

CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion on the peer review of the pesticide risk assessment of the active substance flubendiamide¹

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ABSTRACT

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authority of the rapporteur Member State Greece, for the pesticide active substance flubendiamide are reported. The context of the peer review was that required by Commission Regulation (EU) No 188/2011. The conclusions were reached on the basis of the evaluation of the representative uses of flubendiamide as an insecticide on tomatoes and bell pepper but only when grown in permanent glasshouse structures. The reliable endpoints concluded as being appropriate for use in regulatory risk assessment, derived from the available studies and literature in the dossier peer reviewed, are presented. Missing information identified as being required by the regulatory framework is listed. The risk assessment for aquatic invertebrates from metabolite A 10 (NN1-0001-3-OH-hydroxy-perfluoralkyl) could not be finalised.

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KEY WORDS

flubendiamide, peer review, risk assessment, pesticide, insecticide

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SUMMARY

Flubendiamide is a new active substance for which in accordance with Article 6(2) of Council Directive 91/414/EEC Greece (hereinafter referred to as the 'RMS') received an application from Bayer CropScience for approval. Complying with Article 6(3) of Directive 91/414/EEC, the completeness of the dossier was checked by the RMS. The European Commission recognised in principle the completeness of the dossier by Commission Decision 2006/927/EC.

The RMS provided its initial evaluation of the dossier on flubendiamide in the Draft Assessment Report (DAR), which was received by the EFSA on 1 September 2008. In accordance with Commission Regulation (EU) No 188/2011 Article 11(6) additional information was requested. The RMS's evaluation of the additional information was submitted to the EFSA in the format of addenda to the DAR, which were received by the EFSA on 9 April 2012. The peer review was initiated on 4 May 2012 by dispatching the DAR and the addenda for consultation of the Member States and the applicant Bayer CropScience.

Following consideration of the comments received on the DAR, it was concluded that EFSA should conduct an expert consultation in the area of mammalian toxicology and EFSA should adopt a conclusion on whether flubendiamide can be expected to meet the conditions provided for in Article 5 of Directive 91/414/EEC, in accordance with Article 8 of Commission Regulation (EU) No 188/2011.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of flubendiamide as an insecticide on tomatoes and bell pepper, only when grown in permanent glasshouse structures, as proposed by the applicant. Full details of the representative uses can be found in Appendix A to this report.

In the area of identity, physical/chemical/technical properties and methods of analysis a data gap was identified for a revised specification of the technical material.

No data gap or critical areas of concern were identified in the mammalian toxicology section.

In the area of residues no data gap or areas of concern were identified; however the growing of following crops in greenhouses with a soil based system may have to be restricted to specific crops.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses assessed (which were just situations where greenhouses are permanent structures). The potential for groundwater exposure by flubendiamide and its soil metabolite NNI-0001-des-iodo (A1) above the parametric drinking water limit of 0.1 µg/L, consequent to these uses assessed, was concluded to be low

A low risk to birds, mammals, fish, algae, honey bees, non-target arthropods, earthworms, soil macro-organisms, soil micro-organisms, non-target plants and sewage treatment organisms was concluded. A low risk to aquatic invertebrates was also concluded for the flubendiamide, however, the risk assessment for aquatic invertebrates from metabolite A10 (NNI-0001-3-OH-hydroxy-perfluoroalkyl) could not be finalised with the available data.

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BACKGROUND

In accordance with Article 80(1)(a) of Regulation (EC) No 1107/2009,³ Council Directive 91/414/EEC⁴ continues to apply with respect to the procedure and conditions for approval for active substances for which a decision recognising in principle the completeness of the dossier was adopted in accordance with Article 6(3) of that Directive before 14 June 2011.

Commission Regulation (EU) No 188/2011⁵ (hereinafter referred to as 'the Regulation') lays down the detailed rules for the implementation of Council Directive 91/414/EEC as regards the procedure for the assessment of active substances which were not on the market on 26 July 1993. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States and the applicant for comments on the initial evaluation in the Draft Assessment Report (DAR) provided by the rapporteur Member State (RMS), and the organisation of an expert consultation, where appropriate.

In accordance with Article 8 of the Regulation, EFSA is required to adopt a conclusion on whether the active substance is expected to meet the conditions provided for in Article 5 of Directive 91/414/EEC within 4 months from the end of the period provided for the submission of written comments, subject to an extension of 2 months where an expert consultation is necessary, and a further extension of up to 8 months where additional information is required to be submitted by the applicant(s) in accordance with Article 8(3).

In accordance with Article 6(2) of Council Directive 91/414/EEC Greece (hereinafter referred to as the 'RMS') received an application from Bayer CropScience for approval of the active substance flubendiamide. Complying with Article 6(3) of Directive 91/414/EEC, the completeness of the dossier was checked by the RMS. The European Commission recognised in principle the completeness of the dossier by Commission Decision 2006/927/EC.⁶

The RMS provided its initial evaluation of the dossier on flubendiamide in the DAR, which was received by the EFSA on 1 September 2008 (Greece, 2008). In accordance with Commission Regulation (EU) No 188/2011 Article 11(6) additional information was requested. The RMS's evaluation of the additional information was submitted to the EFSA in the format of addenda to the DAR, which were received by the EFSA on 9 April 2012. The peer review was initiated on 4 May 2012 by dispatching the DAR and the addenda to Member States and the applicant Bayer CropScience for consultation and comments. In addition, the EFSA conducted a public consultation on the DAR. The comments received were collated by the EFSA and forwarded to the RMS for compilation and evaluation in the format of a Reporting Table. The applicant was invited to respond to the comments in column 3 of the Reporting Table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 8(3) of the Regulation were considered in a telephone conference between the EFSA, the RMS, and the European Commission on 7 September 2012. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof it was

³ Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ No L 309, 24.11.2009, p. 1-50.

⁴ Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1-32, as last amended.

⁵ Commission Regulation (EU) No 188/2011 of 25 February 2011 laying down detailed rules for the implementation of Council Directive 91/414/EEC as regards the procedure for the assessment of active substances which were not on the market 2 years after the date of notification of that Directive. OJ No L 53, 26.2.2011, p. 51-55.

⁶ Commission Decision 2006/927/EC of 13 December 2006 recognising in principle the completeness of the dossier submitted for detailed examination in view of the possible inclusion of flubendiamide in Annex I to Council Directive 91/414/EEC. OJ No L 354, 14.12.2006 p. 54-55.

concluded that additional information should be requested from the applicant and the EFSA should organise an expert consultation in the area of mammalian toxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments is reflected in the conclusions set out in column 4 of the Reporting Table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation and the additional information to be submitted by the applicant, were compiled by the EFSA in the format of an Evaluation Table.

The conclusions arising from the consideration by the EFSA, and as appropriate by the RMS, of the points identified in the Evaluation Table, together with the outcome of the expert consultation where this took place, were reported in the final column of the Evaluation Table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in June 2013.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the representative uses as a insecticide on glasshouse tomatoes and bell pepper as proposed by the applicant. A list of the relevant end points for the active substance as well as the formulation is provided in Appendix A. In addition, a key supporting document to this conclusion is the Peer Review Report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The Peer Review Report (EFSA, 2013) comprises the following documents, in which all views expressed during the course of the peer review, including minority views, can be found:

- the comments received on the DAR and the addenda
- the Reporting Table (9 September 2012),
- the Evaluation Table (27 June 2013)
- the report(s) of the scientific consultation with Member State experts (where relevant)
- the comments received on the assessment of the additional information (where relevant),
- the comments received on the draft EFSA conclusion.

Given the importance of the DAR including its addendum (compiled version of June 2013 containing all individually submitted addenda (Greece, 2013)) and the Peer Review Report, both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Flubendiamide is the ISO common name for 3-iodo-*N'*-(2-mesyl-1,1-dimethylethyl)-*N*-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*o*-tolyl}phthalamide (IUPAC).

The representative formulated product for the evaluation was 'BELT 480 SC' (code: NNI-0001 SC 480), a suspension concentrate (SC) containing 480 g/L flubendiamide.

The representative uses evaluated comprise applications by spraying against various lepidopteran species in tomato and bell pepper, only in permanent glasshouse structures. Full details of the GAPs can be found in the list of end points in Appendix A.

CONCLUSIONS OF THE EVALUATION

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

The following guidance documents were followed in the production of this conclusion: SANCO/3030/99 rev.4 (European Commission, 2000) and SANCO/825/00 rev. 8.1 (European Commission, 2010).

The minimum purity of the active substance is 960 g/kg. No FAO specification exists.

The specification of the technical material should be regarded as provisional. The revised specification proposed in the Addendum 1 to Annex C of the DAR (March 2013) would be considered acceptable if the unidentified material is removed. A data gap was identified

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 flubendiamide or the representative formulation. The main data regarding the identity of flubendiamide and its physical and chemical properties are given in appendix A.

Adequate analytical methods are available for the determination of flubendiamide in technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material.

Residues of flubendiamide in food and feed of plant origin can be monitored by LC-MS/MS with LOQs of 0.01 mg/kg for all four types of matrices (dry, high water, high acid and high oil content). A LC-MS/MS method to monitor residues in food of animal origin was properly validated at LOQ of 0.01 mg/kg for muscle, liver, kidney, fat, milk and eggs. Appropriate LC-MS/MS methods exist for the analysis of flubendiamide in soil, water and air with LOQs of 0.5 µg/kg, 0.05 µg/L and 1.8 µg/m³ respectively. Validation of a LC-MS/MS method for the determination of the metabolite NNI-0001-3-OH-hydroxy perfluoralkyl in surface water at LOQ of 0.05 µg/L was also provided. However pending on the data gap identified in Section 5 more sensitive method for analysis of this metabolite in surface water might need to be provided.

A method for residues in body fluids and tissues is not required as the active substance is not classified as toxic or very toxic.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000 rev. 10 - final (European Commission, 2003), SANCO/222/2000 rev. 7 (European Commission, 2004) and SANCO/10597/2003 - rev. 10.1 (European Commission, 2012).

Flubendiamide was discussed in the Pesticides Peer Review meeting 102 in March 2013.

Flubendiamide is poorly absorbed after oral administration in rats (23.5%); it is widely distributed with the highest concentrations in liver, adrenal gland and fat, and extensively metabolised, mainly in male rats. It is mainly excreted through faeces (>91%). It is not acutely toxic via oral, dermal or inhalation routes, it is not a skin and eye irritant, nor a skin sensitiser. The most sensitive species after subchronic repeated doses is the dog, with the relevant No Observed Adverse Effects Levels (NOAELs) of 2.21 and 2.6 mg/kg bw per day, based on shortening of the activated partial thromboplastin time (APTT), increased alkaline phosphatase (ALP), plus increased adrenal weights and histopathological changes (in the 90-day study) and increased liver weight (in the 1-year study). Rat and mouse had similar NOAELs in a 90-day study (11.4 and 11.9 mg/kg bw per day mainly based on liver weight findings). In chronic toxicity and carcinogenicity studies rats showed a decrease eosinophil count, increased absolute liver weight with periportal fatty change, increased incidence of chronic nephropathy (females also showed increased incidence of thyroidal follicular cell hypertrophy) with a NOAEL of 1.7 mg/kg bw per day, whereas in mice the NOAEL was 4.44 mg/kg bw per day, based on liver and thyroid effects (discoloration of the livers in males, increased liver weights with centrilobular hypertrophy and centrilobular microvesicular fatty change of hepatocytes in both sexes, enlarged thyroids and an upward trend in thyroid weights with follicular cell hypertrophy and hydropic change and increased large-sized follicles in both sexes).

Flubendiamide did not show any relevant genotoxicity and carcinogenicity potential. The effects observed in the reproductive toxicity studies with flubendiamide suggest that classification and labelling with R63⁷ (“Possible risk of harm to the unborn child” or H360D “May damage the unborn child”) and R64*⁸ (“May cause harm to breast-fed babies”) are appropriate: exposure via milk of flubendiamide and/or its metabolites cannot be excluded and the experts noted that pup death was observed in the 1 generation study at the highest dose tested and in F1 generation in the 2-generation study that could be linked to exposure via milk. The relevant parental and offspring NOAELs are 12.91 mg/kg bw per day, the relevant reproductive NOAEL is 3.84 mg/kg bw per day. Eye effects were observed in the multigeneration and developmental neurotoxicity studies in rats: the majority of the experts agreed that it cannot be excluded that possible *in utero* exposure in humans would result in the same eye effects as for after birth in rats. The relevant maternal and developmental NOAELs are 10 and 100 mg/kg bw per day, respectively, in rats, and 1000 mg/kg bw per day in rabbits.

The toxicological profile of the flubendiamide metabolite NNI-0001-des-iodo (A-1, not present in the rat metabolism) was investigated in acute oral toxicity study (which showed low oral acute toxicity) and in a negative bacterial mutation assay. No further data are available to establish whether the reference values of flubendiamide apply to NNI-0001-des-iodo as well, neither specific reference values can be set.

The Acceptable Daily Intake (ADI) is 0.017 mg/kg bw per day based on the NOAEL of 1.7 mg/kg bw per day of the long/term toxicity study in rats, with the application of an uncertainty factor (UF) of 100; the Acute Reference Dose (ARfD) is 0.1 mg/kg bw based on the NOAEL of 10 mg/kg bw per day for developmental effects (eye effects) observed in the DNT study (UF of 100). The agreed Acceptable Operator Exposure Level (AOEL) is 0.006 mg/kg bw per day based on an overall NOAEL of 2.6 mg/kg bw per day for dogs, (UF 100 and 23.5% correction for oral absorption). The operator and worker exposure is below the AOEL, even without the use of Personal Protective Equipment (PPE) (except when the Dutch model is applied, leading to the need of considering the use of gloves and coveralls to reduce the exposure below the AOEL). Bystander exposure is not considered for glasshouse uses.

⁷ It should be noted that classification is formally proposed and decided in accordance with Regulation (EC) No 1272/2008. Proposals for classification made in the context of the evaluation procedure under Regulation (EC) No 1107/2009 are not formal proposals.

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3. Residues

The assessment in the residue section below is based on the guidance documents listed in the document 1607/VI/97 rev.2 (European Commission, 1999), and the JMPR recommendations on livestock burden calculations stated in the 2004 and 2007 JMPR reports (JMPR, 2004, 2007).

The metabolism of flubendiamide was investigated in the three crop categories fruit and fruiting vegetables (tomato, apple), leafy vegetables (cabbage) and cereals (maize) using aniline ring labelled and the phthalic acid ring labelled material. Flubendiamide was by far the major component of the total radioactive residues (TRR) accounting for 50% to 94% TRR in the mature crops. Only small proportions of metabolites were detected (individually <1% to 6% TRR) with the exception of metabolite A-1 (NN1-0001-des-iodo) which accounted for more than 10% TRR in the apple and maize metabolism study, but was not a rat metabolite (refer to chapter 2). Oxidative cleavage of a small portion of the parent compound leading to label-specific metabolites was observed in tomatoes and apples, but levels and proportions of these metabolites were not significant.

Both, flubendiamide and the metabolite were determined in the residue trials in tomatoes and peppers grown indoors. Residues of the metabolite A-1 (NN1-0001-des-iodo) has always been below the LOQ in all tested samples. Hence, in terms of the representative uses the residue definition for risk assessment was set as flubendiamide, and it was proposed that also flubendiamide alone is a suitable marker compound for inclusion in the monitoring residue definition. A re-evaluation of whether or not the non-rat metabolite A-1 (NN1-0001-des-iodo) may have to be considered in the risk assessment should be conducted if further uses are requested, and upon availability of residue trial data with such uses.

The effects of processing on the nature of flubendiamide residues have been investigated, and under core processing conditions (sterilisation, pasteurization and baking/brewing/boiling) no degradation of flubendiamide occurred. Therefore for the processed commodities under consideration the same residue definition as for the raw commodities applies.

A sufficient number of residue trials in tomatoes and peppers grown indoors is available. The trial results are supported by storage stability data and validated analytical methods. Processing factors could be derived on the basis of processing residue studies on tomatoes.

Residues in rotational crops were investigated in wheat, Swiss chard, and turnips with flubendiamide radio labelled in the aniline ring and the phthalic acid ring at concentrations in soil slightly higher (≥ 1.25 N) than the estimated plateau concentration. Again, flubendiamide was the major component of the TRR in all crops grown up to a plant back interval of 9 month. The metabolite A-27 (flubendiamide des-iodo alkylphthalimide) was present up to 21% TRR. However, absolute levels of A-27 were very low and did not exceed 0.01 mg/kg. All other metabolites were detected in insignificant amounts and proportions. Therefore, for rotational crops the same residue definition as for raw commodities is applicable. However, the available data indicate that residues of flubendiamide in rotational leafy crops and cereals exceeded 0.01 mg/kg. Hence, in terms of the representative use, there is the potential for residues of flubendiamide to exceed the default MRL of 0.01 mg/kg in crops that could be grown in greenhouses on a soil-based system following the cultivation of tomatoes and peppers. Therefore, residues trials may be necessary to address the potential for uptake of residues in crops realistically expected to be grown as following crops in greenhouses with a soil-based system, depending on individual MS practices. Alternatively, a restriction to grow crops other than tomatoes, peppers and crops already regulated by an MRL higher than the default value of 0.01 mg/kg, in greenhouses with a soil based system, may have to be considered.

Although not required to support the representative uses in tomatoes and peppers, the metabolism of flubendiamide in livestock was investigated in lactating goats and laying hens. The metabolism studies indicated that the residues mainly accumulate in fat. The studies further indicate that for the risk assessment residue definition the sum of flubendiamide and A-14 (NN1-0001-iodophthalimide),

expressed as flubendiamide will be appropriate, and for enforcement purposes flubendiamide alone is considered a sufficient marker. Feeding studies with flubendiamide in hens and dairy cows are also available; however, full evaluation of these studies is only possible on the basis of a dietary burden calculation for feed commodities, which does not apply to the representative uses in tomato and peppers.

The consumer exposure assessment was performed with the EFSA PRIMo. For the calculation of the maximum chronic exposure (TMDI) the proposed MRLs were used. The long-term consumer intake for the European diets was 4 % of the ADI (maximum for WHO cluster diet B). No acute consumer intake concerns were identified regarding the intake of commodities related to the representative uses. The calculated maximum exposure was 13% of the ARfD for peppers (DE child). The intake estimates did not consider potential residues of flubendiamide in crops that could be grown in greenhouses on a soil-based system following the cultivation of tomatoes and peppers.

4. Environmental fate and behaviour

In soil laboratory incubations under aerobic conditions in the dark, flubendiamide exhibited very high persistence, forming the metabolite NNI-0001-des-iodo (A1) (max 7.1% applied radioactivity (AR)), which reached levels triggering a groundwater exposure assessment and exhibited very high persistence. Mineralisation of the phthalic acid and aniline ring ¹⁴C radiolabels to carbon dioxide accounted for only 0.1-0.3 % AR after 90-91 days. The formation of unextractable residues (not extracted by water then acetonitrile) for these radiolabels accounted for 5.2 – 7.1 % AR after 90-91 days. Under the conditions of a laboratory soil photolysis study (where the light energy and quality mimicked natural sunlight and not light energy / quality that is present in a glasshouse) the route of degradation was the same as that in the dark, but metabolite NNI-0001-des-iodo (A1) was formed at higher levels (max 17.6 % AR). In anaerobic soil incubations flubendiamide appeared even more stable than under aerobic conditions. Flubendiamide exhibited low to slight mobility in soil. NI-0001-des-iodo (A1) exhibited medium to low soil mobility. It was concluded that the adsorption of flubendiamide and NNI-0001-des-iodo (A1) was not pH dependent. In satisfactory field dissipation studies carried out at 6 sites across western Europe (spray application to the soil surface on bare soil plots between mid June and the end of August, with grass subsequently emerging), flubendiamide exhibited high to very high persistence with degradation being biphasic. The faster first phase degradation in the experiments was postulated to have been at least partially due to photolysis at the soil surface, which is a process that will be significantly reduced in the context of the representative uses assessed that are under glass. Therefore second slow phase dissipation DT50 were taken forward in the exposure assessments. This is clearly necessary where the compartment being assessed will be under glass. Sample analyses were carried out for the parent flubendiamide, NNI-0001-des-iodo (A1), NNI-0001-benzoic acid (A18) which accounted for maxima of 2.6 % and 3.7 % of applied parent respectively and two other potential transformation products that were either not detected, or detected at <0.15% of the dosed flubendiamide. Second slow phase DT50 values from the biphasic fits were accepted as being reasonable estimates of flubendiamide degradation within the soil matrix, following normalisation of the decline of both phases to FOCUS reference conditions (20°C and -10kPa soil moisture), using the time step normalisation procedure in accordance with FOCUS (2006) kinetics guidance. A geomean value from these normalised slow phase data was used in the groundwater exposure assessments.

In laboratory incubations in dark aerobic natural sediment water systems, flubendiamide exhibited very high persistence. The unextractable sediment fraction (not extracted by acetonitrile followed by heated acetonitrile water/water) was the sink for the phthalic acid and aniline ring ¹⁴C radiolabels, accounting for 9.5 – 16.5 % AR at study end (125 days). Mineralisation of these radiolabels accounted for only 0.4 – 0.9 % AR at the end of the study. Transformation products, as characterised by resolved radioactivity in chromatograms (that was not the test substance) individually did not account for more than 2 % AR. In a laboratory sterile aqueous photolysis experiment flubendiamide formed the major transformation products NNI-0001-des-iodo (A1) (max. 21.6% AR) and NNI-0001-3-OH-hydroxy-perfluoroalkyl (A10) (max 13% AR). In outdoor mesocosm experiments located in Germany, where

non radio labelled test substance was dosed to the water column in May, flubendiamide exhibited medium persistence. NI-0001-des-iodo (A1) never accounted for > 2.1% of applied parent and NNI-0001-3-OH-hydroxy-perfluoroalkyl (A10) was not detected (<0.4% of applied parent). The necessary surface water and sediment exposure assessments (Predicted environmental concentrations (PEC) calculations) were carried out for flubendiamide (water and sediment) and the metabolites NI-0001-des-iodo (A1) and NNI-0001-3-OH-hydroxy-perfluoroalkyl (A10) (water only) assuming 0.1 and 0.2% emission from a glasshouse to an adjacent water body, with the characteristics as defined for FOCUS (2001) step 1 and 2 PEC estimates. This approach has been accepted by Member State experts as an assumption that can be used in EU level surface water exposure assessments for glasshouse uses and is referred to in FOCUS (2008) guidance as being appropriate.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (FOCUS, 2009) scenarios and the model PEARL 4.4.4⁹ for the active substance flubendiamide and NI-0001-des-iodo (A1) assuming 0.2% of the flubendiamide application rate is emitted from a glasshouse to soil in adjacent fields. Also PEARL 4.4.4 was used with the FOCUS scenario soil descriptions, but modified climate files to represent soil temperature and drip irrigation practices in glasshouses in northern and southern Europe, to address leaching potential through the soil column directly under glass houses. The potential for groundwater exposure from the representative uses by flubendiamide and NI-0001-des-iodo (A1) above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations that are represented by all of the 8 pertinent FOCUS and adapted FOCUS groundwater scenarios.

The PEC in soil, surface water, sediment, and groundwater covering the representative uses assessed (which were just situations where greenhouses are permanent structures), can be found in Appendix A of this conclusion.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a, 2002b, 2002c) and SETAC (2001).

A risk assessment for birds and mammals from secondary poisoning was available and indicated a low risk. As the representative use of flubendiamide is to tomatoes and bell peppers in permanent glasshouses only, exposure to birds and mammals from other routes of exposure is not expected and a low risk was concluded.

A risk assessment for aquatic organisms was available and a low risk to fish (acute and chronic) sediment dweller and algae was concluded, however, a high acute and chronic risk to aquatic invertebrates was indicated by the first tier risk assessment. The risk assessment for aquatic invertebrates was refined using a higher tier mesocosm study and a low risk was concluded. Flubendiamide has two aquatic metabolites (A1 (NNI-0001-des-iodo) and A10 (NNI-0001-3-OH-hydroxy-perfluoroalkyl) which needed to be considered in the aquatic risk assessment. No toxicity data were available for metabolite A10 (NNI-0001-3-OH-hydroxy-perfluoroalkyl) and limited data were available for metabolite A1 (NNI-0001-desiodo). Therefore, in the absence of toxicity data, inline with the Aquatic Guidance Document (European Commission, 2002b), a risk assessment was performed by assuming the metabolite is ten times more toxic than the parent substance. The risk assessment indicated a low risk to fish and algae but was not sufficient to indicate a low risk to aquatic invertebrates. The risk assessment for metabolite A1 (NNI-0001-desiodo) was refined using the available mesocosm study where metabolite A1 (NNI-0001-desiodo) was detected at levels greater than the surface water PEC value and a low risk was concluded. Metabolite A10 (NNI-0001-3-OH-hydroxy-perfluoroalkyl) was not detected in the available mesocosm study and no further information was available to refine the risk assessment for aquatic invertebrates. A data gap was therefore

⁹ Simulations complied correctly utilised the agreed Q10 of 2.58 (following EFSA PPR, 2007) and Walker equation coefficient of 0.7.

considered for information to assess the risk to aquatic invertebrates from metabolite A10 (NNI-0001-3-OH-hydroxy-perfluoroalkyl).

A risk assessment for earthworms, soil macro organisms and soil micro organisms was available and indicated a low risk. A low risk was also concluded for honey bees, non-target arthropods, earthworms, non-target plants and organisms involved in sewage treatment processes. Flubendiamide was not toxic to honey bees at the concentrations tested in the available laboratory studies and therefore no concern was raised regarding the risk to pollinators which may be used in glasshouses.

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

6.1. Soil

Compound (name and/or code)	Persistence	Ecotoxicology
flubendiamide	High to very high persistence European field dissipation studies, biphasic kinetics DT ₅₀ 5.8-970 days (DT ₉₀ 855-> 1000 days)	Low risk to soil-dwelling organisms.

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
flubendiamide	Low to slight mobility K _{Foc} 1076-3318 mL/g	No	Yes	Yes	A low risk was indicated in the surface water exposure assessment.
NNI-0001-des-iodo (A1)	medium to low mobility K _{Foc} 234-581 mL/g	No	Yes	Acute oral LD50> 2000 mg/kg bw No genotoxic potential No further data needed	A low risk was indicated in the surface water exposure assessment.

6.3. Surface water and sediment

Compound (name and/or code)	Ecotoxicology
flubendiamide	Low risk to aquatic organisms.
NNI-0001-des-iodo (A1)	Low risk to aquatic organisms.
NNI-0001-3-OH-hydroxy-perfluoroalkyl (A10)	No data available. Data gap.

6.4. Air

Compound (name and/or code)	Toxicology
flubendiamide	No acute toxicity via inhalation

7. List of studies to be generated, still ongoing or available but not peer reviewed

This is a complete list of the data gaps identified during the peer review process, including those areas where a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 7 of Directive 91/414/EEC concerning information on potentially harmful effects).

- Revised specification for the technical material. (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 1)
- Information to address the acute and chronic risk to aquatic invertebrates from metabolite A10 (NNI-0001-3-OH-hydroxy-perfluoroalkyl) (relevant for all representative uses; submission date proposed by the applicant unknown; see section 5)

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

- A restriction to grow crops other than tomatoes, peppers and crops already regulated by an MRL higher than the default value of 0.01 mg/kg, in greenhouses with a soil based system, may have to be considered.

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles of Annex VI to Directive 91/414/EEC and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

1. The risk assessment for aquatic invertebrates from metabolite A 10 (NN1-0001-3-OH-hydroxy-perfluoroalkyl) could not be finalised.

9.2. Critical areas of concern

An issue is listed as a critical area of concern where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles of Annex VI to Directive 91/414/EEC, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

9.3. Overview of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in

Representative use		Tomatoes (permanent glasshouse)	Bell peppers (permanent glasshouse)
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial vertebrates	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised		
Risk to aquatic organisms	Risk identified		
	Assessment not finalised	X ¹	X ¹
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached		
	Parametric value of 10µg/L ^(a) breached		
	Assessment not finalised		
Comments/Remarks			

The superscript numbers in this table relate to the numbered points indicated in sections 9.1 and 9.2. Where there is no superscript number see sections 2 to 6 for further information.

(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

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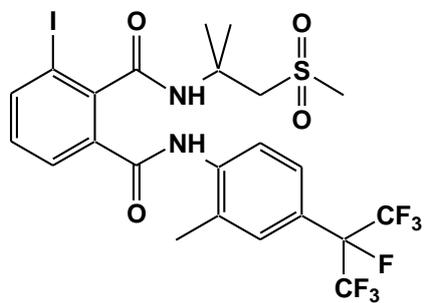
APPENDICES

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

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

Active substance (ISO Common Name) ‡	Flubendiamide
Function (<i>e.g.</i> fungicide)	Insecticide
Rapporteur Member State	Greece
Co-rapporteur Member State	-

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	3-iodo- <i>N</i> '-(2-mesyl-1,1-dimethylethyl)- <i>N</i> -{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]- <i>o</i> -tolyl}phthalamide
Chemical name (CA) ‡	<i>N</i> '-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-3-iodo- <i>N</i> ¹ -[2-methyl-4-[1,2,2,2-tetrafluoro-1--trifluoromethyl)ethyl]phenyl]-1,2-benzenedicarboxamide
CIPAC No ‡	788
CAS No ‡	272451-65-7
EC No (EINECS or ELINCS) ‡	not allocated
FAO Specification (including year of publication) ‡	-
Minimum purity of the active substance as manufactured ‡	960 g/kg
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	None.
Molecular formula ‡	C ₂₃ H ₂₂ F ₇ IN ₂ O ₄ S
Molecular mass ‡	682.4 g/mol
Structural formula ‡	 <p>The image shows the chemical structure of flubendiamide. It consists of a phthalimide core. One nitrogen of the phthalimide is substituted with a 2-methyl-2-(methylsulfonyl)ethyl group. The other nitrogen is substituted with a 4-(1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl)phenyl group. The benzene ring of the phthalimide core has an iodine atom at the 3-position.</p>

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	217.5 – 220.7°C with decomposition (99.6%)
Boiling point (state purity) ‡	No boiling point due to thermal decomposition
Temperature of decomposition (state purity)	255 to 260°C (99.6%)
Appearance (state purity) ‡	Pure a.s.: White Crystalline powder (99.1%)
	Technical a.s.: White Crystalline powder (96.0%)
Vapour pressure (state temperature, state purity) ‡	< 10 ⁻⁴ Pa (at 200°C)
	approximately 3.8x10 ⁻¹⁰ Pa (at 25°C) (99.6%)
Henry's law constant ‡	Calculated values at 20°C:
	< 9 x10 ⁻⁶ Pa m ³ /mol approximately 2x10 ⁻⁹ Pa m ³ /mol (99.6%)
Solubility in water (state temperature, state purity and pH) ‡	Solubility at 20 °C (99.1%) and pH 5.98
	29.90 ± 2.87 µg/L
Solubility in organic solvents ‡ (state temperature, state purity)	At 19.8°C (99.1%):
	Solubilities at 19.8°C: p-xylene: 0.488 g/L n-heptane: 0.000835 g/L methanol: 26.0 g/L 1,2-dichloroethane: 8.12 g/L acetone: 102 g/L ethyl acetate: 29.4 g/L
Surface tension ‡ (state concentration and temperature, state purity)	Not applicable
Partition co-efficient ‡ (state temperature, pH and purity)	At 25 °C:
	pH 4: Log Po/w = 4.13 ± 0.02 pH 7: Log Po/w = 4.14 ± 0.04 pH 9: Log Po/w = 4.11 ± 0.04 (99.6%)
Dissociation constant (state purity) ‡	Not applicable
UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	UV/vis –spectrum
	Absorption maxima's and coefficients: Neutral: 204.4 nm (ε = 39066 L.mol ⁻¹ .cm ⁻¹) Acidic: 203.0 nm (ε = 40500 L.mol ⁻¹ .cm ⁻¹) Basic: 218.0 nm (ε = 24967 L.mol ⁻¹ .cm ⁻¹) (99.0%)
Flammability ‡ (state purity)	Not highly flammable (96.0%, technical) Flubendiamide has no self-ignition temperature (96.0%, technical)
Explosive properties ‡ (state purity)	Flubendiamide is not expected to have explosive properties (97.4%, technical)
Oxidising properties ‡ (state purity)	Flubendiamide is not expected to have oxidizing properties (97.4%, technical)

Summary of representative uses evaluated (*flubendiamide*)

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Tomato	EU	Belt 480 SC	G	Lepidoptera	SC	480g/L	spraying	BBCH 13-89	2	7 days	0.006	500-2000	0.03-0.12	3	240 g/ha max per season only permanent glasshouse structures
Bell pepper	EU	Belt 480 SC	G	Lepidoptera	SC	480g/L	spraying	BBCH 13-89	2	7 days	0.006	500-1600	0.03-0.096	1	192 g/ha max per season only permanent glasshouse structures

Remarks:

(a)	For crops, Codex (or other, e.g. EU) classifications should be used; where relevant, the use situation should be described (e.g. fumigation of a structure)	(h)	Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(b)	Outdoor or field use (F), glasshouse application (G) or indoor application(I)	(i)	g/kg or g/l
(c)	e.g. biting and suckling insects, soil born insects, foliar fungi, weeds	(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
(d)	e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)		

- (e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
- (f) All abbreviations used must be explained
- (g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench

- (k) The minimum and maximum number of application possible under practical conditions of use must be provided
- (l) PHI - minimum pre-harvest interval
- (m) Remarks may include: Extent of use/economic importance/restriction

Methods of Analysis

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

Technical as (analytical technique)	HPLC-UV _{235nm} (internal standard method) HPLC-UV _{230nm} (internal standard method)
Impurities in technical as (analytical technique)	HPLC-UV _{210nm} (external standard method) HPLC-UV _{230nm} (external standard method) GC-FID Karl Fisher titration CIPAC MT 29, EN ISO 3451-1 “The Sulfate Limit Test” of “the Japanese Pharmacopoeia 14 th ed”.
Plant protection product (analytical technique)	HPLC-UV _{235nm} (external standard method) For the determination of flubendiamide in the representative formulation BELT© SC 480.

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin	Flubendiamide
Food of animal origin	Flubendiamide
Soil	Flubendiamide
Water surface	Flubendiamide Open for NNI-0001-3-OH-hydroxy perfluoroalkyl
drinking/ground	Flubendiamide
Air	Flubendiamide

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	<p>Report Number: 00816/M001, Doc No.: MR-087/03 & M-0822086-01-1</p> <p><u>Substrates:</u> citrus, head cabbage (head), oil (olive, cotton), bean (with pod), tomato and wheat (grain)</p> <p><u>Analysis:</u> LC/MS/MS</p> <p><u>Determined analyte:</u> NNI-0001, NNI-0001-des-iodo</p> <p><u>LOQ:</u> 0.01 mg/kg</p> <p>Report Number: P866G, Method Report No: M-246750-01-1. ILV + confirmatory study</p> <p><u>Substrates:</u> tomato, wheat (grain), head cabbage (head), cottonseed oil</p> <p><u>Analysis:</u> LC/MS/MS</p> <p><u>Determined analyte:</u> NNI-0001, NNI-0001-des-iodo</p> <p><u>LOQ:</u> 0.01 mg/kg</p>
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Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)

Method No. BCS 01207 based on the QuEChERS Method (confirmatory study)

Substrates: apple, orange, carrot, dry beans, oilseed rape

Analysis: LC/MS/MS

Determined analyte: NNI-0001, NNI-0001-des-iodo

LOQ: 0.01 mg/kg

Report Number: 00912, Doc No.: MR-149/04 & M-249688-01-1

Substrates: muscle, liver, kidney, fat, milk and poultry egg

Analysis: LC/MS/MS

Determined analyte: NNI-0001, NNI-0001-iodophthalimide

LOQ: 0.01 mg/kg

Doc No.: BAY-0512V & M-250859-02-1. ILV study

Substrates: muscle, fat and egg

Analysis: LC/MS/MS

Determined analyte: NNI-0001, NNI-0001-iodophthalimide

LOQ: 0.01 mg/kg

Soil (principle of method and LOQ)

Report Number: 00921, Doc No.: MR-187/04 & M-258125-01-1

Substrates: soil

Analysis: LC/MS/MS

Determined analyte: NNI-0001, NNI-0001-des-iodo and NNI-0001-benzoic acid

LOQ: 0.5 µg/kg

Report Number: 00849, Doc No.: MR-202/3 & M-082404-01-1

Substrates: soil

Analysis: LC/MS/MS

Determined analyte: NNI-0001, NNI-0001-des-iodo, NNI-0001-3-OH, NNI-0001-3-OH-hydroxy-perfluoroalkyl and NNI-0001-benzoic acid

LOQ: 0.5 µg/kg

Water (principle of method and LOQ)

Report Number: 00838, Doc No.: MR-134/03 & M-080711-01-1

Substrates: surface water

Analysis: LC/MS/MS

Determined analyte: NNI-0001, NNI-0001-des-iodo

LOQ: 0.05 µg/L

Report Number: 00760, Doc No.: MR-188/02 & M-078580-01-1

Substrates: surface water

	<p><u>Analysis</u>: LC/MS/MS <u>Determined analyte</u>: NNI-0001 <u>LOQ</u>: 0.05 µg/L</p> <p>Report Number: MR-12/081, Doc No. M-442265-01-1:</p> <p><u>Substrates</u>: surface water <u>Analysis</u>: LC/MS/MS <u>Determined analyte</u>: NNI-0001, NNI-0001-des-iodo and NNI-0001-3-OH-hydroxyperfluoralkyl <u>LOQ</u>: 0.05 µg/L</p> <p>Drinking water is covered by the abovementioned methods.</p>
<p>Air (principle of method and LOQ)</p>	<p>Doc No: P/B898G & M-253397-01-1</p> <p><u>Substrates</u>: air <u>Analysis</u>: LC/MS/MS <u>Determined analyte</u>: NNI-0001 <u>LOQ</u>: 1.8 µg/m³</p>
<p>Body fluids and tissues (principle of method and LOQ)</p>	<p>As flubendiamide is not classified as toxic or highly toxic, no analytical method is required for its determination in body fluids and tissues.</p>

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

	<p>RMS/peer review proposal</p>
<p>Active substance</p>	<p>None</p>

Impact on Human and Animal Health

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

Rate and extent of absorption ‡	Rapid, 23.5% (radioactivity found in bile, urine, liver, GI tract without content and carcass)
Distribution ‡	Widely distributed to blood and most of the organs/tissues. In liver, adrenal gland and fat higher levels were detected
Potential for accumulation ‡	Moderate accumulation potential-especially in females-after repeated dosing, but with a plateau reached at early phase
Rate and extent of excretion ‡	The main route of excretion was <i>via</i> faeces (>91% of the dose) and bile (♀: 3.28% and ♂: 11.06%) 168 h post last dosing. In urine a minor part of radioactivity was detected (0.15-1.67% of the dose)
Metabolism in animals ‡	Relative intensive metabolism involving oxidation of the methyl groups and resulting in the alcohol, aldehyde and benzoic acid derivatives of flubendiamide (males rats, mice, dogs) In female rats the metabolism was less intensive (no capability of oxidizing the methyl moiety). Most relevant animal-model: male rat
Toxicologically relevant compounds (animals and plants) ‡	Parent compound.
Toxicologically relevant compounds (environment) ‡	

Acute toxicity (Annex IIA, point 5.2)

Rat LD ₅₀ oral ‡	> 2000 mg/kg b.w. (males & females)
Rabbit LD ₅₀ dermal ‡	> 2000 mg/kg b.w. (males & females)
Rat LC ₅₀ inhalation ‡	> 0.0685 mg/L air (MAC, males & females)
Skin irritation ‡	No skin irritant (male Japanese White rabbits)
Eye irritation ‡	No eye irritant (male Japanese White rabbits)
Skin sensitisation ‡	No skin sensitiser (M&K, females)

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	<p><u>Target organs</u>: liver (rat, mouse, dog), thyroid (rat), blood (rat), ovaries (rat, mouse), kidney (rat) and adrenals (dog).</p> <p><u>Effects</u>: increased ALP activity, shortening of APTT, increased relative liver weight at the dose of 1500 ppm in both male and female dogs as well as reduced mean terminal body weight in males only.</p>	
Relevant oral NOAEL ‡	2.21 mg/kg bw per day (1-year, dog) 11.4 mg/kg bw per day (90-day, male rat) 11.9 mg/kg bw per day (90-day, mouse) 2.6 mg/kg bw per day (90-day, dog)	
Relevant dermal NOAEL ‡	NOAEL _{local} : 1000 mg/kg bw per day (30-day, rat) NOAEL _{systemic} : 100 mg/kg bw per day (30-day, rat)	
Relevant inhalation NOAEL ‡	No data - not required	

Genotoxicity ‡ (Annex IIA, point 5.4)

Not a genotoxic agent	
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Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect ‡	<p><u>Rats</u>: anaemia (> 50 ppm, females), liver, thyroid, kidney and skin histopathology (> 1000 ppm), increased adrenal, ovary and testes weights (20000 ppm)</p> <p><u>Mice</u>: liver and thyroid histopathology (> 1000 ppm), increased adrenal weight and pituitary hyperplasia (10000 ppm)</p>	
Relevant NOAEL ‡	1.7 mg/kg bw per day (carcinogenicity, male rat) 4.44 mg/kg bw per day (carcinogenicity, mouse)	
Carcinogenicity ‡	No evidence of a carcinogenic potential	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	Ocular effects in pups; delayed balanopreputial separation and increased ovarian weight	
Relevant parental NOAEL ‡	12.91 mg/kg bw per day (male rat)	R64
Relevant reproductive NOAEL ‡	3.84 mg/kg bw per day (female rat)	
Relevant offspring NOAEL ‡	12.91 mg/kg bw per day (male rat)	

Developmental toxicity

Developmental target / critical effect ‡

Enlargement of eyeballs (DNT study in rats)
Developmental neurotoxicity (eye anatomical and pathology findings, i.e. enlarged eyeballs, exophthalmos and general ocular opacity, confirmed by functional eye lesions) (rats)

Relevant maternal NOAEL ‡

Rat: 10 mg/kg bw per day Rabbit: 1000 mg/kg bw per day	
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Relevant developmental NOAEL ‡

Rat: 100 mg/kg bw per day Rabbit: 1000 mg/kg bw per day	Repr. Cat 3 Xn; R63
Rat: 10 mg/kg bw per day	

Relevant developmental neurotoxicity NOAEL ‡

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡

No neurotoxic potential

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡

ID-I was not affected by NNI-0001, which means that NNI-0001 does not affect thyroid hormone homeostasis. Increased relative thyroid gland weight supported by histopathological changes were assessed as an indirect effect mediated by increased TSH secretion from the pituitary secondary to an increased biliary excretion of thyroid hormones as a result of hepatic microsomal enzyme (UDP-GT) induction. However, the possibility of an additional mechanism that accounts for thyroid gland hypertrophy besides liver enzyme induction cannot be excluded.

Perinatal ocular toxicity study in mice

No effects on perinatal ocular development in mice occurred

Studies on metabolites

NNI-0001-des-iodo:
Acute oral LD₅₀ > 2000mg/kg bw, non genotoxic

NNI-0001-3-OH:
Acute oral LD₅₀ > 2000mg/kg bw, non genotoxic

Medical data‡ (Annex IIA, point 5.9)

- Reports from manufacturing personnel: No adverse effects have been reported
- Symptoms from poisoning incidents: Exposure of the general population has been limited so far. Human poisoning cases are not known and special clinical studies are not available.
- Additional predicted poisoning symptoms based on animal testing: During pregnancy ingestion may adversely affect the developing foetus, without

apparent maternal toxicity. Chronic overexposure may also show evidence of kidney and liver toxicity and endocrine system disruption including delayed sexual maturation, and thyroid, adrenal and gonadal effects.

- First aid measures: No therapeutic regimes can be proposed, as no antidote is known for flubendiamide. Symptomatic treatment is advised

Summary (Annex IIA, point 5.10)

ADI ‡

AOEL ‡

ARfD ‡

Value	Study	Safety factor
0.017 mg/kg bw per day	carcinogenicity study in rats	100
0.006 mg/kg bw per day	90 day & 1 year dog study	100 [oral abs. = 23.5%]
0.1 mg/kg bw	developmental neurotoxicity study in rats	100

Dermal absorption‡ (Annex IIIA, point 7.3)

2% for both diluted and concentrate SC 480 flubendiamide formulation based on *in vivo* monkey data

Exposure scenarios (Annex IIIA, point 7.2)

Operator

Greenhouse - hand held spray application on greenhouse tomatoes & bell peppers
 Max. application rate = 2.25 L product/ha (1.2 kg a.s./ha)
 Lowest intended spray volume = 500 L/ha

IVA study (Mich, 1996) & German model for M/L

No PPE : 60% of AOEL

Dutch Greenhouse model

No PPE: 143% of AOEL

PPE (gloves & coverall): 14% of AOEL

Southern Greenhouse model (ECPA)

PPE (coverall): 45.1% of AOEL

PPE (gloves & coverall): 29.6% of AOEL

Workers

Estimated exposure levels are lower than the AOEL.

Bystanders

No exposure is foreseen since the intended application is to be performed in greenhouse.

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

RMS/peer review proposal

Flubendiamide

Repr. Cat. 3 (development), **Xn**; **R63** “May cause harm to the unborn child”

R64 “May cause harm to breast-fed babies”

S2-13-36/37-46

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

Plant groups covered	Leafy crops (L) (cabbage), Fruits (F) (cherry tomato, apple) and Cereals (C) (corn)
Rotational crops	Spring wheat, Swiss chard and Turnips
Metabolism in rotational crops similar to metabolism in primary crops?	Yes
Processed commodities	Flubendiamide (Hydrolysis study)
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Yes
Plant residue definition for monitoring	Flubendiamide
Plant residue definition for risk assessment	Flubendiamide (representative uses) Reconsideration is required whether inclusion of non-rat metabolite NNI-0001 des-iodo in risk assessment is necessary for other uses.
Conversion factor (monitoring to risk assessment)	Not applicable

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

Animals covered	Lactating goat, Laying Hen
Time needed to reach a plateau concentration in milk and eggs	In eggs: plateau level reached on day 13 after the first dose. In milk: plateau level observed after 7-8 days of dosing
Animal residue definition for monitoring	Flubendiamide
Animal residue definition for risk assessment	Sum of parent flubendiamide (NNI-0001) and NNI-0001-iodo-phthalimide expressed as flubendiamide
Conversion factor (monitoring to risk assessment)	Not applicable
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)

The metabolism of flubendiamide was also investigated in confined rotational crops (spring wheat, Swiss chard and turnips) using the same two radiolabels as for the plant metabolism studies. The metabolism in rotational crops was investigated following spray application of flubendiamide onto soil (day 0). Crops of the first, second and third rotation were sown at day 29, day 135 and day 274, respectively. Representative immature and mature plant samples were analysed. The Total Radioactive Residues (TRRs) were relatively low for all crops and all rotations. Unchanged parent compound was the main component of nearly all confined rotational crop samples. Several metabolites were identified, however all of them at very low levels (less than 0.01 mg/kg in all crops at all rotations).
Only residues of parent flubendiamide exceeded 0.01 mg/kg in rotated cereal and leafy crops, considering the plateau concentration in soil.

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

Residues of flubendiamide and its metabolite NNI-0001 des-iodo are stable under deep frozen conditions for at least 18 months in/on tomato (fruit), vegetable (oil), wheat (grain), head cabbage (head), bean (with pod) and citrus (fruit) and at least 12 months in/on in must of grape.

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

Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)

Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
	No	No	No
	Not relevant	Not relevant	Not relevant
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices : Mean (max) mg/kg		
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-		
Eggs		-	

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)	STM (b)
Tomatoes (Fruiting Vegetables, Solanaceae)	Glasshouse	1X0.02, 2X0.03, 1X0.04, 4X0.06, 1X0.07, 1X0.08, 2X0.09, 3X0.10, 2X0.11, 1X0.012		0.2 mg/kg	0.12 mg/kg	0.075 mg/kg
Peppers (Fruiting Vegetables, Solanaceae)	Glasshouse	1X0.04, 1X0.06, 1X0.07, 1X0.08, 1X0.09, 1X0.10, 2X0.11		0.2 mg/kg	0.11 mg/kg	0.085 mg/kg

(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)

ADI	0.017 mg/kg bw per day
TMDI (% ADI) according to WHO European diet	4% (WHO Cluster B)
TMDI (% ADI) according to national (to be specified) diets	2% (EFSA PRIMo; IT toddler)
IEDI (WHO European Diet) (% ADI)	Not necessary
NEDI (specify diet) (% ADI)	Not necessary
Factors included in IEDI and NEDI	Not applicable
ARfD	0.1 mg/kg bw
IESTI (% ARfD)	Up to 13% ARfD (EFSA PRIMo; DE child)
NESTI (% ARfD) according to national (to be specified) large portion consumption data	Not necessary
Factors included in IESTI and NESTI	Not applicable

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	
Tomatoes/Raw juice	2	<0.48		
Tomatoes/Juice	2	<0.42		
Tomatoes/Fruit, peeled	2	<0.29		
Tomatoes/Preserve	2	<0.29		
Tomatoes/wet pomace	2	3.13		
Tomatoes/paste	2	4.33		
Tomatoes/raw puree	2	2.08		
Tomatoes/washed fruits	2	<0.67		
Tomatoes/puree	2	1.94		

* The mean values of Series A+B are reported here. The TF<mean value results from the fact that single TF were re-calculated for products where the residues were below the LOQ. In this case, the calculated factors are not given as an exact value, which would be misleading, but as being "<" the result of the ratio LOQ in processed commodity / residues in the RAC.

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

Fruiting Vegetables
Solanaceae
 Tomatoes
 Peppers

	0.2 mg/kg
	0.2 mg/kg

.....
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 ‡	0.3 % after 91-120 d, [¹⁴ C-phthalic acid ring]-labelled flubendiamide (n=4) 0.1 % after 90-120 d, [¹⁴ C-aniline ring]-labelled flubendiamide (n=1)
Non-extractable residues after 100 days ‡	5.2-7.1 %, at 90-91 days [¹⁴ C- phthalic acid ring]-labelled flubendiamide (n=4) 5.7% at 90days, [¹⁴ C- aniline ring]-labelled flubendiamide (n=1)
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	NNI-0001-des-iodo (A1) 7.1 % max. value (n= 4) Max. concentrations of unidentified metabolites were 2.7 % and 1.3 % of AR. No label-specific metabolite from cleavage of the molecule in the aniline and phthalic acid moiety was observed.

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

Anaerobic degradation ‡	
Mineralization after 100 days	No ¹⁴ CO ₂ (<0.1 % of AR) was detected at any sampling point during the anaerobic phase of the study.
Non-extractable residues after 100 days	5.7 % at 0 d, 11.7 % after 120 d, [¹⁴ C- phthalic acid ring]-labelled flubendiamide] (n=1) 5.3 % at 0 d, 12.2 after 120 d, [¹⁴ C- aniline ring]-labelled flubendiamide-label (n= 1)
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	No transformation products were observed in the study.
Soil photolysis ‡	
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	DT50 = 36.4 days (July London day) DT50 = 28.8 days (June Athens day) NI-0001-des-iodo (A1) 17.6 % max. value at 11 d, [¹⁴ C-phthalic acid ring]-labelled flubendiamide] (n=1) NNI-0001-oxalinic acid (A-31) 1.5 % max. value at 11 d, [¹⁴ C- phthalic acid ring]-labelled flubendiamide] (n=1) (n=1) NI-0001-des-iodo (A1) 15.5 % max. value at 11 d, [¹⁴ C-aniline acid ring]-labelled flubendiamide] (n=1) NNI-0001-oxalinic acid (A-31) 8.2 % max. value at 11 d, [¹⁴ C- aniline acid ring]-labelled flubendiamide] (n=1)

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	X ¹⁰	PH (CaCl ₂)	t. °C / % MWHC	DT ₅₀ (d)	DT ₅₀ (d) 20°C pF2/10kPa	St. (r ²)	Method of calculation
Sandy loam		6.32	20 ± 2 °C / 50 %	> 1 year *	-	-	No degradation curve could be fitted
Silty loam		6.54	20 ± 2 °C / 50 %	> 1 year*	-	-	No degradation curve could be fitted
Silt		6.7	20 ± 2 °C / 50 %	> 1 year*	-	-	No degradation curve could be fitted
Loamy sand		5.44	20 ± 2 °C / 75 %	> 1 year*	-	-	No degradation curve could be fitted
Geometric mean/median							

* No degradation curve could be fitted and no half-life could be calculated from the above study. Therefore no exact degradation rate for degradation under dark aerobic laboratory conditions could be determined, while it is concluded that the degradation half-life DT₅₀ in soil under these conditions is clearly >1 year.

¹⁰ X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

Parent	Aerobic conditions, soil cores sampled in the field to a depth of 50 cm single application at a rate of 180 g a.s./ha							
Soil type (indicate if bare or cropped soil was used).	Location (country or USA state).	Crop, Maintenance	pH	avg.T (°C) (daily min, max)	DT50/DT90 (d)	DT50/DT90 (d) 20°C pF2/10kPa	breakpoint t _b (d)* k1, k2	Meth od of calculation
Silt loam, Burscheid (Hoefchen)	Germany	Grass, Mulching	7.1	5.8 / 14.2	32.3 / >1000 DFOP k ₂ =0.0006	28.9 / 462	54.9 k1=0.024 k2=0.0015	2x SFO of HS
Clay loam, Vilobi	Spain	Grass [#]	6.5	5.7 / 21.6	28.5 / >1000 DFOP k ₂ =0.0002	21.0 / 1283	10.7 k1=0.033 k2=0.00054	2x SFO of HS
Sandy loam, Monheim (Laacher Hof)	Germany	Grass, Mulching	7.4	7.6 / 15.6	55.4 / >1000 DFOP k ₂ =0.0002	12.6 / 693 28.6/693	11.6 k1=0.055 k2=0.001	2x SFO of HS
Sandy loam, Little Shelford	Great Britain	Grass, kept to <20cm	8.1	6.2 / 13.8	970 / >1000 DFOP k ₂ =0.0003	11.4 / 408	53.1 k1=0.061 k2=0.0017	2x SFO of HS
Silt loam, Vatteville	France	Grass, cut monthly	6.5	6.8 / 14.7	130 / >1000 FOMC	7.5 / 495 7.8/542	5.9 6.2 k1=0.093 k2=0.0014	2x SFO of HS
Loam, Albaro	Italy	Grass, cut monthly	8.0	8.9 / 16.4	5.8 / 855 FOMC	10.8 / 346.6	23.2 k1=0.064 k2=0.002	2x SFO of HS
Geometric mean						14.0 / 553 16.0/562	21.5 19.3	

Disappearance times of the transformation products of NNI-0001, NNNI-0001-des-iodo (A-1) and NNI-0001-benzoic acid (A-18) were not calculated as evaluation of the data was not possible due to the low residues of both compounds in soil.

Metabolites detected under aerobic conditions in the terrestrial field studies, appl. rate: 180 g a.s./ha

NNI-0001-desiodo (A-1)	1.3–4.7 g/ha corresp. to 0.7–2.6 % of the applied A.S.*) two years after application; max. level (4.7 g/ha) detected two years after appl.
NNI-0001-3-OH (A-2)	single detection of 0.3 g/ha corresp. to 0.2 % of the applied A.S.*) at day 28 in a German trial
NNI-0001-benzoic acid (A-18)	1.8-5.4 g/ha corresp. to 1.0-3.0 % of the applied A.S.*) two years after application; max. levels (6.6 and 6.7 g/ha corresp. to 3.7 and 3.7 % of applied) detected 119 and 481 days after application

*) Calculated without correction of the molar mass ratios

The residue levels of these metabolites in the field soil were relatively constant (with small variations in the 2-year observation period) at the mentioned low levels. Therefore no degradation rate could be calculated for these metabolites.

Met 1 – Met 3		Aerobic conditions, soil cores sampled in the field to a depth of 50 cm single application at a rate of 180 g a.s./ha						
Soil type (indicate if bare or cropped soil was used).	Location (country or USA state).	Crop, Maintenance	pH	t. °C / % MWHC	DT50 /DT90 (d)	DT50 (d) 20°C pF2/10kPa	St. (r²)	Method of calculation
Silt loam, Burscheid (Hoefchen)	Germany	Grass, Mulching	7.1	5.8 / 14.2	n.a.*	n.a.*		n.a.*
Clay loam, Vilobi	Spain	Grass [#]	6.5	5.7 / 21.6	n.a.*	n.a.*		n.a.*
Sandy loam, Monheim (Laacher Hof)	Germany	Grass, Mulching	7.4	7.6 / 15.6	n.a.*	n.a.*		n.a.*
Sandy loam, Little Shelford	Great Britain	Grass, kept to <20cm	8.1	6.2 / 13.8	n.a.*	n.a.*		n.a.*
Silt loam, Vatteville	France	Grass, cut monthly	6.5	6.8 / 14.7	n.a.*	n.a.*		n.a.*
Geometric mean					n.a.*	n.a.*		n.a.*

pH dependence (yes / no) (if yes type of dependence)

‡ No pH dependence can be derived from the above summary table.

Soil accumulation and plateau concentration ‡

Plateau concentration calculated at 0.138 mg/kg in the top 20 cm soil reached after 20 years application of 2 x 120 g a.s./ha with a 7-day interval per annum. (bottom of saw tooth curve) see PEC in soil for more details.

Laboratory studies ‡

Parent	Anaerobic conditions						
Soil type	X ¹¹	PH (CaCl ₂)	t. °C / % MWHC	DT ₅₀ /DT ₉₀ (d)	DT ₅₀ (d) 20°C pF2/10kPa	St. (r ²)	Method of calculation

¹¹ X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

Loamy sand		5.44	20 °C / 75 %	> 1 year / - -			No degradation was observed in the anaerobic study period. Thus, it is concluded that under dark, anaerobic conditions in soil NNI-0001 has a degradation half life of > 1 year
Geometric mean/median							

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent ‡							
Soil Type	OC %	Soil pH (CaCl ₂)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Silt	1.56	6.2			18.3	1172	0.9787
Sandy loam	1.47	6.3			23.5	1596	1.0224
Silty clay	1.15	4.8			30.0	2609	1.0004
Loamy sand	0.52	5.4			17.2	3318	1.0190
Loam	2.3	4.7			24.8	1076	0.9648
Arithmetic mean/median					-	1954	0.997
pH dependence (yes or no)			no				

Metabolite NNI-0001-des-iodo (A-1) ‡							
Soil Type	OC %	Soil pH (CaCl ₂)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Silt loam	2.62	6.1			8.365	319	0.96
Sandy loam	1.30	6.0			3.514	270	0.96
Silt loam	1.10	6.4			2.574	234	0.94
Loamy sand	0.52	5.8			1.379	265	0.94
Clay loam	1.10	6.3			6.4	581	0.93
Arithmetic mean/median					-	334	0.95
pH dependence (yes or no)			no				

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

Column leaching ‡	<p>Column leaching studies were not performed. This requirement is covered by the adsorption/desorption studies with the parent compound.</p> <p>Column leaching studies were not performed for metabolites. These studies are not required since none of the metabolites formed under real conditions reached or exceeded 5% of AR at more than one sampling point.</p>
Aged residues leaching ‡	Aged column leaching studies were not performed. This requirement is covered by the adsorption/desorption studies with the parent compound.
Lysimeter/ field leaching studies ‡	The mobility of the NNI-0001 has been assessed on the basis of the adsorption/desorption study and a modelling study of the PEC ground water values following the maximum annual use for tomatoes and bell pepper in the greenhouse. Lysimeter or filed leaching studies were not conducted.

PEC (soil) (Annex IIIA, point 9.1.3)

Parent	DT50 = 2310 days (2nd slow phase DT50 from the field study trial site with the longest overall DT50 from field studies without normalisation)
Method of calculation	
Application data	<p>Crop: tomato/bell pepper under greenhouse conditions</p> <p>Depth of soil layer: 5 cm in the year of application and for residues emitted from a glasshouse (both plateau and in the year of application, 20cm for calculating the accumulated plateau)</p> <p>Soil bulk density: 1.5 g/cm³</p> <p>% plant interception: 50 % early scenario/ 80 % late scenario (refer to tomato)</p> <p>Number of applications: 2</p> <p>Interval (d): 7</p> <p>Application rate(s): 6 g as/hL</p>

Early and late use scenarios of flubendiamide in greenhouses. The crop interception values refer to tomato (FOCUS, 2000 & 2002)

Scenario (tomato)	Application rate (g a.s./hL)	Spray volume (hl/ha)	Application rate (g a.s./ha)	Crop interception	Total annual soil loading (g a.s./ha)
Early (BBCH 13+)	2 x 6	6	2 x 36	50 %	36
Late (BBCH 80+)	2 x 6	20	2 x 120	80 %	48

PEC_(s)	Single	Single	Multiple	Multiple
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(mg/kg)	application Actual	application Time weighted average	application Actual	application Time weighted average
Initial	n/a		0.064	
Short term 24h	n/a	n/a	0.064	0.064
2d	n/a	n/a	0.064	0.064
4d	n/a	n/a	0.064	0.064
Long term 7d	n/a	n/a	0.064	0.064
28d	n/a	n/a	0.063	0.064
50d	n/a	n/a	0.063	0.063
100d	n/a	n/a	0.062	0.063
Plateau concentration	PECsoil_accu valley of saw tooth curve = 0.138 mg/kg (over 20cm)	PECsoil_accu peak of saw tooth curve = 0.202 mg/kg (residue calculated for top 5cm, final years application)		

PEC _(s) (mg/kg) 0.1% exposure rate in greenhouse vicinity	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	n/a		3.2x10 ⁻⁴	
Short term 24h	n/a	n/a	3.2x10 ⁻⁴	3.2x10 ⁻⁴
2d	n/a	n/a	3.19x10 ⁻⁴	3.2x10 ⁻⁴
4d	n/a	n/a	3.19x10 ⁻⁴	3.19x10 ⁻⁴
Long term 7d	n/a	n/a	3.19x10 ⁻⁴	3.19x10 ⁻⁴
28d	n/a	n/a	3.17x10 ⁻⁴	3.18x10 ⁻⁴
50d	n/a	n/a	3.15x10 ⁻⁴	3.17x10 ⁻⁴
100d	n/a	n/a	3.10x10 ⁻⁴	3.15x10 ⁻⁴
Plateau concentration	PECsoil_accu valley of saw tooth curve = 2.76x10 ⁻³ (over 5cm)	PECsoil_accu peak of saw tooth curve = 0.00308 mg/kg (over 5cm)		

PEC _(s) (mg/kg) 0.2% exposure rate in greenhouse vicinity	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	n/a		6.39x10 ⁻⁴	
Short term 24h	n/a	n/a	6.39x10 ⁻⁴	6.39x10 ⁻⁴

	2d	n/a	n/a	6.39×10^{-4}	6.39×10^{-4}
	4d	n/a	n/a	6.39×10^{-4}	6.39×10^{-4}
Long term	7d	n/a	n/a	6.38×10^{-4}	6.39×10^{-4}
	28d	n/a	n/a	6.34×10^{-4}	6.37×10^{-4}
	50d	n/a	n/a	6.30×10^{-4}	6.35×10^{-4}
	100d	n/a	n/a	6.20×10^{-4}	6.30×10^{-4}
Plateau concentration	PECsoil_accu valley of saw tooth curve = 5.53×10^{-3} (over 5cm)		PECsoil_accu peak of saw tooth curve = 0.00617 mg/kg (over 5cm)		

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

Hydrolytic degradation of the active substance and metabolites > 10 % ‡

NNI-0001 is hardly hydrolysed in the range from 4.0 to 9.0 and any environmentally relevant temperature
 NNI-0001-des-iodo is hardly hydrolysed in the range from 4.0 to 9.0 and any environmentally relevant temperature

Photolytic degradation of active substance and metabolites above 10 % ‡

7 experimental days with [phthalic acid ring and aniline ring UL-14C] NNI-0001
 Natural light, 35°N; DT50: 32.5 days at 35°N latitude (Tokyo)
 Natural light from a Xenon light, 40°N; DT₅₀ 5 & 6 days
 NNI-0001-des-iodo (A1): 21.6 % (max. value) AR (7 d)
 NNI-0001-3-OH (A2): 6.1 % (max. value) AR (1 d)
 NNI-0001-3-OH-perfluoroalkyl (A10): 13 % (max. value) (4 d)
 Estimated DT50 at 50°N: 10-15 solar days in June derived from the quantum yield

Quantum yield of direct phototransformation in water at $\Sigma > 290$ nm

Mean of Φ = 0.002408 (Flubendiamide)
 Mean of Φ = 0.0000988 (A-1)
 Mean of Φ = 0.00124 (A-10)

Readily biodegradable ‡
 (yes/no)

No

Degradation in water / sediment

Parent	Distribution (Max., in water 68.1 at 0 d. Max. sed 80.9 % after 59 d)									
Water / sediment system	pH water phase	pH sed (CaCl ₂)	t. °C	DT ₅₀ -DT ₉₀ whole sys.	St. (r ²)	DT ₅₀ -DT ₉₀ water	St. (r ²)	DT ₅₀ -DT ₉₀ sed	St. (r ²)	Method of calculation
Leverkusen, Germany	7.1	6.6		> 1 year -		9.4 -				
Wipperfuert, Germany	6.5	5.9		> 1 year -		4.4 -				

Geometric mean/median										
Geometric mean/median										

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)
Leverkusen, Germany	7.1	6.6	0.4 % after 125 d	9.6 % after 125 d	9.5 % after 125 d
Wipperfuert, Germany	6.5	5.9	0.9 % after 125 d	8.9 % at 59 d	16.5 % after 125

Outdoor mesocosm, test substance not radiolabelled

Parent	Distribution (Max. in water 95.75 after 2 d. Max. sed 14.50 % after 98 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT ₅₀ -DT ₉₀ whole sys.	St. (r ²)	DT ₅₀ -DT ₉₀ water	r ²	DT ₅₀ -DT ₉₀ sed	St. (r ²)	Method of calculation
Nespen, Wiehl, Germany	7.8 – 10.2			55.4 – 72.0 d -		49.8 – 66.9 d -				SFO

Degradation in water / sediment

NNI-0001-des-iodo (A1)	Distribution (Max., in water 62.7 at 0 d. Max. sed 58.7 % after 101 d)									
Water / sediment system	pH water phase	pH sed (CaCl ₂)	t. °C	DT ₅₀ -DT ₉₀ whole sys.	St. (r ²)	DT ₅₀ -DT ₉₀ water	St. (r ²)	DT ₅₀ -DT ₉₀ sed	St. (r ²)	Method of calculation
Lawrence, Kansas	7.9	7.3		Essentially stable		-				
Pikeville, N. Carolina	7.0	4.3		Essentially stable		-				
Geometric mean/median										

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)
Lawrence, Kansas	7.9	7.3	0.4 % after 101 d	1.8 % after 101 d	1.8 % after 101 d
Pikeville, N. Carolina	7.0	4.3	0.3 % after 101 d	2.3 % at 101 d	2.3 % at 101 d

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

Parent

Parameters used in FOCUSsw step 1 and 2

Version control no. of FOCUS calculator: n/a
Molecular weight (g/mol): n/a
Water solubility (mg/L): n/a
 K_{OC}/K_{OM} (L/kg): n/a
DT₅₀ soil (d): n/a
DT₅₀ water/sediment system (d): n/a
DT₅₀ water (d): n/a
DT₅₀ sediment (d): n/a
Crop interception (%): n/a
Flubendiamide :
DT50 water = 9.4 days
DT50 sed=1000 days
Max. amount in water = 100%
Max. amount in sediment = 80.9%
Metabolite A1:
DT50 water = 1000 days
DT50 sed= -
Max. amount in water = 21.6%
Max. amount in sediment = -
Molar mass correction = 0.816
Metabolite A10:
DT50 water = 1000 days
DT50 sed= -
Max. amount in water = 13.0%
Max. amount in sediment = -
Molar mass correction = 0.836

Parameters used in FOCUSsw step 3 (if performed)

Version control no.'s of FOCUS software: n/a
Vapour pressure: n/a
 K_{om}/K_{oc} : n/a
1/n: n/a

Application rate

Crop: tomato/ bell pepper
Crop interception: n/a
Number of applications: 2 x 120 gr a.s. /ha
Exposure rate: 0.1% and 0.2% of applied
Surface water body: static, 0.3 m deep
Interval (d): n/a
Application rate(s): n/a
Application window: n/a

Drift rate 0.10%	Day after overall maximum	PEC _{sw} (µg/L)		PEC _{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Flubendiamide	0 h	0.064		0.484	
	24 h	0.059	0.062	0.484	0.484
	2 d	0.055	0.059	0.484	0.484
	4 d	0.048	0.055	0.483	0.484
	7 d	0.038	0.050	0.482	0.483
	14 d	0.023	0.042	0.480	0.482
	21 d	0.014	0.038	0.477	0.481
	28 d	0.008	0.033	0.475	0.480
	42 d	0.003	0.025	0.470	0.477

Drift rate 0.20%	Day after overall maximum	PEC _{sw} (µg/L)		PEC _{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Flubendiamide	0 h	0.128		0.968	
	24 h	0.119	0.123	0.968	0.968
	2 d	0.110	0.119	0.967	0.968
	4 d	0.095	0.111	0.966	0.967
	7 d	0.076	0.100	0.964	0.966
	14 d	0.045	0.084	0.959	0.964
	21 d	0.027	0.075	0.954	0.961
	28 d	0.016	0.065	0.950	0.959
	42 d	0.006	0.049	0.941	0.954

Drift rate	A1 PEC _{sw} (µg/L)	A10 PEC _{sw} (µg/L)
0.10%	0.014	0.009
0.20%	0.028	0.017

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

Method of calculation and type of study (e.g. modelling, field leaching, lysimeter)

Modelling with FOCUS PEARL 4.4.4
 Scenarios (list of names): Chateadun, Hamburg, Krensmunster, Okehampton, Piacenza, Porto, Sevilla, Thiva
 Modelling with FOCUS PEARL 4.4.4
 Potential exposure of soils inside greenhouses and outside greenhouses due to air emissions of 0.2% of the flubendiamide application rate.
 DT50 flubendiamide = 582 days (slow phase)
 Kom flubendiamide = 1134 l/kg 1/n=1
 DT50 A1 = 1000 days
 Kom A1 = 193.6 l/kg 1/n=0.95
 Formation fraction A1 = 0.076
 Q10=2.58, Walker equation coefficient= 0.7

Application data and crop interception

Early and late use scenarios of flubendiamide in greenhouses. The crop interception values refer to tomato (FOCUS, 2000 & 2002)k

Scenario (tomato)	Application rate (g a.s./hL)	Spray volume (hl/ha)	Application rate (g a.s./ha)	Crop interception	Total annual soil loading (g a.s./ha)
Early (BBCH 13+)	2 x 6	6	2 x 36	50 %	36
Late (BBCH 80+)	2 x 6	20	2 x 120	80 %	48

The late scenario represents the worst case for the soil exposure. The PECsoil calculations for NNI-0001 were based on the late use scenario. 2 x 120 g a.s./ha, at 7 day interval, with 80 % crop interception and 48 g a.s./ha annual soil loading.

Irrigation scheme for the Northern and Southern European greenhouse scenario (all values in mm=L x m⁻² x d⁻¹)

Daily irrigation (mm)	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Annual Sum
N. Europe	0 ^{a)}	0 ^{a)}	1	2	3	4	4	4	3	2	1	0 ^{a)}	~720
S. Europe	1	1	2	3	3	4	0 ^{a)}	0 ^{a)}	3	2	1	1	~630

a) no cultivation

Temperature related statistics

Region	Mean Daily Minimum Temperatures (°C)	Mean Daily Average Temperatures (°C)	Mean Daily Maximum Temperatures (°C)
Northern Europe	13	18	25
Southern Europe	13	19	27

Crop development data of tomato/pepper under European greenhouse conditions

Region	Crop	Emergence date	Date of Max. LAI*	Harvest date
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N. Europe	Tomato	20.04	20.05	10.07
S. Europe	Pepper (representing bell pepper)	10.10	20.11	15.01

*Leaf Area Index

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

Region	FOCUS Scenario	Flubendiamide PECgw (µg/L)	NNI-0001-des-iodo (A1) PECgw (µg/L)
N. Europe	Chateaudun	< 0.001	0.009
	Hamburg	< 0.001	0.008
	Kremsmunster	< 0.001	0.003
	Okehampton	< 0.001	0.001
S. Europe	Piacenza	< 0.001	0.009
	Porto	< 0.001	<0.001
	Sevilla	< 0.001	0.002
	Thiva	< 0.001	0.003

PEC(gw) assuming air emissions of 0.2% of the flubendiamide application rate- FOCUS modelling results (80th percentile annual average concentration at 1m)

FOCUS Scenario	Flubendiamide PECgw (µg/L)	NNI-0001-des-iodo (A1) PECgw (µg/L)
Chateaudun	< 0.001	0.002
Hamburg	< 0.001	0.002
Kremsmunster	< 0.001	0.001
Okehampton	0.001	0.002
Piacenza	0.001	0.002
Porto	0.001	0.002
Sevilla	< 0.001	0.001
Thiva	< 0.001	0.002

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

Direct photolysis in air ‡

Quantum yield of direct phototransformation

Photochemical oxidative degradation in air ‡

Volatilisation ‡

Metabolites

Not studied - no data requested due to the low volatility
Not studied - no data requested due to the low volatility
DT50 of 8.8 hours derived by the Atkinson model (AOP version 1.90). OH concentration assumed = 0.5×10^{-6} radicals cm^{-3} (24 h per day)
from plants : no study conducted, because the low vapour pressure $V_p < 10^{-4}$ Pa at 200°C (approx. $< 3.8 \times 10^{-10}$ Pa at 20°C) suggests that NNI-0001 is absolutely non-volatile
from soil surfaces: see above
Metabolites of NNI-0001 were only formed in minor amounts and are usually more polar (i.e. less volatile)

than the parent

The short half life of 8.8 hours indicates a negligible risk for NNI-0001 to be susceptible for long range transport or accumulation in the air.

PEC (air)

Method of calculation

Non volatile due to the low vapour pressure ($< 3.8 \cdot 10^{-10}$ Pa at 20°C). Henry's law constant ca. 9×10^{-6} Pa m³ mol⁻¹ at 20°C

Residues requiring further assessment

Environmental occurring residues requiring further assessment by other disciplines (toxicology and ecotoxicology) and or requiring consideration for groundwater exposure.

Soil: NNI-0001
 Surface Water: NNI-0001, NNI-0001-des-iodo (A1), and NNI-0001-3-OH-hydroxy-perfluoroalkyl (A10)
 Sediment: NNI-0001
 Ground water: NNI-0001 and NNI-0001-des-iodo (A1)
 Air: NNI-0001

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

Soil (indicate location and type of study)

-

Surface water (indicate location and type of study)

-

Ground water (indicate location and type of study)

-

Air (indicate location and type of study)

-

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

Candidate for R 53

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

Acute toxicity to mammals	LD ₅₀ > 2000 mg/kg bw (rat oral)
Reproductive toxicity to mammals	NOAEL 50 ppm diet, equivalent to 3.68 mg /kg bw per day (rat, reproductive toxicity)
Acute toxicity to birds	LD ₅₀ > 2000 mg /kg bw (bobwhite quail); LD ₅₀ > 2000 mg SC 480/kg bw (bobwhite quail, >796 mg a.s/kg bw)
Dietary toxicity to birds	LD ₅₀ > 5000 ppm diet, equivalent to > 1082 mg/kg bw per day (bobwhite quail); LD ₅₀ > 4535 ppm diet, equivalent to > 1022 mg/kg bw per day (mallard duck)
Reproductive toxicity to birds	NOEL: 102 ppm diet (10.2 mg a.s./kg bw per day) (bobwhite quail) NOEL: 289 ppm diet (26 mg/kg bw per day (mallard duck)

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)
Glasshouse application to tomatoes and peppers, 2 applications of 0.12 kg a.s./ha

Application rate (kg a.s./ha)	Category (e.g. insectivorous bird)	Time-scale	PEC _{fish} or PEC _{earthworm} (mg a.s./kg)	DDD (mg a.s./kg bw/day)	TER	Trigger
0.12	Fish-eating bird	Long-term	0.008 ¹	0.0013 ²	759478	5
0.12	Fish-eating mammal	Long-term	0.008 ¹	0.0012 ³	3199	5
0.12	Earthworm-eating bird	Long-term	0.03 ⁴	0.0315	324	5
0.12	Earthworm-eating mammal	Long-term	0.03 ⁴	0.0384	96	5

¹ Calculated using a lipid normalised (6%) BCF of 66 and a PEC_{sw} of 0.000128 mg a.s./L (drift rate of 0.2 %)

² Calculated using an FIR/bw value of 0.159 for fish-eating birds

³ Calculated using an FIR/bw value of 0.142 for fish-eating mammals

⁴ Calculated using soil PEC value assuming 0.2% emission from glasshouse

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	Endpoint	Toxicity (µg a.s./L)
Laboratory tests				
<i>Oncorhynchus mykiss</i>	a.s.	96 hr (static)	Mortality, LC ₅₀	>61.9 µg a.s./L nom ¹
<i>Lepomis macrochirus</i>	a.s.	96 hr (static)	Mortality, LC ₅₀	> 67.7 µg as/L mm
<i>Pimephales promelas</i>	a.s.	96 hr (static)	Mortality, LC ₅₀	> 66.5 µg as/L mm
<i>Cyprinus carpio</i>	a.s.	96 hr (static)	Mortality, LC ₅₀	> 84.7 µg as/L mm

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	Endpoint	Toxicity ($\mu\text{g a.s./L}$)
<i>Cyprinodon variegatus</i> (marine)	a.s.	96 hr (static)	Mortality, LC ₅₀	> 29.8 $\mu\text{g a.s./L}$ mm
<i>Oncorhynchus mykiss</i>	NNI-0001 SC 480	96 hr (static)	Mortality, LC ₅₀	>250,000 $\mu\text{g form/L nom}$ >1000,000 $\mu\text{g a.s./L}$
<i>Lepomis macrochirus</i>	NNI-0001 SC 480	96 hr (static)	Mortality, LC ₅₀	>250,000 $\mu\text{g form/L nom}$ >1000,000 $\mu\text{g a.s./L}$
<i>Pimephales promelas</i>	a.s.	35 d (flow-through)	NOEC (all endpts.)	60.2 $\mu\text{g a.s./L}$ mm
<i>Crassostrea virginica</i> (Eastern Oysters, marine)	a.s.	96 hr (flow-through)	Shell deposition, EC ₅₀	> 49 $\mu\text{g a.s./L}$ mm
<i>Americamysis bahia</i> (Mysid, marine)	a.s.	96 hr (static)	Mortality, LC ₅₀	> 28 $\mu\text{g a.s./L}$ mm
<i>Americamysis bahia</i> (Mysid, marine)	a.s.	28 d, flow-through	NOEC	19 $\mu\text{g a.s./L}$
<i>Daphnia magna</i>	a.s.	48 h (static)	Mortality, EC ₅₀	>60.0 $\mu\text{g a.s./L nom}$
<i>Daphnia magna</i>	a.s.	21 d (static)	Reproduction, NOEC	33.3 $\mu\text{g a.s./L}$ mm
<i>Daphnia magna</i>	SC480	48 h (static)	Mortality, EC ₅₀	6.5 $\mu\text{g form/L}$ mm 2.6 $\mu\text{g a.s./L}$ mm
<i>Daphnia magna</i>	SC480	48 h (static) with varying algae densities	Mortality, EC ₅₀	no algae present 10.8 $\mu\text{g form/L nom}$ (4.2 $\mu\text{g a.s./L}$) with 10 ⁶ cells/mL algae > 32 $\mu\text{g form/L nom}$ (12.5 $\mu\text{g a.s./L}$)
<i>Daphnia magna</i>	NNI-0001 SC480	21 d (static)	Reproduction, NOEC	1.0 $\mu\text{g form/L nom}$ 0.4 $\mu\text{g a.s./L nom}$
<i>Daphnia magna</i>	NNI-0001-des-iodo (A1)	48 h (static)	Mortality, EC ₅₀	> 881 $\mu\text{g p.m./L}$ mm
<i>Chironomus riparius</i>	SC480	48 h (static)	Mortality, LC ₅₀	1880 $\mu\text{g a.s./L}$ mm ¹
<i>Chironomus riparius</i>	a.s.	28 d (static)	NOEC	35 $\mu\text{g a.s./L}$ mm
<i>Chironomus riparius</i>	NNI-0001-des-iodo (A1)	28 d (static)	NOEC	3.3 $\mu\text{g p.m./L}$ mm
<i>Chironomus riparius</i>	NNI-0001-des-iodo (A1)	28 d (static, spiked)	NOEC	55 $\mu\text{g p.m./ kg dws}$

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	Endpoint	Toxicity (µg a.s./L)
<i>Pseudokirchneriella subcapitata</i>	a.s.	72 h (static)	Biomass: E _b C ₅₀ Growth rate: E _r C ₅₀	>69.3 µg a.s./L mm >69.3 µg a.s./L mm
<i>Pseudokirchneriella subcapitata</i>	Preparation	72 h (static)	Growth rate: E _r C ₅₀	>251 µg a.s./L nom (>100 µg a.s./L)
<i>Lemna gibba</i>	a.s.	14 d (static)	Growth rate, EC ₅₀	>54.6 µg a.s./L mm
Mesocosm test	SC 480	16 w (static). Test substance was sprayed once at concentrations 0.4, 1.0, 2.3, 5.3 and 12 microg/L. The mesocosms were investigated for 16 weeks after treatment. Taxonomic composition of zooplankton, phytoplankton, total and benthic macroinvertebrates and emergence of insects were observed. The most sensitive taxon was <i>D longispina</i>	NOAEC	5.3 µg a.s./L (nom)

Mm: Endpoint based on mean measured concentrations

Nom: Endpoint based on nominal concentrations

¹ Endpoint should be regarded as an estimation due to the presence of undissolved test material in the test chambers

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

Glasshouse application to tomatoes and peppers, 2 applications of 0.12 kg a.s./ha

Time scale	Species	Endpoint µg/L	Drift rate %	PEC _{sw} µg/L	TER	Trigger	
flubendiamide							
Acute	<i>C. variegatus</i>	LC ₅₀	>29.8	0.128	>233	100	
Chronic	<i>P. promelas</i>	NOEC	60.2	0.128	470	10	
Acute	<i>Daphnia magna</i>	EC ₅₀	2.6 ²	0.2	0.128	20.5	100
				0.1	0.064	40.9	
Chronic	<i>Daphnia magna</i>	NOEC	0.4 ²	0.2	0.128	3.3	10
				0.1	0.064	6.6	
Acute	<i>Chironomus riparius</i>	EC ₅₀	18800	0.128	146875	100	
Chronic	<i>Chironomus riparius</i>	NOEC	35	0.128	273	10	

Time scale	Species	Endpoint µg/L		Drift rate %	PEC _{sw} µg/L	TER	Trigger
-	Algae	EC ₅₀	>69.3	0.2	0.128	>233	10
Metabolite A1 (NNI-0001-desiodo)							
Acute	<i>C. variegatus</i>	LC ₅₀	>2.98 ¹	0.2	0.028	>106	100
Chronic	<i>P. promelas</i>	NOEC	6.02 ¹	0.2	0.028	215	10
Acute	<i>Daphnia magna</i>	EC ₅₀	>881	0.2	0.028	>31464	100
Chronic	<i>Daphnia magna</i>	NOEC	0.04 ¹	0.2	0.028	1.5	10
				0.1	0.041	2.9	
Chronic	<i>Chironomus riparius</i>	NOEC	3.3	0.2	0.028	118	10
-	Algae	EC ₅₀	>6.93 ¹	0.2	0.028	>248	10
Metabolite A10 (NNI-0001-3-OH-hydroxy-perfluoroalkyl)							
Acute	<i>C. variegatus</i>	LC ₅₀	>2.98 ¹	0.2	0.017	>175	100
Chronic	<i>P. promelas</i>	NOEC	6.02 ¹	0.2	0.017	354	10
Acute	<i>Daphnia magna</i>	EC ₅₀	0.26 ¹	0.2	0.017	15.3	100
				0.1	0.009	28.9	
Chronic	<i>Daphnia magna</i>	NOEC	0.04 ¹	0.2	0.017	2.4	10
				0.1	0.009	4.6	
Chronic	<i>Chironomus riparius</i>	NOEC	3.3	0.2	0.017	194	10
-	Algae	EC ₅₀	>6.93 ¹	0.2	0.017	>408	10
Refined risk assessment							
<p>A mesocosm study was available where the NOAEC was determined to be 5.3 µg a.s./L based on class 3 effects on <i>Daphnia longispina</i>. Using an assessment factor of 3, this gives a Regulatory Acceptable Concentration (RAC) of 1.77 µg a.s./L. As the surface water PEC values (for both the 0.1% and 0.2% drift rates) are less than the RAC of 1.77 µg a.s./L, a low risk to aquatic invertebrates is concluded.</p> <p>Metabolite A1 (NNI-0001-desiodo) was also detected in the mesocosm study and therefore the risk can be covered by the risk assessment for the parent substance.</p> <p>Metabolite A10 (NNI-0001-3-OH-hydroxy-perfluoroalkyl) was measured for, but not detected, in the mesocosm study; data gap to address the acute and chronic risk to aquatic invertebrates.</p>							

¹ Calculated assuming 10 times more toxic than the parent, flubendiamide

² Taken from a study performed with the formulated product 'SC 480'; endpoint expressed in terms of active substance

Bioconcentration

Bioconcentration factor (BCF)

Annex VI Trigger for the bioconcentration factor

Clearance time

CT₅₀

CT₉₀

73 (active, whole fish)
66 (6% lipid normalised)
12.6 (NNI-0001-des-iodo, whole fish)
1000
4.7 days (active, mean of two concentrations)
2.6 days (NNI-0001-des-iodo)
<21 days (active)
<14 days (NNI-0001-des-iodo)

Level of residues (%) in organisms after the 14-day depuration phase

After 14 days in uncontaminated water 8.8 µg/kg (17 % of the plateau) of the nominal concentration of 0.5 µg/L was observed, and 67.5 µg/kg (14 % of the plateau) of the nominal concentration of 5.0 µg/L was observed. By extrapolation it can be calculated that 95% of the mean plateau radioactivity would have been depurated from whole fish after 20-21 days (active).
 After 14 days in uncontaminated water 3.9 µg/kg (6 % of the plateau) for the nominal concentration exposure of 5.0 µg/L was observed. After 14 days in uncontaminated water 94 % of the mean plateau radioactivity were depurated from whole fish (NNI-0001-des-iodo).

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

Acute oral toxicity

> 200 µg active/bee
 > 200 µg a.s./bee (tested as formulation SC 480)

Acute contact toxicity

> 200 µg active/bee
 > 200 µg a.s./bee (tested as formulation SC480)

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

Glasshouse application to tomatoes and peppers, 2 applications of 0.12 kg a.s./ha

Application rate (kg a.s./ha)	Crop	Route	Hazard quotient	Trigger
Laboratory tests				
0.12	Tomato, Bell pepper	Oral, active	<0.6 ¹	50
		Oral, SC 480	<0.6 ¹	50
		Contact, active	<0.6 ¹	50
		Contact, SC 480	<0.6 ¹	50

¹ HQ values for glasshouse uses not required but included for completeness.

Field or semi-field tests

A honey bee semi-field study was performed with the formulated product ‘NNI-0001 SC 480’. Applications were made to flowering *Phacelia tanacetifolia*.

T1: 1 application of 90 g a.s./ha

T2: 1 application of 180 g a.s./ha

A water control and a toxic reference (Insegar WG 25) were also used.

Colonies condition (strength) and bee brood development, mortality, foraging activity and behaviour on the bees were assessed.

No differences in mortality between the water control and the treatment hives were observed. The study demonstrated a moderate effect on bee brood.

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

Species	Test procedure	Test Substance	Dose (g a.s./ha)	Endpoint	Effect
Laboratory tests					
<i>Typhlodromus pyri</i>	14 d [225-675 g as/ha on glass plates]	NNI-0001 SC 480	225 – 675 g as/ha	mortality	LR ₅₀ > 675 g a.s./ha
<i>Aphidius rhopalosiphi</i>	14 d [120-675 g as/ha on glass plates]	NNI-0001 SC 480	120 – 675 g as/ha	mortality	LR ₅₀ > 675 g a.s./ha
<i>Chrysoperla carnea</i>	extended laboratory study [22.5-180 g as/ha on bean leaves and food]	NNI-0001 SC 480,	180 g as/ha 22.5 – 180.0 g as/ha	Reproduction Mortality	4% LR ₅₀ >180 g a.s. /ha
<i>Coccinella septempunctata</i>	extended laboratory study [17-675 g as/ha on apple leaves]	NNI-0001 SC480,	675 270 17 – 675 g as/ha	Reproduction Reproduction Mortality	16% 3% LR ₅₀ = 407
<i>Coccinella septempunctata</i>	extended laboratory study [22.5-180.0 g as/ha on apple leaves and food]	NNI-0001 SC480,	180 90 22.5 – 180 g as/ha	Reproduction Reproduction Mortality	5% 0% LR ₅₀ = 106
<i>Coccinella septempunctata</i>	extended laboratory aged residue [195 g as/ha on vine leaves and food]	NNI-0001 SC480,	195 195 aged	Mortality, Reproduction, Hatching	No effect at 195 g as/ha
Field or semi-field tests					
Potential arthropod prey of birds and mammals, naturally occurring in vineyards		Field test with NNI-0001 SC 480 [154 g a.s./ha, 4 applications on a vineyard. The residue level of all arthropods generally decreased after the initial peak to levels of 50% of initial in a few days. By the end of the study period residue levels of NTA decreased to 1/5 of the maximum residue levels			

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

Acute toxicity

Reproductive toxicity

14-day LC _{50 corr} >500 mg /kg (active); 14- day LC _{50 corr} >500 mg form./kg (SC 480) (=LC _{50 corr} >194 mg a.s./kg) 14-day LC _{50 corr} >500 mg /kg (NNI-0001-des-iodo)
NOEC _{corr} =500 mg a.s./kg (SC 480) NOEC _{corr} =15.8 mg a.s./kg d.w. soil (SC 480, 28 d Collembola)

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

Glasshouse application to tomatoes and peppers, 2 applications of 0.12 kg a.s./ha

Application rate (kg as/ha)	Species	Soil PEC mg a.s./ kg soil	Time-scale	TER	Trigger
Exposure in-glasshouse					
0.12	Earthworm	0.202	acute	>2475	10
0.12	Earthworm	0.202	long-term	2475	5
0.12	Collembola	0.202	long-term	78	5
Exposure following emission (0.2% drift) from the glasshouse					
0.12	Earthworm	0.00617	acute	>81037	10
0.12	Earthworm	0.00617	long-term	81037	5
0.12	Collembola	0.00617	long-term	2561	5

Field studies, Soil litter degradation

Test substance	Time scale	End point
SC 480	Chronic, 180 days	NOEC \geq 339 μ g a.s./kg d.w. soil

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

Nitrogen mineralisation

-1% effect at day 28 at 7.47 mg form/kg d.w.soil

Carbon mineralisation

4% effect at day 27 at 7.47 mg form/kg d.w.soil

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

Preliminary screening data

No phytotoxic effects at 250 g a.s./ha were observed for the 11 plant species tested.

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

Test type/organism	end point
Activated sludge	EC ₅₀ (3 h) >10000 mg a.s./L

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

Classification according to Council Directive 67/548/EEC:

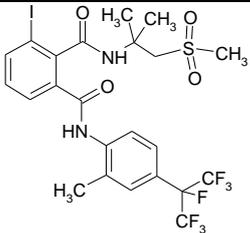
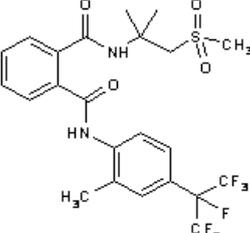
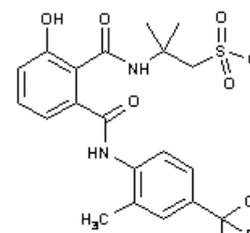
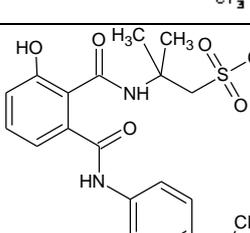
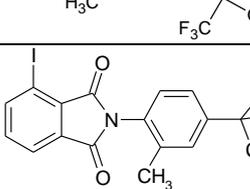
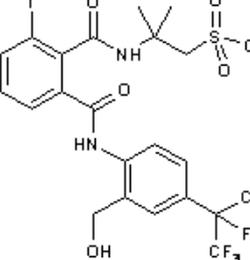
R50/53: very toxic for aquatic organisms. May cause long term effects in the aquatic environment

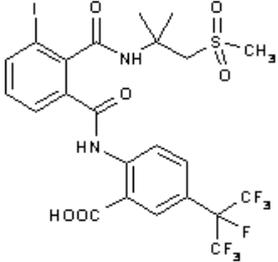
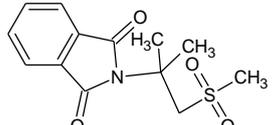
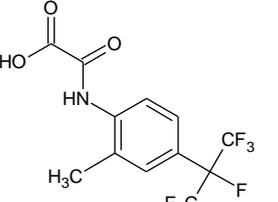
Based on results on fish, invertebrates, algae

Ecotoxicologically relevant compounds

Compartment	
soil	flubendiamide
water	Flubendiamide Data gap for metabolite A10 (NNI-0001-3-OH-hydroxy-perfluoroalkyl)
sediment	flubendiamide
groundwater	flubendiamide

APPENDIX B – USED COMPOUND CODE(S)

Code/Trivial name*	Chemical name**	Structural formula
NNI-0001 (flubendiamide)	3-iodo- <i>N'</i> -(2-mesylyl-1,1-dimethylethyl)- <i>N</i> -{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]- <i>o</i> -tolyl}phthalamide	
NNI-0001-des-iodo A-1	<i>N</i> -[4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-2-methylphenyl]- <i>N'</i> -[2-methyl-1-(methylsulfonyl)propan-2-yl]phthalamide	
NNI-0001-3-OH A-2	<i>N</i> ¹ -[4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-2-methylphenyl]-3-hydroxy- <i>N</i> ² -[2-methyl-1-(methylsulfonyl)propan-2-yl]phthalamide	
NNI-0001-3-OH-hydroxy perfluoroalkyl A-10	<i>N</i> ¹ -[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl]-3-hydroxy- <i>N</i> ² -[2-methyl-1-(methylsulfonyl)propan-2-yl]phthalamide	
NNI-0001-iodo-phthalimide A-14	2-[4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-2-methylphenyl]-4-iodo-1 <i>H</i> -isoindole-1,3(2 <i>H</i>)-dione	
NNI-0001-benzylalcohol A-16	<i>N</i> ¹ -[4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-2-(hydroxymethyl)phenyl]-3-iodo- <i>N</i> ² -[2-methyl-1-(methylsulfonyl)propan-2-yl]phthalamide	

<p>NNI-0001-benzoic acid A-18</p>	<p>5-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-2-[(3-iodo-2-{[2-methyl-1-(methylsulfonyl)propan-2-yl]carbamoyl}benzoyl)amino]benzoic acid</p>	
<p>NNI-0001-des-iodo-alkylphthalimide A-27</p>	<p>2-[2-methyl-1-(methylsulfonyl)propan-2-yl]-1<i>H</i>-isoindole-1,3(2<i>H</i>)-dione</p>	
<p>NNI-0001-oxalinic acid A-31</p>	<p>{[4-(1,1,1,2,3,3,3-heptafluoropropan-2-yl)-2-methylphenyl]amino}(oxo)acetic acid</p>	

* The metabolite name in bold is the name used in the conclusion.

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

ABBREVIATIONS

1/n	slope of Freundlich isotherm
λ	wavelength
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
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 Abstracts Service
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CIPAC	Collaborative International Pesticides Analytical Council Limited
CL	confidence limits
cm	centimetre
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
ELINCS	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
f(twa)	time weighted average factor
FAO	Food and Agriculture Organisation of the United Nations
FID	flame ionisation detector
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
GC	gas chromatography
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
mN	milli-newton
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
NPD	nitrogen phosphorous detector
OECD	Organisation for Economic Co-operation and Development
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 <i>n</i> -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
REACH	Registration, Evaluation, Authorisation of CHemicals
RPE	respiratory protective equipment
RUD	residue per unit dose
SC	suspension concentrate
SD	standard deviation
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
yr

week
year