.1.1), it was decided that the submitted study was sufficient to characterise the metabolism of cyflufenamid in livestock.

Based on the results of the intake calculation (see below), no metabolism studies are required for poultry.

The PRAPeR 40 meeting of experts discussed the residue definitions for animal matrices. It was decided to include the *E*-isomer in the residue definitions for risk assessment and

monitoring in line with the decision for the residue definitions in plant matrices (see section 3.1.1). Concerning the risk assessment, it was noted that the PRAPeR 39 meeting of experts concluded that for the metabolites 149-F1 and 149-F6 the application of ADI and ARfD of cyflufenamid, if needed, would be appropriate, as these metabolites contributed to the toxicity driving the setting of the reference values. Since metabolite 149-F1 was present at significant percentages (31-62%) of the TRR in milk, liver, kidney and muscle, it was decided to include this metabolite in the residue definition for risk assessment. It was proposed to include 149-F1 also in the residue definition for monitoring, as cyflufenamid is not a suitable marker in kidney and liver.

The following residue definition was proposed for animal matrices for monitoring and risk assessment: **sum of cyflufenamid, the *E*-isomer and metabolite 149-F1 expressed as cyflufenamid**.

The rapporteur Member State carried out intake calculations for domestic animals on the basis of the highest and median residues levels for cyflufenamid in cereal grain and straw. For dairy cattle, beef cattle, pigs and chicken, theoretical maximum daily intakes of 0.16, 0.37, 0.07 and 0.06 mg/kg feed (DM) and theoretical mean daily intakes of 0.05, 0.13, 0.02 and 0.02 mg/kg feed (DM) were calculated.

Based on the residue definition for risk assessment, on the metabolism study on goats and on the dietary burden calculation it was concluded by the PRAPeR 40 meeting of experts that residues below 0.01 mg/kg are expected in milk, muscle and kidneys. It was discussed whether the levels of cyflufenamid and 149-F1 in liver and fat were of concern taking into account that cyflufenamid is fat soluble. As the residue plateau in milk is reached quickly and the rate of metabolism and excretion was high, it was assumed that cyflufenamid will not bioaccumulate. Therefore, it was decided not to request a livestock feeding study, but to consider the estimated residue levels of cyflufenamid plus 149-F1 in liver (0.011 mg/kg) and fat (0.004 mg/kg) for the risk assessment.

3.3. Consumer risk assessment

The rapporteur Member State provided a chronic consumer risk assessment for chronic exposure in Addendum 3 (February 2008) taking into account the ADI of 0.04 mg/kg bw/day and intake of cereal grain (STMR) (not peer-reviewed). Chronic intakes calculated for UK and consumption data and for the WHO European diet are all less than 1% of the ADI. The EFSA notes that the assessment does not cover the intake of animal matrices. However, taking account of the estimated residues in fat and liver (see section 3.2), this would not lead to a significant increase of the TMDI.

A calculation carried out by EFSA after the meeting with the EFSA PRAPeR model (PRIMO, rev. 2) on the basis of the proposed MRLs for wheat, rye and barley and the estimated residue levels for fat and liver, showed the WHO Cluster diet B (TMDI = 0.5% ADI) as the most critical models for the chronic intake.

The acute exposure is not expected to exceed the ARfD (0.05 mg/kg bw). NESTIs for consumer/intake combinations calculated by the rapporteur Member State are maximum 2.4% of the ARfD (for intake of cereals by 4-6 year old children). A calculation carried out by EFSA after the meeting with the EFSA PRAPeR model (PRIMO, rev. 2) on the basis of the MRLs proposed for wheat, rye and barley showed that the highest NESTI for the intake of barley by adults (1.4% of ARfD).

The EFSA notes that the consumer risk assessment has to be regarded provisional pending confirmation that the analytical method used in the residue trials covers the residue definition for food in plant matrices with respect to the *E*-isomer. However, no major contribution of the *E*-isomer to the risk assessment is expected.

3.4. Proposed MRLs

In accordance with the proposed residue definition for monitoring (sum of cyflufenamid (*Z*-isomer) plus its *E*-isomer), the following MRLs were proposed by the rapporteur Member State in the DAR:

Wheat, triticale, rye	0.02 mg/kg
Barley	0.1 mg/kg

The EFSA notes that the MRLs are proposed provisionally pending confirmation that the analytical method used in the residue trials covers the residue definition for food in plant matrices with respect to the *E*-isomer.

The PRAPeR 40 meeting of experts decided that MRLs for animal matrices should be proposed at the LOQ of the analytical method for monitoring. An analytical method for monitoring of cyflufenamid residues (in accordance with the residue definition) is not available. A respective data requirement has been formulated.

4. Environmental fate and behaviour

Cyflufenamid was discussed at the PRAPeR 37 meeting of experts on environmental fate and behaviour (December 2007) on the basis of the DAR and addendum 2 of November 2007. All radiolabel-studies performed to investigate the environmental fate and behaviour of cyfluflenamid used fluorinated [phenyl-U-^{14}C] and/or [cyclopropyl-^{14}C] cyflufenamid. The technical grade material contains the *E* isomer in low concentrations, therefore all the end points presented are based on the concentration of the parent compound alone.

4.1. Fate and behaviour in soil

4.1.1. Route of degradation in soil

The environmental fate of cyflufenamid in soil was investigated in a number of laboratory studies using fluorinated [phenyl-U-^{14}C] cyflufenamid. An additional study was performed using [cyclopropyl-2,3-^{14}C] cyflufenamid. Studies carried out at *ca*. 20ºC and 40% MWHC were available for 6 soils dosed with cyflufenamid. Results of degradation of cyflufenamid in a single soil at 10ºC and 40% MWHC were also available. The formation of residues not extracted sequentially with acetone, methanol and ammonium chloride/methanol were a sink for the applied fluorinated phenyl -^{14}C and cyclopropyl-^{14}C radiolabels (36.8% and 27.0% of the applied radiolabel (AR) after 120 and 45 days, respectively). Mineralisation to carbon dioxide represented less than 0.1% AR in the fluorinated phenyl-labelled study, and represented 49.8% AR at 45 days in the cyclopropyl-labelled study. The metabolite **149-F** was a major metabolite representing up to 34.7% AR at 44 days in the soils studied. The metabolite **149-F1** was also a major metabolite representing up to 22.9% AR at the end of the study (120 days). A further major soil metabolite was identified as **149-F11** and represented

up to 18.5% AR at 14 days in the soils studied. A fourth metabolite was characterised as it accounted for more than 5% AR in at least two sequential time points and was identified as **149-F6** (6.9-9.0% AR at 59-90 days).

Residues of the cyflufenamid isomer 149-(*E*)-FB were detected in all soils at up to 5.7% AR at the end of the study (120 days). The technical grade material was noted to contain the isomer at a maximum concentration of 1.5%.

In the DAR there was a reasoned case to argue against the need for additional studies with radiolabelling in the phenyl acetic acid moiety. If degradation of cyflufenamid proceeds via cleavage of the amide, it may result in the formation of the metabolite phenyl acetic acid (PAA) and related compounds. The argumentation provided by the applicant was based on the results of a monitoring study in Japan indicating that the natural background of PAA concentrations in soil are above the worst case soil predicted environmental concentrations (PEC) calculated in the DAR. The validity of this study was discussed at the PRAPeR 37 meeting of experts. It was concluded that despite the shortcomings of the study, it is plausible that PAA is a naturally occurring compound which is formed through metabolism of different substances, and that the potential formation of such a substance from the applied cyflufenamid would have an insignificant effect. The Member State experts agreed that the concern was sufficiently addressed, and that the studies submitted were sufficient to characterise the environmental fate of cyflufenamid in soil.

Data on anaerobic laboratory degradation in soil showed that this route of degradation was insignificant compared to that observed in aerobic incubations, and no radioactive degradation product accounted for more than 5% AR throughout the study.

In a laboratory soil photolysis study, (midsummer sunlight at latitude 40°N), no novel photodegradation products were identified, and degradation of the parent compound cyflufenamid was slow, indicating that photolysis will not significantly contribute to the overall degradation of cyflufenamid in soil under environmental conditions.

4.1.2. Persistence of the active substance and their metabolites, degradation or reaction products

The degradation rates for cyflufenamid were calculated for 7 soils (pH 5.8–8.2, organic carbon (OC) 1.4–3.1 %; clay 8–34 %) by fitting the data to a one-compartment, first order model using non-linear regression analysis. Not normalised (20ºC and 40% maximum water holding capacity (MWHC)) DT_{50} values for cyflufenamid were in the range 7.1-412 days, with a geometric mean of 33.8 days, indicating that the active substance shows low to high persistence in soil.

The rate of degradation of the metabolites identified in section 4.1.1 above (149-F, 149-F1, 149-F6 and 149-F11) was investigated under dark aerobic conditions at 20^{o}C and 40% MWHC in a study with three soils (pH 5.7-7.6, OC 1.4-2.1%; clay 13-34 %). Single first-order DT_{50} were: 5.8-14.4 days for 149-F; 118-329 days for 149-F1; 850-2138 days for 149-F6 and 1.9-3.4 days for 149-F11. After normalisation to FOCUS reference conditions[26] (20°C and -10kPa soil moisture content) the geometric mean of the DT_{50} values were 8.9, 168.5, 1247 and 2.3 days for 149-F, 149-F1, 149-F6 and 149-F11, respectively.

Data from field studies carried out to recognised guidelines to assess rates of cyflufenamid dissipation in the field were available for areas of northern and southern Europe (UK,

[26] Using section 2.4.2 of the generic guidance for FOCUS groundwater scenarios, version 1.1 dated April 2002.

Germany, Northern and Southern France). Cyflufenamid was applied by spray to bare soil plots at approximately 50 g a.s./ha in late May or early June at each site. The samples were analysed for the parent compound and the four main soil metabolites (149-F, 149-F1, 149-F6 and 149-F11). No quantifiable residues of the parent compound or the metabolites were detected in the 10-20cm soil horizons. No residues of the metabolite 149-F6 were detected at any site. No residues of cyflufenamid metabolites were detected above the LOQ (2 ng/g) at the UK and German field sites. Residues of 149-F11 were detected at a maximum concentration of 6.2 ng/g after 30 days at the Northern France site, and residues of 149-F1 were detected at a maximum concentration of 3.0 ng/g after 94 days at the Southern France site. The dissipation of cyflufenamid was modelled assuming simple first-order kinetics using non-linear regression analysis. The DT_{50} and DT_{90} values for cyflufenamid in the 0-10 cm layer were in the range of 10.2-91 days and 35-301 days, respectively.

During the commenting period of the peer review it was questioned whether the field trials were sufficiently worst-case with regard to the rate of degradation of cyflufenamid in view of the fact that in the laboratory studies an apparent dependency on soil organic matter (OM) content for degradation rate was supposed (slowest dissipation in soils with highest OM content), and in field studies only soils with low OM content were investigated. The Member State experts agreed with the rapporteur Member State that a reasonable range of soil types had been selected for the field trials (e.g. sand, loamy sand, clay loam and silty clay), covering both Northern EU and Southern EU conditions and covering a reasonable range of individual soil characteristics (e.g. pH 4.5 to 7.9; clay content 7.10 to 39.36%), and therefore accepted the original data submitted as being sufficient to meet the data requirements.

The experts discussed the maximum accumulated peak PEC soil for metabolites 149-F1 and 149-F6 provided in the DAR, that used arithmetic mean DT_{50} for calculation and not the longest DT_{50} values which is the usual regulatory practice. The experts could not accept these values for use in the EU risk assessment. They asked for new initial PEC soil values to be calculated taking into consideration also the maximum observed formation fractions from the laboratory soil studies (appropriately taking into account the relative molecular masses). These new calculations can be found in appendix A.

4.1.3. Mobility in soil of the active substance and their metabolites, degradation or reaction products

Batch adsorption studies were conducted with cyflufenamid and four soils (pH 5.8-7.1; OC 0.8-2.4%). These resulted in adsorption K_{Foc} values of 1000-2354 mL/g (mean 1595 mL/g), indicating that cyflufenamid exhibits slight to low mobility in soil. Freundlich coefficients (1/n) were 0.87-0.96 (mean 0.93). The K_{Foc} values calculated from the Freundlich adsorption constants for the four soils generally correlated with the organic carbon content of the soil. No influence of soil pH or clay content was observed for the available data set.

Batch adsorption studies were also carried out on the major soil metabolites 149-F, 149-F1, 149-F6 and 149-F11 in the same four soils selected for the parent adsorption studies. The range and mean of K_{Foc} values and Freundlich coefficients (1/n) were as follows:

- 149-F: K_{Foc} range 10.5-43.2 mL/g (mean K_{Foc} was 32 mL/g, mean 1/n was 0.84);
- 149-F1: K_{Foc} range 51-147 mL/g (mean K_{Foc} was 79 mL/g, mean 1/n was 0.94);
- 149-F6: K_{Foc} range 7-13 mL/g (mean K_{Foc} was 8.5 mL/g, mean 1/n was 0.99);
- 149-F11: K_{Foc} range 7-25 mL/g (mean K_{Foc} was 13.6 mL/g, mean 1/n was 0.88).

A field leaching study was also conducted with cyflufenamid applied to winter barley in the United Kingdom on a sandy soil with low water retention and attenuating properties. Two separate spray applications of cyflufenamid at 25 g a.s./ha were made with a 14 days interval. No residues of cyflufenamid were detected in samples from the treated plot at any sampling occasion, and annual average concentrations in soil water leachates were less than 0.05 µg/L for cyflufenamid and its metabolites.

4.2. Fate and behaviour in water

4.2.1. Surface water and sediment

Cyflufenamid was found to be hydrolytically stable at 50°C and pH 4, 5 and 7. The hydrolysis rate at 20°C and pH 9 was determined to be 642 days. Degradation products at pH 9 were identified as 149-(*E*)-FB (the cyflufenamid isomer), 149-F and 149-F1, all present at <10% AR at 20°C after 30 days. Cyflufenamid can therefore be considered to be hydrolytically stable at environmentally relevant conditions.

In an aqueous photolysis study cyflufenamid was not significantly degraded in either the irradiated samples or the dark controls. The DT_{50} was tentatively calculated to be 339 days, which indicated that photolysis was unlikely to be a significant route of dissipation for cyflufenamid. Co-chromatography indicated that 149-(*E*)-FB was the only metabolite detected and represented 0.4-8.4% AR in irradiated samples. The mean lifetime for cyflufenamid in the top 5 cm water layer was calculated to be 127 days at 40° N using the quantum yield (calculated to be 2.49×10^{-4}). Photolysis is unlikely to be a significant route of degradation under these conditions.

Cyflufenamid was classified as 'not readily biodegradable' according to a standard test (OECD 301/B) of ready biodegradability following incubation with an activated sludge inoculum.

In two aerobic laboratory (dark, 20°C) natural water/sediment systems fluorinated [phenyl-U-^{14}C] cyflufenamid dissipated rapidly from the water phase with a first order, two-compartment DT_{50} of 3.58-4.95 days and a DT_{90} of 11.9 and 16.5 days. Cyflufenamid partitioned to the sediment with a peak concentration measured 14 days after dosing of 63.0-64.8% AR. The more prominent degradation products in both systems were 149-F11 and 149-F. The metabolite 149-F11 was detected in the water phase at a maximum of 15.5% AR after 100 days, and was detected in the sediment phase at a peak of 6.8% AR after 59 days. The metabolite 149-F was detected in the water phase at a maximum of 7.1% AR after 59 days, and was detected in the sediment phase at a peak of 8.6% AR after 100 days. Minor amounts of the metabolites 149-F6 and 149-F1 were also found in the water phase of each system (<1.0% AR). The rate of mineralisation was low, reaching a maximum of 3.5% AR after 100 days. First-order one-compartment DT_{50} values of the active substance for the whole systems were calculated to be 46.3-128.8 days. The PRAPeR 37 meeting of experts noted that no information was available on the potential formation of metabolite PPA in the aquatic systems, as only cyflufenamid radiolabelled in the fluorinated ring was investigated in the water/sediment studies (refer to section 4.1.1). The applicant did not justify the deficiency in the full assessment of the degradation pathway of cyflufenamid in aquatic systems, and it was unknown to the experts of the fate and behaviour meeting, if PPA could be potentially toxic to aquatic organisms. It was concluded that a data requirement for a water/sediment study performed with the non-fluorinated phenyl ring is not necessary, although the environmental fate and behaviour of cyflufenamid in water bodies has not been completely characterised.

The available surface water exposure assessment for cyflufenamid and for the metabolites 149-F and 149-F11 only considered the spray drift route of entry to surface water bodies, as the FOCUS surface water scenarios were not available at the time the DAR for cyflufenamid was written. The PECsw calculations were based on the method proposed in the Guidance Document on Aquatic Ecotoxicology and the drift values of Rautmann. The potential exposure of surface water from the parent compound cyflufenamid and the soil major metabolites 149-F, 149-F1 and 149-F11 via the drainage and run-off routes of entry has not been assessed in the available EU level exposure assessment. Member States should therefore carry out a surface water exposure and consequent aquatic risk assessment for cyflufenamid and its soil major metabolites from the run-off and drainage routes of exposure at national level, should cyflufenamid be included in Annex I to Council Directive 91/414/EEC.

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

The potential contamination of ground water by cyflufenamid and its soil metabolites 149-F, 149-F1, 149-F6 and 149-F11, when used according to the proposed representative uses, was assessed in the DAR with FOCUS GW PELMO (v.3.3.2) model and the relevant scenarios. The degradation pathway for cyflufenamid was relatively complex, and it was not considered possible to perform full kinetic analyses that would result in the derivation of reliable formation fractions of all four metabolites in the degradation studies conducted with the parent compound. Therefore, in the original DAR, PEC groundwater calculations were performed by the applicant assuming instantaneous input of the parent compound and considering the maximum accumulation of each metabolite in laboratory degradation studies, as well as the ratio of molecular weights of the parent compound and the metabolite. The Member State experts acknowledged that this simplistic approach does not take into account the potential leaching of the metabolite that may occur during the individual formation phases, which would be simulated if a formation fraction approach had been used. The rapporteur Member State provided a new FOCUS groundwater assessment in the Addendum 2, assuming a formation fraction of 100% for each stage of the metabolic pathway (i.e. parent → 149-F11 → 149-F → 149-F1 → 149-F6). It was agreed by the meeting of experts that this conservative approach is appropriate. It was also recognised that the use of the arithmetic mean of the individual rate constants to derive the degradation input parameters for cyflufenamid and its metabolites is not the best practice. However, it was concluded that the selection of the longer geometric mean of the DT_{50} values, in line with the actual decision-making criteria, would not affect the conclusions of the existing FOCUS groundwater modelling (refer to Addendum 2 for more details).

The results showed that for cyflufenamid and for the metabolites 149-F and 149-F11 no annual average concentration in the percolate at 1m soil depth exceeding 0.001 µg/L is to be expected. The concentrations for metabolite 149-F1 are in the range of 0.011 – 0.546 µg/L. The concentration of 0.1 µg/L is exceeded in 7 out of 9 European FOCUS scenarios parameterised for winter cereals. For the metabolite 149-F6 the estimated PEC_{gw} are > 0.75 µg/L in all the simulated scenarios (80^{th} percentile annual average concentration at 1m ranged from 1.566 µg/L to 5.623 µg/L). These findings trigger, according to the *Guidance document on the assessment of the relevance of metabolites in groundwater of the substances regulated under Council Directive 91/414/EEC*"(SANCO 221/2000, final 2003), a 3-stage hazard assessment comprising of a biological, genotoxicity and toxicity screening. The toxicological assessment was able to conclude that the metabolites 149-F1 and 149-F6 were not relevant regarding groundwater at the expected concentrations (see section 2.8).

4.3. Fate and behaviour in air

The vapour pressure of cyflufenamid was determined to be 3.54×10^{-5} Pa at 20 C. On the basis of this value and the Henry's law constant it can be concluded that due to the low vapour pressure no significant evaporation of cyflufenamid has to be expected after its use.

A theoretical calculation of the potential for photo-oxidation of cyflufenamid in the atmosphere was submitted, using the method of Atkinson using the AOPWIN v1.88 program. An estimated rate constant of 6.25×10^{-12} cm^3/molecule.sec was calculated for the reaction with OH radicals. This corresponded to a first-order DT_{50} value of 20.5 hours assuming an OH radical concentration of 1.5 x 10^6 per cm^3 (equivalent to 1.7 days on a 12 h daylight basis). Therefore, cyflufenamid is not considered to be prone for long-range transport and contamination through the atmosphere.

5. Ecotoxicology

Cyflufenamid was discussed at the PRAPeR 38 meeting of experts on ecotoxicology in December 2007 on basis of the DAR (January 2006). The representative use evaluated for cyflufenamid was the use as fungicide in cereals at 2 x 25 g a.s./ha.

The risk assessment was conducted according to the following guidance documents: Risk Assessment for Birds and Mammals. SANCO/4145/2000 September 2002; Aquatic Ecotoxicology, SANCO/3268/2001 rev.4 final, October 2002; Terrestrial Ecotoxicology, SANCO/10329/2002 rev.2 final, October 2002; Risk Assessment for non-target arthropods, ESCORT 2, March 2000, SETAC.

5.1. Risk to terrestrial vertebrates

The acute and short-term toxicity of cyflufenamid to birds is low with LD_{50} values of >2000 mg a.s./kg bw and >743 mg a.s./kg bw/day, respectively. A NOEC = 98 mg a.s./kg bw/day was obtained in the long-term toxicity study with birds.

The acute toxicity of cyflufenamid to mammals was low with LD_{50} for rat of >5000 mg a.s./kg bw. The long-term toxicity endpoint which drives the risk assessment for mammals was discussed by the experts at the PRAPeR 38 meeting. In the DAR the rapporteur Member State proposed to use a NOEC = 75 mg a.s./kg bw/day from the rat multigeneration study, however this value was questioned. The EFSA asked whether the effects on litter resorption in the rabbit developmental study should be considered. In that case the NOEC should be set at 60 mg a.s./kg bw/day. The ecotoxicological experts agreed to send the following question to the section on mammalian toxicology: "are the effects on foetal weight, ossification and litter resorption seen in the developmental study with rabbits likely to have been caused by the gavage dosing?". The experts on mammalian toxicology considered that these effects observed in the developmental study could not be considered as dose/reaction effects. However, the rapporteur Member State provided a modified risk assessment in the revised list of end points (February 2008) based on a NOEC of 57 mg a.s./kg bw/day, the lower reproduction end point driven from the rat multigeneration study, instead of 75 mg a.s./kg bw/day that was used in the DAR. The use of this end point was not discussed at the PRAPeR 38 meeting of experts on ecotoxicology. However, this end point was agreed by the PRAPeR 39 meeting of experts on mammalian toxicology. The EFSA agreed with the use of this end point.

The risk was calculated for a herbivorous and insectivorous bird and mammal as foreseen in the guidance. Based on the first-tier risk assessment the risk to large herbivorous and insectivorous birds can be regarded as low for the representative uses of cyflufenamid in cereals, as the TER values (131 - >1481) exceed the Annex VI trigger values. Also, the first-tier TER values for mammals (36 - >22727) exceed the Annex VI trigger values indicating a low risk to small herbivorous and insectivorous mammals from the representative uses of cyflufenamid in cereals.

There are similarities between the metabolites and the parent compound in terms of their chemical structure and hydroxylated moieties. These indicate that the toxicities are likely to be comparable. Furthermore, no major metabolites were identified in cereals in the section on Residues, and the section on Mammalian Toxicology assumed that the metabolites are of no greater toxicological concern than the parent compound. Therefore, it is considered that the risk from the metabolites to birds and mammals is covered by the risk assessment for the parent cyflufenamid and hence, also the risk from the metabolites is considered to be low. The LogPow for the metabolites is below 3, therefore the risk to birds and mammals from secondary poisoning from these metabolites is considered to be low.

As the LogPow exceeds 3 for cyflufenamid, the risk to earthworm- and fish-eating birds and mammals was assessed. The risk from secondary poisoning to birds and mammals can be considered as low (revised list of end points February 2008).

The risk to birds and mammals from the uptake of contaminated drinking water was assessed as low (revised list of end points February 2008).

5.2. Risk to aquatic organisms

Algae are the most sensitive aquatic organisms on an acute time scale to cyflufenamid. Aquatic organisms were more sensitive to the lead formulation “NF-149 EW”. Therefore the risk assessment is based on end points from the studies with the lead formulation. Fish and *Daphnia magna* showed a similar sensitivity towards cyflufenamid on a chronic time scale.

The potential exposure of surface water with parent cyflufenamid and the soil major metabolites 149-F, 149-F1 and 149-F11 via the drainage and run-off routes of entry has not been assessed in the available EU level exposure assessment. The EFSA considers that the main input way was the drift. Therefore, if the new PECsw for the run-off and drainage will be done, these would be lower than those obtained with the drift.

The risk to aquatic organisms from exposure via spray drift was calculated. The risk to aquatic organisms for the representative uses of cyflufenamid and its relevant metabolites can be regarded as low for exposure via drift.

Cyflufenamid can be found in a concentration above 10% in the sediment and the NOEC for *D. magna* is below 0.1 mg a.s./L. Therefore a study on *Chironomus riparius* was made available. The risk to *C. riparius* from the representative uses of cyflufenamid can be regarded as low. No metabolites were found in concentrations above 10% in the sediment.

Studies on fish, *D. magna* and algae with aquatic metabolites 149-F, 149-F1, 149-F6 and 149-F11 were submitted. The risk from these metabolites was assessed for the three different exposure routes as was done for the parent compound. In addition, the risk to aquatic organisms from exposure via groundwater was assessed for the metabolites 149-F1 and 149-F6. The risk to aquatic organisms from these metabolites is low for all exposure routes evaluated.

A study on bioconcentration in fish is available as the LogPow exceeds 3. The resulting BCF (528) exceeds the Annex VI trigger value of 100 for not readily biodegradable compounds. Nevertheless, the risk from bioconcentration in fish is considered to be low as more than 95% depuration was observed in 14 days, the long-term risk to fish and the risk to fish-eating birds and mammals (see above) is considered to be low. The LogPow values of the metabolites 149-F, 149-F1, 149-F6 and 149-F11 are all below 3, therefore no studies on bioconcentration in fish for these metabolites are considered necessary.

As cyflufenamid is not an herbicide, no studies on aquatic higher plants, such as *Lemna gibba*, are considered necessary.

5.3. Risk to bees

Acute contact and oral toxicity studies with cyflufenamid and the lead formulation "NF-149 EW" are available. The resulting HQ values do not breach the Annex VI trigger value indicating a low risk to bees for the representative uses of cyflufenamid evaluated.

5.4. Risk to other arthropod species

Standard laboratory studies with *Aphidius rhopalosiphi*, *Typhlodromus pyri*, *Poecilus cupreus* and *Chrysoperla carnea* with the lead formulation "NF-149 EW" are available.

The resulting HQ values for *A. rhopalosiphi* and *T. pyri* are below the Escort II trigger value of 2, both in-field as off-field. This indicates a low risk to non-target arthropods, which is confirmed by the available extended laboratory study on *A. rhopalosiphi* and *T. pyri* and the laboratory studies on *P. cupreus* and *C. carnea.*

Based on the available studies the risk to non-target arthropods can be regarded as low for the representative uses of cyflufenamid evaluated.

5.5. Risk to earthworms

Acute toxicity studies with cyflufenamid, the lead formulation "NF-149 EW", and the soil metabolites 149-F, 149-F1, 149-F6 and 149-F11 are available. Furthermore, chronic toxicity studies with the lead formulation "NF-149 EW" and the metabolites 149-F1 and 149-F6 were submitted. The end points from studies with the active substance, the lead formulation and the metabolites 149-F and 149-F11 were corrected for the organic carbon content in the test soil, as the LogPow of these substances exceeds 2.

The resulting acute and long-term TER values are all above the appropriate Annex VI trigger value indicating a low risk to earthworms from the representative uses of cyflufenamid evaluated and its relevant metabolites.

5.6. Risk to other soil non-target macro-organisms

The $DT_{90field}$ in soil is 300 days for cyflufenamid. No studies on other soil non-target organisms are considered necessary as the effects on soil micro-organisms are less than 25%, the TERlt for earthworms exceeds 5, and the standard arthropod HQ values are below 2. Nevertheless, a 28-day laboratory study on *Folsomia candida* with the lead formulation "NF-149 EW" was made available. However, although considered acceptable by the rapporteur Member State, the experts at the PRAPeR 38 meeting agreed that, due to absence of a clear dose-effect relationship between 0.00355 - 3.55 mg a.s./kg, a reliable NOEC cannot be

determined, and other evidence on non-target arthropods and earthworms would suggest likely low toxicity.

The DT_{90} values in soil for the metabolites 149-F1 and 149-F6 exceed one year. Therefore, the effects of these metabolites on other soil non-target macro-organisms should be assessed. A 28-day laboratory study on *Folsomia candida* with both metabolites is available. Based on these studies the risk from 149-F1 and 149-F6 to collembola can be regarded as low.

During the peer review some Member States proposed that litter-bag studies with the metabolites 149-F1 and 149-F6 were considered necessary, as their DT_{90}-values are above the relevant trigger of 365 days. However, the rapporteur Member State proposed that 149-F1 and 149-F6 are considered to have low biological activity compared to the parent compound. In addition, both metabolites were not acutely or chronically toxic to earthworms, *F. candida* and soil microbial processes, and present a low risk at the predicted exposure levels in soil. The EFSA agrees with the above RMS' explanation.

No studies on other soil non-target macro-organisms with the metabolites 149-F and 149-F11 are considered necessary as the $DT_{90field}$ of these metabolites is below 100 days.

Overall, it was concluded that the risk to soil organisms for the exposure of cyflufenamid and its metabolites was assessed to be low.

5.7. Risk to soil non-target micro-organisms

The effects of cyflufenamid were tested on soil microbial respiration and nitrogen transformation. Effects were less than 25 % at day 28 at 0.294 mg a.s./kg d.w. soil. This tested concentration exceeds the predicted environmental concentrations in soil of 0.0235 mg a.s./kg soil, and therefore the risk to soil non-target micro-organisms from cyflufenamid is considered to be low for the representative uses evaluated.

Given the $DT_{90field}$ for cyflufenamid, a study on soil micro-organisms with the lead formulation should be envisaged. However, as the soil microbial activity deviated <25% control activity in soil treated with cyflufenamid at approximately 2.5 and 12.5x the maximum predicted soil concentration, according to SANCO 10329/2002, this is sufficient indication of low risk from cyflufenamid to soil microbial processes following the proposed use on cereals.

Studies on the effects of metabolites 149-F1 and 149-F6 on soil micro-organisms were made available. Effects on soil microbial respiration and nitrogen transformation were less than 25% at 0.043 mg 149-F1/kg soil, and 0.083 mg 149-F6/kg soil. These test concentrations are above the PEC_{soil} values of 0.00332 mg 149-F1/kg soil and 0.00131 mg 149-F6/kg soil, indicating a low risk to soil micro-organisms from these metabolites for the representative uses evaluated.

The rapporteur Member State explained in the DAR, that no studies on metabolites 149-F and 149-F11 have been submitted. Within their risk assessment in the DAR, the applicant has argued that as the DT_{50} values are <10 days for these two metabolites, their peak concentrations would have occurred during the 28-day study conducted using cyflufenamid. As a result, no further consideration of these two metabolites will be made as the following risk assessment concerning cyflufenamid will also cover 149-F and 149-F11.

The EFSA considered that according to OECD 216 and 217 soil micro-organisms should last at least 28 days. As the study with the parent compound only ran for 28 days, the metabolites will never have been tested long enough. Furthermore, the peak for the metabolite 149-F only appears after 44 days.

The rapporteur Member State suggested the following explanation: it was established that using the DT_{50} for the metabolites 149-F and 149-F11 of 9.8 days and 2.5 days, the PECsoil would be < 10 % of the maximum initial concentration within 28 days. Thus, it can be assumed that there would be significant exposure from the metabolite 149-F1 in soil micro-organism studies using the parent compound, and the absence of > 25 % effect over 28 days is sufficient to establish a low risk for the metabolite 149-F1. However, this justification did not cover the risk for the metabolite 149-F. The rapporteur Member State included a justification for the risk from the metabolite 149-F in the evaluation table rev.1-2 (February 2008): "an approximate 19% decline in cyflufenamid over 28 days is predicted from the PEC_{soil} values. In the soil microbial studies at the highest dose this represents approximately 0.056 mg cyflufenamid degradation. Assuming that degradation follows the proposed soil pathway, this represents formation of 0.045mg 149-F11, which with a DT_{50} of 2.5 days, will have rapidly degraded to 149-F. Thus, it is likely that significant exposure from the metabolite 149-F is probable in this study (maximum PEC_{soil} 149-F=0.0066 mg/kg) without effect on microbial activity. Furthermore, both 149-F and 149-F11 were considered not to significantly accumulate in soil (DAR B.8.3)".

Low risk to earthworms was indicated from 149-F11 and 149-F and its soil metabolite derivatives 149-F1 and 149-F6, the latter also without effect on soil microbial activity. Thus, overall, the rapporteur Member State considered that the weight of evidence, based on likely absence of toxicity and limited transient exposure, indicates that 149-F will be of low risk to soil organisms and processes.

The experts during the PRAPeR 38 meeting agreed with the RMS' justification.

Overall, it was concluded that the risk of cyflufenamid and its relevant soil metabolites was assessed to be low.

5.8. Risk to other non-target-organisms (flora and fauna)

A fungicidal, herbicidal, insecticidal and acaricidal screening study with cyflufenamid and the metabolites 149-F1 and 149-F6 is available. In conclusion, it was considered that the risk to non-target flora and fauna from the use of cyflufenamid or its metabolites was assessed to be low.

5.9. Risk to biological methods of sewage treatment

The respiration rate EC_{50} for cyflufenamid exceeds 100 mg a.s./L. Based on this study the risk to biological methods of sewage treatment is considered to be low for the representative uses of cyflufenamid evaluated.

6. Residue definitions

6.1. Soil

Definition for risk assessment:	cyflufenamid, 149-F, 149-F1, 149-F6, 149-F11
Definition for monitoring:	cyflufenamid

6.2. Water

6.2.1. Ground water

Definition for exposure assessment: cyflufenamid, 149-F, 149-F1, 149-F6, 149-F11

Definition for monitoring: cyflufenamid

6.2.2. Surface water

Definition for risk assessment

in surface water: cyflufenamid, 149-F11; via run-off/drainage from soil: 149-F, 149-F1, 149-F6, 149-F11

in sediment: cyflufenamid; via run-off/drainage from soil: 149-F, 149-F1, 149-F6, 149-F11

Definition for monitoring: cyflufenamid

6.3. Air

Definition for risk assessment: cyflufenamid

Definition for monitoring: cyflufenamid

6.4. Food of plant origin

Definition for risk assessment: sum of cyflufenamid (*Z*-isomer) plus its *E*-isomer (cereal crops only)

Definition for monitoring: sum of cyflufenamid (*Z*-isomer) plus its *E*-isomer (cereal crops only)

6.5. Food of animal origin

Definition for risk assessment: sum of cyflufenamid, the *E*-isomer and metabolite 149-F1 expressed as cyflufenamid

Definition for monitoring: sum of cyflufenamid, the *E*-isomer and metabolite 149-F1 expressed as cyflufenamid

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

6.6.1. Soil

Compound (name and/or code)	Persistence	Ecotoxicology
cyflufenamid	Low to high persistence Single first-order $DT_{50\ lab}$ 7.1-412 days (20°C, 40% MWHC soil moisture)	The risk to earthworms and soil micro-organisms was assessed as low.
149-F	Low to moderate persistence Single first-order $DT_{50\ lab}$ 5.8-14.4 days (20°C, 40% MWHC soil moisture)	The risk to earthworms and soil micro-organisms was assessed as low.
149-F11	Low persistence Single first-order $DT_{50\ lab}$ 1.9-3.4 days (20°C, 40% MWHC soil moisture)	The risk to earthworms and soil micro-organisms was assessed as low.
149-F1	High to very high persistence Single first-order $DT_{50\ lab}$ 118-329 days (20°C, 40% MWHC soil moisture)	The risk to earthworms and soil micro-organisms was assessed as low.
149-F6	Very high persistence Single first-order $DT_{50\ lab}$ 850-2138 days (20°C, 40% MWHC soil moisture)	The risk to earthworms and soil micro-organisms was assessed as low.

6.6.2. 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
cyflufenamid	Slight to low mobility (K_{Foc} 1000-2354 mL/g)	No	Yes	Yes	The risk to aquatic organism was assessed as low.
149-F	Very high mobility (K_{Foc} 10.5-43.2 mL/g)	No	No	No (Available toxicological information: LD_{50}=2697 mg/kg. Ames test negative; present in the rat metabolism)	No
149-F11	Very high mobility (K_{Foc} 7-25 mL/g)	No	No	No (Available toxicological information LD50=1123 mg/kg, Ames test negative)	No

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
149-F1	Very high mobility (K_{Foc} 51-147 mL/g)	FOCUS PELMO v 3.3.2: trigger exceeded in 7 out of 9 scenarios (max 0.546 µg/L for Hamburg scenario)	No	No (Available toxicological information: LD_{50}=349 mg/kg. Ames test negative; present in the rat metabolism)	No
149-F6	Very high mobility (K_{Foc} 7-13 mL/g)	FOCUS PELMO v 3.3.2: trigger exceeded in all 9 scenarios (max 5.623 µg/L for Seville scenario); trigger of 0.75 µg/L exceeded in all 9 scenarios	No	No (Available toxicological information: LD_{50}=686 mg/kg. Ames test negative; present in the rat metabolism)	No

6.6.3. Surface water and sediment

Compound (name and/or code)	Ecotoxicology
cyflufenamid	The risk to aquatic organism was assessed as low.
149-F	The risk to aquatic organism was assessed as low.
149-F11	The risk to aquatic organism was assessed as low.

6.6.4. Air

Compound (name and/or code)	Toxicology
cyflufenamid	Low acute toxicity by inhalation (LC_{50} > 4.76 mg/L/4h)

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

- Amendment to the primary residue monitoring method for food/feed of plant origin regarding batch size and storage of extracts (relevant for all representative uses evaluated, data requirement identified by the PRAPeR 36 meeting of experts (November 2007); date of submission unknown; refer to chapter 1)
- Clarification whether the residue monitoring method for food/feed of plant origin and the analytical method used in the residue trials are able to separate the *E* and *Z* isomers or not (relevant for all representative uses evaluated, data requirement identified by the PRAPeR 36 meeting of experts (November 2007), and the PRAPeR 40 meeting of experts (December 2007), respectively; partial submission received by the rapporteur Member State on 25 November 2008, further information is awaited from the notifier; refer to chapters 1 and 3)
- Analytical method for animal commodities for the following residue definition: sum of cyflufenamid, the *E* isomer and metabolite 149-F1 (relevant for all representative uses evaluated, data requirement identified by the PRAPeR 36 meeting of experts (November 2007) and the PRAPeR 40 meeting of experts (December 2007); submission received by the rapporteur Member State on 25 November 2008; refer to chapters 1 and 3)

CONCLUSIONS AND RECOMMENDATIONS

OVERALL CONCLUSIONS

The conclusion was reached on the basis of the evaluation of the representative uses as fungicide as proposed by the applicant against powdery mildew in winter and spring wheat, triticale, rye and barley, from growth stage of BBCH 30 up to growth stage of BBCH 59, in all EU countries, up to a maximum of two applications at a maximum individual application rate per spray of 25 g a.s./ha, with an interval of 28 days between applications. For full details of the GAP please refer to the attached end points.

The representative formulated product for the evaluation was 'NF-149 EW', an oil-in-water emulsion (EW), containing 50 g/L cyflufenamid.

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.

Adequate methods are available to monitor all compounds given in the respective residue definition in food/feed of plant origin and environmental matrices, however a data requirement was identified in relation to the method for plants. A data requirement was set for a monitoring method for the residues in food of animal origin.

In mammals, cyflufenamid is not acutely toxic via oral, dermal or inhalation routes; it is not a skin or eye irritant or skin sensitiser. In the short-term toxicity studies the dog was the most sensitive species showing alterations in the liver function and brain vacuolation. The relevant oral NOAEL is 4.1 mg/kg bw/ day (1-year dog study). Cyflufenamid did not show any genotoxic potential. Increased incidences of thyroid tumours and hepatocellular adenomas

were observed in male rats and mice, respectively, however, these were not considered to be of relevance for the risk assessment. The relevant NOAEL from the long-term toxicity and carcinogenicity studies is 4.4 mg/kg bw/day (rat study). No specific effect on the reproductive parameters was found in multigeneration studies with rats: the relevant parental and offspring NOAEL is 18 mg/kg bw/day, whereas the reproductive NOAEL is 57 mg/kg bw/day. Tested in developmental toxicity studies, cyflufenamid did not cause malformations in the rat or rabbit: the relevant maternal NOAELs are 100 mg/kg bw/day and 5 mg/kg bw/day (rat and rabbit, respectively); the relevant developmental NOAELs are 1000 mg/kg bw/day (highest dose level tested) for rat, and 10 mg/kg bw/day for rabbit based on skeletal effects (enlarged anterior fontanels and retardation of ossification). The ADI of 0.04 mg/kg bw/day was derived from the chronic rat study applying a safety factor of 100. The ARfD is 0.05 mg/kg bw (NOAEL for maternal toxicity from the developmental rabbit studies, SF of 100). The AOEL of 0.03 mg/kg bw/day (rounded) is based on the 1-year dog study with a correction for oral absorption of 70% and a safety factor of 100. The operator, worker and bystander exposure was estimated to be below the AOEL even without the use of personal protective equipment.

The metabolism of cyflufenamid was investigated in wheat and rotational crops. The metabolism was found to be moderate. Besides cyflufenamid, its *E*-isomer 149-(*E*)-FB and further metabolites (149-F-2-OH-B, 149-F-4-OH-B, 149-F-α-OH-B, 149-F and 149-F4B-Glu) were identified. The meeting of experts decided to include the *E*-isomer in the residue definition for plant matrices, based on the assumption that the analytical methods used in the residue trials and for monitoring cannot separate the two isomers. The notifier was asked to confirm this assumption. Based on the results of a confined rotational crop study, no residues above the LOQ are expected in parts of rotational crops intended for human consumption.

Dietary burden calculations showed a significant intake of cyflufenamid through cereal straw and grain for dairy and beef cattle only. A metabolism study on ruminants was submitted and showed low transfer of residues into milk and tissues. Cyflufenamid was the main radioactive component in fat. However, in other tissues and milk, the metabolite 149-F1 was the main radioactive component. The meeting of experts decided to include 149-(*E*)-FB and 149-F1 in the residue definitions for animal matrices. It was concluded that bioaccumulation of cyflufenamid is not expected, and that no significant residues are expected in food of animal origin after feeding with cereal grain and straw treated according to the notified cGAP.

MRLs for wheat, triticale, rye and barley were proposed provisionally on the basis of residue trials on wheat and barley, pending confirmation that the analytical method used in the residue trials covers the residue definition in for food in plant matrices. MRLs for animal matrices should be set at the LOQ when an analytical method for animal products is available.

A chronic and acute dietary intake estimate was carried out by the rapporteur Member State. The TMDI was below 1% of the ADI and the NESTI maximum 2% for all considered consumer groups.

The information available on the fate and behaviour in the environment for cyflufenamid is sufficient to carry out an appropriate environmental exposure assessment at EU level. The potential exposure of surface water with parent cyflufenamid and the soil major metabolites 149-F, 149-F1 and 149-F11 via the drainage and run-off routes of entry has not been assessed in the available EU level exposure assessment. Member States should therefore carry out a

surface water exposure and consequent aquatic risk assessment for cyflufenamid and its soil major metabolites from the run-off and drainage routes of exposure at national level, should cyflufenamid be included in Annex I to Council Directive 91/414/EEC. For the applied for intended uses, the potential for groundwater exposure by cyflufenamid and the metabolites 149-F and 149-F11 above the parametric drinking water limit of 0.1 µg/L, is low. The concentrations of the metabolite 149-F1 exceeded the trigger of 0.1 µg/L in 7 out of 9 European FOCUS scenarios parameterised for winter cereals. For the metabolite 149-F6 the estimated PEC_{gw} are > 0.75 µg/L in all the simulated scenarios. The toxicological assessment was able to conclude that metabolites 149-F1 and 149-F6 are not relevant regarding groundwater at the expected concentrations.

The acute, short-term and long-term risk to herbivorous and insectivorous birds, and the acute and long-term risk for herbivorous and insectivorous mammals was low for the representative uses in cereals at an application rate of 25 g a.s./ha. The risk from secondary poisoning and from the uptake of contaminated drinking water to birds and mammals can be considered as low.

Aquatic organisms were more sensitive to the lead formulation "NF-149 EW". The potential exposure of surface water with parent cyflufenamid and the soil major metabolites 149-F, 149-F1 and 149-F11 via the drainage and run-off routes of entry has not been assessed. The EFSA considers that the main route of exposure was via drift. Therefore, in case the new PECsw for the run-off and drainage are considered, it is expected that these would be lower than those obtained with the drift.

The risk to aquatic organisms for the representative uses of cyflufenamid and its relevant metabolites can be regarded as low for exposure via drift. The resulting BCF exceeds the Annex VI trigger value of 100 for not readily biodegradable compounds. Nevertheless, the risk from bioconcentration in fish is considered to be low, as more than 95% depuration was observed in 14 days.

Low acute and chronic risk to earthworms was assessed from the representative uses of cyflufenamid and its relevant metabolites.

The risk to bees, non-target arthropods, soil non-target macro-organisms, soil non-target micro-organisms, non-target terrestrial plants and biological methods for sewage treatment was assessed as low.

PARTICULAR CONDITIONS PROPOSED TO BE TAKEN INTO ACCOUNT TO MANAGE THE RISK(S) IDENTIFIED

None.

CRITICAL AREAS OF CONCERN

None.

APPENDICES

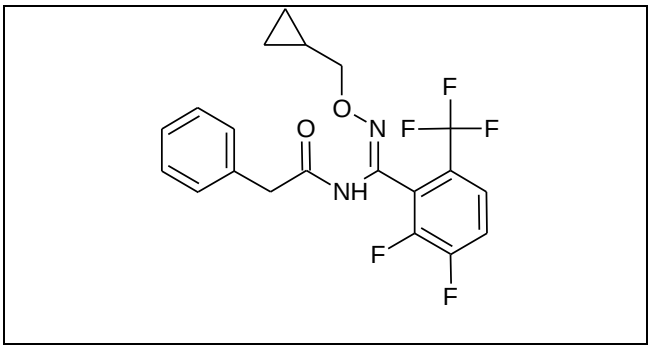
APPENDIX A – LIST OF END POINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

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

Active substance (ISO Common Name) ‡	cyflufenamid
Function (*e.g.* fungicide)	Fungicide
Rapporteur Member State	United Kingdom
Co-rapporteur Member State	Not applicable

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	*(Z)-N*-[α-(cyclopropylmethoxyimino)-2,3-difluoro-6-(trifluoromethyl)benzyl]-2-phenylacetamide
Chemical name (CA) ‡	*(Z)-N*-[[(cyclopropylmethoxy)amino][2,3-difluoro-6-(trifluoromethyl)phenyl]methylene] benzeneacetamide
CIPAC No ‡	759
CAS No ‡	180409-60-3
EC No (EINECS or ELINCS) ‡	Not allocated
FAO Specification (including year of publication) ‡	Not available
Minimum purity of the active substance as manufactured ‡	980 g/kg
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	None
Molecular formula ‡	$C_{20}H_{17}F_5N_2O_2$
Molecular mass ‡	412.36 g/mole

Structural formula ‡	

Physical and chemical properties (Annex IIA, point 2)

Melting point (99.5%) ‡	61.5-62.5 °C
Boiling point (99.5%) ‡	256.8 °C (partial decomposition had occurred)
Temperature of decomposition (99.5%)	>140 °C
Appearance (Pure 99.5%)	White solid
(Techn. 97.3%) ‡	Ivory, reddish yellow pale grey
Vapour pressure (98.7%) ‡	3.54 x 10^{-5} Pa at 20°C
Henry's law constant ‡	2.81x10^{-2} Pa.m^3.mol^{-1} at 20°C
Solubility in water (98.7%) ‡	0.52 mg/l at pH 6.3-6.8 and 20°C 0.014 mg/l at pH 4 and 20°C 0.12 mg/l at pH 10 and 20°C
Solubility in organic solvents ‡ (98.7%)	Dichloromethane >331g/l at 20°C Chloroform >372g/l at 20°C Carbon tetrachloride >399g/l at 20°C Acetone >198g/l at 20°C Tetrahydrofuran >222g/l at 20°C Benzene >220g/l at 20°C Toluene >217g/l at 20°C Xylene >217g/l at 20°C Acetonitrile >196g/l at 20°C Methanol >198g/l at 20°C Ethanol >198g/l at 20°C Ethyl acetate >225 g/l at 20°C Dimethyl sulfoxide >275g/l at 20°C Carbon disulfide >316 g/l at 20°C Dimethylformamide >237g/l at 20°C n-octanol 76.9g/l at 20°C n-hexane 18.6g/l at 20°C n-heptane 15.7g/l at 20°C

Surface tension ‡ (95.9%)	66.5 mN/m at 20 °C (90% saturated solution)
Partition co-efficient ‡ (state temperature, pH and purity)	Log P_{ow} = 4.68 at pH 4.05 and 20°C (98.7%) Log P_{ow} = 4.7 at pH 6.75 and 20°C (98.7%) Log P_{ow} = 4.55 at pH 9.95 and 20°C (98.7%)
Dissociation constant (state purity) ‡	pKa = 12.08 at 20°C (98.7%)
UV/VIS absorption (max.) incl. ε ‡ (99.5%)	207 nm (ε= 2.08 x 10^4 l mol^{-1} cm^{-1}) 238 nm (ε= 1.29 x 10^4 l mol^{-1} cm^{-1}) Acidic - λ_{max} 207 nm (ε= 2.11 x 10^4 l mol^{-1} cm^{-1}) 238 nm (ε= 1.32 x 10^4 l mol^{-1} cm^{-1}) 361nm (ε= 1.78 x 10^2 l mol^{-1} cm^{-1}) Basic - λ_{max}220 nm (ε= 1.30 x 10^4 l mol^{-1} cm^{-1}) 240 nm (ε= 1.18 x 10^4 l mol^{-1} cm^{-1})
Flammability ‡ (98.1%)	Not highly flammable Auto flammability: no self-ignition below 400°C
Explosive properties ‡ (98.1%)	Non-explosive
Oxidising properties ‡ (98.1%)	No oxidising properties

Summary of representative uses evaluated (cyflufenamid)*

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		Application				Application rate per treatment (for explanation see the text in front of this section)			PHI (days) (m)	Remarks
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min/ max (k)	interval between applications (min)	g as/hL min – max (l)	water L/ha min – max	g as/ha min – max (l)		
Winter and spring wheat, triticale rye	Northern Europe Southern Europe	NF-149 EW	F	Powdery mildew	EW	50 g a.s./l	Tractor boom	BBCH30-59 (GS30-59) Spring	1 2	28 days	6..25 12.5	200 400	25	48-78 (NE) 42-63 (SE)	
Winter and spring barley	Northern Europe Southern Europe	NF-149 EW	F	Powdery mildew	EW	50 g a.s./l	Tractor boom	BBCH30-59 (GS30-59) Spring	1 2	28 days	6..25 12.5	200 400	25	48-78 (NE) 42-63 (SE)	

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

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

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

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

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

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

(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**

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

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

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

(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	(m) PHI - minimum pre-harvest interval

Methods of Analysis

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

Technical as (analytical technique)	Dissolution in acetonitrile and analysis by reverse phase HPLC-UV (210nm).
Impurities in technical as (analytical technique)	Organic impurities: dissolution in acetonitrile and analysis by reverse phase HPLC-UV (210 nm). Residual solvents: dissolution in N,N-dimethyl-formamide and analysis by GC-FID.Water: Karl Fisher titration method.
Plant protection product (analytical technique)	Dissolution in n-hexane and analysis by normal phase HPLC-DAD (254nm).

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Sum of cyflufenamid and *E* isomer
Food of animal origin		Sum of cyflufenamid, *E* isomer and metabolite 149-F1
Soil		cyflufenamid
Water	surface	cyflufenamid
	drinking/ground	cyflufenamid
Air		cyflufenamid

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	Matrix: cereal grain Analyte: cyflufenamid Extraction with acetone/methanol (50:50 v/v), cleanup by liquid-liquid partition with dichloromethane followed by GPC, and analysis by GC-MS (m/z 321, 294, 412). LOQ: 0.01 mg/kg. Acceptable ILV submitted.
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Data requirement

Soil (analytical technique and LOQ)	Matrix: Sandy loam and clay loam Analyte: cyflufenamid Extraction with dichloromethane/acetone (1:1 v/v), clean-up by GPC and analysis by GC-MS (223, 294, 321 and 412). LOQ: 0.03 mg/kg
Water (analytical technique and LOQ)	Matrix: Ground, surface and drinking Analyte: cyflufenamid Extraction using a C18 disk cartridge and analysis by GC-MS (412, 188, 294 and 321). LOQ: 0.1 µg/l The above method was validated at the LOQ for m/z 412 only. The additional confirmatory ions were validated at 100 times this level. The following method is therefore used for confirmation of residues. Matrix: leachate water Analytes: cyflufenamid, 149-F, 149-F1, 149-F6, 149-F11 Extraction using tandem C18, SCX solid phase extraction cartridges and analysis by LC-MS (m/z 411 (cyflufenamid), m/z 295 (149-F), m/z 225 (149-F1), m/z 224 (149-F6), m/z 379 (149-F11). LOQ: 0.05 µg/l

Air (analytical technique and LOQ)	Analyte: cyflufenamid Adsorption onto Tenax, then extraction of the Tenax with acetone and analysis by GC-MS (412, 294 and 321). LOQ: 1µg/m3
Body fluids and tissues (analytical technique and LOQ)	Not required.

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

	RMS/peer review proposal
Active substance	None

Impact on Human and Animal Health

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

Rate and extent of oral absorption ‡	Absorption was rapid (Tmax 1-4 hours) and at least 70% (with up to 60% contributed by bile).
Distribution ‡	Tissue concentrations were highest in the GIT plus contents, liver and fat. <1.0 % of the administered dose remained at 168 hours post-dosing. After repeat doses, elimination half lives of tissue radioactivity were two to three times those for plasma.
Potential for accumulation ‡	Some indication for accumulation potential.
Rate and extent of excretion ‡	Excretion was rapid with >80% elimination by 48 hours. About 70% in the faeces.
Metabolism in animals ‡	Metabolism was extensive with no absorbed material being excreted unchanged. Three main pathways: reduction, hydroxylation and methoxylation
Toxicologically relevant compounds ‡ (animals and plants)	Cyflufenamid
Toxicologically relevant compounds ‡ (environment)	Cyflufenamid

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	>5000 mg/kg	-
Rat LD_{50} dermal ‡	>2000 mg/kg	-
Rat LC_{50} inhalation ‡	>4.76mg/l of air (nose only/4h)	-
Skin irritation ‡	Slightly irritant (no classification proposed)	-

Eye irritation ‡	Slightly irritant (no classification proposed)	-
Skin sensitisation ‡	Non-sensitiser (M+K)	-

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Reduced body weight gain, histopathology in the liver and thymus and brain vacuolation in dog 90 day dietary study at dose level of 76 mg/kg bw/d.	
Relevant oral NOAEL ‡	6.5 mg/kg bw/d , 90-day dog 4.1 mg/kg bw/d, 1-y dog 20 mg/kg bw/d , 90-day rat	-
Relevant dermal NOAEL ‡	1000 mg/kg bw/d (highest dose level tested), 28-day rat	-
Relevant inhalation NOAEL ‡	No data, not required.	-

Genotoxicity ‡ (Annex IIA, point 5.4)

	Not genotoxic	-

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

Target/critical effect ‡	**Histopathological changes in the kidneys of males, and in the livers of females in 2 yr rat study.** **Reduced bodyweight gain, liver weight increases and histopathological changes in the liver, heart and lungs in 18 month mouse study.**	
Relevant NOAEL ‡	2 year rat: 4.4 mg/kg bw/day 18 month mouse: 63 mg/kg bw/day	
Carcinogenicity ‡	Thyroid adenomas and carcinomas in male rats at the highest dose. Hepatocellular adenomas in mice. Tumours in both species considered not relevant for human risk assessment.	-

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	Reproductive parameters were not affected. However there was increased liver and thyroid weight in F_0 adults and F_1 and F_2 offspring. Reduced body weight gain in F_1 and F_2 offspring during late lactation.	-
Relevant parental NOAEL ‡	18.0 mg/kg bw/day	-
Relevant reproductive NOAEL ‡	**57 mg/kg bw/day (highest dose tested)**	-
Relevant offspring NOAEL ‡	18.0 mg/kg bw/day	-

Developmental toxicity

Developmental target / critical effect ‡	Maternal: Decreased food consumption and bodyweight and increased liver weight. Development: There were no specific malformations. NOAEL for developmental effects was based on skeletal effects (enlarged anterior fontanels and retardation of ossification)	-
Relevant maternal NOAEL ‡	Rat: 100 mg/kg bw/day Rabbit: 5 mg/kg bw/day	-
Relevant developmental NOAEL ‡	Rat: 1000 mg/kg bw/day (highest dose level tested) Rabbit: 10 mg/kg bw/day	-

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No data – not required	-
Repeated neurotoxicity ‡	13 week neurotoxicity study (rat):- No neurotoxic effects up to highest dose tested (453 mg/kg bw/day) Note: brain vacuolation observed in routine 90-day dog study (see short term toxicity)	-
Delayed neurotoxicity ‡	No data – not required	-

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	A number of supplementary studies were conducted including promoter studies and enzyme inhibition studies. Their findings were used to explain observations in the more routine toxicity studies (e.g. thyroid tumours) and are supporting the non-relevance of tumour findings for humans.
Studies performed on metabolites or impurities ‡	149-F: Oral LD_{50} 2697 ♂, 2993 ♀ mg/kg bw (rat) 149-F1: Oral LD_{50} 434 ♂, 349 ♀ mg/kg bw (rat) 149-F6: Oral LD_{50} 686 ♂, 686 ♀ mg/kg bw (rat) 149-F11: Oral LD_{50} 1123 ♂, 1360 ♀ mg/kg bw (rat) 149-(*E*)-FB: Oral LD_{50} ♂ & ♀ >5000 mg/kg bw (rat) CPCA: Oral LD_{50} 743 ♂, 743 ♀ mg/kg bw (rat) CPMOH: Oral LD_{50} 391 ♂, 639 ♀ mg/kg bw (rat) Ames tests conducted with each of the above metabolites all gave negative results.

Medical data ‡ (Annex IIA, point 5.9)

No evidence of toxicological concern from medical surveillance of manufacturing plant personnel. No cases of poisoning. Limited information since this is a new active substance.

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.04 mg/kg bw/d	2-year rat supported by 1 year dog	100
AOEL ‡	0.03 mg/kg bw/day	1 year dog study	100 (70% correction factor for oral absorption)
ARfD ‡	0.05 mg/kg bw	Rabbit developmental toxicity study.(maternal toxicity)	100

Dermal absorption ‡ (Annex IIIA, point 7.3)

NF-149 5% EW formulation	1% for undiluted preparation 8% for in-use dilution Based on *in vivo* rat study and *in vitro* rat and human skin study performed with 5% EW formulation.

Exposure scenarios (Annex IIIA, point 7.2)

Operator	Tractor-mounted hydraulic boom sprayer German model (no PPE) = 0.0013 mg/kg bw/day (4% of AOEL) UK POEM (no PPE) = 0.009 mg/kg bw/day (30% of AOEL)
Workers	0.0024 mg/kg bw/day (8% of AOEL) German re-entry model
Bystanders	0.00002 mg/kg bw/day (<1 % of AOEL) Lloyd and Bell, 1983

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

	RMS/peer review proposal
Cyflufenamid	No classification proposed.

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

Plant groups covered	Cereal (wheat) foliar application
Rotational crops	Root crop (carrot), leafy crop (lettuce), cereal (wheat)
Metabolism in rotational crops similar to metabolism in primary crops?	Not possible to conclude (limited identification only performed in the available rotational metabolism study).
Processed commodities	Hydrolysis studies not available or required (low residues in grain).
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not studied- see above
Plant residue definition for monitoring	Sum of cyflufenamid (Z-isomer) plus its E-isomer
Plant residue definition for risk assessment	Sum of cyflufenamid (Z-isomer) plus its E-isomer
Conversion factor (monitoring to risk assessment)	Not required

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

Animals covered	Ruminant (goat)
Time needed to reach a plateau concentration in milk and eggs	It appeared that a plateau level in milk was reached after two days
Animal residue definition for monitoring	Sum of cyflufenamid, the E-isomer and 149-F1
Animal residue definition for risk assessment	Sum of cyflufenamid, the E-isomer and 149-F1
Conversion factor (monitoring to risk assessment)	Not required
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	Yes

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

Residues in succeeding cops are not expected to be significant as a result of this proposed GAP

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

Cyflufenamid residues were stable over frozen storage (-18 °C in cereal samples over the period studied (up to 25 months in immature shoots and straw and up to 22 months in grain).

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

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	Yes (0.36 beef cattle based on HRs in straw and grain; 0.13 beef cattle based on STMRs in straw and grain)	No	No
Potential for accumulation (yes/no):	No		
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	No [Residues are expected to be less than 0.01 mg/kg in animal products on the basis of the goat metabolism study conducted at an exaggerated dose rate (low dose: 3N for beef cattle and 7N for dairy cattle); livestock feeding studies are		

	not required]		
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices : Mean (max) mg/kg		
Muscle	Not required	Not required	Not required
Liver	Not required	Not required	Not required
Kidney	Not required	Not required	Not required
Fat	Not required	Not required	Not required
Milk	Not required		
Eggs		Not required	

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

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Wheat	N - field	10 trials grain <0.02 x 9; 0.02 straw <0.10 x 4; 0.10; 0.12; 0.13; 0.14; 0.16; 0.22		0.02 grain	**0.02 (grain)** **0.22 straw**	<0.02 grain 0.11 straw
Wheat	S - field	10 trials grain <0.02 x 10 straw 0.12 x 2; 0.15; 0.17; 0.19; 0.20; 0.21; 0.22 x 2; 0.56		0.02* grain	<0.02 (grain) 0.56 straw	<0.02 grain 0.2 straw
Barley	N-field	10 trials grain <0.02 x 3; 0.02 x 3; 0.03 x 3; 0.05 straw <0.1 x 4; 0.1, 0.11; 0.12 x 2; 0.16; 0.24		0.1 grain	0.05 (grain) 0.24 (straw)	0.02 grain 0.11 straw

Barley	S-field	10 trials grain <0.02 x 5; 0.02; 0.03; 0.03; 0.04; 0.07 straw <0.1; 0.11 x 2; 0.18; 0.19; 0.22; 0.24; 0.34; 0.45; 0.54		0.1 grain	0.07 (grain) 0.54 (straw)	0.02 grain 0.2 straw

(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

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

ADI	0.04 mg/kg bw/day
TMDI (% ADI) according to WHO European diet	0.000065 mg/kg bw/day (or 0.2 % of the ADI)
TMDI (% ADI) according to national (to be specified) diets	-
IEDI (WHO European Diet) (% ADI)	-
NEDI (specify diet) (% ADI)	Highest value for UK consumer groups is toddler NEDI - 0.000195 mg/kg bw/day toddler (UK) less than 1% ADI
Factors included in IEDI and NEDI	STMR
ARfD	0.05 mg/kg bw/day
IESTI (% ARfD)	See below (based on UK diet data)
NESTI (% ARfD) according to national (to be specified) large portion consumption data	NESTI - Highest value for UK consumer groups is 4-6 year old 0.0012 mg/kg bw/day 4-6 year old (UK) [2.4% of ARfD]
Factors included in IESTI and NESTI	No variability factor required for wheat and no processing factors used

(a) EFSA notes that the consumer risk assessment has to be regarded provisional pending confirmation that the analytical method used in the residue trials covers the residue definition for food in plant matrices with respect to the E-isomer. However, no huge contribution of the E-isomer to the risk assessment is expected.

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

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor	Yield factor	
Processing data are not available or required				

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

Wheat grain Rye grain Triticale grain	0.02 (a)
Barley grain	0.1 (a)
Animal matrices	(b)

(a) The MRLs are proposed provisionally pending confirmation that the analytical method used in the residue trials covers the residue definition for food in plant matrices with respect to the E-isomer

(b) The PRAPeR 40 meeting decided that MRLs for animal matrices should be proposed at the LOQ of the analytical method for monitoring. An analytical method for monitoring of cyflufenamid residues (in accordance with the residue definition) is not available (data requirement).

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

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

Mineralization after 100 days ‡	<0.1% AR after 120 d, [^{14}C-fluorinated phenyl]-label (n= 1) 49.8% AR after 45 d, [^{14}C-cyclopropyl]-label (n= 1) Sterile conditions: not determined
Non-extractable residues after 100 days ‡	36.8% AR after 120 d, [^{14}C-fluorinated phenyl]-label (n= 6) 27.0% AR after 45 d, [^{14}C-cyclopropyl]-label (n= 1) Sterile conditions: not determined
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	149-F[27] – 34.7% AR at 44 d (n= 6) 149-F11[28] – 18.5% AR at 14 d (n = 6) [^{14}C-fluorinated phenyl] & [^{14}C-cyclopropyl]-labels 149-F1[29] – 22.9% AR at 120 d (n = 6) 149-F6[30] – 6.9-9.0% AR at 59-90 d (n = 6) [^{14}C-fluorinated phenyl]-label

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

Anaerobic degradation ‡

Mineralization after 100 days	Mineralisation – 0.1% AR after 120 d [^{14}C-fluorinated phenyl]-label
Non-extractable residues after 100 days	Non-extractable residues 7.0% AR after 120 d [^{14}C-fluorinated phenyl]-label
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	None detected at >5% AR [^{14}C-fluorinated phenyl]-label

[27] 149-F: N-cyclopropylmethoxy-2,3-difluoro-6-trifluoromethylbenzamidine
[28] 149-F11: (Z)-N-(α-cyclopropylmethoxyimino-2,3-difluoro-6-trifluoromethylbenzyl)carbamoylacetic acid
[29] 149-F1: 2,3-difluoro-6-trifluoromethylbenzamidine
[30] 149-F6: 2,3-difluoro-6-trifluoromethylbenzamide

Soil photolysis ‡	
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Mineralisation 0.8% AR after 15 d Non-extractable residues 6.4% AR after 15 d Metabolites None detected at >5% AR [^{14}C-fluorinated phenyl]-labell

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

Laboratory studies ‡

Parent	Aerobic conditions						
Soil type	%OC	pH (H_2O)	t. °C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Arrow, Sandy loam	1.8	6.2	20°C / 40%	40.5 / 135	-	0.77	SFO
Arrow*, Sandy loam	1.6	6.1	20°C / 40%	7.1 / 23.6	-	0.95	SFO
Evesham 3	1.9	7.7	20°C / 40%	20.6 / 68.4	-	0.98	SFO
Evesham 3**	1.9	7.7	10°C / 40%	50.7 / 168.4	-	0.95	SFO
Bromsgrove	1.4	5.8	20°C / 40%	8.95 / 29.7	-	0.97	SFO
Speyer 2.2	2.8	6.1	20°C / 40%	121 / 402***	-	0.76	SFO
Abington	2.1	8.2	20°C / 40%	18.9 / 62.8	-	0.99	SFO
Terling	3.1	6.9	20°C / 40%	412*** / 1369***	-	0.67	SFO
Geometric mean/median			-	33.8**** / 20.6	-	-	SFO

*: study conducted with [cyclopropyl-2, 3-^{14}C] cyflufenamid; all others used [fluorinated phenyl-^{14}C] cyflufenamid

**: study conducted at 10°C, all others at 20°C

***: extrapolated beyond the duration of the study

****: Geometric mean calculated from 7 values (the value from the Evesham 3 soil at 10°C was excluded and the two values for the Arrow soil were treated as separate values)

149-F	Aerobic conditions							
Soil type	%OC	pH (H_2O)	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/ k_f	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Bromsgrove	1.4	5.7	20°C / 40%	5.78 / 19.2	-	5.78	1.00	SFO
Evesham 3	1.8	7.6	20°C / 40%	14.4 / 47.8	-	10.9	0.99	SFO
Arrow	2.1	6.8	20°C / 40%	11.2 / 37.2	-	11.2	0.99	SFO
Geometric mean			-	9.8	-	8.9	-	SFO

149-F1	Aerobic conditions							
Soil type	%OC	pH (H_2O)	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/ k_f	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Bromsgrove	1.4	5.7	20°C / 40%	329* / 1093*	-	329*	0.87	SFO
Evesham 3	1.8	7.6	20°C / 40%	118 / 392*	-	89.7	0.84	SFO
Arrow	2.1	6.8	20°C / 40%	163* / 541*	-	163*	0.85	SFO
Geometric mean			-	185	-	168.5	-	SFO

*: extrapolated beyond the duration of the study

149-F6	Aerobic conditions							
Soil type	%OC	pH (H_2O)	t. °C / % MWHC	DT_{50} (d)	f. f. k_{dp}/ k_f	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Bromsgrove	1.4	5.7	20°C / 40%	850*	-	850*	**	SFO
Evesham 3	1.8	7.6	20°C / 40%	1418*	-	1070*	**	SFO
Arrow	2.1	6.8	20°C / 40%	2138*	-	2138*	**	SFO
Geometric mean			-	1371*	-	1247*	-	SFO

*: extrapolated beyond the duration of the study;

**: visually the fits were acceptable, although they were extrapolated well beyond the study duration

149-F11	Aerobic conditions							
Soil type	%OC	pH (H_2O)	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/ k_f	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Bromsgrove	1.4	5.7	20°C / 40%	3.42 / 11.4	-	3.42	0.99	SFO
Evesham 3	1.8	7.6	20°C / 40%	2.5 / 8.3	-	1.9	0.93	SFO
Arrow	2.1	6.8	20°C / 40%	1.86 / 6.2	-	1.86	0.99	SFO
Geometric mean				2.5	-	2.3	-	SFO

Field studies ‡

Parent	Aerobic conditions								
Soil type (indicate if bare or cropped soil was used).	Location (country or USA state).	%OC	pH	Depth (cm)	DT_{50} (d) actual	DT_{90}(d) actual	St. (r^2)	DT_{50} (d) Norm.	Method of calculation
Sand (bare)	Warsop, UK	1.0	6.5	0-10	25.7	87	0.85	-	SFO
Loamy sand (bare)	Brunne, Germany	0.8	4.5	0-10	91	301	0.72	-	SFO
Clay loam (bare)	Villers devant le Thour, North France	1.1	7.9	0-10	10.2	35	0.94	-	SFO
Silty clay (bare)	St. Sulpice de Faleyrens, Southern France	1.7	6.2	0-10	17.3	57	0.70	-	SFO
Geometric mean					25.3	-	-	-	

pH dependence ‡ (yes / no) (if yes type of dependence)	No. Some evidence of increased persistence in high %OC soils in the laboratory
Soil accumulation and plateau concentration ‡	Not determined, DT_{90f} < 1 year

Laboratory studies ‡

Parent	Anaerobic conditions						
Soil type	%OC	pH (H_2O)	t. °C / % MWHC	DT_{50} / DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam	2.0	6.4	20°C / flooded	398* / 1321*	-	<0.7	SFO

*: extrapolated beyond the duration of the study

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Cyflufenamid							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Speyer 2.2,Loamy sand	2.4	6.0	-		56.5	2354	0.96
Arrow,loam	1.8	5.8	-	-	25.9	1439	0.93
Evesham 3,Clay loam	1.9	7.1	-	-	19.0	1000	0.87
Bromsgrove, Sandy loam	0.8	5.8	-	-	12.7	1588	0.95
Arithmetic mean					-	1595	0.93
pH dependence, Yes or No			No				

149-F							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Speyer 2.2, Loamy sand	2.4	6.0	-	-	1.037	43.2	0.87
Arrow, Sandy loam	1.8	5.8	-	-	0.569	31.6	0.90
Evesham 3, Clay loam	1.9	7.1	-	-	0.813	42.8	0.87
Bromsgrove, Sandy loam	0.8	5.8	-	-	0.084	10.5	0.73
Arithmetic mean					-	32	0.84
pH dependence (yes or no)			No.				

149-F1

Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Speyer 2.2, Loamy sand	2.4	6.0	-	-	1.304	54	0.94
Arrow, Sandy loam	1.8	5.8	-	-	1.135	63	0.94
Evesham 3, Clay loam	1.9	7.1	-	-	2.793	147	0.89
Bromsgrove, Sandy loam	0.8	5.8	-	-	0.409	51	0.99
Arithmetic mean					-	79	0.94
pH dependence (yes or no)			No.				

149-F6

Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Speyer 2.2, Loamy sand	2.4	6.0	-	-	0.172	7	0.98
Arrow, Sandy loam	1.8	5.8	-	-	0.125	7	0.99
Evesham 3, Clay loam	1.9	7.1	-	-	0.243	13	0.93
Bromsgrove, Sandy loam	0.8	5.8	-	-	0.055	7	1.06
Arithmetic mean					-	8.5	0.99
pH dependence (yes or no)			No.				

149-F11

Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Speyer 2.2, Loamy sand	2.4	6.0	-	-	0.248	10	0.87
Arrow, Sandy loam	1.8	5.8	-	-	0.211	12	0.93
Evesham 3, Clay loam	1.9	7.1	-	-	0.141	7	0.82
Bromsgrove, Sandy loam	0.8	5.8	-	-	0.199	25	0.89
Arithmetic mean					-	13.6	0.88
pH dependence (yes or no)			No.				

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

Column leaching ‡	No study submitted, none required
Aged residues leaching ‡	No study submitted, none required

Field leaching studies ‡	Location: UK, Nottinghamshire Study type (e.g.lysimeter, field): field Number of applications: 1 year, 2 applications year Application rate: 50 g/ha/year Average annual rainfall + irrigation (mm): >800 mm Annual average concentrations at 120cm: cyflufenamid, 149-F, 149-F1, 149-F6, 149-F11, all <0.05 µg/L.

PEC (soil) (Annex IIIA, point 9.1.3)

Parent Method of calculation	DT_{50} (d): 91 days Kinetics: 1st order Field or Lab: representative worst case from field studies.
Application data	Crop: wheat Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: 50% for first application, 70% for second application Number of applications: 2 Interval (d): 28 Application rate(s): 25 g as/ha

PEC$_{(s)}$ (µg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	16.7	16.7	23.5	23.5
Short term				
24h	16.5	16.5	23.3	23.4
2d	16.4	16.5	23.1	23.3
4d	16.2	16.4	22.8	23.1
Long term				
7d	15.8	16.2	22.2	22.9
28d	13.5	15.0	19.0	21.1
50d	11.4	13.9	16.0	19.5
100d	7.8	11.7	11.0	16.4

Metabolite 149-F	Molecular weight relative to the parent: 294.2
Method of calculation	
Application data	Application rate assumed: 4.95 g as/ha (assumed 149-F is formed at a maximum of 34.7% of the applied dose). Maximum PECsoil = 6.60µg/kg

Metabolite 149-F1	Molecular weight relative to the parent: 224.1
Method of calculation	
Application data	Application rate assumed: 2.49 g as/ha (assumed 149-F1 is formed at a maximum of 22.9% of the applied dose). Maximum PECsoil = 3.32µg/kg (single seasons application) Maximum accumulated peak PECsoil = 6.2 µg/kg after 7 years (based on a DT50 of 329 d derived as the maximum of the un-normalised DT50 values from 3 soils). Note the DT50 used was extrapolated beyond the duration of the study.

Metabolite 149-F6 Method of calculation	Molecular weight relative to the parent: 225.1
Application data	Application rate assumed: 0.98 g as/ha (assumed 149-F6 is formed at a maximum of 9.0% of the applied dose). Maximum PECsoil = 1.31µg/kg kg (single seasons application) Maximum accumulated peak PECsoil = 8.12 µg/kg after 10 years and 11.6 µg/kg after 40 successive years (based on a DT50 of 2138 d derived as the maximum of the un-normalised DT50 values from 3 soils). Note the DT50 used was extrapolated beyond the duration of the study.

Metabolite 149-F11 Method of calculation	Molecular weight relative to the parent: 380.3
Application data	Application rate assumed: 3.41g as/ha (assumed 149-F11 is formed at a maximum of 18.5% of the applied dose). Maximum PECsoil = 4.55µg/kg

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

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	pH 4 and pH 5: 50°C, negligible
	pH 7: 50°C negligible
	pH 9: 20°C DT_{50} > 1 year (1^{st} order) No metabolites > 10% AR
Photolytic degradation of active substance and metabolites above 10 % ‡	Artificial light, equivalent to natural summer sunlight at 40°N; DT_{50} 339 days No metabolites > 10% AR

Quantum yield of direct phototransformation in water at $\Sigma > 290$ nm	2.49×10^{-4}
Readily biodegradable ‡ (yes/no)	No, substance considered not ready biodegradable.

Degradation in water / sediment

Parent	Distribution (Max. water 84.4% AR at 0d, max sed 64.8 % AR after 14d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys. (d)	St. (r^2)	DT_{50}-DT_{90} Water (d) (represents dissipation)	St. (r^2)	DT_{50}-DT_{90} sed (d)	St. (r^2)	Method of calculation
Bury pond / clay loam	7.2	7.9	20° C	128.8* / 427.9*	**	3.58 / 11.9	** 0.93	-	-	SFO
Houghton Meadow / Clay	7.2	7.3	20° C	46.3 / 153.9*	**	4.95 / 16.5	** 0.96	-	-	
Geometric mean				77.2 / 256		-		-		

*: extrapolated beyond the duration of the study
**: visually the fits were acceptable

Distribution of metabolites:-

Water:

149-F max of 6.8-7.1% AR (59-61 days, n= 2)

149-F11 max of 12.1-15.5% AR (100 days, n = 2)

Sediment:

149-F max of 8.6% AR (100 days, n= 2)

149-F11 max of 5.2-6.8% AR (59-100 days, n = 2)

Mineralization and non extractable residues					
Water / sediment system	pH water phase	pH sed	Mineralization x % after n d. (end of the study).	Non-extractable residues in sed. max x % after n d	Non-extractable residues in sed. max x % after n d (end of the study)
Bury pond / clay loam	7.2	7.9	0.5% at 100 d	8.4% at 100 d	8.4% at 100 d
Houghton Meadow / Clay	7.2	7.3	3.5% at 100 d	19.1 % at 100 d	19.1 % at 100 d

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

Note: the surface water assessment has not been conducted using the FOCUSsw models. Spray drift only has been considered.

Parent	DT_{50} (d): 4.95 days
Method of calculation	Kinetics: 1st order Field or Lab: representative worst case from sediment water studies
Application rate	Crop: wheat Number of applications: 2 Interval (d): 28 Application rate(s): 25 g as/ha Depth of water body: 30 cm
Main routes of entry	2.77% drift from 1 metre for single application 2.38% drift from 1 metre for multiple application

$PEC_{(sw)}$ (µg/L)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.231	0.231	0.202	0.202
Short term				
24h	0.201	0.216	0.176	0.189
2d	0.175	0.202	0.153	0.176
4d	0.132	0.177	0.116	0.155
Long term				
7d	0.087	0.147	0.076	0.129

14d	0.033	0.101	0.029	0.089
21d	0.012	0.075	0.011	0.065
28d	0.005	0.058	0.004	0.051
42d	0.0006	0.039	0.001	0.034

149-F

Method of calculation	DT_{50} (d): not determined
Application rate	Crop: wheat Equivalent input into surface water 0.00603 mg/m2 (assumed 149-F is formed at a maximum of 7.1% of the applied dose in water) Depth of water body: 30 cm
Main routes of entry	2.38% drift from 1 metre

$PEC_{(sw)}$ (µg/L)	Single application Actual
Initial	0.020

149-F11

Method of calculation	DT_{50} (d): not determined

Application rate	Crop: wheat Equivalent input into surface water 0.0170 mg/m2 (assumed 149-F11 is formed at a maximum of 15.5% of the applied dose in water) Depth of water body: 30 cm
Main routes of entry	2.38% drift from 1 metre

PEC$_{(sw)}$ (µg/L)	Single application Actual
Initial	0.057

PEC (sediment)

Parent Method of calculation	64.8% partitioning to top 5cm layer of sediment, entry route as for surface water, assuming instantaneous input of 0.1190 mg/m^2, sediment density 1.3 g/cm^3
Application rate	Crop: wheat Number of applications: 2 Interval (d): 28 Application rate(s): 25 g as/ha

PEC$_{(sed)}$ (µg/kg)	Single application Actual
Initial	1.19

149-F	
Method of calculation	8.6% partitioning to top 5 cm layer of sediment, entry route as for surface water, assuming instantaneous input of 0.1190 mg/m^2, sediment density 1.3 g/cm^3
Application rate	Crop: wheat Number of applications: 2 Interval (d): 28 Application rate(s): 25 g as/ha (assumed 149-F is formed at a maximum of 8.6% of the applied dose in sediment)

PEC$_{(sed)}$ (µg/kg)	Single application Actual
Initial	0.112

149-F11	
Method of calculation	6.8% partitioning to top 5 cm layer of sediment, entry route as for surface water, assuming instantaneous input of 0.1190 mg/m^2, sediment density 1.3 g/cm^3
Application rate	Crop: wheat Number of applications: 2 Interval (d): 28 Application rate(s): 25 g as/ha (assumed 149-F11 is formed at a maximum of 6.8% of the applied dose in sediment)

PEC$_{(sed)}$ (µg/kg)	Single application Actual
Initial	0.115

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

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	For FOCUS gw modelling, values used – Modelling using FOCUS model(s), with appropriate FOCUS gw scenarios, according to FOCUS guidance. Model(s) used: FOCUS PELMO (v3.3.2) Scenarios (list of names):Châteaudun; Hamburg, Jokioinen, Kremsmünster, Okehampton, Piacenza, Porto, Seville, Thiva Crop: Winter cereals and Spring cereals Mean first order rate constant from field, 0.0357, equivalent DT_{50f} 19.4 d (All scenarios) K_{foc}: parent, mean 1595, $^1/_n$= 0.93 149-F, mean first order rate constant from laboratory, 0.08169, equivalent DT_{50lab} 8.5 d K_{foc}: 149-F, mean 32, $^1/_n$= 0.84 149-F1, mean first order rate constant from laboratory, 0.00470, equivalent DT_{50lab} 147 d K_{foc}: 149-F1, mean 79, $^1/_n$= 0.94 149-F6, mean first order rate constant from laboratory, 0.000597, equivalent DT_{50lab} 1162 d K_{foc}: 149-F6, mean 8.5, $^1/_n$= 0.99 149-F11, mean first order rate constant from laboratory, 0.3048, equivalent DT_{50lab} 2.3 d K_{foc}: 149-F11, mean 13.6, $^1/_n$= 0.88 NB: DT_{50} values reported above were derived from the arithmetic mean of the individual rate constants. Marginally higher DT_{50} values would have been derived from taking the geometric mean of the DT_{50} values. In the opinion of the RMS the longer DT_{50} values would not have significantly affected the conclusions of the groundwater exposure

	assessment. See rate of degradation section for further details of geomean DT_{50} values.
Application rate	Application rate: 25 g a.s./ha. The RMS has assumed a conservative formation fraction of 100% for each stage of the metabolic pathway in the groundwater modelling (e.g. parent → 149-F11 → 149-F → 149-F1 → 149-F6). No. of applications: 2 (1st application 35 d before maturation, 2nd application 7 d before maturation for winter cereals; 1st application 21 d before maturation, 2nd application 0 d before maturation for spring cereals; See below further details of actual application dates. Time of application (month or season): Spring

Scenario	**Date of maturation of winter cereals assumed in FOCUS PELMO** **(value in brackets represents the corresponding maturation date for spring cereals[a])**	**Date of first application to winter cereals (35 d prior to maturation)**	**Date of second application to winter cereals (7 d prior to maturation)**
Châteaudun	31-May (10-June)	26-Apr	24-May
Hamburg	1-June (5-June)	27-Apr	25-May
Jokioinen	25-June (30-June)	21-May	18-June
Kremsmünster	5-June (5-June)	1-May	29-May
Okehampton	15-May (22-May)	10-Apr	8-May
Piacenza	10-May	5-Apr	3-May
Porto	30-Apr (10-June)	26-Mar	23-Apr
Sevilla	28-Feb	26-Apr	24-May
Thiva	30-Mar	23-Feb	23-Mar

[a]Applications to spring cereals were assumed to take place 21 and 0 days before maturation

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

$PEC_{(gw)}$

Average annual concentration (Results quoted for modelling with FOCUS gw scenarios, according to FOCUS guidance.)	Highest annual average concentrations (80th percentile) according to FOCUS guidance: cyflufenamid: 0.000µg/l 149-F: 0.000µg/L, 149-F1: 0.546µg/L, 149-F6: 5.623µg/L, 149-F11: 0.000µg/L (see detailed results in table below)

Results presented for winter cereals modelled using FOCUS PELMO v3.3.2.

Compound	C	H	J	K	N	P	O	S	T
Cyflufenamid	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
149-F11	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
149-F	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
149-F1	0.286	0.546	0.385	0.395	0.453	0.526	0.061	0.011	0.196
149-F6	3.743	2.385	3.652	2.208	1.566	2.491	2.000	5.623	4.043

C = Châteaudun, H = Hamburg, J = Jokioinen, K = Kremsmünster, N = Okehampton, P = Piacenza,
O = Porto, S = Seville, T = Thiva.

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

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	No data, none required.
Photochemical oxidative degradation in air ‡	DT_{50} of 20.5 hours (equivalent to 1.7 d on a 12 h daylight basis) derived by the Atkinson method of calculation (OH radical concentration assumed to be 1.5 x 10^6 per cm^3)

Volatilisation ‡	No data
Metabolites	None

PEC (air)

Method of calculation	Expert judgement, based on vapour pressure, dimensionless Henry's law constant and information on volatilisation from plants and soil.

$PEC_{(a)}$

Maximum concentration	Negligible (a simple worst case value of 2.5µg a.s./l of air was estimated assuming a single applied dose of cyflufenamid of 25 g a.s./ha partitioned completely into 1m^3 of air)

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).	Soil: cyflufenamid, 149-F, 149-F1, 149-F6, 149-F11 Surface Water: cyflufenamid, 149-F, 149-F11 (via drift) plus cyflufenamid, 149-F, 149-F1, 149-F6, 149-F11 (via runoff/drainage from soil) Sediment: cyflufenamid, 149-F, 149-F11 (via drift) plus cyflufenamid, 149-F, 149-F1, 149-F6, 149-F11 (via runoff/drainage soil) Ground water:cyflufenamid, 149-F, 149-F1, 149-F6, 149-F11 Air: cyflufenamid

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

Soil (indicate location and type of study)	None
Surface water (indicate location and type of study)	None
Ground water (indicate location and type of study)	None

Air (indicate location and type of study)	None

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

Candidate for R53

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

Species	Test substance	Time scale	End point (mg/kg bw/d)	End point (mg/kg feed)
Birds ‡				
C. virginianus	cyflufenamid	Acute	LD50 >2000	-
C. virginianus	cyflufenamid	Short-term	LC50 >743	>5000
C. virginianus	cyflufenamid	Long-term	NOEC = 98	1000
Mammals ‡				
Rat	cyflufenamid	Acute	LD50 >5000	-
Mouse	NF-149EW	Acute	LD50 >5000[1]	-
Rat	cyflufenamid	Long-term[2]	NOEC = 57	800
Additional higher tier studies ‡ - None				

[1] mg preparation/kg/d; [2] based on reproductive NOEC

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

Winter & spring cereals (N/SEU); 2x 0.025 kg a.s./ha (28d spray interval); BBCH30-59

Indicator species/Category	Time scale	ETE	TER	Annex VI Trigger
Tier 1 (Birds)				
Large herbivorous[1]	Acute	1.72	>1163	10
Large herbivorous[1]	Short-term	0.96	>774	10
Large herbivorous[1]	Long-term	0.51	192	5
Small insectivorous[1,2,3]	Acute	1.35	>1481	10
Small insectivorous[1,2,3]	Short-term	0.75	>991	10
Small insectivorous[1,2,3]	Long-term	0.75	131	5
Higher tier refinement (Birds) - not required				

Indicator species/Category	Time scale	ETE	TER	Annex VI Trigger
Tier 1 (Mammals)				
Small herbivorous[1]	Acute	5.43	>921	10
Small herbivorous[1]	Long-term	1.60	36	5
Small insectivorous[2,4]	Acute	0.22	>22727	10
Small insectivorous[2,4]	Long-term	0.08	713	5
Higher tier refinement (Mammals) - not required				

[1] early; [2] late crops; [3] small insects; [4] large insects

Secondary dietary effects in non-target vertebrates:

Cyflufenamid logPow = 4.7, i.e. >3 and assessment required according to SANCO 4145/2000 (Metabolites 149-F, 149-F1, 149-F6 and 149-F11 all logPow = <3)

Winter & spring cereals (N/SEU); 2x 0.025 kg a.s./ha (28d spray interval); BBCH30-59

Indicator species/Category	**Time scale**	**ETE[1]** **(mg a.s./kg bw /d)**	**TER**	**Annex VI Trigger**
Birds				
Earthworm-eating	Long-term	0.417[2]	235[4]	5
Fish-eating	Long-term	0.025[3]	3920[4]	5
Mammals				
Earthworm-eating	Long-term	0.518[2]	110[5]; 19[6]	5
Fish-eating	Long-term	0.016[3]	3563[5]; 625[6]	5
Higher tier bioaccumulation - not required				

[1] see SANCO 4145/2000 for derivation
[2] based on Pow =50118.7, Koc = 1595 mL/g, PECsoil =0.0235 mg a.s./kg
[3] based on BCF = 528, PECsw = 0.000231 mg a.s./L
[4] based on bird reproductive effect in bird (NOEC=98 mg a.s./kg bw/d)
[5] based on reproductive effects in rat (NOAEL=57 mg a.s./kg bew/d)
[6] based on developmental effects in rabbit (NOAEL=10 mg a.s./kg bw/d)

Non-target vertebrate dietary risk from drinking water:

Winter & spring cereals (N/SEU); 2x 0.025 kg a.s./ha (28d spray interval); BBCH30-59

Indicator species/Category	**Time scale**	**ETE[1]**	**TER**	**Annex VI Trigger**
Bird				
Large herbivore (bw 3.0kg)	Acute	1.03[2]	>1948[3]	10
Small insectivore (bw 0.01kg)	Acute	6.74[2]	>297[3]	10
Mammal				
Small herbivore (bw 0.025kg)	Acute	3.58[2]	>1397[4]	10

Indicator species/Category	Time scale	ETE[1]	TER	Annex VI Trigger
Small insectivore (bw 0.01kg)	Acute	3.92[2]	>1275[4]	10
Higher Tier – not required				

[1] see SANCO 4145/2000 for derivation
[2] based on 500L/ha min spray volume; x 0.2 correction for residue dilution
[3] based on acute avian LD50 = >2000 mg a.s./kg bw
[4] based on acute mammalian LD50 = >5000 mg a.s./kg bw

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

Group	Test substance	Time-scale (Test type)	End point	Toxicity mg/L
Laboratory tests ‡				
Fish				
O. mykiss	cyflufenamid	96h (s.static)	Mortality, EC_{50}	1.04[mm]
P. promelas	cyflufenamid	28d (flow thru)	Growth NOEC	0.024[mm]
O. mykiss	NF-149EW	96h (s.static)	Mortality, EC_{50}	0.511(9.81[1])[mm]
O. mykiss	Metabolite 149-F	96h (s.static)	Mortality, EC_{50}	41.3[mm]
O. mykiss	Metabolite 149-F1	96h (s.static)	Mortality, EC_{50}	>103[mm]
O. mykiss	Metabolite 149-F6	96h (s.static)	Mortality, EC_{50}	>98.5[mm]
O. mykiss	Metabolite 149-F11	96h (s.static)	Mortality, EC_{50}	>97.1[mm]
Aquatic invertebrate				
D. magna	cyflufenamid	48h (static)	Mortality, EC_{50}	>1.73[mm]
D. magna	cyflufenamid	21d (static)	Surviv/repro NOEC	0.0406/0.246[mm]
D. magna	NF-149EW	48h (static)	Mortality, EC_{50}	0.491(9.48[1])[mm]
D. magna	Metabolite 149-F	48h (static)	Mortality, EC_{50}	54.6[mm]
D. magna	Metabolite 149-F1	48h (static)	Mortality, EC_{50}	14.1[mm]
D. magna	Metabolite 149-F6	48h (static)	Mortality, EC_{50}	>103[mm]
D. magna	Metabolite 149-F11	48h (static)	Mortality, EC_{50}	>99.6[mm]
Sediment dwelling organisms				
C. riparius	Cyflufenamid[2]	28d (static)	Repro NOEC	1.0[nom]

Group	Test substance	Time-scale (Test type)	End point	Toxicity mg/L
Algae				
P. subcapitata	cyflufenamid	72h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	>0.828[mm] >0.828[mm]
P. subcapitata	NF-149EW	72h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.0364(0.701[1])[m] [m] 0.0844(1.628[1])[m] [m]
P. subcapitata	Metabolite 149-F	72h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	55.3[mm] 77.1[mm]
P. subcapitata	Metabolite 149-F1	72h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	>99.7[mm] >99.7[mm]
P. subcapitata	Metabolite 149-F6	72h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	>101[mm] >101[mm]
P. subcapitata	Metabolite 149-F11	72h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	>97.3[mm] >97.3[mm]
Higher plant - not required				
Microcosm or mesocosm tests - not required				

[nom] nominal; [mm] mean measured; [1] preparation conc., [2] spiked water

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

Note: the surface water assessment has not been conducted using the FOCUSsw models. Spray drift and drainflow have only been considered (see Environmental Fate section).

SPRAY DRIFT & DRAINFLOW

Winter & spring cereals (N/SEU);1x or 2x 0.025 kg a.s./ha (28d spray interval); BBCH30-59

Test substance	Organism	Tox end pt. (mg/L)	Time-scale	PECi (mg/L)	TER	Annex VI
SPRAY DRIFT @ 1m off-field (2.77% 1x application =worse case)						
Preparation / a.s.						
NF-149EW	Fish	0.511	Acute	0.000231	2212	100
Cyflufenamid	Fish	0.024	Chronic	0.000231	104	100
NF-149EW	Aq. inverts.	0.491	Acute	0.000231	2126	10
Cyflufenamid	Aq. inverts.	0.0406	Chronic	0.000231	176	10
NF-149EW	Algae	0.0364	Chronic	0.000231	158	10
Cyflufenamid	Sed. dweller	1.0	Chronic	0.000231	4329	10
Metabolites						
149-F	Fish	41.3	Acute	0.00002	2065000	100
149-F	Aq. inverts.	54.6	Acute	0.00002	2730000	100
149-F	Algae	55.3	Chronic	0.00002	2765000	10
149-F6	Fish	>98.5	Acute	0.0000007	>140000000	100
149-F6	Aq. inverts.	>103	Acute	0.0000007	>147000000	100
149-F6	Algae	>101	Chronic	0.0000007	>144000000	10
149-F11	Fish	>97.1	Acute	0.000057	>1703509	100
149-F11	Aq. inverts.	>99.6	Acute	0.000057	>1747368	100

149-F11	Algae	>97.3	Chronic	0.000057	>1707018	10
DRAINFLOW						
Metabolites						
149-F	Fish	41.3	Acute	0.000723	57123	100
149-F	Aq. inverts.	54.6	Acute	0.000723	75519	100
149-F	Algae	55.3	Chronic	0.000723	76487	10
149-F1	Fish	>103	Acute	0.000134	>768657	100
149-F1	Aq. inverts.	>14.1	Acute	0.000134	105224	100
149-F1	Algae	>99.7	Chronic	0.000134	>744030	10
149-F6	Fish	>98.5	Acute	0.000143	>688811	100
149-F6	Aq. inverts.	>103	Acute	0.000143	>720280	100
149-F6	Algae	>101	Chronic	0.000143	>706294	10

FOCUSsw not assessed

Bioconcentration		
	cyflufenamid	Aq. metabolites
$logP_{O/W}$	4.7	All <3.0
Bioconcentration factor (BCF)[1] ‡	528	-
Annex VI Trigger for the bioconcentration factor	100	-
Clearance time (days) (CT_{50})	1.0 - 1.5d	-
(CT_{90})	5d	-
Level and nature of residues (%) in organisms after the 14 day depuration phase	1.4 - 1.5	-

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)
cyflufenamid ‡	>100	>100
NF-149EW	>15.51 (a.s.)	>15.51(a.s.)
Field or semi-field tests - not required		

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

Winter & spring cereals (N/SEU);1x or 2x 0.025 kg a.s./ha (28d spray interval); BBCH30-59

Test substance	Route	Hazard quotient	Annex VI Trigger
cyflufenamid	Contact	<0.25	50
cyflufenamid	oral	<0.25	50
NF-149EW	Contact	<1.61	50
NF-149EW	oral	<1.61	50

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

Laboratory tests with standard sensitive species

Species	Test Substance	End point	Effect (LR_{50} g/ha[1])
Typhlodromus pyri ‡	NF-149EW	Mortality	>50 (a.s.)
Aphidius rhopalosiphi ‡	NF-149EW	Mortality	50 (a.s.)

Winter & spring cereals (N/SEU);1x or 2x 0.025 kg a.s./ha (28d spray interval); BBCH30-59

Test substance	Species	Effect (LR_{50} g/ha)	HQ in-field	HQ off-field @1.0m (2.38%)	Trigger
NF-149EW	*Typhlodromus pyri*	>50 (a.s.)	<0.85	<0.02	2
NF-149EW	*Aphidius rhopalosiphi*	50 (a.s.)	0.85	0.02	2

Further laboratory and extended laboratory studies ‡

Species	Life stage	Test substance, substrate and duration	Dose (g a.s./ha)	End point	% effect (max)	Trigger value
Chrysoperla carnea	Larvae	NF-149EW	1.25-50	Mortality	8	50 %
Poecilius cupreus	Adult	NF-149EW (14d aged)	1.25-50	Mortality	3.3	50 %
Aphidius rhopalosiphi	Adult	NF-149EW (48h)	5.89-50	11d Mean parasitised aphid/female	-26	50 %
Typhlodromus pyri	Proto Nymph	NF-149EW (14d aged)	0.589-50	21d Mean eggs/female	-7	50 %
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	Test	End point (mg a.s./kg soil)
Earthworms			
	Cyflufenamid ‡	Acute 14d $LC50_{corr}$	>500
	NF-149EW	Acute 14d $LC50_{corr}$	>25
	NF-149EW	Chronic 56d $NOEC_{corr}$	0.667
	Metabolite 149-F	Acute 14d $LC50_{corr}$	139.5
	Metabolite 149-F1	Acute 14d LC50	>1000
	Metabolite 149-F1	Chronic 56d NOEC	1.075
	Metabolite 149-F6	Acute 14d LC50	>1000
	Metabolite 149-F6	Chronic 56d NOEC	2.075
	Metabolite 149-F11	Acute 14d $LC50_{corr}$	>500
Other soil macro-organisms			
Collembola			
	NF-149EW	28d $NOEC_{corr}$	0.0178-1.78
	Metabolite 149-F1	28d NOEC	0.086
	Metabolite 149-F6	28d NOEC	16.6
Soil micro-organisms			
N - mineralisation	Cyflufenamid ‡	28d	<25% effect
	Metabolite 149-F1	28d	<25% effect
	Metabolite 149-F6	28d	<25% effect
C - mineralisation	Cyflufenamid ‡	28d	<25% effect
	Metabolite 149-F1	28d	<25% effect
	Metabolite 149-F6	28d	<25% effect
Field studies - not required			

corr. = corrected for log Pow>2 & 10% soil OM

Toxicity/exposure ratios for soil organisms

Winter & spring cereals (N/SEU);1x or 2x 0.025 kg a.s./ha (28d spray interval); BBCH30-59

Test organism	Test substance	Time scale	Soil PEC[i] (mg/kg soil)	TER	Trigger
Earthworms					
	cyflufenamid ‡	Acute	0.0235	>21277	10
	NF-149EW	Acute	0.0235	>1064	10
	NF-149EW	Chronic	0.0235	28	5
	Metab. 149-F	Acute	0.0066	21136	10
	Metab.149-F1	Acute	0.0062	>16129	10
	Metab.149-F1	Chronic	0.0062	173	5
	Metab.149-F6	Acute	0.0116	>86207	10
	Metab.149-F6	Chronic	0.0116	179	5
	Metab.149-F11	Acute	0.00455	>109890	10
Other soil macro-organisms					
Collembola	NF-149EW ‡	Chronic	0.0235	0.76-76	5
	Metab.149-F1	Chronic	0.0062	14	5
	Metab.149-F6	Chronic	0.0116	1431	5

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

Herbicidal screening - 4 plant spp. - 2.0 kg cyflufenamid/ha post emergent - LR50>2.0 a.s. kg/ha

Laboratory dose response tests - not undertaken

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

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

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

Not undertaken

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

Test type/organism	end point
Activated sludge	EC50 > 100mg a.s./L

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

Compartment	
soil	Cyflufenamid
Surface water	Cyflufenamid
sediment	Cyflufenamid
groundwater	Cyflufenamid

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

	RMS/peer review proposal
Cyflufenamid	N, R50, R53, S60, S61
NF-149EW	N, R50, R53, S35, S57

APPENDIX B – LIST OF ABBREVIATIONS

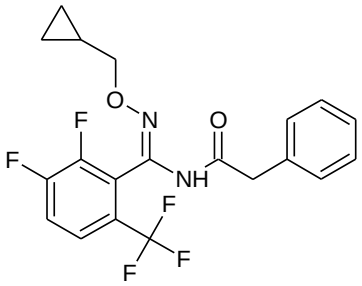
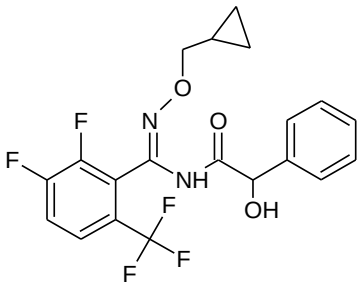
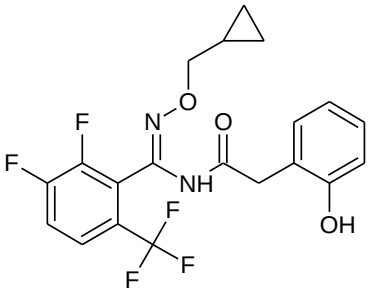
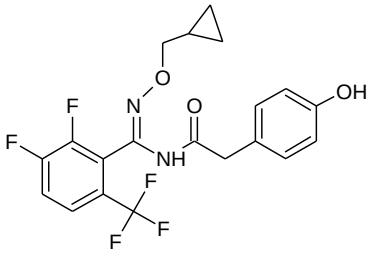
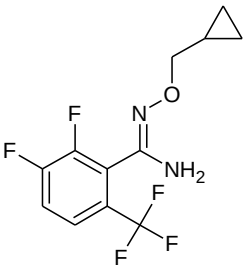
1/n	slope of Freundlich isotherm
ε	decadic molar extinction coefficient
°C	degree Celsius (centigrade)
µg	microgram
µm	micrometer (micron)
a.s.	active substance
AChE	acetylcholinesterase
ADE	actual dermal exposure
ADI	acceptable daily intake
ADME	Absorption, distribution, metabolism, elimination
AF	assessment factor
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
AV	avoidance factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstract Service
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CIPAC	Collaborative International Pesticide Analytical Council Limited
CL	confidence limits
d	day
DAA	days after application
DAR	draft assessment report
DAT	days after treatment
DM	dry matter
DT_{50}	period required for 50 percent disappearance (define method of estimation)
DT_{90}	period required for 90 percent disappearance (define method of estimation)
dw	dry weight
EbC_{50}	effective concentration (biomass)
EC_{50}	effective concentration
ECHA	European Chemical Agency
EEC	European Economic Community

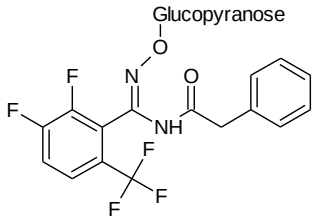
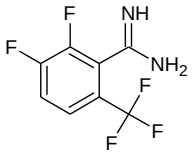
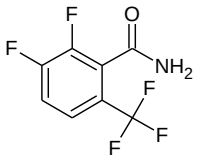
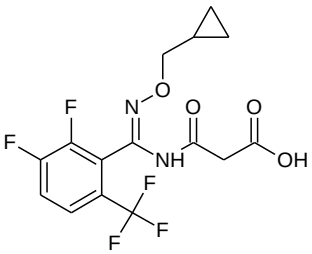
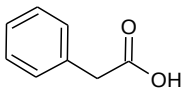
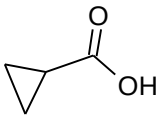
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER_{50}	emergence rate/effective rate, median
ErC_{50}	effective concentration (growth rate)
EU	European Union
EUROPOEM	European Predictive Operator Exposure Model
EW	emulsion, oil in water
f(twa)	time weighted average factor
FAO	Food and Agriculture Organisation of the United Nations
FIR	Food intake rate
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
g	gram
GAP	good agricultural practice
cGAP	critical good agricultural practice
GC	gas chromatography
GC-FID	gas chromatography with flame ionisation detector
GC-MS	gas chromatography-mass spectrometry
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GGT	gamma glutamyl transferase
GM	geometric mean
GS	growth stage
GSH	glutathion
h	hour(s)
ha	hectare
Hb	haemoglobin
Hct	haematocrit
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HQ	hazard quotient
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{doc}	organic carbon linear adsorption coefficient
kg	kilogram
K_{Foc}	Freundlich organic carbon adsorption coefficient

L	litre
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDH	lactate dehydrogenase
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
m	metre
M/L	mixing and loading
MAF	multiple application factor
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
mL	millilitre
mm	millimetre
MRL	maximum residue limit or level
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MWHC	maximum water holding capacity
NESTI	national estimated short-term intake
ng	nanogram
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OC	organic carbon content
OM	organic matter content
Pa	Pascal
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in ground water
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval

PIE	potential inhalation exposure
pK_a	negative logarithm (to the base 10) of the dissociation constant
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
PT	proportion of diet obtained in the treated area
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r^2	coefficient of determination
RPE	respiratory protective equipment
RUD	residue per unit dose
SC	suspension concentrate
SD	standard deviation
SF	safety factor
SFO	single first-order
SSD	species sensitivity distribution
STMR	supervised trials median residue
$t_{1/2}$	half-life (define method of estimation)
TER	toxicity exposure ratio
TER_A	toxicity exposure ratio for acute exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TK	technical concentrate
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UV	ultraviolet
W/S	water/sediment
w/v	weight per volume
w/w	weight per weight
WBC	white blood cell
WG	water dispersible granule
WHO	World Health Organisation
wk	week
yr	year

APPENDIX C – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
149-(*E*)-FB	*N*-{(*E*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-phenylacetamide	
149-F-α-OH-B	*N*-{(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-hydroxy-2-phenylacetamide	
149-F-2-OH-B	*N*-{(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-(2-hydroxyphenyl)acetamide	
149-F-4-OH-B	*N*-{(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}-2-(4-hydroxyphenyl)acetamide	
149-F	*N*'-(cyclopropylmethoxy)-2,3-difluoro-6-(trifluoromethyl)benzenecarboximidamide	

149-F4B-Glu	*N*-{(*Z*)- [2,3-difluoro-6-trifluoromethy α-(β-glucopyranosylimino)benzyl]}-2-phenylacetamide	
149-F1	2,3-difluoro-6-(trifluoromethyl)benzenecarboximidamide	
149-F6	2,3-difluoro-6-(trifluoromethyl)benzamide	
149-F11	3-({(*Z*)-[(cyclopropylmethoxy)imino][2,3-difluoro-6-(trifluoromethyl)phenyl]methyl}amino)-3-oxopropanoic acid	
PAA	phenylacetic acid	
CPCA	cyclopropanecarboxylic acid	
CPMOH	cyclopropylmethanol