European Commission

Combined Draft (Renewal) Assessment Report prepared according to Regulation (EC) N° 1107/2009
and
Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N° 1272/2008

FLONICAMID (ISO);

N-(cyanomethyl)-4-(trifluoromethyl)pyridine-3-carboxamide

Volume 1

Rapporteur Member State: Finland
Co-Rapporteur Member State: Sweden

December 2023

Version History

When	What
May 2022	Initial RAR DRAR was submitted to co-RMS for commenting and to the applicant for editorial comments before submitting it to EFSA and ECHA parallel.
December 2023	First draft RAR submitted to EFSA

The RMS is the author of the Assessment Report. The Assessment Report is based on the validation by the RMS, and the verification during the EFSA peer-review process, of the information submitted by the Applicant in the dossier, including the Applicant's assessments provided in the summary dossier. As a consequence, data and information including assessments and conclusions, validated and verified by the RMS experts, may be taken from the applicant's (summary) dossier and included as such or adapted/modified by the RMS in the Assessment Report. For reasons of efficiency, the Assessment Report should include the information validated/verified by the RMS, without detailing which elements have been taken or modified from the Applicant's assessment. As the Applicant's summary dossier is published, the experts, interested parties, and the public may compare both documents for getting details on which elements of the Applicant's dossier have been validated/verified and which ones have been modified by the RMS. Nevertheless, the views and conclusions of the RMS should always be clearly and transparently reported; the conclusions from the applicant should be included as an Applicant's statement for every single study reported at study level; and the RMS should justify the final assessment for each endpoint in all cases, indicating in a clear way the Applicant's assessment and the RMS reasons for supporting or not the view of the Applicant.

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Level 1

FLONICAMID

1 STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1.1 CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED

1.1.1 Purpose for which the draft assessment report was prepared

This renewal assessment report (RAR) has been prepared in accordance with Commission Regulation (EU) No 844/2012 and Guidance Document SANCO/2012/11251 rev. 4 in order to evaluate the supplementary dossier submitted by ISK Biosciences Europe N.V., and to allow a decision on the renewal of the approval of the active substance flonicamid (IKI-220) under Commission Regulation (EC) No 1107/2009.

The harmonised classification and labelling of flonicamid has been considered previously in the EU (ATP07). The existing entry in Annex VI of CLP Regulation (EU) 1272/2008 is: Acute Tox. 4, H302: Harmful if swallowed.

In the framework of the renewal assessment of flonicamid under Regulation (EC) 1107/2009, RMS proposes no change to the current harmonised classification (Acute Tox. 4; H302) of the active substance. Therefore, in this context, a targeted CLH proposal is presented in this document using the common agreed template for DAR/RAR/CLH report.

An MRL application was included in the renewal dossier and was submitted alongside the renewal dossier in November 2020. The purpose of the MRL application was to modify the existing MRLs for representative uses on cucumber and courgette; dry beans and dry peas; and wheat. As representative uses include melliferous crops, a modification of the honey MRL was also requested. This MRL application was updated in November 2023 to modify also the exiting MRL for non-representative crop potato. This request is handled in parallel within the RAR. Furthermore, honey was removed from the MRL application. A separate routine MRL application under Regulation (EC) N:o 396/2005 will be submitted (in IUCLID format) to modify the MRL for honey at the beginning of 2024.

1.1.2 Arrangements between rapporteur Member State and co-rapporteur Member State

According to Commission Regulation (EU) No 2016/183 Finland was designated Rapporteur Member State (RMS) and Sweden assigned as Co-Rapporteur Member State (Co-RMS).

Finland, as RMS, evaluated the dossier submitted by the applicant and drafted the Renewal Assessment Report for all the sections, whereas Sweden as Co-RMS, conducted a pre-peer review of this report before submitting it to EFSA.

1.1.3 EU Regulatory history for use in Plant Protection Products

Flonicamid (CAS No 158062-67-0) was first included on Annex I of 91/414/EEC on 01/09/2010 under Commission Directive 2010/29/EU. France was the Rapporteur Member State (RMS). The original date of expiration of approval was 31/10/2020 according to the Commission Implementing Regulation 540/2011/EC but

the approval period was extended to 31.8.2023 according to the Commission Implementing Regulation (EU) 2017/2069.

The following documents of the previous evaluation process resulting in the first approval of flonicamid:

- Draft Assessment Report on flonicamid prepared by France, 2005 (DAR)
- Final addendum to the DAR [compiled version of June 2007 containing all individually submitted addenda]
- European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance flonicamid. EFSA Journal 2010; 8(5):1445. DOI:https://doi.org/10.2903/j.efsa.2010.1445
- SANCO Review report for the active substance flonicamid (IKI-220) ANCO/ 10479/2010 final of 12th March 2010
- Commission directive 2010/29/EU and Commission Implementing Regulation (EU) No 540/2011 and (EU) 2017/2069.

The draft review report was finalised in the Standing Committee on the Food Chain and Animal Health on 12 March 2010. Flonicamid was listed in Annex I of Directive 91/414/EEC on 1 September 2010 (Commission Directive 2010/29/EU) with the following specific provisions:

> PART A
> Only uses as insecticide may be authorised.
>
> PART B
> For the implementation of the uniform principles as referred to in Article 29(6) of Regulation (EC) No 1107/2009, the conclusions of the review report on flonicamid, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 22 January 2010, shall be taken into account.
>
> In this overall assessment, Member States must pay particular attention to:
>
> - the risk to operators and re-entry workers
> - the risk to bees
>
> Conditions of authorisation shall include risk mitigation measures where appropriate.
> The Member States shall inform the Commission in accordance with Article 38 of Regulation (EC) No 1107/2009 on the specification of the technical material as commercially manufactured.

EFSA has published the following Reasoned opinions:

- Reasoned opinion on the modification of the existing MRLs for flonicamid in various crops. 6.5.2010. EFSA Journal 2010; 8(5) :1610. DOI: https://doi.org/10.2903/j.efsa.2010.1610
- Reasoned opinion on the review of the existing maximum residue levels (MRLs) for flonicamid according to Article 12 of Regulation (EC) No 396/2005. 18.6.2014. EFSA Journal 2014; 12(6):3740,

49 pp. DOI: https://doi.org/10.2903/j.efsa.2014.3740

- Reasoned opinion on the modification of the existing MRLs for flonicamid in several crops. 28.4.2015. EFSA Journal 2015;13(5):4103. DOI: https://doi.org/10.2903/j.efsa.2015.4103
- Reasoned opinion on the modification of the MRL for flonicamid in herbs and edible flowers. 27.4.2016. EFSA Journal 2016; 14(4):4467. DOI: https://doi.org/10.2903/j.efsa.2016.4467
- Reasoned opinion on the modification of existing maximum residue levels for flonicamid in various commodities. 28.3.2017. EFSA Journal 2017;15(3):4748. DOI: https://doi.org/10.2903/j.efsa.2017.4748
- Reasoned opinion on the modification of existing maximum residue levels for flonicamid in various root crops. 18.9.2018. EFSA Journal 2018; 16(9):5414. DOI: https://doi.org/10.2903/j.efsa.2018.5414
- Reasoned opinion on the modification of existing maximum residue levels for flonicamid in various crops. 25.9.2018. EFSA Journal 2018; 16(9):5410. DOI: https://doi.org/10.2903/j.efsa.2018.5410
- Reasoned opinion on the modification of the existing maximum residue levels for flonicamid in strawberries and other berries. 27.5.2019. EFSA Journal 2019;17(8):5745. DOI: https://doi.org/10.2903/j.efsa.2019.5745
- Reasoned opnion on the evaluation of confirmatory data following the Article 12 MRL review for flonicamid. 13.5.2020. EFSA Journal 2020;18(5):6117. DOI: https://doi.org/10.2903/j.efsa.2020.6117
- Reasoned opinion on the setting of import tolerances for flonicamid in various crops and products of animal origin. 23.6.2020 DOI: https://doi.org/10.2903/j.efsa.2020.6136

1.1.4 Evaluations carried out under other regulatory contexts

US-EPA [EPA–HQ–OPP–2017–0750; FRL–10012–60]; Pesticide Registration Review; Proposed Interim Decisions for Several Pesticides (including flonicamid).

https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-128016_24-Feb-05_a.pdf

https://www.regulations.gov/search?filter=flonicamid

1.2 APPLICANT INFORMATION

1.2.1 Name and address of applicant(s) for approval of the active substance

Name and address:	**ISK Biosciences Europe N.V.** Pegasus Park De Kleetlaan 12B – Bus 9 B-1831 Diegem – Belgium
Telephone	[redacted]
e-mail:	
Contact:	Team leader [redacted]

Alternative contact:	[redacted] Team Leader [redacted]

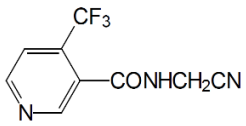
1.2.2 Producer or producers of the active substance

ISK Biosciences Europe N.V.

1.2.3 Information relating to the collective provision of dossiers

ISK Biosciences Europe N.V. is the sole notifier for the active substance Flonicamid.

1.3 IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1 Common name proposed or ISO-accepted and synonyms	FLONICAMID (ISO); N-(cyanomethyl)-4-(trifluoromethyl)pyridine-3-carboxamide
1.3.2 Chemical name (IUPAC and CA nomenclature)	
IUPAC	N-cyanomethyl-4-(trifluoromethyl)nicotinamide
CA	*N*-(cyanomethyl)-4-(trifluoromethyl)-3-pyridinecarboxamide
1.3.3 Producer's development code number	IKI-220
1.3.4 CAS, EEC and CIPAC numbers	
CAS	158062-67-0
EEC	No EC-number available*
CIPAC	763
1.3.5 Molecular and structural formula, molecular mass	
Molecular formula	$C_9H_6F_3N_3O$
Structural formula	
Molecular mass	229.16 g/mol
1.3.6 Method of manufacture (synthesis pathway) of the active substance	CONFIDENTIAL information - data provided separately (Volume 4)
1.3.7 Specification of purity of the active substance in g/kg	Minimum Purity 960 g/kg
1.3.8 Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1 Additives	CONFIDENTIAL information - data provided separately (Volume 4)
1.3.8.2 Significant impurities	CONFIDENTIAL information - data provided separately (Volume 4)
1.3.8.3 Relevant impurities	Toluene max 4 g/kg (notifier's proposal) max 3 g/kg (RMS FI's proposal)
1.3.9 Analytical profile of batches	CONFIDENTIAL information - data provided separately (Volume 4)

* A list number is provided: 605-127-0

1.4 INFORMATION ON THE PLANT PROTECTION PRODUCT

There are 2 representative formulations: Shoori and Teppeki

a) Shoori:

1.4.1 Applicant	Name	ISK Biosciences Europe N.V.
	Address	Pegasus Park De Kleetlaan 12B – Bus 9 B-1831 Diegem – Belgium
	Contact person	[redacted]
	Telephone	
	Fax	
	e-Mail	
1.4.2 Producer of the plant protection product	**Name:** **Address:**	[redacted]
	Contact : **Telephone number :** **Fax number :** **E-mail:**	[redacted]
1.4.3 Trade name or proposed trade name and producer's development code number of the plant protection product	**Trade name:** Shoori **Code number:** IKI-220 100 OD	

1.4.4 Detailed quantitative and qualitative information on the composition of the plant protection product Shoori (IKI-220 100 OD)

1.4.4.1 Composition of the plant protection product

Pure active substance:

content of pure active substance :	**100 g / l**	**10.45 (% w / w)****
limits :*	90 – 110 g / l	9.28 – 11.34 (% w / w)

Technical active substance:

content of technical active substance :	**104 g / l**	**10.89 (% w / w)****
limits :*	93.6 – 114.4 g / l	9.78 – 11.96 (% w / w)

at a minimum purity of the technical active substance of 96.0 %.

* according to Manual on development and use of FAO and WHO specifications for pesticides, prepared by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS), Rome, 2016

** Based on the relative density of the formulation = 0.9569 (rounded values)

1.4.4.2 Information on the active substances

Type	**Name/Code Number**
ISO common name	Flonicamid
CAS No	158062-67-0
EC No	No EC-number available*
CIPAC No	763
Salt, ester anion or cation present	Not relevant

* A list number is provided: 605-127-0

1.4.4.3 Information on safeners, synergists and co-formulants

CONFIDENTIAL information – data provided separately (Volume 4)

1.4.5 Type and code of the plant protection product

oil dispersion [Code : OD]

1.4.6 Function

Insecticide

1.4.7 Field of use envisaged

for use in agricultural crops under field conditions for control of sucking insects like, amongst other, mainly aphid species

1.4.8 Effects on harmful organisms

systemic and translaminar actions confers a generalised and long lasting aphid control

b) Teppeki:

<table>
<tr><td>1.4.9 Applicant</td><td><table>
<tr><td>Name</td><td>ISK Biosciences Europe N.V.</td></tr>
<tr><td>Address</td><td>Pegasus Park
De Kleetlaan 12B – Bus 9
B-1831 Diegem – Belgium</td></tr>
<tr><td>Contact person</td><td>[redacted]</td></tr>
<tr><td>Telephone</td><td></td></tr>
<tr><td>Fax</td><td></td></tr>
<tr><td>e-Mail</td><td></td></tr>
</table></td></tr>
<tr><td>1.4.10 Producer of the plant protection product</td><td>Name:
Address: [redacted]

Contact :
Telephone number :
Fax number :
E-mail: [redacted]</td></tr>
<tr><td>1.4.11 Trade name or proposed trade name and producer's development code number of the plant protection product</td><td>Trade name: Teppeki

Code number: IKI-220 500 WG</td></tr>
</table>

1.4.12 Detailed quantitative and qualitative information on the composition of the plant protection product Teppeki (IKI-220 500 WG)

1.4.12.1 Composition of the plant protection product

Pure active substance:

content of pure active substance:	**500 g / kg**	**50.0 (% w / w)**
limits:	475 – 525 g / kg	47.5 – 52.5 (% w / w)

Technical active substance:

content of technical active substance:	**521 g / kg**	**496 – 546 (% w / w)**
limits:	52.1 g / kg	49.6 – 54.6 (% w / w)

at a minimum purity of the technical active substance of 96.0 %.

1.4.12.2 Information on the active substances

Type	**Name/Code Number**
ISO common name	Flonicamid
CAS No	158062-67-0
EC No	No EC-number available*
CIPAC No	763
Salt, ester anion or cation present	Not relevant

* A list number is provided: 605-127-0

1.4.12.3 Information on safeners, synergists and co-formulants

CONFIDENTIAL information – data provided separately (Volume 4)

1.4.13 Type and code of the plant protection product

water dispersible granules [Code : WG]

1.4.14 Function

Insecticide

1.4.15 Field of use envisaged

for use in agricultural and horticultural/ornamental crops under field and greenhouse (indoor) conditions for control of sucking insects like, amongst other, mainly aphid species

1.4.16 Effects on harmful organisms

Flonicamid exhibits systemic and translaminar activity.

1.5 DETAILED USES OF THE PLANT PROTECTION PRODUCT

Details of the representative uses are summarised in the Table 1.5.1. An MRL application was submitted along the dossier to modify the existing MRLs for representative uses on cucumber and courgette; dry beans and dry peas; and wheat. The relevant GAPs are highlighted in the "Remarks" column.

1.5.1 Details of representative uses

Uses for Teppeki (IKI-220 500 WG) and Shoori (IKI-220 100 OD).

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		Application				Application rate per treatment			PHI (days) (m)	Remarks
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
Uses for Teppeki (IKI-220 500 WG)															
Wheat	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids in spring time; April to June/beginning July; BBCH 39 till PHI 28 days; = BBCH 39 – 77/79	1-2	21 days	0.014-0.035	200-500	0.07	28	GAP included in the MRL application
Wheat	CEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids in spring time; April to June/beginning July; BBCH 37/39 till PHI 28 days; = BBCH 37/39 – 77/79	1-2	21 days	0.014-0.035	200-500	0.07	28	GAP included in the MRL application
Wheat	NEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids in spring time; April to June/beginning July; BBCH 21-77/79 (= BBCH 21 till PHI)	1-2	21 days	0.014-0.035	200-500	0.07	28	GAP included in the MRL application

Crop and/or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Preparation**		**Application**				**Application rate per treatment**			**PHI (days)** (m)	**Remarks**
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
Apple / pears	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 01-70	1	not relevant	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	nr*	
Apple / pears	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 71-85/87	1-2	21 days	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	21	
Apple / pears	CEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 01-70	1	not relevant	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	nr*	
Apple / pears	CEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 71-85/87	1-2	21 days	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	21	
Apple / pears	NEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 01-70	1	not relevant	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	nr*	
Apple / pears	NEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 71-85/87	1-2	21 days	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	21	
Peaches	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 07-70	1	not relevant	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	nr*	
Peaches	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 71-85/87	1-2	21 days	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	14	
Peaches / apricots	CEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 07-70	1	not relevant	0.007-0.014	500 – 1000	0.07	nr*	

Crop and/or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Preparation**		**Application**				**Application rate per treatment**			**PHI (days)** (m)	**Remarks**
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
Peaches / apricots	CEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 71-85	1-2	21 days	0.007-0.014	500 – 1000	0.07	21	
Plums	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 07-70	1	not relevant	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	nr*	
Plums	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 71-85	1-2	21 days	0.007-0.035 (0.005)	200 – 1000 (excep. 1500)	0.07	14	
Plums	CEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 07-70	1	not relevant	0.007-0.014	500 – 1000	0.07	nr*	
Plums	CEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	At arrival of aphids; BBCH 71-85	1-2	21 days	0.007-0.014	500 – 1000	0.07	21	
Cucumber/ courgette	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	BBCH 16/18 till PHI (BBCH 16/18 – 85/87); April to July	3	7 days	0.005-0.0125	400 – 1000	0.05	1	
Cucumber/ courgette	SEZ	IKI-220 500 WG	G	Aphids	WG	500 g/kg	Foliar spraying	BBCH 16/18 till PHI (BBCH 16/18 – 85/87); April to July	3	7 days	0.005-0.0125	400 – 1000	0.05	1	*Non-permanent cultivation*
Cucumber/ courgette	IZ	IKI-220 500 WG	G	Aphids	WG	500 g/kg	Foliar spraying	BBCH 16/18 till PHI*; BBCH 16/18-85/87); year around production	3	7 days	0.007-0.02	400 – 1200	0.08	1	GAP included in the MRL application *Permanent cultivation*
Tomato / eggplant	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	BBCH 16/18 till PHI (BBCH 16/18 – 85/87); April to July	3	7 days	0.006-0.015	400 – 1000	0.06	1	

Crop and/or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Preparation**		**Application**				**Application rate per treatment**			**PHI (days)** (m)	**Remarks**
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
Tomato / eggplant	IZ	IKI-220 500 WG	G	Aphids	WG	500 g/kg	Foliar spraying	BBCH 16/18 till PHI*; BBCH 16/18-85/87); year around production	3	7 days	0.006-0.015	400 – 1000	0.06	1	*Non-permanent cultivation*
Tomato / eggplant	IZ	IKI-220 500 WG	G	Aphids	WG	500 g/kg	Foliar spraying	BBCH 16/18 till PHI*; BBCH 16/18-85/87); year around production	3	7 days	0.006-0.015	400 – 1000	0.06	1	*Permanent cultivation*
Melons	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	BBCH 15 till PHI (BBCH 15 – 85/87); April to July	3	7 days	0.005-0.0125	400 – 1000	0.05	1	
Cherries	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	BBCH 07-70	1	not relevant	0.006-0.014	500 – 1200	0.07	nr*	
Cherries	SEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	BBCH 71-85/87	1-2	21 days	0.006-0.014	500 – 1200	0.07	14	
Cherries	CEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	BBCH 07-70	1	not relevant	0.006-0.014	500 – 1200	0.07	nr*	
Cherries	CEZ	IKI-220 500 WG	F	Aphids	WG	500 g/kg	Foliar spraying	BBCH 71-85/87	1-2	21 days	0.006-0.014	500 – 1200	0.07	14	
Uses for Shoori (IKI-220 100 OD)															
Dry beans (pulses)	SEZ	IKI-220 100 OD	F	Pea/bean aphids: *Acyrthosiphon pisum* (ACYRON) *Aphis fabae* (APHIFA)	OD	100 g/L	Foliar spraying	Spring; April to June/Beg. July BBCH 11-71**	1	not relevant	0.017-0.05	100-300	0.05	nr*	GAP included in the MRL application

Crop and/or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Preparation**		**Application**				**Application rate per treatment**			**PHI (days)** (m)	**Remarks**
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
Dry beans (pulses)	CEZ	IKI-220 100 OD	F	Pea/bean aphids: *Acyrthosiphon pisum* (ACYRON) *Aphis fabae* (APHIFA)	OD	100 g/L	Foliar spraying	Spring; April to June/Beg. July BBCH 11-71**	1	not relevant	0.008-0.025	200-600	0.05	nr*	GAP included in the MRL application.
Dry peas (pulses)	SEZ	IKI-220 100 OD	F	Pea/bean aphids: *Acyrthosiphon pisum* (ACYRON) *Aphis fabae* (APHIFA)	OD	100 g/L	Foliar spraying	Spring; April to June/Beg. July BBCH 11-71**	1	not relevant	0.017-0.05	100-300	0.05	nr*	GAP included in the MRL application
Dry peas (pulses)	CEZ	IKI-220 100 OD	F	Pea/bean aphids: *Acyrthosiphon pisum* (ACYRON) *Aphis fabae* (APHIFA)	OD	100 g/L	Foliar spraying	Spring; April to June/Beg. July BBCH 11-71**	1	not relevant	0.008-0.025	200-600	0.05	nr*	GAP included in the MRL application
Winter and spring wheat	SEZ	IKI-220 100 OD	F	Aphids *Macrosiphum avenae (Syn. Sitobion avenae*) (MACSAV) *Metopolophium dirhodum (Syn.*	OD	100 g/L	Foliar spraying	BBCH 39 till PHI 28 days	1	not relevant	0.017-0.05	100-300	0.05	28	

Crop and/or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Preparation**		**Application**				**Application rate per treatment**			**PHI (days)** (m)	**Remarks**
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
				Macrosiphum dirhodum) (METODR) *Rhopalosiphum padi* (RHOPPA)											
Winter and spring wheat	CEZ	IKI-220 100 OD	F	Aphids *Macrosiphum avenae (Syn. Sitobion avenae*) (MACSAV) *Metopolophium dirhodum (Syn. Macrosiphum dirhodum*) (METODR) *Rhopalosiphum padi* (RHOPPA)	OD	100 g/L	Foliar spraying	BBCH 39 till PHI 28 days	1	not relevant	0.010-0.033	150-500	0.05	28	
Rye	SEZ	IKI-220 100 OD	F	Aphids *Macrosiphum avenae (Syn. Sitobion avenae*) (MACSAV) *Metopolophium dirhodum (Syn. Macrosiphum dirhodum*)	OD	100 g/L	Foliar spraying	BBCH 39 till PHI 28 days	1	not relevant	0.017-0.05	100-300	0.05	28	

Crop and/or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Preparation**		**Application**				**Application rate per treatment**			**PHI (days)** (m)	**Remarks**
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
				(METODR) *Rhopalosiphum padi* (RHOPPA)											
Rye	CEZ	IKI-220 100 OD	F	Aphids *Macrosiphum avenae (Syn. Sitobion avenae*) (MACSAV) *Metopolophium dirhodum (Syn. Macrosiphum dirhodum*) (METODR) *Rhopalosiphum padi* (RHOPPA)	OD	100 g/L	Foliar spraying	BBCH 39 till PHI 28 days	1	not relevant	0.010-0.033	150-500	0.05	28	
Triticale	SEZ	IKI-220 100 OD	F	Aphids *Macrosiphum avenae (Syn. Sitobion avenae*) (MACSAV) *Metopolophium dirhodum (Syn. Macrosiphum dirhodum*) (METODR)	OD	100 g/L	Foliar spraying	BBCH 39 till PHI 28 days	1	not relevant	0.017-0.05	100-300	0.05	28	

Crop and/or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Preparation**		**Application**				**Application rate per treatment**			**PHI (days)** (m)	**Remarks**
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
				Rhopalosiphum padi (RHOPPA)											
Triticale	CEZ	IKI-220 100 OD	F	Aphids *Macrosiphum avenae (Syn. Sitobion avenae*) (MACSAV) *Metopolophium dirhodum (Syn. Macrosiphum dirhodum*) (METODR) *Rhopalosiphum padi* (RHOPPA)	OD	100 g/L	Foliar spraying	BBCH 39 till PHI 28 days	1	not relevant	0.010-0.033	150-500	0.05	28	

nr* Not relevant. PHI determined by growth stage.

** at arrival of aphids in spring-time (commonly BBCH 50-71); before till end of flowering (10% pods formed)

(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and sucking insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(j) Growth stage range from first to last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of applications possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval

1.5.2 Further information on representative uses

For details on number and timing of applications and duration of protection, please refer to GAP table (point 1.5.1)

1.5.3 Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

An MRL application was submitted for non-representative crop potato in late phase of the evaluation in August 2022. The GAP is highlighted in Table 1.5.2. as a non-representative GAP.

Table 1.5.2. Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		Application				Application rate per treatment			PHI (days) (m)	Remarks
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	Growth Stages & season (j)	number min-max (k)	Interval between application min-max	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
Industrial and ware potatoes	NEZ CEZ SEZ	**Teppeki** (IKI-220 50% WG)	F	Aphids	WG	50%	spraying	From BBCH 15 untill BBCH 70/71	2	21	0.016 – 0.040	200 – 500	0.080	n/a (PHI defined by application timing)	Not be used in tank mixes with oil-based adjuvants
Seed potatoes	NEZ CEZ SEZ	**Teppeki** (IKI-220 50% WG)	F	Aphids	WG	50%	spraying	From BBCH 15 untill BBCH 35-39	1	-	0.016 – 0.040	200 - 500	0.080	n/a (PHI defined by application timing)	Tank mixes with oil-based adjuvants possible

Remarks:

(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and sucking insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(j) Growth stage range from first to last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of applications possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval

NEU: outdoor uses in northern Europe
SEU: outdoor uses in southern Europe
G: Greenhouse (indoor uses)

1.5.4 Overview on authorisations in EU Member States

Flonicamid containing products are authorised in most of the Member States (AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE and SI. Please refer to Document D-2 in CP dossier.

Level 2

FLONICAMID

2 SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

Summary of methodology proposed by the applicant for literature review and for all sections

2.1 IDENTITY

2.1.1 Summary or identity

Flonicamid is the ISO accepted common name for N-cyanomethyl-4-(trifluoromethyl)nicotinamide (IUPAC). The minimum purity of Flonicamid technical is 960 g/kg. However, the reference specification is open (rf. EFSA Journal 2010; 8(5):1445). According to the current specification, Flonicamid technical can contain the relevant impurity toluene at levels of up to 3 g/kg, but in the renewal the applicant proposes to increase the value to 4 g/kg while RMS FI would like to keep the level at 3 g/kg. Toxicity of certain impurities was not concluded. The reference specification is still open. (For further details, please, see Vol 4.)

2.2 PHYSICAL AND CHEMICAL PROPERTIES [EQUIVALENT TO SECTION 7 OF THE CLH REPORT TEMPLATE]

2.2.1 Summary of physical and chemical properties of the active substance

Flonicamid (purified) is an off-white powder, whereas Flonicamid technical is light beige powder. It has a melting point of 157.5°C and decomposes before reaching a boiling point. Its vapour pressure is 2.55 x 10^{-6} Pa (calculated value at 25°C). The UV-VIS, NMR, IR and mass spectra are in agreement with the molecular structure of Flonicamid. The water solubility of Flonicamid is 5.3-5.4 g/L at 20°C and is unchanged by different pH values. The solubility in organic solvents was > 100 g/L in acetone, methanol and acetonitrile. The solubility was 34.2 g/L in ethyl acetate, 18.7 g/L in isopropyl alcohol, 4.5 g/L in dichloromethane, 3.0 g/L in n-octanol and 0.55 g/L in toluene. Its solubility in hexane was far below 1 g/L (0.0002 g/L). The surface tension of a 90% saturated solution was 47.3 mN/m at 25°C and that of a 1 g/L solution was 70.5 mN/m at 20°C. Flonicamid does not self-ignite and is not flammable. It has no explosive or oxidizing properties.

Flonicamid has not to be classified for physical-chemical hazards.

Table 1: Summary of physicochemical properties of the active substance

Property	Value	Reference (year)	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	powder: off-white (PAI 99.7%) light beige (TGAI 98.7%)	(2000), Doc. No. 119-002; Report No.: 012575-1 (1999), Doc. No. 119-001; Report No.: 010153-1	visual assessment
Melting/freezing point	157.5°C (PAI 99.7%)	(1999), Doc. No. 119-001; Report No.: 010153-1	measured: endothermic maximum
Boiling point	no boiling point observed decomposition observed at 306-320°C (PAI 99.7%)	(2002a), Doc. No. 112-001; Report No.: 842001	measured: thermal analysis and capillary test
Relative density	mean relative density: 1.531 (20°C/20°C) (TGAI 98.7%) 1.54 (20°C/20°C) (PAI 99.7%)	(2000), Doc. No. 119-002; Report No.: 012575-1 (1999), Doc. No. 119-001; Report No.: 010153-1	measured: pycnometer method
Vapour pressure	2.55 x 10^{-6} Pa at 25°C	(1999), Doc. No. 115-001; Report No.: 010341-1	calculated value (measured at 30°C, 40°C and 50°C and extrapolated to 25°C
Surface tension	47.3 mN/m at 25±1°C (90% saturated solution) (TGAI 98.7%) 70.5 mN/m at 20°C (1 g/L solution) (PAI 99.8%)	(2002), Doc. No. 142-001; Report No.: 20334 (2017h), Doc. No. 116-001; Report No.: XH40MW	measured: plate method harmonised ring method
Water solubility	5.3-5.4 g/L at 20°C (PAI 99.8%; pH 4-10)	(2017a), Doc. No. 114-006; Report No.: BS18LD	measured
Partition coefficient n-octanol/water	log P_{OW} = 0.09-0.1 at 20°C (PAI 99.8%; pH 4-10)	(2017b), Doc. No. 114-001; Report No.: LT76QH	measured: shake flask method
Henry's law constant	4.2 x 10^{-8} Pa m^3 mol^{-1} at 20°C	(1999), Doc. No. 115-001; Report No.: 010341-1	calculated value
Flash point	not applicable	-	-
Flammability	not flammable (TGAI 98.7%)	(2002), Doc. No. 142-001; Report No.: 20334	measured

Property	Value	Reference (year)	Comment (e.g. measured or estimated)
Explosive properties	not explosive	(2001a), Doc. No. 181-001; Report No.: 834028	theoretical assessment
Self-ignition temperature	no relative self-ignition temperature below 400°C (TGAI 98.7%)	(2002), Doc. No. 142-001; Report No.: 20334	measured
Oxidising properties	not oxidising	(2001b), Doc. No. 181-002; Report No.: 834030	theoretical assessment
Granulometry	not applicable	-	-
Solubility in organic solvents and identity of relevant degradation products	acetone: 163.5 g/L ethyl acetate: 34.2 g/L methanol: 104.3 g/L dichloromethane: 4.5 g/L toluene: 0.55 g/L hexane: 0.0002 g/L n-octanol: 3.0 g/L acetonitrile: 132.8 g/L isopropyl alcohol: 18.7 g/L (PAI 99.7%) (at 20°C)	(1999c), Doc. No. 114-003; Report No.: 010250-1	measured: flask method
Dissociation constant	pKa = 11.60 at 20±1°C (PAI 99.7%)	(1999), Doc. No. 115-002; Report No.: 010141-1	measured: spectrophotometric method
Viscosity	not applicable	-	-
Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity	**UV/VIS*:*** neutral solution (pH 7): λ_{max} = 265 nm: ε (L mol^{-1} cm^{-1}) = 3870 acidic solution (pH < 2): λ_{max} = 266 nm: ε (L mol^{-1} cm^{-1}) = 3890 alkaline solution (pH > 12): λ_{max} = 204 nm: ε (L mol^{-1} cm^{-1}) = 13200 λ_{max} = 270 nm: ε (L mol^{-1} cm^{-1}) = 4190 at λ > 290 nm: or ε at 290 nm: 400 L mol^{-1} cm^{-1} (estimated value) **IR:** The IR spectrum confirms the molecular structure.	(1999), Doc. No. 117-001; Report No.: 010043-1 (1999a), Doc. No. 117-003; Report No.: 4855-98-0172-AS-001 (2002b), Doc. No. 117-002; Report No.: 841952	measured: UV/VIS IR ^{1}H-NMR ^{13}C-NMR MS

Property	Value	Reference (year)	Comment (e.g. measured or estimated)
	NMR: The NMR spectra confirm the molecular structure. **MS:** The mass spectrum confirms the molecular structure.		

2.2.1.1 Evaluation of physical hazards [equivalent to section 8 of the CLH report template]

Table 2: **Summary table for relevant physical-chemical properties**

Method	Results	Remarks	Reference (year)
theoretical assessment	Not explosive	-	(2001a), Doc. No. 181-001
Regulation (EC) No 440; A.10	Not flammable	-	(2002), Doc. No. 142-001
Regulation (EC) No 440; A.16	Flonicamid has no relative self-ignition temperature below 400°C	-	(2002), Doc. No. 142-001
theoretical assessment	Not oxidizing	-	(2001b), Doc. No. 181-002

2.2.1.1.1 Explosives *[equivalent to section 8.1 of the CLH report template]*

Table 3: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
Theoretical assessment	Not explosive	-	(2001a), Doc. No. 181-001

2.2.1.1.1.1 Short summary and overall relevance of the provided information on explosive properties

Flonicamid does not possess any chemical groups associated with explosive properties. In addition, the exothermic decomposition energy was determined by DSC. The value obtained was 374 J/g which is below the UN limit of 500 J/g.

2.2.1.1.1.2 Comparison with the CLP criteria

Since flonicamid does not possess any chemical groups associated with explosive properties that are given in Table A6.1 in Appendix 6 of the UN RTDG, Manuals of Tests and Criteria, the classification procedure does not need to be applied according to section 2.1.4.3 of Annex I to CLP. That means flonicamid does not meet the CLP criteria for explosives.

2.2.1.1.1.3 Conclusion on classification and labelling for explosive properties

Data conclusive but not sufficient for classification

2.2.1.1.2 Flammable gases (including chemically unstable gases) *[equivalent to section 8.2 of the CLH report template]*

Table 4: Summary table of studies on flammable gases (including chemically unstable gases)

Method	Results	Remarks	Reference
Not applicable	Not applicable	Not applicable as the substance is a solid	

2.2.1.1.2.1 Short summary and overall relevance of the provided information on flammable gases (including chemically unstable gases)

Not applicable to this substance.

2.2.1.1.2.2 Comparison with the CLP criteria

Not applicable to this substance.

2.2.1.1.2.3 Conclusion on classification and labelling for flammable gases

Hazard class not applicable

2.2.1.1.3 Oxidising gases *[equivalent to section 8.3 of the CLH report template]*

Table 5: Summary table of studies on oxidising gases

Method	Results	Remarks	Reference
Not applicable	Not applicable	Not applicable as the substance is a solid	

2.2.1.1.3.1 Short summary and overall relevance of the provided information on oxidising gases

Not applicable to this substance.

2.2.1.1.3.2 Comparison with the CLP criteria

Not applicable to this substance.

2.2.1.1.3.3 Conclusion on classification and labelling for oxidising gases

Hazard class not applicable

2.2.1.1.4 Gases under pressure *[equivalent to section 8.4 of the CLH report template]*

Table 6: Summary table of studies on gases under pressure

Method	Results	Remarks	Reference
Not applicable	Not applicable	Not applicable as the substance is a solid	

2.2.1.1.4.1 Short summary and overall relevance of the provided information on gases under pressure

Not applicable to this substance.

2.2.1.1.4.2 Comparison with the CLP criteria

Not applicable to this substance.

2.2.1.1.4.3 Conclusion on classification and labelling for gases under pressure

Hazard class not applicable

2.2.1.1.5 Flammable liquids *[equivalent to section 8.5 of the CLH report template]*

Table 7: Summary table of studies on flammable liquids

Method	Results	Remarks	Reference
Not applicable	Not applicable	Not applicable as the substance is a solid	

2.2.1.1.5.1 Short summary and overall relevance of the provided information on flammable liquids

Not applicable to this substance.

2.2.1.1.5.2 Comparison with the CLP criteria

Not applicable to this substance.

2.2.1.1.5.3 Conclusion on classification and labelling for flammable liquids

Hazard class not applicable

2.2.1.1.6 Flammable solids *[equivalent to section 8.6 of the CLH report template]*

Table 8: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
Regulation (EC) No 440; A.10	Not flammable	-	(2002), Doc. No. 142-001

2.2.1.1.6.1 Short summary and overall relevance of the provided information on flammable solids

A study conducted according to the relevant EU test method (A10) is available. The test item melted on contact with the flame and became liquid (as caramel) but did not ignite.

2.2.1.1.6.2 Comparison with the CLP criteria

The test material did not ignite when heated to its melting point. As the screening procedures of method A10 and UN test N.1 are equivalent, on the basis that no combustion occurred it may be concluded that the substance does not meet the CLP criteria for classification as a flammable solid.

2.2.1.1.6.3 Conclusion on classification and labelling for flammable solids

Data conclusive but not sufficient for classification

2.2.1.1.7 Self-reactive substances *[equivalent to section 8.7 of the CLH report template]*

2.2.1.1.7.1 Short summary and overall relevance of the provided information on self-reactive substances

There are no chemical groups present in the molecule associated with explosive or self-reactive properties.

2.2.1.1.7.2 Comparison with the CLP criteria

Since flonicamid does not possess any chemical groups associated with explosive or self reactive properties that are given in Tables A6.1 and A6.2 in Appendix 6 of the UN RTDG, Manuals of Tests and Criteria, the classification procedure does not need to be applied according to section 2.8.4.2 of Annex I to CLP. That means flonicamid does not meet the CLP criteria for self-reactive substances.

2.2.1.1.7.3 Conclusion on classification and labelling for self-reactive substances

Data conclusive but not sufficient for classification

2.2.1.1.8 Pyrophoric liquids *[equivalent to section 8.8 of the CLH report template]*

Table 9: Summary table of studies on pyrophoric liquids

Method	Results	Remarks	Reference
Not applicable	Not applicable	Not applicable as the substance is a solid	

2.2.1.1.8.1 Short summary and overall relevance of the provided information on pyrophoric liquids

Not applicable to this substance.

2.2.1.1.8.2 Comparison with the CLP criteria

Not applicable to this substance.

2.2.1.1.8.3 Conclusion on classification and labelling for pyrophoric liquids

Hazard class not applicable

2.2.1.1.9 Pyrophoric solids *[equivalent to section 8.9 of the CLH report template]*

2.2.1.1.9.1 Short summary and overall relevance of the provided information on pyrophoric solids

Experience shows that flonicamid does not spontaneously ignite in contact with air.

2.2.1.1.9.2 Comparison with the CLP criteria

Since experience in manufacture shows that flonicamid does not ignite spontaneously on coming into contact with air at normal temperatures, the classification procedure for pyrophoric solids need not be applied according to section 2.10.4.1 of Annex I to CLP. That means flonicamid does not meet the CLP criteria for pyrophoric solids.

2.2.1.1.9.3 Conclusion on classification and labelling for pyrophoric solids

Data conclusive but not sufficient for classification

2.2.1.1.10 Self-heating substances *[equivalent to section 8.10 of the CLH report template]*

Table 10: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
Regulation (EC) No 440; A.16	Flonicamid has no relative self-ignition temperature below 400°C	-	(2002), Doc. No. 142-001

2.2.1.1.10.1 Short summary and overall relevance of the provided information on self-heating substances

An auto-ignition test performed according to the relevant EC test guideline (A16) is available. No temperature effect was observed. The conclusion was that flonicamid has no relative self-ignition temperature below 400°C.

2.2.1.1.10.2 Comparison with the CLP criteria

Flonicamid was found not to self-ignite or undergo self-accelerating decomposition on heating. However, methods A.16 and UN test N.4 do not correspond to each other, and method A.16 has no influence on C&L. Thus, it cannot be concluded that flonicamid does not meet the CLP criteria.

2.2.1.1.10.3 Conclusion on classification and labelling for self-heating substances

Data inconclusive

2.2.1.1.11 Substances which in contact with water emit flammable gases *[equivalent to section 8.11 of the CLH report template]*

2.2.1.1.11.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

Flonicamid does not emit flammable gases in contact with water.

2.2.1.1.11.2 Comparison with the CLP criteria

According to the screening procedure in CLP Regulation, Annex I 2.12.4.1, the classification procedure for this class need not be applied because the chemical structure of the substance does not contain metals or metalloids. In addition, experience in production shows that the substance does not react with water (the substance is manufactured with water).

2.2.1.1.11.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

Data conclusive but not sufficient for classification

2.2.1.1.12 Oxidising liquids *[equivalent to section 8.12 of the CLH report template]*

Table 11: Summary table of studies on oxidising liquids

Method	Results	Remarks	Reference
Not applicable	Not applicable	Not applicable as the substance is a solid	

2.2.1.1.12.1 Short summary and overall relevance of the provided information on oxidising liquids

Not applicable to this substance.

2.2.1.1.12.2 Comparison with the CLP criteria

Not applicable to this substance.

2.2.1.1.12.3 Conclusion on classification and labelling for oxidising liquids

Hazard class not applicable

2.2.1.1.13 Oxidising solids *[equivalent to section 8.13 of the CLH report template]*

Table 12: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
Theoretical assessment	Not oxidizing	-	(2001b), Doc. No. 181-002

2.2.1.1.13.1 Short summary and overall relevance of the provided information on oxidising solids

Flonicamid contains oxygen and fluorine, but as these elements are chemically bonded only to carbon, the classification procedure does not need to be applied.

2.2.1.1.13.2 Comparison with the CLP criteria

According to the screening procedure in CLP Regulation, Annex I 2.14.4.1, for organic substances, the classification procedure for this class shall not apply because even though flonicamid contains oxygen and fluorine, these elements are chemically bonded only to carbon.

2.2.1.1.13.3 Conclusion on classification and labelling for oxidising solids

Data conclusive but not sufficient for classification

2.2.1.1.14 Organic peroxides *[equivalent to section 8.14 of the CLH report template]*

Table 13: Summary table of studies on organic peroxides

Method	Results	Remarks	Reference
Not applicable	Not applicable	Not applicable as the substance does not contain any peroxide groups	

2.2.1.1.14.1 Short summary and overall relevance of the provided information on organic peroxides

On the basis of a review of the chemical structure of flonicamid it is noted that the substance does not contain any peroxide functional groups and therefore does not meet the definition as an organic peroxide.

2.2.1.1.14.2 Comparison with the CLP criteria

Not applicable to this substance.

2.2.1.1.14.3 Conclusion on classification and labelling for organic peroxides

Hazard class not applicable

2.2.1.1.15 Corrosive to metals *[equivalent to section 8.15 of the CLH report template]*

Table 14: Summary table of studies on the hazard class corrosive to metals

Method	Results	Remarks	Reference
Not applicable	Not applicable	Not applicable as the substance is not corrosive to metals	

2.2.1.1.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

Corrosion to metals is not a known property of flonicamid.

2.2.1.1.15.2 Comparison with the CLP criteria

It is noted that in the UN RTDG test C.1, only solids with a melting point below 55°C need to be tested. The melting point of flonicamid is 157.5°C, hence the substance is not considered as corrosive to metals (cf. waiver on CLP guidance 2.16.4.1).

2.2.1.1.15.3 Conclusion on classification and labelling for corrosive to metals

Data conclusive but not sufficient for classification

2.2.2 Summary of physical and chemical properties of the plant protection product

Summary of results of IKI-220 100 OD (Shoori):

The appearance of the product is that of homogeneous, light brown and viscous liquid. It is not explosive, has no oxidising properties. The product has no flash point below 234-242°C. It has a self-ignition temperature of 260°C. In 1 % aqueous dilution, it has a pH value around 6.9 at 21°C. The product is surface active.

After 7 days at 0°C and 14 days at 54°C, neither the active ingredient content nor the technical properties were changed. However, after storage at low temperature, phase separation was observed. The stability data indicate a shelf life of at least 3 years at ambient temperature when stored in HDPE/EVOH bottles and for at least two years when stored in F-HDPE bottles.

Its technical characteristics are acceptable for an *OD* formulation.

IKI-220 100 OD does not need to be classified for physico-chemical hazards.

Summary of results of IKI-220 500 WG (Teppeki):

The appearance of the product is that of free-flowing cylindrical granules of brown colour**,** with a slight odour of ammonia. It is not explosive, has no oxidising properties. The product is not flammable. It has a self-ignition temperature of 383°C. In 1 % aqueous dilution, it has a pH value around 8.3 at 22°C.

There is no effect of high temperature on the stability of the formulation, since after 14 days at 54°C, neither the active ingredient content nor the technical properties were changed. The stability data indicate a shelf life of at least 3 years at ambient temperature when stored in HDPE bottles. However, the relevant impurity toluene was not

analysed before and after storage. Thus, a new shelf-life study was initiated. The report of two-year storage in HDPE is now available, and it includes the initial time point, the results after storage for 14 days at 54°C as well as after 2-year storage at room temperature. Note that the concentration of toluene increases by 15% during 1-year storage. Yet, it is still < 3 g/kg, which fulfils the current specification. However, according to the applicant, toluene is a residual solvent which cannot increase during storage, and the 15% difference is related to measurement uncertainty.

The technical characteristics are acceptable for a WG formulation.

The product can be mixed in the tank together with the products Novodor FC 20 % SC (a.s.: bacillus thuringiensis), Score 25 % EC (a.s.: difenoconazole), Dithane DG 75 % WG (a.s.: mancozeb), Decis 2.5 % EC (a.s.: deltamethrin), Karate 5 % EC (a.s.: lambda-cyhalothrin), Shirlan 50 % SC (a.s.: fluazinam), Benomyl 52.4 % WP (a.s.: benomyl), Stroby DF 50 % WG (a.s.: kresoxim-methyl), Kumulus DF 80 % WG (a.s.: sulfur), Phytocap Ultra 80 % WG (a.s.: captan), Juwel Top SE (a.s.: epoxiconazole 125 g/L, kresoxim-methyl 125 g/L, fenpropimorph 150 g/L), Ranman (IBE 3878) 40 % SC (a.s.: cyazofamid) and Wetter (IBE 3869). Studies regarding the combination with the mentioned products were submitted and the application as tank mixture is acceptable.

IKI-220 500 WG does not need to be classified for physico-chemical hazards.

2.3 DATA ON APPLICATION AND EFFICACY

2.3.1 Summary of effectiveness

Flonicamid is applied as foliar treatment and is used in agricultural and horticultural/ornamental crops under field and greenhouse (indoor) conditions for control of sucking insects like, amongst other, mainly aphid species.

2.3.2 Summary of information on the development of resistance

Flonicamid belongs to IRAC insecticide mode of action classification Group 29 ’Chordotonal organ Modulators’ (nerve action; target protein responsible for biological activity is unknown or uncharacterized, IRAC (Insecticide Resistance Action Committee) MoA Classification v 9.3, June 2019). In contrast to Group 9, Group 29 insecticides do not bind to the Nan-lav TRPV channel complex.

According to the Arthropod Pesticide Resistance Database (www.pesticideresistance.org) there are seven reported resistance cases worldwide (USA and South Korea) for Flonicamid for *Aphis gossypii* in cotton and vegetables, yet no resistance is reported in Europe. However, several cases with sensitivity shift has been identified.

2.3.3 Summary of adverse effects on treated crops

No adverse effects on treated crops have been observed. This has been confirmed by the results of the seedling emergence and vegetative vigor studies conducted with the representative formulation as well as by more than ten years of commercial use in various conditions in the field and greenhouses.

2.3.4 Summary of observations on other undesirable or unintended side-effects

No undesirable or unintended side-effects have ever been reported or observed.

2.4 FURTHER INFORMATION

2.4.1 Summary of methods and precautions concerning handling, storage, transport or fire

For information on active substance please see Volume 3CA, B4.
For information on representative formulation please see Volume 3CP, B4 –IKI-2020 100 OD and Volume 3CP, B4 –IKI-220 500 WP.

2.4.2 Summary of procedures for destruction or decontamination

For information on active substance please see Volume 3CA, B4.
For information on representative formulation please see Volume 3CP, B4 –IKI-2020 100 OD and Volume 3CP, B4 –IKI-220 500 WP.

2.4.3 Summary of emergency measures in case of an accident

No undesirable or unintended side-effects have ever been reported or observed.

For information on active substance please see Volume 3CA, B4.
For information on representative formulation please see Volume 3CP, B4 –IKI-2020 100 OD and Volume 3CP, B4 –IKI-220 500 WP.

2.5 METHODS OF ANALYSIS

For details on the analytical methods and their validity assessment see Volume 3CP B5 (IKI-2020 100 OD and IKI-220 500 WG) and Volume 4 (confidential data).

2.5.1 Methods used for the generation of pre-authorisation data

2.5.1.1 Analysis of the active substance as manufactured

Samples of the technical material were dissolved in acetonitrile/tetrahydrofuran/trifluoroacetic acid (100/50/1 v/v/v) and diluted with water. Analysis was carried out by HPLC-UV. For determination of the relevant impurity toluene, samples of the technical material were dissolved in ethyl acetate and analysed by GC-FID.

2.5.1.2 Formulation analysis

IKI-220 50 WG:

Samples of the plant protection product were dissolved in mobile phase (water / acetonitrile / tetrahydrofurane / trifluoroacetic acid 2550:300:150:3 and analysed by HPLC-UV at 265 nm after clean-up. Alternatively, samples of the plant protection product were dispersed in water and diluted with acetonitrile. An aliquot of the solution was diluted with water / acetonitrile (80/20) and filtered. Analysis was carried out by HPLC-UV.

For analysis of toluene, samples of the plant protection product were dispersed in acetone containing internal standard (ethyl benzene) filtered. Analysis was carried out by GC-MS.

IKI-220 100 OD:

A sample of the plant protection product was dispersed in an internal standard solution (dimethyl phthalate), centrifuged and filtered. The filtrate was analysed by HPLC-UV at 265 nm.For determination of toluene, samples of the plant protection product were dispersed in acetonitrile, sonicated and filtered. The filtrate was analysed by HPLC-UV at 207 nm.

2.5.2 Methods for Risk Assessment

2.5.2.1 Methods in soil, water, sediment, air and any additional matrices used in support of environmental fate studies

No studies with analytical methods for the determination of non-isotope labelled residues were submitted.

2.5.2.2 Methods in soil, water and any additional matrices used in support of efficacy studies

No studies with analytical methods for the determination of non-isotope labelled residues were submitted.

2.5.2.3 Methods in feed, body fluids and tissues, air and any additional matrices used in support of toxicological studies

For determination of Flonicamid in test diet, samples of diet were extracted with water / acetonitrile 1:4, filtered and analysed by HPLC-UV at 265 nm. Another method for analysis of Flonicamid in test diet used the same extraction solvent and employed an additional clean-up step using an extraction cartridge prior to analysis by HPLC-UV.

Quantification of Flonicamid in dosing solutions (solutions of carboxymethyl cellulose in water) was done after dilution with acetonitrile / water (8:2). An aliquot of the solution was diluted with water / acetonitrile (8:2) and analysed by HPLC-UV at 265 nm.

2.5.2.4 Methods in body fluids, air and any additional matrices used in support of operator, worker, resident and bystander exposure studies

No studies with analytical methods for the determination of non-isotope labelled residues submitted.

2.5.2.5 Methods in or on plants, plant products, processed food commodities, food of plant and animal origin, feed and any additional matrices used in support of residues studies

One method for analysis of Flonicamid, TFNA, TFNG and TFNA-AM in crops and processed commodities was based on extraction with methanol, clean-up by SPE and derivatisation of metabolites TFNA and TFNG with diazomethane. Analysis was carried out by GC-MS. Another method for analysis of Flonicamid, TFNA, TFNG and TFNA-AM in crops employed extraction with methanol, clean-up by SPE and analysis by HPLC-MS/MS. For analysis of Flonicamid, TFNA, TFNG and TFNA-AM in plums and processed commodities, extraction was carried out with acetonitrile/water/acetic acid (60/40/0.1). After clean-up, analysis was carried out by HPLC-MS/MS. For analysis of Flonicamid, TFNG, TFNA, OH-TFNA-AM and TFNA-AM in animal tissue, samples were extracted with acetonitrile / water (8+2). After clean-up, the samples were analysed by HPLC-MS/MS. Another method for analysis of Flonicamid, TFNG, TFNA, OH-TFNA-AM and TFNA-AM in goat tissue samples, employed acidic extraction under reflux. After work-up, the samples were analysed by HPLC-MS/MS. Analysis of Flonicamid, TFNG, TFNA, OH-TFNA-AM and TFNA-AM in milk was done after extraction with ethanol/water by HPLC-MS/MS. A method for analysis of Flonicamid, TFNA, TFNG and TFNA-AM in crops used extraction with acetonitrile/water/acetic acid (60/40/0.1) and clean-up by liquid-liquid partitioning or by SPE. Analysis was performed by HPLC-MS/MS. A method for analysis of Flonicamid, TFNA and TFNG in crops was done according to the multi-residue method Quechers with analysis by HPLC-MS/MS. For some dry matrices, an additional clean-up step by SPE was included. For analysis of Flonicamid, TFNA and TFNG in processed commodities of wheat, the multi-residue method Quechers including an SPE clean-up step was employed with analysis by HPLC-MS/MS. Analysis of Flonicamid and its metabolites, TFNG, TFNA, TFNG-AM and TFNA-AM in honey was done after extraction with methanol by HPLC-MS/MS. For analysis of Flonicamid, TFNA and TFNG in apricots and peaches, sample preparation comparable to the Quechers method was used employing internal standards. Analysis was carried out by HPLC-MS/MS.

2.5.2.6 Methods in soil, water, sediment, feed and any additional matrices used in support of ecotoxicology studies

For analysis of Flonicamid in avian diet, samples were extracted with acetonitrile / water (80:20) and centrifuged. An aliquot of the extract was diluted into calibration range with acetonitrile / water (80:20) and analysed by HPLC-UV.

Methods for determination of Flonicamid in test water relied on dilution or homogenisation by shaking and analysis by HPLC-UV.

Analysis of sediment for Flonicamid was done by extraction with methanol and analysis by HPLC-UV after clean-

up.

For analysis of TFNA, TFNA-OH, TFNG-AM and TFNA-AM in test water, samples were diluted with acetonitrile, acetonitrile / water (1:1), test water and / or mobile phase and analysed by HPLC-UV.

For analysis of Flonicamid, TFNA, TFNG and TFNA-AM in pollen, nectar and honey, samples were extracted with methanol and cleaned-up by SPE. TFNA and TFNG were derivatised using diazomethane. Analysis was carried out by GC-MS.

A method for determination of Flonicamid in test water used HPLC-MS/MS detection after dilution with acetonitrile / test medium (1:1).

Samples of larval diet, sucrose diet and aqueous stock solution were diluted with acetonitrile / water (1:4) into calibration range and analysed by HPLC-MS/MS for Flonicamid.

For analysis of TFNG, TFNA, TFNG-AM and TFNA-AM, samples of aqueous sugar solutions (50%) were mixed with methanol. An aliquot of the supernatant was diluted with water and analysed by HPLC-MS/MS. Samples of acetone were diluted with methanol/water (1:1) and analysed by HPLC-MS/MS.

Samples of flowers, nectar and pollen were extracted with methanol and aliquot of the supernatant was diluted with water. In case of pollen, the extracts were filtered. Analysis of Flonicamid and its metabolites TFNA, TFNG, TFNG-AM and TFNA-AM was carried out by HPLC-MS/MS.

A method for analysis of the metabolite TFA in aqueous sugar solutions (50%) was based on dilution with methanol, addition of TFA-internal standard and analysis by GC-MS/MS.

Methods for analysis of Flonicamid, TFNA, TFNA-AM and TFNG in leaves, flowers, pollen and nectar relied on extraction with acetonitrile / water (80:20) and analysis by HPLC-MS/MS after work-up.

2.5.2.7 Methods in water, buffer solutions, organic solvents and any additional matrices resulting from the physical and chemical properties tests

For analysis of Flonicamid in organic solvents, samples were filtered, diluted and analysed by HPLC-UV at 265 nm. In case of hexane samples, the samples were evaporated to dryness and resuspended in acetonitrile before analysis by HCPLC-UV.

Quantification of Flonicamid in adsorbent traps was done, after extraction with acetonitrile and analysis by HPLC-UV at 265 nm.

Samples of buffered and unbuffered water were filtered and an aliquot of the filtrate was diluted with acetonitrile / water (1:1) prior to quantification of Flonicamid by HPLC-UV.

For analysis of Flonicamid, samples of water were diluted with the respective buffer solution (saturated with octanol) and further diluted with acetonitrile / water (1:1) prior to analysis by HPLC-UV.

Samples of octanol were diluted with octanol (saturated with buffer solution) and further diluted with acetonitrile and acetonitrile / water (1:1) prior to analysis by HPLC-UV.

For analysis of TFNA-OH, TFNA-AM, TFNG-AM, TFNA and TFNG, samples of water were diluted with acetonitrile / water (1:1) prior to analysis by HPLC-UV.
Samples of octanol were diluted either with acetonitrile and acetonitrile / water (1:1) prior to analysis by HPLC-UV.

2.5.3 Methods for post control and monitoring purposes

Table 2.5.3 - 1: Summary of monitoring methods for the determination of residues of Flonicamid and its metabolites

Matrix type / crop group	Primary Method	Confirmatory method	Independent Lab Validation
High water crops (lettuce, sugar beet root)	CA 4.2 (a)/01	CA 4.2 (a)/01	CA 4.2 (a)/02
High acid crops (orange)	CA 4.2 (a)/01	CA 4.2 (a)/01	CA 4.2 (a)/02
High oil crops (oil seed rape seed)	CA 4.2 (a)/01	CA 4.2 (a)/01	CA 4.2 (a)/02
Dry crops (wheat grain and straw)	CA 4.2 (a)/01	CA 4.2 (a)/01	CA 4.2 (a)/02
Animal origin	CA 4.2 (a)/03	CA 4.2 (a)/03	CA 4.2 (a)/04
Milk	CA 4.2(a)/05	CA 4.2(a)/05	CA 4.2 (a)/06
Soil	CA 4.2 (b)/01	CA 4.2 (b)/01	Not required
Water (drinking, ground and surface water)	CA 4.2 (b)/02	CA 4.2 (b)/02	CA 4.2 (b)/03
Air	CA 4.2 (c)/01	Not required	Not required
Body fluids and tissue (urine, plasma, liver)	CA 4.2 (c)/01	CA 4.2 (c)/01	Not required

2.5.3.1 Plants and plant products

Samples were extracted with acetonitrile containing 1% formic acid after addition of water. After addition of a Quechers extraction kit (containing magnesium sulphate and sodium chloride), the sample was centrifuged. An aliquot of the supernatant was diluted with water containing 0.1% formic acid and analysed by HPLC-MS/MS. The method was validated for Flonicamid, TFNA, TFNG and TFNA-AM. An independent laboratory validation has been successfully carried out.

2.5.3.2 Food of animal origin

Samples were extracted with acetonitrile / water (80:20) containing hydrochloric acid. After clean-up steps by SPE and centrifugation, analysis was performed by HPLC-MS/MS. The method was validated for Flonicamid and TFNA-AM. An independent laboratory validation has been successfully carried out.

2.5.3.3 Soil

Soil samples were extracted twice with methanol/water (30/70). The extracts were combined, diluted with methanol/water (30/70) and analysed by HPLC-MS/MS. The method was validated for Flonicamid, TFNA, TFNA-OH, TFNA-AM, TFNG and TFNG-AM.

2.5.3.4 Water

Water samples were directly analysed without further clean-up and the content of Flonicamid and its metabolites TFNA, TFNA-OH, TFNA-AM, TFNG and TFNG-AM was determined by HPLC-MS/MS. An independent laboratory validation for drinking water is available.

2.5.3.5 Air

Residues of Flonicamid were trapped on solid sorbent material (Orbo-44) which was extracted using acetonitrile. After clean-up, the extract was analysed by HPLC-DAD.

2.5.3.6 Body fluids and tissues

Samples were extracted with acetonitrile / water (80/20) acidified with hydrochloric acid and cleaned-up according to the Quechers multi-residue method. The final extract was diluted with water and analysed by HPLC-MS/MS. The method was validated for Flonicamid and TFNA-AM.

2.6 EFFECTS ON HUMAN AND ANIMAL HEALTH

The data on active substance flonicamid were evaluated during the first Annex I review of flonicamid and were presented in the monograph (Vol.3, Annex B, Section B.6 Toxicology and metabolism, February 2005) and in the Final addendum (June 2007). Proposal for Harmonised Classification and Labelling (CLH report, version number 2, March 2012) was submitted to ECHA and the proposal was based mainly on the information presented in this assessment of flonicamid.

A harmonised classification and labelling for flonicamid has been adopted by the ECHA Committee for Risk Assessment (RAC) on 5 June 2013 (ECHA/RAC/CLH-O-0000002561-80-03/F). The resulting classification is available in COMMISSION REGULATION (EU) 2015/1221 of 24 July 2015 (7th adaptation to technical and scientific progress of Regulation (EC) No 1272/2008) and the classification for human health is the following:

Acute Tox. 4; H302

In addition to the studies evaluated during the first Annex I review of flonicamid, the applicant submitted some new studies on flonicamid during this renewal process mainly to meet the current data requirements of Regulation 283/2013: *in vitro* comparative metabolism studies in mouse, rat, dog rabbit and human; *in vitro* phototoxicity test; studies examining hormonal levels in rats in connection with reproductive toxicity; 28-day oral immunotoxicity study, in vitro micronucleus study and several new toxicity studies on different metabolites. Based on re-evaluation of all old and new studies, no change to the current harmonised classification is proposed by the RMS and the previous classification is still considered valid:

Acute Tox. 4; H302

More detailed results of the studies are presented in Volume 3, section B.6.

2.6.1 Summary of absorption, distribution, metabolism and excretion in mammals *[equivalent to section 9 of the CLH report template]*

Table 15: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Absorption, distribution, metabolism and excretion by oral route Pilot excretion experiment; oral gavage of a single dose of 0.9 and 21 mg/kg (due to calculation error) Pilot pharmacokinetics experiment; oral gavage of a single oral dose of 2 and 50 mg/kg	A rapid and almost complete absorption and rapid elimination of [^{14}C]IKI-220 from plasma following a first order kinetics after a single oral administration of a low (2.0 mg/kg bw) and a high (50 mg/kg bw) dose in rats. Plasma concentrations reached their maximal level between 0.25 – 1h and the Cmax and AUC were directly proportional to the dose level. Excretion occurred predominantly via the urine and considerably less via the feces within the first 24h post dosing. No radiolabel was excreted in expired air. No biologically significant differences were seen between	Due to a calculation error, both the low and the high doses in the pilot excretion experiment were administered at only about 40% of the intended value. The error in this pilot study had no significant	dRAR: B.6.1.1.1, 2001

Method	Results	Remarks	Reference
OECD TG 417 (1984) GLP Acceptable study	sexes and dose levels in the range 2.0 – 50 mg/kg.	impact on the results which could be considered acceptable.	
<u>Absorption, distribution, metabolism and excretion by oral route</u> Pharmacokinetics of an oral dose of [^{14}C]IKI-220 in Sprague-Dawley rats OECD TG 417 (1984) GLP Acceptable study	A rapid absorption and elimination of [^{14}C]IKI-220 from plasma was detected. The pharmacokinetics in both sexes at 2 mg/kg and in females at 400 mg/kg were comparable, but at 400 mg/kg males exhibited a slight prolongation of T_{max} and $T_{1/2}$ of elimination due to an extended plateau in plasma concentration.	-	dRAR: B.6.1.1.2, 2001
<u>Absorption, distribution, metabolism and excretion by oral route</u> Study of the elimination and distribution of radiolabel following a single oral administration of [^{14}C]IKI-220 to Sprague-Dawley rats OECD TG 417 (1984) GLP Acceptable study	A rapid and almost complete absorption and excretion in the urine of [^{14}C]IKI-220 (within 24h post dosing at the low dose level and 48h post dosing at the high dose level) whereas fecal excretion was low, accounting for approx. 5% of the administered dose at both dose levels. Radioactivity was widely distributed throughout the tissues, higher peak concentrations occuring in liver, kidneys, adrenals and thyroid tissue, but there was no accumulation of radioactivity in any tissue. The rate of oral absorption, the route and rate of excretion and the tissue distribution of flonicamid were not significantly affected by dose level or sex.	-	dRAR: B.6.1.1.3, 2002
<u>Absorption, distribution, metabolism and excretion by oral route</u> Study of the elimination and distribution of radiolabel following multiple oral administration of [^{12}C/^{14}C]IKI-220 to Sprague-Dawley rats OECD TG 417 (1984) GLP Acceptable study	A rapid and almost complete absorption and excretion of [^{14}C] IKI-220 predominantly in the urine within 24h post dosing, whereas fecal excretion was low, accounting for approx. 7% of the administered dose. The distribution of radioactivity was comparable to that after a single dose of 2 mg/kg, i.e. widely distributed throughout the tissues, with higher peak concentrations occurring in liver, kidneys, adrenals, thyroid and ovarian tissue, but there was no accumulation of radioactivity in any tissue. The rate of oral absorption, the tissue distribution and the route and rate of excretion were not affected by treatment regimen or sex. In the rat, repeated dosing of a low dose had no effect on the disposition of IKI-220 compared to a single dose at the same dose level.	-	dRAR: B.6.1.1.4, 2002

Method	Results	Remarks	Reference
Absorption, distribution, metabolism and excretion by oral route Study of the biliary elimination of radiolabel following oral administration of [^{14}C]IKI-220 to Sprague-Dawley rats OECD TG 417 (1984) GLP Acceptable study	Rapid absorption and predominant elimination in the urine of [^{14}C]IKI-220 (approx. 70 – 80% of the administered dose); fecal and biliary elimination were minor routes of excretion in the rat, accounting each for 3- 5% of the administered dose. There was no accumulation in the carcass. With the exceptions of slightly prolonged biliary excretion in high dose males and higher blood levels in both sexes at the high dose, the dose level and sex did not influence the route, extent and time course of elimination.	-	dRAR: B.6.1.1.5, 2002
Absorption, distribution, metabolism and excretion by oral route Identification and quantification of [^{14}C]IKI-220 and metabolites (TFNA-AM *N*-oxide conjugate; TFNA conjugate, TFNA-AM *N*-oxide, OH-TFNA-AM, TFNG-AM, TFNA-AM, INKI-220 *N*-oxide, TFNG, TFNA) in Sprague-Dawley rats that received single and/or or multiple oral doses of the test substance OECD TG 417 (1984) GLP Acceptable study	The metabolic profile in urine was generally quantitatively and qualitatively similar between the sexes and after single and multiple doses of 2 mg/kg bw and no appreciable induction of metabolism was seen. The major urinary residue in both sexes after single or multiple administrations was [^{14}C]IKI-220 parent compound which occurred at up to 71.99% of administered dose. A major urinary metabolite was TFNA-AM, which occurred at up to 27.34% of administered dose. All other metabolites occurred at ≤ 3.7% administered dose. [^{14}C]IKI-220 parent compound was the predominant residue in bile, but all metabolites and parent compound each accounted for ≤ 3.32% administered dose. The metabolic profile in the liver of males was generally quantitatively and qualitatively similar after single and multiple treatments of 2 mg/kg bw. [^{14}C]IKI-220 parent was the predominant residue at ≤ 2.35% administered dose. Two significant, but minor, metabolites were also formed, TFNG at ≤ 1.10 % and TFNA-AM at ≤ 1.19 % administered dose. The predominant residues in faeces were [^{14}C]IKI-220 parent, TFNA-AM and TFNA, but none accounted for more than 1.2% administered dose. TFNA-AM *N*-oxide conjugate also occurred after administration of 400 mg/kg bw at up to 1.0% administered dose.	-	dRAR: B.6.1.1.6, 2002
Absorption, distribution, metabolism and excretion by oral route Metabolic fate of IKI-220 [II] - absorption,	TFNA and TFNG were rapidly and entirely excreted in urine and faeces. 24 h after the intake of ^{14}C-TFNA, 95.6 to 98.6% of the doses (0.5 mg/kg and 100 mg/kg respectively) were already excreted as well as for ^{14}C-TFNG (102.6% and 94.4% of the doses) and at the end of	The study was not conducted under GLP and no official guideline was mentioned. Only male rats	dRAR: B.6.1.1.7, 1998

Method	Results	Remarks	Reference
distribution and excretion in male IGS rats- single oral dose of ([^{14}C]IKI-220 at 100 mg/kg or ^{14}C-TFNG and ^{14}C-TFNA at 0.5 mg/kg bw or 100 mg/kg bw, respectively No guideline was mentioned, was mainly conducted in compliance with OECD TG 417 (1984) Supportive study	the experiment 99.8% and 100.5% of the doses of ^{14}C-TFNA and of ^{14}C-TFNG, 104.8% and 97.7%, were excreted. Short term analysis showed that a few hours after administration, TFNA and TFNG were found mainly in kidney, stomach and intestine which are also in accordance with fast eliminations of the molecules via faeces and urine. Low biliary excretion of IKI-220 or the two metabolites was observed.	were used but no justification for the sex of the animals used was provided. Number of replicates was low, unclear why only one rat was used in the ([^{14}C]IKI-220 100 mg/kg dose group.	
Absorption, distribution, metabolism and excretion by other routes - *In vitro* comparative metabolism Assessment of the *in vitro* metabolism of IKI-220 by using mouse, rat, dog rabbit and human liver S9 fractions, in order to compare the *in vitro* metabolite pattern (TFNA, TFNA-AM, TFNG, TFNG-AM) occurring in animal and human test systems. There is no specific OECD test guideline available for this type of study. The study was perfomed mainly in accordance with EFSA Supporting publication 2019:EN-1618. Supportive study	This is a new *in vitro* comparative metabolism study that was performed in order to comply with the data requirements of Reg (EU) 283/2013. The study has not been evaluated previously. ^{14}C]IKI-220 essentially remained as unchanged parent following incubation with each of mouse, rat, dog, rabbit and human liver S9 fractions for up to 120 minutes. Three metabolites (designated M1 – M3) were detected across the five species at low levels (< 5%). Metabolite M1 eluted with the same retention time as TFNA-AM. These results also correlate well with the *in vivo* results. Taken together, under the conditions of this study there were no human-specific or disproportionate human metabolites detected.	No claim of GLP compliance was made and the exposures were perfomed only as single samples, which can reduce the reliability and statistical power of the study. Hence, the study is considered as supportive.	dRAR: B.6.1.2.1, 2017
Absorption, distribution, metabolism and excretion by other routes - *In vitro* comparative metabolism	This is a new *in vitro* comparative metabolism study that was performed in order to comply with the data requirements of Reg (EU) 283/2013. The study has not been evaluated previously. [^{14}C]IKI-220 essentially remained as unchanged parent following incubation	-	dRAR: B.6.1.2.2, 2018

Method	Results	Remarks	Reference
Assessment of the *in vitro* metabolism of IKI-220 by using mouse, rat, dog rabbit and human liver S9 fractions, in order to compare the *in vitro* metabolite pattern (TFNA, TFNA-AM, TFNG, TFNG-AM) occurring in animal and human test systems. There is no specific OECD test guideline available for this type of study. The study was perfomed mainly in accordance with EFSA Supporting publication 2019:EN-1618. Acceptable study	with mouse, rat, dog, rabbit and human liver S9 fractions for up to 120 minutes. Three metabolites (designated M1 – M3) were detected across the five species at low levels (< 5%). Metabolite M1 eluted with the same retention time as TFNA-AM. Taken together, under the conditions of this study there were no human-specific or disproportionate human metabolites detected.		
<u>Absorption, distribution, metabolism and excretion by other routes</u> - <u>*In vitro* comparative metabolism</u> Assessment of the *in vitro* metabolism of IKI-220 by using mouse, rat, dog rabbit and human hepatocytes, in order to determine the relevance of the toxicological animal data. There is no specific OECD test guideline available for this type of study. The study was perfomed mainly in accordance with EFSA Supporting publication 2019:EN-1618. Acceptable study	This is a new *in vitro* comparative metabolism study that was performed in order to comply with the data requirements of Reg (EU) 283/2013. The study has not been evaluated previously. [^{14}C]IKI-220 was slowly metabolised by mouse, rat, rabbit, dog and human hepatocytes, with < 34% metabolism being observed after 48 h incubation. The main metabolite detected in all species except human was found to be TFNA-AM. An additional metabolite, M1 (< 2% sample radioactivity after 48 h), was the main component in addition to parent detected in incubations with human hepatocytes. M1 was also detected at similar amounts in rat and rabbit incubations, why it can be concluded that no human-specific metabolites were observed. These *in vitro* results in hepatocytes are comparable to the situation in rat metabolism studies *in vivo*, where about 50 % of IKI-220 is excreted unchanged and a single metabolite, TFNA-AM, was found quantitatively.	-	dRAR: B.6.1.2.3, 2020

2.6.1.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Six studies have been performed to investigate the oral absorption, distribution, metabolism and excretion of flonicamid (IKI-220) in Sprague-Dawley rats and these studies were evaluated in the DAR (2005) (B.6.1.1.7 only partly). Initially, a pilot excretion and pharmacokinetics study was performed using oral dose levels in the range 0.85 – 50 mg/kg bw in which expired air was collected for 48 h post-treatment. Since no radioactivity was detected in the 24 – 48 h samples, expired air was not collected in the subsequent main studies. [^{14}C]IKI-220 labelled in the pyridyl-3 position was used for the studies in which single oral doses of 2 or 400 mg/kg bw, or multiple doses of 2 mg/kg bw, were investigated.

Flonicamid is rapidly and almost completely absorbed (> 93%) from the gastrointestinal tract of the rat and is rapidly eliminated from plasma following single oral doses of 2 or 400 mg/kg and multiple oral doses of 2 mg/kg for 14 consecutive days. Excretion occurs predominantly in the urine, none is detected in expired air. Total urinary elimination after 7 days amounts to 72.0 - 77.8% of administered dose for both sexes in the dose range 2 – 400 mg/kg bw. Fecal elimination amounts to no more than 6.4%, almost all of which is eliminated within 48 h. Biliary elimination is a minor route of excretion after single oral doses of 2 or 400 mg/kg bw and only up to 4.63% of administered dose is eliminated by this route during the 48 h post administration. With the exception of slightly prolonged biliary excretion in males at 400 mg/kg bw, the dose level and sex of the animals do not influence the extent and time course of biliary elimination.

Elimination of flonicamid follows first order kinetics and the pharmacokinetics is not markedly influenced by sex or dose level in the range of 2.0 – 400 mg/kg bw. However, at 400 mg/kg bw, males exhibit a slight prolongation of T_{max} (0.9 h vs. 0.5 h) and $T_{1/2}$ of elimination (11.6 h vs. 4.5 - 6.8 h) due to an extended plateau in plasma concentration. The AUC values are approximately proportional to dose level in both sexes. The AUC ratios are 263 and 265 in males and females, respectively, for a dose ratio of 200. The maximum plasma concentrations (C_{max}) of radioactivity are comparable in both sexes at 2 mg/kg (2.07/2.11 µg-eq/g), but at 400 mg/kg the C_{max} for females (367.6 µg-eq/g) is higher than for males (249.6 µg-eq/g) which is considered to reflect the prolonged plateau in plasma concentrations in males at 400 mg/kg bw. The ratio of C_{max} values shows an approximate proportionality to dose, 120 and 174 in males and females, respectively, but the ratio in males is depressed as a consequence of the prolonged plateau in plasma concentrations at 400 mg/kg bw.

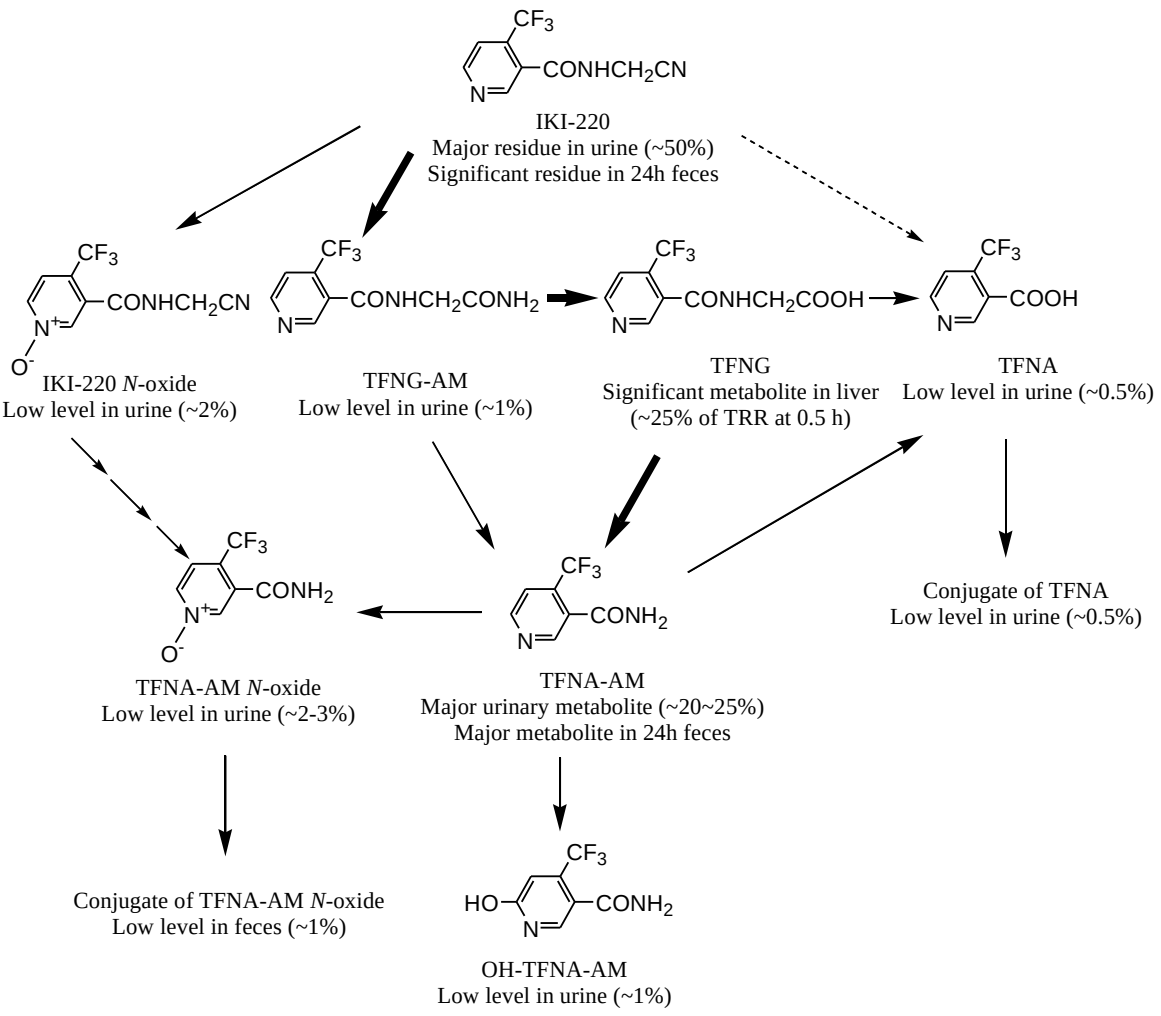
The tissue distribution of flonicamid is not affected by dose level or sex. Following a single oral dose of [^{14}C]IKI-220, radioactivity is rapidly and widely distributed throughout the tissues of the body. Tissue levels are broadly in line with blood concentration, but higher peak concentrations occur in liver, kidneys, adrenals and thyroid tissue. Radioactivity is rapidly cleared from the tissues and there is no accumulation in any tissue. The tissue distribution of [^{14}C]IKI-220 is not affected by dose level or sex.

Multiple administrations (14+1) of low dose (2 mg/kg bw) of ^{14}C]IKI-220 are rapidly absorbed from the gastrointestinal tract and rapidly eliminated from the plasma and tissues, predominantly in the urine. Radioactivity is rapidly and widely distributed throughout the tissues of the body broadly in line with blood concentration, but higher peak concentrations occur in liver, kidneys, adrenals, thyroid and ovarian tissue. There is no accumulation of

radioactivity in any tissue. The rate of oral absorption, the tissue distribution and the route and rate of excretion of [^{14}C]IKI-220 are not affected by treatment regimen or sex.

The metabolic profile in urine is generally quantitatively and qualitatively similar between the sexes and after single and multiple doses of 2 mg/kg bw and in general the induction of metabolism is low. The major urinary residue is IKI-220 parent compound which accounts for up to 72% of administered dose after 48 h. A major urinary metabolite is TFNA-AM, which occurs at up to 27.3% of administered dose. All other metabolites each occur at ≤ 3.7% of administered dose. IKI-220 is the predominant residue in bile, but all metabolites and parent compound each account for ≤ 3.3% of administered dose. The metabolic profile in the liver of males is generally quantitatively and qualitatively similar after single and multiple treatments of 2 mg/kg bw. IKI-220 parent compound is the predominant residue at ≤ 2.35% of administered dose. Two significant, but minor, metabolites are also formed, TFNG at ≤ 1.10% and TFNA-AM at ≤ 1.19% of administered dose. The predominant residues in faeces are IKI-220 parent compound, TFNA-AM and TFNA, but none accounts for more than 1.2% of administered dose. TFNA-AM N-oxide conjugate also occurs after administration of 400 mg/kg bw at up to 1.0% of administered dose.

Proposed metabolic pathway for flonicamid in rat



Three new *in vitro* comparative metabolism studies (dRAR: B.6.1.2.1 - B.6.1.2.3) not previously evaluated were performed for this renewal evaluation in order to comply with the data requirements of Reg (EU) 283/2013. In these studies both human and different animal (mouse, rat, dog and rabbit) derived liver S9 fractions and hepatocytes were used. IKI-220 remained mainly as unchanged parent following liver S9 incubations in each of the tested species. Similarly the test substance was slowly metabolised by hepatocytes in all tested species. Based on the studies no human-specific metabolites were detected.

2.6.2 Summary of acute toxicity

2.6.2.1 Acute toxicity - oral route [equivalent to section 10.1 of the CLH report template]

Table 16: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD TG 401 (1987) GLP Acceptable study	Sprague-Dawley rats 2 rats/sex/dose level in the range finding study; 5 rats/sex/dose level in the main study	IKI-220 technical, purity 98.7%	Range finding study: 1000, 2000 or 5000 mg/kg bw Main study: 625, 1250, 2500 or 5000 mg/kg bw Single oral gavage	Males: 884 mg/kg bw Females: 1768 mg/kg bw	dRAR: B.6.2.1.1, 2001

Table 17: Summary table of human data on acute oral toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data available				

Table 18: Summary table of other studies relevant for acute oral toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other data available				

2.6.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

No new acute oral toxicity data was submitted for the ongoing re-evaluation of flonicamid. The LD_{50} values were calculated as 884 and 1768 mg/kg for males and females, respectively.

The main clinical signs recorded in rats dying within 4 h post dosing included decreased activity, loss of mobility, laboured breathing, prostration, convulsions, cold to touch and hypersensitivity to noise; subsequently, clinical signs occurred mainly in females at all dose levels and comprised laboured breathing, rales, prostration, cold to touch,

tremors, anogenital staining and few or no feces; ataxia was a common finding in females. Surviving rats gained weight during the observation period, with the exception of 1 female in each of the 625 mg/kg and the 2500 mg/kg groups that had weight loss at day 14. Gross lesions at necropsy considered to be treatment-related were confined to dark red-black foci on the serosal surface of the stomach in 1 male at 1250 mg/kg, 2 females at 2500 mg/kg and 2 females at 5000 mg/kg. All other gross findings were non-specific (diffuse dark red color in lungs of 1 female, red discharge and/or staining in the anogenital area in 2 females, dark red black spots in the thymus in 2 females).

2.6.2.1.2 Comparison with the CLP criteria regarding acute oral toxicity

The acute oral LD_{50} values of flonicamid for male and female rats were 884 and 1768 mg/kg bw, respectively. Classification for acute oral toxicity in category 4 under Regulation (EC) No 1272/2008 (Section 3.1) is required for substances with an acute oral LD_{50} value (or estimated LD_{50} value) of $300 < ATE \leq 2000$ mg/kg bw. The lowest acute oral LD_{50} for flonicamid was 884 mg/kg bw.

2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity

This hazard class was not re-assessed in the current dossier as no new acute oral toxicity data was submitted for the ongoing AIR4 evaluation. The acute oral LD_{50} values for male and female rats were 884 and 1768 mg/kg bw, respectively. Since the lowest LD_{50} is 884 mg/kg bw for male rats, the ATE (oral exposure) for flonicamid can be set at 884 mg/kg bw. Based on the available data flonicamid meets the criteria to be classified for acute oral toxicity Acute Tox.4 , H302. Hence, the current harmonised classification Acute Tox. 4; H302 (Harmful if swallowed) is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F). The proposed ATE value (oral exposure) is 884 mg/kg bw.

2.6.2.2 Acute toxicity - dermal route [equivalent to section 10.2 of the CLH report template]

Table 19: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD TG 402 (1987) GLP Acceptable study	Sprague-Dawley rats 2 rats/sex in the range finding study; 5 rats/sex in the main study	IKI-220 technical, purity 98.7%	A single dermal application of 5000 mg/kg bw, (24 h)	Both sexes: >5000 mg/kg bw	dRAR: B.6.2.2.1, 2000

Table 20: Summary table of human data on acute dermal toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data available				

Table 21: Summary table of other studies relevant for acute dermal toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other data available				

2.6.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

No new acute dermal toxicity data was submitted for the ongoing re-evaluation of flonicamid. The acute dermal LD_{50} value of flonicamid for male and female rats was >5000 mg/kg bw.

No deaths occurred during the observation periods, neither in the range finding nor the main study. Minor, treatment-related clinical signs were seen in both sexes and included coloured material around the nose and eyes (until day 3 and day 1, respectively), and anogenital staining (on day 1 only). No treatment-related clinical signs occurred after day 3. Body weights were increased in all rats at end of the 14 day observation period (males: 38.6 ± 15.8 g; females: 21.2 ± 10.8 g), with the exception of one male that showed a weight loss of 3 g during week 1 post dosing. There were no gross lesions at necropsy other than one male with localised hair loss.

2.6.2.2.2 Comparison with the CLP criteria regarding acute dermal toxicity

The acute dermal LD_{50} value of flonicamid for male and female rats was >5000 mg/kg bw. Classification for acute dermal toxicity under CLP Regulation (EC) No 1272/2008 (Section 3.1) is required for substances with an acute dermal LD_{50} value of ≤ 2000 mg/kg bw. As flonicamid has an acute dermal LD_{50} value of > 2000 mg/kg, no classification is required for acute dermal toxicity.

2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

This hazard class was not assessed in the current dossier as no new acute dermal toxicity data was submitted for the ongoing AIR4 evaluation. The dermal LD_{50} value to rats was was estimated to be greater than 5000 mg/kg bw. Hence, no classification for acute dermal toxicity is warranted and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.2.3 Acute toxicity - inhalation route [equivalent to section 10.3 of the CLH report template]

Table 22: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
OECD TG 403 (1981) GLP Acceptable study	Sprague-Dawley rats 5 rats/sex	IKI-220 technical, purity 98.7% MMAD: 4.8 ± 2.4µm	4.9 mg/L 4 hours, nose only	> 4.9 mg/L	dRAR: B.6.2.3.1, 2000

Table 23: Summary table of human data on acute inhalation toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data available				

Table 24: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other data available				

2.6.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

No new acute inhalation toxicity data was submitted for the ongoing re-evaluation of flonicamid. The inhalation LC_{50} value of flonicamid for male and female rats was > 4.9 mg/L.

No deaths occurred in any groups and no treatment-related effects on body weigh gain, food and water consumption were observed. Clinical signs included exaggerated breathing in some treated rats (from 30 min after the start of exposure and in all treated rats within 3 h, persisting until day 2 of the observation period) and brown staining around the snout and jaws in all treated rats post-exposure (persisting up to day 2 in females). All other clinical signs (soiling of fur with excreta) occurred in both treated and control rats and were therefore not considered as treatment-related. There were no treatment related macroscopic findings at necropsy, but 2 treated rats showed congestion of the lungs (minimal in 1 male, severe with small dark foci on the lungs in the other male). The weights of the lungs, liver and kidneys were not affected by exposure to the test substance.

2.6.2.3.2 Comparison with the CLP criteria regarding acute inhalation toxicity

The inhalation LC_{50} value of flonicamid was > 4.9 mg/L for males and females combined. Classification for acute inhalation toxicity under Regulation (EC) No 1272/2008 (Section 3.1 of Annex I) is required for substances (dusts and mists) with an acute inhalation LC_{50} value of ≤ 5 mg/L. Although the mean measured concentration during the 4 h inhalation exposure was marginally lower (4.9 mg/L) than the limit concentration of 5 mg/L for classification, no death or adverse clinical signs were seen and hence it can be concluded that the 4-h LC_{50} value is > 4.9 mg/L air by nose-only inhalation of aerosol particles in the respirable range. Therefore classification is not required for acute inhalation toxicity.

2.6.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

This hazard class was not re-assessed in the current dossier as no new acute inhalation toxicity data was submitted for the ongoing AIR4 evaluation. The inhalation LC_{50} value to rats was estimated to be greater than 4.9 mg/L air for males and females. Hence, no classification for acute inhalation toxicity is warranted and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.2.4 Skin corrosion/irritation [equivalent to section 10.4 of the CLH report template]

Table 25: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Results** **- Observations and time point of onset[2]** **- Mean scores/animal** **- Reversibility**	**Reference**
OECD TG 404 (1992)	Six male New Zealand	IKI-220 technical,	0.5 g of test substance	All six rabbits survived until termination and no abnormal clinical or dermal findings were observed. No erythema/eschar formation or	dRAR: B.6.2.4.1, 2000

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results - Observations and time point of onset[2] - Mean scores/animal - Reversibility	Reference
GLP Acceptable study	White rabbits	purity 98.7%	wettened with 1 ml distilled water 4 h, skin reactions evaluated at 1 h, 24 h, 48 h, and 72 h.	oedema was observed in the rabbits throughout the study which was therefore terminated after the 72 h examination. The EU primary irritation indices were 0.0 for both erythema/eschar formation and oedema.	

Table 26: Summary table of human data on skin corrosion/irritation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data available				

Table 27: Summary table of other studies relevant for skin corrosion/irritation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other data available				

2.6.2.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

No new skin irritation data was submitted for the ongoing re-evaluation of flonicamid. Six adult male New Zealand White rabbits were applied with 0.5 g of IKI-220 technical wetted with approx. 1 mL distilled water to the clipped intact thoracic dorsal skin (6 cm^2) under semi-occlusive dressing for 4 h. As a vehicle control, distilled water was applied to a similar area of skin on the opposite side of each rabbit under semi-occlusive dressing. After removal of the patch, each test and control site was wiped with warm water. All six rabbits survived until termination and no abnormal clinical or dermal findings were observed. No erythema/eschar formation or oedema was observed in the rabbits throughout the study which was therefore terminated after the 72 h examination. The EU primary irritation indices were 0.0 for both erythema/eschar formation and oedema.

2.6.2.4.2 Comparison with the CLP criteria regarding skin corrosion/irritation

Classification of a substance as skin corrosive (Category 1) is required if destruction of skin tissue (visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours. Classification of a substance for skin irritation (Category 2) is required on the basis of an animal study showing a mean value of ≥ 2.3 - ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from three consecutive days after the onset of skin reactions. Classification is also required for inflammation that persists to the end of the observation period (normally 14 days) in at least 2 animals, particularly taking into account findings such as alopecia, hyperkeratosis, hyperplasia, and

scaling. Classification may also be required in some cases where there is pronounced variability of response among animals, with very definite positive effects related to exposure in a single animal but less than the criteria listed above. None of the skin corrosion/irritation criteria for categories 1 or 2 are fulfilled by the flonicamid skin irritation data.

2.6.2.4.3 Conclusion on classification and labelling for skin corrosion/irritation

This hazard class was not re-assessed in the current dossier as no new skin corrosion/irritation toxicity data was submitted for the ongoing AIR4 evaluation. No classification is warranted for skin irritation according to the CLP Regulation (EC) No. 1272/2008 and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.2.5 Serious eye damage/eye irritation [equivalent to section 10.5 of the CLH report template]

Table 28: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels duration of exposure**	**Results** **- Observations and time point of onset[2]** **- Mean scores/animal** **- Reversibility**	**Reference**
OECD TG 405 (1987) GLP Acceptable study Topical anesthetics and systemic analgesics were not used in this study	Six male New Zealand White rabbits	IKI-220 technical, purity 98.7%	Single instillation into the lower conjunctival sac of the right eye of 0.1 mL (approx. 70 mg), observation at 1 h, 24 h, 48 h and 72 h after instillation	All rabbits survived until termination and no corneal and iridal effects were seen in any of the animals at any observation point. Conjunctival effects, including redness (grade 2), chemosis (grades 1-2) and discharge (grades 1-3), were observed in all animals at 1 h post application. Redness became less severe at 24 h post application and completely cleared within 72 h post application. Chemosis cleared in most of the animals within 24 h post application. Discharge cleared in all the animals within 24 h post application. No additional ocular findings or non-ocular effects were observed in any of the animals throughout the study. The individual mean 24 – 72 h scores did not exceed 0.7 for conjunctival effects. Ocular examinations using fluorescein, revealed no corneal epithelial damage in any of the animals at any observation. Therefore, mean scores for corneal and iridial effects in all animals were zero.	dRAR: B.6.2.5.1, 2000

Table 29: Summary table of human data on serious eye damage/eye irritation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No human data available				

Table 30: Summary table of other studies relevant for serious eye damage/eye irritation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other data available				

2.6.2.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

No new eye irritation data was submitted for the ongoing re-evaluation of flonicamid. Six male New Zealand White rabbits were each given a single instillation into the lower conjunctival sac of the right eye of 0.1 mL (approx. 70 mg) of IKI-220 technical. The upper and lower eyelids were held together immediately after administration to minimize the loss of test material. The left eye remained untreated to serve as a reference control. All rabbits were observed twice daily for mortality/morbidity throughout the study period and all were sacrificed without necropsy. Both eyes of all rabbits were examined for ocular irritation reactions approx. 1 h, 24 h, 48 h and 72h after instillation. All rabbits survived until termination and no corneal and iridal effects were seen in any of the animals at any observation point. Conjunctival effects, including redness (grade 2), chemosis (grades 1-2) and discharge (grades 1-3), were observed in all animals at 1 h post application. Redness became less severe at 24 h post application and completely cleared within 72 h post application. Chemosis cleared in most of the animals within 24 h post application. Discharge cleared in all the animals within 24 h post application. No additional ocular findings or non-ocular effects were observed in any of the animals throughout the study. The individual mean 24 – 72 h scores did not exceed 0.7 for conjunctival effect. No corneal epithelial damage was observed in any of the animals at any observation. Therefore, mean scores for corneal and iridial effects in all animals were zero.

2.6.2.5.2 Comparison with the CLP criteria regarding serious eye damage/eye irritation

The individual mean 24 – 72 h scores did not exceed 0.7 for conjunctival effect. No corneal epithelial damage was observed in any of the animals at any observation. Therefore, mean scores for corneal and iridial effects in all animals were zero. Since the mean scores after 24 to 72 hours for corneal opacity, iritis, conjunctival redness and conjunctival oedema were below the criteria for classification and labelling in eye irritation category 2, flonicamid should not be classified for eye corrosion/irritation in accordance with CLP Regulation (EC) No 1272/2008.

2.6.2.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

This hazard class was not re-assessed in the current dossier as no new eye irritation data was submitted for the ongoing AIR4 evaluation. No classification is warranted for eye irritation according to the CLP Regulation (EC) No. 1272/2008 and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.2.6 Respiratory sensitisation [equivalent to section 10.6 of the CLH report template]

No data on respiratory sensitisation is available. Flonicamid showed low inhalation toxicity and skin sensitisation (see below), hence, it is unlikely that it would induce respiratory sensitisation.

Table 31: Summary table of animal studies on respiratory sensitisation

Method, guideline, deviations[1] if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
No animal data available					

Table 32: Summary table of human data on respiratory sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data available				

Table 33: Summary table of other studies relevant for respiratory sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Medical supervision statement	Flonicamid	Yearly medical examination of workers involved in the synthesis of flonicamid	No health problems related to the manufacturing operations have been reported between 2006-2020.	dRAR B.6.9.1

2.6.2.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No relevant *in vitro, in vivo* or human data is available for flonicamid for classification of respiratory sensitisation. No evidence of respiratory tract irritation or functional impairment of the respiratory system was seen in the acute rat inhalation toxicity study.

The notifier has provided a statement on medical supervision of IKI-220 production workers. No health problem related to the manufacturing operations has been reported in the detailed periodic medical examinations (interview by doctor, chest X-ray test, urinalysis, haematology, liver function test, renal function test, lipid metabolism, glucose metabolism and others) for the workers engaged in IKI-220 production.

Flonicamid has no skin sensitizing potential. According to the CLP criteria, a substance which is negative in a skin sensitisation assay, most probably also lacks the potential for respiratory allergy.

2.6.2.6.2 Comparison with the CLP criteria regarding respiratory sensitisation

In the absence of relevant human or non-human data and supported by the findings of low systemic toxicity with skin and mucous membranes, flonicamid is not classified as a respiratory sensitiser.

2.6.2.6.3 Conclusion on classification and labelling for respiratory sensitisation

There is no positive evidence of a respiratory sensitisation potential of flonicamid in humans. In addition, the absence of relevant respiratory sensitisation data and with the support of negative acute inhalation and skin sensitisation data, flonicamid does not require classification for respiratory sensitisation according toRegulation (EC) No 1272/2008.

2.6.2.7 Skin sensitisation [equivalent to section 10.7 of the CLH report template]

Table 34: Summary table of animal studies on skin sensitisation

Method, guideline, deviations[1] if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels duration of exposure**	**Results**	**Reference**
OECD TG 406 (1992) GLP Acceptable study	Guinea pigs of the Hartley albino strain	IKI-220 technical, purity 98.7%	4 range finding experiments with a total of 16 guinea pigs: intradermal injection with 0.1 mL of the vehicle alone and 0.1, 1, 5 and 10% IKI-220 (w/v) in mineral oil, or topical application of the vehicle and 10, 25, 50 and 75% IKI-220 (w/v) in mineral oil Main study Intradermal injection with 10% w/v in mineral oil Topical application with 50% (w/v) in mineral oil Challenge application with 10% (w/v) in mineral oil	Range finding study: concentrations of IKI-220 selected for the main study were 10% (w/v) for intradermal induction and 50% (w/v) for topical induction application and 10% for topical challenge. Main study: Following intradermal induction injection, the IKI-220 test animals showed localised dermal reactions at all sites ranging from moderate (grade 2) to intense (grade 3) erythema, with oedema, but without necrosis or ulceration. Following topical induction application, 8 of the 20 IKI-220 test guinea pigs and 2 of the 20 controls guinea pigs exhibited mild erythema but without further dermal reactions. After challenge, 2/20 IKI-220 test animals showed mild erythema at 24 and 48 h after challenge and 2/20 control animals showed mild erythema at 48 h only.	dRAR: B.6.2.6.1, 2000

Table 35: Summary table of human data on skin sensitisation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No human data available				

Table 36: Summary table of other studies relevant for skin sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other data available				

2.6.2.7.1 Short summary and overall relevance of the provided information on skin sensitisation

No new skin sensitisation data was submitted for the ongoing re-evaluation of flonicamid.

The skin sensitization potential of flonicamid in guinea pigs was examined following intradermal and topical exposure using the Magnusson & Kligman maximisation method. 10-20 males guinea pigs of the Hartley albino strain were used. Dinitrochlorobenzene was used as positive control and the Freund's Complete Adjuvant (FCA) was used for preparation of mixtures of the test substance, positive control and vehicle control during the intradermal induction phase of the sensitisation study.

Range finding study: The concentrations of flonicamid selected for the main study were 10% (w/v) for intradermal induction and 50% (w/v) for topical induction application and 10% for topical challenge, mineral oil being selected as the vehicle. From a separate experiment using 0.1, 0.15 and 0.20% DNCB (w/v) in mineral oil, the selected concentrations of DNCB were 0.1% for intradermal and topical inductions and 0.08% for challenge.

Main study: All guinea pigs survived and all gained weight throughout the study period. Following intradermal induction injection, the IKI-220 test animals showed localised dermal reactions at all sites ranging from moderate (grade 2) to intense (grade 3) erythema, with oedema, but without necrosis or ulceration. The IKI-220 control animals showed moderate to intense erythema at all sites in response to FCA with 2 animals also showing necrosis after 48 h. The mineral oil vehicle produced mild (grade 1) erythema only. Following topical induction application, 8 of the 20 IKI-220 test guinea pigs and 2 of the 20 control guinea pigs exhibited mild erythema but without further dermal reactions. On the other hand, 9/10 DNCB test animals showed intense erythema (score 3) at 24 and 48 h after patch removal, with oedema, necrosis and eschar formation in most animals at 24 – 48 h. After challenge, 2/20 IKI-220 test animals showed mild erythema at 24 and 48 h after challenge and 2/20 control animals showed mild erythema at 48 h only. On the other hand, DNCB produced mild to intense erythema in 9 animals at 24 h and 10 animals at 48 h, compared to a zero incidence of positive reactions in the DNCB conttrol group.

2.6.2.7.2 Comparison with the CLP criteria regarding skin sensitisation

According to the CLP Regulation (EC) No. 1272/2008, a sensitising potential of a substance is identified if a significant effect has been obtained in an acceptable *in vivo* test. In the guinea pig maximisation test erythema observed (Score ≥ 1) in ≥ 30% of the test animals is considered as a positive result. IKI-220 technical induced a mild erythema in 10% of the guinea pigs which is below the 30% threshold for classification.

2.6.2.7.3 Conclusion on classification and labelling for skin sensitisation

This hazard class was not re-assessed in the current dossier as no new skin sensitisation data was submitted for the ongoing AIR4 evaluation. No classification is warranted for skin sensitisation according to the CLP Regulation (EC) No. 1272/2008 and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.2.8 Phototoxicity

A new phototoxicity study was submitted for this AIR4 evaluation which has not previously been evaluated.

Table 37: Summary table of studies on phototoxicity

Method, guideline, deviations[1] if any	Test substance	Dose levels duration of exposure	Results	Reference
In vitro 3T3 neutral red uptake phototoxicity test OECD TG 432 (2004) GLP Acceptable study	IKI-220 technical, purity 99.6%	0.0128, 0.064, 0.32, 1.6, 8 40, 200, and 1000 µg/mL, 1 h incubation with test item, half of the samples were irradiated for 50 min, o/n incubation, after 18-22 h treatment with neutral red solution for 3 h	An IC_{50} value could not be obtained for IKI-220 in the absence and presence of UVA, since at the highest concentration of 1000 µg/mL, no reduction in neutral red uptake was measured. Without IC_{50} values it was neither possible to obtain a PIF value. No phototoxic potential of IKI-220 was demonstrated in this *in vitro* 3T3 NRU phototoxicity test and hence no classification for phototoxicity is warranted.	dRAR: B.6.2.7.1, 2016

Table 38: Summary table of human data on phototoxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data available				

Table 39: Summary table of other studies relevant for phototoxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other data available				

No phototoxic potential of IKI-220 was demonstrated in the *in vitro* 3T3 NRU phototoxicity test and hence no classification for phototoxicity is warranted.

2.6.2.9 Aspiration hazard [equivalent to section 10.13 of the CLH report template]

No data on aspiration hazard are available. Flonicamid is not a hydrocarbon.

Table 40: Summary table of evidence for aspiration hazard

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available				

2.6.2.9.1 Short summary and overall relevance of the provided information on aspiration hazard

No specific studies on aspiration hazard are available. However, on the basis of existing animal studies and expert judgment that takes into account chemical structure (flonicamid is not a hydrocarbon) aspiration hazard is not expected.

2.6.2.9.2 Comparison with the CLP criteria regarding aspiration hazard

No relevant data on aspiration hazard are available. An aspiration hazard is identified when the kinematic viscosity is ≤ 20.5 mm2 /s at 40 °C and the substance is a hydrocarbon. Measurements for kinematic viscosity are not available for flonicamid and it is not a hydrocarbon. Therefore, based on the available information, an aspiration hazard is not expected.

2.6.2.9.3 Conclusion on classification and labelling for aspiration hazard

Based on lack of relevant hazard data and due to the fact that flonicamid is not a hydrocarbon, a classification for aspiration hazard according to CLP Regulation (EC) No 1272/2008 is not warranted.

2.6.2.10 Specific target organ toxicity-single exposure (STOT SE) [equivalent to section 10.11 of the CLH report template]

The acute toxicity studies which are relevant for the assessment of the specific target organ toxicity of IKI-220 after single exposure are assessed in the acute toxicity section 2.6.2. In addition, an acute neurotoxicity study was performed (assessed in section 2.6.7).

Table 41: Summary table of animal studies on STOT SE (specific target organ toxicity-single exposure)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
Acute oral, dermal and inhalation toxicity studies in rats Acceptable studies	IKI-220 technical, purity 98.7%, assessed in acute toxicity section 2.6.2	No specific target organ toxicity has been identified after single exposure.	Assessed in acute toxicity sections 2.6.2.1 – 2.6.2.3
Acute oral neurotoxicity study in rats (single oral gavage) Acceptable study	IKI-220 technical, purity 98.7%, assessed in neurotoxicity section 2.6.7	No specific target organ toxicity has been identified after single exposure.	Assessed in neurotoxicity section 2.6.7

Table 42: Summary table of human data on STOT SE (specific target organ toxicity-single exposure)

Type of data/report	**Test substance**	**Route of exposure Relevant information about the study (as applicable)**	**Observations**	**Reference**
No human data available.				

Table 43: Summary table of other studies relevant for STOT SE (specific target organ toxicity-single exposure)

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other data available.				

2.6.2.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure (STOT SE)

No new data concerning specific target organ effects after single exposure was submitted for the ongoing re-evaluation of flonicamid.

In the acute oral toxicity study, no specific effects on target organs were observed. The studies on acute dermal and inhalation toxicity demonstrated a low acute toxic potential of flonicamid with a dermal LD_{50} value of > 5000 mg/kg bw and an inhalation LC_{50} value of > 4.9 mg/L. In the acute oral neurotoxicity study no neurohistopathological changes in central and peripheral nervous tissue were observed and no signs of neurobehavioral toxicity was evident.

2.6.2.10.2 Comparison with the CLP criteria regarding STOT SE (specific target organ toxicity-single exposure)

According to the CLP Regulation (EC) No 1272/2008, specific target organ toxicity (single exposure) is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance or mixture (i.e. significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not covered by acute toxicity, skin corrosion / irritation, eye damage / irritation, respiratory or skin sensitisation, genotoxicity, carcinogenicity and reproductive toxicity should be taken into consideration). There was no indication of any sex-specific susceptibility in any of the acute studies. No specific, non lethal target organ toxicity, or other significant health effects that can impair function, either reversible or irreversible, immediate and/or delayed, arising from a single exposure were seen in the acute toxicity studies with flonicamid, and therefore flonicamid does not warrant classification in category STOT SE.

2.6.2.10.3 Conclusion on classification and labelling for STOT SE (specific target organ toxicity-single exposure)

This hazard class was not re-assessed in the current dossier as no new specific target organ toxicity data-single exposure data was submitted for the ongoing AIR4 evaluation. No effects observed in the acute toxicity studies were observed that would warrant classification for STOT SE according to the CLP Regulation (EC) No. 1272/2008 and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.3 Summary of repeated dose toxicity (short-term and long-term toxicity) [section 10.12 of the CLH report]

2.6.3.1 Specific target organ toxicity-repeated exposure (STOT RE) [equivalent to section 10.12 of the CLH report template]

Table 44: Summary table of animal studies on repeated dose toxicity (short-term and long-term toxicity) STOT RE (specific target organ toxicity - repeated exposure)

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
28-day oral (dietary) toxicity No guideline referred (dose range finding study) Groups (6/sex) of male and female Wistar rats Deviations: Histopathological examination was performed on liver, kidney and spleen only GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 50, 100, 500, 1000, 5000 ppm Corresponding dietary intake: 0, 3.613, 7.47, 36.45, 73.8 and 353.4 mg/kg bw/d Females: 0, 100, 500, 1000, 5000, 10000 ppm Corresponding dietary intake: 0, 8.36, 41.24, 81.9, 372.6 and 642 mg/kg bw/d Duration of exposure: 28 days	The NOEL was 50 and 1000 ppm in males and females, respectively (corresponding to 3.6 and 81.9 mg/kg bw/d in males and females, respectively). The male NOEL is based on increased hyaline droplet deposition in the kidneys at doses ≥ 100 ppm. The female NOEL is based on liver functional changes, enlargement and hepatocellular hypertrophy at 5000 ppm, and reduced weight gain and food consumption at 10000 ppm. As increased hyaline droplet formation in the kidneys has been shown to be mediated by the male rat-specific protein, α2μglobulin, a relevant NOAEL in the male for all other effects (reduced weight gain and food consumption, liver functional changes, enlargement and hepatocellular hypertrophy, and granular casts in the kidneys at 5000 ppm) could be set at 1000 ppm (73.8 mg/kg bw/d).	dRAR: B.6.3.1.1, 2002
28-day oral toxicity, dose range finding study OECD TG 409 (1998) Groups (2/sex) of beagle dogs Deviations: The duration of treatment was 28 or 35 days and the number of animals	IKI-220 technical, purity 98.7% Dose levels: 2, 10 and 50/20 mg/kg bw/d. One male died after one dose of 50 mg/kg bw/day why the group was taken off dose for 6 days and the treatment re-started at 20 mg/kg bw/d.	The highest dose, 50 mg/kg bw/d clearly exceeded the maximum tolerated dose (MTD) level. The NOAEL was established as 20 mg/kg bw/d, based on the absence of unequivocal treatment-related effects.	dRAR: B.6.3.1.2, 2001

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
used was 2/sex/group GLP Acceptable study	Duration of exposure: 28 days		
90-day oral toxicity (rats) OECD TG 408 (1998) Groups (12/sex) of Wistar rats Deviations : Endocrine sensitive endpoints were not measured including at least serum total T4, T3 and TSH GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 50, 200, 1000 and 2000 ppm (corresponding to 0, 3.079, 12.11, 60.0 and 119.4 mg/kg bw/d) Females: 0, 200, 1000 and 5000 ppm (corresponding to 0, 14.52, 72.3 and 340.1 mg/kg bw/d) Duration of exposure: 13 weeks	As the increased hyaline droplet formation in kidneys seen only in male mice at doses ≥ 200 ppm is considered to be related to the male rat-specific protein, α2u-globulin, the relevant NOAEL for males was 1000 ppm (equal to 60.0 mg/kg bw/d) based on reduced food consumption, reduced plasma triglyceride concentration and hepatocellular hypertrophy at 2000 ppm. The NOAEL in females was 1000 ppm (equal to 72.3 mg/kg bw/d) based on the occurrence of reduced food consumption, reduced plasma triglyceride concentration, liver enlargement, hepatocellular hypertrophy and cytoplasmic vacuolation of renal tubular cells at 5000 ppm.	dRAR: B.6.3.2.1, 2002
90-day oral toxicity (mice), Deviations : Designed as a dose ranging study for subsequent carcinogenicity studies; no ophthalmoscopy was performed, only liver, kidneys and spleen were weighed at necropsy and only bone marrow, liver, kidneys, gross lesions and	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 100, 1000 and 7000 ppm (corresponding to 0, 15.3, 153.9 and 1069 mg/kg bw/d) Females: 0, 100, 1000 and 7000 ppm (corresponding to	The NOEL was 100 ppm for both sexes (15.3 and 20.1 mg/kg bw/d in males and females, respectively) based on the occurrence of hepatocellular hypertrophy in males and increased splenic extramedullary hematopoiesis in both sexes at 1000 ppm, and additionally changes in electrolyte homeostasis and anemia coupled with histopathological alterations in both sexes and hepatocellular hypertrophy in females at 7000 ppm	dRAR: B.6.3.2.2, 2001

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
spleen were subjected to histopathological evaluation OECD TG 408 (1998) Groups (10/sex) of Swiss-derived mice [redacted]:CD-1®[redacted] strain) GLP Acceptable study	0, 20.1, 191.5 and 1248 mg/kg bw/d) Duration of exposure: 13 weeks		
90-day oral toxicity (beagle dogs) OECD TG 409 (1998) Groups of 4/sex beagle dogs GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 3, 8 and 20 mg/kg bw/d Females: 0, 3, 8, 20 and 50 mg/kg bw/d Duration of exposure: 90 days	50 mg/kg bw/d to females clearly exceeded the MTD. The relevant NOAEL was 8 mg/kg bw/d in both sexes, based on the occurrence of reduced bw gain and food consumption in both sexes and reduced thymus weight in males at 20 mg/kg bw/d	dRAR: B.6.3.2.3, 2001
52-week oral toxicity (beagle dogs) OECD TG 409 (1998) Groups of 6/sex beagle dogs GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: Males and females: 0, 3, 8, 20 and 50 mg/kg bw/d Duration of exposure: 52 weeks	No specific target organs were affected. The NOAEL was 8 mg/kg bw/d in both sexes, based on the occurrence of hematological changes suggesting mild anemia in both sexes, and reduced bw gain in females, at 20 mg/kg bw/day.	dRAR: B.6.3.2.4, 2003
28-day dermal toxicity (rats)	IKI-220 technical, purity 98.7%	No clear treatment-related effects were observed in either sex or at any dose level. Therefore, the NOAEL was higher than 1000	dRAR: B.6.3.3.1, 2001

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
OECD TG 410 (1981) Groups of 10/sex Sprague-Dawley derived rats GLP Acceptable study	Dose levels: Males and females: 0, 20, 150 and 1000 mg/kg bw/d Duration of exposure: 28 days	mg/kg bw/d, which was the highest dose tested.	
28-day oral (dietary) immunotoxicity (mice) OPPTS 870.7800 (1998) Female [redacted]:CD1[redacted] mice, 10 mice/group GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: 0, 100, 600, 6000 ppm equal to 0, 23.2, 141.8, 1540.2 mg/kg bw/d Duration of exposure: 28 days	This study was assessed in section 2.6.8.4. No statistically significant increases in spleen cell number or specific activity were observed but treatment-related increases in total spleen activity were seen at all tested doses. As the study was designed to provide information about possible immunosuppression and did not comprehensively assess the immune function, IKI-220 was considered not immunotoxic in female CD-1 mice after 28-days of treatment via diet. The NOAEL for immunosuppression was > 6000 ppm (corresponding to 1540 mg/kg bw/d).	dRAR: B.6.8.2.6, 2012

Table 45: Summary table of human data on repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of data/report	**Test substance**	**Route of exposure** **Relevant information about the study (as applicable)**	**Observations**	**Reference**
No human data available.				

Table 46: Summary table of other studies relevant for repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No other data available.				

2.6.3.1.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure (short-term and long-term toxicity)

Oral route (old, previously evaluated data):

The short-term effects of flonicamid after oral administration were studied in rats (28- and 90-day studies), in dogs (28/35-day, 90-day, and 1-year studies) and in mice (90-day study). The target organs were the liver (rats, mice), the kidney (rats) and the haematopoietic system (anaemia, mice). In the rat studies, the adverse effects on the kidneys were considered to be mediated by the male rat specific protein, alpha-2-microglobulin, and were not regarded as relevant to humans. Therefore, the short-term NOAEL in rats was 60 mg/kg bw/d from the 90-day study. In the dog studies, the relevant NOAEL was 8 mg/kg bw/d, based on reduced body weight gain, reduced thymus weight in males (90-day study), and mild anaemia (1-year study). In the mouse study, the NOAEL was 15.3 mg/kg bw/d based on hepatocellular hypertrophy and splenic extramedullary haematopoiesis (related to anaemia).

Dermal route (old, previously evaluated data):

In the 28-day dermal toxicity study in rats, the NOAEL was higher than 1000 mg/kg bw/d (highest dose tested).

28-day oral immunotoxicity (new study):

No statistically significant increases in spleen cell number or specific activity were observed but treatment-related increases in total spleen activity were seen at all tested doses. As the study was designed to provide information about possible immunosuppression and did not comprehensively assess the immune function, flonicamid was considered not immunotoxic under current test conditions. The NOAEL for immunosuppression was > 6000 ppm (corresponding to 1540 mg/kg bw/d, highest dose tested).

For the purpose of STOT RE classification, adverse findings should generally be at or below the oral guidance value of 100 mg/kg bw/d (for category 2) or 10 mg/kg bw/d (for category 1) obtained from a 90-day rat study. Equivalent guidance values are available for 28-days and should be extrapolated where appropriate (i.e. increased by a value of 3 for a 28-day study). Adjusted guidance values for categories 1 and 2 are summarised in the table below. Adjusted values are calculated according to Haber's rule (Guidance on the Application of the CLP Criteria, Version 5.0 – July 2017; Table 3.16 Equivalent guidance values for 28-day and 90-day studies):

Table 47: Adjusted guidance values for categories 1 and 2

Duration	Adjusted guidance values (mg/kg bw/d)
28-days	Cat 1 = 30 Cat 2 = 300
90-days	Cat 1 = 10 Cat 2 = 100
12-months	Cat 1 = 2.5 Cat 2 = 25

Table 48: Extrapolation of the guidance values given for 90-day repeated-dose studies if studies of greater or lesser duration than 90 days are reported

Study reference	Effective dose (mg/kg/day)	Length of exposure	Guidance value/extrapolated guidance value when extrapolated to the exposure duration other than 90 days	Classification supported by the study
dRAR: B.6.3.1.1, 2002	Males: 353.4 mg/kg bw/day Females: 372.6 mg/kg bw/day	28 days	Cat 1 = 30 Cat 2 = 300	No
dRAR: B.6.3.1.2, 2001	50 mg/kg bw/d	28 days	Cat 1 = 30 Cat 2 = 300	No
dRAR: B.6.3.2.4, 2003	20 mg/kg bw/d	12 months	Cat 1 = 2.5 Cat 2 = 25	No
dRAR: B.6.3.3.1, 2001	No treatment-related findings at the highest dose (1000 mg/kg bw/d)	28 days	Cat 1 = 30 Cat 2 = 300	No
dRAR: B.6.8.2.6, 2012	No treatment-related findings at the highest dose (1540 mg/kg bw/d)	28 days	Cat 1 = 30 Cat 2 = 300	No

Two of the studies reported in Table 48 would fall into category 2 classification based on Haber's rule. In the 28-day (dRAR: B.6.3.1.2, 2001) dose range finding oral study, the highest effective dose, 50 mg/kg bw/d clearly exceeded the maximum tolerated dose (MTD) level. The NOAEL was established as 20 mg/kg bw/d, based on the absence of unequivocal treatment-related effects. In the 52-week oral toxicity study in beagle dogs (dRAR: B.6.3.2.4, 2003) no specific target organs were affected. The NOAEL was 8 mg/kg bw/d in both sexes, based on the occurrence of hematological changes suggesting mild anemia in both sexes, and reduced bw gain in females, at 20 mg/kg bw/day (effective dose). In summary, as no significant toxic effects of relevance to human health, were observed, no STOT RE classification is required.

2.6.3.1.2 Comparison with the CLP criteria regarding STOT RE (specific target organ toxicity-repeated exposure)

According to the CLP Regulation (EC) No 1272/2008, specific target organ toxicity (repeated exposure) is defined as specific, target organ toxicity arising from a repeated exposure to a substance or mixture (i.e. significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed). There was no indication of any sex-specific susceptibility in any of the acute studies. As flonicamid does not exert significant specific target organ toxicity after repeated exposure, no classification in category STOT RE is warrranted in accordance with CLP Regulation (EC) No. 1272/2008.

2.6.3.1.2 Conclusion on classification and labelling for STOT RE (specific target organ toxicity-repeated exposure)

Data on specific target organ toxicity-repeated exposure is mainly based on old data already evaluated during the Annex I review of flonicamid in 2005. One new, not previously evaluated repeated dose study (28-day oral dietary

immunotoxicity in mice; dRAR: B.6.8.2.6, 2012) was submitted for the current evaluation. In this study, effects indicating immunotoxicity were not detected, no statistically significant increases in spleen cell number or specific activity were observed but treatment-related increases in total spleen activity were seen at all tested doses. Based on all the available information, none of the effects observed in the repeated dose toxicity studies would warrant classification for STOT RE according to the CLP Regulation (EC) No. 1272/2008 and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.4 Summary of genotoxicity / germ cell mutagenicity [equivalent to section 10.8 of the CLH report template]

Table 49: Summary table of genotoxicity/germ cell mutagenicity tests *in vitro*

Method, guideline, deviations[1] if any	**Test substance**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations /Results**	**Reference**
Reverse mutation test OECD TG 471 (1997) GLP Acceptable study	IKI-220 technical, purity 98.7%	Based on dose range finding test two independent experiments were performed. <u>Main experiments</u> 1st experiment on all five tester strains: TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2 *uvrA* of *E. coli :* 0, 61.7, 185, 556, 1667 and 5000 µg/plate 2nd experiment: 0, 313, 625, 1250, 2500 and 5000 µg/plate With and without metabolic (S9) activation.	In the preliminary dose range-finding test, precipitation of the test substance and cytotoxicity did not occur in any strain at any dose level with or without metabolic activation. Therefore, 5000 µg/plate was selected as the highest dose level for both main experiments. Main experiments: No precipitation of the test substance and no cytotoxicity occurred in any strain at any dose level with or without metabolic activation. IKI-220 technical did not induce gene mutations in any of the tested strains up to 5000 µg/plate.	dRAR: B.6.4.1.1, 2002
In vitro chromosome aberration test in Chinese hamster CHL cells OECD TG 473 (1997) GLP Acceptable study	IKI-220 technical, purity 98.7%	Based on preliminary cytotoxicity test the applied doses of IKI-220 technical were 573, 1145 and 2290 µg/mL (2290 µg/mL = 10 mM). The ability of test substance to cause chromosomal aberrations in Chinese hamster CHL cells in a short term 6-h exposure (±	In the <u>preliminary cytotoxicity test</u>, no inhibition of cell growth up to 50% of the solvent controls at any concentration for the short-term and continuous exposures was shown. Precipitation of the test substance did not occur in any culture and thus the highest concentration for both the short-term and continuous exposures used in the main test was 2290 µg/mL (corresponding to 10 mM). <u>Main test, 6-h expoure</u>	dRAR: B.6.4.1.2, 2002

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
200 metaphase cells instead of 300 cells were evaluated. Relative Population Doubling (RPD) or Relative Increase in Cell Count (RICC) were not used for evaluation of cytotoxicity.		metabolic activation) and continuous 24-h and 48-h exposures (without metabolic activation) was examined.	No cytotoxicity or test substance precipitation was seen at any of the tested doses. Frequencies of metaphases with structural chromosome aberrations excluding gaps ranged from 0 - 1.0% at all concentrations both ± S9 mix. There were no statistically significant increases in the incidences of aberrations in the test groups when compared with the solvent control group and no statistically significant increases in the frequencies of polyploid metaphases (range 0 - 1.0%) at any exposure concentration. <u>Continuous 24-h and 48-h exposures</u> The relative cell growth of cultures was reduced, however, the reductions amounted to only 24 and 27%, respectively, at the highest dose tested. Continuous exposure for 24 or 48 h did not induce any statistically significant increases in the incidences of chromosome aberrations excluding gaps (range 0 - 1.0%) or polyploid metaphases **(**range 0 - 0.5%) at any dose level when compared with the solvent control group.	
In vitro mammalian cell gene mutation test in mouse lymphoma L5178Y/TK$^{+/-}$ cells OECD TG 476 (1997) GLP Acceptable study Gobal evaluation Factor (GEF) was not applied. Suspension growth was not evaluated.	IKI-220 technical, purity 98.7%	Tested doses in first experiment: 28.3, 84.8, 254, 763 and 2290 µg/mL in the presence and absence of metabolic (S9) activation. Tested doses in second experiment: 143, 286, 573, 1145 and 2290 µg/mL ± metabolic activation Dose selection based on a preliminary toxicity test.	Minimal or no cytotoxicity was observed in the main experiments at concentrations up to 2290 µg/mL The test substance did not induce gene mutations in L5178Y TK$^{+/-}$ mouse lymphoma cells *in vitro*, either in the presence or absence of S9 metabolic activation.	dRAR: B.6.4.1.3, 2002

Method, guideline, deviations[1] if any	**Test substance**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations /Results**	**Reference**
In vitro micronucleus test in Chinese hamster CHL/IU cells OECD TG 487 (2016) GLP Acceptable study	IKI-220 technical, purity 99.5%	1st experiment (3-h exposure): 500, 1000, 2000 µg/mL in the presence and absence of metabolic (S9) activation (+ cytoB) 2nd experiment (24-h exposure): 500, 1000, 2000 µg/mL in the absence of metabolic (S9) activation (+ cytoB) The highest concentration was selected on the basis of the test guideline.	Precipitation of the test substance occurred at 2000 µg/mL at the beginning of treatment in each treatment with and without metabolic activation. No cytotoxicity was observed at any dose level with or without metabolic activation. There were no statistically significant increases in the frequencies of micronucleated binucleate cells at any concentration of the test substance when compared with the solvent control in any treatment. Hence, no evidence for clastogenic or aneugenic potential was observed.	dRAR: B.6.4.1.4, 2023

Table 50: Summary table of genotoxicity/mutagenicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations[1] if any	**Test substance**	**Relevant information about the study (as applicable)**	**Observations/Results**	**Reference**
Micronucleus assay in mouse bone marrow cells OECD TG 474 (1997) GLP Supportive study; sufficient bone marrow exposure not sufficiently demonstrated, only 2000 polychromatic erythrocytes per mouse instead of 4000 were evaluated.	IKI-220 technical, purity 98.7%	Administration of [redacted] mice (5/sex/dose) by gavage at 250, 500 and 1000 mg/kg bw/d (males) and 125, 250 and 500 mg/kg bw/d (females). Dose selection was based on a range-finding study where the maximum tolerated dose levels in males and females were considered to be 1000 and 500 mg/kg bw, respectively.	No significant increase in the no. of micronucleated PCEs were observed in any test substance treated group at any sampling time. As no clear change in the ratio of PCEs/total erythrocytes in the exposed groups compared to negative control was evident, uncertainty remains if sufficient bone marrow exposure (at high enough concentration for long enough time) occurred to allow the test substance to actually reach the target tissue, which is required for micronucleus formation.	dRAR: B.6.4.2.1, 2002
In vivo DNA repair (UDS) test using rat hepatocytes OECD TG 486 (1997) GLP Acceptable study, however, the UDS test is no longer recommended as a follow-up study to positive *in vitro* tests.	IKI-220 technical, purity 98.7%	Male (5 rats/dose) Sprague-Dawley-derived rats were given by gavage a single dose of 600 or 2000 mg/kg IKI-220 technical. Dose selection was based on a range-finding study where the maximum tolerated dose level was approx. 2000 mg/kg .	IKI-220 technical did not induce unscheduled DNA synthesis in Sprague-Dawley rat liver cells.	dRAR: B.6.4.2.2 2003
The comet assay to detect DNA strand breaks using mouse colon, liver and lung cells No applicable OECD guideline was available at the time when the study was conducted and hence it was performed mainly according to the method of Tice et *al.* (Environ. Mol. Mutagen., 35:206-221, 2000). Considered as supportive study by RMS due to following limitations/deviations; the administration of the test substance was not clearly defined, only 50	IKI-220 technical, purity 98.7%	Groups (4 mice/group) of ddY male were given a single oral dose of of 375, 750 and 1500 mg/kg bw of IKI-220 technical. Dose selection was based on a preliminary range-finding study.	All mice survived to the scheduled sacrifice and no clinical signs occurred in any group at any dose level. IKI-220 did not induce DNA damage in mouse colon, liver or lung cells as measured by the comet assay. Due to certain limitations/deviations (described in column 1) of the performed assay, RMS considers the results as supportive.	dRAR: B.6.4.2.3, 2002

Method, guideline, deviations[1] if any	Test substance	Relevant information about the study (as applicable)	Observations/Results	Reference
cells/animal in four animals/dose were scored (recommended 150) acceptability and evaluation criteria were not specified in the original study report, no recommendations for how to achieve a sensitive and reproducible response in tissues other than liver are available.				

Table 51: Summary table of human data relevant for genotoxicity / germ cell mutagenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data available				

2.6.4.1 Short summary and overall relevance of the provided information on genotoxicity / germ cell mutagenicity

The potential of flonicamid to induce gene mutations or chromosomal damage was tested using *in vitro* gene mutation assays in bacterial and mammalian cells, *in vitro* and *in vivo* chromosome studies (incl. a mouse micronucleus test), and *in vivo* unscheduled DNA synthesis (UDS) and comet assays.

Three *in vitro* and three *in vivo* genotoxicity studies with IKI-220 technical submitted for this dossier were already evaluated in the DAR (2005). The *in vitro* studies were all considered acceptable and the conclusion that they all were negative has not been changed. The results of the *in vivo* studies neither indicate any genotoxic potential of IKI-220, however due to certain limitations and deviations of the available *in vivo* micronucleus and comet assay tests compared to current test guidelines, the studies are considered as supportive by the RMS. The applicant submitted additionally an *in vitro* micronucleus test in order to compensate the deviations of the *in vivo* micronucleus test.

In vitro studies

The *in vitro* genotoxicity of IKI-220 technical was examined by using the Ames test, *in vitro* mammalian cell gene mutation test, *in vitro* chromosome aberration test and *in vitro* micronucleus test. All of the studies were considered acceptable. Based on the results all of the tests were negative; no mutagenicity in bacteria, no induction of gene mutations in L5178Y mouse lymphoma cells, no increase of chromosomal aberrations in Chinese hamster CHL cells and no increase of micronucleus induction were detected.

In vivo studies

The *in vivo* genotoxicity of IKI-220 technical was assessed by the *in vivo* micronucleus assay, unscheduled DNA synthesis (UDS) assay and *in vivo* comet assay. The results of the micronucleus assay in [redacted] mouse bone marrow

cells were negative, however, due to some limitations in the study design (only 2000 polychromatic erythrocytes per mouse instead of 4000 were evaluate) and the uncertainty of adequate bone marrow exposure, which is required for micronucleus formation, the study is considered supportive by the RMS. The UDS assay in rat primary hepatocytes was negative, but as the UDS test is no longer recommended as a follow-up study to positive *in vitro* tests, an additional test (e.g. *in vivo* comet assay) would be recommended to enable a final conclusion to be drawn. The *in vivo* comet assay in mouse colon, liver and lung cells was negative. No applicable OECD guideline was available at the time when the study was conducted and it was performed mainly according to the method of Tice *et al.* (Environ. Mol. Mutagen., 35:206-221, 2000). RMS considers that the study had essential limitations/deviations when compared to the current OECD TG 489, which are important to take into consideration when making a final conclusion and therefore the study is considered supportive. The limitations included lack of a clear definition of the administration of the test substance and no specified acceptability and evaluation criteria. In addition in the current OECD TG 489 (2016) it is recommended that 150 cells/animal in at least five animals/dose should be scored for DNA damage – in this study only 50 cells/animal in four animals/dose were scored. As a general limitation to the *in vivo* comet assay it is mentioned in Annex 3 of the OECD TG 489 that no inter-laboratory studies have been conducted in tissues other than liver and stomach, therefore no recommendations for how to achieve a sensitive and reproducible response in tissues other than liver are available, such as expected positive and negative control ranges. For the liver, an agreement on setting a lower limit to the negative control value has not been reached. The interpretation of results is therefore difficult, when taking these limitations and the fact that also lung cells were studied, into consideration.

Based on the available data, it can be concluded that IKI-220 does not cause gene mutations and it is not clastogenic or aneugenic.

2.6.4.2 Comparison with the CLP criteria regarding genotoxicity / germ cell mutagenicity

No human epidemiological data is available for flonicamid. Flonicamid does not produce gene mutations in prokaryotic or eukaryotic cells *in vitro*, either in the presence or absence of a mammalian metabolic activation system and it is not clastogenic in an *in vitro* chromosome aberration test in Chinese Hamster CHL cells. Flonicamid does not cause micronuclei in an *in vitro* micronucleus test showing no potential for clastogenicity or aneugenicity. Flonicamid does not produce DNA damage, as assessed by unscheduled DNA synthesis in rat hepatocytes. Flonicamid did not induce chromosomal damage or DNA strand breaks as measured by the micronucleus and comet assays. Hence, no genotoxic potential of flonicamid was indicated based on the available *in vivo* somatic cell mutagenicity or *in vitro* mutagenicity studies, which were all negative.

Based on the available data, it can be concluded that flonicamid does not cause gene mutations and it is not clastogenic or aneugenic.

2.6.4.3 Conclusion on classification and labelling for genotoxicity / germ cell mutagenicity

The available data (including new acceptable *in vitro* micronucleus test with negative result) indicate no classification regarding genotoxicity / germ cell mutagenicity and this is also in agreement with the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

Based on the available data, it can be concluded that flonicamid does not cause gene mutations and it is not clastogenic or aneugenic.

2.6.5 Summary of long-term toxicity and carcinogenicity [equivalent to section 10.9 of the CLH report template]

The long-term toxicity of IKI-220 was examined in a combined chronic toxicity and carcinogenicity study in Wistar rats and in two oncogenicity studies in CD-1 mice.

Table 52: Summary table of animal studies on long-term toxicity and carcinogenicity

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
Oral (dietary) chronic toxicity and carcinogenicity OECD TG 453 (1981) Groups of male and female Wistar rats Main group: 52 rats/sex, satellite group 1: 14 rats/sex, satellite group 2: 10 rats/sex GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 50, 100, 200, 1000 ppm Corresponding dietary intake: 1.84, 3.68, 7.32, 36.5 mg/kg bw/day Females: 0, 200, 1000, 5000 ppm Corresponding dietary intake: 8.92, 44.1, 219 mg/kg bw/day Duration of exposure: Main group: 104 weeks, satellite group 1: 52 weeks, satellite group 2: 26 weeks	**NOAEL for carcinogenicity:** > 1000 ppm (36.5 mg/kg bw/d) for males and > 5000 ppm (219 mg/kg bw/d) for females **NOAEL for systemic toxicity in males:** 200 ppm (7.32 mg/kg bw/d) based on the occurrence of reduced body weight and nephropathy at 1000 ppm **NOAEL for systemic toxicity in females:** 1000 ppm (44.1 mg/kg bw/d) based on the occurrence of reduced body weight gain, mild anemia, hepatic hypertrophy, hepatic dysfunction, renal tubular vacuolation, chronic nephropathy and accelerated age-related eye and muscle lesions at 5000 ppm **Non-neoplastic findings** High females (5000 ppm) at terminal sacrifice: in the liver (increased incidence of hepatic hypertrophy and eosinophilic cell foci), the kidney (increased incidence of vacuolation and brown pigment deposition in renal proximal tubular cells), in the striated muscle (increased incidences of muscle fiber atrophy) and the eye (retinal atrophy); high dose decedent females exhibited similar effects, with the exception that liver changes were not seen and that increased incidence of cataract were found. The increased incidences of muscle atrophy, retinal atrophy and cataract commonly seen in ageing rats were considered unlikely to reflect direct toxicity of test substance. Increased incidence of chronic nephropathy was found in high dose males (1000 ppm) at terminal sacrifice, whereas decedent males exhibited an increased incidence of hyaline droplet deposition in the proximal renal tubules. Increased incidences of forestomach erosion/ulceration were also found in decedent at 1000 ppm in both sexes and at 5000 ppm (females) but not in surviving rats at terminal sacrifice; this lesion is therefore not likely to be treatment related. No significant changes were	dRAR: B.6.5.1, 2002

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
		seen in either sex at 100 ppm, except a significant increase of bile duct hyperplasia in males at terminal kill and a significant decrease in the incidence of hyaline droplet deposition in the proximal tubular kidney cells in decedent and all rats. **Neoplastic findings** No consistent cause of death was evident in decedent. The nature and incidence of all tumor types were similar in all groups of animals scheduled to be killed after 104 weeks, including the decedent. Statistically significant changes in tumor incidences between treated and control groups were confined to reduced incidences of anterior pituitary adenoma in males at 1000 ppm and mammary gland adenoma in females at 5000 ppm. Treatment-related rare tumor types did not occur in either sex and the multiplicity of tumors and latencies did not indicate a treatment effect in either sex at any dose level. Additional data was provided by the applicant (DAR Volume 3 - B.6 addendum 3 (December 2006)) concerning squamous cell carcinomas in the nasal cavity, the incidence of cerebellum granular cell tumors in the high dose female group and the apparent increased hematopoiesis in all treatment groups, confirming that the observed lesions were formed spontaneously and were not related to IKI-220 treatment.	
Oral (dietary) oncogenicity OECD TG 451 (1981) Groups of male and female Swiss mice [redacted]:CD-1® [redacted] VAF/Plus strain) Main group: 60 mice/sex, satellite groups: 10 mice/sex GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 250, 750, 2250 ppm Corresponding dietary intake: 29, 88, 261 mg/kg bw/day Females: 0, 250, 750, 2250 ppm Corresponding dietary intake: 38, 112, 334 mg/kg bw/day Duration of exposure: Main group: 78 weeks, satellite	**NOAEL for carcinogenicity could not be determined:** < 250 ppm (corresponding to < 29 and < 38 mg/kg bw/d in males and females, respectively) based on increased lung adenoma and carcinoma incidences **NOAEL for systemic toxicity could not be determined** based on the occurrence of increased incidences of hepatic hypertrophy in males at ≥ 250 ppm and in females at ≥ 2250 ppm, increased incidences of splenic extramedullary hematopoiesis in males at ≥ 250 ppm and in females at ≥ 750 ppm, reduced bone marrow cellularity in both sexes at ≥ 750 ppm, and increased incidences of lung hyperplasia/hypertrophy at ≥ 250 ppm in both sexes. **Non-neoplastic findings** were seen in the liver, spleen and bone marrow Liver: In satellite groups, minimal to moderate centrilobular hepatocyte hypertrophy occurred only in males at 2250 ppm; in the main group, this finding was found in males at all dose levels in	dRAR: B.6.5.2, 2003

Method, guideline, deviations[1] if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
	groups of 26 and 52 weeks	which it exhibited dose dependent severity and in females at 2250 ppm. Spleen: In satellite groups, increased splenic extramedullary hematopoiesis and pigment deposition (both graded as minimal to moderate) occurred in both sexes at 2250 ppm at both interim kills. In the main group, this finding was seen in males at all dose levels and in females at the two highest dose levels and increased pigment deposition (golden brown granular material consistent with hemosiderin) occurred in both sexes at 2250 ppm. Bone marrow: In satellite groups, an increased incidence of minimal to moderate bone marrow hypocellularity was evident at low incidence in both sexes after 26 weeks and in males only after 52 weeks, two 2 males also showed pigment deposition after 26 weeks. In the main groups, increased incidence of minimal bone marrow hypocellularity accompanied by pigment deposition was evident in both sexes at 750 or 2250 ppm, suggesting a treatment-related effect on erythrogenesis. Other changes: Increased incidences of enlargement and increased eosinophilia of the epithelial cells lining the terminal bronchioles occurred in a large proportion of mice in all treated groups, but there was no clear dose-response relationship. This treatment-related finding was attributed to an increased size and granularity of the cytoplasm of these epithelial cells (presumably Clara cells) and was considered as suggestive of an induction of cytochrome enzymes. Although hypertrophy localized within airway cells appeared to be the principal change, increased cell numbers could not be precluded. Therefore, the alteration was referred to as hypertrophy/hyperplasia. **Neoplastic findings** Statistically significant increased incidences of primary lung tumors in both sexes at all doses. Initial histopathological examination showed that the overall incidences of treated mice with any primary lung tumor (including alveolar/bronchiolar adenoma and carcinoma) were in the range 36.7 - 60.0% compared with control incidences of 16.7 and 15.0% in males and females, respectively; there were also increased incidences of focal alveolar/bronchiolar hyperplasia of epithelial cells (most likely Clara cells) in terminal bronchioles in both sexes at all dose levels. The diagnoses were confirmed by a pathology working group. Although a very small number of diagnoses were modified on	

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
		peer review, the group incidences of both benign and malignant tumors were comparable to the original incidences. There were clear dose related increased incidences of malignant tumors and of the number of mice with multiple tumors Only a small proportion of incidental deaths in all treatment groups had a primary lung tumor and most were diagnosed in animals killed at termination at week 78, indicating that the lung tumors were generally not life-threatening. Historical incidences of benign tumours in [redacted]:CD-1® [redacted] strain were reported to be approx. 14% and 8% in males and females, respectively and the incidence of malignant tumors was reported to be approx. 7% and 4% in males and females, respectively.	
Oral (dietary) oncogenicity OECD TG 451 (1981) Male and female Swiss mice [redacted]CD-1® [redacted] strain), groups of 50 mice/sex GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 10, 25, 80, 250 ppm Corresponding dietary intake: 1.20, 3.14, 10.0, 30.3 mg/kg bw/day Females: 0, 10, 25, 80, 250 ppm Corresponding dietary intake: 1.42, 3.66, 11.8, 36.3 mg/kg bw/day Duration of exposure: 78 weeks	**NOAEL for carcinogenicity and systemic toxicity:** 80 ppm (corresponding to 10 mg/kg bw/d in males and 11.8 mg/kg bw/d in females) based on the elevated incidence of pulmonary adenoma in males and hyperplasia in both sexex at 250 ppm **Non-neoplastic findings** Lungs: statistically significant increases in the incidences of pulmonary hyperplasia/hypertrophy of the terminal bronchiolar epithelium in both sexes treated at 250 ppm which were only seen in mice killed at termination (after 78 weeks). At the lower doses, the incidences of these changes did not differ statistically significantly from that of controls in both sexes. The lesions were graded as slight in all groups. Other tissues: A slight, but significantly increased incidence of centrilobular hepatocellular fatty change in the liver in the 250 ppm females which were subjected to unscheduled necropsy (considered as incidental **Neoplastic findings** Lung: Statistically significant increase of single or multiple alveolar/bronchiolar adenomas of the lungs in males at 250 ppm; the total number of males at 250 ppm bearing either type of pulmonary tumor was significantly higher compared to controls. The latency of pulmonary tumor formation in these males was not affected by treatment since the first pulmonary neoplastic changes were seen in decedent mice after 64, 75, 68, 53 and 56 weeks of treatment in the control, 10 ppm, 25 ppm, 80 ppm and 250 ppm groups, respectively. The incidences of pulmonary epithelial adenoma and carcinoma in males treated at	dRAR: B.6.5.3, 2004

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
		up to 80 ppm, and in females at all doses up to 250 ppm, were not significantly different from the control incidences.	

Table 53: Summary table of human data on long-term toxicity and carcinogenicity

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No human data available.				

Table 54: Summary table of other studies relevant for long-term toxicity and carcinogenicity

Based on the increased incidence of lung tumours observed in the first mouse oncogenicity study, five mechanistic studies were performed to examine the etiology of the observed tumours.

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
Examination of cell proliferation in lung epithelial cells of CD-1 mice using the bromodeoxyuridine (BrdU) labelling technique No OECD guideline available Not conducted under GLP Acceptable study	IKI-220 technical, purity 98.7%	Groups of five male mice ([redacted]CD-1[redacted] strain) were administered dietary concentrations of 0, 80, 250, 750 and 2250 ppm of IKI-220 technical for three consecutive days (72 h). The mice were given 100 mg/kg bw BrdU by intraperitoneal injection at 14 and 2 h prior to the termination of treatment. The terminal kill was performed at 72 h after initiation of feeding administration and all mice were subjected to necropsy; the lungs were removed with the trachea, which was subjected to immunohistopathological examination using BrdU labelling. 1000 BrdU-negative and positive nuclei in epithelial cells of the terminal bronchiolar region of the lung were scored for BrdU uptake.	Dose-dependent increase in cell proliferation in the epithelial cells of the terminal bronchiolar region of the lung after dietary administration at 250 – 2250 ppm, corresponding to doses of 40.9 - 339.3 mg/kg bw/d. As suggested by the study author, a threshold for the stimulation of lung epithelial cell proliferation by IKI-220 appeared to lie in the range of 80 – 250 ppm, equivalent to a dose range of 12.3 - 40.9 mg/kg bw/d. The NOEL for cell proliferation was 80 ppm, equivalent to a dose of 12.3 mg/kg bw/d.	dRAR: B.6.8.2.1, 2003
Comparison of the BrdU labelling index in the terminal	IKI-220 technical,	Groups of five female mice [redacted]:CD-1[redacted] strain) were given dietary concentrations of	The cell proliferation elicitated by IKI-220 differed between CD-1	dRAR: B.6.8.2.2, 2003

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
bronchial epithelial lung cells in mice and rats after dietary administration of IKI-220 for three or seven days. No OECD guideline available Not conducted under GLP Acceptable study	purity 98.7%	0 or 2250 ppm IKI-220 technical for 3 or 7 consecutive days and groups of 5 female Wistar rats were given dietary concentrations of 0 or 5000 ppm of the test substance for 3 or 7 consecutive days. The dose levels used were the highest doses used in the oncogenicity studies in rats and mice. All animals were given intraperitoneal injections of 100 mg/kg bw of BrdU at 2 h prior to the termination of treatment. The terminal kills were performed at 3 or 7 days after initiation of feeding administration and all animals were subjected to necropsy; the lungs were removed with the trachea which was subjected to immunohistopathological examination using BrdU labelling. 1000 BrdU-negative and positive nuclei in epithelial cells of the terminal bronchiolar region of the lung were scored for BrdU uptake.	mice and Wistar rats; an increase in cell proliferation in epithelial cells of the terminal bronchiolar region of the lung in female mice after 3 or 7 days of treatment at an average dose level of 380 mg/kg bw/day was observed, but not in female rats at an average dose level of 398 mg/kg bw/day.	
Investigation of the reversibility of IKI-220 induced effects in terminal bronchial epithelial cells of CD-1 mice by measuring BrdU uptake. In addition, the expected target cells, Clara (club) cells, were identified by immunohistochemical staining to detect a possible increase in number and altered morphology after exposure to the test substance. No OECD guideline available Not conducted under GLP Acceptable study	IKI-220 technical, purity 98.7%	Groups of 20 male mice [redacted]j:CD-1([redacted] strain) were administered dietary concentrations of 0 or 2250 ppm IKI-220 technical for 28 consecutive days. The dose level selected for this study was the highest dose level used in the oncogenicity study in mice. Five mice/group were killed at 0, 7, 14 or 28 days after the end of treatment. Mice were given intraperitoneal injections of 100 mg/kg bw of BrdU at 2h prior to the terminal scheduled kill (i.e 5 mice/group at 0, 7, 14 or 28 days after the end of treatment). The lungs were removed with the trachea which was subjected to immunohistopathological examination using BrdU labelling. An additional section of lung tissue from each animal was similarly treated but using polyclonal	IKI-220 induced an increase in cell proliferation in epithelial cells of the terminal bronchiolar region of the lung in CD-1 mice after 28 days of treatment at an average dose of 303 mg/kg bw/d, which was fully reversible within 7 days of the end of treatment. IKI-220 induced a fully reversible elongation and hypertrophy/hyperplasia of the Clara (Club) cells in the terminal bronchiolar region of the lung, but did not exert a cytotoxic effect on the activated Clara cell. Hence, it can be anticipated that the pathological progressive effects originating for the mitogenic potency of IKI-220 were rapidly and completely reversible.	dRAR: B.6.8.2.3, 2003

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		antibody against Clara cells as the primary antibody (CC-10 staining) and immunohistochemically stained for Clara (Club) cells. 1000 BrdU-negative and positive nuclei in epithelial cells of the terminal bronchiolar region of the lung were scored for BrdU uptake and Clara cell numbers were confirmed by electron microscopy.		
The aim was to examine if the increased increased incidences of lung bronchiolar/alveolar tumours seen in the mouse carcinogenicity study were caused by the parent compound IKI-220 or one of its metabolites (TFNG, TFNA or TNFA-AM) by using BrdU labelling. No OECD guideline available Not conducted under GLP Acceptable study	IKI-220 technical, purity 98.7%; TFNG, purity 99.4%; TFNA, purity 99.4%; TFNA-AM, purity 100%	Groups of 10 male mice [redacted]:CD-1([redacted]) strain) were administered dietary concentrations of 0, 2250 ppm of IKI-220 technical or 2250 ppm of TFNG or 2250 ppm of TFNA or 2250 ppm of TFNA-AM. 5 mice/group were killed after either 3 or 7 days of treatment. The mice were given an intraperitoneal injection of 100 mg/kg bw of BrdU 2 h prior to the scheduled sacrifice i.e. after 3 or 7 days of treatment. The lungs were removed with the trachea which was subjected to immunohistopathological examination using BrdU labelling. 1000 BrdU-negative and positive nuclei in epithelial cells of the terminal bronchiolar region of the lung were scored for BrdU uptake.	At 2250 ppm, equivalent to a dose of 389/330 (3/7 days) mg/kg bw/day, IKI-220 induced an increase in cell proliferation in the epithelial cells of the terminal bronchiolar region of the lung in male mice as measured by BrdU incorporation. The metabolites TFNG, TFNA and TFNA-AM did not, however, affect the BrdU labelling index, why the cell proliferation effect of IKI-220 can be considered to be due to the parent molecule rather than one of the metabolites tested.	dRAR: B.6.8.2.4, 2003
The aim of the study was to determine if different mouse strains (CD-1, B6C3F1 and C57), known to have different background levels of spontaneous tumours in the bronchioalveolar region of the lung, would differ in their cell proliferation after IKI-220 treatment. CD-1 mice are known to have a high incidence of spontaneous tumours, C57 to have a low incidence and	IKI-220 technical, purity 98.7%	Groups of 5 male mice of the three different mouse strains [redacted]:CD-1 [redacted] , [redacted]:B6C3F1 and C57/6J] were administered dietary concentrations of 0 or 2250 ppm of IKI-220 technical or 2250 ppm of isoniazid for 3 consecutive days. The mice were given an intraperitoneal injection of 100 mg/kg bw of BrdU at 2 h prior to the scheduled sacrifice i.e. after 3 days of treatment. The lungs were removed with the trachea which was subjected to immunohistopathological examination using BrdU labelling. 1000 BrdU-negative and positive nuclei in	Cell proliferation of the lung terminal bronchiolar epithelial cells (BrdU index) was significantly increased after 3-day dietary administration of 2250 ppm IKI-220 in CD-1 mice only, but not in B6C3F1 nor in C57 mice. However, the 3-day dietary administration of 2250 ppm isoniazid induced a more pronounced proliferation of lung terminal bronchiolar epithelial cells compared to IKI-220 in CD-1 mice, and less marked in B6C3F1 and C57 mice. In contrast to the differential response seen among the 3 strains of mice	dRAR: B.6.8.2.5, 2003

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
B6C3F1 to be intermediate between CD-1 and C57 with respect to backround levels of spontaneous lung tumours. Isoniazid, which has been shown to induce lung tumours in mice, was used to compare the effects with IKI-220 treated mice. No OECD guideline available Not conducted under GLP Acceptable study		epithelial cells of the terminal bronchiolar region of the lung were scored for BrdU uptake. An additional section of lung tissue from each mouse was similarly treated but using polyclonal antibody against Clara cells as the primary antibody (CC-10 staining) and immunohistochemically stained for Clara cells. . The number of CC-10 positive cells in the control groups of each mouse strain was also recorded and expressed as a percentage of the cells scored.	with respect to cell turnover, the proportion of Clara cells in the terminal bronchiolar region of mouse lung was similar among all tested strains, namely 80% of the terminal bronchiolar cells were Clara cells. CD-1 mice appeared to exhibitd strain-specificity to the cell proliferating effect of IKI-220 which was not evident after isoniazid treatment. In Wistar rats, the proportion of Clara cells in the terminal bronchiolar region of the lung was low in relation to mouse lung.	

2.6.5.1 Short summary and overall relevance of the provided information on long-term toxicity and carcinogenicity

No new carcinogenicity data was submitted for the ongoing re-evaluation of flonicamid. The oral long-term toxicity of flonicamid was investigated via dietary administration in a combined chronic toxicity and carcinogenicity study in Wistar rats, and in oncogenicity studies in the CD-1 mouse.

In Wistar rats the liver and the kidneys were identified as specific target organs following long-term administration of IKI-220 and the lesions were similar to the findings of the 13 week study. In the liver, centrilobular hepatic hypertrophy occured with signs of liver dysfunction, evident only in females at the highest dose (5000 ppm). Kidney effects occurred in both sexes, but there was a clear difference between the sexes in lesion morphology. In the males, the nephrotoxicity closely resembled α2-microglobulin nephropathy and was characterized by tubular epithelial hyaline droplet deposition occurring in parallel with an increased incidence of tubular basophilia up to 52 weeks of treatment and hyaline degeneration was accompanied by an increased incidence of chronic nephropathy after 104 weeks of treatment. In the females, morphological alterations were confined to proximal tubular vacuolation, chronic nephropathy and increased incidences of brown pigment deposition; female rats also developed signs of mild anemia and accelerated expression of the common age-related lesions, such as cataract, retinal atrophy and striated muscle fibre atrophy. The incidence of lesions in the nerves supplying the muscles were unaffected by treatment. The lowest NOAEL value established in the rat for non-neoplastic effects was 200 ppm in males and 1000 ppm in females i.e. 7.32 and 44.1 mg/kg bw/d, respectively. In addition, as documented the DAR Volume 3 - B.6 addendum 3 (December 2006), the applicant submitted two additional reports (Report No. [redacted] and Flonicamid 04-04) and a position paper regarding the details about the tumours observed in the current rat study. These data concerned the incidence of squamous cell carcinomas in the nasal cavity, the incidence of cerebellum granular cell tumors in the high dose female group and the apparent increased hematopoiesis in all treatment groups. Based on a detailed re-analysis of the histopathological data, it was concluded that the slight non-statistically significant increase in

incidence of these tumors was not a IKI-220 treatment-related effect but that the observed lesions were formed spontaneously.

In CD-1 mice, the liver, spleen, bone marrow and lung were identified as target organs for non-neoplastic effects: increased incidences of hepatic hypertrophy, splenic extramedullary hematopoiesis with pigment deposition, lung hyperplasia/hypertrophy and reduced bone marrow cellularity occurred. Hepatic hypertrophy and splenic extramedullary hematopoiesis in males and lung hyperplasia / hypertrophy in both sexes occurred at the lowest dose level. A NOEL could not be established for neoplastic effects in the first CD-1 mouse study in which increased incidences of primary lung tumours (alveolar/bronchiolar adenomas and carcinomas) were seen in both sexes at all doses in the range of 250 – 2250 ppm, equivalent to 29 – 334 mg/kg bw/d. Most of the tumours were diagnosed in mice killed at termination at week 78, indicating that the lung tumours were generally not life-threatening In the second mouse stud with lower doses (10 – 250 ppm), a NOEL for lung hyperplasia / hypertrophy could be determined as 80 ppm (equivalent to 10 and 11.8 mg/kg bw/d) in males and females, respectively. IKI-220 did not affect the incidence of neoplasia in any other tissue or organ in the mouse.

Based on the increased incidence of lung tumours observed in the first mouse oncogenicity study, five mechanistic studies were performed to examine the etiology of the observed tumours. Based on these studies it was concluded that IKI-220 exhibited a species-specific cell proliferating effect in the CD-1 mice. In addition, this effect was strain-specific as the response was more pronounced in the CD-1 mouse, conversely to isoniazid whose effect does not exhibit s+train-specificity. Moreover the CD-1 mice show a considerably higher spontaneous rate of lung lesions (historical control data in addendum 2, October 2006) than the B6C3F1mice, which again have a higher incidence of lesions than the C57BL mice. Increased mitogenesis was demonstrated as the most plausible mode of action of IKI-220 and the sequence of events for mouse lung tumours has been delineated as predominantly arising from bronchiolar Club (formerly Clara) cells undergoing increased proliferation followed by hyperplasia, leading to adenomas and ultimately carcinomas. More importantly, there is also evidence that in absence of early changes of increased proliferation and hyperplasia, adenomas and carcinomas do not develop later.

Based on all the available data, IKI-220 is not likely to be carcinogenic in humans based on the mode of action seen only in CD-1 mice. In conclusion, the collective IKI-220 data strongly support no classification for carcinogenic potential and a NOAEL of 7.32 mg/kg body weight/day based on the chronic rat study was proposed.

2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity

Flonicamid showed no carcinogenic potential in rats. The mechanism of lung tumour formation in CD-1 mice is not relevant for humans. The CLP criteria for classification as a Category 2 carcinogen are as follows:“The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.” On the basis of an extensive assessment of historical control data, mechanistic information and comparison with isoniazid, flonicamid does not have intrinsic properties to induce cancer in rats, and the effects observed in mice have been demonstrated to be species- and

strain-specific and not relevant to humans. Therefore the existing experimental evidence does not fulfil the criteria for classification for carcinogenicity according to Regulation (EC) No 1272/2008.

Table 55: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	**Tumour type and background incidence**	**Multi-site responses**	**Progression of lesions to malignancy**	**Reduced tumour latency**	**Responses in single or both sexes**	**Confounding effect by excessive toxicity?**	**Route of exposure**	**MoA and relevance to humans**
Rat, Wistar	Squamous cell carcinomas in the nasal cavity, cerebellum granular cell tumors	No	No	No	Squamous cell carcinomas in the nasal cavity in both sexes, cerebellum granular cell tumors in the high dose female group	No	Oral	Additional data was provided that confirmed spontaneous formation of observed tumors.
Mouse, CD-1	Lung tumors	No	No	No	Response in both sexes	NOAEL could not be determined	Oral	Increased mitogenesis in bronchiolar Club cells, species and strain specific effect not relevant to humans
Mouse, CD-1	Lung tumors	No	No	No	Response in males	No	Oral	Increased mitogenesis in bronchiolar Club cells, species and strain specific effect not relevant to humans

2.6.5.3 Conclusion on classification and labelling for carcinogenicity

This hazard class was not re-assessed in the current dossier as no new carcinogenicity data was submitted for the ongoing AIR4 evaluation. Taking into accoutn the weight of evidence analysis of the available data, it is concluded

that the low increase in frequency of benign lung tumors in highly susceptible mice with a clear threshold for lung benign tumor induction through a mechanism which is not relevant for other strains of mice and for rats, does not constitute even a limited evidence of carcinogenicity. Therefore, based on the available data, flonicamid does not require classification for carcinogenicity in accordance with the CLP Regulation (EC) No. 1272/2008 and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.6 Summary of reproductive toxicity [equivalent to section 10.10 of the CLH report template]

2.6.6.1 Adverse effects on sexual function and fertility – generational studies [equivalent to section 10.10.1 of the CLH report template]

Table 56: Summary table of animal studies on adverse effects on sexual function and fertility – generational studies

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL**	**Reference**
Reproductive toxicity study Preliminary study **<u>Guideline</u>** No guideline was stated. GLP Rat, Wistar 8/sex/group Low parental toxicity. Low parental toxicity would not be questionable if the dosing would be done up to the limit dose 1000 mg/kg bw/d. Study is **acceptable as a range-finding study.**	Flonicamid (batch no 9809, purity 98.7 %) 0, 50, 200, 1000, or 2000 ppm. (correspond to 0, 2.86, 11.49, 57.7 and 114.2 mg/kg bw/d males and 5.28, 20.8, 103.7 and 214 mg/kg bw/d females). Oral, diet Pre-mating and through mating, gestation and lactation	**Adults:** NOAEL for male parental animals 200 ppm, equivalent to 11.5 mg/kg bw/d, based on the occurrence of histopathological adverse effects on the kidneys at dose levels of ≥ 1000 ppm. NOAEL for female parental animals > 2000 ppm, equivalent to 214 mg/kg bw/d, based on the absence of effects at this highest dose level. **Offspring:** A NOAEL > 2000 ppm, equivalent to 214 mg/kg bw/d, based on the absence of effects at this highest dose level. **Reproduction:** A NOAEL > 2000 ppm, equivalent to 214 mg/kg bw/d, based on the absence of effects at this highest dose level.	dRAR: B.6.6.1.1, 2002a
Two-generation reproduction study in rats **<u>Guideline</u>** OECD Test Guideline 416 (1983) GLP **<u>Deviations</u>**	Flonicamid (batch no. 9809, purity 98.7 %) 0 ,50, 300 and 1800 ppm [correspondig of 0, 3.07, 18.3, 109.1 mg/kg bw/d (for parental (P)	**Adults:** NOAEL 300 ppm (equivalent to 18.3 / 28.2 mg/kg bw/day) based on reduced ovary/adrenal weights and renal tubular vacuolation at 1800 ppm in parental females, and reduced 17β-estradiol concentration in F1 females. The thyroid weight was reduced in parental males and degenerative renal tubular lesions were observed at 1800 ppm in both parental and F1 males.	dRAR: B.6.6.1.2, 2002b

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Several deviations were observed in humidity and/or ventilation but this did not affect the study results. Rat, Wistar 24/sex/group **Study is acceptable** Low parental toxicity would not be questionable if the dosing would be done up to the limit dose 1000 mg/kg bw/d in the preliminary study.	males); 4.67, 28.2, 163.8 mg/kg bw/d (for P females); 3.39, 20.7, 124.8 mg/kg bw/d (for first filial (F1) males), 4.95, 30.5, 176.8 mg/kg bw/d (for F1 females)] Oral, diet Pre-mating and through mating, gestation and lactation	**Offspring:** NOAEL 300 ppm (equivalent to 30.5 mg/kg bw/d) based on delayed vaginal opening and reduced uterus weights in F1 female progeny only. **Reproduction:** NOEL > 1800 ppm (equivalent to 109.1 and 163.8mg/kg bw/d in males and females, respectively), based on the absence of effects at these dose levels.	
Hormonal examination No guideline No GLP Rat, Wistar 75 females 6-8 /group **Study is acceptable**	No test substance The blood samples were taken on detailed date and time of blood sampling for each group.	**Effects:** The serum levels of 17β-estradiol seemed to be higher at 14:00 - 16:00 but gradually decreased at 18:00 - 20:00. On the other hands, LH levels revealed a clear surge pattern as the peak at 18:00. FSH also showed same pattern with LH but the differences between each time point were very minor.	dRAR: B.6.6.1.3 2006
Flonicamid effects on hormonal levels in 28-day and 90-day feeding studies in rats **<u>Guideline</u>** No guideline No GLP Rat, Wistar 75 females 6-8 /group **Study is acceptable**	Flonicamid (lot 9809), purity 98.7% 0, 50, 100, 300 and 1800 ppm (corresponding to 3.7 – 4.3, 7.5 – 8.7, 22.4 – 26.8, 136.0-154.1 mg/kg bw/day) Oral diet	**Effects:** No differences in the hormone levels of LH, FSH, and 17β-estradiol were observed in the study when rats are treated with flonicamid up to 1800 ppm via diet for 28 days or 90 days.	dRAR: B.6.6.1.4, 2006
Developmental toxicity study, rat Range-finding study **<u>Guideline</u>** No guideline was stated No GLP Rat, Sprague-Dawley rats [redacted]:SD)	Flonicamid (lot. No 970213, purity 97.4%) 0, 10, 100, or 500 mg/kg bw/day Oral, gavage Days 6-19 of gestation (14 days)	**Maternal effects**: NOAEL 100 mg/kg bw/day based on treatment-related effects (increase of liver weight) at the 500 mg/kg bw/day group **Embryotoxicity/teratogenicity**. NOAEL 500 mg/kg bw/day as no treatment-related fetal malformations occurred at any dose level.	dRAR: B.6.6.2.1, 2006

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
20 females, 5/group **Study is acceptable as a range-finding study.**			
Developmental toxicity study, rat Range-finding study **Guideline** No guideline was stated but the study is generally in line with OECD 414 (2001) GLP Rat, Wistar 6/group **Study is acceptable as a range-finding study.**	Flonicamid (batch no 9809, purity 98.7 %) 0, 30, 100, 300 and 1000 mg/kg bw/day Oral, gavage Days 6-19 of gestation (14 days)	**Maternal effects**: NOAEL 300 mg/kg bw/d, based on the occurrence of maternal death and reduced weight gain at 1000 mg/kg bw/d. **Embryotoxicity/teratogenicity**. NOAEL > 1000 mg/kg bw/d, based on the absence of foetal effects at this dose level, although only 2 litters were available for evaluation	dRAR: B.6.6.2.2, 2002a
Developmental toxicity study, rat **Guideline** OECD Test Guideline 414, 2001 GLP **Deviations** The exposure period was from day 6 not from day 5 Not including investigations of thyroid hormones in dams, of anogenital distance in foetuses, of external vs gonadal foetal sex, of investigation for incomplete testicular descent/cryptorchidism Rat, Wistar 24 /group **Study is acceptable.**	Flonicamid (batch no 9809, purity 98.7 %) 0, 20, 100 and 500 mg/kg bw/day Oral, gavage Days 6-19 of gestation (14 days)	**Maternal toxicity:** NOAEL 100 mg/kg bw/d, based on effects observed in the kidneys and liver. **Embryotoxicity/teratogenicity** NOAEL 100 mg/kg bw/day based an increased incidence of skeletal variations, namely extra cervical ribs	dRAR: B.6.6.2.3, 2002b
Developmental toxicity study, rabbit Range-finding study	Flonicamid (batch no 9809, purity 98.7 %)	**Maternal effects**: NOAEL 10 mg/kg bw/d, based on maternal body weight loss and reduced food consumption.	dRAR: B.6.6.2.4, 2002c

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Guideline No guideline was stated. GLP **Deviations** Daily monitoring revealed a temporal rise on seven days in humidity following cleaning of the animal room or owing to a stop of a cooling machine. However, these deviations were not considered to affect the results of this study. Rabbit Japanese White 6/group **Study is acceptable as a range-finding study.**	0, 3, 10 and 30 mg/kg bw/day Oral, gavage Days 6-27 of gestation (22 days)	**Embryotoxicity/teratogenicity**: A NOAEL 10 mg/kg bw/d, based on and reduced live foetus number at 30 mg/kg bw/d.	
Developmental toxicity study, rabbit **Guideline** OECD Test Guideline 414 (2001) GLP **Deviations** As for humidity, daily monitoring revealed temporal rises on 15 separate days. These deviations were due to a cleaning of the animal room or owing to a stop of a cooling machine. However, these were not considered to affect the results of this study. No ED-sensitive endpoints (AGD in foetuses and thyroid hormones in dams) were measured.	Flonicamid (batch no 9809, purity 98.7 %) 0, 2.5; 7.5 and 25 mg/kg bw/day Oral, gavage Days 6-27 of gestation (22 days)	**Maternal toxicity:** NOAEL 7.5 mg/kg bw/d based on the occurrence of reduced weight gain and food consumption at 25 mg/kg bw/d. **Embryotoxicity/teratogenicity:** NOAEL > 25 mg/kg bw/d based on the absence of developmental toxicity at the highest dose level employed. A number of external, skeletal and visceral anomalies were observed; however, they were not dose-related, and they fall within the historical control data and can thus be considered as incidental.	dRAR: B.6.6.2.5, 2002d

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Rabbit Japanese White [redacted]:JW), 25/group **Study is acceptable.**			

Table 57: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available.				

Table 58: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
28-day oral (dietary) toxicity No guideline referred (dose range finding study) GLP Acceptable study	IKI-220 technical, purity 98.7%	Groups (6/sex) of male and female Wistar rats Dose levels: Males: 0, 50, 100, 500, 1000, 5000 ppm Corresponding dietary intake: 0, 3.613, 7.47, 36.45, 73.8 and 353.4 mg/kg bw/d Females: 0, 100, 500, 1000, 5000, 10000 ppm Corresponding dietary intake: 0, 8.36, 41.24, 81.9, 372.6 and 642 mg/kg bw/d	A statistically significant decrease in absolute ovary weight was observed in high dose females (-25% compared with control; $p<0.05$). This decrease was considered to be secondary to body weight change (-9% compared with controls, $p<0.05$) and not a direct effect on ovaries.	dRAR: B.6.3.1.1, 2002
90-day oral toxicity (beagle dogs) OECD TG 409 (1998) Groups of 4/sex beagle dogs GLP Acceptable study	IKI-220 technical, purity 98.7%	Groups of 4/sex beagle dogs Dose levels: Males: 0, 3, 8 and 20 mg/kg bw/d Females: 0, 3, 8, 20 and 50 mg/kg bw/d Duration of exposure: 90 days	An increased absolute weight of epididymes was observed at the lowest tested dose (3 mg/kg bw/d). Increased absolute and relative prostate weight at 8 mg/kg bw/d and increased absolute prostate weight at 3 mg/kg bw/d was also observed. These changes were not considered as treatment-related as they occurred only in low or mid dose groups, but not in high dose males (20 mg/kg bw/d).	dRAR: B.6.3.2.3, 2001

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Oral (dietary) chronic toxicity and carcinogenicity OECD TG 453 (1981) GLP Acceptable study	IKI-220 technical, purity 98.7%	Groups of male and female Wistar rats Main group: 52 rats/sex, satellite group 1: 14 rats/sex, satellite group 2: 10 rats/sex Dose levels: Males: 0, 50, 100, 200, 1000 ppm Corresponding dietary intake: 1.84, 3.68, 7.32, 36.5 mg/kg bw/day Females: 0, 200, 1000, 5000 ppm Corresponding dietary intake: 8.92, 44.1, 219 mg/kg bw/day Duration of exposure: Main group: 104 weeks, satellite group 1: 52 weeks, satellite group 2: 26 weeks	A statistically significantly reduced incidence of mammary gland adenoma was observed (1/52 compared with 7/52 in controls) in the high dose females (5000 ppm equivalent to 219 mg/kg bw/d). The observation is considered to be associated with age-related tumours and may be due to normal variation in incidence at this age of the animal. Due to the effect direction (decrease of incidence) it is considered not adverse. A statistically significantly decreased incidence of ovarian cysts was observed at Week 104 in the high dose animals treated with 219 mg/kg bw/d (2/31 compared with 10/31 in controls). The observation is considered not to be adverse or treatment-related and may be related to the age of the animals.	dRAR: B.6.5.1, 2004
Oral (dietary) oncogenicity OECD TG 451 (1981) Male and female Swiss mice ([redacted]CD-1® [redacted] strain), groups of 50 mice/sex GLP Acceptable study	IKI-220 technical, purity 98.7%	Dose levels: Males: 0, 10, 25, 80, 250 ppm Corresponding dietary intake: 1.20, 3.14, 10.0, 30.3 mg/kg bw/day Females: 0, 10, 25, 80, 250 ppm Corresponding dietary intake: 1.42, 3.66, 11.8, 36.3 mg/kg bw/day Duration of exposure: 78 weeks	An increased incidence of thickened uterus wall (assessed at week 78) was observed (20/37 compared with 14/44 in the controls; $p<0.05$) in the high dose females (36.3 mg/kg bw/d). This observation did not correspond to an increased incidence of any particular microscopic uterine alteration and was therefore not considered as adverse.	dRAR: B.6.5.3, 2004
In vitro mechanistic	IKI-220, purity 99.6%	E-modality (Estrogen (ER) receptor signalling in hERα-HeLa-9903 cells)	Negative evidence for ER-related endocrine activity.	dRAR; B.6.8.3.6, 2020
In vitro mechanistic	IKI-220, purity 99.6%	A-modality (Androgen receptor (AR) signalling in CV-1 cells)	Negative evidence for AR-related endocrine activity.	dRAR; B.6.8.3.6, 2020
In vitro mechanistic	IKI-220, purity 99.5%	Aromatase inhibition – aromatase is the enzyme responsible for converting androgens to	No effect, supporting negative evidence for S-related endocrine activity.	dRAR; B.6.8.3.7, 2020

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		estrogens during steroidogenesis.		
In vitro mechanistic	IKI-220, purity 99.5%	Steroidogenesis assay - production of estradiol and testosterone in human H295R adreno-carcinoma cells	No significant effect on the production of estradiol. A slight, but stat. sign. inhibition of testosterone production at the two highest doses, 316 µM and 1 mM, indicating a positive response. No clear dose-response was evident and the range 0.81-1.03 was small. A revision of the OECD Test Guideline 456 is under preparation where incorporation of a 1.5-fold threshold has been discussed. In conclusion, the observed slight inhibition of testosterone production was not considered as clear evidence for an endocrine disrupting effect.	dRAR; B.6.8.3.8, 2021

2.6.6.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility – generational studies

A preliminary and a 2-generation dietary reproductive toxicity study have been performed in the rat. Additional observations on serum gonadotrophin and sex hormone levels and estrogen receptor binding affinity were performed on F1 progeny of the 2-generation study to investigate the etiology of observed effects.

In the rat 2-generation reproductive toxicity study (dRAR: B.6.6.1.2), flonicamid in the diet at concentrations of 0, 50, 300 and 1800 ppm did not affect fertility or reproductive ability in either sex. However, effects suggestive of interference with the normal sexual maturation of female progeny were seen at 1800 ppm (reduced uterus weights in the F1 & F2 generation and slightly delayed vaginal opening in F1 progeny) but all other aspects of F1 development and, specifically the reproductive capacity, were unaffected by treatment with flonicamid. Reduced ovary weights were also apparent in P generation female rats at the end of lactation, but the relevance of this finding is questionable since ovary weights are not affected in subsequent generations, or in nulliparous females treated for 13 weeks at up to 5000 ppm from 6 weeks of age. A statistically significant ($p < 0.01$) increase in the absolute and relative thyroid weights of P parental males at 1800 ppm were observed. Decreased testes weight (absolute), increased liver weight (relative), and increased seminal vesicles weight (relative) in the Fl generation was observed. In the 300-ppm group, the relative weight of kidneys and thyroids of Fl males were significantly higher than the controls. These differences in organ weights in the 300 and 1800 ppm groups were judged not to be biologically significant because they were only found in one generation, except for the thyroids, they were only seen in absolute or relative to body weight but not in both and they were not accompanied by any adverse histopathology findings. Sperm analysis did not reveal any treatment effect on sperm count and morphology. The only other effects of flonicamid administration identified in the 2-generation study were related to the kidney. Morphologically distinct histopathological alterations occurred in the kidneys of males and females in both the P and F1 generation. These renal lesions were already seen in previous short-term toxicity studies. In males, the kidney changes were considered

to be mediated by the male rat-specific protein, alpha-2-microglobulin; and in females the kidney changes consisted of vacuolation of proximal tubular cells. F1 males and females were not more susceptible than the P generation to these renal lesions.

The NOEL for fertility and reproductive performance was > 1800 ppm (equivalent to 109.1 and 163.8 mg/kg bw/d in males and females, respectively), based on the absence of effects at these dose levels. The NOAEL for parental systemic effects was established at 300 ppm (equivalent to 18.3 / 28.2 mg/kg bw/day) based on reduced ovary/adrenal weights and renal tubular vacuolation at 1800 ppm in parental females, and reduced 17β-estradiol concentration in F1 females. The thyroid weight was reduced in parental males and degenerative renal tubular lesions were observed at 1800 ppm in both parental and F1 males. The NOAEL for the offspring was 300 ppm (equivalent to 30.5 mg/kg bw/d) based on delayed vaginal opening and reduced uterus weights in F1 female progeny only. In this study, parental toxicity was very low raising a question whether the dose levels tested have been high enough.

Table 59: Main observations in two-generation reproduction study

Dose levels	**0 ppm**		**50 ppm**		**300 ppm**		**1800 ppm**	
	P	**F1**	**P**	**F1**	**P**	**F1**	**P**	**F1**
BODY WEIGHT GAIN (g)								
Males								
Premating								
w 0-1	51±3	43±3	50±2	42±4	49±4	42±4	48±4**	41±4
w0-10	263±22	339±24	266±23	336±25	257±26	334±23	262±23	325±22
Treatment w 0-18	318±27	394±29	313±26	388±39	311±28	392±29	316±25	382±28
Females								
Premating								
w 0-1	27±5	34±2	36±3	34±2	26±4	33±2	37±3	32±2***
w0-10	138±14	184±11	136±11	189±13	136±12	187±19	132±10	180±14
Gestation d 0-20	107±9	104±17	103±20	107±13	105±14	111±15	101±10	113±11
Lactation d 0-21	18±11	16±14	23±14	8±16	28±15*	13±20	36±15***	25±13
Treatment w 0-18	170±13	222±12	169±10	228±14	167±13	226±20	171±16	222±16
No examined	24	24	24	24	24	23	24	24
Estrous Cycle length [days]	4.0	4.1	4.0	4.0	4.0	4.0	4.0	4.0
Normal cycling[a] [%]	100	100	100	100	100	100	100	100
% Mating								
Males	100	100	95.8	100	100	100	100	95.8
Females	100	100	100	100	100	100	100	100
No of d until mating	1.0	1.0	1.6	1.0	1.0	1.0	1.2	1.6
Fertility index[b] (%)	91.7	87.5	100	91.7	95.8	91.3	91.7	100

Gestation index[c] (%)	100	100	91.7	100	100	100	100	100
Duration of gestation (d)	22.1	22.0	22.3	22.2	22.3	22.2	22.5*	22.1
N implants (± SD)	15.0±1.4	13.2±3.4	13.9±4.1	13.9±3.2	13.9±3.1	14.5±3.0	13.5±2.4	14.5±1.3
N pups (± SD)	13.5±1.3	12.5±3.4	13.8±2.0	12.4±3.2	12.7±3.0	13.2±3.2	12.6±2.4	14.0±1.3
Sex ratio	54.7	57.9	50.8	48.9*	52.2	54.3	48.2	53.1

F1: first filial generation; No.: Number; P: parental generation; ppm: parts per million
* p≤ 0.05, ** p≤ 0.01., *** p≤ 0.001
[a] proportion of females showing normal estrous cyclicity; [b] no. pregnant / no. mated x 100; [c] no. normal parturitions / no. pregnancies x 100

Table 60: Group mean age and weight at completion of preputial separation or vaginal opening, and ano-genital distance of F1 and F2 pups

Generation	**Group (ppm)**	N° M / F examined	**Preputial separation complete**		**Vaginal opening complete**	
			Age (days)	**bw (g)**	**Age (days)**	**bw (g)**
F1	**0**	24 / 24	41.9 ± 1.1	187.5 ± 10.7	32.6 ± 1.3	106.7 ± 6.7
	50	24 / 24	41.6 ± 1.4	185.9 ± 10.8	32.5 ± 2.0	107.6 ± 13.1
	300	24 / 23	41.7 ± 1.3	187.6 ± 9.5	32.7 ± 2.2	107.2 ± 11.6
	1800	24 / 24	41.9 ± 1.7	186.0 ± 11.6	34.1 ± 2.0**	112.0 ± 11.8
F2	**0**	24 / 24	-	-	32.3 ± 1.5	101.8 ± 9.8
	50	24 / 24	-	-	32.7 ± 1.6	107.4 ± 8.5
	300	24 / 24	-	-	32.0 ± 1.5	104.6 ± 9.0
	1800	24 / 24	-	-	33.1 ± 1.6	107.5 ± 9.5

			Males			**Females**		
			Bw (g)	**Ano-genital distance**		**Bw (g)**	**Ano-genital distance**	
				(mm)	**(relative[a])**		**(mm)**	**(relative[a])**
F2	**0**	24 / 24	10.6	6.06±0.88	0.276	10.1	2.86±0.39	0.133
	50	24 / 24	10.8	6.58±0.64	0.298	10.3	3.12±0.32	0.144
	300	24 / 23	10.9	6.41±0.68	0.289	10.5	3.10±0.32	0.142
	1800	24 / 24	10.5	6.33±0.54	0.289	10.2	3.12±0.30	0.144

[A]day 0 = pups alive on day 0 / pups born x 100, day 4 = pups alive on day 4 / pups alive on day 0 x 100, day 21 = pups alive on day 21 / pups alive on day 4 x 100, * p < 0.05

In order to assess potential anti-oestrogenic effects of flonicamid as a cause of findings in the rat reproduction study (i.e. delayed vaginal opening, reduced absolute and relative uterus weight observed in the 1800 ppm group), along with equivocal results on some hormone levels (isolated increased LH at 300 ppm, increased LH and FSH and decreased 17β-estradiol at 1800 ppm), two additional studies were performed in the rat.

First study was carried out to investigate normal fluctuation of LH, FSH and 17β-oestradiol levels in normal female Wistar rats of nulliparous animals at pro-oestrous. The serum levels of 17β-estradiol seemed to be higher at 14:00 - 16:00 but gradually decreased at 18:00 - 20:00. On the other hand, LH levels revealed a clear surge pattern as the peak at 18:00. FSH also showed same pattern with LH but the differences between each time point were very minor. LH values during the 13h00-15h00 interval vary from 0.71 to 42.72 ng/mL, study results strongly indicate that the minor changes observed at 300 and 1800 ppm in LH levels are within the range of basal oscillation at pro-oestrous in normal female Wistar rats. It is therefore concluded that the increase in LH levels observed in the 300 and 1800 ppm groups of the reproduction study was not a treatment-related effect, but an observation induced by experimental bias.

The second study investigated the hormonal effects of flonicamid to the female Wistar rats administered continuously for a period of 28 or 90 days. Flonicamid was administered in the diet at concentrations of 0, 50, 100, 300 and 1800 ppm. An additional 100 ppm group was included in the present studies to check the potential threshold level of the effect. There were no differences in the levels of LH, FSH and 17β-estradiol compared with controls after administration of flonicamid in the diet for 28 days or 90 days.

The applicant has also included a position paper about the several changes indicating any anti-estrogenic effects, including prolonged gestation, reduced ovary weight, and delayed sexual development in parental females, and reduced uterine weight of female weanlings, which were noted in females of the top dose group in the rat reproduction study. The conclusion of this position paper was that it is indicated that a slightly higher LH level noted in the middle dose group in the rat reproduction toxicity study has no biological significance but originated by experimental bias.

Findings in subchronic toxicity and chronic toxicity / carcinogenicity studies

In the repeated dose 28-day oral toxicity study in Wistar rats (dose range finding study) (dRAR: B.6.3.1.1) a statistically significant decrease in absolute ovary weight was observed in high dose females (-25% compared with control; $p<0.05$). This decrease was considered to be secondary to body weight change (-9% compared with controls, $p<0.05$) and not a direct effect on ovaries.

In the repeated dose 90-day oral toxicity study in beagle dogs ((dRAR: B.6.3.2.3) an increased absolute weight of epididymes was observed at the lowest tested dose (3 mg/kg bw/d). Increased absolute and relative prostate weight at 8 mg/kg bw/d and increased absolute prostate weight at 3 mg/kg bw/d was also observed. These changes were not considered as treatment-related as they occurred only in low or mid dose groups, but not in high dose males (20 mg/kg bw/d).

In the rat carcinogenicity study (dRAR: B.6.5.1), a statistically significantly reduced incidence of mammary gland adenoma was observed (1/52 compared with 7/52 in controls) in the high dose females (5000 ppm equivalent to 219 mg/kg bw/d). The observation is considered to be associated with age-related tumours and may be due to normal variation in incidence at this age of the animal. Due to the effect direction (decrease of incidence) it is considered not adverse. In the same study, a stat. significantly decreased incidence of ovarian cysts was observed at Week 104 in the high dose animals treated with 219 mg/kg bw/d (2/31 compared with 10/31 in controls). The observation is considered not to be adverse or treatment-related and may be related to the age of the animals.

In the dietary carcinogenicity study in CD-1 mice (dRAR: B.6.5.3) an increased incidence of thickened uterus wall (assessed at week 78) was observed (20/37 compared with 14/44 in the controls; $p<0.05$) **i**n the high dose females (36.3 mg/kg bw/d). This observation did not correspond to an increased incidence of any particular microscopic uterine alteration and was therefore not considered as adverse.

2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility

This hazard class was not re-assessed in the current dossier as no new reproductive data was submitted for the ongoing AIR4 evaluation. According to the RMS evaluation, flonicamid was not found to be toxic to fertility or sexual function in animal experiments. Thus, it does not fulfil the criteria for classification for reproductive toxicity, and no classification is required for flonicamid in accordance with the CLP Regulation (EC) No. 1272/2008 and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.6.2 Adverse effects on development [equivalent to section 10.10.4 of the CLH report template]

Table 61: Summary table of animal studies on adverse effects on development

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ - critical effects at the LOAEL**	**Reference**
Developmental toxicity study, rat Range-finding study **Guideline** No guideline was stated No GLP Rat, Sprague-Dawley rats [redacted]:SD) 20 females, 5/group **Study is acceptable as a range-finding study.**	Flonicamid (lot. no. 970213, purity 97.4%) 0, 10, 100, or 500 mg/kg bw/day Oral, gavage Days 6-19 of gestation (14 days)	**Maternal effects**: NOAEL 100 mg/kg bw/day based on treatment-related effects (increase of liver weight) at the 500 mg/kg bw/day group **Embryotoxicity/teratogenicity**. NOAEL 500 mg/kg bw/day as no treatment-related fetal malformations occurred at any dose level.	dRAR: B.6.6.2.1 , 2006
Developmental toxicity study, rat Range-finding study **Guideline** No guideline was stated but the study is generally in line with OECD 414 (2001) GLP Rat, Wistar 6/group **Study is acceptable as a range-finding study.**	Flonicamid (batch no. 9809, purity 98.7 %) 0, 30, 100, 300 and 1000 mg/kg bw/day Oral, gavage Days 6-19 of gestation (14 days)	**Maternal effects**: NOAEL 300 mg/kg bw/d, based on the occurrence of maternal death and reduced weight gain at 1000 mg/kg bw/d. **Embryotoxicity/teratogenicity**. NOAEL > 1000 mg/kg bw/d, based on the absence of foetal effects at this dose level, although only 2 litters were available for evaluation	dRAR: B.6.6.2.2, 2002a
Developmental toxicity study, rat **Guideline**	Flonicamid (batch no. 9809, purity 98.7 %)	**Maternal toxicity:** NOAEL 100 mg/kg bw/d, based on effects observed in the kidneys and liver.	dRAR: B.6.6.2.3, 2002b

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for parent, offspring and for developmental effects)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
OECD Test Guideline 414, 2001 GLP **<u>Deviations</u>** The exposure period was from day 6 not from day 5 Not including investigations of thyroid hormones in dams, of anogenital distance in foetuses, of external vs gonadal foetal sex, of investigation for incomplete testicular descent/cryptorchidism Rat, Wistar 24 /group **Study is acceptable.**	0, 20, 100 and 500 mg/kg bw/day Oral, gavage Days 6-19 of gestation (14 days)	**Embryotoxicity/teratogenicity** NOAEL 100 mg/kg bw/day based an increased incidence of skeletal variations, namely extra cervical ribs	
Developmental toxicity study, rabbit Range-finding study **<u>Guideline</u>** No guideline was stated GLP **<u>Deviations</u>** Daily monitoring revealed a temporal rise on seven days in humidity following cleaning of the animal room or owing to a stop of a cooling machine. However, these deviations were not considered to affect the results of this study. Rabbit Japanese White 6/group	Flonicamid (batch no. 9809, purity 98.7 %) 0, 3, 10 and 30 mg/kg bw/day Oral, gavage Days 6-27 of gestation (22 days)	**Maternal effects**: NOAEL 10 mg/kg bw/d, based on maternal body weight loss and reduced food consumption **Embryotoxicity/teratogenicity**: A NOAEL 10 mg/kg bw/d, based on and reduced live foetus number at 30 mg/kg bw/d	dRAR: B.6.6.2.4, 2002c

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for parent, offspring and for developmental effects)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Study is acceptable as a range-finding study.			
Developmental toxicity study, rabbit **Guideline** OECD Test Guideline 414 (2001) GLP **Deviations** As for humidity, daily monitoring revealed temporal rises on 15 separate days. These deviations were due to a cleaning of the animal room or owing to a stop of a cooling machine. However, these were not considered to affect the results of this study. No ED-sensitive endpoints (AGD in foetuses and thyroid hormones in dams) were measured. Rabbit Japanese White [redacted]:JW), 25/group **Study is acceptable.**	Flonicamid (batch no. 9809, purity 98.7 %) 0, 2.5; 7.5 and 25 mg/kg bw/day Oral, gavage Days 6-27 of gestation (22 days)	**Maternal toxicity:** NOAEL 7.5 mg/kg bw/d based on the occurrence of reduced weight gain and food consumption at 25 mg/kg bw/d. **Embryotoxicity/teratogenicity:** NOAEL > 25 mg/kg bw/d based on the absence of developmental toxicity at the highest dose level employed. A number of external, skeletal and visceral anomalies were observed; however, they were not dose-related, and they fall within the historical control data and can thus be considered as incidental.	dRAR: B.6.6.2.5, 2002d

Table 62: Summary table of human data on adverse effects on development

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available				

Table 63: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Two-generation reproduction study in rats **Supportive in studying developmental effects**	Flonicamid (batch no. 9809, purity 98.7 %)	Dose 0 ,50, 300 and 1800 ppm [correspondig of 0, 3.07, 18.3, 109.1 mg/kg bw/d (for parental (P) males); 4.67, 28.2, 163.8 mg/kg bw/d (for P females); 3.39, 20.7, 124.8 mg/kg bw/d (for first filial (F1) males), 4.95, 30.5, 176.8 mg/kg bw/d (for F1 females)] Oral, diet Pre-mating and through mating, gestation and lactation	**Offspring:** NOAEL 300 ppm (equivalent to 30.5 mg/kg bw/d) based on delayed vaginal opening and reduced uterus weights in F1 female progeny only. **Reproduction:** NOEL > 1800 ppm (equivalent to 109.1 and 163.8mg/kg bw/d in males and females, respectively), based on the absence of effects at these dose levels.	dRAR: B.6.6.1.2, 2002b

2.6.6.2.1 Short summary and overall relevance of the provided information on adverse effects on development

Developmental toxicity studies (oral gavage), with associated range-finding studies, have been performed in rats and rabbits.

In the rat developmental toxicity study (dRAR: B.6.6.2.3) there were no treatment-related effects on reproductive parameters at any dose level. No external abnormalities were found in any live fetuses in the control and treated groups. Visceral malformations (Table 64:) were observed only in 2 fetuses in the 20 mg/kg group (each one case of retroesophageal subclavian and right-sided aortic arch) and 1 fetus in the 500 mg/kg group (malpositioned ovary). As for visceral variations, thymic remnant in the neck, malpositioned subclavian branch (right subclavian artery originating from aorta) and/or left umbilical artery were observed with low incidences in all groups including the control. However, there was no statistically significant relationship between the incidences of these variations and the dose level.

There was a treatment-related increase in the incidence of skeletal variations at 500 mg/kg bw/d (Table 64:). The effect was due entirely to a significant ($p < 0.001$) increase in the incidence of cervical (supernumerary) rib. The foetal incidences of cervical rib were 6.5, 2.3, 3.2 and 34.1 % in the groups treated at 0, 20, 100 and 500 mg/kg bw/d, respectively. The only other statistically significant differences between control and treated groups were reduced total incidences ($p < 0.05$) of skeletal variations at 20 and 100 mg/kg bw/d. The nature and incidence of all other skeletal variations at all dose levels were comparable in the treated and control groups

Skeletal examination revealed a variety of malformations (Table 64:) in the control and treated groups with low frequencies; i.e., absent rib, fused rib, fused rib cartilage, absent thoracic arch, fused thoracic arch, dumbbell-shaped cartilage of thoracic centrum, fused thoracic centrum, hemicentric thoracic centrum, split cartilage of thoracic centrum, unilateral thoracic centrum cartilage, and spilt cartilage of lumbar centrum. However, the incidences were comparable between the control and treated groups.

Table 64: Summary of reproduction data of the rat developmental toxicity study

Parameter	**Group values for animals treated at [mg/kg bw/d]:**			
	0	**20**	**100**	**500**
No. pregnant / no. mated	22 / 24	24 / 24	24 / 24	24 / 24
No. of live foetuses	298	337	302	341
No of litters	22	24	23	24
No. dams with live foetuses	22	24	23 [a]	24
Gravid uterus weight [g]	68	71	67	73
Mean no. corpora lutea/dam	15.9	15.9	15.7	15.7
Mean no. implantation sites/dam	14.9	15.0	14.1	14.8
Pre-implantation loss [%]	5.8	5.2	10.7	5.2
Total no. dead foetuses	0	3	0	1
Total post-implantation loss [%]	9.4	6.6	6.4	4.2
Mean no. live foetuses/dam	13.5	14.0	13.1	14.2
Sex ratio (% males)	51	51	49	49
Mean male foetal weight [g]	3.25	3.21	3.33	3.22
Mean female foetal weight [g]	3.05	3.02	3.13	3.01
Placental weight [g]	0.433	0.459	0.456	**0.475****
Visceral variations				
No. foetuses examined	143	160	146	165
No. of foetuses with visceral variations	2 (1.4%)	3 (1.9%)	4 (2.7%)	6 (3.6%)
Incidence in litters	2	3	3	6
-Thymic remnant in the neck	1	1	0	1
-Left umbilical artery	0	2	3	2
-Malpositioned subclavian branch: right subclavian artery originating from aorta	1	0	1	3
Visceral malformations				
No. foetuses examined	143	160	146	165
No. of foetuses with visceral malformations	0	2 (1.3%)	0	1 (0.6%)
Incidence in litters	0	2	0	1
-Retroesophageal subclavian	0	1	0	0
-Right-sided aortic arch	0	1	0	0
-Malpositioned ovary	0	0	0	1
Skeletal variations				
No. foetuses examined	155	177	156	176
No. of foetuses with skeletal malformations	18 (11.6%)	**8*** (4.5%)	**8*** (5.1%)	**70*****(**39.8%)
Incidence in litters	11	6	6	**23*****
-Misaligned sternebra	1	1	1	0
-Cervical rib	10	4	5	**60*****
-Supernumerary rib	3	1	1	7
-Bipartite ossification of thoracic centrum	1	0	0	2
-Dumbbell ossification of thoracic centrum	5	1	0*	6
-Dumbbell ossification of lumbar centrum	1	1	1	1
-27 presacral vertebrae	0	0	0	1
Skeletal malformations				
No. foetuses examined	155	177	156	176

Parameter	Group values for animals treated at [mg/kg bw/d]:			
	0	**20**	**100**	**500**
No. of foetuses with skeletal malformations	2 (1.3%)	1 (0.6%)	1 (0.6%)	1 (0.6%)
Incidence in litters	1	1	1	1
-Absent rib	1	1	0	0
-Fused rib	2	0	0	0
-Fused rib cartilage	0	1	0	1
-Absent thoracic arch	1	1	0	0
-Fused thoracic arch	1	0	0	0
-Dumbbell-shaped cartilage of thoracic centrum	0	0	1	0
-Fused thoracic centrum	1	0	0	0
-Hemicentric thoracic centrum	1	1	0	0
-Split cartilage of thoracic centrum	1	0	0	0
-Unilateral thoracic centrum cartilage	1	0	0	0
-Split cartilage of lumbar centrum	1	0	0	0

No.: Number
* P<0.05, ** p<0.01 ***P<0.001.
[a] one dam had implantation sites visible only by staining and was excluded from calculation of mean data

In order to clarify the relevance of the increased incidence of cervical rib (categorized as variation), a re-assessment was performed and summarised in a position paper (year 2006, "cervical ribs observed in the teratogenicity study in rats treated with Flonicamid), examining this finding in detail, e.g by analysing the presence or absence of cartilage (Table 65:). This position paper was also included and referred in the DAR Addendum 3 (2006). The occurrence of skeletal variation, i.e. an increase in the incidence of cervical rib in the rat at a dose level of 500 mg/kg bw/d. is considered not to be toxicologically relevant because only 2 foetuses (from the same litter) out of 60 exhibited cervical ribs with distal cartilage, which is not significantly different compared to control animals. Furthermore, it occurs in the absence of other treatment-related abnormalities.

Table 65: Incidence of cervical rib in the rat developmental toxicity study

Finding		Control	20	100	500
			[mg/kg bw/d]		
Total skeletal variations		18 (11.6%)	8* (4.6%)	8* (5.1%)	70*** (39.8%)
Cervical rib	Foetal incidence	10 (6.5%)	4 (2.3%)	5 (3.2%)	60*** (34.1%)
	Without cartilage	10	4	5	58***
	With cartilage	0	0	0	2
	Litter incidence	7 (31.8%)	4 (16.7%)	3 (13.0%)	23*** (95.8%)

*p<0.05 ***p<0.001

Cervical ribs with distal cartilage are permanent structures in contrast to cervical ribs without distal cartilage, which are transient and disappear post-natally. With the exception of two foetuses from one litter, all of the observations of cervical rib lacked distal cartilage. The incidence of cervical ribs with distal cartilage was not significantly elevated and therefore not considered to be related to treatment. Other cervical ribs adjacent to the 7th cervical vertebra (uni- or bilaterally) were completely ossified and rudimentary (or small). As the majority of the supernumerary ribs showed no distal cartilage and they are transient variations which disappear post-natally, they

should not be regarded as an indication for a teratogenic potential of flonicamid. Moreover, these effects were observed at a dose level which caused toxicity to the dams (liver hypertrophy, vacuolation of renal tubular cells and increased placental weight).

Since the apparently treatment-related increase in the incidence of skeletal variations at 500 mg/kg bw/d was due entirely to a significant ($p < 0.001$) increase in the incidence of cervical ribs, skeletal variations in foetuses are no indication of a teratogenic effect. The findings of extra-cervical ribs are considered as minor defects which are not sufficient for classification. The NOAELs in the rat are 100 mg/kg bw/d for maternal rats and 100 mg/kg bw/d for rat foetuses.

In the rabbit teratogenicity study (dRAR: B.6.6.2.5) the pregnancy incidence in all experimental groups was uniformly high and 23, 22, 21 and 23 females treated at 0, 2.5, 7.5 and 25 mg/kg bw/d, respectively, had viable young on Day 28. There were no treatment-related effects at any dose level on gravid uterus weight, the numbers of corpora lutea and implantations, pre-implantation loss, number of live foetuses, and post-implantation loss from resorption and foetal death.

Higher incidences of abnormal foetuses occurred in all groups treated with flonicamid (Table 66:). However, the total foetal and litter incidences of abnormal foetuses in the groups treated at 2.5 or 25 mg/kg bw/d were not significantly ($p > 0.05$) different from control values and showed no dose dependency. The incidence of foetuses with visceral abnormalities and the overall litter incidence of abnormalities at 7.5 mg/kg bw/d were significantly higher ($p < 0.05$) than the control values. Visceral examination revealed several types of malformations in the control and/or treated groups. Among these malformations, abnormal lung lobation and absent kidney accompanied by absent ureter were observed only in the two-higher dose groups. However, no statistically significant differences were noted in the incidences of these visceral malformations in the treated groups when compared to those in the control group. Visceral variations observed were malpositioned innominate, malpositioned subclavian branch, and thymic remnant in the neck. Among these findings, the incidence of thymic remnant in the neck was significantly lower in the 2.5 mg/kg group than that in the control group. However, it was thought to be unrelated to test substance treatment because incidences in the other treated groups were comparable to the control group.

Skeletal examination disclosed a variety of malformations in the sternebra, ribs, vertebral arches and bodies, limbs, and/or phalanges. In some cases, multiple malformations occurred in the same fetuses. The control and treated groups were comparable for the incidences of these skeletal malformations (Table 66:). As for skeletal variations, cervical rib, supernumerary rib, 27 presacral vertebrae, and lumbosacral transitional vertebra were observed in all groups including the control. In addition, misaligned sternebra was observed in the control and 2.5 mg/kg groups. No statistically significant differences were noted in the incidences of these skeletal variations in the treated groups when compared to those in the control group.

Statistically significant differences were noted in the incidence of females having fetuses with malformations and the incidence of fetuses with visceral malformations between the control group and the 7.5 mg/kg group. However, this increase was thought to be incidental because no specific types of malformations were significantly increased in either 7.5 mg/kg or other treated groups.

Table 66: Summary incidences of external, visceral and skeletal findings in rabbit teratogenicity study

Parameter	**No. and [%] foetuses at [mg/kg bw/d]:**			
	0	**2.5**	**7.5**	**25**
No. litters evaluated (external)	23	22	21	23
No. foetuses evaluated (external)	173	167	156	170
External abnormalities	0 (0.0)	2 (1.2)	2 (1.3)	1 (0.6)
No. litters evaluated (visceral)	23	22	21	23
No. foetuses evaluated (visceral)	173	167	156	170
Abnormal foetuses (visceral)	1 (0.6)	2 (1.2)	**6*** (3.8)	5 (2.9)
No. litters evaluated (skeletal)	23	22	21	23
No. foetuses evaluated (skeletal)	173	167	156	170
Abnormal foetuses (skeletal)	0 (0.0)	3 (1.8)	3 (1.9)	3 (1.8)
Total abnormal foetuses	1[a] (0.6)	7[b] (4.2)	11[c] (7.1)	9[d] (5.3)
Total abnormal litters	1 (4.3)	4 (18.2)	**6*** (28.6)	3 (13.0)
Foetuses with visceral variations	7 (4.0)	**1*** (0.6)	10 (6.4)	7 (4.1)
Foetuses with skeletal variations	55 (31.8)	59 (35.3)	43 (27.6)	65 (38.2)

No.: Number

[a] one foetus with malpositioned testis

[b] 2 foetuses with malpositioned testis, one foetus with anal atresia, one foetus with omphalocele, 2 foetuses with fused sternebrae, one foetus with absent cervical vertebral arch

[c] one foetus with local edema, one foetus with omphalocele, one foetus with multiple malformations (retroesophageal subclavian aortic arch, absent kidney and ureter, fused rib and supernumerary thoracic vertebral arch and centrum), 2 foetuses with abnormal lung lobation, one foetus with narrowed pulmonary trunk, one foetus with small lung, one foetus with malpositioned testis, one foetus with fused sternebrae, one foetus with absent rib and hemicentric thoracic vertebral centrum, one foetus with supernumerary thoracic vertebral arch

[d] one foetus with amelia, short tail and gastroschisis, one foetus with ventricular septal defect and interrupted aortic arch, one foetus with fused sternebrae, one foetus with absent lung, 2 foetuses with abnormal lung lobation, one foetus with absent kidney and ureter with small bladder, one foetus with fused caudal vertebral centrum, one foetus with multiple vertebral and long-bone abnormalities

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Historical control data from the testing facility (years 1992-2001) was available. A total of 15 teratogenicity studies were performed and a total of 2177 fetuses were examined. Literature historical control data was also presented. Japan Pharmaceutical Manufacturers Association (JPMA) collected historical control data from developmental and reproductive toxicity studies, which conducted by the member companies and associated contract laboratories between 1986 and 1993. The data include spontaneous incidences of fetal morphological alterations and other observations made at terminal cesarean sections in rats, rabbits and mice. Data from [redacted]:JW rabbits was received from 25 facilities. All observed visceral malformations in rabbit fetuses of dams exposed to flonicamid occur spontaneously with varying frequency in the Japanese testing facility where the study has been performed. The number and frequency of visceral malformations in fetuses was low, not dose-related and was within the historical control values (HCV) in the same laboratory (HCV [redacted] as well as historical control values reported in the survey of JPMA literature.

The maternal NOEL is 7.5 mg/kg bw/d based on reduced food consumption and body weight gain, but the rabbit fetal NOEL is > 25 mg/kg bw/d, the highest dose level of the study. Therefore, the lowest relevant NOAEL for developmental effects is 25 mg/kg bw/d, established in the rabbit.

In the RAC opinion (5 June 2013) visceral malformation in rabbits have been discussed. Flonicamid is not teratogenic in either the rat or in the rabbit, but it does elicit a marked increase in the incidence of cervical rib in the rat at a dose level of 500 mg/kg bw/d. The increased incidence of this skeletal variant is considered not to be relevant

for human risk assessment because it occurs at high dose levels only which also induce overt maternal effects, notably liver hypertrophy, vacuolation of renal tubular cells and increased placental weight. Also, in the 2-generation reproductive toxicity study, flonicamid did not affect the estrus cycle, mating behavior, fertility or fecundity of the parental and F1 generation, or viability and physical development of the progeny. The analysis of the developmental studies indicates that flonicamid is not foetotoxic and it does not have intrinsic properties to induce visceral malformations in rabbits or in rats.

2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development

This hazard class was not re-assessed in the current dossier as no new reproductive data was submitted for the ongoing AIR4 evaluation. The evaluation of the developmental studies indicates that flonicamid is not foetotoxic and it does not have intrinsic properties to induce visceral malformations in rabbits or in rats. The observed malformations in rabbits were spontaneous developmental anomalies not related to exposure to flonicamid, the frequency of which did not significantly increase with dose, even though the dose of 25 mg/kg bw/d induced maternal toxicity. This hazard class was not re-assessed in the current dossier as no new reproductive data was submitted for the ongoing AIR4 evaluation. Thus, it does not fulfil the criteria for classification for reproductive toxicity, and no classification is required for flonicamid in accordance with the CLP Regulation (EC) No. 1272/2008 and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.6.6.3 Adverse effects on or via lactation [equivalent to section 10.10.7 of the CLH report template]

Table 67: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
Two-generation reproduction study in rats **Guideline** OECD Test Guideline 416 (1983) GLP **Deviations** Several deviations were observed in humidity and/or ventilation but	Flonicamid (batch no. 9809, purity 98.7 %) Dose 0 ,50, 300 and 1800 ppm [correspondig of 0, 3.07, 18.3, 109.1 mg/kg bw/d (for parental (P) males); 4.67, 28.2, 163.8 mg/kg bw/d (for P females); 3.39, 20.7, 124.8 mg/kg bw/d (for	**Adults:** NOAEL 300 ppm (equivalent to 18.3 / 28.2 mg/kg bw/day) based on reduced ovary/adrenal weights and renal tubular vacuolation at 1800 ppm in parental females, and reduced 17β-estradiol concentration in F1 females. The thyroid weight was reduced in parental males and degenerative renal tubular lesions were observed at 1800 ppm in both parental and F1 males. **Offspring:** NOAEL 300 ppm (equivalent to 30.5 mg/kg bw/d) based on delayed vaginal opening and reduced uterus weights in F1 female progeny only.	dRAR: B.6.6.1.2, 2002b

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
this did not affect the study results. Rat, Wistar 24/sex/group **Study is acceptable** Low parental toxicity would not be questionable if the dosing would be done up to the limit dose 1000 mg/kg bw/d in the preliminary study.	first filial (F1) males), 4.95, 30.5, 176.8 mg/kg bw/d (for F1 females)] Oral, diet Pre-mating and through mating, gestation and lactation	**Reproduction:** NOEL > 1800 ppm (equivalent to 109.1 and 163.8mg/kg bw/d in males and females, respectively), based on the absence of effects at these dose levels.	

Table 68: Summary table of human data on effects on or via lactation

Type o data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available.				

Table 69: Summary table of other studies relevant for effects on or via lactation

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available.				

2.6.6.3.1 Short summary and overall relevance of the provided information on effects on or via lactation

Two-generation reproduction study in rats is the same as the study in Section 2.6.6.1.

In the rat dietary two-generation reproductive toxicity study (dRAR: B.6.6.1.2) with flonicamid there was no effect of treatment at any dose level in either sex or generation on group mean pup body weights during lactation. Daily clinical examination of F1 and F2 pups revealed no treatment related abnormalities during the lactation and post-weanling periods. Similarly, pup viability throughout lactation was unaffected by treatment (similar numbers of pups were lost due to maternal cannibalism in all groups including controls) and all viability indices were comparable to the control values, except for the d4 viability index for F1 progeny at 50 ppm which was significantly greater than the control value (no pups were lost in this group). There was no effect of treatment at any dose level in either sex or generation on group mean pup bw during lactation.

Sexual development of male F1 progeny, as assessed by body weight and age at the time of balano-preputial separation, was unaffected by treatment at all dose levels. However, vaginal opening in F1 females at 1800 ppm was significantly ($p < 0.01$) delayed by a mean of 1.5 days, at which time their body weights were slightly greater than the controls. The effect was not apparent at lower dose levels. Although vaginal opening in F2 females was, on average, 0.8 days later and body weights were slightly greater than the controls, the differences were not statistically significant ($p > 0.05$). The group mean ano-genital distances in both sexes of F2 progeny on Day 4 of lactation were not significantly ($p > 0.05$) different from control values at all dose levels and were considered not have been affected by treatment. There were no treatment-related effects on the incidence of clinical signs, body weight gains, food consumption and gross findings at necropsy of the F2 females selected for examination of vaginal opening.

No treatment-related gross lesions were evident at necropsy in F1 and F2 pups, including pups dead on Day 0 of lactation, neonatal deaths, pups culled on Day 4 and pups dying or killed subsequently. There were no treatment-related effects at any dose level in progeny of either generation on the absolute and relative organ weights of brain, thymus and spleen. However, the absolute and relative uterus weights in F1 progeny at 1800 ppm were significantly ($p < 0.05$) reduced in relation to control weights, but there was no statistically significant difference in F2 progeny.

As the pups of this study have been exposed during pregnancy and pups begin to eat solid food before weaning, it is not possible to differentiate between effects via lactation, exposure in uterus and exposure via solid food. No specific information is available on the quality of the milk produced by the dams, nor was the rat milk analysed for the presence of flonicamid or its metabolites. On the other hand, the RAR study in ruminants (please see dRAR Volume 3, CA B-7, point B.7.4.2) included the residue levels in milk. The actual average doses administered were 0.088, 0.239 and 0.800 mg/kg bw/day (expressed as the parent compound – corrected by the RMS) in the low, mid and high dose group. The test substance was flonicamid/TFNG (1:1 w:w mixture). Flonicamid was not detected in milk. In some extent of metabolite TFNA-AM was excreted in milk. All values were below the LOD of 0.005 mg/kg in the control and low dose groups, at the highest the residue values were 0.03 mg/kg in mid dose group and 0.09 mg/kg in the high dose group.

The metabolism of flonicamid in lactating goats (dRAR Volume 3, CA B-7, point B.7.2.5) was also investigated. The actual daily dose was 1.66 -1.72 mg/kg body weight. TFNA-AM was identified as a major metabolite in goat milk (97% of TRR). The metabolite TFNA-AM was excreted in some extent to goat milk (0.082-0.084 mg/kg).

It should be noted that there were no adverse effects on the body weight and body weight gain in females of the F1 and/or F2 generation during the lactation period 0-21 days in study submitted. Since there was no clear evidence of a treatment related adverse effect on the offspring due to transfer of flonicamid in milk or due to effects of flonicamid on lactation, no classification for adverse effects on or via lactation is proposed.

2.6.6.3.2 Comparison with the CLP criteria regarding effects on or via lactation

Adverse effects on or via lactation are included under reproductive toxicity, but for classification purposes such effects are treated separately. Classification in the additional category for effects on or via lactation will be considered irrespective of a classification into other reproductive hazard classes. Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the

potential to cause adverse effects on the offspring via lactation.

According to the ruminant's residue study and the goat metabolite study, flonicamid itself is not excreted to the milk, however small amounts its metabolite can be found in milk. It is not possible to differentiate if the adverse effects of pups (decreased absolute and relative uterus weight and slightly greater vaginal opening) in the rat two-generation study are caused by exposure in uterus, via lactation or exposure via solid food. Therefore, classification for effects on or via lactation is not appropriate.

2.6.6.4 Conclusion on classification and labelling for reproductive toxicity

No classification for sexual function and fertility, developmental toxicity or effects on or via lactation is proposed.

2.6.7 Summary of neurotoxicity

The neurotoxic potential of IKI-220 was examined in Sprague-Dawley rats in an acute oral neurotoxicity study (dRAR: B.6.7.1.1) and a 90-day oral neurotoxicity study (dRAR: B.6.7.1.3). In addition, a 28-day dose-ranging oral study (dRAR: B.6.7.1.2) was performed for the selection of doses for the subsequent 90-day study.

Table 70: Summary table of animal studies on neurotoxicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL**	**Reference**
Acute oral neurotoxicity (single oral gavage) OECD TG 424 (1997) Male and female Sprague-Dawley rats, (10 rats/sex at doses 100 and 300 mg/kg bw/day, 10 males at 600 mg/kg bw/day and 5 males/10 females at 1000 mg/kg bw/day) GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 100, 300, 600, 1000 mg/kg bw/day Females: 0, 100, 300, 1000 mg/kg bw/day Duration of exposure: 14-day observation period (at 30/60 minutes, 7 and 14 days)	**NOEL for acute neurotoxicity:** > 600 mg/kg bw/d for males and > 1000 mg/kg bw/d for females **NOEL for general systemic effects:** 600 mg/kg bw/d for males and 300 mg/kg bw/d for females based on the occurrence of transient behavioural effects at 1000 mg/kg bw	dRAR: B.6.7.1.1, 2002
28-day oral (dietary) neurotoxicity, dose-ranging study for the subsequent 90-day neurotoxicity study	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 200, 500, 1000, 5000, 10000 ppm	**NOAEL for general systemic effects:** 84 mg/kg bw/d for males and 429 mg/kg bw/d for females based on slightly and/or transiently reduced weight gain and food consumption at 5000 ppm in males and 10000 ppm in females	dRAR: B.6.7.1.2, 2003

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL**	**Reference**
OECD TG 424 (1997) Male and female Sprague-Dawley rats, 5 rats/sex at doses 200, 500, 1000, 5000, 10000 ppm and additional 5 females at 20000 ppm GLP Acceptable study	Corresponding dietary intake: 0, 17, 41, 84, 388 and 712 mg/kg bw/day Females: 0, 200, 500, 1000, 5000, 10000, 20000 ppm Corresponding dietary intake: 18, 46, 84, 429, 807, 1012 mg/kg bw/day Duration of exposure: 28 days		
90-day oral (dietary) neurotoxicity study OECD TG 424 (1997) Male and female Sprague-Dawley rats, (10 rats/sex at doses 100 and 300 mg/kg bw/day, 10 males at 600 mg/kg bw/day and 5 males/10 females at 1000 mg/kg bw/day) GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: Males: 0, 200, 1000, 10000 ppm Corresponding dietary intake: 0, 13, 67, 625 mg/kg bw/day Females: 0, 200, 1000, 10000 ppm Corresponding dietary intake: 0, 16, 81, 722 mg/kg bw/day Duration of exposure: 90 days	**NOAEL for neurotoxicity:** > 625 mg/kg bw/d for males and > 722 mg/kg bw/d for females **NOAEL for general systemic effects:** 67 mg/kg bw/d for males and 81 mg/kg bw/d for females based on reduced body weight gain and food consumption at 10000 ppm	dRAR: B.6.7.1.3, 2003

2.6.8 Summary of other toxicological studies

2.6.8.1 Toxicity studies of metabolites and impurities

Toxicity studies of seven flonicamid metabolites: TFNA, TFNA-AM, TFNA-AM N-Oxide, TFNA-OH, TFNG, TFNG-AM and TFA have been submitted.

TFNA, TFNA-AM, TFNA-OH, TFNG, TFNG-AM and TFA were the major degradation products of flonicamid observed in soil degradation studies, exceeding 10 % at any time point of the applied dose or 5 % on two consecutive time points or 5 % at the end of the study for which the maximum of formation is not yet reached. All the above mentioned metabolites were assessed for their leaching potential to groundwater. TFNA-AM did not fulfil any of the three criteria above, but leaching potential was still assessed. The concentration of TFNA, TFNA-AM, TFNG and TFNG-AM in groundwater did not exceed 0.1 µg/L in any of the applied uses.

Metabolites TFNA, TFNA-AM, TFNA-AM N-Oxide, TFNA-OH, TFNG, TFNG-AM and hydroxyl TFNA-AM were identified in plant and livestock metabolism studies. Hydroxyl TFNA-AM was found in livestock metabolism studies only, where TFNA-AM was the predominant metabolite (> 90 % in poultry tissues and eggs, 50-74 % in goat tissues and > 90 % in milk).

TFNA was studied in an Ames test, *in vitro* mammalian cell gene mutation test, *in vitro* chromosome aberration test and *in vitro* micronucleus test. All these tests gave negative results. LD_{50} of TFNA in rat was > 2000 mg/kg bw. No treatment-related effects were observed in a 90-day rat study: NOAEL was > 136 and 409 mg/kg bw/day in males and females, respectively. Since the study was performed at such low dose levels that did not show any toxic effects, it is not possible to conclude on the toxicological profile and target organs of this metabolite. Additionally, there were several other deviations in the study, including lower animal number and missing endocrine-related endpoints. Hence, the study was considered as supplementary information only. However, 90-day study of TFNA revealed that subchronic toxicity of this metabolite is likely lower than subchronic toxicity of flonicamid indicating that toxicological profile of TFNA differs from the one of flonicamid. *In silico* analyses indicated that the metabolite TFNA unlikely poses a risk for carcinogenicity, reproductive toxicity or developmental toxicity though only one reliable analysis was available for reproductive toxicity. Based on this information, it is possible to apply the reference values of flonicamid to the risk assessment of TFNA.

TFNA-AM gave a negative result in an Ames test, *in vitro* mammalian cell gene mutation test, *in vitro* chromosome aberration test and *in vitro* micronucleus test. LD_{50} of TFNA-AM in rat was > 2000 mg/kg bw. No assessment of repeated toxicity was provided. TFNA-AM is a major urinary metabolite in rat metabolism comprising 20-25 % of administered dose. Therefore, its toxicity is considered to have been covered in toxicity studies of flonicamid.

There are no studies of OH-TFNA-AM. This metabolite is assumed to be a downstream derivate of TFNA-AM. Hydroxylation is generally considered not to increase toxicity of a compound. Therefore, toxicity of OH-TFNA-AM can be considered to have been studied in the available toxicity tests of the dossier.

TFNA-AM N-oxide was negative in an Ames test, *in vitro* mammalian cell gene mutation test and *in vitro* micronucleus test. LD_{50} of TFNA-AM N-oxide in rat was > 2000 mg/kg bw. No assessment of repeated toxicity was provided.

TFNA-OH was studied in an Ames test, *in vitro* mammalian cell gene mutation test, *in vitro* chromosome aberration test and *in vitro* micronucleus test; all with negative results. LD_{50} of TFNA-OH in rat was > 2000 mg/kg bw. Toxicity studies of flonicamid do not cover toxicity of this minor metabolite. The applicant submitted by request a 90-day study in which the NOAEL was 346 and 400 mg/kg bw/day in males and females, respectively, with hardly any treatment-related effects. The 90-day study of TFNA-OH revealed that subchronic toxicity of this metabolite is lower than subchronic toxicity of flonicamid indicating that toxicological profile of TFNA-OH differs from the one of flonicamid. *In silico* analyses indicated that the metabolite TFNA-OH unlikely poses a risk for carcinogenicity, reproductive toxicity or developmental toxicity. Based on this information, it is possible to apply the reference values of flonicamid to the risk assessment of TFNA-OH. According to the modelling data, TFNA-OH can occur in groundwater up to the concentration of 0.449 µg/L.

TFNG was negative in an Ames test, *in vitro* mammalian cell gene mutation test, *in vitro* chromosome aberration test and *in vitro* micronucleus test. LD_{50} of TFNG in rat was > 2000 mg/kg bw. No treatment-related effects were observed in a 90-day rat study: NOAEL was > 135 and 411 mg/kg bw/day in males and females, respectively. Since the study was performed at such low dose levels that did not show any toxic effects, it is not possible to conclude on the toxicological profile and target organs of this metabolite. Additionally, there were several other deviations in the study, including lower animal number and missing endocrine-related endpoints. Hence, the study was considered as supplementary information only. However, 90-day study of TFNG revealed that subchronic toxicity of this metabolite is likely lower than subchronic toxicity of flonicamid indicating that toxicological profile of TFNG differs from the one of flonicamid. *In silico* analyses indicated that the metabolite TFNG unlikely poses a risk for carcinogenicity, reproductive toxicity or developmental toxicity though only one reliable analysis was available for reproductive toxicity and developmental toxicity. Based on this information, it is possible to apply the reference values of flonicamid to the risk assessment of TFNG.

TFNG-AM was negative in an Ames test, *in vitro* mammalian cell gene mutation test, *in vitro* chromosome aberration test and *in vitro* micronucleus test. LD_{50} of TFNG-AM in rat was > 2000 mg/kg bw. No assessment of repeated toxicity was provided.

TFA was negative in an Ames test and *in vitro* mammalian cell gene mutation test. The result of an *in vitro* chromosome aberration test was negative, but because of the uncertainties in dose selection the study was considered as supplementary information only. TFA was negative in an *in vitro* micronucleus assay showing that there was no clastogenic and aneugenic potential of this metabolite. LD_{50} of TFA in rat was > 2000 mg/kg bw. In a 90-day rat study, statistically significantly increased absolute and relative liver weights with concomitant histopathological findings (increased incidence of hypertrophy) and statistically significant changes in clinical chemistry parameters (reduced glucose and bilirubin concentrations) in both sexes as well as changes in urinalysis (increased ketone levels) were observed from the dose levels of 98/123 mg/kg bw/day in males and females, respectively. The NOAEL was 9.9 and 12.2 mg/kg bw/day in males and females, respectively. There are two rat developmental toxicity studies in the flonicamid dossier. In the first study which was performed with low animal number and two dose levels only, very slight toxic effects were observed at the highest dose level of 150 mg/kg bw/day; the study is acceptable as supplementary data. The second developmental toxicity study was performed in another laboratory with the highest dose of the same level which showed only slight maternal toxicity. No treatment-related effects were observed in foetuses in any of the dose levels tested; the NOAEL for foetal toxicity is higher than the highest administered dose of 150 mg/kg bw/day. Since the study has possibly been performed at too low dose levels it was considered supplementary only. Toxicity of TFA and flonicamid, in general, seem to be of the same level based on the data from 90-day studies, although it is not possible to conclude the thorough toxicological profile of TFA. Further, the data provided does not exclude developmental effects because the highest tested dose 150 mg/kg bw/day did not show any maternal toxicity and is far from the limit dose of 1000 mg/kg bw/day; the study was performed at too low dose levels if the meaning was to study developmental effects.

According to the PECgw modelling data, TFA can occur in groundwater up to the concentration of 13.428 µg/L in the applied uses. TFA has not been observed in primary crop metabolism studies, however, as a soil metabolite, its occurrence in rotational crops is possible. Both metabolism and magnitude of residue study on rotational crops

were provided for the current review. The studies showed that significant amount of residues of TFA may occur in rotationally grown crops.

TFA is a known breakdown product of numerous pesticides and many industrial chemicals. Notification under Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful or unacceptable effects of TFA was submitted on 7 January 2021 to EFSA, the European Commission and Member States by the notifier Bayer of the REACH registration dossier on TFA and the REACH lead registrant and producer of TFA under Regulation (EC) No 1907/2006. [redacted]

Table 71: Summary table of toxicity studies of metabolites

Metabolite	Test	Test object	Concentration	Result	Reference
TFNA	*In vitro* bacterial reverse mutation (Ames test)	*Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 *Escherichia coli* WP2 *uvrA*	Exp. 1 (plate incorporation): 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate in the presence and absence of S9 Exp. 2 (pre-incubation): 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate in the presence and absence of S9	Negative	dRAR: B.6.8.1.2 Acceptable study
TFNA	*In vitro* mammalian cell gene mutation	Mouse lymphoma L5178Y $TK^{+/-}$ cells	Exp. 1 (3-hour exposure): 0, 118.8, 237.5, 475, 950 and 1900 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 118.8, 237.5, 475, 950 and 1900 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.3 Acceptable study

Metabolite	Test	Test object	Concentration	Result	Reference
TFNA	*In vitro* chromosome aberration test	Chinese hamster lung CHL/IU cells	Exp. 1 (6-hour exposure): 0, 475, 950 and 1900 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 475, 950, 1500 and 1900 µg/mL in the absence of S9 Exp. 2 (48-hour exposure): 0, 475, 950 and 1900 µg/mL in the absence of S9 **(not acceptable)**	Negative	dRAR: B.6.8.1.4 Acceptable study
TFNA	*In vitro* micronucleus test	TK6 human lymphoblastoid cells	Exp. 1 (3-hour exposure): 0, 480, 960 and 1920 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 480, 960 and 1920 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.5 Acceptable study
TFNA	Acute oral toxicity	Rat	2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	dRAR: B.6.8.1.1 Acceptable study
TFNA	90-day dietary study	Rat	0, 50 and 2000 ppm (males) 0, 200 and 5000 ppm (females)	NOAEL > 136/409 mg/kg bw/day	dRAR: B.6.8.1.6 **Supplementary information**

Metabolite	Test	Test object	Concentration	Result	Reference
TFNA	(Q)SAR analyses			**Carcinogenicity:** no alerts (Derek Nexus, TopKat) **Reproductive toxicity:** only one reliable analysis: Derek Nexus, no alerts **Developmental toxicity:** no alerts (Derek Nexus, TopKat)	dRAR: B.6.8.1.41 **Supplementary information**
TFNA-AM	*In vitro* bacterial reverse mutation (Ames test)	*Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 *Escherichia coli* WP2 *uvrA*	Exp. 1 (plate incorporation): 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate in the presence and absence of S9 Exp. 2 (pre-incubation): 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate in the presence and absence of S9	Negative	dRAR: B.6.8.1.8 Acceptable study
TFNA-AM	*In vitro* mammalian cell gene mutation	Mouse lymphoma L5178Y $TK^{+/-}$ cells	Exp. 1 (3-hour exposure): 0, 237.5, 475, 950 and 1900 mg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 237.5, 475, 950 and 1900 mg/mL in the absence of S9	Negative	dRAR: B.6.8.1.9 Acceptable study
TFNA-AM	*In vitro* chromosome aberration test	Chinese hamster lung CHL/IU cells	Exp. 1 (6-hour exposure): 0, 475, 950 and 1900 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 475, 950 and 1900 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.10 Acceptable study

Metabolite	Test	Test object	Concentration	Result	Reference
TFNA-AM	*In vitro* micronucleus test	TK6 human lymphoblastoid cells	Exp. 1 (3-hour exposure): 0, 478, 955 and 1910 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 478, 955 and 1910 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.11 Acceptable study
TFNA-AM	Acute oral toxicity	Rat	2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	dRAR: B.6.8.1.7 Acceptable study
TFNA-AM N-oxide	*In vitro* bacterial reverse mutation (Ames test)	*Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 *Escherichia coli* WP2 *uvrA*	Exp. 1 (pre-incubation): 0, 313, 625, 1250, 2500 and 5000 µg/plate in the presence and absence of S9 Exp. 2 (pre-incubation): 0, 313, 625, 1250, 2500 and 5000 µg/plate in the presence and absence of S9	Negative	dRAR: B.6.8.1.13 Acceptable study
TFNA-AM N-oxide	*In vitro* mammalian cell gene mutation	Mouse lymphoma L5178Y $TK^{+/-}$ cells	Exp. 1 (3-hour exposure): 0, 250, 500, 1000 and 2000 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 250, 500, 1000 and 2000 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.14 Acceptable study

Metabolite	Test	Test object	Concentration	Result	Reference
TFNA-AM N-oxide	*In vitro* micronucleus test	TK6 human lymphoblastoid cells	Exp. 1 (4-hour exposure): 0, 500, 1000 and 2000 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 500, 1000 and 2000 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.15 Acceptable study
TFNA-AM N-oxide	Acute oral toxicity	Rat	2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	dRAR: B.6.8.1.12 Acceptable study
TFNA-OH	*In vitro* bacterial reverse mutation (Ames test)	*Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 *Escherichia coli* WP2 *uvrA*	Exp. 1 (plate incorporation): 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate in the presence and absence of S9 Exp. 2 (pre-incubation): 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate in the presence and absence of S9	Negative	dRAR: B.6.8.1.17 Acceptable study
TFNA-OH	*In vitro* mammalian cell gene mutation	Mouse lymphoma L5178Y $TK^{+/-}$ cells	Exp. 1 (3-hour exposure): 0, 129, 259, 518, 1035 and 2070 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 129, 259, 518, 1035 and 2070 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.18 Acceptable study

Metabolite	Test	Test object	Concentration	Result	Reference
TFNA-OH	*In vitro* chromosome aberration test	Chinese hamster lung CHL/IU cells	Exp. 1 (6-hour exposure): 0, 259, 518, 1035 and 2070 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 259, 518, 1035 and 2070 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.19 Acceptable study
TFNA-OH	*In vitro* micronucleus test	TK6 human lymphoblastoid cells	Exp. 1 (3-hour exposure): 0, 500, 1000 and 2000 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 500, 1000 and 2000 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.20 Acceptable study
TFNA-OH	Acute oral toxicity	Rat	2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	dRAR: B.6.8.1.16 Acceptable study
TFNA-OH	90-day dietary study	Rat	0, 2000, 5000 and 10000 ppm	NOAEL 346/400 mg/kg bw/day	dRAR: B.6.8.1.40 Acceptable study

Metabolite	Test	Test object	Concentration	Result	Reference
TFNA-OH	(Q)SAR analyses			**Carcinogenicity:** no alerts (Derek Nexus, TopKat) **Reproductive toxicity:** no alerts (Derek Nexus, Danish (Q)SAR) **Developmental toxicity:** no alerts (Derek Nexus, Danish (Q)SAR); no alerts with moderate reliability (TopKat)	dRAR: B.6.8.1.43 **Supplementary information**
TFNG	*In vitro* bacterial reverse mutation (Ames test)	*Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 *Escherichia coli* WP2 *uvrA*	Exp. 1 (plate incorporation): 0, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate in the presence and absence of S9 Exp. 2 (pre-incubation): 0, 50, 150, 500, 1500 and 5000 µg/plate in the presence and absence of S9	Negative	dRAR: B.6.8.1.22 Acceptable study
TFNG	*In vitro* mammalian cell gene mutation	Mouse lymphoma L5178Y $TK^{+/-}$ cells	Exp. 1 (3-hour exposure): 0, 155, 310, 620, 1240 and 2480 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 155, 310, 620, 1240 and 2480 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.23 Acceptable study

Metabolite	Test	Test object	Concentration	Result	Reference
TFNG	*In vitro* chromosome aberration test	Chinese hamster lung CHL/IU cells	Exp. 1 (6-hour exposure): 0, 620, 1240 and 2480 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 620, 1240 and 2480 µg/mL in the absence of S9 Exp. 2 (48-hour exposure): 0, 620, 1240 and 2480 µg/mL in the absence of S9 **(not acceptable)**	Negative	dRAR: B.6.8.1.24 Acceptable study
TFNG	*In vitro* micronucleus test	TK6 human lymphoblastoid cells	Exp. 1 (3-hour exposure): 0, 500, 1000 and 2000 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 500, 1000 and 2000 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.25 Acceptable study
TFNG	Acute oral toxicity	Rat	2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	dRAR: B.6.8.1.21 Acceptable study
TFNG	90-day dietary study	Rat	0, 50 and 2000 ppm in males (0, 3.56 and 135 mg/kg bw/day) 0, 200 and 5000 ppm in females (0, 16.5 and 411 mg/kg bw/day)	NOAEL > 135/411 mg/kg bw/day	dRAR: B.6.8.1.26 **Supplementary information**

Metabolite	Test	Test object	Concentration	Result	Reference
TFNG	(Q)SAR analyses			**Carcinogenicity:** no alerts (Derek Nexus, TopKat) **Reproductive toxicity:** only one reliable analysis: Derek Nexus, no alerts **Developmental toxicity:** only one reliable analysis: Derek Nexus, no alerts	dRAR: B.6.8.1.41 **Supplementary information**
TFNG-AM	*In vitro* bacterial reverse mutation (Ames test)	*Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 *Escherichia coli* WP2 *uvrA*	Exp. 1 (plate incorporation): 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate in the presence and absence of S9 Exp. 2 (pre-incubation): 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate in the presence and absence of S9	Negative	dRAR: B.6.8.1.28 Acceptable study
TFNG-AM	*In vitro* mammalian cell gene mutation	Mouse lymphoma L5178Y $TK^{+/-}$ cells	Exp. 1 (3-hour exposure): 0, 310, 620, 1240 and 2480 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 310, 620, 1240 and 2480 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.29 Acceptable study

Metabolite	Test	Test object	Concentration	Result	Reference
TFNG-AM	*In vitro* chromosome aberration test	Chinese hamster lung CHL/IU cells	Exp. 1 (6-hour exposure): 0, 620, 1240 and 2480 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 620, 1240 and 2480 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.30 Acceptable study
TFNG-AM	*In vitro* micronucleus test	TK6 human lymphoblastoid cells	Exp. 1 (4-hour exposure): 0, 500, 1000 and 2000 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 500, 1000 and 2000 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.31 Acceptable study
TFNG-AM	Acute oral toxicity	Rat	2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	dRAR: B.6.8.1.27 Acceptable study
TFA	*In vitro* bacterial reverse mutation (Ames test)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA102	Exp. 1 (plate incorporation): 0, 1.6, 8, 40, 200, 1000 and 5000 µg/plate in the presence and absence of S9 Exp. 2 (pre-incubation): 156.25, 312.5, 625, 1250, 2500 and 5000 µg/plate in the presence of S9 Exp. 2 (plate incorporation): 156.25, 312.5, 625, 1250, 2500 and 5000 µg/plate in the absence of S9	Negative	dRAR: B.6.8.1.33 Acceptable study

Metabolite	Test	Test object	Concentration	Result	Reference
TFA	*In vitro* mammalian cell gene mutation	Mouse lymphoma L5178Y $TK^{+/-}$ cells	Exp. 1 (3-hour exposure): 0, 360, 560, 760, 960, 1160 and 1360 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 360, 560, 760, 960, 1160 and 1360 µg/mL in the absence of S9 Exp. 2 (3-hour exposure): 0, 360, 560, 760, 960, 1160 and 1360 µg/mL in the presence of S9	Negative	dRAR: B.6.8.1.34 Acceptable study
TFA	*In vitro* chromosome aberration test	Human blood lymphocytes	Exp. 1 (3-hour exposure): 0, 340.0, 680.0 and 1360 µg/mL in the presence and absence of S9 Exp. 2 (3-hour exposure): 0, 340.0, 680.0 and 1360 µg/mL in the presence of S9 Exp. 2 (20-hour exposure): 85.00, 170.0, 340.0 and 1360 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.35 **Supplementary information**

Metabolite	Test	Test object	Concentration	Result	Reference
TFA	*In vitro* micronucleus test	TK6 human lymphoblastoid cells	Exp. 1 (3-hour exposure): 0, 285, 570 and 1140 µg/mL in the presence and absence of S9 Exp. 2 (24-hour exposure): 0, 285, 570 and 1140 µg/mL in the absence of S9	Negative	dRAR: B.6.8.1.36 Acceptable study
TFA	Acute oral toxicity	Rat	2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	dRAR: B.6.8.1.32 Acceptable study
TFA	90-day dietary study	Rat	0, 160, 1600 and 16000 ppm (0, 9.9, 98 and 1043 mg/kg bw/day in males; 0, 12.2, 123 and 1216 mg/kg bw/day in females)	NOAEL 160 ppm (9.9/12.2 mg/kg bw/day) (increased absolute and relative liver weights with increased incidence of hypertrophy; changes in clinical chemistry parameters (reduced glucose and bilirubin concentrations) and urinalysis (increased ketone levels)	dRAR: B.6.8.1.37 Acceptable study
TFA	Developmental toxicity	Rat	0, 75 and 150 mg/kg bw/day	NOAEL for maternal toxicity 75 mg/kg bw/day (increased relative liver and kidney weights at 150 mg/kg bw/day) NOAEL for foetal toxicity > 150 mg/kg bw/day)	dRAR: B.6.8.1.38 **Acceptable as a range-finding study**

Metabolite	Test	Test object	Concentration	Result	Reference
TFA	Developmental toxicity	Rat	0, 37.5, 75 and 150 mg/kg bw/day	NOAEL for maternal toxicity 75 mg/kg bw/day (slightly increased absolute liver and kidney weights at 150 mg/kg bw/day) NOAEL for foetal toxicity > 150 mg/kg bw/day)	dRAR: B.6.8.1.39 **Supplementary information**

2.6.8.2 Supplementary studies on the active substance

Immunotoxicity

A new study, not previously evaluated, on the potential of IKI-220 to induce immunotoxicity was submitted. The immunotoxicity was investigated in female ([redacted]CD1[redacted] mice after 28-day oral exposure via diet. IKI-220 was considered not immunotoxic in female CD-1 mice after 28-days of treatment via diet (dRAR: B.6.7.1.1)

Table 72: Summary table of animal studies on immunotoxicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL**	**Reference**
28-day oral (dietary) immunotoxicity study OPPTS 870.7800 (1998) Female [redacted]:CD1([redacted] mice, 10 mice/group GLP Acceptable study	IKI-220 technical, purity 98.7% Dose levels: 0, 100, 600, 6000 ppm equal to 0, 23.2, 141.8, 1540.2 mg/kg bw/d Duration of exposure: 28 days	No statistically significant increases in spleen cell number or specific activity were observed but treatment-related increases in total spleen activity were seen at all tested doses. As the study was designed to provide information about possible immunosuppression and did not comprehensively assess the immune function, IKI-220 was considered not immunotoxic in female CD-1 mice after 28-days of treatment via diet. **The NOAEL for immunosuppression** was > 6000 ppm (corresponding to 1540 mg/kg bw/d).	dRAR: B.6.8.2.6, 2012

2.6.9 Summary of medical data and information

The notifier has provided a statement on medical supervision of IKI-220 production workers. No health problem related to the manufacturing operations has been reported in the detailed periodic medical examinations (interview by doctor, chest X-ray test, urinalysis, haematology, liver function test, renal function test, lipid metabolism, glucose metabolism and others) for the workers engaged in IKI-220 production. This is considered to be due to the relatively low intrinsic toxicity of IKI-220 to humans and effective uses of personal protective equipment. Based on a review of published literature, it is concluded that there are no known epidemiological studies involving IKI-220.

2.6.10 Toxicological end points for risk assessment (reference values)

Table 73: Overview of relevant studies for derivation of reference values for risk assessment

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Beagle dog	28-day oral toxicity study (dose range finding study) OECD TG 409 (1998)	IKI-220 technical, purity 98.7%	No treatment related effects were observed except unspecific signs of toxicity at the highest dose (50 mg/kg bw/d) which clearly exceeded the MTD level.	20 mg/kg bw/d	50 mg/kg bw/d	dRAR: B.6.3.1.2, 2001
Wistar rat	90-day oral toxicity study OECD TG 408 (1998)	IKI-220 technical, purity 98.7%	Reduced food consumption, reduced plasma triglyceride concentration and hepatocellular hypertrophy	60 mg/kg bw/d	119.4 mg/kg bw/d	dRAR: B.6.3.2.1, 2002
CD-1 mice	90-day oral toxicity study OECD TG 408 (1998)	IKI-220 technical, purity 98.7%	Hepatocellular hypertrophy in males and increased splenic extramedullary hematopoiesis in both sexes	15.3 mg/kg bw/d	153.9 mg/kg bw/d	dRAR: B.6.3.2.2, 2001
Beagle dog	90-day oral toxicity study OECD TG 409 (1998)	IKI-220 technical, purity 98.7%	Reduced body weight gain and food consumption in both sexes and reduced thymus weight in males.	8 mg/kg bw/d	20 mg/kg bw/d	dRAR: B.6.3.2.3, 2001
Beagle dog	52-week oral toxicity study OECD TG 409 (1998)	IKI-220 technical, purity 98.7%	No specific target organs were affected. Hematological changes suggesting mild anemia in both sexes, and reduced body weight gain in females.	8 mg/kg bw/d	20 mg/kg bw/d	dRAR: B.6.3.2.4, 2003
Sprague-Dawley rat	28-day dermal toxicity study OECD TG 410 (1981)	IKI-220 technical, purity 98.7%	No clear treatment-related effects were observed in either sex or at any dose level.	> 1000 mg/kg bw/day	> 1000 mg/kg bw/day	dRAR: B.6.3.3.1, 2001

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
CD-1 mice (female)	28-day oral (immunotoxicity) toxicity study OPPTS 870.7800 (1998)	IKI-220 technical, purity 98.7%	No stat. sign. increases in spleen cell number or specific activity but treatment-related increases in total spleen activity at all tested doses. As the study provided information on immunosuppression and did not comprehensively assess the immune function, IKI-220 was considered not immunotoxic.	> 1540 mg/kg bw/d	> 1540 mg/kg bw/d	dRAR: B.6.8.2.6, 2012
Wistar rat	Oral (dietary) chronic toxicity and carcinogenicity study (main group 104 weeks) OECD TG 453 (1981)	IKI-220 technical, purity 98.7%	Reduced body weight and nephropathy	7.32 mg/kg bw/d	36.5 mg/kg bw/d	dRAR: B.6.5.1, 2002
CD-1 mice	Oral (dietary) carcinogenicity study (main group 78 weeks) OECD TG 451 (1981)	IKI-220 technical, purity 98.7%	Increased incidences of hepatic hypertrophy	Could not be determined	29 mg/kg bw/d	dRAR: B.6.5.2, 2003
CD-1 mice	Oral (dietary) carcinogenicity study OECD TG 451 (1981)	IKI-220 technical, purity 98.7%	Elevated incidence of pulmonary adenoma in males and hyperplasia in both sexes.	10 mg/kg bw/d	30.3 mg/kg bw/d	dRAR: B.6.5.3, 2004
Wistar rats	Two-generation reproduction study OECD TG 416 (1983)	IKI-220 technical, purity 98.7%	Parental: Thyroid weight was reduced and degenerative renal tubular lesions were observed Offspring: Delayed vaginal opening and reduced uterus weights	Parental: 18.3 mg/kg bw/d Offspring: 30.5 mg/kg bw/d Reproduction: > 109.1 mg/kg bw/d	Parental: 109.1 mg/kg bw/d Offspring: 176.8 mg/kg bw/d Reproduction: > 109.1 mg/kg bw/d	dRAR: B.6.6.1.2, 2002b

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
			Reproduction: No effects in reproduction			
Wistar rats	Developmental toxicity study OECD. 414 (2018)	IKI-220 technical, purity 98.7%	Maternal: Effects observed in the kidneys and liver. Developmental: Increased incidence of skeletal variations, namely extra cervical ribs.	Maternal: 100 mg/kg bw/d Developmental: 100 mg/kg bw/d	Maternal: 500 mg/kg bw/d Developmental: 500 mg/kg bw/d	dRAR: B.6.6.2.3, 2002b
Japanese white rabbit	Developmental toxicity study OECD. 414 (2018)	IKI-220 technical, purity 98.7%	Maternal: Reduced weight gain and food consumption Developmental: No developmental toxicity at the highest dose tested.	Maternal: 7.5 mg/kg bw/d Developmental: > 25 mg/kg bw/d	Maternal: 25 mg/kg bw/d Developmental: > 25 mg/kg bw/d	dRAR: B.6.6.2.5, 2002d

2.6.10.1 Toxicological end point for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake)

The estimation of the Acceptable Daily Intake (ADI) is based on the relevant lowest no-observed adverse effect level (NOAEL) observed in studies with respect to subchronic and chronic toxicity, neurotoxicity, carcinogenicity and reproductive toxicity.

The liver and kidney were demonstrated to be the primary target organs of chronic flonicamid exposure. In the first Annex I review of flonicamid the most relevant NOAEL for derivation of the ADI was considered to be 2.5 mg/kg bw/d based on the teratogenicity study in rabbits (dRAR: B.6.6.2.5, 2002d), showing on some indications of foetotoxicity. However, based on the current new evaluation and the RAC opinion (adopted 5 June 2013) of flonicamid, the maternal NOAEL in the rabbit teratogenicity study has been revoked and was established as 7.5 mg/kg bw/d based on the occurrence of reduced weight gain and food consumption at 25 mg/kg bw/d. Therefore, the next critical dose descriptor representing the most sensitive biological/toxicological test substance-related long term effect in mammals is the NOAEL of 7.32 mg/kg bw/d from the 2-year rat study in Wistar rats (dRAR: B.6.5.1) based on the occurrence of reduced body weight and nephropathy at 36.5 mg/kg bw/d. Hence, the proposed ADI of flonicamid is 0.073 mg/kg bw/d, based on the NOAEL of 7.32 mg/kg bw/d from the combined toxicity and carcinogenicity study in Wistar rats (dRAR: B.6.5.1) by applying a safety factor of 100.

2.6.10.2 Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

The liver and kidney were demonstrated as the primary target organs of short term flonicamid exposure to rats. In the first Annex I review of flonicamid the most relevant NOAEL for derivation of the ArfD was considered to be 2.5 mg/kg bw/d based on the teratogenicity study in rabbits (dRAR: B.6.6.2.5, 2002d), showing on some indications of foetotoxicity. However, based on the current new evaluation and the RAC opinion (adopted 5 June 2013) of flonicamid, the maternal NOAEL in the rabbit teratogenicity study has been revoked and was established as 7.5 mg/kg bw/d based on the occurrence of reduced weight gain and food consumption at 25 mg/kg bw/d. Hence, an ARfD of flonicamid is proposed at 0.075 mg/kg bw, based on the NOAEL of 7.5 mg/kg bw/d from the teratogenicity study in rabbits (dRAR: B.6.6.2.5, 2002d) and a safety factor of 100.

2.6.10.3 Toxicological end point for assessment of occupational, bystander and residents risks – AOEL (acceptable operator exposure level)

The systemic AOEL is usually based on a suitable (mostly oral) short-term study. In the first Annex I review of flonicamid the most relevant NOAEL for derivation of the AOEL was considered to be 2.5 mg/kg bw/d based on the teratogenicity study in rabbits (dRAR: B.6.6.2.5, 2002d), showing on some indications of foetotoxicity. However, based on the current new evaluation and the RAC opinion (adopted 5 June 2013) of flonicamid, the maternal NOAEL in the rabbit teratogenicity study has been revoked and was established as 7.5 mg/kg bw/d based on the occurrence of reduced weight gain and food consumption at 25 mg/kg bw/d.

Therefore, the next critical dose descriptor representing the most sensitive biological/toxicological test substance-related long term effect in mammals is the NOAEL of 7.32 mg/kg bw/d from the 2-year rat study in Wistar rats (dRAR: B.6.5.1) based on the occurrence of reduced body weight and nephropathy at 36.5 mg/kg bw/d. Flonicamid was not carcinogenic in the rat study and the NOAEL for carcinogenicity was considered higher than the highest dose tested. Oral absorption was >80% why no correction for oral absorption is needed. An uncertainty factor of 100 has been applied. Hence, the proposed AOEL of flonicamid is 0.073 mg/kg bw/d, based on the NOAEL of 7.32 mg/kg bw/d from the combined toxicity and carcinogenicity study in Wistar rats (dRAR: B.6.5.1) by applying a safety factor of 100.

2.6.10.4 Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL (acute acceptable operator exposure level)

An AAOEL was not derived during the last EU review of flonicamid. Currently no EU-wide, harmonised guidance for the derivation of an AAOEL is available. The AAOEL is proposed to be established using the same basis as for the ARfD (Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. COMMISSION GUIDANCE DOCUMENT SANTE-10832-2015 rev. 1.7. 24 January 2017). Therefore AAOEL is proposed at 0.075 mg/kg bw/d, based on the NOAEL of 7.5 mg/kg bw/d from the teratogenicity study in rabbits (dRAR: B.6.6.2.5, 2002d) and a safety factor of 100.

2.6.11 Summary of product exposure and risk assessment

There were presented two representative formulations for renewal of approval of flonicamid.

2.6.11.1 Summary of the IKI-220 100 OD exposure and assessment

The representative formulation IKI-220 100 OD is an oil dispersion (OD) containing 100 g/L flonicamid and acts as an insecticide. Based on the toxicological studies performed with the formulation, the product has low oral, dermal and inhalation toxicity. It is not irritating to skin in a three-dimensional human epidermis model. Irritancy to the eye was inconclusive in a Bovine Corneal Opacity and Permeability (BCOP) test and was not irritating to the rabbit eye in vivo. IKI-220 100 OD induced skin sensitisation in mouse LLNA test why the following labelling in accordance with CLP Regulation (EC) No 1272/2008 is warranted: **Skin Sens. 1; H317 (May cause an allergic skin reaction).** Also, an additional labelling **EUH066 (Repeated exposure may cause skin dryness or cracking)** is proposed.

Table 2.6.11.1-1 Summary of acute toxicity studies of IKI-220 100 OD

Reference	Study type	Species / strain	Comments	Results
dRAR: B.6.1.1	LD_{50} oral (14 days)	Wistar rat	No test substance related signs of toxicity	LD_{50} >5000 mg/kg bw
dRAR: B.6.1.2	LD_{50} dermal (14 days)	Wistar rat	No test substance related signs of toxicity	LD_{50} >2000 mg/kg bw
dRAR: B.6.1.3	LC_{50} inhalation (14 days)	Sprague Dawley rat	4 hours “nose only”-exposure to aerosol atmosphere	LC_{50} > 5.08 mg/L air
dRAR: B.6.1.4	Skin irritation	*In vitro* (reconstructed human epidermis)		Non-irritant to skin
dRAR: B.6.1.5 Study 1	Eye irritation	*In vitro* (bovine corneal opacity and permeability (BCOP))	Irritation score: 10.30 (positive control: 54.05; negative control: -0.39	Inconclusive
dRAR: B.6.1.5 Study 2	Eye irritation	New Zealand White rabbit	Mild irritant effects, fully reversible within 5 days	Non-irritant to eyes
dRAR: B.6.1.6	Skin sensitisation, LLNA	CBA/[redacted] mouse	Calculation of EC3 not possible (stimulation indices of all concentrations > 3)	Sensitising to skin **Skin Sens. 1; H317**

The representative insecticidal uses of IKI-220 100 OD are intended for field applications on dry beans and dry peas (pulses) as well as on cereals (winter and spring wheat, rye and triticale). According to the GAP, all uses have

identical application rates and IKI-220 100 OD is applied to all crops by tractor mounted foliar spray. For IKI-220 100 OD, the product dose rates for the crops intended are fixed at 50 g a.s./ha by foliar treatments in the representative uses: the recommended volumes of water range, depending on the crop and region, from 100 to 600 L/ha. IKI-220 100 OD is applied once per crop and season. The timing is from April to June/beginning of July for pulses. For winter and spring wheat, rye and triticale, IKI-220 100 OD can be applied from BBCH 39 till PHI of 28 days. For pulses (dry beans and dry peas) IKI-220 100 OD can be applied from BBCH 11 – 71.

The dermal absorption values for respectively the neat formulation and the spray dilution were considered 3.4% and 29%. The obtained predicted exposure was compared with the appropriate AOEL (0.073 mg/kg bw/day)/ AAOEL (0.075 mg/kg/bw per day) and expressed as % of AOEL/AAOEL.

The following exposure models were used for assessment of exposure of operators, workers, residents and bystanders:

> EFSA Guidance: Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874

Operators

Following calculations using the EFSA model it was demonstrated that there is no undue risk of exposure for operators to cereals or pulses in fields when standard protected workwear (e.g., arms, body and legs covered). However, the product IKI-220 100 OD is classified as skin sensitizer and therefore protective gloves are recommended during mixing/loading or other tasks where exposure is possible.

Bystander and resident

According EFSA calculators there is no undue risk for bystander's adults and for children when IKI-220 100 OD is applied as intended use. For resident, there is no unacceptable risk anticipated for an adult or a child resident incidentally exposed to IKI-220 100 OD in cereal or pulse field.

Worker

According to EFSA calculator, there is no unacceptable risk anticipated for a worker wearing working clothing when re-entering cereal or pea/bean fields.

2.6.11.2 Summary of the IKI-220 500 WG exposure and assessment

The representative formulation IKI-220 500 WG is a wettable granule (WG) containing 500 g flonicamid/kg use as insecticide. The toxicological studies (i.e., acute oral and dermal toxicity, skin and eye irritation, skin sensitisation studies) have been performed with the formulation IKI-220 500 WG. IKI-220 500WG has low toxicity with respect to acute oral, inhalation and dermal routes of administration and is not irritating to the rabbit skin. It has been found that the product should be classified for irritancy to rabbit eye according to Regulation (EC) 1272/2008. The formulation IKI-220 500 WG is not a skin sensitizer.

Table 2.6.11.2-1 Summary of acute toxicity studies of IKI-220 500 WG

Reference	Study type	Species / strain	Vehicle/Solvent	Comments	Results
dRAR: B.6.1.1, 2001	LD_{50} oral (14 days)	Wistar rat	Distilled water	No test substance related signs of toxicity	LD_{50} >2000 mg/kg bw
dRAR: B.6.1.2, 2002	LD_{50} dermal (14 days)	Wistar rat	Distilled water	Occasional and transient slight erythema	LD_{50} >2000 mg/kg bw
dRAR: B.6.1.3, 2002	LC_{50} inhalation (14 days)	Sprague Dawley rat	None (used as supplied)	4 hours "nose only"-exposure to aerosol atmosphere	LC_{50} > 5.36 mg/L air
dRAR: B.6.1.4, 2001a	Skin irritation	New Zealand White rabbit	Distilled water		Non-irritant to skin
dRAR: B.6.1.5, 2001b	Eye irritation	New Zealand White rabbit	Distilled water	Mildly irritant effects	**Eye Irrit. 2; H319** - Causes serious eye irritation
dRAR: B.6.1.6.1, 2002	Skin sensitisation, Buehler test	Guinea pig	Distilled water		No skin sensitisation
dRAR: B.6.1.6.2, 2004	Skin sensitisation, Buehler test	Guinea pig	Distilled water		No skin sensitisation
dRAR: B.6.1.6.3, 2005	Skin sensitisation, LLNA	CBA/[redacted] mouse	N.N-dimethylformamide (DMF)	Stimulation indices < 3 at all concentrations	No skin sensitisation

According to the Regulation (EC) No. 1272/2008, IKI-220 500 WG should be classified as follows:
Eye Irrit. 2; H319 (Causes serious eye irritation).

The representative insecticidal uses of IKI-220 500 WG are intended for field and greenhouse applications. Field applications are intended on cereals (wheat), pome fruits (apples, pears), stone fruits (peaches, apricots, plums, cherries) and fruiting vegetables (cucumber, courgette, tomato, eggplant, melons). Greenhouse applications are intended on fruiting vegetables (cucumber, courgette, tomato, eggplant).

For IKI-220 500 WG, the product dose rates are varying, depending on the crop-pest combinations from 50 to max. 80 g a.s./ha by foliar treatments in the representative uses: the recommended volumes of water range, depending on the crop, from 200 to 1200 L/ha (exceptionally 1500 L for foliar treatments in some orchard crops).
The concentrations in the spraying water will then, theoretically vary from 50 g a.s. in 1000 L (0.05 g/l) to 70 g a.s. in 200 L water (0.35 g/l), respectively, for unprotected vegetables and cereals and various orchards in field conditions.

For foliar treatments, the maximum number is depending on the crop-pest combinations; up to 2 or 3 treatments are currently registered; due to resistance management considerations and potential regulatory limitations, some of these maximum allowed number of treatments may change. The interval between treatments under field conditions is crop dependent and varies from 1-3 weeks (relates to the climatic conditions and speed of re-instalment of aphid populations). Under greenhouse conditions the interval at continued pressure is limited to only 7 days.

The dermal absorption values for respectively the neat formulation and the spray dilution were considered 0.1% and 16%. The obtained predicted exposure was compared with the appropriate AOEL (0.073 mg/kg bw/day)/ AAOEL (0.075 mg/kg/bw per day) and expressed as % of AOEL/AAOEL.

The following exposure models were used for assessment of exposure of operators, workers, residents and bystanders:

• Guidance on the assessment of exposure of operators, workers, residents, and bystanders in risk assessment for plant protection products (EFSA Journal 2014;12(10):3874) - including an exposure calculation spread sheet ("EFSA model"). Calculator version: 30.03.2015.

• EUROPOEM 1996, The development, maintenance, and dissemination of a European Predictive Operator Exposure Model (EUROPOEM) Database, AIR3-CT93-1370. DGVI.FII3 [Ctgb – College voor de toelating van gewasbeschermingsmiddelen en biociden, Wageningen, The Netherlands, ("EUROPOEM"). CORDIS_project_AIR21370_en.pdf and https://english.ctgb.nl/binaries/ctgb-en/documenten/assessment-framework-ppp/2016/10/27/calculation-model-operator-europoem-1/guidance+operator+europoem+i+v01-2.xls

• Mich, G. (1996); Operator Exposure in Greenhouses During Practical Use of Plant Protection Products; exposure model based on data conducted under the sponsorship of the German Industry association, the IVA (Industrieverband Agrar) ("German greenhouse model").

• Southern European glasshouse model (SE glasshouse model). Documented in: EFSA AGREEMENT NUMBER EFSA/PPR/2007/01 FINAL REPORT (28 November 2008): Project to assess current approaches and knowledge with a view to develop a Guidance Document for pesticide exposure assessment for workers, operators, bystanders, and residents. Prepared by the Pesticides Safety Directorate, UK (Paul Hamey, Neil Byron, Louise Hanley, Wendy Leslie & Neil Morgan) in collaboration with Ghent University, BE (Walter Steurbaut, Eline de Backer & Sofie Vergucht), pp. 34-39.

Operators

Following calculations using the EFSA model and three different greenhouse models (EUROPOEM, German greenhouse model and Southern Europe glasshouse model) it was demonstrated that there is no undue risk of exposure for operators to field or greenhouse crops when standard protected workwear (e.g., arms, body and legs covered) were worn. However, the product IKI-220 500 WG is classified as eye irritating and therefore protective

glasses or face shield are recommended during mixing/loading or other tasks where exposure is possible.

Bystander and resident

According EFSA calculators there is no undue risk for bystander's adults and for children when IKI-220 500 WG is applied as intended use. For resident, there is no unacceptable risk anticipated for an adult or a child resident incidentally exposed to IKI-220 500 WG in intended field uses.

IKI-220 500 WG is also intended for glasshouse uses on fruiting vegetables (cucumber, courgette, tomato, eggplant). Applying IKI-220 500 WG in a greenhouse does not lead to relevant exposures of bystanders and residents, because a re-entry into exposed areas is restricted to workers. In addition, the risk of bystander and resident exposure via spray drift or vapour at the time of application or thereafter is very limited and will in any case be covered by the exposure calculations of the operator.

Worker

According to the EFSA model, the predicted level of worker exposure to flonicamid is well within the acceptable range for outdoor and greenhouse uses if gloves are applied for the re-entry in pome fruits/stone fruit (outdoor) as well as for fruiting vegetables in the greenhouse.

2.7 RESIDUE

2.7.1 Summary of storage stability of residues

Deep frozen storage stability of flonicamid and the metabolites TFNA and TFNG included in the residue definitions of flonicamid were investigated in all required commodity types including high water, high acid, high starch, high protein and high oil content commodities. In addition, stability was also tested in cereal straw and honey, included in the others group. Tested minimum stability in these commodities are shown in Table 2.7.1.-1. Stability of the three compounds were similar in all commodities except for in cereal processed commodity bread in which stability of TFNA was lower compared to flonicamid and TFNG (3 vs. 15 months).

Table 2.7.1.-1. Summary of storage stability of flonicamid and its metabolites in various commodities.

Commodity category	Commodity	Storage period [months]	Reference
RAC samples			
Flonicamid			
High water commodity	Apple	18	KCA 6.1/01
	Plums	29	KCA 6.1/02
High acid commodity	Orange (whole fruit)	24	KCA 6.1/04
High starch commodity	Wheat grain	18	KCA 6.1/01
		43	KCA 6.1/02
	Potato	18	KCA 6.1/01
High oil commodity	Oilseed rape seeds	12	KCA 6.1/03
High protein commodity	Dry bean	12	KCA 6.1/03
Others	Wheat straw	18	KCA 6.1/01
		43	KCA 6.1/02
	Honey	6	KCA 6.1/06
TFNG			
High water commodity	Apple	18	KCA 6.1/01
High acid commodity	Orange (whole fruit)	24	KCA 6.1/04
High starch commodity	Wheat grain	18	KCA 6.1/01
		43	KCA 6.1/02
	Potato	18	KCA 6.1/01
High oil commodity	Oilseed rape seeds	12	KCA 6.1/03
High protein commodity	Dry bean	12	KCA 6.1/03
Others	Wheat straw	18	KCA 6.1/01
		43	KCA 6.1/02
	Honey	6	KCA 6.1/06
TFNA			
High water commodity	Apple	18	KCA 6.1/01
High acid commodity	Orange (whole fruit)	24	KCA 6.1/04
High starch commodity	Wheat grain	18	KCA 6.1/01
		43	KCA 6.1/02
	Potato	18	KCA 6.1/01
High oil commodity	Oilseed rape seeds	12	KCA 6.1/03

High protein commodity	Dry bean	12	KCA 6.1/03
Others	Wheat straw	18	KCA 6.1/01
		43	KCA 6.1/02
	Honey	6	KCA 6.1/06
TFNA-AM			
High water commodity	Apple	18	KCA 6.1/01
High starch commodity	Wheat grain	18	KCA 6.1/01
		43	KCA 6.1/02
	Potato	18	KCA 6.1/01
Others	Wheat straw	18	KCA 6.1/01
		43	KCA 6.1/02
	Honey	6	KCA 6.1/06
TFNG-AM			
Others	Honey	6	KCA 6.1/06
Processed			
Flonicamid, TFNG, TFNA-AM			
Processed	Bread	15	KCA 6.1/05
TFNA			
Processed	Bread	3	KCA 6.1/05

Storage stability of metabolites TFNA-AM and TFNG-AM not included in the residue definitions were also tested in few commodity types (see Table 2.7.1.-1.).

No storage stability data were provided for metabolite TFA. Storage stability data on TFA is necessary to support the magnitude of residue studies in rotational crops.

No storage stability studies of the analytes in livestock commodities were submitted or evaluated. Storage stability of analytes were tested within the feeding studies evaluated in the present RAR. In the poultry feeding study (KCA 6.4.1/01), flonicamid, TFNG, TFNA, TFNA-AM and OH-TFNA-AM were stable in egg, muscle, liver, and fat for or 299, 251, 253 and 243 days when stored at -20°C. In the ruminant feeding study (KCA 6.4.2/01), acceptable storage stability of 374, 374, 374 and 315 days for muscle, liver, kidney and fat, respectively, was demonstrated when stored at -20°C.

Storage stability of flonicamid and its metabolites in several different crop extracts were also tested. The extracts were stored at refrigerator temperatures.

Table 2.7.1.-2. Stability of flonicamid and its metabolites in extracts of various commodities.

Extract type	Extract/ solvent	Minimum stability (days)							Study
		Flonicamid	TFNG	TFNA	TFNA-AM	TFNG-AM	TFNA-OH	TFA	
potato	acetone	20	20	20	20				CA 6.1/01
apple	acetone	20	20	20	20				CA 6.1/01
	acetonitrile	15	20	20					CA 6.1/07
plum	acetone	7	7	7	7				CA 6.1/02

lettuce	acidified water	16	16	16	16	16	16	15	CA 6.1/08
orange	acetonitrile	3	3	3					CA 6.1/04
	acetonitrile	13	13	13					CA 6.1/07
	acidified water							25	CA 6.1/08
sunflower seed	acetonitrile	13	13	13					CA 6.1/07
OSR seed	acetonitrile/ water	5	5	5					CA 6.1/03
	acidified water							42	CA 6.1/08
dry beans	acetonitrile/ water	6	3	6					CA 6.1/03
wheat grain	acetone	20	20	20	20				CA 6.1/01
	acetone	4	4	4	4				CA 6.1/02
	acetonitrile	15	15	15					CA 6.1/07
	acidified water	20	20	20	20	20	20	13	CA 6.1/08
wheat straw	acetone	20	20	20	20				CA 6.1/01
	acetone	3	3	3	3				CA 6.1/02
	acidified water	8	8	8	8	8	8	14	CA 6.1/08
Sugar beet root	acidified water							14	CA 6.1/08
honey	methanol/ water	3	3	11	3	3			CA 6.1/06

The analytical methods used in the storage stability studies were all acceptably validated and deemed fit for purpose.

Within the feeding studies, storage stability of flonicamid, TFNG, TFNA, TFNA-AM and OH-TFNA-AM were investigated in poultry and cow matrices. Acceptable storage stability of 299, 251, 253 and 243 days was demonstrated for poultry egg, muscle, liver, and fat, respectively. Acceptable storage stability of 374, 374, 374 and 315 days was demonstrated the analytes in cow muscle, liver, kidney and fat, respectively.

2.7.2 Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

Primary crops

During the previous active substance evaluation (DAR 2005 & addenda -2011 by France, EFSA 2010), studies on metabolism of flonicamid after foliar application of ^{14}C ring labelled substance was submitted for three crop groups; cereals (wheat), root/tuber crop (potatoes) and fruit crop (peaches). An additional metabolism study on pepper was evaluated in the addendum 7 (France, March 2009). In addition, new studies on metabolism of flonicamid in wheat forage and hay and in potato were submitted for the current review.

Wheat (cereal crops)

A study on metabolism of flonicamid in mature wheat commodities grain, straw and chaff at 21 DAT was evaluated in the DAR (2005) and the present RAR. In addition, a supplementary study on wheat forage (14 DAT) and hay (7 DAT) was provided for the present review. In the study with mature wheat, plants were treated with a PHI of 21 days in accordance with the critical GAP, however, the application rate 100 g a.s./ha was only 0.7N compared to the critical GAP (2x 70 g a.s./ha). In the study with forage and hay, rate of 1x 100 g a.s./ha (0.7N) was used with 7 days (hay) and 14 days (forage) PHIs. The radiolabel in both studies was in the ^{14}C-3-pyridyl position.

The metabolic pattern can be expected to be in main parts similar in mature and immature wheat commodities.

In mature wheat grain, metabolite TFNG formed the main residue 39% of TRR (0.11 mg/kg) and parent was responsible for 30% of TRR (0.08 mg/kg). Other significant metabolites in grain were TFNA (8% of TRR / 0.022 mg/kg) and TFNA-AM (6% of TRR / 0.017 mg/kg). Minor metabolites in grain included TFNG-AM (3% / 0.009 mg/kg) and N-oxide TFNA-AM (3% / 0.008 mg/kg), the latter only detected in grain at higher 3.6N rate.

Parent flonicamid was responsible for main part of residues in mature straw and chaff (50% and 41% of TRR, respectively / 1.0-1.5 mg/kg) TFNG was the second highest compound in straw and chaff (20% and 17% of TRR, respectively / 0.40-0.57 mg/kg). Other significant metabolites in straw and chaff included TFNA (2% / 0.041 mg/kg and 6% / 0.204 mg/kg), TFNG-AM (4.5% / 0.091 mg/kg and 5.4% / 0.193 mg/kg) and TFNA-AM (1.8% / 0.036 mg/kg and 2.5% / 0.088 mg/kg).

1N HCl treatment released only minor amounts of metabolites in grain. In straw, the main metabolite released was TFNA (0.045 mg/kg) which is equivalent to the free amount (0.041 mg/kg). In chaff, highest released residues were due to TFNG (2% / 0.074 mg/kg) and TFNG-AM (2% / 0.067 mg/kg).

In addition, an unknown metabolite M10 (molecular weight 375) was found at level of 4.9%/0.176 mg/kg in chaff but was not further identified. Chaff may be used as feed. The molecular weight is high and the compound may be, for example, a simple sugar conjugate. As 71% of TRR in chaff were identified, identification of the metabolite M10 was not considered necessary.

Main metabolites in wheat forage and hay collected at 14 and 7 DAT were parent flonicamid (43% of TRR and 22% of TRR, respectively) and TFNG (33% and 53%). Other significant metabolites were TFNA (3.8-6.5% / 0.036-0.039 mg/kg) and TFNG-AM (11-13% / 0.066-0.122 mg/kg), while TFNA-AM was minor metabolite (max. 1% / 0.01 mg/kg in hay).

Extractability of residues was high in all wheat commodities (76-96% of TRR). Main part of radioactivity in the non-extractable residue of straw and chaff was shown to be associated in lignin (50-58% of bound residue) and in smaller extent to carbohydrates (14-20% of bound residue).

In the magnitude of residue trials, mostly flonicamid, TFNG and TFNA were measured. Flonicamid and TFNG formed the main residues in collected green plant at 0-7 DALA, while TFNG was dominant residue in mature grain. In mature straw, parent compound and TFNG were usually both present. Levels of TFNA were generally low in all commodities, however, in mature grain it was usually measured at higher level than the parent compound. Level of TFNA-AM were measured in grain and straw in 3 studies, but residue levels were <LOQ in nearly all samples. Residues above LOQ were measured in one stem sample at 14 DALA (0.03 mg/kg), grain at 21 DALA (0.07 mg/kg), and mature gain at 30 DALA (0.09 mg/kg), the latter was <LOQ at analysis of replicate sample. The magnitude of residue studies thus show similar residue pattern in cereal products as detected in the nature of residue studies.

Relevance of TFNA-AM and TFNG-AM in wheat feed items (straw, chaff, forage and hay) was further considered by the RMS: In wheat straw and chaff, TFNA-AM was found at levels of 1.8-2.5% of TRR/ 0.036-0.088 mg/kg in the NoR studies with 0.7N rate, while TFNG-AM was found at >2-fold higher amounts 0.091-0.193 mg/kg / 4.5-5.4% of TRR. TFNA-AM was analysed in straw in several MoR studies but was not found at levels >LOQ. It should be noted, however, that levels of TFNG-AM were higher than those of TFNA-AM or even TFNA in wheat straw, forage and hay in the metabolism studies. In wheat forage and hay, TFNA-AM was found at low levels (max. 1% / 0.01 mg/kg) while TFNG-AM was found at significant levels of 11-13% of TRR / 0.066-0.122 mg/kg. As these levels are even higher than those of TFNA (0.04 mg/kg / 4-7% of TRR), TFNG-AM can be regarded as a significant metabolite in cereal forage and hay. TFNA-AM or TFNG-AM were not analysed for in the magnitude of residue studies of forage and hay, and thus no proper conversion factor (CF) can be derived for possible inclusion of TFNG-AM in residue definitions of livestock feed items. However, as the levels of TFNG-AM were low compared to the levels of main metabolites flonicamid and TFNG in primary cereal crop feed items, RMS did not consider inclusion of TFNG-AM necessary in feed residue definitions.

Potatoes (root and tuber crops)

The critical GAP for potatoes according to import tolerance (USA) is 3x 100 g a.s./ha with PHI of 7 days (EFSA 2020 / Finland 2019). Compared to this, the GAPs followed in the two potato metabolism studies is slightly less critical (2x 100 g a.s./ha i.e. approx. 0.7N, and PHI 14 d). Compared to the GAP of the MRL application in the present RAR (2x 80 g a.s./ha), the rate in the study was 1.3N.

Older study [redacted] 2002, CA 6.2/03) was evaluated in the DAR (2005) whereas the new study [redacted] 2018, CA 6.2/04) was submitted for the current re-evaluation. Both studies were considered acceptable and metabolism of flonicamid in potatoes as sufficiently studied. In the older study, the radiolabel was on the ^{14}C-3-pyridyl position and in the ^{14}C-4-pyridyl position in the more recent study.

Translocation of residues to tubers from treated foliage was shown to be low in both studies in the studied time frame of 14 days. Residues in tubers were 0.016-0.106 mg/kg whereas residue levels in foliage were 1.5-65 mg/kg at 1.3-1.4N application rate. It should be noted, however, that in potato field studies higher residues were detected at longer PHIs (see Vol3 B7 section B.7.3.2.). Thus, translocation of residues from foliage to tubers does occur but it is slow.

Main metabolites in tubers were identified as TFNG and TFNA, representing 27-39% and 34-69% of TRR at 1.3-1.4N rate, respectively. No other metabolites were identified in the new potato metabolism study whereas in the older study, also parent flonicamid (5.6% of TRR / 0.006 mg/kg) and a putative sugar conjugate of TFNA (6% of TRR / 0.006 mg/kg) were detected. Minor metabolites TFNG-AM and TFNA-AM represented at maximum 1% of TRR (<0.002 mg/kg). In the more recent study KCA 6.2.1/04, the radiolabel was positioned in the 4-position of the pyridyl ring, allowing the detection of possible metabolite TFA. TFA was not analysed in the study, but no major fractions of unidentified metabolites were present either.

Although not required by the guideline, the metabolites in foliage were analysed. Main metabolites in foliage detected in the older study were TFNG (36% of TRR), TFNA (17% of TRR) and flonicamid (10% of TRR), whereas only parent flonicamid (representing 92% of TRR) was detected in the new study. Minor metabolites detected in the older study were TFNA conjugate, TFNG-AM and TFNA-AM, which were found at level of 3-8% of TRR (max 0.08 mg/kg at 0.7N group). Unidentified metabolites PM-1a and PM-1b were found at level of 2-4% of TRR (max 0.06 mg/kg at 1.3N group).

Extractability of residues from tubers was 91-96% and from foliage 89-97%. Unextractable residue was <10% of TRR / <0.01 mg/kg in tubers. In foliage, the unextractable residue was higher, 11% / 0.17 mg/kg (older study) and 3% / 2.2 mg/kg (newer study) at the 1.3-1.4N treatment group. The high level of unextractable residues in foliage may have warranted further examination in both studies, but this is not considered a major deviation as potato foliage is not a feed item.

The two studies showed similar metabolic profile in potato tubers with TFNA and TFNG as the main metabolites. In foliage, however, only parent was detected in the new study, whereas similar metabolic pattern was detected in tubers and foliage in the older study. In addition, residue levels in tuber were significantly lower in the new study compared to levels detected in the older study, however, levels in foliage were significantly higher in the new study. Reason for this discrepancy may be (presumably) later application growth stage in the new study (BBCH 91 & 95). The foliage looked rather dry at the second application stage and at harvest which may have concentrated the residues and maybe also limited translocation to tubers. This is, however, difficult to confirm as no BBCH growth stage was given for the older study and thus, no reliable comparison can be given. It should also be noted that the new study was performed in a greenhouse which may have affected the levels of parent and metabolites. According to the fate section (see Vol1 soil photolysis), DT50 values for irradiated and dark samples were 22.4 days (irradiated samples) and 53.3 days (dark samples). Thus, the greenhouse environment may have some effect on the detected residue pattern in respect to photolytic degradation.

Peaches and peppers (fruit crops)

Metabolism of flonicamid in fruit crops was studied in peaches and bell peppers. Study on peaches was evaluated in the original DAR (2005) and the additional study on peppers in its addendum vol 7 (France, March 2009). In the

older study, the radiolabel was on the ^{14}C-4-pyridyl position and in the ^{14}C-3-pyridyl position in the more recent study.

The critical GAP for peach in the current renewal assessment includes 2x 70 g a.s./ha with 21 d interval and 14-21 d PHI. The application rates used in the study were more critical (1.4N & 7.1N) while PHI was 21 d.

No specific GAP is available for bell peppers as it is not among representative uses. The critical GAPs for fruits and fruiting vegetables in the current renewal assessment includes 3x 70 g a.s./ha with 7 days interval and 1 day PHI for melon (non-edible peel) and 3x 80 g a.s./ha with 7 days interval and 1 day PHI for greenhouse-cultivated cucumber and courgette. The GAP followed in the study is thus less critical in respect of both application rate (0.4N) and PHI (7 & 14 days vs. 1 day).

Main residues in peach fruit was formed by TFNA (49% of TRR / 0.049 mg/kg) and parent flonicamid (30% of TRR / 0.030 mg/kg) in fruits treated at 1.4N rate. At the exaggerated rate, parent flonicamid formed the main residue (61% of TRR) while TFNA was found at lower rate (18%). Minor metabolites (TFNG, and TFNA-AM & TFNG-AM) were responsible for <6% of TRR / <0.01 mg/kg each.

In bell peppers, the parent compound was responsible for the main residue in surface wash and the fruit extract (in total 91% of TRR / 0.155 mg/kg at 7 days PHI and 77% / 0.082 mg/kg at 14 days PHI). Minor metabolites included TFNG and TFNA which were both detected at <0.01 mg/kg and 2.8-7.8% of TRR and 0.9-3.7% of TRR, respectively.

The quantitative difference in levels of parent and the metabolites between peaches and peppers may be due to longer PHI of 21 days used for peaches vs. PHI of 7 and 14 days for peppers. It should also be noted that the pepper study was performed in greenhouse conditions (see considerations on photolysis in case of potato metabolism studies above).

Metabolism of flonicamid in foliage was also investigated in both crops. Main residue in peach leaves was due to flonicamid (33%), TFNG (19%) and TFNA (16% of TRR), while the AM metabolites of TFNG and TFNA were responsible for 3-4% of TRR. Nearly similar metabolic pattern was observed in pepper leaves: main residues in leaves were due to parent flonicamid (31-38% of TRR) and TFNG (12-28% of TRR), while TFNA and TFNA-AM were detected at <2.5% of TRR / <0.045 mg/kg. The proportion of TFNA in both peach foliage and fruits were higher than in peppers, possibly due to longer PHI.

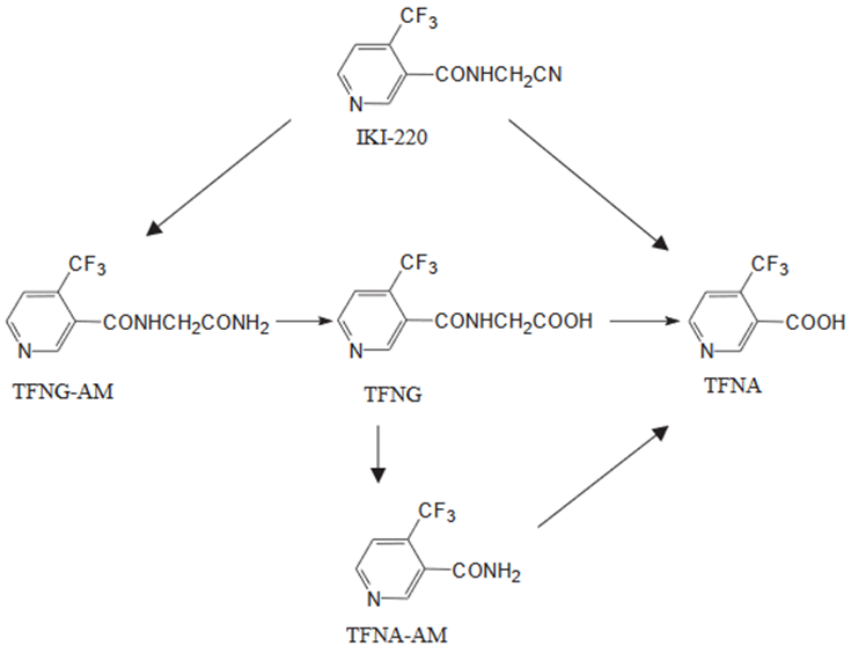
Extractability of residues was high for both fruit crops (98-99% of TRR) and for leaves (89-97%). Unextractable residue was low in both studies for fruits <5% and <0.01 mg/kg. while in leaves it was at highest 11% / 0.67 mg/kg in peach foliage. As leaves have no significance as food/feed, no further extraction is considered necessary.

While parent flonicamid and TFNA were major residues in the metabolism studies, flonicamid, TFNG and TFNA were all detected at significant levels with somewhat differing proportions in different crops in the magnitude of

residue studies on fruit crops (peach, plum, cucumber, tomato, melon and cherry – see Vol 3 part B.7). Thus, also TFNG may be considered as a significant metabolite in fruit crops.

As a summary, the overall qualitative metabolism was similar in all plant commodities. The major metabolic routes of flonicamid in plants is presented in Figure 2.7.3.-1.

Figure 2.7.3.-1. Metabolism of flonicamid (IKI-220) in primary crops.



Succeeding crops

Two studies on metabolism of flonicamid in rotational crops were provided for the current evaluation.

In the first study, ^{14}C-flonicamid labelled at the 3-position of the pyridyl ring was applied at a rate of 2x 100 g a.s./ha (1.1N). Plant-back intervals (PBIs) of 30, 120 and 360 days were investigated. Taking into account that no crop interception was present, it is reasonable to assume that no residues above LOQ are expected in leafy crops and root & tuber crops even at the shortest PBI of 30 days. In wheat grain, residues above LOQ are also not expected. At the shortest investigated PBI of 30 days, low levels of residues of TFNA-OH, TFNG, and TFNG-AM may be present in feed commodities (0.013-0.033 mg/kg). Compared to the metabolism in primary crops, proportions of metabolites TFNG-AM, TFNA-AM and TFNA-OH were higher in rotationally grown wheat. However, no new metabolites were identified in rotational crops compared to primary crops.

Metabolite trifluoroacetic acid (TFA) is a potential soil metabolite. This metabolite was not analysed for in the primary crop metabolism studies or the above old study on rotational crops. TFA may be detected only if the parent compound is labelled in the 4-carbon position of the pyrimidine ring. The radiolabel was positioned in 4-carbon of the ring structure in two primary crop metabolism studies evaluated in the present review (KCA 6.2.1/04 potato

study and 6.2.1/05 peach study). No significant unknown compounds were characterised in these studies. As TFA is a soil metabolite, it is assumed to be more relevant for succeeding crops.

A new rotational crop metabolism study using ^{14}C-flonicamid labelled at the 4-position of the pyridyl ring was provided for the current evaluation. Application rate in the study was 1x 240 g a.s./ha (1.3N) and PBIs were 30, 160 and 345 days. The study was performed in greenhouse conditions. Compared to the study with 3-carbon labelled active substance and slightly lower application rate (1.1N), TRRs in this study were higher and above LOQ of 0.01 mg/kg in all commodities at all sampling time points. TFA was the main metabolite in all tested commodities at all PBIs. In lettuce, TFA represented 94-97% of TRR, and 66-93% of TRR in carrot root. In wheat forage, hay and straw, TFA represented 53-96% of TRR, and in grain 24-73% of TRR. The only other identified metabolite, hexose conjugate of a TFA intermediate, KB-2179- ßS, was detected in wheat forage, hay and straw at PBIs of 30-160 days, representing 2.3-16.5% of TRR / 0.002-0.021 mg/kg. No parent compound, TFNG, TFNA, TFNG-AM or TFNA-OH were detected. As the application rate was 1.3N compared to the cGAP in the present RAR, residues of TFA above 0.01 mg/kg are possible at all PBIs in leafy crops (lettuce), at 30-day PBI in mature carrot, in wheat grain and forage at PBI of 30 days, and at all PBIs in wheat hay and straw.

Based on the new study with ^{14}C-flonicamid labelled at the 4-position of the pyridyl ring, it is evident that TFA represents the major metabolite in succeeding crops while parent or the other metabolites detected in primary crops are either not detected or present in very low concentrations.

Livestock commodities

Poultry

One study on metabolism of flonicamid in laying hen was provided for the previous active substance evaluation (DAR 2005) as well as for the current RAR.

Laying hen received a dose of 0.78 mg a.s./kg bw/day, corresponding to 11.8N of the maximal evaluated dietary burden, for 5 consecutive days. Dosing was carried out for 5 days instead of 7 days as recommended in guideline. Plateau level was not reached in egg yolk.

Extractability of residues from poultry matrices with acetonitrile + acidified acetonitrile:water was generally high, 94.6-99.9% of TRR, except for kidney for which extractable residues represented 81.2% of TRR.

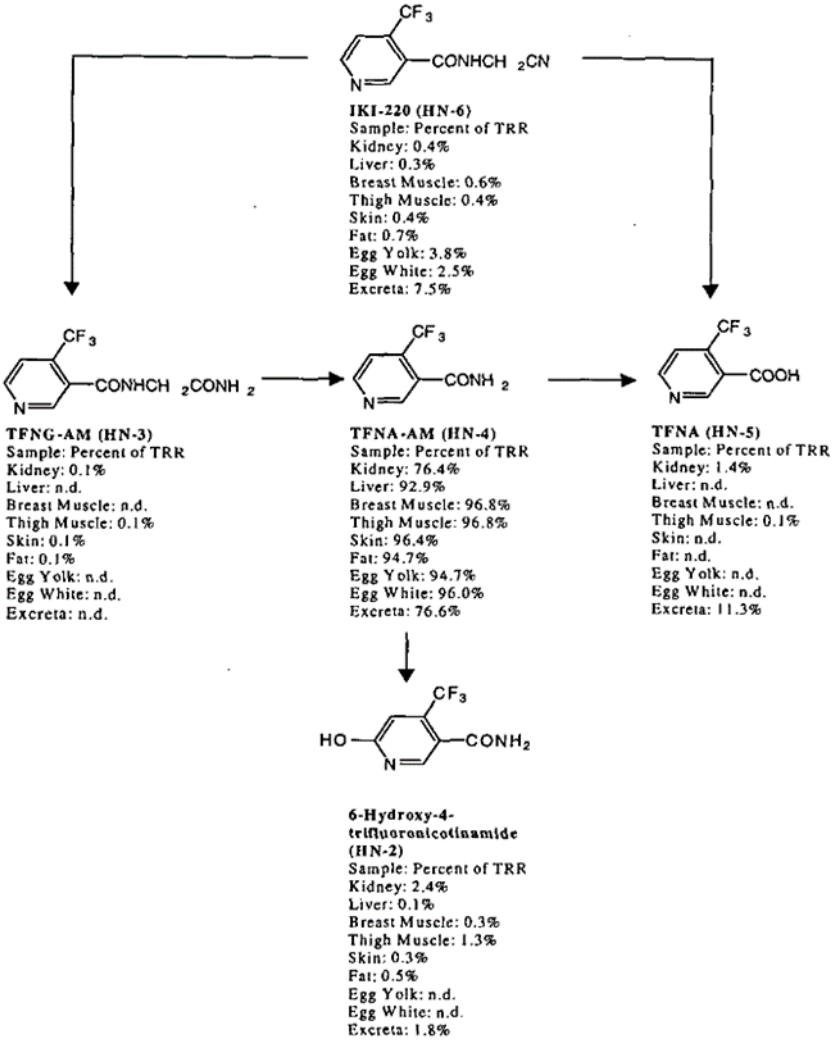
Metabolite TFNA-AM was responsible for the main part of residues in all poultry matrices, representing 92.9-96.8% of TRR (0.47-1.10 mg/kg) in tissues and egg commodities, except for kidney, where the metabolite was present at level of 76.4% of TRR (1.08 mg/kg). TFNA-AM was also the main residue released after acid or protease treatment of kidney and liver PES.

No other significant metabolites were identified in poultry matrices. Metabolite 6-hydroxy-TFNA-AM was detected at highest 2.4% of TRR (0.0335 mg/kg) in kidney. Further strong acid hydrolysis of kidney released additional 6-

OH-TFNA-AM (0.9%/0.0122 mg/kg) and TFNA (1.5%/0.0211 mg/kg). Parent flonicamid was detected at highest in egg white and yolk at similar level of 2.5% of TRR (0.0184 mg/kg) and 3.8% of TRR (0.0188 mg/kg), respectively. Given the high overdosing of the study birds compared to the calculated dietary burden (11.8N), no significant residues of parent or the minor metabolites are expected in poultry commodities.

The proposed metabolism of flonicamid in poultry is presented in Figure 2.7.3.-2.

Figure 2.7.3.-2. Metabolism of flonicamid (IKI-220) in poultry.



Unextractable residues were <2% for most of the commodities with the exception of liver (5.4%) and kidney (18.8%). Radioactivity in liver and kidney was nearly completely released by acid and protease treatments. From both commodities, an unknown component representing 2.9-3.6% of TRR (0.04 mg/kg) was released. The identity of the component was not investigated further. At the present maximal dietary burden level, the component is not expected to occur at level >0.01 mg/kg.

According to the livestock dietary burden calculation, the main feed items responsible for residues for poultry are wheat straw and gluten. Main residues in these feed items are expected to be parent flonicamid and TFNG, and in lower amounts, TFNA, TFNG-AM and TFNA-AM. The main metabolite in poultry was TFNA-AM, whereas only

very low amount of tentative TFNG-AM was found. It seems as the amide bond in the parent molecule is primarily broken in poultry metabolism, yielding TFNA from which further metabolites TFNA-AM and 6-OH-TFNA-AM are formed. It is reasonable to suggest that the amide bond in TFNG and TFNG-AM is hydrolysed in identical way as that in the parent molecule, and thus, the metabolism study conducted with the parent molecule is acceptable. This assumption is supported by the results of the poultry feeding study, where 1:1 mixture of flonicamid:TFNG was used. In the feeding study, no TFNG was found, while the main residue species was TFNA-AM.

Ruminants

One study on metabolism of flonicamid in lactating goats was provided for the previous active substance evaluation (DAR 2005) as well as for the current RAR.

Lactating goats received a dose of approximately 1.7 mg a.s./kg bw/day, corresponding to 19-20N of the maximal evaluated dietary burden (calculated for lamb), for 5 consecutive days.

Plateau level in milk was reached at approximately day 3 of dosing. Residues were not considered fat soluble as the TRR in fat tissues was significantly lower compared to other tissues and as no radioactivity was detected in the hexane extract of milk samples.

Extractability of residues from ruminant matrices with acetonitrile + acidified aqueous acetonitrile (latter not performed for muscle samples) was generally low for tissues: 42-57% of TRR. Fat tissues had somewhat higher extractability of 81-86% of TRR. Extractability was highest for milk: 97-98% of TRR. Further acid or protease hydrolyses were performed for the tissue samples. Strong acid hydrolysis effectively released 97-100% of residual radioactivity from fat tissues while protease treatment was most effective for all other tissues, releasing 81-100% of residual radioactivity. However, only liver hydrolysis fractions and the strong acid hydrolysis fractions of kidney and loin muscle were analysed, whereas the hydrolysed fat tissue and rear leg samples, as well as the mild acid and protease hydrolysis samples of kidney and muscle tissues were not analysed for due to high matrix interference, or low residue levels. The non-analysed fractions of fat tissues represented 14% of TRR / 0.02 mg/kg and the mild acid hydrolysis fractions containing 3% of TRR/0.02 mg/kg for kidney (and 2% of TRR / <0.01 mg/kg for muscles).

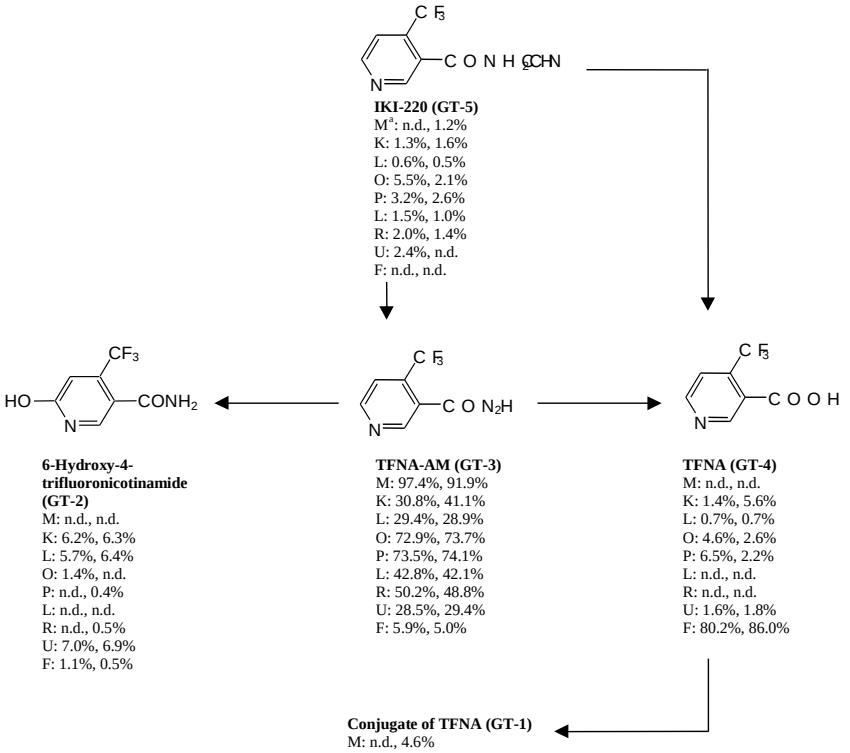
The residual residues exceeded 10% of TRR/0.05 mg/kg for several samples. The unextractable residues after protease hydrolysis represented 10.2% of TRR/0.123 mg/kg for liver, while unextractable residues after acid hydrolyses were 12.3% of TRR/0.08 mg/kg for kidney, 15% of TRR/0.05 mg/kg for rear leg muscle and 17% of TRR/0.06 mg/kg for loin muscle.

In the readily extractable fractions, metabolite TFNA-AM was responsible for the main part of residues in all ruminant matrices, representing 29-50% of TRR (0.16-0.36 mg/kg) in liver, kidney and muscles, 73-74% (0.04-0.11 mg/kg) in fat tissues and 92-97% of TRR (0.08 mg/kg) in milk. TFNA-AM was also the main residue released after acid or protease treatment of kidney, liver and muscle PES (21-31% of TRR / 0.12-0.34 mg/kg). In faeces, TFNA was the main residue (80-86% of TRR) and its unstable conjugate in urine (55-58% of TRR).

No other significant metabolites exceeding 10% of TRR were identified in ruminant matrices, with the exception of unstable TFNA conjugate in one of the kidney samples (11.9% of TRR/0.08 mg/kg). The finding may be due to the presence of this metabolite in urine. Absolute concentrations of metabolites TFNA unstable conjugate and 6-OH TFNA-AM exceeded 0.05 mg/kg in liver samples (0.05-0.08 mg/kg and 0.07-0.08 mg/kg, respectively), however, their relative amount was low (4-7% of TRR). Metabolite 6-OH-TFNA was also released by acid hydrolyses (4-7% of TRR / 0.05-0.08 mg/kg).

The proposed metabolism of flonicamid in ruminants is presented in Figure 2.7.3.-3.

Figure 2.7.3.-2. Metabolism of flonicamid (IKI-220) in ruminants.



[a]M = milk, Day 3, K = kidney, L = liver, O = omental fat, P = perirenal fat, L = loin muscle, R = rear leg muscle, U = urine, day 2 and F = feces, day 3.
The values given are % TRR distribution for the samples from goat replicates 1 and 2, respectively.

According to the livestock dietary burden calculation, the main feed items for ruminants are wheat straw and gluten. Main residues in these feed items are expected to be parent flonicamid and TFNG, and in lower amounts, TFNA, TFNG-AM and TFNA-AM. The main metabolite in ruminants was shown to be TFNA-AM while no TFNG or TFNG-AM were found in any of the tissues, milk or excreta. It seems as the amide bond in the parent molecule is primarily broken in ruminant metabolism, yielding TFNA from which the further metabolites TFNA-AM and 6-

OH-TFNA-AM are formed. It is reasonable to suggest that the amide bond in TFNG and TFNG-AM is hydrolysed in identical way as that in the parent molecule, and thus, the feeding study conducted with the parent molecule is acceptable. The cow feeding study performed with 1:1 mixture of flonicamid and TFNG that was provided for the current evaluation supports the assumption, as no TFNG was found in tissues or milk and as the main residue detected was due to TFNA-AM.

During the previous active substance review, the experts of the PRAPeR 10 meeting noted that the metabolism studies in animals have been carried out with flonicamid solely, whereas TFNA and TFNG residues were also found in feed items at significant levels. Since TFNG is an interim-metabolite in the main metabolic pathway to TFNA-AM, the experts agreed that the metabolism study performed with flonicamid is assumed to cover the metabolites formed upon administration of TFNG to livestock. Conversly, however, TFNA being a final metabolite, a possible accumulation in animal tissues may be suspected, since no information was provided on its rate of elimination via TFNA-conjugates. Therefore, the experts proposed a data gap for the submission of metabolism studies in goat and hen with TFNA. This point was re-discussed by the PRAPeR 70 meeting, taking into account the new elimination study performed in rat with ^{14}C-TFNA and presented in the addendum 4 of February 2007. After ingestion, TFNA was rapidly and entirely excreted in urine and faeces, confirming that no accumulation is expected in any tissue. This observation is in line with the rat and ruminant metabolism studies performed with the parent flonicamid, where TFNA (free and conjugated) was the predominant compound excreted in urine in faeces (56% to 88% TRR in the goat study). Based on this information, the experts concluded that accumulation of TFNA is not expected in ruminant matrices, and a metabolism study using this metabolite is no longer necessary. For poultry there are still some uncertainties since, in the metabolism study performed with the parent, the vast majority of the residue in the excreta was TFNA-AM (77% TRR), TFNA accounting for 11% TRR only. However, considering the exaggerated dose rate, at which the study was performed (10 mg flonicamid/kg DM) when compared to the estimated residue intake (0.3 mg/kg DM), it was concluded that no further TFNA metabolism study needs to be requested on poultry.

Metabolite TFA was not analysed for or identified in the livestock studies. Radiolabel position in the poultry and ruminant studies was at C3 in the ring, which does not allow measurement of this metabolite. Thus, occurrence of TFA in livestock commodities cannot be ruled out. Flonicamid labelled on the C3 position was also used in rat metabolism studies. Opening and degradation of the ring structure in animal metabolism may not be as significant as the other metabolic routes, however.

Pigs

Based on the animal dietary burden calculation (please refer to M-CA 6.2.2.1) it is evident, that the maximum dietary burden of pigs is above the trigger value of 0.004 mg/kg bw/d (see Table 6.2.2-2). However, since metabolism in rats and ruminants was demonstrated to be similar, the findings in ruminants can also be extrapolated to pigs. Consequently, a pig metabolism study is not required.

Fish

As given in the fish working document (SANCO/11187/2013, rev. 3), the accumulation of compounds of relatively low lipophilicity (log Pow < 3) via the diet is known to be negligible and thus, fish metabolism studies are only required for active substances, where the log Pow is greater than or equal to three.

As for Flonicamid, TFNG, TFNA and TFA the log Pow is -0.24, -0.2, 0.4 and -2.6, respectively, no metabolism study in fish is required.

2.7.3 Definition of the residue

Residue definition for plant commodities

The residue definition concluded during the Annex I inclusion (2010) and confirmed during later MRL evaluations (EFSA 2014, 2017 and 2020) was set as "the sum of flonicamid + TFNG + TFNA, expressed as flonicamid" for both enforcement and risk assessment in primary and succeeding crops as well as their processed commodities.

At the final conclusion following Annex I inclusion EFSA stated that "Although there are currently no indications that metabolites from flonicamid may be generated from other compounds, clarification as to whether the TFNA metabolite could be a common metabolite to other active substances would still be desirable (minor deficiency)." The issue was discussed during PRAPeR residue expert meeting 10 (29 November – 01 December 2006) and meeting 70 (5 May – 8 May 2009). In the addendum 8 (France, 2009) RMS stated that "Looking to all pesticide active substances authorised, forbidden and superseded worldwide, RMS considered that TFNA was unlikely to be a common metabolite to other active substances." The notifier was asked to confirm RMS's position. The notifier submitted in September 2009 a position paper to answer the open point and the RMS evaluated the data in Addendum 9 (April 2011). The notifier screened available Data Bases for possible matches using keywords relevant to TFNA, CAS number and chemical structure similarity. The screening resulted in only two found molecules: pyroxsulam and flonicamid itself. The notifier stated that "During the different evaluations made on pyroxsulam by the European commission (UK, 2008 - still pending), Australia (2008) or US-EPA (2007), TFNA was never identified as a metabolite of pyroxsulam. Hence it can be considered that TFNA is specific to flonicamid only." RMS FI agrees with the conclusions presented in Addendum 9 by the previous RMS (FR) and the notifier that TFNA can be regarded as specific metabolite for flonicamid.

Based on the provided metabolism studies in primary crops, the following residue definition for **both enforcement and risk assessment** is suggested for **primary crops:**

"The sum of flonicamid, TFNG and TFNA, expressed as flonicamid"

According to the nature and magnitude of residue studies in primary crops, flonicamid and metabolites TFNG and TFNA are relevant residues to be included in the residue definitions for enforcement and risk assessment. None of

the compounds alone is a suitable marker for monitoring as their proportions differ in different crops. In addition, the new potato metabolism study showed that flonicamid may not be present at levels >LOQ in harvested tubers.

Metabolite TFNA-AM was analysed for in several of the magnitude of residue studies, however, it was not found above LOQ, except for in one wheat stem sample in study KCP 8.3.1/01 (0.03 mg/kg) and in one grain sample in study KCP 8.3.1/02. In the latter study, TFNA-AM was found at level of 0.09 mg/kg in one grain sample, but upon re-analysis in was not found >LOQ. Thus, this metabolite is not considered significant in any of the primary crops.

Stability of parent flonicamid and metabolites TFNG and TFNA in standard processing conditions was confirmed, and no separate residue definition is needed for processed commodities. No data on stability of TFA in standard processing conditions was provided for the current evaluation.

The metabolism of flonicamid in rotational crops was not deemed similar as in primary crops, as the soil metabolite TFA was found to represent major proportion of residues in succeeding crops. In the two primary crop studies with ^{14}C-4-pyridyl labelled flonicamid (one potato and one peach study), no TFA was identified. As TFA is a common metabolite of several other perfluoro-substances used as pesticides (listed in "Setting of MRLs for saflufenacil and dietary risk assessment for its metabolite TFA", EFSA Journal 2014;12(2):3585 Appendix C), it is not a good candidate for enforcement residue definition.

Based on the provided metabolism and magnitude of residue studies in succeeding crops, the following residue definition for **risk assessment** is suggested for **succeeding crops:**

"TFA, expressed as TFA"

For enforcement, the same residue definition as for primary crops is considered sufficient for succeeding crops.

Toxicological profile of the metabolite TFA could not be concluded (data gap, see section 2.6.8).

According to the primary crop metabolism studies, metabolite TFNG-AM occurred at significant levels in wheat feed commodities, especially in forage and hay (11% and 13% of TRR), whereas TFNA represented <10% of TRR in these commodities. TFNG-AM was found also in straw at higher levels compared to the metabolite TFNA (0.09 mg/kg vs. 0.04 mg/kg; 0.7N feeding level). In succeeding crop metabolism studies, TFNG-AM represented >10% of TRR in wheat forage and chaff and >20% of TRR in straw. However, as the levels of TFNG-AM are low compared to the levels of main metabolites flonicamid and TFNG in primary cereal crop feed items, the RMS does not propose a separate residue definition for cereal feed items. TFNG-AM has not been analysed for in any of the magnitude of residue studies. TFNG-AM was tested negative in the genotoxicity tests. As TFGN-AM shares similar structure with TFNG (primary amide group instead of carboxylic acid group in the side chain), it may be assumed to behave in similar manner in livestock metabolism as TFNG, producing the main metabolite TFNA-AM (see details in section 2.7.2.).

Residue definition for livestock commodities

The residue definition concluded during the Annex I inclusion (2010) and was set as "the sum of flonicamid and TFNA-AM, expressed as flonicamid" for both enforcement and risk assessment in livestock commodities.

Based on the provided metabolism studies in laying hen and lactating goats, the RMS does not consider that a change in the existing residue definition for enforcement is necessary. Thus, **the following residue definition for enforcement is suggested for livestock commodities:**

"The sum of flonicamid and TFNA-AM, expressed as flonicamid"

In hen and goat metabolism studies, TFNA was a minor metabolite in all tissues and eggs. TFNA or its unstable conjugate was found in significant levels only in excreta and urine. In cow feeding studies, however, TFNA was found in significant levels in kidney where it was responsible for the highest residue. Notably, it was the only compound found above LOQ at the lowest 1N dose level. In other tissues or milk, TFNA was not found above LOQ in the feeding studies. The reason for the presence of TFNA in kidney may be its high and rapid excretion into urine. As no accumulation of TFNA is expected, the RMS did not consider inclusion of TFNA in residue definitions necessary.

A significant proportion of TFNA-AM was found as bound residue in poultry kidney (15.3% of TRR) and in ruminant liver (28.2% of TRR), kidney (25.2% of TRR) and muscle (31.2% of TRR) in the metabolism studies. The bound residue was liberated by 6N HCl acid treatment (ruminant kidney and muscle) or protease treatment (ruminant liver and poultry kidney). Thus, the residues are potentially bioavailable also in human digestion. In the cow feeding study, hydrolysis treatment liberated TFNA-AM residues especially in liver. Thus, **the following residue definition for risk assessment is suggested for livestock commodities:**

"The sum of flonicamid and TFNA-AM (free and bound), expressed as flonicamid"

Tentative conversion factors for livestock commodities were calculated by the RMS (Table 2.7.3.-1.; see Vol 3 B.7 for details). Inclusion of the bound residue to the residue definition for enforcement was not suggested in order to enable the use of the analytical method in multiresidue screening methods.

Table 2.7.3.-1. Conversion factors for livestock commodities

Commodity	Conversion factor according to the metabolism study	Conversion factor according to the feeding study
Poultry kidney	**1.20**	not analysed
Ruminant liver	1.94	2.6; 2.2 (**average 2.4**)
Ruminant kidney	1.79	1.5; 1.2 (average **1.4**)
Ruminant muscle	**1.70**	not analysed

As the metabolite TFNA-AM was found to be a major metabolite in rat urine, its toxicity is considered to be covered by the parent.

Based on the most recent nature and magnitude of residue studies on rotational crops as well as the livestock dietary burden estimation based on residue levels detected in the MoR study on rotational crops (see chapter 2.7.6.), it is evident that livestock is exposed to significant amounts of soil metabolite TFA via succeeding crop feed items. However, no feeding studies performed on TFA are available for the current evaluation. Further, the livestock metabolism studies were performed with such radiolabel that TFA could not be detected. Thus, the need for inclusion of TFA in the residue definition for risk assessment in livestock commodities cannot be concluded.

Metabolite OH-TFNA-AM was found in low levels in ruminant metabolism and feeding studies. In metabolism study, the highest level was found in kidney (3.3% of TRR / 0.05 mg/kg) at 12N feeding level. In feeding study, however, OH-TFNA-AM was found above LOQ only in muscle tissue at the highest feeding level 26N (max. 0.02 mg/kg). In goat metabolism study, OH-TFNA-AM was found at highest in liver (9.9% of TRR / 0.12 mg/kg) and kidney (8.1% of TRR / 0.05 mg/kg) at 20N feeding level, while its levels were <0.01 mg/kg in other tissues and milk. In cow feeding study, OH-TFNA-AM was found at the two highest dose levels 3N and 9N in milk (max. 0.01 and 0.03 mg/kg), liver (max. 0.01 and 0.05 mg/kg) while in kidney it was found only at the highest dose level (max. 0.04 mg/kg). Thus, the metabolite is considered minor and is not suggested to be included in residue definitions. Hydroxylation is generally considered not to increase toxicity of a compound. Therefore, toxicity of OH-TFNA-AM can be considered to have been studied in the available toxicity tests of the dossier.

The RMS also likes to point out that parent flonicamid was a minor compound in livestock commodities in the evaluated metabolism studies. Its levels were above 0.01 mg/kg only in eggs (0.019 mg/kg; 12N dose level) and in one sample of goat kidney (0.0104 mg/kg; 20N dose level) and it represented at highest 5.5% of TRR in goat omental fat. In feeding studies, it was not found at all above LOQ in cow samples, and in hen only in eggs (maximum 0.02 mg/kg and 0.09 mg/kg at 7.5N and 26N dose levels). Thus, inclusion of the parent in livestock residue definitions seems not necessary. However, as the residue definition used to derive CODEX MRLs include the parent, changing the residue definition might not be practical.

The residue definition for honey and other bee products is suggested as *"the sum of flonicamid, TFNG and TFNA, expressed as flonicamid"*, based on the detected residues in the honey magnitude of residue trials, metabolism studies in primary crops and the demonstrated stability of the analytes in standard hydrolysis conditions. However, this residue definition does not take into account possible residues of soil metabolite TFA in rotationally grown melliferous crops. No data on TFA in rotationally grown melliferous crops is available for the current evaluation.

2.7.4 Summary of residue trials in plants and identification of critical GAP

2.7.4.1 Representative uses

In the present evaluation, two representative formulations were included. Formulation Teppeki (IKI-220 500 WG) is the same as in the previous assessment while Shoori (IKI-220 100 OD) is a new formulation.

The identified critical GAPs for representative crops are presented in Table 2.7.4.-1.

Table 2.7.4.-1. Representative critical GAPs and GAPs for MRL setting for the target crops.

Crop	Zones	Major/ minor[a]	Use F/G[b]	MRL mg/kg[c]	cGAP/ MRL	timing	Rate and PHI
Product IKI-220 500 WG (Teppeki)							
Apples & pears[c]	SEU, CEU & NEU	Major	F	0.3		BBCH 01-70	1x 70 g a.s./ha, no PHI
					cGAP	BBCH 71-87	1-2x 70 g a.s./ha, interval 21 d, PHI 21 d
Peaches[d]	SEU	Major	F	0.4		BBCH 07-70	1x 70 g a.s./ha, no PHI
					cGAP	BBCH 71-87	1-2x 70 g a.s./ha, interval 21 d, PHI 14 d
Peaches and apricots[d]	CEU & NEU	Minor NEU, major SEU	F	peach 0.4; apricot 0.3		BBCH 07-70	1x 70 g a.s./ha, no PHI
					cGAP	BBCH 71-85	1-2x 70 g a.s./ha, interval 21 d, PHI 21 d
Cherries[d]	SEU	Minor	F	0.4		BBCH 07-70	1x 70 g a.s./ha, no PHI
					cGAP	BBCH 71-87	1-2x 70 g a.s./ha, interval 21 d, PHI 14 d
	CEU	Major				BBCH 07-70	1x 70 g a.s./ha, no PHI
					cGAP	BBCH 71-87	1-2x 70 g a.s./ha, interval 21 d, PHI 14 d
Plums[d]	SEU	Major	F	0.3		BBCH 07-70	1x 70 g a.s./ha, no PHI
					cGAP	BBCH 71-85	1-2x 70 g a.s./ha, interval 21 d, PHI 14 d
	CEU & NEU					BBCH 07-70	1x 70 g a.s./ha, no PHI
					cGAP	BBCH 71-85	1-2x 70 g a.s./ha, interval 21 d, PHI 21 d
Tomato & aubergine	SEU	Tomato major	F	0.5		BBCH 16-87	3x 60 g a.s./ha, interval 7 d, PHI 1 d
	CEU & SEU		G		cGAP	BBCH 16-87	3x 60 g a.s./ha, interval 7 d, PHI 1 d
Cucumber & courgette	SEU	Cucumber major in NEU, courgette in SEU	F	0.5		BBCH 16-87	3x 50 g a.s./ha, interval 7 d, PHI 1 d
	CEU & SEU		G		cGAP & MRL	BBCH 16-87	3x 80 g a.s./ha, interval 7 d, PHI 1 d
Melon	SEU	Major	F	0.4	cGAP	BBCH 15-87	3x 50 g a.s./ha, interval 7 d, PHI 1 d
Wheat	SEU	Major	F	2.0	cGAP & MRL	BBCH 39-79	1-2x 70 g a.s./ha, interval 21 d, PHI 28 d
	CEU					BBCH 37-79	
	NEU					BBCH 21-79	
Product IKI-220 100 OD (Shoori)							
Dry beans	CEU & SEU	Major	F	0.03*	cGAP & MRL	BBCH 11-71	1x 50 g a.s./ha, no PHI
Dry peas							
Wheat	CEU & SEU	Major	F	2.0		BBCH 39 onwards	1x 50 g a.s./ha, PHI 28 d
Rye					cGAP		
Triticale							

[a] According to SANTE/2019/12752 Rev. 4
[b] F=field; G=greenhouse
[c] Reg. (EU) 2022/85
[d] Early and late treatments are optional – both are not to be applied to same crops.

2.7.4.1.1 Wheat

The most critical use for wheat in both Northern and Southern zone is 2x 70 g a.s./ha at latest BBCH 79 with application interval of 21 d and PHI of 28 days. The trials supporting the most critical GAP performed with the WG formulated product were also used to support the MRL application for wheat.

Summary of trials supporting the most critical GAP on wheat are presented in Table 2.7.4.-2a. In total 15 independent trials were performed in both the Northern and Southern zones during 5 (NEU) or 4 (SEU) different cultivation seasons. In the Northern zone, 6 decline trials and 6 at-harvest trials (and 3 combined trials) were performed. In the Southern zone, 5 decline trials and 8 at-harvest trials (and 2 combined trials) were performed. The product formulation used in majority of the trials was IBE 3894 (IKI-220 500 WG / IKI-220 50% WG / "TEPPEKI") while in some trials a similar product formulation IBE 3880 was used. In all trials, the application rate was within 25% of the target rate. Storage intervals were acceptable in all trials when compared to the demonstrated storage stability times of flonicamid and metabolites TFNG and TFNA, with the exception of the metabolites in forage samples in study KCP 8.3.1/03.

The residues analysed for in wheat commodities in the magnitude of residue studies included flonicamid, TFNG and TFNA. TFNA-AM was analysed in three studies but was not found at levels >LOQ except in one stem sample in study KCP 8.3.1/01 (0.03 mg/kg) and in one grain sample in study KCP 8.3.1/02. In the latter study, TFNA-AM was found at level of 0.09 mg/kg in one grain sample, but upon re-analysis in was not found >LOQ.

Main proportion of the residue in wheat grain was due to TFNG (median concentration 0.52 mg/kg), while flonicamid and TFNA were found at lower levels (median concentrations 0.01 mg/kg and 0.04 mg/kg, respectively).

Table 2.7.4.-2a. Summary of magnitude of residue trials on wheat supporting the critical GAP (2x 70 g a.s./ha).

Zone	Commodity	Residues (mg/kg)[a]			Values for risk assessment (mg/kg)		MRL (mg/kg)[b]
					STMR	HR	
NEU zone	grain	0.07	0.08	0.14	0.50	1.27	2
		0.23	0.35	0.485			
		0.49	0.50	0.54			
		0.59	0.81	0.84			
		0.91	1.20	1.27			
	straw	<0.06	0.13	0.15	0.42	1.52	3
		0.14	0.18	0.25			
		0.27	0.42	0.48			
		0.66	0.69	1.03			
		1.06	1.09	1.52			
SEU zone	grain	0.04	0.105	0.20	**0.57**	2.35	4
		0.23	0.35	0.47			
		0.52	0.57	0.74			
		0.96	1.06	1.22			
		1.57	2.09	2.35			

	straw	<0.06	0.06	0.11	0.32	**2.19**	3
		0.14	0.15	0.20			
		0.225	0.32	0.33			
		0.47	0.445	0.78			
		0.93	0.47	2.19			
NEU + SEU	grain	Above residues combined			0.53	2.35	3
	straw	Above residues combined			0.33	2.19	3

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

According to Mann-Whitney U-Test, data populations of both grain and straw are similar in the different climatic zones. As also the critical GAP is same in the zones, the residue data can be combined. The current MRL for wheat grain is 2.0 mg/kg (Reg. (EU) 2022/85). An MRL-application was also submitted along the dossier. A new MRL of 3.0 mg/kg is proposed for wheat grain. The evaluated residue data supports the proposed MRLs for wheat grain.

The residue results supporting the most critical GAP concerning the product Teppeki was used for consumer exposure assessment for wheat items, and for wheat and triticale feed items in livestock dietary burden calculation. It is noted that the highest calculated STMR of 0.435 mg/kg for wheat straw resulted from the Norther zone data set of the less critical GAP (1x70 g a.s./ha, see Table 2.7.4.-2b). This value was used in the livestock dietary burden calculation for wheat and triticale straw.

Table 2.7.4.-2b. Summary of magnitude of residue trials on wheat supporting the less critical GAP (1x 70 g a.s./ha).

Zone	Commodity	Residues (mg/kg)[a]				Values for risk assessment (mg/kg)		MRL (mg/kg)[b]
						STMR	HR	
NEU zone	grain	<0.03	<0.03	0.04	0.05	0.14	0.83	2
		0.22	0.40	0.67	0.83			
	straw	0.08	0.12	0.26	0.37	**0.435**	1.38	3
		0.50	0.70	0.99	1.38			
SEU zone	grain	0.07	0.13	0.15	0.20	0.205	0.72	1.5
		0.21	0.26	0.60	0.72			
	straw	0.10	0.12	0.21	0.25	0.265	1.30	3
		0.28	0.96	1.03	1.30			
NEU + SEU	grain	Above residues combined				0.205	0.83	1.5
	straw	Above residues combined				0.325	1.38	3

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

2.7.4.1.2 Wheat, rye and triticale (representative GAP for rye)

Summary of trials supporting the less critical GAP on wheat with the OD-formulated product Shoori are presented in Table 2.7.4.-3. The residue trials supporting the less critical GAPs included in total 8 independent trials on both the NEU and the SEU zones and performed during 2 different cultivation seasons. Used product formulation in the trials were IBE 4131 (WG) and IBE 4084 (OD).

Table 2.7.4.-3. Summary of magnitude of residue trials on wheat supporting the less critical GAP for product Shoori.

Zone	Commodity	Residues (mg/kg)[a]				Values for risk assessment (mg/kg)		MRL (mg/kg)[b]
						STMR	HR	
NEU zone	grain	<0.03	<0.03	0.06	0.08	**0.155**	0.61	1.5
		0.23	0.25	0.54	0.61			
	straw	0.37	0.38	0.43	0.26	**0.375**	**0.74**	1.5
		0.09	0.1	0.56	0.74			
SEU zone	grain	0.04	0.13	0.1	0.14	0.135	0.57	0.9
		0.09	0.19	0.27	0.57			
	straw	0.29	0.48	0.11	0.66	0.275	0.66	1.5
		0.08	0.18	0.26	0.4			
NEU + SEU	grain	Above residues combined				0.135	0.61	1
	straw	Above residues combined				0.33	0.74	1.5

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

According to Mann-Whitney U-Test, data populations of both grain and straw are similar in the different climatic zones. As also the critical GAP is same in the zones, the residue data can be combined. The current MRL for rye grain is 2.0 mg/kg (Reg. (EU) 2022/85). No exceedance of the current MRL is expected.

The residue results supporting the less critical GAP concerning the OD formulation (product Shoori) were used for the consumer exposure assessment and livestock dietary burden calculations for rye products, as this GAP was the only representative use for rye. According to SANTE/2019/12752 rev.4, residue results of wheat can be extrapolated to rye when application occurs after formation of the edible part (BBCH 51 for cereals).

2.7.4.1.3 Apples

The critical GAP for apples and pears in the present evaluation includes 2x 70 g a.s./ha with 21-day interval at BBCH 71-85/87 and a PHI of 21 days for all zones. Three new studies compiling 8 trials on Northern and Southern zones each performed during the growing seasons 2020 and 2021 was provided for the current evaluation.

Summary of trials supporting the critical GAP on apples are presented in Table 2.7.4.-4. In total 16 independent trials were performed (8 in the Southern and 8 in the Northern zones) during two cultivation season. Two of the Northern zone trials and one of the Southern zone trials were decline trials. As the application of the product is

performed when the consumable part was exposed (at or after BBCH 65), half of the trials should be residue decline trials according to Reg. (EU) 283/2013.

The product formulation used in all trials was IBE 3894 (IKI-220 500 WG / IKI-220 50% WG / "TEPPEKI"). In all trials, the application rate was within 25% of the target rate. Storage intervals were acceptable in all trials when compared to the demonstrated storage stability times of flonicamid and metabolites TFNG, TFNA and TFNA-AM.

Table 2.7.4.-4. Summary of magnitude of residue trials on apples supporting the critical GAP.

Zone	Commodity	Residues (mg/kg)[a]			Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
					STMR	HR	
NEU zone	whole apple fruit	0.03	0.04	0.07	0.07	0.22	0.4
		0.07	0.07	0.12			
		0.17	0.22				
SEU zone	whole apple fruit	<0.03	0.04	0.05	0.055	0.15	0.3
		0.05	0.06	0.07			
		0.09	0.15				
NEU + SEU	whole apple fruit	above trials combined			**0.07**	**0.22**	0.3

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

2.7.4.1.4 Peaches and nectarines

The critical GAP in the Southern zone for peaches is 2x 70 g a.s./ha with interval of 21 days and PHI of 14 d. The critical GAP in the Northern and Central zones for peaches and apricots is 2x 70 g a.s./ha with interval of 21 days and PHI of 21 days.

Summary of trials supporting the most critical GAP on peaches and apricots are presented in Table 2.7.4.-5. In total 10 independent trials were performed in the Southern zone during 3 different cultivation seasons. Three of the trials were decline trials and seven of the trials were at-harvest trials. In the northern zone, in total 4 independent trials (one with peach and 3 with apricots) were performed during 2 different cultivation seasons. Three of the trials were decline trials and one at-harvest trial. The product formulation used in majority of the trials was IBE 3894 (IKI-220 500 WG / IKI-220 50% WG / "TEPPEKI") while in some Southern zone trials, a similar product formulation IBE 3880 was used. In all trials, the application rate was within 25% of the target rate. Storage intervals were acceptable in all trials when compared to the demonstrated storage stability times of flonicamid and metabolites TFNG, TFNA and TFNA-AM, with the exception of the metabolites TFNG, TFNA and TFNA-AM in study KCP 8.3.3/01. The results of this trial were thus not included in the MRL and residue calculations.

Table 2.7.4.-5. Summary of magnitude of residue trials on peaches and apricot supporting the critical GAP.

Zone	Commodity	Residues (mg/kg)[a]	Values for risk assessment (mg/kg)[a]	MRL (mg/kg)[b]

				STMR	HR	
NEU zone	whole fruit (1 peach + *3 apricots*)	*0.05*	0.06	0.09	0.15	0.3
		0.12	*0.15*			
SEU zone	whole peach fruit	0.04	0.05	0.07	0.30	0.4
		0.05	0.05			
		0.05	0.08			
		0.09	0.09			
		0.11	0.30			

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

The residues analysed for in peach and apricot commodities in the magnitude of residue studies included flonicamid and metabolites TFNG and TFNA. Metabolite TFNA-AM was analysed in three studies (KCP 8.3.3/01-03) but was not found at levels >LOQ.

Main proportion of the residue in peach and apricot fruit was due to parent flonicamid (median concentrations 0.05 mg/kg in both zones), while TFNG and TFNA were found at slightly lower levels (median concentrations 0.02-0.03 mg/kg in both zones).

As the application of the product is performed when the consumable part was exposed (at or after BBCH 65), half of the trials should be residue decline trials according to Reg. (EU) 283/2013. Of the Southern zone trials, only 3 trials out of 10 were residue decline trials, while of the Northern zone trials, 3 out of 4 trials were residue decline trials. Thus, more decline trials would be needed to complete the data set in the Southern zone.

The current MRL for peaches is 0.4 mg/kg and 0.3 mg/kg for apricots (Reg. (EU) 2022/85). These MRL are not exceeded according to the evaluated trials.

2.7.4.1.5 Plums

The critical GAP in the Southern zone is 2x 70 g a.s./ha with interval of 21 days and PHI of 14 days. The critical GAP in the Central zone is 2x 70 g a.s./ha with interval of 21 days and PHI of 21 days.

Summary of trials supporting the most critical GAP on plums are presented in Table 2.7.4.-6. In total 9 independent trials were performed in the Southern zone during 3 different cultivation seasons. Three of the trials were at-harvest trials and six decline trials. In the northern zone, in total 8 independent trials were performed during 2 different cultivation seasons. All trials were decline trials. The product formulation used in majority of the trials was IBE 3894 (IKI-220 500 WG / IKI-220 50% WG / "TEPPEKI"). In all trials, the application rate was within 25% of the target rate. Storage intervals were acceptable in all trials when compared to the demonstrated storage stability times of flonicamid and metabolites TFNG, TFNA and TFNA-AM, with the exception of storage of extracts in study KCP 8.3.4/01 (considered as minor deviation).

Table 2.7.4.-6. Summary of magnitude of residue trials on plums supporting the critical GAP.

Zone	Commodity	Residues (mg/kg)[a]			Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
					STMR	HR	
NEU zone	whole plum fruit	0.03	0.04	0.05	0.06	0.07	0.2
		0.06	0.06	0.06			
		0.07	0.07				
SEU zone	whole plum fruit	0.03	0.04	0.05	0.05	0.13	0.3
		0.05	0.05	0.09			
		0.09	0.11	0.13			

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

The residues analysed for in plum commodities in the magnitude of residue studies included flonicamid and metabolites TFNG and TFNA. Metabolite TFNA-AM was analysed in six studies (KCP 8.3.3/01-03) but was not found at levels >LOQ.

Main proportion of the residue in plum fruit was due to parent flonicamid (median concentrations 0.03 mg/kg in both zones) and metabolite TFNG (median concentration 0.02 mg/kg in both zones) while TFNA was found at slightly lower levels (median concentrations 0.01 mg/kg in both zones).

The current MRL for plums is 0.3 mg/kg. Theis MRL is not exceeded according to the evaluated trials.

2.7.4.1.6 Cucumber and courgette

Unprotected cucumber and courgette

The critical GAP in the Southern zone for unprotected cucumber and courgette is 3 x 50 g a.s./ha with interval of 7 d and PHI of 1 d.

Summary of trials supporting the critical GAP on unprotected cucumber and courgette is presented in Table 2.7.4.-7. In total 8 independent trials were performed in the Southern zone during two different cultivation seasons. Two of the trials were at-harvest trials and the rest semi or residue decline trials. The trials were performed with IBE 3894 (IKI-220 500 WG/ IKI-220 50% WG / "TEPPEKI"). All trials were conducted within ± 25% of the supported GAP. Storage intervals were acceptable in all trials when compared to the demonstrated storage stability times of flonicamid and metabolites TFNG, TFNA and TFNA-AM.

The residues analysed for cucumbers in the magnitude of residue studies included flonicamid and metabolites TFNG and TFNA. The analytical method used to analyse the residue trial samples has been sufficiently validated and was proven to be fit for purpose. The validity of analytical method for cucumber was furthermore confirmed by procedural recovery samples within the residue trials.

Table 2.7.4.-7. Summary of magnitude of residue trials on unprotected cucumber and courgette supporting the critical GAP.

Zone	Commodity	Residues[a] (mg/kg)	Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
			STMR	HR	
SEU	Cucumber	2 x 0.05, 0.06, 3 x 0.09, 0.10, 0.16	0.075	0.16	0.3

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

The proportion of the residues of flonicamid (median concentration 0.03 mg/kg), TFNG (median concentration 0.03 mg/kg) and TFNA (median concentration 0.02 mg/kg) were nearly the same in cucumber at the desired harvest, at PHI 1 d (in a case that higher residues were found at longer interval, those trials were selected).

The current MRL for cucumbers with edible peel is 0.5 mg/kg (Reg. (EU) 2022/85). This MRL is not exceeded according to the evaluated trials.

Protected cucumber and courgette

The critical GAP for indoor cucumber and courgette is 3 x 80 g a.s./ha with interval of 7 d and PHI of 1 d.

Summary of trials supporting the critical GAP on indoor cucumber and courgette is presented in Table 2.7.4.-8. In total 9 independent trials were performed on indoor cucumber during two different cultivation seasons. Four of the trials were at-harvest trials and the rest residue decline trials. The trials were performed with IBE 3894 (IKI-220 500 WG/ IKI-220 50% WG / "TEPPEKI"). All trials were conducted within ± 25% of the supported GAP. Storage intervals were acceptable in all trials when compared to the demonstrated storage stability times of flonicamid and metabolites TFNG, TFNA and TFNA-AM in study KCP 8.3.3/01.

Table 2.7.4.-8. Summary of magnitude of residue trials on protected cucumber and courgette supporting the critical GAP.

Zone	Commodity	Residues[a] (mg/kg)	Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
			STMR	HR	
G	Cucumber	0.08, 0.11, 2 x 0.14, 0.15, 0.16, 0.24, 0.34, 0.62[c]	0.15	0.62	0.6[d] or 0.9[e]

G = Greenhouse
[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator
[c] An oulier according to the Dixon's Q-test, [d] Derived from 8 trials excluding the statistical outlier, [e] Derived from 9 trials without excluding the statistical outlier

The residues analysed for cucumbers in the magnitude of residue studies included flonicamid and metabolites TFNG, TFNA and TFNA-AM. The analytical method used to analyse the residue trial samples has been sufficiently validated and was proven to be fit for purpose. The validity of analytical method for cucumber was furthermore confirmed by procedural recovery samples within the residue trials.

The current MRL for cucumbers with edible peel is 0.5 mg/kg (Reg. (EU) 2022/85). This MRL is exceeded according to the evaluated trials. Consequently, an MRL-application was submitted along the dossier. According to the Commission Technical guidelines document on extrapolation SANTE/2019/12752 (European Commission, 2020) extrapolation from cucumber to whole group of cucumbers with edible peel is possible when the treatment is before and/or after of edible part of the crop. New MRLs were not requested to the whole group of cucurbits with edible peel but cucumbers and courgettes only. Therefore, new MRLs are proposed for cucumbers and courgettes solely. Further risk management discussions required on the appropriate MRL proposal between 0.9 mg/kg (derived from 9 trials without excluding the statistical outlier) or 0.6 mg/kg (derived from 8 trials excluding the statistical outlier). The derived MRL of 0.9 mg/kg is higher than the requested MRL of 0.6 mg/kg of the applicant. The applicant excluded the highest residue result of 0.62 mg/kg (CP 8.3.8/02, trial FA-22-03-05/02) from the MRL calculation since it is an outlier according to the Dixon's Q-test. The RMS, however, did not find any clear reason from the trial to suggest the result unreliable. Thus, the result was included in the data set. The most critical risk assessment values, an HR of 0.62 mg/kg and an STMR of 0.16 mg/kg (derived from 9 trials without excluding the statistical outlier) were used for the consumer risk assessment.

2.7.4.1.7 Tomato and aubergine

The critical GAP for tomatoes for both the outdoor uses in the Southern zone and the greenhouse uses in all zones is 3x 60 g a.s./ha with interval of 7 days and PHI of 1 day.

Summary of trials supporting the most critical GAP on tomatoes are presented in Table 2.7.4.-9. For Southern zone outdoor uses, in total 8 independent trials were performed during 2 different cultivation seasons. Four of the trials were decline trials and four at-harvest trials (the latter with two sampling time points at PHI of 1 and 3 days). For the greenhouse uses in all zones, in total 12 independent trials were performed during 2 different cultivation seasons. Eight of the trials were decline trials and four at-harvest trials (the latter with two sampling time points at PHI of 1 and 3 days). The product formulation used in majority of the trials was IBE 3894 (IKI-220 500 WG / IKI-220 50% WG / "TEPPEKI").

In half of the outdoor trials and in all of the greenhouse trials, the application rate exceeded 25% of the target rate. Thus, the whole data set was scaled to the representative 1N application rate, as according to EFSA's document "Residue trials and MRL calculations" (2015).

Storage intervals were acceptable in all trials when compared to the demonstrated storage stability times of flonicamid and metabolites TFNG, TFNA and TFNA-AM, with the exception of storage of extracts in study KCP 8.3.9/01 (considered as minor deviation).

The highest residue level 0.334 mg/kg detected in the greenhouse trial in study KCP 8.3.9/04 was shown to be an outlier by the Dixon Outlier Calculator. However, this result is from a trial with cherry tomatoes, and no major deviations were noted in the study. Thus, the result was included in the data set.

Table 2.7.4.-9. Summary of magnitude of residue trials on tomato supporting the critical GAP.

Zone	Commodity	Residues (mg/kg)[a]			Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
					STMR	HR	
SEU zone outdoor	whole tomato fruit	0.04	0.04	0.05	0.05	0.11	0.2
		0.05	0.05	0.06			
		0.08	0.11				
NEU+SEU zone greenhouse	whole tomato fruit	0.06	0.06	0.06	0.10	0.33	0.5
		0.07	0.07	0.08			
		0.13	0.13	0.17			
		0.17	0.20	0.33			

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

The residues analysed for in the tomato magnitude of residue studies included flonicamid and metabolites TFNG and TFNA. Metabolite TFNA-AM was analysed in all except for one study (KCP 8.3.9/04) but was not found at levels >LOQ.

Main proportion of the residue in tomato was due to parent flonicamid (median concentrations 0.04 mg/kg in outdoor trials and 0.12 mg/kg in greenhouse trials). Metabolites TFNG and TFNA were present at low levels: median concentration was 0.01 mg/kg for both. Levels of TFNA were <0.01 mg/kg in all trials except for three trials in the same study where 0.03 mg/kg was found.

The current MRL for tomatoes and aubergines is 0.5 mg/kg. The MRL is not exceeded according to the evaluated trials.

2.7.4.1.8 Melons

The critical GAP for uses on melon in the Southern zone is 3x 50 g a.s./ha with interval of 7 days and PHI of 1 day.

Summary of trials supporting the most critical GAP on melons are presented in Table 2.7.4.-10. For Southern zone outdoor uses, in total 8 independent trials were performed during 2 different cultivation seasons. Four of the trials were semi-decline trials (2 time points) and four at-harvest trials. The product formulation used in all of the trials was IBE 3894 (IKI-220 500 WG / IKI-220 50% WG / "TEPPEKI").

The residues analysed for in the melon magnitude of residue studies included flonicamid and metabolites TFNG and TFNA. Metabolite TFNA-AM was not analysed in any of the studies.

Table 2.7.4.-10. Summary of magnitude of residue trials on melon supporting the critical GAP.

Zone	Commodity	Residues (mg/kg)[a]			Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
					STMR	HR	
SEU	Melon peel	0.05	0.13	0.16	0.185	0.35	-

		0.18 0.33	0.19 0.35	0.29			
	Melon pulp	0.03 0.05 0.10	0.04 0.05 0.13	0.04 0.07	0.05	0.13	-
	Melon whole fruit	0.03 0.09 0.19	0.06 0.12 0.21	0.09 0.13	0.105	0.21	0.4

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

Main proportion of the residue in melon whole fruit was due to metabolite TFNA (median concentrations 0.065 mg/kg). Parent flonicamid and metabolite TFNG were present at lower levels and roughly at equal levels (median concentration was 0.02 mg/kg for both).

Major part of the residues were located in the peel of the fruit (STMR 0.185 mg/kg) while lower levels were detected in the pulp (STMR 0.05 mg/kg). In two of the residue decline trials, higher residues were measured in samples at longer PHI of 3 days (see Vol3 section B.7.3.7). RMS did not consider it likely that significant increase in residues would occur in melon at longer PHIs (>1 day).

Peeling factor was calculated for melon based on residues measured at the magnitude of residue trials. Results are shown in Table 2.7.4.-11.

Table 2.7.4.-11. Calculated individual and median and average peeling factors for melon.

Study	Individual values	Median value	Average value
KCP 8.3.11/01	0.62; 0.56; 0.21; 0.31	0.70	0.64
KCP 8.3.11/02	1.00; 0.78; 0.83; 0.83		

The current MRL for melons is 0.4 mg/kg. The MRL is not exceeded according to the evaluated trials.

2.7.4.1.9 Cherries

The critical GAP for uses on cherry in both the Southern and Central zone is 2x 70 g a.s./ha with interval of 21 days and PHI of 14 days.

Summary of trials supporting the most critical GAP on cherries are presented in Table 2.7.4.-12. For the Southern zone uses, in total 4 independent trials were performed during 2 different cultivation seasons. For the Norther zone uses, in total 8 independent trials were performed during 3 different cultivation seasons. Half of the trials were at-harvest trials in both zones and rest of the trials were decline studies. The product formulation used in all of the trials was IBE 3894 (IKI-220 500 WG / IKI-220 50% WG / "TEPPEKI"). As the GAPs in the different zones are identical and as the data sets were deemed similar, the data of the two zones was combined.

Table 2.7.4.-12. Summary of magnitude of residue trials on cherry supporting the critical GAP.

Zone	Commodity	Residues (mg/kg)[a]	Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
			STMR	HR	
NEU	whole cherry fruit	0.07 0.10 0.10 0.12 0.14 0.15 0.16 0.17	0.13	0.17	0.4
SEU	whole cherry fruit	0.09 0.12 0.13 0.14	0.13	0.14	0.4
NEU + SEU	whole cherry fruit	above trials combined	0.13	0.17	0.4

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

The residues analysed for in the cherry magnitude of residue studies included flonicamid and metabolites TFNG, TFNA and TFNA-AM (the latter in two of the three studies). Main proportion of the residue in cherry whole fruit was due to parent flonicamid (median concentration 0.09 mg/kg). Metabolites TFNA and TFNG were found at lower rates (median concentration 0.02 mg/kg for both). TFNA-AM was not found above LOQ.

Residue levels were analysed in the fruit flesh at the target PHI and residues in whole fruit were calculated by taking into account the weight of the pit. Residue levels were slightly higher in flesh compared to the whole fruit. Similar data was not available for other stone fruit peaches and plums, for which data was provided mostly for flesh only, except for some plum trials where no difference in flesh vs. whole fruit was observed. The reason for this may be due to greater proportion of flesh in bigger fruits.

RMS calculated “de-pitting” or ”pit-spitting” factor for cherry based on residues measured in cherry flesh in the magnitude of residue trials. Results are shown in Table 2.7.4.-13. The calculated factor may be used in risk assessment to correct the STMR and HR residue values given as whole fruit.

Table 2.7.4.-13. Calculated individual, median and average de-pitting / pit-spitting factors for cherry.

Study	Individual values	Median value	Average value
KCP 8.3.12/01	1.11; 1.08; 1.00; 1.06	1.09	1.08
KCP 8.3.12/02	1.08; 0.93; 1.10; 1.10		
KCP 8.3.12/02	1.15; 1.10; 1;11; 1.09		

The current MRL for cherry is 0.4 mg/kg. The MRL is not exceeded according to the evaluated trials.

2.7.4.1.10 Pulses (dry beans and peas)

The critical GAP in the Northern and Southern zone for unprotected dry beans and dry peas is 1 x 50 g a.s./ha at BBCH 11-71, PHI is determined by growth stage.

In total of sixteen independent residue trials were performed on dry beans and dry peas over two growing seasons (8 trials in NEU, 8 trials in SEU). Half of the trials were at-harvest trials in both zones and rest of the trials were

decline studies. The trials were performed with IBE 4084 (IKI-220 100 OD). All trials were conducted within ± 25% of the cGAP.

A previously validated analytical method was used in the trials. The validity of analytical method for dry beans and dry peas was confirmed by procedural recovery samples. Procedural recovery samples were within acceptable range of 70-110%. The linearity of the detector was demonstrated. The LOQ was 0.01 mg/kg for each of flonicamid, TFNG and TFNA (expressed as original compound).

The samples were stored deep frozen prior to extraction. The maximum interval between sampling and extraction was 243 d. Flonicamid and its metabolites TFNG and TFNA have demonstrated to stay stable in dry matrices for at least 18 months under deep frozen conditions. The maximum extraction to quantification interval was 18 d which is covered by the demonstrated extract stability of 20 d.

Summary of trials supporting the the critical GAP on dry beans and peas are presented in Table 2.7.4.-14. As the GAPs in the different zones are identical and as the data sets were deemed similar, the data of the two zones was combined. Based on the available data an MRL of 1.5 mg/kg, a HR of 0.82 mg/kg and a STMR of 0.36 mg/kg are derived.

Table 2.7.4.-14. Summary of magnitude of residue trials on dry beans and peas supporting the critical GAP.

Zone	Commodity	Residues (mg/kg)[a]	Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
			STMR	HR	
NEU	Dry beans	0.15, 0.32, 0.36, 0.53	-	-	-
SEU	Dry beans	0.13, 0.20, 0.21, 0.48	-	-	-
NEU	Dry peas	0.36, 0.61, 0.75, 0.82	-	-	-
SEU	Dry peas	0.14, 0.18, 0.74, 0.77	-	-	-
NEU + SEU	Dry beans + dry peans	0.13, 0.14, 0.15, 0.18, 0.20, 0.21, 0.32, 0.36, 0.36, 0.48, 0.53, 0.61, 0.74, 0.75, 0.77, 0.82	0.36	0.82	1.5

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

The current MRL for dry beans and dry peas is 0.8 mg/kg (Reg. (EU) 2022//85. This MRL is exceeded according to the evaluated trials. Consequently, an MRL-application was submitted along the dossier.

It is also highlighted that the MRL seting (EFSA Journal 2020; 16(6):6136) based on import tolerance of dry beans and dry peas of a more critical US GAP is still pending.

2.7.4.2 MRL Application (non-representative uses)

The critical GAP for uses on seed potatoes in NEU and SEU is 1 x 80 g a.s./ha with latest application BBCH 35-39, PHI is not relevant (covered by growth stage). According to the label, tank mixes with oil-based adjuvants are

possible. The critical GAP for uses on industrial and ware potatoes in NEU and SEU is 2 x 80 g a.s./ha, with latest application BBCH 70/71, PHI is not relevant (covered by growth stage).

Sixteen independent residue trials (8 in NEU, 8 in SEU) were conducted on potatoes according to the critical GAP for seed potato as well as for industrial and ware potatoes. The study design was a reverse decline curve trial. The trials were performed with IKI-220 500 WG.

Samples were analysed based on a method validated successfully within the study. The LOQ was 0.01 mg/kg for each of flonicamid, TFNG and TFNA (expressed as original compound).

Residue samples were stored in compliance with the demonstrated period of storage stability conditions.

Summary of trials supporting the critical GAP on potatoes are presented in Table 2.7.4.2-1. For few NEU trials a higher, exaggerated application rate was applied. The entire data set was scaled. The scaling factors were 0.48-1.07. The individual scaling factors are presented in Vol3, B.7. As the GAPs in the different zones are identical and the data sets were deemed similar according to the Mann Whitney's U-test, the data of the two zones was combined. Based on the available data an MRL of 0.4 mg/kg, a HR of 0.26 mg/kg and a STMR of 0.098 mg/kg are derived for potatoes.

Table 2.7.4.2-1. Summary of magnitude of residue trials on potatoes supporting the critical GAP.

Zone	Commodity	Residues (mg/kg)[a]	Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
			STMR	HR	
NEU	Seed potato	0.030, 0.032, 0.037, 0.045, 0.051, 0.058, 0.093, 0.100	-	-	-
SEU	Seed potato	0.034, 0.046, 0.051, 0.086, 0.127, 0.128, 0.233, 0.260	-	-	-
NEU + SEU	Seed potato	0.030, 0.032, 0.034, 0.037, 0.045, 0.046, 0.051, 0.051, 0.058, 0.086, 0.093, 0.100, 0.127, 0.128, 0.233, 0.260	0.055	0.26	0.4
NEU	Ware potato	0.060, 0.060, 0.063, 0.071, 0.086, 0.098, 0.142, 0.148	-	-	-
SEU	Ware potato	0.051, 0.074, 0.097, 0.098, 0.116, 0.131, 0.233, 0.242	-	-	-
NEU + SEU	Ware potato	0.051, 0.060, 0.060, 0.063, 0.071, 0.074, 0.086, 0.097, 0.098, 0.098, 0.116, 0.131, 0.142, 0.148, 0.233, 0.242	0.098	0.24	0.4

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

The current MRL for potatoes is 0.09 mg/kg (Reg. (EU) 2022//85. This MRL is exceeded according to the evaluated trials. Consequently, an MRL-application was submitted along the dossier.

2.7.5 Summary of feeding studies in poultry, ruminants, pigs, and fish

2.7.5.1 Representative uses

In addition to flonicamid and the metabolites TFNA and TFNG included in the residue definition for primary crops, livestock are exposed to the soil metabolite TFA via residues in succeeding crops. Thus, livestock dietary burden was estimated separately for both residue definitions: for primary crops (sum of flonicamid, TFNA and TFNG) and for rotational crops (TFA) (see Vol3 B7).

Proposed representative uses of the active substance on apples, wheat, rye, triticale and dry peas and beans in the current RAR resulted in detectable residues in feed items. The input values for calculation of livestock dietary burden are presented in Table 2.7.5.-1.

Table 2.7.5.-1. Input values for livestock dietary burden for flonicamid.

Commodity	Median dietary burden		Maximum dietary burden	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Residue definition for risk assessment in primary crops: Flonicamid, TFNG and TFNA				
Apple pomace	0.07 x 5	STMR (NEU/SEU) x PF (default)	0.07 x 5	STMR (NEU/SEU) x PF (default)
Wheat straw	0.435	STMR (NEU – less critical WG formulation GAP)	2.19	HR (SEU – WG formulation cGAP)
Rye straw	0.375	STMR (NEU – wheat OD formulation)	0.74	HR (NEU – wheat OD formulation)
Triticale straw	0.435	STMR (NEU – wheat, WG formulation less critical GAP)	2.19	HR (SEU – wheat WG formulation cGAP)
Wheat grain	0.57	STMR (SEU – WG formulation)	0.57	STMR (SEU – WG formulation)
Rye grain	0.155	STMR (NEU – OD formulation)	0.155	STMR (NEU – OD formulation)
Triticale grain	0.57	STMR (SEU – WG formulation)	0.57	STMR (SEU – WG formulation)
Dry peas	0.36	STMR (NEU+SEU)	0.36	STMR (NEU+SEU)
Dry beans	0.36	STMR (NEU+SEU)	0.36	STMR (NEU+SEU)
Distiller's grain	0.57 x 3.3	STMR (NEU) x PF (default)	0.57 x 3.3	STMR (NEU) x PF (default)
Wheat, gluten, meal	0.57 x 1.8	STMR (NEU) x PF (default)	0.57 x 1.8	STMR (NEU) x PF (default)
Wheat, milled by-products	0.57 x 1	STMR (NEU) x PF (this RAR)	0.57 x 1	STMR (NEU) x PF (this RAR)

Livestock dietary burden for flonicamid + TFNG and TFNA (see calculations in Vol 3 B.7.4.) exceeded the trigger value of 0.004 mg/kg bw for all livestock commodities. Livestock feeding studies are thus justified for all livestock species. Dietary burden results are summarised in Table 2.7.5.-2.

Table 2.7.5.-2. Dietary burden calculation for flonicamid for ruminants, swine and poultry.

Revelant groups	Dietary burden expressed in				Most critical commodity	Trigger (0.004 mg/kg bw) exceeded (Yes/No)	Previous assessment [(a)] Max burden mg/kg bw
	mg/kg bw per day		mg/kg DM				
	Median	Maximum	Median	Maximum			
Cattle (beef)	0.018	0.027	0.74	1.14	Wheat straw	**Yes**	0.077
Cattle (dairy)	0.033	0.049	0.86	1.27	Wheat straw	**Yes**	
Sheep (lamb)	0.051	0.083	1.20	1.96	Wheat straw	**Yes**	0.077
Sheep (ram/ewe)	0.039	0.065	1.17	2.00	Wheat straw	**Yes**	
Swine (breeding)	0.020	0.020	0.86	0.86	Distiller's grain	**Yes**	0.048
Swine (finishing)	0.026	0.026	0.86	0.86	Distiller's grain	**Yes**	
Poultry (broiler)	0.050	0.050	0.70	0.70	Wheat gluten	**Yes**	0.063
Poultry (layer)	0.052	0.065	0.75	0.95	Wheat straw	**Yes**	
Poultry (turkey)	0.041	0.041	0.58	0.58	Wheat gluten	**Yes**	

(a) Art. 6 framework (EFSA Journal 2017;15(3):4748)

The residue definition for risk assessment in succeeding crops suggested in the current RAR as *«TFA, expressed as TFA»*

Exposure of livestock for the soil metabolite TFA via rotational crops was estimated based on the residue levels measured in the study KCA 6.6.2/02 (see Vol 3 B.7 Table B.7.6.2.-13.). The input values for calculation of livestock dietary burden are presented in Table 2.7.5.-3. Animal Model 2017 calculator was used for the livestock dietary burden estimation. Results are presented in Table 2.7.5.-4. As the default processing factors for potato processed feed items are rather high (20 and 38), the calculation also was performed by setting the potato processing factors to value 1 (see results in Table 2.7.5.-5.).

Table 2.7.5.-3. Input values for livestock dietary burden for TFA.

Commodity	Median dietary burden		Maximum dietary burden	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Residue definition for risk assessment in rotational crops: TFA				
Alfalfa, clover forage	0.30	STMR wheat forage (PBI 30 d)	0.43	HR wheat forage (PBI 30 d)
Barley, oat, rye, triticale and wheat forage	0.30	STMR wheat forage (PBI 30 d)	0.43	HR wheat forage (PBI 30 d)
Barley, oat, rye, triticale and wheat straw	0.66	STMR wheat straw (PBI 365 d)	0.84	HR wheat straw (PBI 30 d)
Beet mangel fodder	0.08	STMR carrot root (PBI 120 d)	0.18	HR carrot root (PBI 120 d)
Beet and turnip tops	0.26	STMR carrot tops (PBI 120 d)	0.68	HR carrot tops (PBI 120 d)

Cabbage heads and kale	0.08	SMTR mature lettuce (PBI 30 d)	0.34	HR mature lettuce (PBI 120 d)
Carrot, potato, swede and turnip roots	0.08	STMR carrot root (PBI 120 d)	0.18	HR carrot root (PBI 120 d)
Barley, oat, rye, wheat and triticale grain	0.22	STMR wheat grain (PBI 365 d)	0.22	STMR wheat grain (PBI 365 d)
Brewer's grain	0.22 x 3.3	STMR wheat grain x PF (default)	0.22 x 3.3	STMR wheat grain x PF (default)
Distiller's grain	0.22 x 3.3	STMR wheat grain x PF (default)	0.22 x 3.3	STMR wheat grain x PF (default)
Potato process waste	0.08 x 20	STMR carrot root x PF (default)	0.18 x 20	HR carrot root x PF (default)
Potato dried pulp	0.08 x 38	STMR carrot root (PBI 120 d)	0.18 x 38	HR carrot root (PBI 120 d)
Wheat, gluten, meal	0.22 x 1.8	STMR wheat grain x PF (default)	0.22 x 1.8	STMR wheat grain x PF (default)
Wheat, milled by-products	0.22 x 1	STMR wheat grain x PF (default)	0.22 x 1	STMR wheat grain x PF (default)

Table 2.7.5.-4. Dietary burden calculation for TFA (including potato default PFs).

Revelant groups	Dietary burden expressed in				Most critical commodity	Trigger (0.004 mg/kg bw) exceeded (Yes/No)
	mg/kg bw per day		mg/kg DM			
	Median	Maximum	Median	Maximum		
Cattle (beef)	0.144	0.158	6.01	6.60	potato process waste	**Yes**
Cattle (dairy)	0.185	0.204	4.80	5.30	potato process waste	**Yes**
Sheep (lamb)	0.153	0.173	3.61	4.07	potato process waste	**Yes**
Sheep (ram/ewe)	0.202	0.218	6.05	6.60	potato process waste	**Yes**
Swine (breeding)	0.076	0.087	3.28	3.78	potato process waste	**Yes**
Swine (finishing)	0.038	0.051	1.28	1.72	Swede roots	**Yes**
Poultry (broiler)	0.069	0.077	0.98	1.09	Potato dried pulp	**Yes**
Poultry (layer)	0.060	0.071	0.88	1.03	Potato dried pulp	**Yes**
Poultry (turkey)	0.044	0.052	0.61	0.73	Wheat milled byproducts	**Yes**

Table 2.7.5.-5. Dietary burden calculation for TFA (excluding potato default PFs).

Revelant groups	Dietary burden expressed in				Most critical commodity	Trigger (0.004 mg/kg bw) exceeded (Yes/No)
	mg/kg bw per day		mg/kg DM			
	Median	Maximum	Median	Maximum		
Cattle (beef)	0.027	0.047	1.13	1.98	Turnip tops	**Yes**
Cattle (dairy)	0.051	0.070	1.33	1.82	Swede roots	**Yes**

Sheep (lamb)	0.067	0.085	1.57	2.01	Swede roots	**Yes**
Sheep (ram/ewe)	0.047	0.064	1.42	1.90	Swede roots	**Yes**
Swine (breeding)	0.031	0.044	1.36	1.89	Swede roots	**Yes**
Swine (finishing)	0.038	0.051	1.28	1.72	Swede roots	**Yes**
Poultry (broiler)	0.045	0.053	0.63	0.75	Swede roots	**Yes**
Poultry (layer)	0.048	0.058	0.70	0.85	Swede roots	**Yes**
Poultry (turkey)	0.044	0.052	0.61	0.73	Wheat milled byproducts	**Yes**

Livestock dietary burden for metabolite TFA exceeded the trigger value of 0.004 mg/kg bw for all livestock commodities. Livestock metabolism studies would thus be required for TFA. However, no metabolism studies for TFA were available for the current evaluation.

Poultry

Magnitude of residues in laying hen was investigated in one study using a 1:1 mixture (w:w) of flonicamid and TFNG. A control group and 4 dose levels corresponding to 0.249, 2.413, 7.174 and 24.797 mg/kg feed or 0.018, 0.174; 0.522 and 1.739 mg/kg bw/day (expressed as the parent compound) were used. Plateau level was reached in eggs at approximately day 4. Residue levels in fat tissue vs. other tissues did not indicate that the studied compounds would be fat soluble. The main residue in poultry tissues was TFNA-AM which supports the findings in the poultry metabolism studies. OH-TFNA-AM was found only in muscle tissue at the highest dose group (26N). Flonicamid was found in eggs mainly at the two highest dose groups, while no TFNG was found. This indicates that TFNG is rapidly metabolised in poultry. The study was considered acceptable.

Ruminants

Magnitude of residues in lactating cows was investigated in one study using a 1:1 mixture (w:w) of flonicamid and TFNG. A control group and 3 dose levels corresponding to 2.40, 6.61 and 22.74 mg/kg feed or 0.088, 0.239 and 0.800 mg/kg bw/day (expressed as the parent compound) were used. Plateau level was reached in milk at approximately day 2. Residue levels in fat tissue vs. other tissues did not indicate that the compounds would be fat soluble.

Metabolite OH-TFNA-AM was detected in milk in the two highest dose group (3N and 9N) while in the goat metabolism study, this metabolite was not detected at all in goat milk at N rate of 20. The concentration of OH-TFNA-AM (0.013-0.019 mg/kg in highest dose group) was higher than that of the parent which was not detected above LOQ. TFNA-AM was detected at level of 0.03-0.09 mg/kg in the highest dose group.

Residues in cow muscle tissues were due to TFNA-AM only and it was detected above LOQ in the two highest dose groups. The residues measured in the study were analysed using a method that included hydrolysis, and thus, the bound TFNA-AM is included in the residue results. This contradicts with the DoR for enforcement proposed in the

current RAR which contains only free parent and TFNA-AM. Thus, the values used for MRL determination are potentially overestimating the residue levels.

In liver, the main residue was due to TFNA-AM and it was detected above LOQ in the two highest dose groups (0.04 and 0.11 mg/kg, respectively). No residues were detected in the lowest dose group. Higher residue levels were measured with the analysis method which included hydrolysis step, which indicates that bound residues were present in liver. These findings are in line with the goat metabolism study. Metabolite OH-TFNA-AM was also found in liver at the two highest dose groups (0.01-0.04 mg/kg, respectively) and measured residues were higher with the method that did not use hydrolysis. Levels of OH-TFNA-AM were only slightly lower than those of TFNA-AM in the feeding study, while the levels of OH-TFNA-AM were significantly lower compared to those of TFNA-AM in the metabolism study (6% of TRR vs. 31-41% of TRR). The difference may be due to longer dosing time in the feeding study (28 days vs. 5 days in the metabolism study).

In kidney, metabolite TFNA was responsible for the main residue while levels of TFNA-AM were slightly lower. OH-TFNA-AM was also found at the highest dose group. As no significant difference in levels of residues were found between the two methods, the residues in kidney were mostly in free form. These finding contradict with the findings of the metabolism study where only low levels of TFNA and OH-TFNA-AM were found, and major part of TFNA-AM was protein-bound. The differences in residue levels of metabolites in the present study and the metabolism study may be due to longer dosing time in the present feeding study (28 days vs. 5 days in the metabolism study). However, the results of the present feeding study in respect to levels of TFNA in kidney should be taken into account when deciding on the relevance of this metabolite for residue definitions. It should be noted that in the lowest dose group, only residues of TFNA were found whereas the levels of other metabolites were <LOQ.

In fat tissue, low residue levels of metabolite TFNA-AM were found only at the highest dose group. This indicates that the residue is not fat soluble.

Calculated residue levels and MRLs for livestock commodities are presented in Table 2.7.6.-6. No exceedances of the current MRLs (Reg. (EU) 2022/85) were identified.

Table 2.7.5.-6. Calculated residue levels and MRLs of flonicamid in ruminants, swine and poultry matrices.

Animal commodity	**Residues at the closet feeding level** (mg/kg)		**Estimated value at 1N level**		**MRL proposal** (mg/kg)	**CF**	**STMR** (mg/kg)	**HR** (mg/kg)
	Mean	Highest	$STMR_{Mo}$ (mg/kg)	HR_{Mo} (mg/kg)				
Cattle (all diets) Closest feeding level:	0.088 mg/kg bw		1.8N Dairy cattle (highest diet)					
Muscle	0.04	0.04	0.04	0.01	**0.01**	n.c.	0.04	0.01
Fat	0.01	0.01	0.01	0.00	**LOQ**	n.c.	0.01	0.00
Liver	0.02	0.02	0.02	0.01	**0.006**	2.2	0.03	0.01
Kidney	0.02	0.02	0.02	0.01	**0.008**	1.2	0.02	0.01
Cattle (dairy only)	0.088 mg/kg bw		1.8N Dairy cattle					

Closest feeding level:								
Milk	0.02	0.02	0.02	0.01	**0.007**	n.c.	0.02	0.01
Sheep (all diets) Closest feeding level:	0.088 mg/kg bw		1.1N Lamb (highest diet)					
Muscle	0.04	0.04	0.04	0.03	**0.04**	n.c.	0.04	0.03
Fat	0.01	0.01	0.01	0.01	**0.008**	n.c.	0.01	0.01
Liver	0.02	0.02	0.02	0.01	**0.015**	2.2	0.03	0.03
Kidney	0.02	0.02	0.02	0.02	**0.015**	1.2	0.02	0.01
Sheep (dairy only) Closest feeding level:	0.088 mg/kg bw		1.3N Ewe					
Milk	0.02	0.02	0.02	0.01	**0.015**	n.c.	0.02	0.01
Swine Closest feeding level:	0.088 mg/kg bw		3.4N Finishing (highest diet)					
Muscle	0.04	0.04	0.04	0.01	**0.006**	n.c.	0.04	0.01
Fat	0.01	0.01	0.01	0.00	**LOQ**	n.c.	0.01	0.00
Liver	0.02	0.02	0.02	0.00	**0.003**	2.2	0.03	0.01
Kidney	0.02	0.02	0.02	0.00	**0.004**	1.2	0.02	0.00
Poultry (all diets) Closest feeding level:	0.0175 mg/kg bw		0.3N Layer (highest diet)					
Muscle	0.02	0.02	0.03	0.04	**0.04**	n.c.	0.03	0.04
Fat	0.02	0.02	0.02	0.03	**0.03**	n.c.	0.02	0.03
Liver	0.02	0.02	0.03	0.04	**0.04**	n.c.	0.03	0.04
Poultry (layer only) Closest feeding level:	0.0175 mg/kg bw		0.3N Layer					
Eggs	0.02	0.02	0.06	0.09	**0.09**	n.c.	0.06	0.09

Pigs

Intake calculations show that dietary burden of pigs exceed the trigger value of 0.004 mg/kg bw/day. Metabolism of flonicamid in rats and ruminants was deemed qualitatively and quantitatively similar with metabolite TFNA-AM being the major metabolite in all species. According to guideline 7031/VI/95 rev. 4, pig feeding study is thus not required.

Fish

In the working document on the nature of residues in fish (SANCO/11187/2013 rev. 3), a fish metabolism study is required if the log Pow is >3 and the dietary intake is > 0.1 mg/kg total diet (dry matter). The parent compound flonicamid is a strong base and has lipophilicity logPow of -0.24. The logPow of metabolites TFNG and TFNA are -0.2 and 0.4, respectively. Thus, estimation of fish dietary burden is not required.

Honey

See Section 2.7.9.

2.7.5.2 MRL Application (non-representative uses)

Potatoes can be fed to animals. Therefore, animal dietary burden has to be calculated. In addition to uses on potatoes considered in this MRL application, all feed items which might be treated with flonicamid have to be considered. For feed items from previous evaluations, reference is be made to the previous EFSA Reasoned Opinions. In a case that higher risk assessment values were obtained for crops under evaluation of this RAR, these values were selected.

An experimental processing factor (PF) of 0.38 was used for potato waste. Five experimental replicate trials (mean PF 0.43) for potato wet peel were evaluated in the framework of the current MRL application (see Table 2.7.6.-3). Two experimental replicate trials for potato wet peel (PF 0.33 and 0.34, mean 0.34) were assessed in the context of previous import tolerance application for flonicamid (Finland, 2019). Thus, the mean PF is 0.38 (0.43+0.34/2).

Calculations were performed using the "Animal model 2017", an Excel calculator proposed by EFSA (2017b). The input values are shown in Table 2.7.5-7.

Table 2.7.5.-7 Input values for the dietary burden calculation of Flonicamid

Feed commodity	Median dietary burden		Maximum dietary burden	
	(mg/kg)	Comment	(mg/kg)	Comment
Feed items related to previous evaluation(s)				
Barley (straw)	0.05	STMR (EFSA, 2015)	0.07	HR (EFSA, 2015)
Beet, sugar (tops)	0.09	STMR (EFSA, 2017a)	0.20	HR (EFSA, 2017a)
Cabbage, heads (leaves)	0.14	STMR (EFSA, 2017a)	0.23	HR (EFSA, 2017a)
Oat (straw)	0.05	STMR (EFSA, 2015)	0.07	HR (EFSA, 2015)
Turnip tops (leaves)	0.07	STMR (EFSA, 2018a)	0.29	HR (EFSA, 2018a)
Carrot (culls)	0.05	STMR (EFSA, 2018a)	0.15	HR (EFSA, 2018a)
Swede (roots)	0.05	STMR (EFSA, 2018a)	0.15	HR (EFSA, 2018a)
Turnip (roots)	0.05	STMR (EFSA, 2018a)	0.15	HR (EFSA, 2018a)
Barley (grain)	0.14	STMR (EFSA, 2015)	0.14	STMR (EFSA, 2015)
Bean (seed, dry)	0.39	STMR (EFSA, 2020b)	0.39	STMR(EFSA, 2020b)
Cotton (undelinted seed)	0.04	STMR (EFSA, 2015)	0.04	STMR (EFSA 2015)
Lupin (seed)	0.39	STMR(EFSA, 2020b)	0.39	STMR(EFSA, 2020b)
Oat (grain)	0.14	STMR (EFSA, 2015)	0.14	STMR (EFSA, 2015)

Feed commodity	Median dietary burden		Maximum dietary burden	
	(mg/kg)	Comment	(mg/kg)	Comment
Pea (seed, dry)	0.39	STMR(EFSA, 2020b)	0.39	STMR(EFSA, 2020b)
Rye (grain)	0.35	STMR (EFSA, 2014)	0.35	STMR (EFSA, 2014)
Apple (pomace, wt)	0.30	0.06 STMR x 5 PF[(a)] (EFSA, 2014)	0.30	0.06 STMR x 5 PF[(a)] (EFSA, 2014)
Beet, sugar (dried pulp)	1.62	0.09 STMR x 18 PF[(a)] (EFSA, 2017a)	1.62	0.09 STMR x 18 PF[(a)] (EFSA, 2017a)
Beet, sugar (ensiled pulp)	0.27	0.09 STMR x 3 PF[(a)] (EFSA, 2017a)	0.27	0.09 STMR x 3 PF[(a)] (EFSA, 2017a)
Beet, sugar (molasses)	2.52	0.09 STMR x 28 PF[(a)] (EFSA, 2017a)	2.52	0.09 STMR x 28 PF[(a)] (EFSA, 2017a)
Brewer's grain	0.46	0.14 STMR x 3.3 PF[(a)] (EFSA, 2014)	0.46	0.14 STMR x 3.3 PF[(a)] (EFSA, 2014)
Citrus (dried pulp)	0.40	0.04 STMR x 10 PF[(a)] (EFSA, 2014)	0.40	0.04 STMR x 10 PF[(a)] (EFSA, 2014)
Cotton (meal)	0.05	0.04 STMR x 1.3 PF[(a)] (EFSA, 2015)	0.05	0.04 STMR x 1.3 PF[(a)] (EFSA, 2015)
Lupin seed (meal)	0.43	0.39 STMR x 1.1 PF[(a)] (EFSA, 2020b)	0.43	0.39 STMR x 1.1 PF[(a)] (EFSA, 2020b)
Current RAR				
Rye (straw)	0.375	STMR (NEU)	0.74	HR (NEU)
Triticale (straw)	0.435	STMR (NEU – wheat, WG formulation less critical GAP)	2.19	HR (SEU – WG formulation cGAP)
Wheat (straw)	0.435	STMR (NEU – wheat, WG formulation less critical GAP)	2.19	HR (SEU – WG formulation cGAP)
Wheat (grain)	0.57	STMR (NEU – OD formulation)	0.57	STMR (NEU – OD formulation)
Triticale (grain)	0.57	STMR (NEU – OD formulation)	0.57	STMR (NEU – OD formulation)
Dry peas	0.36	STMR (NEU+SEU)	0.36	STMR (NEU+SEU)
Dry beans	0.36	STMR (NEU+SEU)	0.36	STMR (NEU+SEU)
Wheat (grain)	0.57	STMR (NEU – OD formulation)	0.57	STMR (NEU – OD formulation)
Apple, pomace wet	0.35	0.07 STMR (NEU/SEU) x 5 PF[(a)]	0.35	0.07 STMR (NEU/SEU) x 5 PF[(a)]
Wheat gluten (meal)	1.03	0. 57 STMR (NEU) x 1.8 PF[(a)]	1.03	0. 57 STMR (NEU) x 1.8 PF[(a)]

Feed commodity	Median dietary burden		Maximum dietary burden	
	(mg/kg)	Comment	(mg/kg)	Comment
Distiller's grain (dried)	1.88	0. 57 STMR (NEU) x 3.3 PF[(a)]	1.88	0. 57 STMR (NEU) x 3.3 PF[(a)]
Wheat (milled by-product)	0.57	0. 57 STMR (NEU) x 1 PF (this RAR)	0.57	0. 57 STMR (NEU) x 1 PF (this RAR)
Feed items related to the MRL application on potatoes				
Potato (culls)	0.098	STMR	0.26	HR
Potato (process waste)	0.042	0.098 STMR x 0.38 PF (this RAR; FI, 2019)	0.042	0.098 STMR x 0.38 PF (this RAR; FI, 2019)
Potato (dried pulp)	3.72	0.098 STMR x 38 PF[(a)]	3.72	0.098 STMR x 38 PF[(a)]

(a): Default processing factor (PF) as given in the Animal Model 2017 (EFSA, 2017b).

Livestock dietary burden for metabolite flonicamid exceeded the trigger value of 0.004 mg/kg bw for all livestock commodities as summarised in Table B.2.7.5.-8.

The additional feed commodities under consideration in the MRL application do not result in a significant increase of the animal burdens, compared to the intakes estimated in the previous evaluation (EFSA, 2020b), for dairy and beef cattle, Ram/Ewe and lamb and pig (breeding) and pig (finishing), burden calculations are reported in the Table B.2.7.5-9. For poultry broiler, poultry layer and turkey, the dietary burdens are slightly above the intakes estimated in the previous evaluation (EFSA, 2020b).

Table B.2.7.5.-8. Results of the livestock dietary burden for flonicamid calculation.

Animal burden calculation

According to: "OECD Guidance Document, Series on testing and assessment No 64 and Series on pesticides No 32" and "OECD Guidance Document on Residues in livestock, Series on Pesticides No 73"

Maximum Intake	Cattle						Sheep					
	Beef (500 kg / 12 kg)			Dairy (650 kg / 25 kg)			Ram/Ewe (75 kg / 2,5 kg)			Lamb (40 kg / 1,7 kg)		
(mg/kg bw/d)	0,039	mg/kg bw/d	%	0,064	mg/kg bw/d	%	0,100	mg/kg bw/d	%	0,100	mg/kg bw/d	%
Contributor 1	Wheat	straw	20	Wheat	straw	20	Potato	dried pulp	40	Potato	dried pulp	20
Contributor 2	Beet, sugar	ensiled pulp	25	Beet, sugar	ensiled pulp	40	Wheat	straw	40	Wheat	straw	40
Contributor 3	Swede	roots	40	Potato	culls	30	Swede	roots	20	Swede	roots	30
Contributor 4	Triticale	grain	15	Triticale	grain	10			0	Triticale	grain	10
Median intake	0,0232	mg/kg bw/d		0,0447	mg/kg bw/d		0,0683	mg/kg bw/d		0,0566	mg/kg bw/d	

Maximum Intake	Swine					
	Breeding (260 kg / 6 kg)			Finishing (100 kg / 3 kg)		
(mg/kg bw/d)	0,033	mg/kg bw/d	%	0,051	mg/kg bw/d	%
Contributor 1	Potato	dried pulp	10	Potato	dried pulp	20
Contributor 2	Cabbage, heads	leaves	10	Potato	culls	50
Contributor 3	Potato	culls	50	Triticale	grain	30
Contributor 4	Triticale	grain	30			
Median intake	0,023	mg/kg bw/d		0,040	mg/kg bw/d	

Intakes >0.004 mg/kg bw/d are highlighted

Maximum Intake	Poultry								
	Broiler (1,7 kg / 0,12 kg)			Layer (1,9 kg / 0,13 kg)			Turkey (7 kg / 0,5 kg)		
(mg/kg bw/d)	0,102	mg/kg bw/d	%	0,099	mg/kg bw/d	%	0,060	mg/kg bw/d	%
Contributor 1	Potato	dried pulp	20	Potato	dried pulp	15	Wheat gluten	meal	10
Contributor 2	Swede	roots	10	Wheat	straw	10	Potato	culls	20
Contributor 3	Wheat	grain	70	Swede	roots	10	Wheat	grain	50
Contributor 4				Wheat	grain	65			
Median intake	0,095	mg/kg bw		0,081	mg/kg bw		0,048	mg/kg bw	

Intakes expressed on the dry mater basis (mg/kg DM)

mg/kg DM	Cattle		Sheep		Swine	
	Beef	Dairy	Ram/Ewe	Lamb	Breeding	Finishing
Maximum	1,64	1,67	3,0	2,36	1,42	1,69
Median	0,97	1,16	2,05	1,33	1,01	1,34

	Poultry		
	Broiler	Layer	Turkey
Maximum	1,44	1,45	0,84
Median	1,34	1,18	0,67

Intake >0.1 mg/kg DM in red characters

Table 2.7.5.-9. Dietary burden calculation for flonicamid for ruminants, swine and poultry.

Animal	Median burden (mg/kg bw)	Maximum burden (mg/kg bw)	>0.004 mg/kg bw (Y/N)	Highest contributing commodity[(a)]	Previous assessment Maximum burden (mg/kg bw)
Dairy cattle	0.045	0.064	Y	Wheat straw	0.143 (EFSA 2020b) Dairy cattle
Beef cattle	0.023	0.039	Y	Wheat straw	
Ram/Ewe	0.068	0.100	Y	Potato dried pulp	0.158 (EFSA 2020b) Ram/Ewe
Lamb	0.056	0.100	Y	Potato dried pulp	
Pig (breeding)	0.023	0.033	Y	Potato dried pulp	0.066 (EFSA 2020b) Swine (breeding)
Pig (finishing)	0.040	0.051	Y	Potato dried pulp	
Poultry broiler	0.095	0.102	Y	Potato dried pulp	0.071 (EFSA 2020b) Poultry layer
Poultry layer	0.081	0.099	Y	Potato dried pulp	
Turkey	0.048	0.060	Y	Wheat gluten meal	

(a): Considering the maximum dietary animal burden

Calculated residue levels and MRLs for livestock commodities are presented in Table 2.7.6.-10. No exceedances of the current MRLs (Reg. (EU) 2022/85) were identified.

Table 2.7.6.-10 Calculated residue levels and MRLs of flonicamid in ruminants, swine and poultry matrices.

Animal commodity	Residues at the closet feeding level (mg/kg)		Estimated value at 1N level		MRL proposal (mg/kg)	CF	STMR (mg/kg)	HR (mg/kg)
	Mean	Highest	$STMR_{Mo}$ (mg/kg)	HR_{Mo} (mg/kg)				
Cattle (all diets) Closest feeding level[a]:	0,088	mg/kg bw	1,4	N Dairy cattle (highest diet)				
Muscle	0.04	0.04	0.04	0.04	**0.04**	n.c.	0.04	0.04
Fat	0.01	0.01	0.01	0.01	**0.01**	n.c.	0.01	0.01
Liver	0.02	0.02	0.02	0.02	**0.015**	n.c.	0.02	0.02
Kidney	0.02	0.02	0.02	0.02	**0.015**	n.c.	0.02	0.02
Cattle (dairy only) Closest feeding level[a]:	0.088	mg/kg bw	1.4	N Dairy cattle				
Milk[b]	0.02	0.02	0.02	0.02	**0.02**	n.c.	0.02	0.02
Sheep (all diets) Closest feeding level[a]:	0.088	mg/kg bw	0.9	N Lamb (highest diet)				
Muscle	0.04	0.04	0.04	0.04	**0.04**	n.c.	0.04	0.04
Fat	0.01	0.01	0.01	0.01	**0.01**	n.c.	0.01	0.01
Liver	0.02	0.02	0.02	0.02	**0.02**	n.c.	0.02	0.02
Kidney	0.02	0.02	0.02	0.02	**0.02**	n.c.	0.02	0.02
Sheep (dairy only) Closest feeding level[a]:	0.088	mg/kg bw	0.9	N Ewe				
Milk[b]	0.02	0.02	0.02	0.02	**0.02**	n.c.	0.02	0.02
Swine Closest feeding level[a]:	0.088	mg/kg bw	1.7	N Finishing (highest diet)				
Muscle	0.04	0.04	0.04	0.04	**0.04**	n.c.	0.04	0.04
Fat	0.01	0.01	0.01	0.01	**0.01**	n.c.	0.01	0.01
Liver	0.02	0.02	0.02	0.02	**0.015**	n.c.	0.02	0.02
Kidney	0.02	0.02	0.02	0.02	**0.015**	n.c.	0.02	0.02
Poultry (all diets) Closest feeding level[a]:	0.174	mg/kg bw	1.7	N Broiler (highest diet)				
Muscle	0.07	0.08	0.04	0.05	**0.06**	n.c.	0.04	0.05
Fat	0.04	0.05	0.03	0.03	**0.04**	n.c.	0.03	0.03
Liver	0.07	0.09	0.05	0.06	**0.06**	n.c.	0.05	0.06
Poultry (layer only) Closest feeding level[a]:	0.174	mg/kg bw	1.8	N Layer				
Eggs[c]	0.11	0.13	0.09	0.08	**0.08**	n.c.	0.09	0.08

(a): Closest feeding level and N dose rate related to the maximum dietary burden.

(b): Highest residue level from day D1 to day D2 (daily mean of X cows).

(c): Highest residue level from day D1 to day D2 (daily mean of Y laying hens).

2.7.6 Summary of effects of processing

2.7.6.1 Representative uses

Nature of residues

Nature of residues of radiolabelled flonicamid, TFNG and TFNA were investigated in standard processing

conditions simulating pasteurisation (90°C and pH 4 for 20 min), baking, brewing and boiling (100°C and pH 5 for 60 min) and sterilisation (120°C and pH 6 for 20 min). All compounds were shown to be stable. Formation of unknown degradation products was at highest 1.7% of applied radioactivity for flonicamid, while no degradation products were detected for TFNG and TFNA.

For TFNA-AM, residues above the threshold value 0.01 mg/kg may be expected in some livestock commodities (eggs, poultry tissues, and sheep muscle), and thus, nature of residue studies would be required. TFNA-AM shares considerable structural similarity with the parent compound and TFNG, as well as TFNA, which were all shown to be stable in standard hydrolytic conditions. Parent compound and TFNG have secondary amide structure while TFNA-AM has a primary amide group in the side chain. Amides generally resist hydrolysis well. Thus, also TFNA-AM may be assumed to be stable in these conditions.

TFA may be present in significant levels in rotationally grown crops. No data on stability of TFA in standard hydrolytic conditions were provided for the current evaluation. Given the prevalence of the compound in environmental compartments and its long degradation time, TFA may be considered as stable in hydrolytic conditions. However, studies are still necessary to confirm this.

Magnitude of residues

Distribution of the residue between peel and pulp

The distribution in peel and pulp is relevant for the representative use on melons. Residue levels in peel and pulp were measured in the residue studies conducted in melons in the Southern zone (studies KCP 8.3.11/01-02). The measured residue levels and calculated peeling factors are presented in Table 2.7.6.-1.

Table 2.7.6.-1. Residues in melon peel, pulp and whole fruit, and derived peeling factors.

Study	Product	Residue sum (mg/kg)*	Peeling factor	Median PeF
KCP 8.3.11/01	Peel	0.33	0.62	0.70
	Pulp	0.13		
	Whole fruit	0.21		
	Peel	0.16	0.56	
	Pulp	0.05		
	Whole fruit	0.09		
	Peel	0.35	0.21	
	Pulp	0.04		
	Whole fruit	0.19		
	Peel	0.29	0.31	
	Pulp	0.04		
	Whole fruit	0.13		
KCP 8.3.11/02	Peel	0.05	1.00	
	Pulp	0.03		
	Whole fruit	0.03		
	Peel	0.18	0.78	
	Pulp	0.07		
	Whole fruit	0.09		
	Peel	0.18	0.78	

	Pulp	0.07	
	Whole fruit	0.09	
	Peel	0.19	
	Pulp	0.1	0.83
	Whole fruit	0.12	

* According to the DoR for monitoring and risk assessment: The sum of flonicamid, TFNG and TFNA, expressed as flonicamid

Follow-up studies

Processing studies were provided for wheat, peach, plum and tomato, all of which may contain residues above the threshold concentration of 0.1 mg/kg. These commodities were considered sufficient to represent the proposed uses on cereals, apples, peaches/nectarines, plums, cucumber, tomato/aubergine, melons, cherries and pulses. Summary of the processing factors derived from the follow-up studies are presented in Table 2.7.6.-2.

The studies were considered acceptable, although recoveries were poor (<70%) for many analytes in the fruit processing studies:

- TFNA (canned peach) – study KCA 6.5.3/05
- TFNA (canned plum) and TFNG (jam, juice and washed plum) - KCA 6.5.3/8
- flonicamid (plums, jam and dried plum) and TFNA (juice and washed plum) - study KCA 6.5.3/9
- recovery from plum pyree was not investigated in study KCA 6.5.3/9
- TFNA (ketchup) - study KCA 6.5.3/13).

For dried plums only one study was available. Tentative processing factor is based on this data point, but one additional study would be desirable.

Finally, storage time of the bread samples in the wheat processing studies KCA 6.5.3/02 and KCA 6.5.3/03 exceeded the demonstrated storage time of the metabolite TFNA in bread. However, as the decline in recovery of residues in study KCA 6.1/05 seemed rather stable at 7 months to 15 months (62-65% of nominal fortification level vs. recovery of 71% at 3 months). Furthermore, the major proportion of residues in bread and also in cereal grain were due to TFNG. Thus, the calculated PF for bread can be considered as tentative.

No data on TFA in processed commodities were provided for the current assessment. Residues >0.10 mg/kg in rotationally grown cereals and roots crops may be expected, based on the field study evaluated in this RAR.

Table 2.7.6.-2. Overview on the derived processing factors

Processed commodities	Number of trials	Individual processing factors	Mean/Median Processing factors*	Reference
Sum of Flonicamid + TFNG + TFNA, expressed as Flonicamid				
Wheat				
Aspirated grain	2	~~7.98,~~ 0.38	0.38	KCA 6.5.3/03
Total bran	2	1.04, 1.29	0.95	KCA 6.5.3/03
Bran	1	0.53		KCA 6.5.3/02
Wheat flour (white and whole meal)	4	White meal: 0.99, 0.67 Whole meal: 1.00, 1.33	White meal: 0.83 Whole meal: 0.86 Combined: 0.85	KCA 6.5.3/03
Wheat flour (whole meal)	1	Whole meal: 0.26		KCA 6.5.3/02
Milled by-products	2	1.04, 0.86	0.95	KCA 6.5.3/03, DMC-17-29935 (Doc. No. 634-4003)
Bread (white bread and whole meal bread)	4	White bread: 0.73 0.48, Whole meal bread: 0.80, 0.90	White bread: 0.60 Whole meal bread: 0.73	KCA 6.5.3/03
Bread (whole meal)	4	0.61, 0.78, 0.36, 0.88		KCA 6.5.3/02
Dry gluten	2	<0.04, <0.14	-	KCA 6.5.3/03
Dry starch	2	0.08, 0.11	0.10	KCA 6.5.3/03
Middling	1	0.32	-	KCA 6.5.3/02
Peaches				
Canned peaches	4	0.6, 0.8, 0.6, 1.4	0.7	KCA 6.5.3/05
Fruit juice	4	1.0, 1.0, 0.6, 0.9	1	KCA 6.5.3/05
Jam	4	1.4, 1.0, 1.0, 0.7	1	KCA 6.5.3/05
Purée	4	0.8, 1.0, 1.0, 1.1	1	KCA 6.5.3/05
Peel	1	0.6	-	KCA 6.5.3/05
Plum				
Jam	4 (4)	0.7, 1.3, 0.5, 0.5	0.6	KCA 6.5.3/08, KCA 6.5.3/09
Purée	4 (4)	0.8, 3.1, 1.0, 0.8	0.9	KCA 6.5.3/08, KCA 6.5.3/09
Juice	4 (4)	0.5, 1.7, 0.7, 0.6	0.7	KCA 6.5.3/08, KCA 6.5.3/09
Canned plums	4 (4)	0.5, 2.0, 0.6, 0.6	0.6	KCA 6.5.3/08, KCA 6.5.3/09
Washed plums	1 (1)	0.9	-	KCA 6.5.3/08, KCA 6.5.3/09
Dried plums	1 (1)	1.5	1.5	KCA 6.5.3/08, KCA 6.5.3/09
Tomatoes				
Wet pomace	4	0.9, 1.4, 0.7, 0.8	0.9	KCA 6.5.3/13
Dry pomace	4	3.8, 4.9, 2.4, 2.8	3.3	KCA 6.5.3/13
Tomato juice	4	0.8, 1.0, 0.7, 0.8	0.8	KCA 6.5.3/13

Purée	4	2.1, 2.0, 0.9, 1.8	1.9	KCA 6.5.3/13
Ketchup	4	2.9, 2.8, 0.5, 1.4	2.1	KCA 6.5.3/13
Canned Tomatoes	4	0.9, 0.9, 0.3, 0.6	0.8	KCA 6.5.3/13
Peeled Tomatoes	1	0.6	-	KCA 6.5.3/13
Peel	1	0.8	-	KCA 6.5.3/13

* The mean/median processing factor is obtained by calculating the mean/median of the individual processing factors of each processing study. If results from two field test sites are available, the processing factor is the mean of the single factors from each site. In case of three or more processing test sites, the processing factor is the median of the single factors from each test site.

na not applicable

2.7.6.2 MRL Application (non-representative uses)

Magnitude of residues

A total of four processing trials (1 balance trial / 3 follow-up trials) was performed on potatoes. The median processing factors are presented in Table below :

Table 2.7.6.-3. Overview on the derived processing factors

Processed commodities	Number of trials	Individual processing factors	Median processing factors	Reference
Sum of Flonicamid + TFNG + TFNA, expressed as Flonicamid				
Potato				
Washed and peeled potato	1[a]	1.20[a] (1.43, 3 x 1.29, 0.71)	1.20[a]	ISK,2022 (Report RDE-21-50691, Doc. No. 638-008)
Wet peels	1[a]	0.43[a] (5 x 0.43)	0.43[a]	
Peeled potato	4[b]	1.14, 1.78, 0.67, 1.90	1.46	
Cooked potato	4[b]	1.29, 2.00, 0.83, 1.60	1.45	
Microwaved potato	4[b]	0.86, 1.33, 0.42, 1.10	0.98	
French fries	4[b]	1.57, 2.89, 1.25, 2.25	1.91	
Potato crisps	4[b]	1.29, 3.33, 1.25, 3.10	2.20	
Potato flakes	4[b]	3.43, 5.00, 2.92, 2.80	3.18	

a: a: 1 independent trial (results are given as a mean value of 5 analytical replicates)
b: 1 balance trial, 3 follow-up trials

It was indicated that residues of flonicamid (sum of residues of Flonicamid, TFNG and TFNA expressed as Flonicamid) concentrated in peeled potatoes, cooked potatoes, French fries, potato crisp and potato flakes. Microwaving has no or little effects on the residues (processing factor 0.098).

2.7.7 Summary of residues in rotational crops

Two magnitude of residue studies were provided for the current review. The first study was performed in the USA in climatic conditions representing Southern European conditions. The application of the a.s. was performed on a primary crop cotton at rate of 3x 100 g a.s./ha (1.7N). After harvest of the primary crop,. rotational crops wheat and turnip were planted 30 and 60 days after the treatment of the primary crop. The treatment of the primary crop was performed at reasonably late growth stage of BBCH 81-88 in September/October and the succeeding crops were planted in the autumn, thus representing winter crops. This scenario cannot be regarded as the most critical situation due to high crop interception and long growing time / PHI for the succeeding crops (131-225 days for wheat and 83-155 days for turnip). Furthermore, leafy crops were not included in the study. According to the more recent metabolism study on rotational crops, TRR >0.01 mg/kg may occur also in leafy crops.

No residues of flonicamid, TFNA, TFNG or TFNA-AM >LOQ were found in any of the crops. Low levels of TFGN residues between the LOD and LOQ (0.01 and 0.02 mg/kg) were detected in the control samples. Reason for the detected concentrations was not clarified. Metabolite TFA was not analysed for in the study.

In the second study, application of the active substance was performed on bare soil at rate of 240 g a.s./ha (1.3N). Rotational crops wheat, lettuce and carrot was planted at PBIs of 30, 120 and 365 days. At the time of writing, an interim report was available, from which some results of the 120-day PBI were still missing. However, main part of results were available in the interim report. No residues above LOQ of 0.01 mg/kg of flonicamid or metabolites TFNA, TFNG, TFNA-AM, TFNA-OH and TFNG-AM were detected in the rotational crops at any PBIs. Metabolite TFA, however, was detected in all crops and all PBIs, except in lettuce at PBI of 365 days. Highest residue levels were found in wheat feed commodities (at highest 0.84 mg/kg in wheat straw at PBI of 30 days) and in wheat grain (at highest 0.48 mg/kg in wheat grain at PBI of 365 days). Residues of TFA in mature lettuce were at highest 0.34 mg/kg (PBI 120 days), in mature carrot root 0.18 mg/kg and in tops 0.68 mg/kg (PBI 120 days). Summary of TFA levels in rotational crops is presented in Table 2.7.7.-1.

Table 2.7.7.-1. Summary of TFA residues in rotational crops

Commodity	TFA residues (mg/kg)								
	PBI 30 days			PBI 120 days			PBI 365 days		
	Single	SMTR	HR	Single	SMTR	HR	Single	SMTR	HR
Wheat forage	0.08; *0.28*; *0.43*; 0.32	**0.30**	**0.43**	tba; *0.31*; *0.30*; 0.07	0.30	0.31	nd; *<0.05*; *0.29*; 0.15	0.15	0.29
Wheat hay	0.23; *0.76*; *0.70**; 0.48*	-	0.76	tba; *0.71*; *0.70*; 0.62	**0.70**	0.71	0.15; *0.68*; *0.79*; 0.47	0.58	**0.79**
Wheat grain	0.08; *0.10*; *0.24*; 0.45	0.17	0.45	tba; *0.11*; *0.22*; 0.30	0.22	0.30	0.09; *0.23*; *0.20*; 0.48	**0.22**	0.48
Wheat straw	0.35; *0.34*; *0.84*; 0.48*	0.35	**0.84**	tba; *0.19*; *0.69*; 0.64	0.64	0.69	0.17; *0.80*; *0.73*; 0.59	**0.66**	0.80
Immature lettuce	0.06; *0.12*; *<0.05*; 0.06	0.06	0.12	<0.05; *<0.05*; *<0.05*; 0.48	0.05	0.48	<0.05*; <0.05*; *<0.05*; <0.05	<0.05	<0.05
Mature lettuce	<0.05; *0.11*; *<0.05*; 0.19	**0.08**	0.19	<0.05; *<0.05*; *<0.05*; 0.34	0.05	**0.34**	<0.05; *<0.05*; *<0.05*; <0.05	<0.05	<0.05
Immature carrot	<0.05; *0.29*; *0.10*; 0.16	0.13	0.29	<0.05; *0.14*; *0.16*; 0.41	0.15	0.41	<0.05; *0.08*; *0.12*; 0.13	0.10	0.13
Mature carrot root	<0.05; *0.07*; *<0.05*; 0.08	0.06	0.08	<0.05; *0.06*; *0.09*; 0.18	**0.08**	**0.18**	<0.05; *<0.05*; *0.07*; 0.11	0.06	0.11
Mature carrot leaves	<0.05; *0.20*; *0.20*; 0.19	0.20	0.20	<0.05; *0.10*; *0.68*; 0.42	**0.26**	**0.68**	0.05; *0.10*; *0.35*; 0.26	0.18	0.35

Italics: Southern zone trials
* Concentration in untreated control higher than in treated sample – value not included in STMR calculation
Bolded: used in livestock DB and/or consumer risk assessment calculations.

Metabolite TFA has a long DT90 of >1000 days. The most critical PEC values for the metabolite TFA were calculated for wheat field use at growth stage BBCH 21 and 2x 70 g a.s./ha application rate. The PECaccu of 0.083 mg/kg of TFA translates to application rate of 63 g TFA/ha. The rate of parent would thus be m(TFA) * M(flonicamid) / M(TFA) = 127 g flonicamid/ha. The nature of residue studies were performed with application rates of 200-240 g flonicamid/ha on bare soil, and the magnitude of residue studies with rates of 300 g flonicamid/ha (on primary crop) and 240 g flonicamid/ha (on bare soil). Thus, the application rates used in all studies are considered to cover the accumulation of the metabolite TFA. However, the calculation does not take into consideration the occurence rate of TFA from parent flonicamid (22.5%; seeVol1 table 2.8.7.1-2.). If this value is taken into consideration, the application rate of parent would be (100/22.5) * 127 = 563 g flonicamid/ha, which is not covered by the rates used in the rotational crop studies.

Residues of TFA were found in untreated samples of carrot and wheat. However, as TFA can be expected to be a common contaminant in many agricultural soils dut to its formation from many other plant protection products, the measured values were considered to be representative and were used in further risk assessment.

Due to the long degradation time of TFA, it may also accumulate in soil and be transferred to following years's harvests of permanent crops, especially after several years of use in previous seasons (relevant for pome and stone fruits in the present evaluation).

2.7.8 Summary of other studies

According to Regulation (EU) No. 283/2013, the objective of studies on effect on the residue level in pollen and bee products is to determine the residues in these products for human consumption resulting from residues taken up by honeybees from crops at blossom. The approach taken to address this requirement follows current guidance in technical guideline SANTE/11956/2016 rev. 9 (European Commission, 2018).

Regarding to the representative uses for IKI-220 500 WG, wheat and tomatoes are classified as non-melliferous crops according to this technical guideline. Thus, these crops do not provide enough pollen, nectar, propolis and/or honeydew to honeybees to produce honey and respective residue data are not required for the use of flonicamid on whereas apples, pears, peaches, apricots, plums, cucumber, courgette, eggplants, melons and cherries are classified as melliferous crops in accordance to SANTE/11956/2016 rev.9.

Regarding to the representative uses for IKI-220 OD, wheat, rye and triticale are classified as non-melliferous crops according to technical guideline SANTE/11956/2016 rev. 9. Consequently, residue data in honey are not required for these crops. Instead, dry beans and dry peas are classified as melliferous according to this technical guideline.

Hence, in order to support the melliferous uses for IKT-220 500 WG and IKI-220 100 OD, a residue study in honey

with the GAP covering the worst cGAP of the melliferous crops have been conducted. Four semi-field (tunnel) trials were conducted in different locations in Northern and Southern Europe in order to investigate the magnitude of residues of flonicamid and its metabolites TFNA and TFNG in honey. Flonicamid was applied once at 128 g a.s./ha immediately before flowering (BBCH 59) of *Phacelia tanacetifolia*. This application rate was calculated by using a multiple application factor (MFA) and it is considered to represent the cGAP (3 x 80 g as/ha). Honey was sampled when it has reached commercial maturity. Sampling took place from 15 to 22 d after the application, at BBCH 68-69. The analytical method used to analyse the residue trial samples has been sufficiently validated and was proven to be fit for purpose. Storage intervals were acceptable in all trials when compared to the demonstrated storage stability times of flonicamid and metabolites TFNG and TFNA.

Summary of the residue trials on honey are presented in Table 2.7.9.-1. The residue data indicate that flonicamid in honey are expected to be below 0.069 mg/kg when applied one at a rate of 128 g as/ha just prior to flowering. The study design was considered appropriate to use the results of the trials for deriving a MRL proposal of 0.15 mg/kg for honey. It is, however, noted that the MRL application included in the RAR did not request a modification of the existing MRL for honey. A separate routine MRL application under Regulation (EC) N:o 396/2005 will be submitted (in IUCLID format) to modify the MRL for honey.

Table 2.7.9.-1. Summary of magnitude of residue trials on honey covering representative uses of IKI-220 500 WG and IKI-220 100 WG

Zone	Commodity	Residues[a] (mg/kg)	Values for risk assessment (mg/kg)[a]		MRL (mg/kg)[b]
			STMR (mg/kg)	HR (mg/kg)	
NEU + SEU (semi-field trials)	Honey	<0.03, 2 x 0.06, 0.069	0.06	0.069	0.15

[a] According to residue definition for enforcement and risk assessment, i.e. the sum of flonicamid, TFNG and TFNA, expressed as flonicamid.
[b] According to OECD MRL calculator

2.7.9 Estimation of the potential and actual exposure through diet and other sources

2.7.9.1 Representative uses (primary crops & livestock)

In the framework of the current renewal assessment, a change to the toxicological reference values of flonicamid were proposed as following (see Vol1 2.6.9.1 and 2.6.9.2):

ADI: 0.073 mg/kg bw/day ARfD: 0.075 mg/kg bw

The toxicological profile of metabolites TFNG and TFNA have been reviewed in the present RAR, and it was concluded that the reference values of the parent can be used for these metabolites (see section 2.6.8).

Chronic and acute consumer dietary exposure resulting from the representative uses was calculated using revision 3.1 of the EFSA PRIMo tool using the refined calculation mode. For the TMDI calculations, the current MRLs were used as input values. Input values and conversion factors used in the exposure estimation are summarized in table 2.7.9.-1.

Table 2.7.9.-1. Input values for the consumer exposure assessment of flonicamid (primary crops and livestock commodities)

Commodity	TMDI	Chronic risk assessment		Acute exposure assessment	
	MRL (mg/kg)	Input (mg/kg)	Comment	Input (mg/kg)	Comment
Apple and pear	0.3	0.07	STMR whole fruit (NEU)	0.22	HR whole fruit (NEU)
Peaches and apricots	apricots 0.3; peaches 0.4	0.09	STMR whole fruit (NEU)	0.30	HR whole fruit (SEU)
Plums	0.3	0.06	STMR whole fruit (NEU)	0.13	HR whole fruit (SEU)
Cucumber and courgette	0.9	0.15	STMR whole fruit (indoor use)	0.62	HR whole fruit (indoor use)
Tomato and aubergine	0.5	0.104	STMR whole fruit (indoor use)	0.334	HR whole fruit (indoor use)
Melons	0.4	0.105 x 0.7	STMR whole fruit (SEU) x peeling factor (this RAR)	0.21 x 0.7	HR whole fruit (SEU) x peeling factor (this RAR)
Cherries	0.4	0.13	STMR whole fruit (NEU & SEU)	0.17	HR whole fruit (NEU)
Dry pulses	1.5 (beans & peas)	0.36	STMR (NEU+SEU)	0.36	STMR (NEU+SEU)
Wheat	3	0.57	STMR (SEU)	0.57	STMR (SEU)
Rye	2	0.155	STMR (NEU)	0.155	STMR (NEU)
Bovine** muscle	0.15	0.038*	STMR	0.01	HR
Bovine fat	0.05	0.01*	STMR	0.01*	HR
Bovine liver	0.2	0.015* x 2.2	STMR x CF (this RAR)	0.006 x 2.2	HR x CF (this RAR)
Bovine kidney	0.2	0.015* x 1.2	STMR x CF (this RAR)	0.007 x 1.2	HR x CF (this RAR)
Milk	0.15	0.02*	STMR	0.006	HR
Sheep** muscle	0.15	0.038*	STMR	0.032	HR
Sheep fat	0.05	0.01*	STMR	0.008	HR
Sheep liver	0.2	0.015* x 2.2	STMR x CF (this RAR)	0.015* x 2.2	HR x CF (this RAR)
Sheep kidney	0.2	0.015* x 1.2	STMR x CF (this RAR)	0.012 x 1.2	HR x CF (this RAR)
Sheep milk	0.15	0.02*	STMR	0.013	HR
Swine muscle	0.15	0.038*	STMR	0.005	HR
Swine fat	0.05	0.01*	STMR	0.01*	HR
Swine liver	0.2	0.015* x 2.2	STMR x CF (this RAR)	0.003 x 2.2	HR x CF (this RAR)
Swine kidney	0.2	0.015* x 1.2	STMR x CF (this RAR)	0.004 x 1.2	HR x CF (this RAR)
Poultry muscle	0.1	0.031	STMR	0.039	HR
Poultry fat	0.05	0.023	STMR	0.028	HR
Poultry liver	0.1	0.032	STMR	0.041	HR
Eggs	0.15	0.06	STMR	0.09	HR

Commodity	TMDI	Chronic risk assessment		Acute exposure assessment	
	MRL (mg/kg)	Input (mg/kg)	Comment	Input (mg/kg)	Comment
Honey	0.15	0.06	STMR	0.069	HR

* LOQ
****** According to EFSA's guidance document (September 2015), estimated STMR, HR, and MRL of bovine commodities were extrapolated to horse, and the results of ewe to goat.

In addition, following processing factors available in PRIMo rev. 3.1 were used: Peaches/juice 1.0 ; peaches/canned 0.7 ; plums/juice 0.7 ; tomatoes/sauce/puree 1.9 ; tomatoes/juice 0.8 ; wheat/bread (wholemeal) 0.73 ; wheat/bread/pizza 0.6 ; wheat/milling (wholemeal) -baking 0.86 ; wheat/milling (flour) 0.83.

Results of the consumer dietary exposure are shown in Figures 2.7.10.-1. and -2. TMDI using the present and proposed MRLs was at highest 45% of ADI (NL toddler), wheat and milk as the highest contributors. Highest calculated IEDI was 7% of ADI (GEMS/Food G06 and NL toddler), wheat, milk, apples and tomatoes as the highest contributors. Highest calculated IESTI was 54% of ARfD for cucumbers (child).

For the proposed new MRLs, the highest IESTI new was 58% of ARfD for wheat (child), 47% of ARfD for cucumbers (child) and 37% of ARfD for beans (child). Thus, the proposed MRLs are safe for consumers.

Figure 2.7.9.-1. Results of the chronic consumer exposure estimation for flonicamid.

EFSA PRIMo revision 3.1; 2019/03/19

Flonicamid

LOQs (mg/kg) range from:	0,02	to:	0,10
Toxicological reference values			
ADI (mg/kg bw/day):	0,073	ARfD (mg/kg bw):	0,075
Source of ADI:	RAR	Source of ARfD:	RAR
Year of evaluation:	2023	Year of evaluation:	2032

Input values

Details - chronic risk assessment | Supplementary results - chronic risk assessment

Details - acute risk assessment/children | Details - acute risk assessment/adults

Comments:

Refined calculation mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

	Calculated exposure (% of ADI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	Exposure resulting from: MRLs set at the LOQ (in % of ADI)	Exposure resulting from: commodities not under assessment (in % of ADI)
TMDI/NEDI/IEDI calculation (based on average food consumption)	7%	GEMS/Food G06	4,97	6%	Wheat	0,5%	Tomatoes	0,1%	Cucumbers		7%
	7%	NL toddler	4,93	3%	Wheat	2%	Milk: Cattle	1%	Apples		7%
	6%	DK child	4,38	3%	Wheat	1%	Rye	0,3%	Milk: Cattle		6%
	6%	DE child	4,29	3%	Wheat	1%	Apples	0,5%	Milk: Cattle		6%
	6%	IT toddler	4,16	5%	Wheat	0,2%	Tomatoes	0,1%	Apples		6%
	5%	RO general	3,70	4%	Wheat	0,3%	Milk: Cattle	0,3%	Tomatoes		5%
	5%	FR child 3 15 yr	3,70	4%	Wheat	0,6%	Milk: Cattle	0,2%	Apples		5%
	5%	NL child	3,66	3%	Wheat	0,7%	Milk: Cattle	0,6%	Apples		5%
	5%	ES child	3,34	3%	Wheat	0,3%	Milk: Cattle	0,1%	Tomatoes		5%
	5%	UK toddler	3,29	3%	Wheat	0,6%	Milk: Cattle	0,4%	Beans		5%
	4%	GEMS/Food G15	3,23	4%	Wheat	0,2%	Milk: Cattle	0,2%	Tomatoes		4%
	4%	GEMS/Food G08	2,98	3%	Wheat	0,2%	Tomatoes	0,2%	Milk: Cattle		4%
	4%	GEMS/Food G07	2,96	3%	Wheat	0,2%	Milk: Cattle	0,2%	Tomatoes		4%
	4%	FR toddler 2 3 yr	2,88	2%	Wheat	0,8%	Milk: Cattle	0,3%	Apples		4%
	4%	UK infant	2,82	2%	Wheat	1%	Milk: Cattle	0,2%	Beans		4%
	4%	GEMS/Food G10	2,82	3%	Wheat	0,2%	Tomatoes	0,2%	Milk: Cattle		4%
	4%	IT adult	2,68	3%	Wheat	0,2%	Tomatoes	0,1%	Apples		4%
	4%	SE general	2,62	2%	Wheat	0,3%	Milk: Cattle	0,2%	Bovine: Muscle/meat		4%
	4%	GEMS/Food G11	2,60	3%	Wheat	0,2%	Milk: Cattle	0,1%	Apples		4%
	4%	PT general	2,56	3%	Wheat	0,1%	Tomatoes	0,1%	Apples		4%
	3%	IE adult	1,98	2%	Wheat	0,1%	Peas	0,1%	Milk: Cattle		3%
	3%	DE women 14-50 yr	1,98	2%	Wheat	0,3%	Milk: Cattle	0,2%	Apples		3%
	2%	DE general	1,82	1%	Wheat	0,3%	Milk: Cattle	0,2%	Apples		2%
	2%	ES adult	1,82	2%	Wheat	0,1%	Milk: Cattle	0,1%	Tomatoes		2%
	2%	FR adult	1,68	2%	Wheat	0,1%	Milk: Cattle	0,1%	Apples		2%
	2%	NL general	1,60	2%	Wheat	0,2%	Milk: Cattle	0,1%	Apples		2%
	2%	UK vegetarian	1,55	2%	Wheat	0,2%	Beans	0,1%	Milk: Cattle		2%
	2%	UK adult	1,26	1%	Wheat	0,1%	Beans	0,1%	Milk: Cattle		2%
	2%	LT adult	1,20	0,8%	Wheat	0,2%	Rye	0,2%	Apples		2%
	2%	FI 3 yr	1,12	0,9%	Wheat	0,2%	Cucumbers	0,1%	Rye		2%
	2%	DK adult	1,12	0,9%	Wheat	0,1%	Milk: Cattle	0,1%	Rye		2%
	1%	FR infant	1,05	0,6%	Wheat	0,5%	Milk: Cattle	0,2%	Apples		1%
	1%	FI 6 yr	0,93	0,8%	Wheat	0,1%	Cucumbers	0,1%	Rye		1%
	1%	IE child	0,80	0,9%	Wheat	0,1%	Milk: Cattle	0,0%	Apples		1%
	0,6%	FI adult	0,47	0,3%	Wheat	0,1%	Rye	0,1%	Tomatoes		0,6%
	0,4%	PL general	0,32	0,2%	Apples	0,1%	Tomatoes	0,0%	Pears		0,4%

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of Flonicamid is unlikely to present a public health concern.

Figure 2.7.9.-2. Results of the acute consumer exposure estimation for flonicamid.

Acute risk assessment /children	Acute risk assessment / adults / general population	Acute risk assessment /children	Acute risk assessment / adults / general population
Details - acute risk assessment /children	Details - acute risk assessment/adults	Hide IESTI new calculations	Show IESTI new calculations

The acute risk assessment is based on the ARfD.
The calculation is based on the large portion of the most critical consumer group.

IESTI new calculations:
The calculation is performed with the MRL and the peeling/processing factor (PF), taking into account the residue in the edible portion and/or the conversion factor for the residue definition (CF). For case 2a, 2b and 3 calculations a variability factor of 3 is used. Since this methodology is not based on internationally agreed principles, the results are considered as indicative only.
Since this methodology is not based on internationally agreed principles, the results are considered as indicative only.

Show results of IESTI calculation only for crops with GAPs under assessment

Unprocessed commodities

Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
54%	Cucumbers	0,9 / 0,62	41
41%	Pears	0,3 / 0,22	30
38%	Courgettes	0,9 / 0,62	29
38%	Peaches	0,4 / 0,3	29
32%	Apples	0,3 / 0,22	24
30%	Melons	0,4 / 0,15	22
26%	Tomatoes	0,5 / 0,33	19
14%	Apricots	0,3 / 0,3	10
11%	Aubergines/egg plants	0,5 / 0,33	8,4
11%	Wheat	3 / 0,57	8,2
9%	Beans	1,5 / 0,36	6,6
7%	Plums	0,3 / 0,13	5,5
3%	Milk: Cattle	0,15 / 0,02	2,5
3%	Peas	1,5 / 0,36	2,4
3%	Cherries (sweet)	0,4 / 0,17	2,1

Expand/collapse list

Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)

Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
23%	Cucumbers	0,9 / 0,62	17
19%	Courgettes	0,9 / 0,62	14
12%	Aubergines/egg plants	0,5 / 0,33	9,0
9%	Pears	0,3 / 0,22	6,7
8%	Apples	0,3 / 0,22	6,2
8%	Melons	0,4 / 0,15	5,8
7%	Peaches	0,4 / 0,3	5,6
7%	Tomatoes	0,5 / 0,33	5,3
6%	Wheat	3 / 0,57	4,8
4%	Apricots	0,3 / 0,3	3,3
3%	Beans	1,5 / 0,36	2,4
3%	Plums	0,3 / 0,13	2,3
2%	Cherries (sweet)	0,4 / 0,17	1,7
2%	Peas	1,5 / 0,36	1,2
1%	Other farmed animals:	0,15 / 0,15	0,84

IESTI new
Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI new

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
58%	Wheat	3 / 3	43
47%	Cucumbers	0,9 / 0,9	35
37%	Beans	1,5 / 1,5	27
34%	Melons	0,4 / 0,28	25
29%	Peaches	0,4 / 0,4	22
25%	Milk: Cattle	0,15 / 0,15	19
25%	Apples	0,3 / 0,3	18
24%	Courgettes	0,9 / 0,9	18
24%	Pears	0,3 / 0,3	18
20%	Tomatoes	0,5 / 0,5	15
20%	Apricots	0,3 / 0,3	15
17%	Rye	2 / 2	13
13%	Peas	1,5 / 1,5	9,8
10%	Plums	0,3 / 0,3	7,7
10%	Aubergines/egg plants	0,5 / 0,5	7,5

Total number of commodities found exceeding the ARfD/ADI in children and adult diets (IESTI new calculation)

IESTI new
Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI new

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
34%	Wheat	3 / 3	25
20%	Cucumbers	0,9 / 0,9	15
16%	Plums	0,3 / 0,3	12
14%	Courgettes	0,9 / 0,9	11
14%	Pears	0,3 / 0,3	11
13%	Beans	1,5 / 1,5	9,9
13%	Rye	2 / 2	9,7
13%	Aubergines/egg plants	0,5 / 0,5	9,7
13%	Tomatoes	0,5 / 0,5	9,6
12%	Apples	0,3 / 0,3	9,0
11%	Peaches	0,4 / 0,4	8,1
9%	Melons	0,4 / 0,28	6,6
8%	Milk: Cattle	0,15 / 0,15	5,8
7%	Peas	1,5 / 1,5	5,0
5%	Cherries (sweet)	0,4 / 0,4	4,0

Processed commodities

Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
29%	Courgettes / boiled	0,9 / 0,62	22
8%	Wheat / milling (flour)	3 / 0,47	5,7
7%	Peaches / canned	0,4 / 0,21	5,5
5%	Apples / juice	0,3 / 0,07	3,8
3%	Peas / canned	1,5 / 0,14	2,6
3%	Wheat / milling (wholemeal)-l	3 / 0,42	2,3
3%	Pears / juice	0,3 / 0,07	2,3
3%	Tomatoes / sauce/puree	0,5 / 0,2	1,9
2%	Tomatoes / juice	0,5 / 0,08	1,6
2%	Peaches / juice	0,4 / 0,09	1,5
0,7%	Rye / boiled	2 / 0,16	0,56
0,7%	Rye / milling (wholemeal)-bal	2 / 0,16	0,54
0,5%	Plums / juice	0,3 / 0,04	0,40
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!

Expand/collapse list

Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
19%	Courgettes / boiled	0,9 / 0,62	14
3%	Beans / canned	1,5 / 0,36	2,6
3%	Apples / juice	0,3 / 0,07	2,3
3%	Wheat / pasta	3 / 0,57	2,2
2%	Peaches / canned	0,4 / 0,21	1,7
2%	Tomatoes / sauce/puree	0,5 / 0,2	1,6
2%	Wheat / bread/pizza	3 / 0,34	1,5
2%	Wheat / bread (wholemeal)	3 / 0,42	1,5
1%	Peas / canned	1,5 / 0,14	0,95
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!

Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI new

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
40%	Wheat / milling (flour)	3 / 2,49	30
26%	Courgettes / boiled	0,9 / 0,9	19
22%	Apples / juice	0,3 / 0,3	16
16%	Wheat / milling (wholemeal)-	3 / 2,19	12
14%	Peas / canned	1,5 / 0,6	11
13%	Pears / juice	0,3 / 0,3	9,8
12%	Tomatoes / sauce/puree	0,5 / 0,95	9,1
10%	Tomatoes / juice	0,5 / 0,4	7,6
10%	Rye / boiled	2 / 2	7,3
9%	Rye / milling (wholemeal)-	2 / 2	7,0
9%	Peaches / juice	0,4 / 0,4	6,6
7%	Peaches / canned	0,4 / 0,28	5,4
3%	Plums / juice	0,3 / 0,21	2,0
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!

Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI new

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
19%	Courgettes / boiled	0,9 / 0,9	14
15%	Wheat / pasta	3 / 3	11
14%	Beans / canned	1,5 / 1,5	11
13%	Apples / juice	0,3 / 0,3	10,0
11%	Wheat / bread/pizza	3 / 1,8	7,9
10%	Tomatoes / sauce/puree	0,5 / 0,95	7,8
10%	Wheat / bread (wholemeal)	3 / 2,19	7,7
5%	Peas / canned	1,5 / 0,6	4,0
3%	Peaches / canned	0,4 / 0,28	2,3
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!
#LUKU!	#LUKU!	#LUKU!	#LUKU!

Conclusion:
No exceedance of the toxicological reference value was identified for any unprocessed commodity.
A short term intake of residues of Flonicamid is unlikely to present a public health risk.
For processed commodities, no exceedance of the ARfD/ADI was identified.

2.7.9.2 Rotational crops (metabolite TFA)

In the framework of the current renewal assessment, no new toxicological reference values could be set for TFA (data gap). Although EFSA has set tentative toxicological reference values for TFA (EURL-SRM – Residue Findings Report; Residues of DFA and TFA in Samples of Plant Origin, Version 1 (last update: 5.06.2017)) as an ADI of 0.05 mg/kg bw/day and an ARfD of 0.05 mg/kg bw, these were not considered applicable due to data gaps in the toxicological properties of TFA (see section 2.6.8.1).

2.7.9.3 MRL Application (non-representative uses)

The consumer dietary exposure calculations were performed by using the refined calculation mode of the revision 3.1 of the EFSA Pesticide Residues Intake Model "PRIMo" (EFSA, 2018a).

For the chronic dietary exposure assessment, the following uses were taken into consideration:

- The uses related to the MRL application
- Representative uses considered in this RAR
- Uses considered in previous assessments(s) and supporting the existing MRLs listed in Regulation (EC) No 396/2005

For the acute dietary exposure assessment, the only use considered was related to the MRL application under consideration, i.e. potatoes.

In addition, the following median experimental processing factors were used for processed fractions of potato: 2.98 for potato flakes, 1.57 for potato crisps/chips and 1.91 for French fries (See Table 2.7.6.-3). The processing factors are based on the processing study evaluated in the context of the current MRL application. In addition, for potato crisps/chips and potato flakes results from two replicate trials (potato crisps/chips: mean 1.57 of values 1.52, 1.62); potato flakes: mean 2.98 of values 2.85, 3.11) from the previous import tolerance application (Finland, 2019) were also taken into account.

The input values are presented in Table 2.7.9.-3.

Table 2.7.9-3. Input values for the consumer exposure assessment of flonicamid (primary crops and livestock commodities)

Commodity	Chronic risk assessment		Acute exposure assessment	
	Input (mg/kg)	Comment	Input (mg/kg)	Comment
Food items related to the MRL application				
***Products of plant origin RD-Mo=RD-RA**: Sum of Flonicamid, TFNG and TFNA expressed as Flonicamid*				

Commodity	Chronic risk assessment		Acute exposure assessment	
	Input (mg/kg)	Comment	Input (mg/kg)	Comment
Potatoes	0.098	STMR	0.26	HR
Food items related to the current RAR				
***Products of plant origin RD-Mo=RD-RA**: Sum of flonicamid, TFNG and TFNA expressed as Flonicamid*				
***Products of animal origin RD-Mo=RD-RA:** Sum of flonicamid and TFNA-AM (free and bound), expressed as flonicamid*				
Apple and pear	0.07	STMR whole fruit (NEU)	-	The acute exposure assessment was performed only for the commodity under consideration in this MRL application. .
Peaches and apricots	0.09	STMR whole fruit (NEU)	-	
Plums	0.06	STMR whole fruit (NEU)	-	
Cucumber and courgette	0.15	STMR whole fruit (indoor use)	-	
Tomato and aubergine	0.104	STMR whole fruit (indoor use)	-	
Melons	0.105 x 0.7	STMR whole fruit (SEU) x peeling factor (this RAR)	-	
Cherries	0.13	STMR whole fruit (NEU & SEU)	-	
Dry pulses	0.36	STMR (NEU+SEU)	-	
Wheat	0.57	STMR (SEU)	-	
Rye	0.155	STMR (NEU)	-	
Swine, Bovine, Sheep, Goat, Equine: liver	0.015* x 2.2	STMR x CF (this RAR)	-	
			-	
			-	
Swine, Bovine, Sheep, Goat, Equine: kidney	0.015* x 1.2	STMR x CF (this RAR)	-	
			-	
			-	
Swine, Bovine, Sheep, Goat, Equine: edible offals	0.015* x 2.2	STMR x CF (this RAR)	-	
			-	
			-	
Honey	0.06	MRL	-	
Food items related to previous evaluation(s)				
***Products of plant origin RD-Mo=RD-RA:** Sum of flonicamid, TFNG and TFNA expressed as Flonicamid*				
***Products of animal origin RD-Mo=RD-RA:** Sum of flonicamid and TFNA-AM expressed as Flonicamid*				

Commodity	Chronic risk assessment		Acute exposure assessment	
	Input (mg/kg)	Comment	Input (mg/kg)	Comment
Strawberries	0.14	STMR (EFSA, 2019)	-	
Blueberries	0.23	STMR (EFSA, 2019)	-	
Cranberries	0.23	STMR (EFSA, 2019)	-	
Currants	0.23	STMR (EFSA, 2019)	-	
Gooseberries	0.23	STMR (EFSA, 2019)	-	
Blackberries	0.36	STMR (EFSA, 2018a)	-	
Raspberries	0.36	STMR (EFSA, 2018a)	-	
Beetroots	0.05	STMR (EFSA, 2018b)	-	
Carrots	0.05	STMR (EFSA, 2018b)	-	
Celeriacs	0.05	STMR (EFSA, 2018b)	-	
Horseradishes	0.05	STMR (EFSA, 2018b)	-	
Jerusalem	0.05	STMR (EFSA, 2018b)	-	
Parsnips	0.05	STMR (EFSA, 2018b)	-	
Parsley root	0.05	STMR (EFSA, 2018b)	-	
Radishes	0.22	STMR (EFSA, 2018a)	-	
Salsifies	0.05	STMR (EFSA, 2018b)	-	
Swedes	0.05	STMR (EFSA, 2018b)	-	
Turnips	0.05	STMR (EFSA, 2018b)	-	
Peppers	0.06	STMR (EFSA, 2015)	-	
Brussels sprouts	0.07	STMR (EFSA, 2015)	-	
Head cabbage	0.14	STMR (EFSA, 2017a)	-	
Lettuce and other	0.03	STMR (EFSA, 2018a)	-	
Herbs	0.71	STMR (EFSA, 2016)	-	
Beans (with pods)	0.34	STMR (EFSA, 2017)	-	
Peas (with pods)	0.34	STMR (EFSA, 2017)	-	
Peas (w/o pods)	0.20	STMR (EFSA, 2015)	-	
Lentiles	0.16	STMR (EFSA, 2018b)	-	
Lupins	0.16	STMR (EFSA, 2018b	-	
Cotton seed	0.04	STMR (EFSA, 2015)	-	
Barley	0.17	STMR (EFSA, 2015)	-	
Oats	0.17	STMR (EFSA, 2015)	-	
Sugar beet ((root)	0.03	STMR (EFSA, 2017a)	-	
Hops	0.61	STMR (EFSA, 2014)	-	
	0.06	STMR (FAO, 2016)	-	

Commodity	Chronic risk assessment		Acute exposure assessment	
	Input (mg/kg)	Comment	Input (mg/kg)	Comment
Swine, Bovine, Sheep, Goat, Equine:			-	
			-	
Swine, Bovine, Sheep, Goat, Equine: fat	0.02	STMR (FAO, 2016)	-	
			-	
			-	
Poultry: meat, fat, liver, edible offal	0.04	STMR (FAO, 2016)	-	
			-	
Milk and cream	0.05	STMR (FAO, 2016)	-	
Bird's eggs	0.08	STMR (FAO, 2016)	-	

The calculations were compared to the toxicological reference values proposed for flonicamid, ADI of 0.073 mg/kg bw/d and ARfD of 0.075 mg/kg bw.

The chronic dietary exposure did not exceed the ADI for any of the commodities under consideration. The highest IEDI was calculated for NL toddler, representing 11% of the ADI. Cattle milk was the highest contributing commodity representing 4 % of the ADI. Contribution of potatoes to the total intake was less than 1% in all diets.

The acute dietary exposure did not exceed the ARfD for the raw agricultural commodity considered in this MRL application. The highest acute exposure of 53% of the ARfD was obtained for potatoes. The acute dietary exposure did not exceed the ARfD for the potato processed commodities in this MRL application. The highest acute exposure of 62% of the ARfD was obtained for fried potatoes.

The detailed results of the calculations are given in Figure 2.7.9.-4.

Figure 2.7.9.-4. Results of the chronic and acute consumer exposure estimation for flonicamid.

European Food Safety Authority

EFSA PRIMo revision 3.1; 2019/03/19

Flonicamid

LOQs (mg/kg) range from: 0,02 to: 0,10

Toxicological reference values

ADI (mg/kg bw/day):	0,073	ARfD (mg/kg bw):	0,075
Source of ADI:	RAR	Source of ARfD:	RAR
Year of evaluation:	2023	Year of evaluation:	2032

Input values

Details - chronic risk assessment | Supplementary results - chronic risk assessment

Details - acute risk assessment/children | Details - acute risk assessment/adults

Comments:

Refined calculation mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

	Calculated exposure (% of ADI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	Exposure resulting from MRLs set at the LOQ (in % of ADI)	Exposure resulting from commodities not under assessment (in % of ADI)
TMDI/NEDI/IEDI calculation (based on average food consumption)	11%	NL toddler	8,01	4%	Milk: Cattle	3%	Wheat	1%	Apples		11%
	8%	DE child	5,73	3%	Wheat	1%	Milk: Cattle	1%	Apples		8%
	8%	GEMS/Food G06	5,53	6%	Wheat	0,5%	Tomatoes	0,3%	Potatoes		8%
	7%	NL child	5,25	3%	Wheat	2%	Milk: Cattle	0,6%	Apples		7%
	7%	DK child	5,23	3%	Wheat	1%	Rye	0,9%	Milk: Cattle		7%
	7%	FR child 3 15 yr	5,13	4%	Wheat	2%	Milk: Cattle	0,2%	Beans (with pods)		7%
	7%	RO general	4,79	4%	Wheat	0,8%	Milk: Cattle	0,5%	Potatoes		7%
	6%	UK infant	4,69	3%	Milk: Cattle	2%	Wheat	0,4%	Potatoes		6%
	6%	UK toddler	4,61	3%	Wheat	1%	Milk: Cattle	0,5%	Potatoes		6%
	6%	FR toddler 2 3 yr	4,53	2%	Wheat	2%	Milk: Cattle	0,4%	Beans (with pods)		6%
	6%	IT toddler	4,38	5%	Wheat	0,2%	Tomatoes	0,1%	Potatoes		6%
	6%	GEMS/Food G15	4,33	4%	Wheat	0,5%	Milk: Cattle	0,5%	Potatoes		6%
	6%	ES child	4,25	3%	Wheat	0,9%	Milk: Cattle	0,2%	Potatoes		6%
	6%	GEMS/Food G08	4,06	3%	Wheat	0,5%	Potatoes	0,4%	Milk: Cattle		6%
	5%	GEMS/Food G07	4,01	3%	Wheat	0,5%	Potatoes	0,4%	Milk: Cattle		5%
	5%	SE general	3,88	2%	Wheat	0,8%	Milk: Cattle	0,6%	Potatoes		5%
	5%	GEMS/Food G10	3,81	3%	Wheat	0,4%	Potatoes	0,4%	Milk: Cattle		5%
	5%	GEMS/Food G11	3,66	3%	Wheat	0,5%	Milk: Cattle	0,5%	Potatoes		5%
	4%	PT general	3,21	3%	Wheat	0,7%	Potatoes	0,1%	Tomatoes		4%
	4%	IE adult	2,88	2%	Wheat	0,3%	Potatoes	0,3%	Milk: Cattle		4%
	4%	IT adult	2,87	3%	Wheat	0,2%	Tomatoes	0,1%	Potatoes		4%
	4%	DE women 14-50 yr	2,78	2%	Wheat	0,8%	Milk: Cattle	0,2%	Apples		4%
	4%	DE general	2,68	1%	Wheat	0,8%	Milk: Cattle	0,2%	Apples		4%
	3%	NL general	2,44	2%	Wheat	0,6%	Milk: Cattle	0,3%	Potatoes		3%
	3%	ES adult	2,39	2%	Wheat	0,3%	Milk: Cattle	0,1%	Potatoes		3%
	3%	FR adult	2,12	2%	Wheat	0,3%	Milk: Cattle	0,1%	Beans (with pods)		3%
	3%	FR infant	2,07	1%	Milk: Cattle	0,6%	Wheat	0,3%	Potatoes		3%
	3%	UK vegetarian	1,94	2%	Wheat	0,2%	Milk: Cattle	0,2%	Potatoes		3%
	3%	FI 3 yr	1,84	0,9%	Wheat	0,6%	Potatoes	0,2%	Cucumbers		3%
	2%	LT adult	1,81	0,8%	Wheat	0,4%	Potatoes	0,3%	Milk: Cattle		2%
	2%	UK adult	1,62	1%	Wheat	0,2%	Milk: Cattle	0,2%	Potatoes		2%
	2%	DK adult	1,55	0,9%	Wheat	0,4%	Milk: Cattle	0,2%	Potatoes		2%
	2%	FI 6 yr	1,51	0,8%	Wheat	0,5%	Potatoes	0,1%	Cucumbers		2%
	1%	IE child	1,01	0,9%	Wheat	0,2%	Milk: Cattle	0,1%	Potatoes		1%
	1%	PL general	0,77	0,5%	Potatoes	0,2%	Apples	0,1%	Tomatoes		1%
	1,0%	FI adult	0,70	0,3%	Wheat	0,2%	Potatoes	0,1%	Rye		1,0%

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of Flonicamid is unlikely to present a public health concern.

Acute risk assessment /children	Acute risk assessment / adults / general population	Acute risk assessment /children	Acute risk assessment / adults / general population
Details - acute risk assessment /children	Details - acute risk assessment/adults	Hide IESTI new calculations	Show IESTI new calculations

The acute risk assessment is based on the ARfD.
The calculation is based on the large portion of the most critical consumer group.

IESTI new calculations:
The calculation is performed with the MRL and the peeling/processing factor (PF), taking into account the residue in the edible portion and/or the conversion factor for the residue definition (CF). For case 2a, 2b and 3 calculations a variability factor of 3 is used. Since this methodology is not based on internationally agreed principles, the results are considered as indicative only.
Since this methodology is not based on internationally agreed principles, the results are considered as indicative only.

Show results of IESTI calculation only for crops with GAPs under assessment

Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
55%	Pears	0,3 / 0,3	42
54%	Cucumbers	0,9 / 0,62	41
53%	Potatoes	0,09 / 0,26	40
51%	Peaches	0,4 / 0,4	38
43%	Apples	0,3 / 0,3	32
39%	Tomatoes	0,5 / 0,5	29
38%	Courgettes	0,9 / 0,62	29
30%	Melons	0,4 / 0,15	22
29%	Head cabbages	0,5 / 0,5	22
27%	Oranges	0,15 / 0,15	20
25%	Carrots	0,3 / 0,3	19
24%	Sweet peppers/bell peppers	0,3 / 0,3	18
23%	Beans (with pods)	1,5 / 1,5	17
23%	Beetroots	0,3 / 0,3	17
22%	Celeriacs/turnip rooted	0,3 / 0,3	17

Expand/collapse list

Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)

Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
28%	Head cabbages	0,5 / 0,5	21
23%	Cucumbers	0,9 / 0,62	17
19%	Courgettes	0,9 / 0,62	14
18%	Aubergines/egg plants	0,5 / 0,5	14
15%	Beans (with pods)	1,5 / 1,5	12
14%	Swedes/rutabagas	0,3 / 0,3	10
12%	Pears	0,3 / 0,3	9,2
11%	Apples	0,3 / 0,3	8,4
11%	Blackberries	1 / 1	8,2
11%	Tomatoes	0,5 / 0,5	7,9
10%	Potatoes	0,09 / 0,26	7,8
10%	Peaches	0,4 / 0,4	7,5
10%	Blueberries	0,8 / 0,8	7,3
10%	Parsley	6 / 6	7,2
9%	Beetroots	0,3 / 0,3	6,9

IESTI new
Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI new

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
58%	Wheat	3 / 3	43
47%	Cucumbers	0,9 / 0,9	35
37%	Beans	1,5 / 1,5	27
34%	Melons	0,4 / 0,28	25
29%	Peaches	0,4 / 0,4	22
25%	Milk: Cattle	0,15 / 0,15	19
25%	Apples	0,3 / 0,3	18
24%	Courgettes	0,9 / 0,9	18
24%	Pears	0,3 / 0,3	18
23%	Beans (with pods)	1,5 / 1,5	17
20%	Tomatoes	0,5 / 0,5	15
20%	Apricots	0,3 / 0,3	15
18%	Head cabbages	0,5 / 0,5	13
17%	Rye	2 / 2	13
16%	Peas (with pods)	1,5 / 1,5	12

Total number of commodities found exceeding the ARfD/ADI in children and adult diets (IESTI new calculation)

IESTI new
Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI new

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
34%	Wheat	3 / 3	25
20%	Cucumbers	0,9 / 0,9	15
17%	Head cabbages	0,5 / 0,5	13
16%	Plums	0,3 / 0,3	12
15%	Beans (with pods)	1,5 / 1,5	12
14%	Courgettes	0,9 / 0,9	11
14%	Pears	0,3 / 0,3	11
13%	Beans	1,5 / 1,5	9,9
13%	Rye	2 / 2	9,7
13%	Aubergines/egg plants	0,5 / 0,5	9,7
13%	Tomatoes	0,5 / 0,5	9,6
12%	Apples	0,3 / 0,3	9,0
11%	Blackberries	1 / 1	8,2
11%	Peaches	0,4 / 0,4	8,1
10%	Blueberries	0,8 / 0,8	7,3

Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
62%	Potatoes / fried	0,09 / 0,5	46
29%	Courgettes / boiled	0,9 / 0,62	22
25%	Beans (with pods) / boiled	1,5 / 1,5	19
20%	Turnips / boiled	0,3 / 0,3	15
20%	Parsnips / boiled	0,3 / 0,3	15
18%	Beetroots / boiled	0,3 / 0,3	13
14%	Peas / canned	1,5 / 0,6	11
10%	Salsifies / boiled	0,3 / 0,3	7,7
10%	Jerusalem artichokes / boilec	0,3 / 0,3	7,7
10%	Peaches / canned	0,4 / 0,28	7,3
9%	Currants (red, black and whi	0,8 / 0,23	6,6
9%	Lentils / boiled	0,8 / 0,8	6,5
8%	Brussels sprouts / boiled	0,6 / 0,6	6,1
8%	Wheat / milling (flour)	3 / 0,47	5,7
6%	Raspberries / juice	1 / 0,36	4,2

Expand/collapse list

Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
19%	Courgettes / boiled	0,9 / 0,62	14
16%	Beetroots / boiled	0,3 / 0,3	12
14%	Beans / canned	1,5 / 1,5	11
9%	Parsnips / boiled	0,3 / 0,3	6,4
8%	Turnips / boiled	0,3 / 0,3	5,7
7%	Celeriacs / boiled	0,3 / 0,3	5,5
7%	Peas (with pods) / boiled	1,5 / 1,5	5,1
5%	Peas / canned	1,5 / 0,6	4,0
4%	Currants (red, black and	0,8 / 0,23	2,9
3%	Salsifies / boiled	0,3 / 0,3	2,5
3%	Jerusalem artichokes /	0,3 / 0,3	2,4
3%	Apples / juice	0,3 / 0,07	2,3
3%	Peaches / canned	0,4 / 0,28	2,3
3%	Peas (without pods) / boiled	0,7 / 0,7	2,2
3%	Wheat / pasta	3 / 0,57	2,2

IESTI new
Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI new

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
40%	Wheat / milling (flour)	3 / 2,49	30
30%	Currants (red, black and	0,8 / 0,8	23
26%	Courgettes / boiled	0,9 / 0,9	19
25%	Beans (with pods) / boiled	1,5 / 1,5	19
22%	Apples / juice	0,3 / 0,3	16
16%	Wheat / milling (wholemeal)-	3 / 2,19	12
16%	Raspberries / juice	1 / 1	12
14%	Carrots / juice	0,3 / 0,3	11
14%	Peas / canned	1,5 / 0,6	11
13%	Pears / juice	0,3 / 0,3	9,8
12%	Tomatoes / sauce/puree	0,5 / 0,95	9,1
11%	Oranges / juice	0,15 / 0,15	7,9
10%	Tomatoes / juice	0,5 / 0,4	7,6
10%	Potatoes / fried	0,09 / 0,17	7,5
10%	Rye / boiled	2 / 2	7,3

IESTI new
Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI new

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
19%	Courgettes / boiled	0,9 / 0,9	14
15%	Wheat / pasta	3 / 3	11
14%	Beans / canned	1,5 / 1,5	11
14%	Currants (red, black and white) /	0,8 / 0,8	10
13%	Apples / juice	0,3 / 0,3	10,0
11%	Wheat / bread/pizza	3 / 1,8	7,9
10%	Tomatoes / sauce/puree	0,5 / 0,95	7,8
10%	Wheat / bread (wholemeal)	3 / 2,19	7,7
7%	Peas (with pods) / boiled	1,5 / 1,5	5,1
7%	Beetroots / boiled	0,3 / 0,3	5,0
6%	Head cabbages / canned	0,5 / 0,5	4,7
5%	Peas / canned	1,5 / 0,6	4,0
4%	Celeriacs / boiled	0,3 / 0,3	3,3
4%	Barley / beer	0,4 / 0,08	2,9
4%	Parsnips / boiled	0,3 / 0,3	2,7

2.7.9.4 Estimation of consumer exposure via groundwater

Metabolite TFNA-OH may occur in groundwater up to concentration of 0.449 µg/L. According to the toxicological information evaluated in this RAR (see section 2.6.8.1), the metabolite is less toxic compared to the parent. Thus, the toxicological reference values of the parent are applicable to metabolite TFNA-OH. However, as the concentrations of TFNA-OH in ground water are below 0.75 µg/L in all scenarios, and as no significant consumer exposure is expected via food commodities, no consumer risk assessment was performed for the metabolite according to the requirements of SANCO/221/2000 rev.11.

As the non-relevance of TFA in ground water could not be concluded (see section 2.12), no uses resulting in exceedance of 0.1 µg/L of TFA residues in ground water can be accepted. Thus, no consumer exposure for TFA via drinking water was performed.

2.7.10 Proposed MRLs and compliance with existing MRLs

2.7.10.1 Representative uses

An overview of the proposed MRLs and compliance with existing MRLs for flonicamid are summarised in tables below:

IKI-200 500 WG:

Table 2.7.10.-1 Overview of the proposed MRLs and compliance with existing MRLs for flonicamid covering representative uses of IKI-220 500 WG

Commodity	Region	STMR (mg/kg)	HR (mg/kg)	Proposed MRL (mg/kg)	Exsting MRL[a] (mg/kg)	Remarks
Apples and pears	NEU + SEU	0.07	0.22	0.3	0.3	The GAP is covered by the existing MRL
Apricots and peaches	NEU	0.09	0.15	0.3	Apricots: 0.3 Peaches: 0.4	The GAP is covered by the existing MRL.
Peaches	SEU	0.07	0.30	0.4	0.4	The GAP is covered by the existing MRL.
Cherries	NEU + SEU	0.13 (flesh)	0.17 (flesh)	0.4 (whole fruit)	0.4	The GAP is covered by the existing MRL.
Plums	NEU	0.06	0.07	0.2	0.3	The GAP is covered by the existing MRL.
	SEU	0.05	0.13	0.3		
Tomato	SEU	0.05	0.11	0.2	0.5	The GAPs are covered by the existing MRL Extrapolation to aubergine.
	GH	0.10	0.33	0.5	0.5	
Melon	SEU	0.06 (pulp)	0.13 (pulp)	0.4 (whole fruit)	0.4	The GAP is covered by the existing MRL.

Cucumbers	SEU	0.075	0.16	0.3	0.5	The GAP is covered by the existing MRL.
	G	0.15	0.62	**0.6**[b] **or 0.9**[c]	0.5	The proposed MRL is higher than the existing MRL. The MRL is to be increased. Extrapolation is proposed to courgette.
Wheat (2 x 70 g as/ha)	NEU + SEU	0.53	3	**3**	2	The proposed MRL is higher than the existing MRL. The MRL is to be increased
Wheat (1 x 70 g s/ha)	NEU + SEU	0.21	0.83	0.4	2	The GAP is covered by the existing MRL.

NEU = Northern Europe, SEU = Southern Europe, G = Greenhouse,
[a] Regulation (EU) 2022/85, [b] Derived from 8 trials excluding the statistical outlier, [c] Derived from 9 trials without excluding the statistical outlier
In case that two MRLs for one crop were calculated, the highest MRL is written in bold

IKI-220 100 OD:

Table 2.7.10.-2 Overview of the proposed MRLs and compliance with existing MRLs for flonicamid covering representative uses of IKI-220 100 OD

Commodity	Region	STMR (mg/kg)	HR (mg/kg)	Proposed MRL (mg/kg)	Existing MRL[1] (mg/kg)	Remarks
Dry beans[2] and dry peas[3]	NEU + SEU	0.36	0.82	**1.5**	0.8	The proposed MRL is higher than the existing MRL. The MRL is to be increased.
Wheat, rye and triticale	NEU + SEU	0.135	0.61	1	2	The GAP is covered by the existing MRL.

NEU = Northern Europe, SEU = Southern Europe, G = Greenhouse
[1] Regulation (EU) 2022/85
[2] Beans (0300010) in the group of "Pulses", peas (0300030) in the crop group of "Pulses"

Honey:

Table 2.7.10.-3 Overview of the proposed MRLs and compliance with existing MRLs for flonicamid in honey covering representative uses of IKI-220 500 WG and IKI 220 100 OD

Commodity	Region	STMR (mg/kg)	HR (mg/kg)	Proposed MRL (mg/kg)	Existing MRL[1] (mg/kg	Remarks
Honey	NEU + SEU (semi field trials)	0.06	0.07	**0.15**	0.05 (*)	The proposed MRL is higher than the existing MRL. However, is is notes that the MRL application included in the RAR did not seek a modification of the existing MRL for honey. A separate routine MRL application under Regulation (EC) N:o 396/2005 will be submitted (in IUCLID

						format) to modity the MRL for honey.

NEU = Northern Europe, SEU = Southern Europe, G = Greenhouse
[1] Regulation (EU) 2022/85
(*) indicates lower limit of analytical determination

Other products of animal origin:

Table 2.7.10.-4 Overview of the proposed MRLs and compliance with existing MRLs for flonicamid in animal products covering representative uses of IKI-220 500 WG and IKI 220 100 OD

Commodity	Highest STMR (mg/kg)	Highest HR (mg/kg)	Highest Proposed MRL (mg/kg)	Existing MRL[1] (mg/kg	Remarks
Swine, Bovine, Sheep, Goat, Equine: muscle/meat	0.04	0.03	0.04	0.15	The existing MRL is not exceeded.
Swine, Bovine, Sheep, Goat, Equine: fat	0.01	0.01	0.008	0.05	The existing MRL is not exceeded.
Swine, Bovine, Sheep, Goat, Equine: liver	0.03	0.03	0.015	0.2	The existing MRL is not exceeded.
Swine, Bovine, Sheep, Goat, Equine: kidney	0.02	0.01	0.015	0.2	The existing MRL is not exceeded.
Poultry muscle, liver	0.03	0.04	0.04	0.1	The existing MRL is not exceeded.
Poultry fat	0.02	0.03	0.03	0.05	The existing MRL is not exceeded.
Eggs	0.06	0.09	0.09	0.15	The existing MRL is not exceeded.
Milks	0.02	0.01	0.015	0.15	The existing MRL is not exceeded.

[1] Regulation (EU) 2022/85

2.7.10.2 MRL application (non-representative uses)

An overview of the proposed MRLs and compliance with existing MRLs for flonicamid are summarised in tables below:

Table 2.7.10.-5 Overview of the proposed MRL and compliance with existing MRL for flonicamid in potatoes covering intended uses of IKI-220 500 WG

Commodity	Region	STMR (mg/kg)	HR (mg/kg)	Proposed MRL (mg/kg)	Existing MRL[1] (mg/kg)	Remarks
Potatoes	NEU + SEU	0.098	0.26	**0.4**	0.09	The proposed MRL is higher than the existing MRL. The MRL is to be increased.

NEU = Northern Europe, SEU = Southern Europe
[1] Regulation (EU) 2022/85
(*) indicates lower limit of analytical determination

Table 2.7.10.-6 Overview of the proposed MRLs and compliance with existing MRLs for flonicamid

in animal products covering intended uses of IKI-220 500 WG

Commodity	Highest STMR (mg/kg)	Highest HR (mg/kg)	Highest Proposed MRL (mg/kg)	Existing MRL[1] (mg/kg	Remarks
Swine, Bovine, Sheep, Goat, Equine: muscle/meat	0.04	0.04	0.04	0.15	The existing MRL is not exceeded.
Swine, Bovine, Sheep, Goat, Equine: fat	0.01	0.01	0.01	0.05	The existing MRL is not exceeded.
Swine, Bovine, Sheep, Goat, Equine: liver	0.02	0.02	0.02	0.2	The existing MRL is not exceeded.
Swine, Bovine, Sheep, Goat, Equine: kidney	0.02	0.02	0.02	0.2	The existing MRL is not exceeded.
Poultry fat	0.03	0.03	0.04	0.05	The existing MRL is not exceeded.
Poultry tissues other than fat	0.05	0.06	0.06	0.1	The existing MRL is not exceeded.
Eggs	0.09	0.08	0.08	0.15	The existing MRL is not exceeded.
Milks	0.02	0.02	0.02	0.15	The existing MRL is not exceeded.

[1] Regulation (EU) 2022/85

2.7.11 Proposed import tolerances and compliance with existing import tolerances

Import tolerances are not proposed in the framework of renewal for flonicamid.

2.8 FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1 Summary of fate and behaviour in soil

2.8.1.1 Degradation of the active substance and its metabolites in soil

Aerobic degradation studies of flonicamid in soil

Route of aerobic degradation of flonicamid in soil under dark conditions at 20°C was investigated in three separate laboratory studies in a total of eight soils – and at 10 °C in one study using one soil. The old two studies used flonicamid labelled in 3rd position of the pyridyl ring allowing the detection of metabolites TFNG-AM, TFNG, TFNA-AM, TFNA, and TFNA-OH and the new study flonicamid labelled in 4th position allowing of the detection of metabolites TFNG-AM, TFNG, TFNA-AM, TFNA, TFNA-OH + TFA (trifluoroacetic acid) containing the three fluorides from the original structure of flonicamid (see Figure 2.8.1-1 below). These studies are considered to present adequate variety of soil properties and adequate positions of ^{14}C labelling to cover all possible metabolites and therefore satisfies the data requirements under Regulation 1107/2009. Provided studies are summarized below:

Old studies (evaluated in FR DAR 2005 and re-evaluated in Vol 3, CA, Point B.8.1.1.1); additionally, degradation kinetics evaluated in Vol 3, CA Point B.8.1.1.1):

- Study B.8.1.1.1/02 (2002): An aerobic soil metabolism study with [^{14}C] IKI-220. Report 6933-96-0186-EF-001-001
- Study B.8.1.1.1/03 (2002a): Rate of degradation of [^{14}C]IKI-220 in soil. Report 013066-1

A new study (evaluated in this RAR; additionally, degradation kinetics evaluated in Vol 3, CA, Point B.8.1.1.1):

- Study B.8.1.1.1/01 (2021): [^{14}C]-IKI-220 Aerobic degradation and metabolism in four soils at 20 °c in the dark (final report)

The proposed route of degradation in soil in shown in Figure B.2.8.1.1-1.

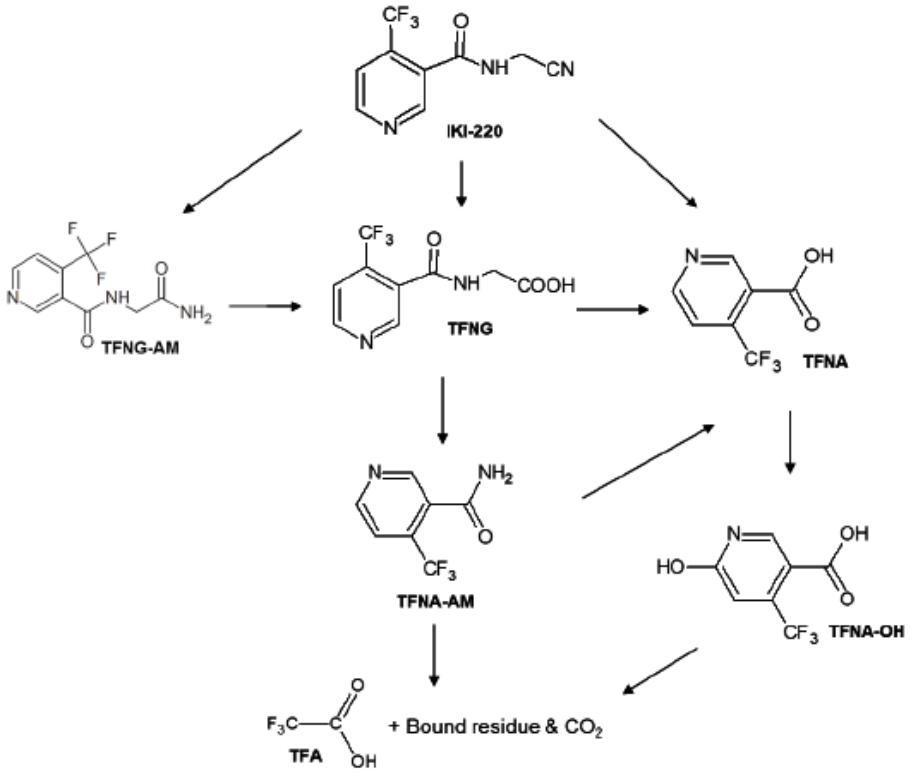


Figure B.2.8.1.1-1: The proposed degradation pathway of flomicamid in soil

A summary of soils used to investigate the aerobic degradation of flonicamid is presented in table below. pH of the soils varied from 6.15. to 7.44. Difference in pH range of the tested soils is considered adequate as flonicamid is hydrolytically stable in water with pH ranging from 5 to 9 ([redacted] 2002). Organic carbon contents were within the OECD 307 recommendations.

Table 2.8.1.1-1: Soils used to investigate the aerobic degradation of flonicamid

Study	**Study B.8.1.1.1/01 (2021)**				**Study B.8.1.1.1/02 (2002)**	**Study B.8.1.1.1/03 (2002a)**		
Name	Lufa 2.2	Lufa 2.4	Clipstone	Brierlow	Madison Ohio 072	Bedfordshire 188, UK # 21	Birmingham 189, UK # 39	Speyer 180, Lufa 2.1
Textural class (USDA scheme)	Sand	Silt loam	Loamy sand	Silt loam	Loamy sand	Loamy sand	Sandy loam	Sand
Origin	Germany	Germany	UK	UK	USA	UK	UK	Germany
(USDA scheme): sand (0.05–2 mm) silt (0.002–0.05 mm) clay (< 0.002 mm)	 87 12.8 0.2	 38.5 51.2 10.3	 87 6.5 6.5	 31.4 61.9 6.6	 79.2 14.0 6.8	 82.0 12.0 6.0	 62.0 26.0 12.0	 92.0 6.0 2.0
Organic carbon [%]	1.82	2.05	1.18	3.93	0.57	1.4	2.7	0.5
Organic matter [%]	3.14	3.53	2.03	6.78	0.98	2.4	4.6	0.9
Microbial biomass [colony forming units/g] [1)]	15.3 [2)]	37.0 [2)]	35.6 [2)]	24.3 [2)]	Bacteria: 7×10^6 Fungi: 22×10^3	Bacteria: 1.3×10^7 Fungi: 4.2×10^6	Bacteria: 1.1×10^7 Fungi: 2.2×10^5	Bacteria: 6.3×10^6 Fungi: 6.6×10^4

Study	Study B.8.1.1.1/01 (2021)				Study B.8.1.1.1/02 (2002)	Study B.8.1.1.1/03 (2002a)		
CEC [meq/100g]	17.4	35.5	12.3	34.0	3.7	8.5	16.9	3.3
pH [$CaCl_2$]	5.36	7.15	5.58	5.46	7.2	-	-	-
pH [H_2O]	6.15	7.44	6.53	6.34	-	-	-	-
pH [not known]	-	-	-	-	7.2	6.9	7.0	6.2
MWC [w/w %]	46.66	54.37	39.03	62.31	16.16	41.0	64.8	29.5
FC [w/w %], 0.33 bar	18.82	28.55	37.36	13.36	8.83	-	-	-
Bulk density[g/cm^3]	-	-	-	-	1.62	-	-	-

[1)] At the beginning of the test
[2)] Values below 1 % of the TOC but since degradation of the test item was observed, soil was seen to be biologically active

Flonicamid (IKI-220) degrades very rapidly in soil with best fit half-lives varying between 0.30 days and 1.92 days (SFO, FOMC) when incubated at 20°C in darkness (Table 2.8.1.1-4). Lower temperature slows down the degradation process, but the degradation is still very fast. A half-life of 2.4 days was calculated from samples incubated at 10°C.

Aerobic degradation studies of flonicamid metabolites

Since IKI-220 degrades rapidly in soil, the fate and behaviour of the major metabolites of flonicamid was also investigated in order to determine their relevance. Separate degradation studies with five soil metabolites of flonicamid were performed to investigate their route and rate of degradation in detail. All metabolites, except for TFA, were found to rapidly degrade in soil at 20°C as well as at 10°C. The terminal step in the metabolism and degradation of all metabolites is the mineralization to CO_2 and the binding to the soil matrix. No other metabolites were found in these studies.

Following five separate studies (presented below) provided during the Annex I Inclusion on the degradation of flonicamid metabolites (TFNG-AM, TFNG, TFNA-AM, TFNA and TFNA-OH) in soil under aerobic conditions in the dark at 20 °C in the laboratory using radiolabel in 3rd position of the pyridyl ring have been re-evaluated:

- Study B.8.1.1.2/01 (2002c): Rate of degradation of [^{14}C]TFNG-AM in soil. Report 012697-1
- Study B.8.1.1.2/02 (2002b): Rate of degradation of [^{14}C]TFNG in soil. Report 012065-1
- Study B.8.1.1.2/03 (2002d): Rate of degradation of [^{14}C]TFNA-AM in soil. Report 012696-1
- Study B.8.1.1.2/04 (2002): Rate of degradation of [^{14}C]TFNA in soil. Report 012064-1
- Study B.8.1.1.2/05 (2002): Rate of degradation of [^{14}C]TFNA-OH in soil. Report 012066-1

During the evaluation procedure Applicant wanted to send two new metabolite studies. RMS promised to evaluate these studies so that the studies would be evaluated at EU level instead of evaluation at and zonal level.

- Study B.8.1.1.2/06 (2022): [^{14}C]TFNA-AM Aerobic Degradation and Metabolism in 3 Soils at 20 °C in the Dark. Report S20-08229
- Study B.8.1.1.2/10 (2022): [^{14}C]TFNA-OH Aerobic Degradation and Metabolism in 3 Soils at 20 °C in the Dark. Report S20-08230

A summary of soils used to investigate the aerobic degradation of flonicamid metabolites is presented in the table below (Table 2.8.1.1-2). pH of the soils varied from 5.7 to 6.8 in metabolite studies with TFNG, TFNA and TFNA-OH and from 6.2 to 7.0 in metabolite studies with TFNG-AM and TFNA-AM. Difference in pH range is quite small.

However, all metabolites were also analysed in parent studies in which soil pHs ranged from 6.15 to 7.44. All the other metabolites in these studies, except the part were the three fluorides (trifluoroacetic acid), are degraded very fast (DT_{50} < 5 days) showing that the chemical structure of the active substance is easily biodegradable. Organic carbon contents were within the OECD 307 recommendations.

Table 2.8.1.1-2: Soils used to investigate the aerobic degradation of flonicamid metabolites

Study	**Study B.8.1.1.2/02 (TFNG) Study B.8.1.1.2/04 (TFNA) Study B.8.1.1.2/05 (2002) (TFNA-OH)**			**Study B.8.1.1.2/01 (TFNG-AM) Study B.8.1.1.2/03 (TFNA-AM)**			**Study B.8.1.1.2/06 (TFNA-AM) Study B.8.1.1.2/10 (TFNA-OH)**		
Name	**165, UK # 21**	**166, UK # 39**	**167, Lufa 2.1**	**188, UK # 21**	**189, UK # 39**	**180, Lufa 2.1**	**Lufa 2.2**	**Lufa 2.4**	**Clipstone**
Soil designation	Bedfordshire	Birmingham	Speyer	Bedfordshire	Birmingham	Speyer	Hanhofen	Leimersheim	Nottinghamshire
Textural class (USDA scheme)	Loamy sand	Sandy loam	Sand	Loamy sand	Sandy loam	Sand	Loamy sand	Loam	Loamy sand
Origin	UK	UK	Germany	UK	UK	Germany			
(USDA scheme): sand (0.05 – 2 mm) silt (0.002 – 0.05 mm) clay (< 0.002 mm)	 86.4 10.7 2.9	 61.4 23.8 14.8	 89.6 8.1 2.3	 82.0 12.0 6.0	 62.0 26.0 12.0	 92.0 6.0 2.0	 77.7 15.7 6.6	 36.7 49.5 13.8	 87.1 8.5 4.4
Organic carbon [%]	0.73	3.18	0.60	1.4	2.7	0.5	1.85	2.24	1.07
Organic matter [%][1)]	1.25	5.49	1.03	2.4	4.6	0.9	3.19	3.86	1.84
Microbial biomass [colony forming units/g][2)]	Bacteria: 1.7×10^7 Fungi: 2.2×10^5	Bacteria: 3.0×10^7 Fungi: 3.4×10^5	Bacteria: 1.2×10^6 Fungi: 9.4×10^5	Bacteria: 2.1×10^7 Fungi: 3.3×10^5	Bacteria: 3.8×10^7 Fungi: 1.0×10^5	Bacteria: 3.6×10^6 Fungi: 1.4×10^5	$22.1^{2,3)}$ $19.7^{2,4)}$ $15.1^{5,7)}$ $16.0^{6,7)}$	$81.0^{2,3)}$ $87.0^{2,4)}$ $59.6^{5)}$ $66.1^{6)}$	$16.2^{2,3)}$ $20.0^{2,4)}$ $8.0^{5,7)}$ $7.7^{6,7)}$
CEC [meq/100g]	4.97	13.01	2.02	8.5	16.9	3.3	20.8	36.4	10.6
pH [not known]	6.8	6.4	5.7	6.9	7.0	6.2			
pH ($CaCl_2$)							5.67	7.42	5.88
pH (H_2O)							6.59	8.11	6.73
MWC [w/w %]	21.23	39.88	18.41	41.0	64.8	29.5	19.8	28.8	11.9

[1)] Calculated from organic carbon according to OM = OC : 0.58
[2)] At the beginning of the test; (microbial activity values are from [redacted] 2002 b, c; minor deviation was in other studies; do not affect the results of these studies)
[3)] Treated soil
[4)] Untreated soil
[5)] At the end of the test, untreated soil
[6)] At the end of the test, treated soil
[7)] Slightly below 1 % of TOC

Route of aerobic degradation of flonicamid and its metabolites in soil

The major metabolites observed, exceeding 10 % or two times 5 % of the applied dose, were TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA (Table 2.8.1.1-3). The hydrolysis of the cyano-group of flonicamid led to the formation of the metabolites TFNG-AM and TFNG. These metabolites underwent an immediate degradation resulting in the formation of TFNA. Metabolite TFNG-AM was found with a maximum amount of 12.6 % of applied radioactivity. TFNG, found with maximum amounts of 51.3 % of applied radioactivity, degraded further to TFNA and TFNA-AM by hydrolysis of the amide bond. The latter was found up to 7.6 % of applied dose. TFNA was found in amounts of up to 52.5 % of the applied dose. In the flonicamid study B.8.1.1.1/01 (2021), TFA was found with maximum amounts of 22.5 % of applied radioactivity. All six metabolites are regarded therefore as significant metabolites of flonicamid in soil. Two additional studies investigating the formation of metabolite TFA from precursor metabolites TFNA-AM and TFNA-OH were provided during the evaluation procedure. TFA was found max of 18.4 % and 16.2 % of the applied radioactivity, respectively.

Degradation studies with metabolites showed that these metabolites are rapidly degraded, except metabolite TFA.

After 120 days in the new study with flonicamid, 31.8 % -71.1 % of the applied radioactivity was to 14CO2 and 52.8 % - 71.1 % of the applied dose was bound to the soil matrix (Table 2.8.1.1-3).

Table 2.8.1.1-3: Degradation of flonicamid and its metabolites in percentage of applied radioactivity at 20°C (max values given during the study period)

Parent study	Soil	Percentage of the applied radioactivity (%)							
	Name	TFNG-AM	TFNG	TFNA	TFNA-OH	TFNA-AM	TFA	CO_2	NER
Flonicamid 30 days	Madison	9.6	2.5	36.4	20.2	6.9	-	47.0	35.2
	Bedfordshire	9.7	2.9	30.6	21.3	3.6	-	56.6	37.7
	Birmingham	7.8	2.7	19.2	12.1	3.6	-	48.3	43.3
	Speyer 2.1	10.2	3.9	12.2	17.6	7.6	-	56.2	29.6
Flonicamid 120 days [1)]	Lufa 2.2	12.5	38.5	9.8	20.8	4.8	22.6	38.1 [2)]	58.7 [2)]
	Lufa 2.4	8.6	41.1	52.4	9.7	3.6	14.7	43.7 [2)]	52.8 [2)]
	Clipstone	9.7	18.5	17.6	25.3	3.7	17.6	37.0 [2)]	57.3 [2)]
	Brierlow	6.7	51.3	8.7	20.3	3.3	13.9	31.8 [2)]	71.1 [2)]
TFNG-AM 30 days	Bedfordshire	-	11.5	52.5	23.7	-	-	57.0	42.3
	Birmingham	-	6.2	45.4	12.4	-	-	56.8	40.9
	Speyer 2.1	-	9.8	29.4	20.4	-	-	71.2	31.0
TFNG 30 days	Bedfordshire	-	-	51.4	36.2	-	-	46.8	38.3
	Birmingham	-	-	46.0	31.5	-	-	36.0	48.8
	Speyer 2.1	-	-	24.5	39.6	-	-	50.3	27.1
TFNA 30 days	Bedfordshire	-	-	-	46.0	-	-	45.3	42.3
	Birmingham	-	-	-	41.6	-	-	37.3	48.9
	Speyer 2.1	-	-	-	54.9	-	-	54.6	24.7
TFNA-OH 30 days	Bedfordshire	-	-	-	-	-	-	49.8	42.4
	Birmingham	-	-	-	-	-	-	41.5	48.0
	Speyer 2.1	-	-	-	-	-	-	60.0	30.0
TFNA-OH	Lufa 2.2 [3)]	-	-	-	-	-	16.2	33.0	64.9

Parent study	Soil	Percentage of the applied radioactivity (%)							
	Name	TFNG-AM	TFNG	TFNA	TFNA-OH	TFNA-AM	TFA	CO_2	NER
120 days	Lufa 2.4 [3)]	-	-	-	-	-	14.6	34.2	64.8
	Clipstone [3)]	-	-	-	-	-	11.8	35.2	61.9
TFNA-AM 30 days	Bedfordshire	-	-	2.3	1.1	-	-	63.9	40.4
	Birmingham	-	-	5.4	1.8	-	-	54.1	43.1
	Speyer 2.1	-	-	0.6	0.4	-	-	53.6	26.9
TFNA-AM 120 days	Lufa 2.2 [3)]	-	-	-	-	-	18.4	31.1	50.0
	Lufa 2.4 [3)]	-	-	-	-	-	17.4	35.7	59.7
	Clipstone [3)]	-	-	-	-	-	14.8	28.1	58.1

1) TFA could be identified in this study B.8.1.1.1/01 (2021) as flonicamid was labelled in 4th carbon in pyridyl ring for which the trifluoro moiety is attached, in other flonicamid and metabolite studies (applied as parent) substances were labelled in 3rd carbon in pyridyl ring, except for TFNA-OH and TFNA-AM (see footnote 3)
2) Mean of two values(
3) TFA could be identified in additional studies with metabolites TFNA-AM (Study B.8.1.1.2/06, 2022) and TFNA-OH (Study B.8.1.1.2/10, 2022) as metabolites were labelled in 4th carbon in pyridyl ring

Rate of the aerobic degradation of flonicamid and its metabolites in soil

The data from the previous presented studies were re-assessed according to FOCUS degradation kinetics guidance documents (2006, 2014) using the software KinGUI 2. This kinetic assessment was performed to re-evaluate the degradation kinetics of flonicamid and its major soil metabolites TFNG-AM, TFNG, TFNA-AM, TFNA, TFNA-OH and TFA. Only statistically reliable endpoints were acted to derive geometric mean modelling DT_{50} values and arithmetic mean formation fractions for flonicamid and its metabolites TFNG-AM, TFG, TFNA, TFNA-OH, TFNA-AM and TFA.

Stepwise approach for the kinetic evaluation of degradation to obtain DT_{50} and DT_{90}

A stepwise approach for the kinetic evaluation of data to obtain persistence and modelling endpoints were used (FOCUS DegKinetics Report 2006,2014). The DT_{50} and DT_{90} values were derived in Steps 1 to 7, from kinetic assessment of parent alone or in conjunction with the formed metabolite(s) in a stepwise approach as the parent degraded up to a tertiary metabolite. For parent, at Step 1 = parent alone, assessed with 4 models (SFO, FOMC, DFOP and HS); at Step 2 to Step 7: at Step 2 = parent fixed and primary metabolites free fitted, at Step 3 = free fitting of all compounds with optimized parameters, at Step 4 = parent and primary metabolites fixed, secondary metabolites free fitted, at Step 5 = all compounds free fitted with optimized parameters, at Step 6 = parent, primary and secondary metabolites fixed, tertiary metabolite free fitted, Step 7 = all compounds free fitted with optimized parameters). For metabolites, in studies where metabolite was dosed as parent, Steps from 1 to 5 were used: Step 1 = metabolite as parent, was assessed also with 4 models; at Step 2 to Step 5 as explained above).

Persistence endpoints

For all compounds, the best fit DT_{50} values were determined by fitting the parent data and metabolite as parent data alone (Step 1 according to FOCUS stepwise approach). Worst case persistence endpoints for each compound are marked in bold in Table 2.8.1.1-4 below. For TFA, no separate metabolite study was available, therefore DT_{50} values were obtained only from the parent study (Study B.8.1.1.1/01, 2021). Applicant provided two new metabolite studies with TFNA-OH and TFNA-AM as precursor metabolites to study. All studies soils were incubated at 20°C and field

capacity, except Lufa 2.4 and Clipstone A2 for field capacity. Non-normalised DT_{50} values for these two soils have been presented in the table below for persistence evaluation. Normalised values for flonicamid and formed metabolites in this study have been presented in Table 2.8.1.1-5.

Flonicamid degraded fast in the eight soils studied with best fit DT_{50} values ranging from 0.30 days to 1.92 days at 20°C (Table 2.8.1.1-4). Degradation followed SFO kinetics, except for soil Madison and Birmingham (FOMC) soils. DT_{90} values are presented in the same table. Additionally, also soil major metabolites TFNG-AM, TFNG, TFNA, TFNA-OH and TFNA-AM degraded fast in the studied soils. The last metabolite in the chain i.e., TFA (trifluoroacetic acid) is very slowly degrading compound in soil (Table 2.8.1.1-4). Ultimate mineralization to $^{14}CO_2$ was shown by a steady increase throughout each of the experiments in addition to increased amounts of bound residues (Table 2.8.1.1-3 above).

Worst case non-normalised persistence DT_{50} endpoints for flonicamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA are 1.92, 1.01, 1.32, 0.58, 4.57, 5.10 and >1000 days, respectively. The respective DT_{90} values are 6.37, 3.36, 4.40, 1.94, 15.18, 16.93 and >1000 days.

Table 2.8.1.1-4: Summary of best fit $DT_{50/90}$ values of flonicamid and its relevant metabolites TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM - <u>persistence endpoints</u>

'Parent' study [a)]	Soil		DT_{50}	DT_{90}	Model	Chi^2 error
	Name	Soil ID				
Flonicamid	Lufa 2.2 [c)]	2.2	0.29	0.97	SFO	6.4
	Lufa 2.4 [c)]	2.4	0.30	0.98	SFO	5.3
	Clipstone A2 [c)]	A2	0.92	3.02	SFO	4.1
	Brierlow E1 [c)]	E1	0.38	1.25	SFO	5.6
	Madison	72	0.97	5.35	FOMC	6.2
	Bedfordshire	188	0.64	2.11	SFO	3.2
	Birmingham	189	0.58	2.31	FOMC	2.7
	Speyer	180	**1.92** [b)]	**6.37** [b)]	SFO	0.8
TFNG-AM	Bedfordshire	188	0.13	0.51	DFOP	0.8
	Birmingham	189	0.29	0.97	SFO	7.1
	Speyer	180	**1.01** [b)]	**3.36** [b)]	SFO	3.2
TFNG	Bedfordshire	165	0.18	0.61	SFO	11.1
	Birmingham	166	0.30	0.98	SFO	7.3
	Speyer	167	**1.32** [b)]	**4.40** [b)]	SFO	5.1
TFNA	Lufa 2.4	2.4	**2.47** [b)]	**8.22** [b)]	SFO	10.8
	Bedfordshire	165	0.58	1.94	SFO	4.0
	Birmingham	166	0.29	0.96	SFO	0.7
	Speyer	167	0.51	1.69	SFO	2.4
TFNA-OH	Bedfordshire	165	1.93	6.24	SFO	7.5
	Birmingham	166	1.51	5.03	SFO	4.2
	Speyer	167	**4.57** [b)]	**15.18** [b)]	SFO	8.2
	Lufa 2.2	2.2	0.95 [d)]	3.14 [d)]	SFO	3.3
	Lufa 2.4	2.4	0.98 [d)]	3.25 [d)]	SFO	10.6
	Clipstone	A2	2.42 [d)]	8.05 [d)]	SFO	5.3
TFNA-AM	Bedfordshire	188	1.40	4.64	SFO	4.1
	Birmingham	189	1.12	3.73	SFO	7.3

'Parent' study [a)]	Soil		DT_{50}	DT_{90}	Model	Chi^2 error
	Name	Soil ID				
	Speyer	180	3.74	12.43	SFO	3.5
	Lufa 2.2	2.2	3.92 [d)]	13.01 [d)]	SFO	7.7
	Lufa 2.4	2.4	3.11 [d)]	10.33 [d)]	SFO	3.7
	Clipstone	A2	**5.10** [b,d)]	**16.93** [b,d)]	SFO	5.4
TFA	Lufa 2.4	2.4	>1000	>1000	SFO	12.2
	Clipstone A2	A2	705.8	>1000	SFO	5.3
	Brierlow E1	E1	**>1000**	**>1000**	SFO	15.1

[a)] Fitting Step according to FOCUS 'stepwise approach' where best fit could be determined
[b)] Worst case value to be used for persistence evaluation
[c)] Values from the final report of study B.8.1.1.1/01, 2021
[d)] Values from the new metabolite studies provided during the evaluation procedure

Modelling endpoints

As explained above, DT_{50} values for soils Lufa 2.4 and Clipstone A2 from study B.8.1.1.1/01 (2021) needs to be normalised for field capacity for use in modelling. Normalised values for flonicamid and formed metabolites TFNG-AM, TFNA and TFA are presented in table below:

Table 2.8.1.1-5: Normalisation of flonicamid and its metabolites for study B.8.1.1.1/01 (2021)

Substance	Soil	Moisture correction factor	t °C / % MWHC	DT_{50} (d)	DT_{50} (d) 20 °C pF2/10kPa
Flonicamid	Lufa 2.2	1.0	20 / 50	0.29	0.29
	Lufa 2.4	**0.966**	**20 / 50**	**0.30**	**0.29**
	Clipstone A2	**0.635**	**20 / 50**	**0.92**	**0.58**
	Brierlow E1	1.0	20 / 50	0.38	0.38
TFNG-AM	Lufa 2.2	1.0	20 / 50	0.07	0.07
	Lufa 2.4	**0.966**	**20 / 50**	**0.04**	**0.04**
	Brierlow E1	1.0	20 / 50	0.04	0.04
TFNA	**Lufa 2.4**	**0.966**	**20 / 50**	**2.47**	**2.39**
	Clipstone A2	**0.635**	**20 / 50**	**0.44**	**0.27**
	Brierlow E1	1.0	20 / 50	0.40	0.51
TFA	**Lufa 2.4**	**0.966**	**20 / 50**	**>1000**	**1000**
	Clipstone A2	**0.635**	**20 / 50**	**705.8**	**448.0**
	Brierlow E1	1.0	20 / 50	1000	1000

Summary of the normalised DT_{50} values for modelling purposes are presented below in Table 2.8.1.1-6:

Applicant has performed kinetic re-evaluation of the parent study labelled in 4^{th}-C in pyridyl ring (B.8.1.1.1/01 2021, final report) and additionally the parent study together with the new metabolite studies with TFNA-OH (Study B.8.1.1.2/10, 2022) and TFNA-AM (Study B.8.1.1.2/06, 2022) also labelled in 4^{th}-C in pyridyl ring. Therefore, two sets on DT_{50} values (Table 2.8.1.1-6) and formation fraction (Table 2.8.1.1-7) are available for some of the metabolites. Applicant has provided PECgw and PECsw/PECsed modelling using both sets of values, later, called as Parameter Set 1 and Parameter Set 2. The main difference occurs in the DT_{50} value of TFA. DT_{50} values of 765.2 days and 505.2 days are obtained with Parameter Set 1 and 2, respectively. Single bolded worst case DT50 values are used for PECsoil calculation.

Table 2.8.1.1-6: Summary of normalized DT50 values of flonicamid and its relevant metabolites TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA – modelling endpoints (normalised)

Parent study	Soil		Step [1]	Compound DT_{50} [d]						
	Name	Kinetic model		Flonicamid	TFNG-AM	TFNG	TFNA	TFNA-OH	TFNA-AM	TFA
Flonicamid	Lufa 2.2.	SFO	7	0.29	0.06	*n.r.*	*n.r.*	*n.r.*	*n.r.*	*n.r.*
	Lufa 2.4	SFO	7	0.29	0.04	*n.r.*	**2.39**	*n.r.*	*n.r.*	>1000
	Clipstone A2	SFO	7	0.58	*n.r.*	*n.r.*	0.27	2.35	*n.r.*	448.0
	Brierlow E1	SFO	7	0.38	0.04	*n.r.*	0.51	*n.r.*	*n.r.*	>1000
	~~Madison~~ [2]	~~FOMC~~	~~3~~	~~1.11~~	~~0.23~~		~~2.88~~			
	Bedfordshire	SFO	3	0.63	0.12		0.70			
	Birmingham	FOMC	3	0.62	0.14		0.49			
	Speyer 2.1	SFO	3	**1.92**	0.66		1.16			
TFNG-AM	Bedfordshire	DFOP	5		0.14	0.03	0.46			
	Birmingham	SFO	5		0.29	0.02	0.65			
	Speyer 2.1	SFO	5		**1.01**	0.14	1.12			
TFNG	Bedfordshire	SFO	2			0.18	0.77		1.16	
	Birmingham	SFO	1			0.30	*n.r.*		*n.r.*	
	Speyer 2.1	SFO	1			**1.32**	*n.r.*		*n.r.*	
TFNA	Bedfordshire	SFO	3				0.59	1.69		
	Birmingham	SFO	3				0.29	1.53		
	Speyer 2.1	SFO	3				0.51	2.56		
TFNA-OH	Bedfordshire	SFO	1					1.93		
	Birmingham	SFO	1					1.51		
	Speyer 2.1	SFO	1					**4.57**		
	Lufa 2.2[3]	SFO	3					0.95		nr
	Lufa 2.4[3]	SFO	3					1.05		157.5
	Clipstone[3]	SFO	3					2.57		524.7
TFNA-AM	Bedfordshire	SFO	1						1.40	
	Birmingham	SFO	1						1.12	
	Speyer 2.1	SFO	1						3.74	
	Lufa 2.2[3]	SFO	3						13.7	340.1
	Lufa 2.4[3]	SFO	3						2.98	338.4
	Clipstone[3]	SFO	3						**5.12**	**1000**
Geometric mean [without metabolite studies labelled in the 4th-position of the pyridyl ring]				**0.59**	**0.15**	**0.13**	**0.71**	**2.14**	**1.61**	**765.2**
Geometric mean [incl. metabolite studies labelled in the 4th-position of the pyridyl ring]				**0.59**	**0.15**	**0.13**	**0.71**	**1.87**	**2.82**	**505.5**

n.r. = not reliable

[1] Fitting Step according to FOCUS 'stepwise approach' where adequate modelling parameters could be determined

[2] Fitting was not acceptable for this soil, therefore, DT_{50} value is deleted from the data set

[3] New metabolite studies provided during evaluation procedure; metabolite labelled in the 4th carbon of pyridyl ring

Following normalised geomean DT_{50} values were obtained for flonicamid and its metabolites: 0.059 days for flonicamid in eight soils, 0.15 days for TFNG-AM in 9 soils, 0.13 days for TFNG in 6 soils, 0.64 and 0.71 days for TFNA in 13 soils (Parameter Sets 1 and 2), 2.14 days and 1.87 days for TFNA-OH in 10 soils (Parameter Sets 1 and 2), 1.61 days and 2.82 days for TFNA-AM in 7 soils (Parameter Sets 1 and 2) and 765.2 days and 505.2 days for TFA (Parameter Sets 1 and 2) (Table 2.8.1.1-6). RMS considers that it is justified to use the Parameter Set 2 values for TFA and other metabolites, since also for other metabolites results (DT_{50} values) obtained from a parent or precursor metabolite studies have been accepted. However, as Applicant provided modelling results with both Parameter Sets, these have been presented in this dRAR for completeness.

Formation fractions of the metabolites

Summary of formation fractions of flonicamid and its relevant metabolites TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA is given in Table 2.8.1.1-7. In the parent study, flonicamid was metabolised to TFNG-AM, TFNA and TFA with arithmetic mean formation fractions of 0.751, 0.16 and 0.157 (Parameter Sets 1 and 2) and 0.339 and 0.258 (via metabolite TFNA-OH) (Parameter Sets 1 and 2), respectively. In the metabolite study, TFNG-AM was further metabolised to TFNG and TFNA with arithmetic mean formation fractions of 0.983 and 0.88 and 0.875 (Parameter Sets 1 and 2), respectively. In the metabolite study, TFNG was further metabolized to TFNA and TFNA-AM with formation fractions of 0.76 and 0.1 (single ff values available), respectively. In the metabolite study, TFNA was further metabolized to TFNA-OH with a mean arithmetic formation fraction of 0.777. In the parent study, TFNA-OH and TFNA-AM were further metabolized to TFA with formation fractions of 0.339 and 0.334, respectively. When the new studies with precursor metabolites TFNA-OH and TFNA-AM labelled in 4th carbon in pyridyl ring were taken into account together with the parent study the obtained formation fractions for the metabolite TFA were 0.258 and 0.239, respectively.

Table 2.8.1.1-7: Summary of formation fractions of flonicamid and its relevant metabolites TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA

Parent study	Soil		Step*	Metabolite formation fractions					
	Name	Nr.		TFNG-AM	TFNG	TFNA	TFNA-OH	TFNA-AM	TFA
Flonicamid	Madison	72	3	0.70 1)		0.30 1)			
	Bedfordshire	188	3	0.81 1)		0.00 1)			
	Birmingham	189	3	0.57 1)		0.30 1)			
	Speyer 2.1	180	3	0.54 1)		0.13 1)			
	Speyer 2.2	2.2	7	0.88 1)	n.r.	n.r.	n.r.	n.r.	
	Speyer 2.4	2.4	7	0.87 1)	n.r.	0.13 1)	n.r.	n.r.	0.384 5) 0.00 6)
	Clipstone	A2	7	n.r.	n.r.	0.12 1)	n.r.	n.r.	0.256 5) 1.00 6)
	Brierlow	E1	7	0.89 1)	n.r.	0.11 1)	n.r.	n.r.	0.378 5) 0.003 6)
TFNG-AM	Bedfordshire	188	5		1.00 2)	0.94 3)			
	Birmingham	189	5		1.00 2)	1.00 3)			
	Speyer 2.1	180	5		0.95 2)	0.80 3)			

Parent study	Soil		Step*	Metabolite formation fractions					
	Name	Nr.		TFNG-AM	TFNG	TFNA	TFNA-OH	TFNA-AM	TFA
TFNG	Bedfordshire	165	2			0.76 3)		0.10 3)	
	Birmingham	166	*2*			n.r.		n.r.	
	Speyer 2.1	167	*2*			n.r.		n.r.	
TFNA	Bedfordshire	165	3				0.81 4)		
	Birmingham	166	3				0.69 4)		
	Speyer 2.1	167	3				0.83 4)		
TFNA-OH	Lufa 2.2	2.2	3						n.r.
	Lufa 2.4	2.4	3						0.150 5)
	Clipstone A2	A2	3						0.124 5)
TFNA-AM	Lufa 2.2	2.2	3						0.196 6)
	Lufa 2.4	2.4	3						0.112 6)
	Clipstone A2	A2	3						0.124 6)
Arithmetic mean Excl. metabolite dosed studies labelled in the 4th -position of the pyridine ring				**0.751**	**0.983**	**0.16** (from Flonicamid) **0.88** (from TFNG)	**0.777**	**0.10**	**0.339** (from TFNA-OH) **0.334** (from TFNA-AM)
Arithmetic mean Incl. metabolite dosed studies labelled in the 4th -position of the pyridine ring				**0.751**	**0.983**	**0.157** (from Flonicamid) **0.875** (from TFNG)	**0.777**	**0.10**	**0.258** (from TFNA-OH) **0.239 (**from TFNA-AM)

n.a. = not reliable
1) Formed from parent
2) Formed from TFNG-AM as precursor
3) Formed from TFNG as precursor
4) Formed from TFNA as precursor
5) Formed from TFNA-OH as precursor
6) Formed from TFNA-AM as precursor
*) Fitting Step according to FOCUS 'stepwise approach' where adequate modelling parameters could be determined

Anaerobic degradation of the active substance and its metabolites in soil

Anaerobic degradation of flonicamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-OH and TFNA-AM is not considered to be relevant for further consideration since the degradation under aerobic conditions is rapid, and according to good agricultural practices, it is not expected that the applications will happen while anaerobic conditions are present. However, a new aerobic degradation study using flonicamid labelled in 4th position of pyridyl ring (B.8.1.1.1/01, 2021) is provided and a new metabolite i.e., TFA (trifluoroacetic acid) is formed a with a geomean DT_{50} of 765.2 days (4 soils) and a max DT_{50} of >1000 days. Additionally, no water/sediment studies are available using flonicamid labelled in 4th position of pyridyl ring.

The use of the product is during late spring – summer, a time for which anaerobic conditions is not expected to occur. However, due to long degradation time of TFA, it cannot be ruled out that the metabolite would not be exposed to anaerobic conditions.

If an anaerobic degradation study would be required with TFA, RMS is uncertain how to use the possible DT_{50} value obtained in this study.

Field studies

Soil dissipation studies

Soil dissipation studies needs not to be required due to the very rapid degradation of flonicamid (IKI-220) as well as its metabolites TFNG-AM, TFNG, TFNA, TFNA-OH and TFNA-AM in soil with a DT_{50} of less than 5 days. As explained above a new metabolite i.e., TFA (trifluoroacetic acid) is formed a with a geomean DT_{50} of 765.2 days (4 soils) and a max DT_{50} of >1000 days.

Based on the data requirement regulation (EU/283/2013), soil dissipation study shall be conducted for the active substance, its metabolites, breakdown and reaction products if one of the following conditions is fulfilled:
(a) $DegT_{50}$ lab for active substance, $DegT_{50}$ lab or $DisT_{50}$ lab for metabolites, breakdown and reaction products, in one or more soils determined at 20 °C and at a moisture content of the soil related to a pF value of 2 (suction pressure) is greater than 60 days.
Both the geomean DT_{50} and max DT_{50} values for TFA are clearly above the trigger and therefore a data gap for a soil dissipation study is triggered. However, due to very high expected leaching potential of TFA (a default Koc value of 0 was used in PECgw and PECsw modelling) it might be difficult to analyse reliable residue levels in the field study soils. Water solubility data on TFA is not available but based on public sources TFA is miscible to water. RMS suggests that the data gap would be discussed in an expert meeting.

Soil accumulation studies

Based on the data requirement regulation (EU/283/2013), soil accumulation studies shall provide sufficient information to evaluate the possibility of accumulation of residues of the active substance and of metabolites, breakdown and reaction products. The study can be replaced if reliable information can be provided by a model calculation or another appropriate assessment.
However, only degradation studies using flonicamid labelled in 3rd position in pyridyl ring has been considered by the Applicant in its statement above. However, a new aerobic degradation study using flonicamid labelled in 4th position of pyridyl ring (B.8.1.1.1/01, 2021) was provided and a new metabolite i.e., TFA (trifluoroacetic acid) was formed. Both the geomean DT_{50} and max DT_{50} values for TFA are clearly above the triggers. However, instead of a soil accumulation study, accumulation of TFA (PECsoil,plateau and PECsoil,acc) can be obtained using the worst-case laboratory DT_{50} value. PECsoil values were calculated using DT_{50} value of 1000 days. Three DT_{50} values were available (geomean 765.2 days, max >1000 days).

Soil photolysis

Irradiation seems to have an accelerating effect on the degradation since the half-life of exposed soil samples was significantly reduced compared to the samples incubated in darkness. DT_{50} values for irradiated and dark samples were re-evaluated according to recommendations of the FOCUS Degradation Kinetics Report (2006, 2014) and resulted in values of 22.9 days (irradiated samples) and 52.8 days (dark samples). In comparison to the soil metabolism and degradation studies (geomean DT_{50} of 0.60 days, worst case DT_{50} of 1.92 days), flonicamid

degraded clearly more slowly in the photolysis study. This may be explained by the reduced microbial activity in the test, caused by a very dry soil in the experimental set up of the study. Fast degradation in dark laboratory studies shows that microbial degradation is a key driver in the degradation behaviour of flonicamid.

2.8.1.2 Assessment in relation to P/vP -criteria for soil compartment

The criteria for persistence in soil, as stated in Annex II to Regulation (EC) 1107/2009, are DT_{50} 120 days (PBT) and 180 days (POP and vPvB). For results derived by other kinetic models than SFO the RMS has divided the FOMC DT_{90}s by 3.32 and DFOP k_2 by $\ln(2)/k_2$ to obtain pseudo SFO DT_{50} values, respectively.

Table 2.8.1.2-1 : Evaluation of the active substance against POP/PBT/vPvB criteria

POP						
	soil > 180 days	**water > 60 days**	**sediment > 180days**	**bioaccumulation > 5 000 or logKow >5**	**toxicity high**	**LRT >2 days**
Flonicamid, 20 °C	0.59 [1]					
Flonicamid, 12 °C	1.3 [1]					
PBT						
	soil > 120 days	**water > 40 days**	**sediment > 120days**	**bioaccumulation >2 000**	**NOEC 0.01 mg/L**	
Flonicamid, 20 °C	0.59 [1]					
Flonicamid, 12 °C	1.3 [1]					
vPvB						
	soil > 180 days	**water > 60 days**	**sediment > 180days**	**bioaccumulation > 5 000**		
Flonicamid, 20 °C	0.59 [1]					
Flonicamid, 12 °C	1.3 [1]					

[1] Normalised geometric mean DT_{50} value of 8 soils

The presented evaluation shows that flonicamid does not fulfil the persistence criteria for POP, PBT or vPvB.

2.8.1.3 Adsorption and desorption in soil

Applicant has provided a new adsorption study according to the OECD Test Guideline 121 (2001; Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC); 2017), but this study was not evaluated by RMS as the study author concluded that no reliable Koc value could be determined. Adsorption of the active substance flonicamid has been studied in one test which was evaluated during the process of Annex I inclusion and was then considered acceptable (EFSA Scientific Report for Flonicamid (2010: 8(5), 1445). In the study, the adsorption of flonicamid was determined according to the OECD Test Guideline 106 (1981).

- in 4 soils under standard conditions of batch equilibrium test with one test concentration for 24 h at 20 ± 2 °C following application of [3-^{14}C]flonicamid (Study B.8.1.2.1/01, 2000); soil pH values ranged from pH 6.5 to 7.6 an expert meeting(solution not indicated) and organic carbon contents from 0.7 to 3.0 %

This study has been re-evaluated by RMS and is still considered valid even though there were few minor deviations from the current OECD Test Guideline 106 (2000).

Flonicamid, in soil/solution ratios 1:5 (with or without $HgCl_2$) and 1:2 (with $HgCl_2$), showed very low adsorption percentages in four soil (EFSA OECD 106 Calculator: ≤ 15.21 %). $HgCl_2$ was used to prevent degradation of the active substance. Tier 3 test to determine the Freundlich adsorption isotherms was not conducted as 'Kd * soil/solution ratio' was below 0.3. Therefore, only Kd and Kdoc values are available. Provided study is considered fit for the purpose to describe the adsorption of flonicamid.

Only Kd and Kdoc values obtained with soil/solution ratio 1:2 was listed in the LoEPs of EFSA conclusion on Flonicamid (2010). During the Annex I inclusion, the original Kd and Kdoc values with soil/solution ratio of 1:2 (with $HgCl_2$) was re-calculated by the RMS FR in the DAR (2005). RMS FR stated that "Water content of the soils used in this study was not negligible and was not taken into account. Accordingly, the decrease in concentration in supernatant could partly result from dilution and thus adsorption measurements would not be reliable". Kd and Kdoc values were recalculated by the RMS FR taking account of "this phenomenon" as expressed by Applicant. Moisture corrected Kd and Kdoc values for flonicamid [^{14}C-IKI-220] of 0.03 - 0.17 L/kg and 2.5 - 8.7 (mean 5.9 L/kg; geomean 5.4 L/kg), respectively, were obtained (Table 2.8.1.3-1) for the 4 soils tested. These re-calculated values are listed in the LoEP of EFSA conclusion of flonicamid (2010).

Table 2.8.1.3-1: Adsorption of flonicamid on soils (5 mg/L, 1:2 ratio, with $HgCl_2$) re-calculated by FR during Annex I inclusion

Soil	**Bedfordshire U.K. (097)**	**Birmingham U.K. (099)**	**LUFA 2.3 Germany (101)**	**Madison, Ohio USA (072)**
Classification* (USDA)	loamy sand	sandy loam	sandy loam	loamy sand
Cs (soilless control) [mg/L]	4.88	4.88	4.88	4.88
Ce (after adsorption) [mg/L]	4.66 (97.0 %)	4.18 (93.6 %)	4.49 (97.5 %)	4.55 (98.1 %)
Soil moisture [%]	6.29	16.39	8.58	8.50
V total water phase [mL]	5.16 [1)]	5.41 [1)]	5.21 [1)]	5.21 [1)]
% AR on soil	1.45	7.3	4.1	2.8
Kd [mL/g]	0.03	0.17	0.09	0.06
OC [%]	1.2	3.0	1.3	0.7
Kdoc [mL/g]	**2.5**	**5.7**	**6.9**	**8.7**

Figures into brackets account for purity (parent in fraction).
V total water phase = added solution (5 mL) + initial soil moisture content.

RMS did not find any guidance whether soil moisture content should be taken into account when calculating Kd and Kdoc values using indirect method when looking at OECD TG 106 (2000) or EFSA Report on the Outcome of the pesticides peer review meeting on the OECD 106 evaluators checklist (2017). Therefore, RMS has again presented the original Kd and Kdoc values reported in the study report (Table 2.8.1.3-2). RMS has also calculated the Kd and Kdoc values using EFSA OECD 106 Calculator but without correction of soil moisture content to check

the original calculations. Kd and Kdoc values obtained with EFSA OECD 106 Calculator are almost equal to the original Kd and Kdoc values (Table 2.8.1.3-2).

The slightly different Kd and Kdoc values results from a slightly different approach that is used to calculate the $mass_{soil}^{ads,eq}$ (which divided by soil mass (g) will give $C_{soil}^{ads,eq}$) in indirect method.

1) in the original study report, measured soilless controls (=G; µg a.s./mL) were used to calculate $mass_{soil}^{ads,eq}$ (=(G*Vo)-($C_{aq}^{ads,eq}$*Vo)); in FR DAR, the recalculated Kd values are based on these values but the water volume of the soils based on soil moisture content of the soils were included in the volume of the supernatant (Vo+soil water).

2) EFSA OECD 106 Calculator uses the measured initial concentrations in supernatants (Cini; µg a.s./mL) in place of soilless control to calculate $mass_{soil}^{ads,eq}$ (=(Cini*Vo)-($C_{aq}^{ads,eq}$*Vo))

The original Kd and Koc values reported for flonicamid (without moisture correction) were 0.09 – 0.34 mL/g and 7.9-20.7 mL/g (geomean 12.5 mL/g), respectively, with soil/solution ratio of 1:2 with $HgCl_2$, the soil:solution ratio, which was used to determine Kd and Kdoc values during the Annex I inclusion (Table 2.8.1.3-2). Calculations with EFSA OECD 106 Calculator resulted in Kd and Kdoc values of 0.12 - 0.36 mL/g and 9.7 - 23.7 mL/kg (geomean 14.3 mL/g) with soil/solution ratio of 1:2 (Table 2.8.1.3-2), respectively.

Table 2.8.1.3-2: Adsorption of flonicamid on soils (5 mg/L, 1:2 ratio, with $HgCl_2$) reported in the studies provided and using EFSA OECD 106 Calculator (2016)

Soil	**Units**	**Bedfordshire**	**Birmingham**	**Lufa 2.3**	**Madison**	**Geomean Kdoc**
Adsorption method	**-**	**Indirect**	**Indirect**	**Indirect**	**Indirect**	
Soil:solution ratio	(g dw/mL)	1:2	1:2	1:2	1:2	
Mass balance of ^{14}C 1)	%	97.0	93.6	97.5	98.1	
Adsorbed percentage	%	4.1	14.34	7.99	6.76	
Kd value	mL/g dw	0.094	0.335	0.174	0.145	
Kdoc value	mL/g OC	7.9	11.2	13.4	20.7	**12.5**
Kd × (soil:solution ratio)		0.047	0.1675	0.087	0.0725	
Adsorbed percentage by EFSA tool	**%**	**5.48**	**15.21**	**8.92**	**7.71**	
Kd by EFSA tool	mL/g dw	**0.12**	**0.36**	**0.20**	**0.17**	
Kdoc by EFSA tool	mL/g OC	**9.7**	**12.0**	**15.1**	**23.7**	**14.3**
Kd × (soil:solution ratio)		0.06	0.18	0.10	0.09	

RMS has also presented the results obtained with soil/solution ratio 1:5. Slightly higher values were obtained with soil/solution ratio of 1:5 with $HgCl_2$ (Table 2.8.1.3-3) and without $HgCl_2$ (Table 2.8.1.3-4) than with soil solution ratio 1:2. Almost equal values were obtained in test systems either with or without $HgCl_2$. RMS has also provided results obtained with EFSA OECD 106 Calculator. Combining both 1:5 soil/solution ratios (with or without $HgCl_2$) Kd values of 0.14 - 0.35 mL/g (EFSA OECD 106 Calculator: 0.09 – 0.40 mL/g) (geomean 0.21 mL/g) and Kdoc values of 12.1 – 42.1 mL/kg (EFSA OECD 106 Calculator: 7.9 – 34.7 mL/g) (geomean 19.9 mL/g) were obtained, respectively.

Table 2.8.1.3-3: Adsorption of flonicamid on soils (5 mg/L, 1:5 ratio, with $HgCl_2$) reported in the studies provided and using EFSA OECD 106 Calculator (2016)

Soil	Units	Bedfordshire	Birmingham	Lufa 2.3	Madison	Geomean Kdoc
Adsorption method	**-**	**Indirect**	**Indirect**	**Indirect**	**Indirect**	
Soil:solution ratio	(g dw/mL)	1:5	1:5	1:5	1:5	
Mass balance of ^{14}C	%	98.0	96.4	97.5	98.4	
Adsorbed percentage	%	3.74	7.40	4.65	5.57	
Kd	mL/g dw	0.19	0.40	0.24	0.30	
Kdoc value	mL/g OC	16.2	13.3	18.8	42.1	**20.3**
Kd × (soil:solution ratio)		0.038	0.08	0.048	0.06	
Adsorbed percentage by EFSA tool	**%**	**2.78**	**6.48**	**3.70**	**4.63**	
Kd by EFSA tool	mL/g dw	**0.14**	**0.35**	**0.19**	**0.24**	
Kdoc by EFSA tool	mL/g OC	**11.9**	**11.6**	**14.8**	**34.7**	**16.3**
Kd × (soil:solution ratio)		0.028	0.07	0.038	0.048	

Table 2.8.1.3-4: Adsorption of flonicamid on soils (5 mg/L, 1:5 ratio, without $HgCl_2$) reported in the studies provided and using EFSA OECD 106 Calculator (2016)

Soil	Units	Bedfordshire	Birmingham	Lufa 2.3	Madison	Geomean Kdoc
Adsorption method	**-**	**Indirect**	**Indirect**	**Indirect**	**Indirect**	
Soil:solution ratio	(g dw/mL)	1:5	1:5	1:5	1:5	
Mass balance of ^{14}C	%	95.1	85.2	95.0	97.7	
Adsorbed percentage	%	2.82	8.32	5.57	4.65	
Kd	mL/g dw	0.1451	0.4539	0.2950	0.2441	
Kdoc value	mL/g OC	12.1	15.1	22.7	34.9	**19.5**
Kd × (soil:solution ratio)		0.029	0.091	0.059	0.049	
Adsorbed percentage by EFSA tool	%	**1.85**	**7.31**	**4.63**	**3.70**	
Kd by EFSA tool	mL/g dw	**0.09**	**0.40**	**0.24**	**0.18**	
Kdoc by EFSA tool	mL/g OC	**7.9**	**13.3**	**18.7**	**27.5**	**15.2**
Kd × (soil:solution ratio)		0.018	0.080	0.048	0.036	

RMS agrees that it would be reasonable to select Kd and Kdoc values obtained only from soil/solution ratio of 1:2 as OECD 106 (2000) recommends a 1:1 soil/solution ratio in cases where low adsorption occurs. RMS considers that the original Kd and Kdoc values obtained in the study report would be more appropriate than the soil moisture corrected values provided by FR. At least, Kd values for the flonicamid metabolites were not corrected for soil moisture in FR DAR (2005) or Final Addendum (2007).

Applicant has used the geomean Kdoc value of 5.4 L/kg in groundwater modelling which is obtained with the 'French approach' which takes into account the soil moisture content of the soils used in the adsorption study. The calculated Kdoc values have been corrected with the soil moisture contents (CA, Volume 3, Table B.8.1.2.1-1). This Kdoc value is lower than obtained in the original study report (12.5 L/kg) or the value calculated with the EFSA OECD 106 Calculator. Therefore, RMS considers that no new groundwater modelling is needed as the lowest Kdoc value has been used.

Adsorption of the metabolites

Applicant has provided new adsorption studies for metabolites TFNG-AM, TFNG, TFNA, TFNA-AM and TFNA-OH according to the OECD Test Guideline 121 (2001; Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC); 2017), but these studies were not evaluated by RMS as the study authors concluded that no reliable Koc value could be determined as the obtained Koc values were below the determination limit of the method for all metabolites.

Studies listed below were evaluated during the process of Annex I inclusion and were then considered acceptable (EFSA Scientific Report for Flonicamid (2010: 8(5), 1445). These studies were performed according to the OECD TG 106 (1981) and were re-evaluated by RMS according to the OECD TG 106 (2000). Some deficiencies were noted but studies are still considered valid. Kd and Kdoc values for the metabolites were not corrected with soil moisture content. This is not a common procedure in adsorption value calculations, but this is clarified here as in FR DAR Kd and Kdoc values for flonicamid were corrected with soil moisture content and were listed in LoEPs of EFSA conclusion on Flonicamid (2010). No adsorption study was provided with the metabolite TFA; however, Applicant has used Koc value of 0 in the modelling.

- TFNG-AM: application of [3-^{14}C]TFNA on 4 soils in a preliminary study and on 5 soils in a main study under standard conditions of batch equilibrium test with one test concentration for 24 h at 20 ± 2 °C in the dark (Study B.8.1.2.2/03, 2002); pH values ranged from pH 5.6 to 7.2 in H_2O and with organic carbon contents of 0.60 to 3.2 for the four soils with adequate recovery % (no degradation of TFNG-AM)
- TFNG: application of [3-^{14}C]TFNG on 4 soils under standard conditions of batch equilibrium test with one test concentration for 24 h at 20 ± 2 °C in the dark (Study B.8.1.2.2/05, 2002); pH values ranged from pH 5.7 to 7.2 in H_2O and with organic carbon contents of 0.73 to 3.18 %
- TFNA: application of [3-^{14}C]TFNA on 4 soils under standard conditions of batch equilibrium test with one test concentration for 24 h at 20 ± 2 °C in the dark (Study B.8.1.2.2/01, 2002); pH values ranged from pH 5.7 to 7.2 in H_2O and with organic carbon contents of 0.73 to 3.18 %
- TFNA-OH: application of [3-^{14}C]TFNA-OH on 4 soils under standard conditions of batch equilibrium test with one test concentration for 24 h at 20 ± 2 °C in the dark (Study B.8.1.2.2/02, 2002); pH values ranged from pH 5.7 to 7.2 in H_2O and with organic carbon contents of 0.73 to 3.18 %
- TFNA-AM: application of [3-^{14}C]TFNA-AM on 4 soils in a preliminary study and on 5 soils in a main study under standard conditions of batch equilibrium test with one test concentration for 24 h at 20 ± 2 °C in the dark (Study, B.8.1.2.2/04, 2002); pH values ranged from pH 5.7 to 7.2 in H_2O and with organic carbon contents of 0.60 to 3.2

The adsorption of flonicamid metabolites TFNG-AM, TFNG, TFNA, TFNA-AM and TFNA-OH were investigated on four to nine soil types covering a range of different properties (see above).

Results from the adsorption of [^{14}C]TFNG-AM showed adsorption of 2.66 to 27.24 % in 4 soils out of 9 soil tested with acceptable recovery in sterile soils (EFSA OECD 106 Calculator: 2.69 to 27.21 %) (for further information, please see Vol 3, CA, Tables B.8.1.2.2-6 and B.8.1.2.2-7 and RMS comments). The calculated adsorption coefficients Kd ranged from 0.04 to 0.32 (EFSA OECD 106 Calculator: 0.03 to 0.37). Correction for percent organic

carbon in each soil resulted in the calculated soil adsorption constants (Kdoc) ranging from 5.50 to 13.2 (EFSA OECD 106 Calculator: 3.78 to 12.06). In correlation to the low binding of the test compound, the results from the adsorption phase predict very high mobility for the test substance [^{14}C]TFNG-AM in 4 soil sterilised soil types tested with a geomean of 8.7 mL/g (Table 2.8.1.3-5 below) (EFSA OECD 106 Calculator: 7.9 mL/g).

Results from the adsorption of [^{14}C]TFNG (adsorbed percentage: < 1.7 %) showed less than 5 % binding of the applied test compounds to 3 soils with acceptable recovery (for further information, please see Vol 3, CA, Table B.8.1.2.2-10 and RMS comments) of the 4 soils tested. The calculated adsorption coefficients Kd for TFNG ranged from 0.00 to 0.03 (EFSA OECD 106 Calculator: 0.00 to 0.02). The Kdoc values ranged from 0.20 to 4.05 (EFSA OECD 106 Calculator: 0.00 to 3.02). In correlation to the low binding of the test compound, the results from the adsorption phase predict very high mobility for the test substance [^{14}C]TFNG in 3 of the 4 types tested with a geomean of 1.0 mL/g (Table 2.8.1.3-5 below) (EFSA OECD 106 Calculator: 1.7 mL/g).

Results from the adsorption of [^{14}C]TFNA (adsorbed percentage: <1.7 %) showed less than 5 % binding of the applied test compounds to each soil type tested. The calculated adsorption coefficient Kd for TFNA ranged from 0.00 to 0.02 (EFSA OECD 106 Calculator: 0.00 to 0.03) (for further information, please see Vol 3, CA, Table B.8.1.2.2-2 and RMS comments). Correction for percent organic carbon in each soil resulted in calculated soil adsorption constants (Kdoc) ranging from 0.00 to 3.05 (EFSA OECD 106 Calculator: 0.00 to 2.70). In correlation to the low binding of the test compound, the results from the adsorption phase predict very high mobility for the test substance [^{14}C]TFNA in 4 soil types tested with a geomean of 1.4 mL/g (Table 2.8.1.3-5 below) (EFSA OECD 106 Calculator: 2.3 mL/g).

Results from the adsorption of [^{14}C]TFNA-AM showed adsorption of 2.83 to 16.16 % (EFSA OECD 106 Calculator: 2.16 to 16.13 %) of the applied test compound to the 9 soil types tested. The calculated adsorption coefficients Kd ranged from 0.03 to 0.20 (EFSA OECD 106 Calculator: 0.02 to 0.19) (for further information, please see Vol 3, CA, Tables B.8.1.2.2-8 and B.8.1.2.2-9 and RMS comments). Correction of the Kd for percent organic carbon in each soil resulted in calculated soil adsorption constants (Kdoc) ranging from 2.8 to 12.1 (EFSA OECD 106 Calculator: 1.8 to 11.3). In correlation to the low binding of the test compound, the results from the adsorption phase predict very high mobility for the test substance [^{14}C]TFNA-AM in all 9 the soil types tested (Table 2.8.1.3-5 below).

Results from the adsorption of [^{14}C]TFNA-OH (adsorbed percentage: < 3.9 %) showed less than 5 % binding of the applied test compounds to each soil type tested. The calculated adsorption coefficients Kd for TFNA-OH ranged from 0.01 to 0.06 (EFSA OECD 106 Calculator: 0.01 to 0.04) (for further information, please see Vol 3, CA, Table B.8.1.2.2-4 and RMS comments) and corresponding Kdoc values of 1.60 to 4.39 (EFSA OECD 106 Calculator: 1.22 to 3.57). In correlation to the low binding of the test compound, the results from the adsorption phase predict very high mobility for the test substance [^{14}C]TFNA-OH in 4 soil types tested with a geomean of 2.7 mL/g (EFSA OECD 106 Calculator: 2.0 mL/g) (Table 2.8.1.3-5).

For all metabolites, the obtained Kd and Kdoc values calculated in the respective studies and with EFSA OECD 106 Calculator are very similar in both soil/solution ratios.

Table 2.8.1.3-5: Kdoc values for metabolites in tested soils based on the values in the study reports

Soil	**TFNG-AM [1)]**	**TFNG**	**TFNA**	**TFNA-AM**	**TFNA-OH**
Adsortion method	**Indirect**	**Indirect**	**Indirect**	**Indirect**	**Indirect**
Soil:solution ratio	**1:1**	**1:1**	**1:1**	**1:1**	**1:1**
Bedfordshire	**5.5**	0.20	0.35	5.5	1.60
Birmingham	2.5	1.05	0.00	2.8	1.92
Lufa 2.1	0.0	1.29	3.05	5.2	4.19
Madison (USA)	**13.2**	4.05	2.67	4.8	4.39
Madison OH (USA)	**10.51**			5.5	
Hillsburo (USA)	9.25			10.1	
Lufa 2.1	**7.56**			5.0	
Painesville (USA)	4.24			4.5	
Glasgow (USA)	15.84			12.1	
Geomean of all soils	**8.7**	**1.02**	**1.4**	**5.6**	**2.7**
Geomean of all soils with EFSA tool	7.9	1.26	1.3	4.9	2.0

[1)] Only values from soils with acceptable recovery of TFNG-AM are used in the geomean calculations (marked bold)

2.8.2 Summary of fate and behaviour in water and sediment [equivalent to section 11.1 of the CLH report template]

Applicant has provided two new studies, one on the ready biodegradability of flonicamid and another one on aerobic mineralisation of flonicamid in surface water to comply with the new data requirements. Other data points covering the degradation of flonicamid and its metabolites in aquatic systems were covered with studies submitted during the Annex I Inclusion. These studies are still considered valid by RMS FI. Degradation kinetics for flonicamid and its metabolites were evaluated according to FOCUS DegKin' Report (2006, 2014).

2.8.2.1 Rapid degradability of organic substances

2.8.2.1.1 Ready biodegradability

Ready biodegradability of flonicamid in aquatic systems was investigated in the following new study:

- Evaluation of aerobic biodegradability on "IKI-220 TGAI" (flonicamid) (Study B.8.2.2.1/01, 2016)

Ready biodegradability study of flonicamid in aquatic systems was conducted in compliance with OECD No. 310 (2006) instead of OECD No. 301 which is the valid current guideline. The provided study adequately describes the ready biodegradability of flonicamid under aerobic dark conditions at 20 °C. It was shown that flonicamid is not readily biodegradable.

Method	Results	Key or Supportive study	Remarks	Reference
Guideline: OECD 310 (2006) GLP Deviations: None from current requirement OECD 301 - Temperature (20 ± 2 °C) was slightly below the recommended 22 ± 2 °C. Not considered to invalidate the study as reference substance performed well in the study.	The test item flonicamid was investigated for its biodegradability in a 28-day inorganic carbon (IC) test. - The test water was prepared according to testing guidelines. - The amount of developed inorganic carbon was measured and reported in comparison to the blank. - The test sample had a starting concentration of 20.30 mg/L of organic carbon (TOC). - As reference substance sodium benzoate was used at a starting concentration of 20.43 mg/L of organic carbon (TOC). - Samples were taken on day 0 (treatment day), 1, 7, 14, 21 and 28 of the incubation periods for detection of the inorganic carbon concentration (TIC). - Determination of total inorganic carbon has been done using an automatic TOC analyser.	Key study	Non-labelled flonicamid	B.8.2.2.1/01 (2016) Report No. S-2016-03899 AM

	- The carbon dioxide generated by oxidation has been detected using an infrared gas analyser (NDIR). - Sodium benzoate was completely biodegraded within 7 days of exposure. - After 28 days only 2 % of biodegradation was measured in the flasks containing test item and inoculum. Flonicamid is not a readily biodegradable substance when considering CPL labelling. **For further details, please see CA, Vol 3, Point B.8.2.2.1 Ready biodegradability, study B.8.2.2.1/01**			

2.8.2.1.2 BOD5/COD

No tests measuring BOD5/COD were provided.

2.8.2.2 Other convincing scientific evidence

No other scientific evidence was provided to show that flonicamid would be a readily biodegradable compound.

2.8.2.2.1 Aquatic simulation tests

Data package submitted for inclusion of flonicamid in Annex I of Directive 91/4141/EEC did not include a study on aerobic mineralization in surface water. Applicant has provided a new aerobic mineralisation study in surface water which complies with the new data requirements.

Aerobic mineralisation of flonicamid in natural surface water has been investigated in the following new study:

- Aerobic mineralisation of ^{14}C-Flonicamid in surface water (Study B.8.2.2.2/01, 2017)

Aerobic mineralisation of flonicamid has been studied in the laboratory at two concentrations (10.5 and 97.3 µg/L) in natural surface water (pelagic test). Flonicamid did not degrade, and no major metabolites occurred during the study.

Method	**Results**	**Key or Supportive study**	**Remarks**	**Reference**
Guideline: OECD 309 (2004) GLP Deviations: None	Degradation of [^{14}C]flonicamid was performed under aerobic conditions in the dark with two different concentrations (10.5 µg/L and 97.3 µg/L) in natural aerobic surface water from a large water body.	Key study	Radiolabelled flonicamid	B.8.2.2.2/01 (2017) Report No. S16-04742

	- Test water had a dissolved organic carbon content of 7.8 mg/L and a BOD of 1.9 mg/L O_2. - Test water was incubated at 20 ± 2 °C. Flasks were aerated by a flow-through system and complete incubation time was 59 days. - Duplicate samples were taken for analysis at 0, 2, 7, 14, 21, 30 and 59 days after application. - Radioactivity was quantified by LSC and characterized by reverse HPLC. TLC was used for confirmation of selected samples. - Recoveries in low-test concentration was from 101.1 % to 105.1 % applied radioactivity (AR) and in high-test concentration from 98.1 % to 104.1 % AR. - CO_2 was observed in amounts up to 3.7 % AR for the low- and high-test concentration, respectively. - No organic volatiles were observed. There were no major metabolites of [^{14}C]flonicamid detected for both concentrations. - The test system was validated with the reference substance sodium benzoate. After 14 days 79.3 % AR of the reference item was mineralized. - DT_{50} values for [^{14}C]flonicamid were >10000 days (low concentration) and 3430 days (high concentration). - Max CO_2 evolved was 3.7 % during 59-day study. <u>Flonicamid is not a readily biodegradable substance when considering CPL criteria.</u> **For further details, please see CA, Vol 3, Point B.8.2.2.2, aerobic mineralization in surface water, study B.8.2.2.2/01.**			

2.8.2.2.2 Field investigations and monitoring data (if relevant for C&L)

Field data

Not relevant for C & L labelling.

No field data are available due to the very rapid degradation of flonicamid (IKI-220) as well as its metabolites TFNG-AM, TFNG, TFNA, TFNA-OH and TFNA-AM in soil with a DT_{50} of less than 5 days. However, a new

aerobic degradation study using flonicamid labelled in 4th position of pyridyl ring (B.8.1.1.1/01, 2021) was provided and a new metabolite i.e., TFA (trifluoroacetic acid) was formed with a geomean DT_{50} of 765.2 days (4 soils) and max lab DegT90 > 1000 days.

Monitoring data

Not relevant for C & L labelling.

2.8.2.2.3 Inherent and enhanced ready biodegradability tests

Please see Point 2.8.2.1.1.

2.8.2.2.4 Soil and sediment degradation data

Soil degradation data

Flonicamid degraded very fast in eight studied soils (Table 2.8.2.2.4-1). For further information for soil compartment, please see Point 2.8.1.1.

Table 2.8.2.2.4-1: $DT_{50/90}$ values obtained for flonicamid in eight soils.

Parent study	Soil		DT_{50}	DT_{90}	Model	Chi^2 error
	Name	Soil ID				
Flonicamid	Lufa 2.2	2.2	0.30	1.01	SFO	8.9
	Lufa 2.4	2.4	0.30	0.98	SFO	8.2
	Clipstone A2	A2	0.92	3.04	SFO	5.0
	Brierlow E1	E1	0.38	1.27	SFO	7.6
	Madison	72	0.97	5.35	FOMC	6.2
	Bedfordshire	188	0.64	2.11	SFO	3.2
	Birmingham	189	0.58	2.31	FOMC	2.7
	Speyer	180	**1.92** b)	**6.37** b)	SFO	0.8

Water/sediment system degradation data

Degradation of flonicamid in water/sediment systems was investigated in the following study:

- Aerobic aquatic sediment metabolism of [^{14}C]IKI-220 (Study B.8.2.2.3/01, 2002) (kinetic evaluation of the degradation in B.8.2.2.3/02, 2020; report: PP261-00025/7-3)

The degradation route is proposed to be similar to the degradation route in soil studies (see Figure 2.8.2.2.4-1 below). Under aerobic aquatic conditions flonicamid was rapidly and extensively degraded in both river and pond water/sediment systems. It should be noted that flonicamid was labelled in 3rd carbon of pyridyl ring and therefore the metabolite TFA (trifluoroacetic acid) could not be determined in the study. The degradation of this metabolite in soil was very slow with DT_{50} values ranging from 274 days to >1000 days in four soils in a study B.8.1.1.1/01 (2021). In the pond system, TFNA-OH and TFNA were the major metabolites exceeding 10 % of the applied dose. TFNG and TFNA-AM were formed as intermediate metabolites in both test systems. TFNG reached maximum 3 - 4 % of AR and TFNA-AM maximum 1 % of AR. In the river system, no major metabolites were formed. Further degradation of the radioactive residues resulted in mineralization to $^{14}CO_2$ and incorporation into the soil organic

matter i.e., bound residues. $^{14}CO_2$ accounted for 59.1 % and 15.6 % of AR in river and pond systems, respectively, and bound residues increased to 38.4 % (river) and 75.4 % of AR (pond) by the end of the study.

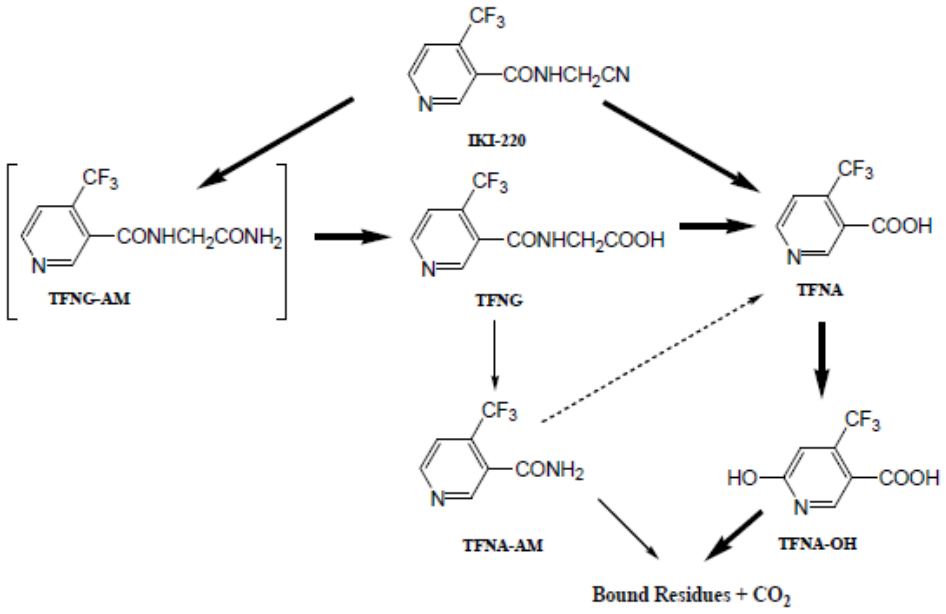


Figure 2.8.2.2.4-1 : Proposed degradation pathway of flonicamid in water and sediment

The degradation kinetics were re-assessed according to FOCUS Degradation kinetic guidance (2006, 2014). Degradation rates and formation fractions could be derived for both major metabolites found in pond system for the modelling and persistence endpoints. The geometric mean DT_{50} value for flonicamid of the total system was calculated to be 39.8 days (Table 2.8.2.2.4-2). Persistence endpoints were derived by calculating the worst case DT_{50} value of flonicamid for the total system, corresponding to 44.6 days, and the DT_{90} corresponding to 148.1 days. For the water phase, the worst-case $DisT_{50}$ and $DisT_{90}$ were calculated to be 27.9 days and 120.2 days and for the sediment layer 67.5 days and 224.2 days, respectively.

Table 2.8.2.2.4-2: Summary of DT_{50} and DT_{90} values of flonicamid in water/sediment systems (PI level)

Degradation	River	Pond	River	Pond	River	Pond
	Total system ($DegT_{50}$)	**Total system** ($DegT_{50}$)	**Water phase** ($DisT_{50}$)	**Water phase** ($DisT_{50}$)	**Sediment layer** ($DisT_{50}$)	**Sediment layer** ($DisT_{50}$)
DT_{50} [d] (modelling endpoint)	44.6	35.5	36.5	29.1 *	67.5	42.5
Geomean	**39.8**		**n.r.**		**n.r.**	
DT_{50} [d] (persistence endpoint)	44.6	35.5	27.9	5.53	67.5	42.5
Worst case	**44.6**		**27.9**		**67.5**	

Degradation	River	Pond	River	Pond	River	Pond
	Total system ($DegT_{50}$)	**Total system** ($DegT_{50}$)	**Water phase** ($DisT_{50}$)	**Water phase** ($DisT_{50}$)	**Sediment layer** ($DisT_{50}$)	**Sediment layer** ($DisT_{50}$)
DT_{90} [d] (persistence endpoint)	148.1	117.9	120.2	73.1	224.2	141.1
Worst case	**148.1**		**120.2**		**224.2**	

n.r. =not relevant
* DT_{50} derived from slow k (DFOP)

For the metabolites TFNA-OH and TFNA degradation based on combined fitting with the parent was also determined. Table 2.8.2.2.4-3 presents the DT_{50} and DT_{90} values (MI level, combined fitting) derived for the parent and metabolites TFNA-OH and TFNA in the pond system in a stepwise approach (i.e. Step 2 = parent fixed to best fit parameters and primary metabolites included, Step 3 = free fitting parent and primary metabolites with optimized parameters). The DT_{50} and DT_{90} values selected for modelling purposes were derived from free fitting (Step 3) with optimized parameters. Due to new input parameter requirements (i.e., formation fraction) for surface water models of FOCUS Step 3, the results of the combined fitting of parent and metabolite are applicable for PECsw/sed calculation at Step 3.

For the river system no adequate data was available for the determination of metabolite degradation kinetics.

Table 2.8.2.2.4-3: Summary of DT_{50} and DT_{90} values and the formation fractions of the flonicamid, metabolites TFNA-OH and TFNA in water/sediment systems (MI level). Degradation in the total system based on combined fitting, pond system

Degradation	Flonicamid	TFNA-OH	TFNA
DT_{50} [d] modelling endpoint	35.5	39.0	33.5
DT_{50} [d] persistence endpoint	35.5	39.0	33.5
DT_{90} [d] persistence endpoint	117.9	129.5	111.3
Formation fraction (from flonicamid)	-	0.25	0.45

Considering the low leaching potential of flonicamid and its other metabolites, except metabolite TFA, due to its rapid degradation under realistic outdoor conditions, and in view of groundwater modelling results, transport into the saturated zone is unlikely to occur. Therefore, a study concerning the degradation in the saturated zone is not required.

Method	Results	Key or Supportive study	Remarks	Reference
Guideline: SETAC 1995 BBA (IV,5-1, 1990 US EPA162-4 GLP	Flonicamid labelled in the 3rd position of the pyridyl ring, was applied to individual samples from each of two different water/sediment test systems at an application rate of 0.03 mg/L.	Key study	Radiolabelled flonicamid	B.8.2.2.3/01 2002 Report No. 011052-1

Deviations: Only 22-25 g soil dw was used in the test flasks instead of 50 g dw recommended. This is not considered to have affected the results obtained. Otherwise, the study followed the current test guideline OECD 308.	- The test systems were sampled at intervals over a 145-day (River; EFS-163) and 136-day (Pond; EFS-164) period under aerobic conditions. - At each sampling interval the water and sediment phases of the sample were separated and analysed for flonicamid and metabolites. - Release of radioactivity as $^{14}CO_2$ and radiolabelled volatiles was monitored for the duration of the study. - LSC analyses permitted detection of radiolabel in samples to < 0.01 % of the applied radioactivity (LOD) which fulfils the sensibility required. - Mass balance of the applied radioactivity (i.e., based on the sum of the water phase, sediment extracts, volatile and bound radioactivity) was greater than 90 % in both water/sediment systems at all sampling points, averaging 99.1 % in the River system samples and 103.1 % in the Pond system samples. - Sediment organic carbon contents differed more than 2 % as recommended - Sediment 'clay+silt' contents differed more than 20 % as recommended - Sediment/solution ratio was 1:4 as recommended - Redox potential measurements showed that water phase was aerobic and sediment anaerobic below the surface of sediment, as required. - For DT_{50} values, see Table 2.8.2.2.4-2 above. - CO_2 evolved was 59.1 % and 15.6 % of applied RA in River and Pond system, respectively. Flonicamid is not a readily biodegradable substance when considering CPL labelling. **For further details, please see CA, Vol 3, Point B.8.2.2.3, aerobic mineralization in surface water, study B.8.2.2.3/01.**			

2.8.2.2.5 Hydrolysis

The hydrolysis of flonicamid and its metabolite TFNA has been investigated under abiotic and biotic conditions in the following studies:

- A hydrolysis study of ^{14}C-IKI-220 (flonicamid) in water (B.8.2.1.1/01, 2002; kinetic evaluation of the degradation in B.8.2.1.1./02, 2020; report: PP261-00027/7-5)
- A hydrolysis study of ^{14}C-TFNA in water (B.8.2.1.1/03, 2002)

Hydrolysis of flonicamid was investigated in buffered aqueous solutions at pH 5, 7 and 9 and different temperatures at 25, 40 and 50 °C. No hydrolysis was observed at pH 5 and pH 7 in samples incubated at 25 °C and very slow hydrolysis under alkaline conditions with a half-life value of 204 days at pH 9 (Table 2.8.2.2.5-1). Extensive and rapid hydrolysis occurred only at pH 9 and at elevated temperatures, with half-life values of 17 days at 40 °C and 9 days at 50 °C, respectively. In a kinetic re-assessment according to FOCUS (2006, 2014) of the relevant data at 25 °C, flonicamid was found to be stable at pH 5 and 7 and very slowly degrading at pH 9 (DT_{50} of 203.3 days: Table 2.8.2.2.5-1). The hydrolysis of the nitrile moiety of flonicamid augmented by alkaline conditions (and high temperature) leads to the formation of TFNG-AM, the only major product at 25 °C. The results of this study indicate that aqueous abiotic hydrolysis of flonicamid would be minimal under environmental conditions associated with expected use and/or exposure.

Table 2.8.2.2.5-1: Calculated values of the $DT_{50/90}$ from the hydrolysis of IKI-220

Study conditions	DT_{50} [days]	DT_{90} [days]	Kinetic model
25 °C, pH 5	> 1000	> 1000	SFO
25 °C, pH 7	> 1000	> 1000	SFO
25 °C, pH 9	203.3	675.4	SFO

TFNA

The route and rate of hydrolysis of ^{14}C-labelled TFNA was determined in sterile buffer solutions prepared at pH 5, 7 and 9 incubated at 25 °C and 50 °C. The results indicate that aqueous abiotic hydrolysis of TFNA would not be expected under environmental conditions associated with anticipated use and/or exposure.

Summary of fate and behaviour in water and sediment [equivalent to section 11.1 of the CLH report template]

Method	Results	Key or Supportive study	Remarks	Reference
Guideline: OECD TG 111 GLP Deviations: None	The rate and route of hydrolysis of ^{14}C-labelled flonicamid was determined in sterile buffer solutions as a function of pH and temperature. Buffer solutions prepared and treated with [^{14}C]flonicamid (ca. 1 µg/mL) were incubated - at pH 5, 7 and 9 for 30 days (120 days for pH 9 samples) at 25 ± 1 °C - at pH 4, 5, 7 and 9 for 120 days at 50 ± 1°C in darkness. - at pH 4, 5, 7 and 9 at 40 ± 1 °C for up to 59 days. - Flonicamid is hydrolytically stable at environmentally realistic pH values of pH 5, 7 and 9 and at environmentally realistic temperature of 25 °C. - Kinetic evaluation of the results has been conducted by [redacted] (2020; Report No. PP261-00027/7-5). Calculated $DT_{50/90}$ values for hydrolysis of flonicamid:	Key study	Radiolabelled study Study considered valid for evaluation of hydrolytic degradation.	Study B.8.2.1.1/01 (2002) Report No. 008076-2

	<table><tr><th>Study conditions</th><th>DT_{50} [days]</th><th>DT_{90} [days]</th><th>Kinetic model</th></tr><tr><td>25 °C, pH 5</td><td>> 1000</td><td>> 1000</td><td>SFO</td></tr><tr><td>25 °C, pH 7</td><td>> 1000</td><td>> 1000</td><td>SFO</td></tr><tr><td>25 °C, pH 9</td><td>203.3</td><td>675.4</td><td>SFO</td></tr></table> Mineralisation was not measured. Flonicamid is not a readily biodegradable substance when considering CPL labelling. **For further details, please see CA, Vol 3, Point B.8.2.1.1 Hydrolytic degradation, study B.8.2.1.1/01.**			

2.8.2.2.6 Photochemical degradation

Direct photolysis of flonicamid in water under natural sunlight conditions has been investigated in the following study:

- A photolysis study of ^{14}C-IKI-220 (flonicamid) in water (B.8.2.1.2/01, 2002; kinetic evaluation of the degradation in B.8.2.1.2/02, 2020; report: PP261-00027/7-6)

Direct photolysis of flonicamid in water under natural sunlight conditions showed only minor amounts of metabolites. A kinetic assessment was performed to re-evaluate the photolytic degradation kinetics of flonicamid in water under aerobic laboratory conditions showing that flonicamid is photolytically stable at pH 7 and 23 °C in aqueous buffer solutions, with $DT_{50/90}$ values being > 1000 days. There are no reliable indications from other available data that route and rate of degradation in the water phase can be significantly influenced by indirect photo degradation, therefore corresponding degradation studies are not required.

Summary of fate and behaviour in water and sediment [equivalent to section 11.1 of the CLH report template]

Method	Results	Key or Supportive study	Remarks	Reference
Guideline: SETAC 1995 GLP Deviations: None from current OECD 316	[^{14}C]flonicamid (IKI-220) at a concentration of 1.0 µg/mL in pH 7.00 ± 0.05 phosphate buffer was continuously exposed to simulated sunlight (xenon arc lamp with filters) for 15 days at a temperature of 23 ± 2 °C. At selected intervals, (days 0, 1, 3, 7, 10 and 15) two replicates of light-exposed and dark control samples were analysed directly by HPLC with radiochemical flow detection (HPLC-RAD) to determine the distribution of radioactivity. - The selected pH of the buffer solution is considered acceptable as flonicamid is hydrolytically stable at the pH and temperature maintained in the study.	Key study	Radiolabelled study Study considered valid for evaluation of direct photochemical degradation in sterile buffer at pH 7	Study B.8.2.1.2/01 (2002) Report No. 011050-1

	- Additionally, wavelength > 290 nm were filtered off. The suntest apparatus used with xenon lamp is in line with OECD 316. - The collected six sampling dates with two replicates per sampling time fulfil the requirement of the test guideline. - Study met the quality criteria of the test guideline since the recovery ranged from 96.7 to 104.3 % during the study period. The kinetic evaluation of the results has been conducted by [redacted] (2020; Report No. PP261-00027/7-6). The kinetic evaluation of the degradation of flonicamid followed the FOCUS DegKinetics Report (2006, 2014). The obtained DT_{50} value of >1000 days show no photolytic degradation. Calculated $DT_{50/90}$ values for photolysis of flonicamid: **Phosphate buffer at pH 7** | **DT_{50} [days]** | **DT_{90} [days]** | **Kinetic model** Exposed samples | > 1000 | > 1000 | SFO Mineralisation was not measured. <u>Flonicamid is not a readily biodegradable substance when considering CPL labelling.</u> **For further details, please see CA, Vol 3, Point B.8.2.1.2: Photolytic degradation, study B.8.2.1.2/01.**			

Flonicamid is not a readily biodegradable substance based on study results on hydrolysis and photolysis in water, ready biodegradability test, aerobic mineralisation test in water and water/sediment test. This conclusion is also in line with the previous classification of flonicamid in accordance with the CLP Regulation (EC) No. 1272/2008 (Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).

2.8.2.2.7 Other / Weight of evidence

No other data has been provided.

2.8.3 Summary of fate and behaviour in air

2.8.3.1 Route and rate of degradation in air

No new studies have been submitted. The photo-oxidative degradation in air of flonicamid was estimated via the Atkinson method.

The photochemical and oxidative decomposition of flonicamid (IKI-220) in air was evaluated on theoretical calculation according to Atkinson. The calculation was performed with the help of the programme AOPWIN, Atmospheric Oxidation Programme v1.70 considering a concentration of OH radicals in the troposphere of 1.5×10^6 molecule cm^{-3} and 12 hours irradiation per day. The total estimated rate constants obtained enabled the calculation of the atmospheric half-life of flonicamid based upon average atmospheric concentrations of hydroxyl radicals. For flonicamid, the overall rate constant resulted in $k_{OH} = 0.779 \times 10^{-12}$ cm^3 $molecule^{-1}$ sec^{-1}.

Using this data, the half-life of flonicamid was calculated as 13.74 days when a 12-hour day is considered and 6.87 days when a 24-hour day is considered.

Table 2.8.3.1-1 Calculated half-lives of flonicamid

Parameters	Flonicamid
Half-life (12-hour day)	13.74
Half-life (24-hour day)	6.87

2.8.3.2 Transport via air

As the vapour pressure of 9.43×10^{-7} Pa (20 °C) of flonicamid is below the trigger for volatilisation from plant surfaces of 1×10^{-5} Pa, volatilisation is negligible. Therefore, there is no potential for short- and long-range transport via volatilisation from plant surfaces.

TFA formed as degradation product from flonicamid was found in the soil compartment (could not be found in water or sediment as only flonicamid labelled in 3rd C in pyridyl ring was used). The vapour pressure derived with EpiSuite 4.1 of 1.55×10^4 Pa (25 °C) shows a high potential of volatilisation. However, as expounded in the RAR on Flufenacet (*quotes in italics*) (Volume 3 CP, 19), "*the determination of the Henry´s law constant for TFA demonstrated that the compound displayed high affinity towards water, therefore atmospheric water, either in form of clouds or as fog, may be an effective sink for that compound*". Further it is explained, that TFA formed as degradation product from active substances of plant protection products "*will be present as trifluoroacetate – the dissociated form* (due to a pKa of 1.x 1.6 Vol 3 CA, B.2.8) *displaying very low volatility potential and as such not posing any substantial threat to the atmosphere.*" The very low volatility is proven by the low vapour pressure of the sodium salt of TFA ($<1.0 \times 10^{-6}$ Pa (20 °C), CA, Vol 3, B.2.2).
"*The examination of the available literature data showed that the presence of the TFA in the atmosphere was not expected to be related to the degradation in that environmental compartment of the active substances of the plant protection products containing in their molecules the CF_3-functional groups, nor to the possible volatilisation from soil of TFA formed there as a result of degradation of such agrochemicals*."

As TFA evolved from flonicamid only occurred in the aerobic soil degradation studies (B.8.1.1.1/01) and did not occur in the volatile traps, a volatilisation to air from soil is very unlikely. As the substance is highly affine towards water, the substance will be associated to the soil water.

Local and global effects

Neither local nor global effects as described in the EU Regulation No. 283/2013 are expected for flonicamid due to

the low vapour pressure of 9.43 x 10^{-7} Pa (20 °C).

Furthermore, Flonicamid does not contain unsaturated carbon-carbon bonds in the molecule and therefore an ozone depletion potential is not expected.

2.8.3.3 Assessment in relation to long range transport in air

The criteria for long range transport in relation via air as stated in Annex II to Regulation (EC) 1107/2009 are following:

An active substance fulfils the potential for long-range environmental transport criterion where:

— measured levels of the active substance in locations distant from the sources of its release is of potential concern,

— monitoring data show that long-range transport of the active substance may have occurred via air, or

— environmental fate properties and/or model results demonstrate that the active substance has a potential for long-range environmental transport through air in locations distant from the sources of its release. For an active substance that migrates significantly through the air, its DT_{50} in air is to be greater than 2 days.

Table 2.8.3.3-1: Evaluation of the active substance in relation to POP criteria of long-range transport in air

POP						
	soil > 180 days	**water > 60 days**	**sediment > 180days**	**bioaccumulation > 5 000 or logKow >5**	**toxicity high**	**LRT >2 days**
Flonicamid, 20 °C	0.59 [1)]	27.9 [2)]	67.5 [2)]			13.7 [3)]
Flonicamid, 12 °C	1.3 [1)]	59.3 [2)]	143.4 [2)]			
PBT						
	soil > 120 days	**water > 40 days**	**sediment > 120days**	**bioaccumulation >2 000**	**NOEC 0.01 mg/L**	
Flonicamid, 20 °C	0.59 [1)]	27.9 [2)]	67.5 [2)]			
Flonicamid, 12 °C	1.3 [1)]	59.3 [2)]	143.4 [2)]			
vPvB						
	soil > 180 days	**water > 60 days**	**sediment > 180days**	**bioaccumulation > 5 000**		
Flonicamid, 20 °C	0.59 [1)]	27.9 [2)]	67.5 [2)]			
Flonicamid, 12 °C	1.3 [1)]	59.3 [2)]	143.4 [2)]			

[1)] Normalised geometric mean DT_{50} value of 8 soils

[2)] Worst case $DisT_{50}$ value of two water/sediment system; water phase and sediment separately; worst case total system $DegT_{50}$ 44.6 days at 20 °C

[3)] Atkinson method; Vapour pressure 9.43 x 10^{-7} Pa (20 °C), water solubility 5.2 g/L → low volatilisation expected

The POP criteria of DT_{50} in air of 2 days is set for active substances that is known or expected to have a potential for long-range environmental transport through air. However, the vapour pressure of 9.43 x 10^{-7} Pa (20 °C) and water solubility 5.2 g/L of flonicamid indicate that no long-range transport would occur. Hence, RMS considers that flonicamid does not fulfil the POP criteria for long-range transport.

2.8.3.4 Hazardous to the ozone layer

Summary table of studies on hazards to the ozone layer.

Method	Results	Remarks	Reference
Regulation (EC) 2037/2000 of the European Parliament and of the Council of 29 June 2000 on substances that deplete the ozone layer	- Based on the chemical structure flonicamid is not listed in the Annex I of the regulation.		
Chemical structure	- flonicamid does not contain unsaturated carbon-carbon bonds in the molecule - flonicamid does not contain non-aromatic carbon-carbon double and triple bounds, calculations of decomposition reactions with ozone were not applicable. -therefore, an ozone depletion potential is not expected as stated by Applicant.		
EEC A.4 OECD 104 (gas saturation method)	- low vapour pressure of 9.43 x 10^{-7} Pa - based on low vapour pressure flonicamid is not expected to volatilise from plant and soil surfaces and is therefore not expected to occur in air.	Acceptable	Doc. No. 115-001 Vol 3, CA, Section B.2, Point B.2.2/01 (1999)
Calculation based	- Henry's Law constant of 4.2 x 10^{-8} Pa*m3*mol^{-1} at 20°C (based on the vapour pressure of Flonicamid of 9.43 x 10^{-7} Pa at 20°C and the water solubility of 5.2 g/L). - based on Henry's Law constant flonicamid is not expected to volatilise from water and is therefore not expected to occur in air.	Acceptable	Doc. No. 115-001 Vol 3, CA, Section B.2, Point B.2.2/02 (1999)

2.8.3.4.1 Short summary and overall relevance of the provided information on hazards to the ozone layer

Provided information on the vapour pressure and Henry's Law constant are relevant for the evaluation of the volatilisation properties of flonicamid and therefore its probability to occur in air and reach the stratosphere.

2.8.3.4.2 Comparison with the CLP criteria

Based on the Regulation (EC) 2037/2000 on substances that deplete the ozone layer and on the vapour pressure and Henry's Law constant of flonicamid it is very unlikely that flonicamid would reach the stratosphere.

2.8.4 Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

Groundwater

For groundwater, data were available from NL (since 2006, flonicamid was found 3 times with a maximum value of ≤ 0.01 µg/L; DE (1850 measurement sites – all values were below the LOD 0.02 µg/L); DK (flonicamid was not detected within the last years in any of the investigated regions).

Surface water

For surface water, data were available from NL, DE, DK, FI.

NL: In the years 2009-2019, 3359 locations were monitored with 1172 detections from 0.005 to 0.21 µg/L and a maximum concentration of 0.21 µg/L (2009) in a surface water sample. The mean concentration for 2019 is 0.187µg/L. This value is below the max. concentration estimated for PECsw in STEP 3 which is considered to be safe with regard to environmental risk assessment.

DE: In 2013, investigations were conducted at 4 sampling sites. The maximum detected concentration of flonicamid was 0.057 µg/L. This detection was below relevant trigger value of 0.1 µg/L and can therefore be considered as not relevant.

FI: From 2014 onwards, Water framework Directive data is available for 502 multiresidue samples. Flonicamid has not been found in any of the samples. LOD was mainly 0.01 µg/L.

2.8.5 Definition of the residues in the environment requiring further assessment

The residues for risk assessment are defined in Table 2.8.5-1.

In addition to flonicamid, six metabolites (TFNA, TFNA-OH, TFNG-AM, TFNG, TFNA-AM and TFA) are present in significant amounts in soil and should be included in the definition of the residue in soil and groundwater. However, all soil metabolites are relevant for surface water.

In addition to flonicamid, two metabolites (TFNA, TFNA-OH) can be found in significant amounts in surface water. It should be noted that the water/sediment study provided was performed with flonicamid labelled at 3rd carbon of pyridyl ring. Therefore, the occurrence of TFA (attached to 4th carbon of pyridyl ring) in water sediment system could not be analysed. Hence, flonicamid, TFNG-AM, TFNG, TFNA, TFNA-AM, TFNA-OH and TFA should be included in the definition of the residue in surface water. In the water/sediment study, only flonicamid was found in sediment above 10 % of the applied radioactivity. As explained above, TFA could not be identified in the study and is therefore included in the definition of residues for risk assessment for sediment.

Currently no guideline for definition of residue in air is given. However, due to the low vapour pressure of flonicamid it is concluded that it is unlikely that significant residues will occur in the air.

Table 2.8.5-1: Definition of the residues for risk assessment

	Residue definition
Soil	Flonicamid, TFNG-AM, TFNG, TFNA, TFNA-AM, TFNA-OH, TFA
Groundwater	Flonicamid, TFNG-AM, TFNG, TFNA, TFNA-AM, TFNA-OH, TFA

Surface water	Flonicamid, TFNG-AM, TFNG, TFNA, TFNA-AM, TFNA-OH, TFA
Sediment	Flonicamid, TFNG-AM[1], TFNG[1], TFNA[1], TFNA-AM[1], TFNA-OH[1], TFA[2]
Air	Flonicamid
[1] These metabolites are not found in sediment in amounts above 10 % of applied radioactivity [2] Flonicamid was not labelled into 4th carbon of pyridyl ring in water/sediment system and therefore TFA could not be analysed	

2.8.6 Definition of the residue for monitoring

Based on the ecotoxicological risk assessment for soil and water organisms, flonicamid is considered to be the only relevant residue in the environment for monitoring purposes (see Table 2.8.6-1).

Based on FOCUS modelling neither flonicamid nor its metabolites TFNG-AM, TFNG, TFNA and TFNA-AM are expected to exceed 0.1 µg/L in groundwater. Only metabolites TFNA-OH and TFA breach the trigger of 0.1 µg/L, TFNA-OH max 0.419 µg/L and TFA max 9.728 µg/L. Toxicological assessment of the metabolites in groundwater is presented in Vol 3, CA, Section 6, Point 6.8.1. The relevance of these two metabolites needs to be studied with further toxicological data (see Vol 1, level 3, point 3.1.1.4: Criteria for the approval of an active substance, relevance of metabolites) according to (Sanco/221/2000 –rev.11, 21 October 2021). Therefore, these two metabolites are included in the residue definition for monitoring now but might be adapted based on the outcome of the pending toxicological assessment.

Table 2.8.6-1: Definition of the residues for monitoring

	Residue definition
Soil	Flonicamid
Groundwater	Flonicamid and TFA depending on the outcome on the evaluation on the toxicological relevance of this metabolite
Surface water	Flonicamid
Sediment	Not required

2.8.7 Summary of exposure calculations and product assessment

2.8.7.1 Predicted environmental concentrations in soil (PECs)

In the following table the used endpoints for the PECsoil calculations are presented for both metabolites. In accordance with the FOCUS report on soil persistence models (1997), homogenous distribution within 5 cm soil depth, a bulk density of 1.5 g/cm³ was assumed for risk assessment.
Due to the very fast degradation rates of flonicamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-OH and TFNA-AM no PECsoil,acc value were calculated, however, for the persistent metabolite TFA, PECsoil,acc values were calculated for each applied use.

Beside the initial PECsoil which represent the predicted environmental concentrations immediately after application, actual and time weighted concentrations were calculated and reported as short-term (≤ 4 days after application) and as long-term values.

PECsoil immediately after the first application were calculated using FOCUS guidance (Boesten, J., 1997) with the following equation:

$$PEC_{ini} = \frac{A \cdot (1 - f_{int})}{100 \cdot d \cdot bd}$$

The PEC values after various time points were calculated as follows:

$$PEC_{act}(t) = PEC_{ini} \cdot e^{(-t \cdot \frac{\ln 2}{DT_{50}})}$$

where A = application rate [g/ha]
f_{int} = fraction intercepted by plant cover
d = depth of the soil layer [cm]
bd = bulk density [g/cm³]
DT_{50} = half-life for dissipation [d]
t = time period concerned [d]

The PECsoil,plateau for TFA were calculated as follows:

$$PEC_{soil,plateau} = Z_{eco}/Z_{til} * PEC_{ini} * e^{-k*t} / (1 - e^{-k*t})$$

with $PEC_{soil,plateau}$ = background concentration at steady state [mg/kg]
PEC_{ini} = initial concentration in total soil [mg/kg]
Z_{eco} = ecotoxicological averaging depth (5 cm)
Z_{til} = ploughing depth (20 cm)
t = interval between application seasons (365 days) [d]
k = degradation rate (ln 2 / DT_{50}) [1/d]

RMS has calculated the accumulation PEC_S values for wheat at BBCH 21 with 2 x 70 g a.s./ha (interception 20 %) as these calculations were missing. Second application after 21 days interval has also been calculated with 20 % interception even though the latter application occurs around BBCH 36 (AppDate Program, GW side) together with interception of 80 %. This is a worst-case approach only for TFA as for flonicamid and its other metabolites complete or almost complete degradation (all DT_{50} < 5 days) occur during the interval of 21 days. The $PECsoil_{plateau,average}$ and $PECsoil_{acc,max}$ values are given in Table 2.8.7.1-11 for formulation IKI-220 100 OD and 2.8.7.1-12 to 2.8.7.1-19 for formulation IKI-220 500 WG, respectively.

Additionally, RMS has calculated $PECsoil_{plateau,average}$ values for the metabolite TFA for 5 cm depth as a worst-case approach for all uses, using the following equation from FOCUS guidance (Boesten, J., 1997):

Plateau average PEC_S = Initial PEC_S for 1 application / ki

$PECsoil_{acc,max}$ has been calculated summing the PECact +PECsoil plateau.

These values have been reported in the tables below.

Following input values were used for the active substance and metabolites.

Table 2.8.7.1-1: Input parameter / Endpoints for the active substance flonicamid and relevant metabolites used for PECsoil calculation

Parameter	Value	Remark /Reference
Flonicamid		
Molecular weight [g/mol]	229.2	Vol 3, CA, B.1.7
DT_{50} [d]	1.92	Vol 3, CA, study B.8.1.1.1/03
TFNG-AM		
Molecular weight [g/mol]	247.2	
DT_{50} [d]	1.01	Vol 3, CA, study B.8.1.1.2/01
Maximum occurrence soil [%]	12.6	Vol 3, CA, study B.8.1.1.1/01
TFNA		
Molecular weight [g/mol]	191.1	
DT_{50} [d]	2.88	Vol 3, CA, study B.8.1.1.1/02
Maximum occurrence soil [%]	52.4	Vol 3, CA, study B.8.1.1.1/01
TFNG		
Molecular weight [g/mol]	248.2	
DT_{50} [d]	1.32	Vol 3, CA, study B.8.1.1.1/02
Maximum occurrence soil [%]	51.3	Vol 3, CA, study B.8.1.1.1/01
TFNA-OH		
Molecular weight [g/mol]	207.1	
DT_{50} [d]	4.57	Vol 3, CA, study B.8.1.1.1/02
Maximum occurrence soil [%]	25.3	Vol 3, CA, study B.8.1.1.1/01
TFNA-AM		
Molecular weight [g/mol]	190.1	
DT_{50} [d]	5.10	Vol 3, CA, study B.8.1.1.2/10
Maximum occurrence soil [%]	7.6	Vol 3, CA, study B.8.1.1.1/02
TFA		
Molecular weight [g/mol]	114.0	
DT_{50} [d]	1000	Vol 3, CA, study B.8.1.1.1/01
Maximum occurrence soil [%]	22.5	Vol 3, CA, study B.8.1.1.1/01

A factor of difference in the molecular weights of active substance and metabolites and the occurrence of the metabolites in soil has been calculated (Table 2.8.7.1-2).

Table 2.8.7.1-2: Difference in the molecular weights of the active substance and the metabolites and the occurrence of the metabolites in soil

Substance	Molecular weight	Occurrence in soil (% of AR)	$MW_{met}/MW_{a.s.}$ * soil occurrence
flonicamid	229.2		
TFNG-AM	247.2	12.6	0.136
TFNA	191.1	52.4	0.437
TFNG	248.2	51.3	0.556
TFNA-OH	207.1	25.3	0.229
TFNA-AM	190.1	7.6	0.063

Substance	Molecular weight	Occurrence in soil (% of AR)	$MW_{met}/MW_{a.s.}$ * soil occurrence
TFA	114	22.5	0.112

Formulation IKI-220 100 OD

The formulation IKI-220 100 OD is to be used in dry beans, dry peas and cereals (winter and spring wheat, rye, triticale). For all representative uses, the mode of application is overall spraying. The most conservative conditions (i.e., the highest application rates and conservative interception values) were chosen for each use from the GAP and are presented in Table 2.8.7.1-3. Interception by plants and corresponding soil deposition rates were assumed according to the respective EFSA guidance document (EFSA 2014[1]).

Table 2.8.7.1-3: **Representative GAP for flonicamid in formulation IKI-220 100 OD**

Crop	Growth stage (BBCH)	Number of applications (Interval)	Application rate per treatment g a.s./ha	Interception (%)	Deposition rate per treatment (g a.s./ha)
Beans	BBCH 11 - 71	1 (-)	50	Early: **25** covering Late: 70	37.5
Peas	BBCH 11 - 71	1 (-)	50	Early: **35** covering Late: 85	32.5
Cereals	BBCH 39 - PHI	1 (-)	50	Early: **80** covering Late: 80	10.0

A summary of the initial soil concentrations of flonicamid and its metabolites are presented in the table below. The difference in the molecular weights of the active substance and metabolites and the occurrence of the metabolites in soil has been taken into account when calculating the initial soil concentrations of metabolites.

Table 2.8.7.1-4: Initial PEC soil values for flonicamid and its metabolites

Substance	Molecular weight	Occurrence in soil (% of AR)	MWmet/MW a.s. factor* soil occurrence	PECs,initial in soil (mg/kg soil dw)		
				Beans	Peas	Cereals
Flonicamid	229.2			0.050	0.043	0.013
TFNG-AM	247.2	12.6	0.136	0.007	0.006	0.002
TFNG	248.2	51.3	0.556	0.028	0.024	0.009
TFNA	191.1	52.4	0.437	0.022	0.019	0.006
TFNA-AM	190.1	7.6	0.063	0.003	0.003	0.001
TFNA-OH	207.1	25.3	0.229	0.011	0.010	0.003
TFA	114.0	22.5	0.112	0.006	0.005	0.002
				0.022*	0.019*	0.006*
				0.028**	0.024**	0.008**

* Plateau conc. 5 cm ; **$PECsoil_{acc,max}$ = PECact + PECplateau conc. in 5 cm soil depth

[1] EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014 ; 12(5):3662

Beside the initial PECsoil which represent the predicted environmental concentrations immediately after application, actual and time weighted concentrations were calculated and reported as short-term (≤ 4 days after application) and as long-term values.

Table 2.8.7.1-5: Summary of the PECsoil values for flonicamid - 1 x 0.05 kg a.s. /ha

PECsoil [mg/kg]		Beans		Peas		Cereals	
		Actual	TWA	Actual	TWA	Actual	TWA
Initial		0.050		0.043		0.013	
Short term	24h	0.035	0.042	0.030	0.036	0.009	0.011
	2d	0.024	0.036	0.021	0.031	0.007	0.010
	4d	0.012	0.027	0.010	0.023	0.003	0.007
Long term	7d	0.004	0.018	0.004	0.016	0.001	0.005
	14d	< 0.001	0.010	< 0.001	0.009	< 0.001	0.003
	21d	< 0.001	0.007	< 0.001	0.006	< 0.001	0.002
	28d	< 0.001	0.005	< 0.001	0.004	< 0.001	0.001
	50d	< 0.001	0.003	< 0.001	0.002	< 0.001	0.001
	100d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
Plateau conc. 5 cm		-	-	-	-	-	-
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.

A summary of the actual and TWA soil concentrations of TFNG-AM in beans, peas and cereals is presented below:

Table 2.8.7.1-6: Summary of the PECsoil values for TFNG-AM - 1 x 0.05 kg a.s. /ha

PECsoil [mg/kg]		Beans		Peas		Cereals	
		Actual	TWA	Actual	TWA	Actual	TWA
Initial		0.007		0.006		0.002	
Short term	24h	0.003	0.005	0.003	0.004	0.001	0.001
	2d	0.002	0.004	0.002	0.003	0.001	0.001
	4d	< 0.001	0.002	< 0.001	0.002	< 0.001	0.001
Long term	7d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
	14d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
	21d	< 0.001	0.001	< 0.001	< 0.001	< 0.001	< 0.001
	28d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	50d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	100d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Plateau conc. 5 cm		-	-	-	-	-	-
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.

A summary of the actual and TWA soil concentrations of TFNG in beans, peas and cereals is presented below:

Table 2.8.7.1-7: Summary of the PECsoil values for TFNG - 1 x 0.05 kg a.s. /ha

PECsoil [mg/kg]		Beans		Peas		Cereals	
		Actual	TWA	Actual	TWA	Actual	TWA
Initial		0.028		0.024		0.009	
Short term	24h	0.017	0.022	0.014	0.019	0.004	0.005
	2d	0.010	0.017	0.009	0.015	0.002	0.004
	4d	0.003	0.012	0.003	0.010	0.001	0.003
Long term	7d	0.001	0.008	0.001	0.007	< 0.001	0.002
	14d	< 0.001	0.004	< 0.001	0.003	< 0.001	0.001
	21d	< 0.001	0.003	< 0.001	0.002	< 0.001	0.001
	28d	< 0.001	0.002	< 0.001	0.002	< 0.001	<0.001
	50d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
	100d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
Plateau conc. 5 cm		-	-	-	-	-	-
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.

A summary of the actual and TWA soil concentrations of TFNA in beans, peas and cereals is presented below:

Table 2.8.7.1-8: Summary of the PECsoil values for TFNA - 1 x 0.05 kg a.s. /ha

PECsoil [mg/kg]		Beans		Peas		Cereals	
		Actual	TWA	Actual	TWA	Actual	TWA
Initial		0.022		0.019		0.006	
Short term	24h	0.017	0.020	0.015	0.017	0.005	0.005
	2d	0.014	0.018	0.012	0.015	0.004	0.005
	4d	0.008	0.014	0.007	0.012	0.002	0.004
Long term	7d	0.004	0.011	0.004	0.009	0.001	0.003
	14d	0.001	0.006	0.001	0.006	< 0.001	0.002
	21d	< 0.001	0.004	< 0.001	0.004	< 0.001	0.001
	28d	< 0.001	0.003	< 0.001	0.003	< 0.001	0.001
	50d	< 0.001	0.002	< 0.001	0.002	< 0.001	0.001
	100d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
Plateau conc. 5 cm		-	-	-	-	-	-
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.

A summary of the actual and TWA soil concentrations of TFNA-AM in beans, peas and cereals is presented below:

Table 2.8.7.1-9: Summary of the PECsoil values for TFNA-AM - 1 x 0.05 kg a.s. /ha

PECsoil [mg/kg]		Beans		Peas		Cereals	
		Actual	TWA	Actual	TWA	Actual	TWA
Initial		0.003		0.003		0.001	
Short term	24h	0.003	0.003	0.002	0.002	0.001	0.001

PECsoil [mg/kg]		Beans		Peas		Cereals	
		Actual	**TWA**	**Actual**	**TWA**	**Actual**	**TWA**
	2d	0.002	0.003	0.002	0.002	0.001	0.001
	4d	0.002	0.002	0.001	0.002	< 0.001	0.001
Long term	7d	0.001	0.002	0.001	0.002	< 0.001	< 0.001
	14d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
	21d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
	28d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
	50d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	100d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Plateau conc. 5 cm		-	-	-	-	-	-
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.

A summary of the actual and TWA soil concentrations of TFNA-AM in beans, peas and cereals is presented below:

Table 2.8.7.1-10: Summary of the PECsoil values for <u>TFNA-OH</u> - 1 x 0.05 kg a.s. /ha

PECsoil [mg/kg]		Beans		Peas		Cereals	
		Actual	**TWA**	**Actual**	**TWA**	**Actual**	**TWA**
Initial		0.011		0.010		0.003	
Short term	24h	0.010	0.011	0.009	0.009	0.003	0.003
	2d	0.008	0.010	0.007	0.009	0.002	0.003
	4d	0.006	0.009	0.005	0.007	0.002	0.002
Long term	7d	0.004	0.007	0.003	0.006	0.001	0.002
	14d	0.001	0.005	0.001	0.004	< 0.001	0.001
	21d	< 0.001	0.003	< 0.001	0.003	< 0.001	0.001
	28d	< 0.001	0.003	< 0.001	0.002	< 0.001	0.001
	50d	< 0.001	0.002	< 0.001	0.001	< 0.001	< 0.001
	100d	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001
Plateau conc. 5 cm		-	-	-	-	-	-
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.

A summary of the actual and TWA soil concentrations of TFA in beans, peas and cereals is presented below:

Table 2.8.7.1-11: Summary of the PECsoil values for <u>TFA</u> - 1 x 0.05 kg a.s. /ha

PECsoil [mg/kg]		Beans		Peas		Cereals	
		Actual	**TWA**	**Actual**	**TWA**	**Actual**	**TWA**
Initial		0.006		0.005		0.002	
Short term	24h	0.006	0.006	0.005	0.005	0.002	0.002
	2d	0.006	0.006	0.005	0.005	0.002	0.002
	4d	0.006	0.006	0.005	0.005	0.002	0.002

PECsoil [mg/kg]		Beans		Peas		Cereals	
		Actual	TWA	Actual	TWA	Actual	TWA
Long term	7d	0.006	0.006	0.005	0.005	0.002	0.002
	14d	0.006	0.006	0.005	0.005	0.002	0.002
	21d	0.006	0.006	0.005	0.005	0.002	0.002
	28d	0.006	0.006	0.005	0.005	0.002	0.002
	50d	0.005	0.006	0.005	0.005	0.001	0.002
	100d	0.005	0.005	0.005	0.005	0.001	0.001
Plateau conc. 5 cm		0.022	-	0.019	-	0.006	-
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		0.028	-	0.024	-	0.008	-

PECsoil value for the formulation IKI-220 100 OD

The formulation IKI-220 100 OD is intended to be used in dry beans, dry peas and cereals (winter and spring wheat, rye, triticale). For all representative uses, the mode of application is overall spraying. The most conservative conditions (i.e., the highest application rate and conservative interception value) was chosen for the PECsoil calculation for the formulation. Worst case PECsoil value for Flonicamid was obtained in beans with application rate of 1 x 0.05 g a.s./ha (see Table 2.8.7.1-12) i.e., 0.5 L formulation/ha. PECsoil value for the formulation was calculated as explained for the active substance in the beginning of this section B.8.2. Formulation density of 0.9569 kg/L was taken into account. PECsoil value for the formulation is presented in table below:

Table 2.8.7.1-12: Worst case PECsoil value for the formulation - 1 x 0.5 L form. /ha

Crop	Application rate L/ha [1)]	Interception %	Bulk density kg/L	PECsoil mg form./kg soil dw
Beans	1 x 0.478	25	1.5	0.478

[1)] Formulation density 0.9569 kg/L taken into account; see CP, Volume 3, B.2.6 for IKI-220 100 OD

Formulation IKI-220 500 WG

The formulation IKI-220 500 WG OD is to be used in wheat, pome and stone fruit early and late, cucumber/courgette/melon and tomato/eggplant. For all representative uses, the mode of application is overall spraying. The most conservative conditions (i.e., the highest application rates and conservative interception values) were chosen for each use from the GAP and the values used are presented in Table 2.8.7.1-13. Interception by plants and corresponding soil deposition rates were assumed according to the respective EFSA guidance document (EFSA 2014[2]).

[2] EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014;12(5):3662

Table 2.8.7.1-13 : **Representative GAP for flonicamid**

Crop	Growth stage (BBCH)	Number of applications (Interval)	Application rate per treatment g a.s./ha	Interception (%)	Deposition rate per treatment (g a.s./ha)
Wheat	NZ : BBCH 21-77/79 BBCH 39 - 77/79	2 (21 d)	70	Early: **20** (BBCH 21) Early: 80 (BBCH 39) covering Late: 80	14
Pome fruit early Stone fruit early	BBCH 01-70 BBCH 07-70	1	70	Early: **50** covering Late: 60	35
Pome fruit late Stone fruit late	BBCH 71-85/87	2 (21 d)	70	Late: **65**	24.5
Cucumber / courgette	BBCH 16/18 - 85/87 field use covering greenhouse use and melon (BBCH 15 - 85/87)	3 (7 d)	50	Early: **50** [1] covering Late: 80	25
Cucumber / courgette	BBCH 16/18 - 85/87, greenhouse	3 (7 d)	80	Early: **50** [1] covering Late: 80	40
Tomato / eggplant	BBCH 16/18 - 85/87, field use covering greenhouse use	3 (7 d)	60	Early: **50** covering Late: 80	30

[1] Tomatoes were used as a surrogate crop for Cucumber /Courgette

A summary of the initial soil concentrations of flonicamid and its metabolites are presented in the table below. The difference in the molecular weights of the active substance and metabolites and the occurrence of the metabolites in soil has been taken into account when calculating the initial soil concentrations of metabolites.

Table 2.8.7.1-14: Initial PEC soil values for flonicamid and its metabolites in all applied uses

Crop	Flonicamid	TFNG-AM	TFNA	TFNG	TFNA-OH	TFNA-AM	TFA initial	TFA acc,max *
	[mg/kg]							
wheat BBCH 21	0.075	0.010	0.042	0.033	0.005	0.017	0.017	0.083
wheat, BBCH 39-	0.019	0.003	0.008	0.010	0.004	0.005	0.004	0.020
pome fruit, stone fruit, early	0.047	0.006	0.021	0.026	0.011	0.003	0.005	0.026
pome fruit stone fruit, late	0.033	0.004	0.014	0.018	0.008	0.002	0.007	0.036
cucumber / courgette (F, G)	0.036	0.005	0.018	0.019	0.011	0.003	0.011	0.055
cucumber / courgette (G)	0.058	0.007	0.029	0.031	0.018	0.005	0.018	0.088
tomato / eggplant	0.043	0.005	0.022	0.023	0.013	0.004	0.013	0.066

(F) = field, (G) = greenhouse

* $PECsoil_{acc,max} = PEC_{act} + PEC_{soil,plateau}$ in 5 cm soil depth

Beside the initial PECsoil which represent the predicted environmental concentrations immediately after application, actual and time weighted concentrations were calculated and reported as short-term (≤ 4 days after application) and as long-term values.

Table 2.8.7.1-15: Summary of the PECsoil values for flonicamid and its metabolites in wheat after second application 2 x 0.07 kg a.s./ha at BBCH 21

PECsoil [mg/kg]		Wheat (2 x 0.07 kg a.s. /ha)						
		flonicamid	TFNG-AM	TFNG	TFNA	TFNA-AM	TFNA-OH	TFA
Initial		0.075	0.010	0.042	0.033	0.005	0.017	0.017
Short term	24h	0.052	0.005	0.025	0.019	0.004	0.015	0.017
	2d	0.036	0.003	0.015	0.011	0.003	0.013	0.017
	4d	0.018	0.001	0.005	0.004	0.002	0.010	0.017
Long term	7d	0.006	< 0.001	0.001	0.001	0.001	0.006	0.017
	14d	<0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.002	0.016
	21d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.001	0.016
	28d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.016
	42d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.016
	50d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.016
	100d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.015
TWA	21d	0.002	0.001	0.001	0.001	0.001	0.004	0.016
Plateau conc. 5 cm		-	-	-	-	-	-	0.066
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.	0.083

Table 2.8.7.1-16: Summary of the PECsoil values for flonicamid and its metabolites in wheat after second application 2 x 0.07 kg a.s./ha at BBCH 39-

PECsoil [mg/kg]		Wheat (2 x 0.07 kg a.s. /ha)						
		flonicamid	TFNG-AM	TFNG	TFNA	TFNA-AM	TFNA-OH	TFA
Initial		0.019	0.003	0.010	0.008	0.005	0.004	0.004
Short term	24h	0.013	0.001	0.006	0.007	0.004	0.004	0.004
	2d	0.009	0.001	0.004	0.005	0.003	0.003	0.004
	4d	0.004	< 0.001	0.001	0.003	0.003	0.002	0.004
Long term	7d	0.001	< 0.001	< 0.001	0.002	0.002	0.002	0.004
	28d	< 0.001	< 0.001	< 0.001	< 0.001	0.001	< 0.001	0.004
	50d	< 0.001	< 0.001	< 0.001	< 0.001	0.001	< 0.001	0.004
	100d	< 0.001	< 0.001	< 0.001	< 0.001	0.001	< 0.001	0.004
TWA	21d	0.002	< 0.001	0.001	0.002	0.003	0.001	0.004
Plateau conc. 5 cm		-	-	-	-	-	-	0.016
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.	0.020

Table 2.8.7.1-17: Summary of the PECsoil values for flonicamid and its metabolites for pome/stone fruit early after single (1 x 0.07 kg a.s. /ha)

PECsoil [mg/kg]		Pome/stone fruit, early (1 x 0.07 kg a.s. /ha)						
		flonicamid	TFNG-AM	TFNG	TFNA	TFNA-AM	TFNA-OH	TFA
Initial		0.047	0.006	0.026	0.021	0.003	0.011	0.005
Short term	24h	0.033	0.003	0.016	0.016	0.002	0.009	0.005
	2d	0.023	0.002	0.009	0.013	0.002	0.008	0.005
	4d	0.011	< 0.001	0.003	0.008	0.001	0.006	0.005
Long term	7d	0.004	< 0.001	0.001	0.004	0.001	0.004	0.005
	28d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.005
	50d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.005
	100d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.005
TWA	21d	0.006	< 0.001	0.002	0.004	0.001	0.003	0.005
Plateau conc. 5 cm		-	-	-	-	-	-	0.021
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.	0.026

Table 2.8.7.1-18: Summary of the PECsoil values for flonicamid and its metabolites for pome/stone fruit late after second application of (2 x 0.07 kg a.s. /ha)

PECsoil [mg/kg]		Pome/stone fruit, late (2 x 0.07 kg a.s./ha)						
		flonicamid	TFNG-AM	TFNG	TFNA	TFNA-AM	TFNA-OH	TFA
Initial		0.033	0.004	0.018	0.014	0.002	0.008	0.007
Short term	24h	0.023	0.002	0.011	0.011	0.002	0.007	0.007
	2d	0.016	0.001	0.006	0.009	0.001	0.006	0.007
	4d	0.008	0.001	0.002	0.006	0.001	0.004	0.007
Long term	7d	0.003	< 0.001	< 0.001	0.003	0.001	0.003	0.007
	28d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.007
	50d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.007
	100d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.007
TWA	21d	0.004	< 0.001	0.002	0.003	0.001	0.002	0.007
Plateau conc. 5 cm		-	-	-	-	-	-	0.029
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.	0.036

Table 2.8.7.1-19: Summary of the PECsoil values for flonicamid and its metabolites for cucumber (field and greenhouse covering melon) after third application (3 x 0.05 kg a.s./ha)

PECsoil [mg/kg]		Cucumber (3 x 0.05 kg a.s. /ha)						
		flonicamid	TFNG-AM	TFNG	TFNA	TFNA-AM	TFNA-OH	TFA
Initial		0.036	0.005	0.019	0.018	0.003	0.011	0.011
Short term	24h	0.025	0.002	0.011	0.014	0.002	0.010	0.011
	2d	0.018	0.001	0.007	0.011	0.002	0.008	0.011
	4d	0.009	< 0.001	0.002	0.007	0.001	0.006	0.011
Long term	7d	0.003	< 0.001	< 0.001	0.003	0.001	0.004	0.011
	14d	< 0.001	< 0.001	< 0.001	0.001	< 0.001	0.001	0.011
	21d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.011
	28d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.011
	50d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.011
	100d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.010
TWA	21d	0.005	< 0.001	0.002	0.004	0.001	0.003	0.011
Plateau conc. 5 cm		-	-	-	-	-	-	0.044
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.	0.055

Table 2.8.7.1-20: Summary of the PECsoil values for flonicamid and its metabolites for cucumber/courgette greenhouse use early after third application (3 x 0.08 kg a.s./ha)

PECsoil [mg/kg]		cucumber/courgette, greenhouse (3 x 0.08 kg a.s. /ha)						
		flonicamid	TFNG-AM	TFNG	TFNA	TFNA-AM	TFNA-OH	TFA
Initial		0.058	0.007	0.031	0.029	0.005	0.018	0.018
Short term	24h	0.040	0.004	0.018	0.023	0.004	0.015	0.018
	2d	0.028	0.002	0.011	0.018	0.003	0.013	0.018
	4d	0.014	0.001	0.004	0.011	0.002	0.010	0.018
Long term	7d	0.005	< 0.001	0.001	0.005	0.001	0.006	0.018
	14d	< 0.001	< 0.001	< 0.001	0.001	< 0.001	0.002	0.018
	21d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.001	0.018
	28d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.018
	50d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.017
	100d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.017
TWA	21d	0.008	0.001	0.003	0.006	0.001	0.005	0.018
Plateau conc. 5 cm		-	-	-	-	-	-	0.070
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.	0.088

Table 2.8.7.1-21: Summary of the PECsoil values for flonicamid and its metabolites for tomato after third application (3 x 0.06 kg a.s./ha)

PECsoil [mg/kg]		Tomato (3 x 0.06 kg a.s. /ha)						
		flonicamid	TFNG-AM	TFNG	TFNA	TFNA-AM	TFNA-OH	TFA
Initial		0.043	0.005	0.023	0.022	0.003	0.013	0.013
Short term	24h	0.030	0.003	0.014	0.017	0.003	0.012	0.013
	2d	0.021	0.001	0.008	0.013	0.002	0.010	0.013
	4d	0.010	< 0.001	0.003	0.008	0.002	0.007	0.013
Long term	7d	0.003	< 0.001	0.001	0.004	0.001	0.005	0.013
	14d	< 0.001	< 0.001	< 0.001	0.001	< 0.001	0.002	0.013
	21d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.001	0.013
	28d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.013
	50d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.013
	100d	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.013
TWA	21d	0.006	< 0.001	0.002	0.004	0.001	0.004	0.013
Plateau conc. 5 cm		-	-	-	-	-	-	0.053
$PEC_{acc,max} = PEC_{act} + PEC_{plateau}$ conc.		No acc.	No acc.	No acc.	No acc.	No acc.	No acc.	0.066

Formulation IKI-220 500 WG

Formulation IKI-220 500 WG is intended to be used outdoor in wheat, pome/stone fruits early and late, cucumber/courgette and tomato/eggplant. For all representative uses, the mode of application is overall spraying. The most conservative conditions (i.e., the highest application rate and conservative interception value) was chosen for the PECsoil calculation for the formulation. Worst case PECsoil value for Flonicamid was obtained in wheat, early with application with application of 1 x 0.07 g a.s./ha (see Table 2.8.7.1-22) i.e., 0.14 L formulation/ha. PECsoil value for the formulation was calculated as explained in the beginning of this section B.8.2 for the active substance. PECsoil value for the formulation is presented in table below:

Table 2.8.7.1-22: Worst case PECsoil value for the formulation - 1 x 0.14 L form. /ha

Crop	Application rate L/ha	Interception %	Bulk density kg/L	PECsoil mg form./kg soil dw
Wheat (NZ)	1 x 0.14	20	1.5	0.149

2.8.7.2 Predicted environmental concentrations in groundwater (PECgw)

Input data used in PECgw modelling for flonicamid (Table 2.8.7.2-1) and its metabolites TFNG-AM, TFNG and TFNA (Table 2.8.7.2-2), TFNA-OH, TFNA-AM and TFA (Table 2.8.7.2-3) using FOCUS PELMO 5.5.3, FOCUS PEARL 4.4.4 and MACRO 5.5.4 are given below.

Two sets of input parameters were calculated concerning the studies labelled in the 4th-position of the pyridyl ring. One with the soil degradation study (CA, Vol. 3, B.8.1.1.1/01) alone and one set including additionally the metabolite studies labelled in the 4th-position (CA, Vol. 3, B.8.1.1.2/06 and B.8.1.1.2/10).

Parameter Set 1 = parent study (CA, Vol. 3, 8.1.1.1/01) **without** metabolite studies labelled in the 4th-position of the pyridyl ring. (CA, Vol. 3, B.8.1.1.2/06 and B.8.1.1.2/10).
Parameter Set 2 = parent study (CA, Vol. 3, B.8.1.1.1/01) **including** metabolite studies labelled in the 4th-position of the pyridyl ring (CA, Vol. 3, B.8.1.1.2/06 and B.8.1.1.2/10).

Table 2.8.7.2-1: Summary of input parameters for flonicamid for the leaching simulation models FOCUS PELMO 5.5.3, FOCUS PEARL 4.4.4 and MACRO 5.5.4 for the determination of PECgw

Parameter	Values	Remarks
Physico-Chemical parameters		
Molecular weight [g/mol]	229.2	CA, Vol 3, B.1.1.5
Water solubility [mg/L] (20 °C)	5200	CA, Vol 3, B.2.5
Water solubility [mg/L] (25 °C)	6262	Calculated with Van´t Hoff equation
Water solubility [mg/L] (30 °C)	7500	Calculated with Van´t Hoff equation

Parameter	Values	Remarks
Vapour pressure [Pa] (20 °C)	9.43 x 10^{-7}	CA, Vol 3, B.2.2
Vapour pressure [Pa] (25 °C)	2.55 x 10^{-6}	CA, Vol 3, B.2.2
Vapour pressure [Pa] (30 °C)	6.48 x 10^{-6}	Calculated with Van´t Hoff equation
Degradation in soil		
DT_{50} soil [d]	0.59	CA, Vol 3, B.8, Table B.8.1.1.6-6
Temperature correction function Reference temperature [°C] MACRO: [K-1] PRZM: Q10 [-]	 20 0.095 2.58	 FOCUS recommendation EFSA recommendation EFSA recommendation
Moisture correction function Reference moisture [-] PRZM / MACRO: moisture exponent [-]	 pF 2 0.7	 FOCUS recommendation
Transformation rate [1/day]	1.174826	Calculated from ln(2)/DT_{50}
Formation fractions [-] used in PEARL	0.751 to TFNG-AM 0.160 to TFNA 0.089 to CO_2	CA, Vol 3, B.8, Table B.8.1.1.6-7 Used for Set 1
	0.751 to TFNG-AM 0.157 to TFNA 0.092 to CO_2	CA, Vol 3, B.8, Table B.8.1.1.6-7 Used for Set 2
Formation fractions [-] used in MACRO	0.75 to TFNG-AM 0.74 to TFNG 0.81 as w.c. to TFNA 0.63 to TFNA-OH 0.07 to TFNA-AM 0.21 to TFA (path 1) 0.02 to TFA (path 2)	Directly from parent to metabolite as only a less complex pathway can be realized in MACRO Used for Set 1
	0.75 to TFNG-AM 0.74 to TFNG 0.81 as w.c. to TFNA 0.63 to TFNA-OH 0.07 to TFNA-AM 0.16 to TFA (path 1) 0.02 to TFA (path 2)	Directly from parent to metabolite as only a less complex pathway can be realized in MACRO Used for Set 2
Proportional transformation rates [1/day]	0.862294 to TFNG-AM 0.187972 to TFNA 0.104560 to CO_2	CA, Vol 3, B.8, Table B.8.1.1.6-7, e.g. to TFNG-AM ($k_{TFNG-AM} = k_{parent} * 0.76_{ff}$) to TFNA ($kTFNA = kparent * 0.16_{ff}$) to CO_2 ($k_{CO2} = k_{parent} - (k_{TFNG-AM} + k_{TFNA})$) Used for <u>Set 1</u>
	0.882294 to TFNG-AM 0.184448 to TFNA 0.108084 to CO_2	CA, Vol 3, B.8, Table B.8.1.1.7 Used for <u>Set 2</u>
Sorption to soil		
Koc [L/kg]	14.3	CA, Vol 3, B.8, Table B.8.1.3.4-2 geometric mean (n=4); calc. by RMS
Kom [L/kg]	8.3	Kf,om = Kf,oc / 1.724
Exponent of the Freundlich Isotherm 1/n [-]	1.0	Worst case
Plant uptake factor [-]	0	Worst case

[1)] Value calculated by RMS with EFSA OECD 106 Calculator tool (2016)

Table 2.8.7.2-2: Summary of input parameters for the flonicamid metabolites TFNG-AM, TFNG and TFNA for the leaching simulation models FOCUS PELMO 5.5.3, FOCUS PEARL 4.4.4 and MACRO 5.5.4

Parameter	TFNG-AM	TFNG	TFNA	Remarks
Molecular weight [g/mol]	247.2	248.2	191.1	-
Water solubility [mg/L]	10000	10000	10000	Worst case
Vapour pressure [Pa] (20 °C)	0	0	0	Default
Degradation in soil				
DT_{50} soil [d]	0.15	0.13	0.71	CA, Vol 3, B.8, Table B.8.1.1.6-6
Transformation rate [1/day]	4.620981	5.143803	0.976264	Calculated from ln(2)/DT_{50}
Formation fractions [-] to be used in Pearl	0.983 to TFNG	0.880 to TFNA 0.1 to TFNA-AM	0.777 to TFNA-OH	CA, Vol 3, B.8, Table B.8.1.1.6-7 Used for Set 1
	0.983 to TFNG	0.875 to TFNA 0.1 to TFNA-AM	0.777 to TFNA-OH	CA, Vol 3, B.8, Table B.8.1.1.6-7 Used for Set 2
Proportional transformation rates [1/day] to be used in Pelmo	4.542425 to TFNG 0.078557 to CO_2	4.692073 to TFNA 0.533190 to TFNA-AM 0.106638 CO_2	0.758557 to TFNA-OH 0.217707 to CO_2	CA, Vol 3, B.8, Table B.8.1.1.6-7 Used for Set 1
	4.542425 to TFNG 0.078557 to CO_2	4.665414 to TFNA 0.533190 to TFNA-AM 0.133298 to CO_2	0.758557 to TFNA-OH 0.217707 to CO_2	CA, Vol 3, B.8, Table B.8.1.1.6-7 Used for Set 2
Sorption to soil				
Koc [mL/g]	7.9[1)]	1.3[1)]	1.3[1)]	CA, Vol 3, B.8, Table B.8.1.3.4-5
Kom [mL/g]	4.6	0.8	0.8	Kf,om = Kf,oc / 1.724
1/n [-]	1	1	1	Worst case
Plant uptake factor [-]	0	0	0	Default

[1)] Value calculated by RMS with EFSA OECD 106 Calculator tool (2016)

Table 2.8.7.2-3: Summary of input parameters for the Flonicamid metabolites TFNA-OH, TFNA-AM and TFA for the leaching simulation models FOCUS PELMO 5.5.3, FOCUS PEARL 4.4.4 and MACRO 5.5.4

Parameter	TFNA-OH	TFNA-AM	TFA	Remarks
Molecular weight [g/mol]	207.1	190.1	114.0	-
Water solubility [mg/L]	10000	10000	10000	Worst case
Vapour pressure [Pa] (20 °C)	0	0	0	Default
Degradation in soil				
DT_{50} soil [d]	2.14	1.61	765.2	CA, Vol 3, B.8, Table B.8.1.1.6-6, used for Set 1
	1.87	2.82	505.5	CA, Vol 3, B.8, Table B.8.1.1.6-6, used for Set 2
Transformation rate [1/day]	0.323901 0.370667	0.429197 0.245797	0.000906 0.001371	Calculated from ln(2)/DT_{50}

Parameter	TFNA-OH	TFNA-AM	TFA	Remarks
Formation fractions [-]	0.339 to TFA	0.344 to TFA	-	CA, Vol 3, B.8, Table B.8.1.1.6-7, used for Set 1
	0.258 to TFA	0.239 to TFA	-	CA, Vol 3, B.8, Table B.8.1.1.6-7, used for Set 2
Proportional transformation rates [1/day]	0.109802 to TFA 0.214098 to CO_2	0.145927 to TFA 0.283270 to CO_2	0.000906 to CO_2	CA, Vol 3, B.8, B.8.1.1.6-7 Used for Set 1
	0.095632 to TFA 0.275035 to CO_2	0.058745 to TFA 0.187051 to CO_2	0.001371 to CO_2	CA, Vol 3, B.8, B.8.1.1.6-7 Used for Set 2
Sorption to soil				
Koc [mL/g]	2.0[1)]	4.9[1)]	0	CA, Vol 3, B.8, Table B.8.1.3.4-5, except for TFA
Kom [mL/g]	1.2	2.8	0	Kf,om = Kf,oc / 1.724
1/n [-]	1	1	1	Worst case
Plant uptake factor [-]	0	0	0	Default

[1)] Value calculated by RMS with EFSA OECD 106 Calculator tool (2016)

The predicted environmental concentration of flonicamid in groundwater has been assessed with the models FOCUS PELMO 5.5.3, FOCUS PEARL 4.4.4 and MACRO 5.5.4. Relevant predefined scenarios for the respective crops were chosen.

For the calculations of the metabolites with the model MACRO 5.5.4 individual formation fractions were multiplied to achieve a formation fraction from the parent. For the primary metabolite TFNG-AM, the kinetic assessed formation fraction of 0.76 was used. For the secondary metabolite TFNG both fractions, from parent to TFNG-AM and from TFNG–AM to TFNG were multiplied, resulting in a formation fraction of 0.74. The value of 0.74 (parent to TFNG) was further multiplied with 0.1 (formation of TFNA-AM) and multiplied with 0.34 (formation of TFA from TFNA-AM), resulting in a formation fraction of 0.024 from the parent to TFA (path 1). For the second path, the 0.74 formation to TFNG was multiplied with 1 (worst-case formation to TFNA) then multiplied with 0.78 (formation of TFNA-OH from TFNA) and last multiplied with 0.27 (formation of TFA from TFNA-OH), resulting in a formation fraction of 0.156 from the parent (path 2). PECgw values for TFA resulting from both paths were summarized. For metabolites TFNA-OH and TFNA-AM worst case formations of 1 from the respective precursors were assumed, resulting in formation fractions of 0.78 and 0.1 from the parent, respectively.

Formulation IKI-220 100 OD

Predicted environmental concentrations in groundwater (PECgw) following applications of IKI-220 100 OD according to GAP, were calculated in accordance with the guidance of the FOCUS groundwater workgroup European Commission (2003), FOCUS (2009), FOCUS (2000) under consideration of recent updates (FOCUS, 2011, 2012 and 2014).

The leaching potential of flonicamid in the product IKI-220 100 OD in soil and their concentrations in the leachate at 1 meter soil depth were calculated in order to predict their concentrations in the groundwater (PECgw). The major

metabolites occurring in soil are TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA. The formulated product IKI-220 100 OD is intended to be applied to beans, peas, and spring and winter wheat (covering rye and triticale) according to the GAP. The most conservative conditions (i.e., the highest application rates and conservative interception rates) were chosen for each use from the GAP in Table 2.8.7.2-4. A single application in peas, beans and wheat is foreseen per growing season. Interception by plants and corresponding soil deposition rates were assumed according to the respective EFSA guidance document (EFSA 2014).

Table 2.8.7.2-4: Representative GAP for flonicamid (IKI-220 100 OD)

Crop (GAP)	Focus Crop	Growth stage (BBCH)	Number of applications (Interval)	Application rate per treatment [kg a.s./ha]	Inter-ception [%]	Effective soil exposure rate [kg a.s./ha]
Dry Beans	Beans	11 - 71	1	0.05	Early: 25 Late: 70	Early: 0.0375 Late: 0.015
Dry Peas	Peas	11 - 71	1	0.05	Early: 35 Late: 85	Early: 0.0325 Late: 0.0075
Winter and spring wheat, rye, triticale	Winter and spring cereals	39 - PHI	1	0.05	Early: 80 Late: 80	Early: 0.01 Late: 0.01

Application timing was assumed under consideration of the appropriate expected growth stages and the FOCUS emergence dates for early uses and FOCUS harvest dates for late uses. For beans at BBCH 11, the 1st application was considered to start 3 days after emergence, for the late use at BBCH 71 it was considered that the last application ends 30 d before harvest. For the use in peas at BBCH 11, the 1st application was considered to start 4 days after emergence for the late use at BBCH 71 it was considered that the last application ends 30 d before harvest. The 1st application date for the use in spring and winter wheat at BBCH 39 starts 10 days after the spring point and the last application was selected to be 28 days (PHI) before harvest. Application dates for the different scenarios are summarised in Table 2.8.7.2-5 to Table 2.8.7.2-8.

Table 2.8.7.2-5: Application dates for flonicamid on <u>peas</u> covering dry peas, CEZ, SEZ (IKI-220 100 OD)

Scenario	Early application at BBCH 11	Late application at BBCH 71
	1. Appl.	1. Appl.
Châteaudun	08/04	16/07
Hamburg	13/04	26/07
Jokioinen	28/05	26/07
Okehampton	08/04	16/07

Table 2.8.7.2-6: Application dates for flonicamid on beans covering dry beans, CEZ, SEZ (IKI-220 100 OD)

Scenario	Early application at BBCH 11	Late application at BBCH 71
	1. Appl.	1. Appl.
Hamburg	14/04	26/07
Kremsmünster	14/04	26/07
Okehampton	19/03	16/08
Porto	14/03	01/08
Thiva, 1st crop	05/04	16/05
Thiva, 2nd crop	12/07	31/08

Table 2.8.7.2-7: Application dates for flonicamid on winter cereals covering winter wheat, rye, triticale, CEZ, SEZ (IKI-220 100 OD)

Scenario	Early application at BBCH 39	Late application at BBCH (PHI)
	1. Appl.	1. Appl.
Châteaudun	01/05	17/06
Hamburg	14/05	13/07
Jokioinen	24/05	18/07
Kremsmünster	04/05	13/07
Okehampton	01/05	04/07
Piacenza	29/04 (29.3.)	03/06
Porto	29/04 (29.3.)	02/06
Sevilla	29/04 (29.3.)	03/05
Thiva	29/04 (29.3.)	02/06

Table 2.8.7.2-8: Application dates for flonicamid on spring cereals covering spring wheat, rye, triticale, CEZ, SEZ (IKI-220 100 OD)

Scenario	Early application at BBCH 39	Late application at BBCH (PHI)
	1. Appl.	1. Appl.
Châteaudun	09/04 (03/05)	22/06
Hamburg	01/05	23/07
Jokioinen	17/06	28/07
Kremsmünster	01/05	23/07
Okehampton	01/05	23/07
Porto	09/04 (03/05)	22/06

Based on the PECgw modelling the results can be summarised as follows:

PECgw was modelled with two sets of input values (set 1 without the 2 new studies with metabolites TFNA-OH and TFNA-AM labelled in 4th carbon in pyridyl-ring) and (set 2 with the 2 new studies with metabolites TFNA-OH and TFNA-AM labelled in 4th carbon in pyridyl-ring). Additionally, PECgw was modelled using triennial application interval with set 1 input values.

PECgw values for Flonicamid are ≤ 0.001 µg/L for all FOCUS scenarios modelled with PELMO 5.5.3, PEARL 4.4.4 and MACRO 5.5.4. The same applies to the metabolites TFNG-AM, TFNG, TFNA, TFNA-AM. For the metabolite TFNA-OH, PECgw values were below 0.01 µg/L. In conclusion, all PECgw values for Flonicamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-AM and TFNA-OH are below the legal drinking water limit of 0.1 µg/L (all modelling results available in LoEPs).

Metabolite TFA

PELMO and PEARL

For the metabolite TFA, the PECgw values exceeded 0.1 µg/L for all uses and all scenarios with annual application. With triennial application, the PECgw exceeded 0.1 µg/L for all uses and all scenarios, except:

- peas, late in Hamburg (PELMO) and Okehampton scenarios (PEARL) (Table 2.8.7.2-9)
- beans, late in Porto scenario (both models) (Table 2.8.7.2-10)
- winter cereals, late in Okehampton and Porto scenarios (both models) (Table 2.8.7.2-11)
- spring cereals, late in Okehampton and Porto scenarios (both models) (Table 2.8.7.2-12)

The PECgw for the metabolite TFA exceeded 0.75 µg/L for the following uses and scenarios with annual application (Set 1 input values used):

Peas (Table 2.8.7.2-9):

- PELMO 5.5.3: all scenarios in peas early, except in Okehampton scenario
- PEARL 4.4.4: all scenarios in peas early

Table 2.8.7.2-9: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation model FOCUS PELMO and PEARL for peas (1 x 0.05 kg a.s./ha)

Scenario	Peas, early Set 1 annual	Peas, early Set 2 annual	Peas, early Set 2 triennial	Peas, late Set 1 annual	Peas, late Set 2 annual	Peas, late Set 2 triennial
PELMO 5.5.3						
Châteaudun	**2.146**	**1.611**	0.554	0.538	0.404	0.136
Hamburg	**1.886**	**1.416**	0.405	0.434	0.326	0.096
Jokioinen	**2.470**	**1.854**	0.611	0.572	0.429	0.146
Okehampton	**0.994**	0.746	0.205	0.229	0.172	0.049
PEARL 4.4.4						
Châteaudun	**3.103**	**2.106**	0.707	0.732	0.502	0.174
Hamburg	**2.664**	**1.931**	0.534	0.659	0.482	0.127
Jokioinen	**3.044**	**2.217**	0.655	0.655	0.480	0.153
Okehampton	**1.128**	**0.813**	0.232	0.249	0.182	0.055

Bolded values >0.75 µg/L

Beans (Table 2.8.7.2-10):

- PELMO 5.5.3: all scenarios in beans early, except in Porto scenario

- PEARL 4.4.4: all scenarios in beans early, except in Porto scenario, and in beans late, except in Jokioinen, Okehampton, Porto and Thiva, 1st crop

Table 2.8.7.2-10: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation model FOCUS PELMO and PEARL for beans (1 x 0.05 kg a.s./ha)

Scenario	Beans, early Set 1 annual	Beans, early Set 2 annual	Beans, early Set 2 triennial	Beans, late Set 1 annual	Beans, late Set 2 annual	Beans, late Set 2 triennial
PELMO 5.5.3						
Hamburg	**2.084**	**1.564**	0.443	**0.824**	0.619	0.183
Jokioinen	**1.637**	**1.229**	0.445	0.585	0.439	0.176
Okehampton	**1.128**	**0.847**	0.243	0.471	0.354	0.101
Porto	**0.817**	0.613	0.173	0.372	0.279	0.071
Thiva, 1st crop	**1.975**	**1.482**	0.631	**0.787**	0.591	0.251
Thiva, 2nd crop	**2.077**	**1.559**	0.663	**0.861**	0.647	0.262
PEARL 4.4.4						
Hamburg	**2.658**	**1.928**	0.557	**1.146**	**0.839**	0.230
Jokioinen	**1.506**	**1.089**	0.446	0.579	0.421	0.170
Okehampton	**1.389**	**1.004**	0.288	0.555	0.408	0.119
Porto	**1.048**	0.744	0.188	0.395	0.285	0.079
Thiva, 1st crop	**2.510**	**1.667**	**0.834**	**1.018**	0.671	0.330
Thiva, 2nd crop	**2.663**	**1.790**	**0.875**	**1.126**	**0.754**	0.349

Bolded values >0.75 µg/L

Winter cereals (Table 2.8.7.2-11):

- PELMO 5.5.3: all scenarios in winter cereals early and late, except in Hamburg, Kremsmünster, Okehampton, Piacenza, Porto, and Sevilla
- PEARL 4.4.4: all scenarios in winter cereals early and late, except in Hamburg, Kremsmünster, Okehampton, Piacenza and Porto

Table 2.8.7.2-11: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation model FOCUS PELMO and PEARL for winter cereals (1 x 0.05 kg a.s./ha)

Scenario	Winter cereals, early Set 1 annual	Winter cereals, early Set 2 annual	Winter cereals, early Set 2 triennial	Winter cereals, late Set 1 annual	Winter cereals, late Set 2 annual	Winter cereals, late Set 2 triennial
PELMO 5.5.3						
Châteaudun	**0.949**	0.712	0.247	**0.968**	0.726	0.259
Hamburg	0.597	0.448	0.127	0.615	0.461	0.130
Jokioinen	**0.834**	0.626	0.225	**0.839**	0.630	0.230
Kremsmünster	0.452	0.339	0.121	0.417	0.313	0.125
Okehampton	0.330	0.248	0.071	0.331	0.248	0.072
Piacenza	0.664	0.498	0.128	0.574	0.431	0.123
Porto	0.324	0.243	0.062	0.323	0.242	0.062
Sevilla	0.559	0.419	0.176	0.574	0.431	0.177
Thiva	**0.770**	0.578	0.304	**0.792**	0.594	0.317

Scenario	Winter cereals, early Set 1 annual	Winter cereals, early Set 2 annual	Winter cereals, early Set 2 triennial	Winter cereals, late Set 1 annual	Winter cereals, late Set 2 annual	Winter cereals, late Set 2 triennial
PEARL 4.4.4						
Châteaudun	**1.081**	0.740	0.243	**1.073**	0.733	0.250
Hamburg	0.643	0.468	0.133	0.699	0.511	0.134
Jokioinen	**1.030**	0.750	0.221	**0.987**	0.721	0.224
Kremsmünster	0.392	0.285	0.129	0.359	0.260	0.112
Okehampton	0.337	0.245	0.072	0.333	0.242	0.071
Piacenza	0.650	0.449	0.110	0.539	0.371	0.105
Porto	0.371	0.263	0.071	0.374	0.265	0.067
Sevilla	**1.352**	0.725	0.706	**1.357**	0.732	0.723
Thiva	**1.797**	**1.123**	0.548	**1.830**	**1.157**	0.559

Bolded values >0.75 µg/L

Spring cereals (Table 2.8.7.2-12):

- PELMO 5.5.3: in none of the scenarios in spring cereals early and late
- PEARL 4.4.4: scenarios in spring cereals early and late, except Kremsmünster, Okehampton and Porto

Table 2.8.7.2-12: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation model FOCUS PELMO and PEARL for spring cereals (1 x 0.05 kg a.s./ha)

Scenario	Spring cereals, early Set 1 annual	Spring cereals, early Set 2 annual	Spring cereals, early Set 2 triennial	Spring cereals, late Set 1 annual	Spring cereals, late Set 2 annual	Spring cereals, late Set 2 triennial
PELMO 5.5.3						
Châteaudun	0.621	0.466	0.163	0.642	0.482	0.170
Hamburg	0.574	0.430	0.122	0.567	0.425	0.125
Jokioinen	0.733	0.550	0.175	0.743	0.558	0.180
Kremsmünster	0.475	0.356	0.128	0.415	0.312	0.127
Okehampton	0.321	0.241	0.068	0.323	0.243	0.069
Porto	0.305	0.229	0.054	0.310	0.233	0.054
PEARL 4.4.4						
Châteaudun	**0.809**	0.551	0.176	**0.824**	0.564	0.181
Hamburg	**0.818**	0.594	0.168	**0.937**	0.686	0.170
Jokioinen	**0.881**	0.644	0.211	**0.825**	0.606	0.212
Kremsmünster	0.436	0.315	0.138	0.411	0.298	0.125
Okehampton	0.356	0.259	0.076	0.348	0.254	0.078
Porto	0.356	0.253	0.063	0.356	0.256	0.065

Bolded values >0.75 µg/L

All the PECgw values for TFA were below 10 µg/L.

MACRO

The PECgw for the metabolite TFA exceeded 0.75 µg/L for the peas early and winter cereals early and late (both sets of input values given) in FOCUS MACRO 5.5.4 (Table 2.8.7.2-13). All uses resulted in PECgw values below 10 µg/L.

Table 2.8.7.2-13: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation model FOCUS MACRO 5.5.4 for all crops

Scenario	Peas[a] early	Peas[a] late	Winter cereals early	Winter cereals late	Spring cereals early	Spring cereals late
Châteaudun (set 1)	**2.068**	0.490	**1.129**	**1.112**	0.667	0.675
Châteaudun (set 2)	**1.444**	0.346	**0.769**	**0.760**	0.462	0.472

Bolded values >0.75 µg/L
[a] Crop in MACRO 5.5.4 is legumes which covers beans

In conclusion:

The 80%. annual average concentration of TFA exceeds the limit values of 0.1 µg/L in almost all scenarios and 0.75 µg/L in many scenarios with the applied crops (GAP) and therefore the relevance of the metabolite TFA needs to evaluated according the Sanco/221/2000 –rev.11, 21 October 2021: guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under regulation (EC) No 1107/2009.

Formulation IKI-220 500 WG

Predicted environmental concentrations in groundwater (PECgw) following applications of formulation IKI-220 500 WG according to GAP, were calculated in accordance with the guidance of the FOCUS groundwater workgroup European Commission (2003), FOCUS (2009), FOCUS (2000) under consideration of recent updates (FOCUS, 2011, 2012 and 2014).

The leaching potential of flonicamid in the product IKI-220 500 WG in soil and their concentrations in the leachate at 1 meter soil depth were calculated in order to predict their concentrations in the groundwater (PECgw). The major metabolites occurring in soil are TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA. The formulated product IKI-220 500 WG is intended to be applied to the crops spring and winter wheat, apples, pears, peaches, apricots, plums, cherries, cucumbers, courgette, tomatoes, eggplants, and melons according to the GAP. The most conservative conditions (i.e., the highest application rates and conservative interception rates) were chosen for each use from the GAP in Table 2.8.7.2-14. Interception by plants and corresponding soil deposition rates (Table 2.8.7.2-15) were assumed according to the respective EFSA guidance document (EFSA 2014).

Table 2.8.7.2-14: Representative GAP for flonicamid (IKI-220 500 WG).

Crop	Growth stage (BBCH)	Number of applications (Interval)	Application rate per treatment g a.s./ha	Interception (%)	Deposition rate per treatment (g a.s./ha)
Wheat	BBCH 21 (NZ) BBCH 39 - 77/79 (SZ)	2 (21 d)	70	Early, BBCH 21: **20** Early: 80 covering Late: 80	56 14
Pome /stone fruit early	BBCH 01-70 BBCH 07-70	1	70	Early: **50** covering Late: 60	35
Pome /stone fruit late	BBCH 71-85/87	2 (21 d)	70	Late: **65**	24.5
Cucumber / courgette	BBCH 16/18 - 85/87 field use covering greenhouse use and melon (BBCH 15 - 85/87)	3 (7 d)	50	Early: **50** [1] covering Late: 80	25 10
Cucumber / courgette	BBCH 16/18 - 85/87, greenhouse	3 (7 d)	80	Early: **50** [1] covering Late: 80	40 16
Tomato / eggplant	BBCH 16/18 - 85/87, field use covering greenhouse use	3 (7 d)	60	Early: **50** covering Late: 80	30 12

[1] Tomatoes were used as a surrogate crop for Cucumber/courgette and melon

Application timing was assumed under consideration of the appropriate expected growth stages and the FOCUS emergence dates for early uses and FOCUS harvest dates for late uses. For winter cereals at BBCH 21 the 1st

application was considered to start 14 days before spring point for the early use in NEZ, 10 days after spring point for CEZ and SEZ for BBCH 37/39, and for late application and BBCH 79 28 days (PHI) before harvest. For the use in spring cereals BBCH 21 in NEZ the 1st application was considered to start 14 days after emergence and 30 days after emergence for BBCH 37/39 in CEZ and SEZ. For late application at BBCH 79, 28 days before harvest was assumed. For the use in apples at BBCH 01/07-70 the application at emergence was assumed, for BBCH 70 emergence plus 75 days. For the apples late at BBCH 71 application was set to 75 days after emergence. For apples late with BBCH 85-87 application 21 days (PHI) before harvest was chosen. For tomatoes early application 7 days after emergence and for tomatoes late 1 day before harvest was assumed. Application dates for the different scenarios are summarised in Table 2.8.7.2-15 to Table 2.8.7.2-18.

Table 2.8.7.2-15: Application dates for flonicamid on spring cereals covering wheat, CEZ, SEZ, NEZ (IKI-220 500 WG)

Scenario	Early application at BBCH 21 (NEZ)		Early application at BBCH 37/39 (CEZ, SEZ)		Late application at BBCH 79	
	1. Appl.	2. Appl.	1. Appl.	2. Appl.	1. Appl.	2. Appl.
Châteaudun	24/03	14/04	09/04	30/04	01/06	22/06
Hamburg	15/04	06/05	01/05	22/05	02/07	23/07
Jokioinen	01/06	22/06	17/06	08/07	07/07	28/07
Kremsmünster	15/04	06/05	01/05	22/05	02/07	23/07
Okehampton	15/04	06/05	01/05	22/05	02/07	23/07
Porto	24/03	14/04	09/04	30/04	01/06	22/06

RMS used the AppDate Program (prepared in Fraunhofer-Institute, DE, by M. Klein; model version 2018) to derive realistic application dates for early application at BBCH 39 as in the Appendix A of FOCUS Groundwater Report (2000) only emergence and harvest dates are provided, and therefore it is difficult to determine realistic application dates for BBCH 39 for winter cereals. For most of the scenarios, the selected days for early application were ± 5 days given by the AppDate for BBCH 39. In case not, application dates calculated by AppDate Program are given in brackets (see Table 2.8.7.2-16). At present no new modelling is required as RMS waits comments from SZ MSs whether the application dates used in the groundwater modelling are realistic for their agroclimatic conditions and crop development.

Table 2.8.7.2-16: Application dates for flonicamid on winter cereals covering wheat, CEZ, SEZ, NEZ (IKI-220 500 WG)

Scenario	Early application at BBCH 21 (NEZ)		Early application at BBCH 37/39 (CEZ, SEZ)		Late application at BBCH 79	
	1. Appl.	2. Appl.	1. Appl.	2. Appl.	1. Appl.	2. Appl.
Châteaudun	07/04 (01/04)	28/04	01/05	22/05	27/05	17/06
Hamburg	20/04	11/05	14/05	04/06	22/06	13/07
Jokioinen	30/04	21/05	24/05	14/06	27/06	18/07
Kremsmünster	10/04	01/05	04/05	25/05	22/06	13/07
Okehampton	07/04	28/04	01/05	22/05	13/06	04/07
Piacenza	05/04	26/04	29/04	20/05	13/05	03/06
Porto	05/04	26/04	29/04	20/05	12/05	02/06
Sevilla	05/04	26/04	29/04	20/05	12/04	03/05
Thiva	05/04	26/04	29/04	20/05	12/05	02/06

Table 2.8.7.2-17: Application dates for flonicamid on apples, covering apples and pears, peaches/apricots, plums and cherries, CEZ, SEZ, NEZ (IKI-220 500 WG)

Scenario	Early application at BBCH 01/07-70	Late at BBCH 70 (=1 week before BBCH 71)	Intermediate application at BBCH 71-85/87 [2]		Late application at BBCH85/87 (PHI = 21 d) [2]		Late application at BBCH85/87 (PHI = 14 d) [2]	
	1. Appl.	1. Appl.	1. Appl. [1]	2. Appl.	1. Appl.	2. Appl.[3]	1. Appl.	2. Appl.[3]
Châteaudun	01/04	08/06	15/06	06/07	20/08	10/09	27/08	17/09
Hamburg	15/04	22/06	29/06	20/07	18/09	09/10	25/09	16/10
Jokioinen	10/05	17/07	24/07	14/08	03/09	24/09	10/09	01/10
Kremsmünster	15/04	22/06	29/06	20/07	18/09	09/10	25/09	16/10
Okehampton	25/03	01/06	08/06	29/06	04/08	25/08	11/08	01/09
Piacenza	01/04	08/06	15/06	06/07	20/09	11/10	27/09	18/10
Porto	15/03	22/05	29/05	19/06	19/09	10/10	26/09	17/10
Sevilla	15/03	22/05	29/05	19/06	03/09	24/09	10/09	01/10
Thiva	15/03	22/05	29/05	19/06	08/09	29/09	15/09	06/10

[1] for PECgw calculation for only one application, the date for the 1st application (earlier) was used
[2] for PECgw calculation for two applications, both dates were used
[3] for PECgw calculation for only one application late, the date for the 2nd application (later) was used

Table 2.8.7.2-18: Application dates for flonicamid on tomatoes covering cucumber/courgette, eggplants, and melons, (IKI-220 500 WG)

Scenario	Early application at BBCH 15, 16/18			Late application at BBCH 85/87		
	1. Appl.	2. Appl.	3. Appl.	1. Appl.	2. Appl.	3. Appl.
Châteaudun	17/05	24/05	31/05	10/08	17/08	24/08
Piacenza	17/05	24/05	31/05	10/08	17/08	24/08
Porto	22/03	29/03	05/04	16/08	23/08	30/08
Sevilla	22/04	29/04	06/05	16/06	23/06	30/06
Thiva	17/04	24/04	01/05	26/08	02/09	09/09

Predicted environmental concentrations in groundwater (PECgw)

Two sets of input parameters were calculated concerning the studies labelled in the 4th-position of the pyridyl ring. One with the soil degradation study (CA, Vol. 3, B.8.1.1.1/01; parent study) alone and one set including additionally the metabolite studies labelled in the 4th-position (CA, Vol. 3, B.8.1.1.2/06: TFNA-AM → TFA and B.8.1.1.2/10: TFNA-OH → TFA).

Parameter Set 1 = parent study (CA, Vol. 3, 8.1.1.1/01) **without** metabolite studies labelled in the 4th-position of the pyridyl ring. (CA, Vol. 3, B.8.1.1.2/06 and B.8.1.1.2/10).

Parameter Set 2 = parent study (CA, Vol. 3, B.8.1.1.1/01) **including** metabolite studies labelled in the 4th-position of the pyridyl ring (CA, Vol. 3, B.8.1.1.2/06 and B.8.1.1.2/10).

Flonicamid and metabolites TFNG-AM, TFNG, TFNA and TFNA-AM

PECgw values for flonicamid are below 0.001 µg/L and PECgw values for the metabolites TFNG-AM, TFNG, TFNA and TFNA-AM of flonicamid are below 0.1 µg/L for all FOCUS scenarios calculated with PELMO 5.5.3, PEARL 4.4.4 and MACRO 5.5.4 i.e., all these PECgw are below the legal drinking water limit of 0.1 µg/L (all modelling results available in LoEPs). PECgw values for metabolite TFA exceeded the limit 0.1 µg/L for all uses and all scenarios and 0.75 µg/L for many uses and scenarios (Tables 2.8.7.2-19 to 2.8.7.2-27) and exceeded >10 µg/L in few uses and scenarios. PECgw values for the metabolite TFNA-OH exceeded the limit 0.1 µg/L in few scenarios in pome/stone fruits but remained below 0.75 µg/L (Table 2.8.7.2-28).

Metabolite TFA

PELMO and PEARL

For the metabolite TFA, the PECgw values exceeded 0.1 µg/L for all uses and all scenarios. Additionally, PECgw values exceeded 0.75 µg/L for most of the applied uses and scenarios. PECgw values are presented in tables below and note that the values <0.75 µg/L are bolded.

Winter cereals (Table 2.8.7.2-19):

- PELMO 5.5.3: all scenarios, except for Okehampton and Porto at BBCH 37/39 and 79 (Set 2)
- PEARL 4.4.4: all scenarios, except for Okehampton and Porto at BBCH 37/39 and 79 (Set 2)

Table 2.8.7.2-19: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation models FOCUS PELMO and PEARL for winter cereals (2 x 0.07 kg a.s./ha)

Scenario	Winter cereals BBCH 21 Set 1	Winter cereals BBCH 21 Set 2	Winter cereals BBCH 37/39 Set 1	Winter cereals BBCH 37/39 Set 2	Winter cereals BBCH 79 Set 1	Winter cereals BBCH 79 Set 2
PELMO 5.5.3						
Châteaudun	6.719	5.042	2.648	1.988	2.676	2.008
Hamburg	4.230	3.174	1.679	1.260	1.711	1.284

Scenario	Winter cereals BBCH 21 Set 1	Winter cereals BBCH 21 Set 2	Winter cereals BBCH 37/39 Set 1	Winter cereals BBCH 37/39 Set 2	Winter cereals BBCH 79 Set 1	Winter cereals BBCH 79 Set 2
Jokioinen	5.806	4.358	2.343	1.759	2.354	1.767
Kremsmünster	3.145	2.360	1.264	0.948	1.215	0.912
Okehampton	2.340	1.756	0.934	**0.701**	0.916	**0.688**
Piacenza	4.527	3.398	1.720	1.291	1.671	1.254
Porto	2.255	1.693	0.903	**0.678**	0.902	**0.677**
Sevilla	3.929	2.948	1.613	1.211	1.589	1.192
Thiva	5.353	4.018	2.175	1.632	2.196	1.648
PEARL 4.4.4						
Châteaudun	7.563	5.186	2.979	2.040	2.973	2.031
Hamburg	4.469	3.249	1.839	1.341	1.911	1.397
Jokioinen	7.226	5.251	2.886	2.104	2.803	2.049
Kremsmünster	2.707	1.967	1.104	0.803	1.070	0.778
Okehampton	2.399	1.743	0.959	**0.698**	0.916	**0.667**
Piacenza	4.306	3.009	1.582	1.075	1.539	1.064
Porto	2.564	1.816	1.034	**0.733**	1.038	**0.736**
Sevilla	9.481	5.092	3.810	2.057	3.805	2.047
Thiva	**12.570**	7.857	5.076	3.191	5.104	3.218

Bolded values <0.75 µg/L
Blue value >10 µg/L

Spring cereals (Table 2.8.7.2-20):

- PELMO 5.5.3: in all scenarios, except for Okehampton and Porto at BBCH 37/39 and 79 (Set 2)
- PEARL 4.4.4: in all scenarios, except for Okehampton and Porto at BBCH 37/39 and 79 (Set 2)

Table 2.8.7.2-20: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation models FOCUS PELMO and PEARL for spring cereals (2 x 0.07 kg a.s./ha)

Scenario	Spring cereals BBCH 21 Set 1	Spring cereals BBCH 21 Set 2	Spring cereals BBCH 37/39 Set 1	Spring cereals BBCH 37/39 Set 2	Spring cereals BBCH 79 Set 1	Spring cereals BBCH 79 Set 2
PELMO 5.5.3						
Châteaudun	4.387	3.292	1.745	1.310	1.780	1.336
Hamburg	4.018	3.016	1.604	1.204	1.565	1.175
Jokioinen	5.100	3.829	2.067	1.551	2.082	1.562
Kremsmünster	3.311	2.485	1.328	0.997	1.186	0.890
Okehampton	2.265	1.700	0.894	**0.671**	0.892	**0.669**
Porto	2.152	1.615	0.855	**0.642**	0.864	**0.649**
PEARL 4.4.4						
Châteaudun	5.693	3.883	2.262	1.543	2.306	1.576
Hamburg	5.739	4.170	2.319	1.688	2.544	1.861
Jokioinen	6.187	4.516	2.457	1.798	2.376	1.742
Kremsmünster	3.029	2.184	1.212	0.876	1.158	0.842
Okehampton	2.530	1.836	1.002	**0.728**	0.958	**0.699**
Porto	2.502	1.772	1.001	**0.711**	0.992	**0.713**

Bolded values <0.75 µg/L

Apples, BBCH stages 01/07, 70 and 71 (Table 2.8.7.2-21):

- PELMO 5.5.3: in all scenarios, except for Porto at all BBCH stages (Set 1 and 2)
- PEARL 4.4.4: in all scenarios, except for Porto at BBCH 01/07 (Set 1) and at BBCH 70 and 71 (Set 1 and 2)

Table 2.8.7.2-21: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation models FOCUS PELMO and PEARL for apples , 1 x 0.07 kg a.s./ha

Scenario	Apples BBCH 01/07 Set 1	Apples BBCH 01/07 Set 2	Apples BBCH 70 Set 1	Apples BBCH 70 Set 2	Apples BBCH 71 Set 1	Apples BBCH 71 Set 2
PELMO 5.5.3						
Châteaudun	2.428	1.822	1.828	1.372	1.583	1.188
Hamburg	2.235	1.677	1.800	1.351	1.581	1.187
Jokioinen	2.807	2.108	2.275	1.708	1.969	1.477
Kremsmünster	1.989	1.493	1.473	1.106	1.296	0.973
Okehampton	1.397	1.049	1.069	0.802	0.933	0.701
Piacenza	1.428	1.072	1.061	0.796	0.916	0.688
Porto	**0.703**	**0.528**	**0.593**	**0.445**	**0.507**	**0.381**
Sevilla	6.983	5.241	5.172	3.882	4.492	3.372
Thiva	4.566	3.427	3.342	2.508	2.906	2.181
PEARL 4.4.4						
Châteaudun	2.488	1.804	1.976	1.430	1.720	1.246
Hamburg	3.829	2.785	3.164	2.318	2.787	2.044
Jokioinen	4.158	3.036	3.356	2.471	2.914	2.142
Kremsmünster	1.620	1.175	1.258	0.912	1.088	0.793
Okehampton	1.399	1.018	1.104	0.803	0.955	0.693
Piacenza	2.057	1.445	1.708	1.204	1.492	1.052
Porto	0.853	**0.617**	**0.664**	**0.477**	**0.585**	**0.421**
Sevilla	3.078	2.200	2.377	1.702	2.072	1.482
Thiva	4.613	3.201	3.731	2.605	3.237	2.260

Bolded values <0.75 µg/L

Apples, BBCH stages 71-85/87 , PHI 21 days (Table 2.8.7.2-22):

- PELMO 5.5.3: in all scenarios, except for Porto at BBCH 71-85/87 (Set 2) and at PHI 21 days (Set 1) and for Porto, Okehampton and Piacenza for PHI 21 d (Set 2)
- PEARL 4.4.4: in all scenarios, except for Porto at PHI 21 days (Set 1 and 2)

Table 2.8.7.2-22: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation models FOCUS PELMO and PEARL for apples, late

Scenario	Apples BBCH 71-85/87 Set 1; 2 x 0.07 kg a.s./ha	Apples BBCH 71-85/87 Set 2; 2 x 0.07 kg a.s./ha	Apples PHI 21 d Set 1; 1 x 0.07 kg a.s./ha	Apples PHI 21 d Set 2; 1 x 0.07 kg a.s./ha	Apples PHI 21 d Set 2; 2 x 0.07 kg a.s./ha	Apples PHI 21 d Set 2; 2 x 0.07 kg a.s./ha
PELMO 5.5.3						
Châteaudun	3.123	2.344	1.476	1.108	2.952	2.215
Hamburg	3.086	2.316	1.636	1.230	3.202	2.404
Jokioinen	3.965	2.977	1.858	1.401	3.798	2.862
Kremsmünster	2.530	1.899	1.247	0.937	2.481	1.862
Okehampton	1.865	1.399	0.959	**0.720**	1.920	1.441
Piacenza	1.732	1.300	0.857	**0.644**	1.571	1.180
Porto	0.978	**0.734**	**0.642**	**0.482**	1.216	0.915
Sevilla	8.884	6.667	4.156	3.119	8.199	6.154
Thiva	5.772	4.332	2.934	2.202	5.790	4.346
PEARL 4.4.4						
Châteaudun	3.297	2.391	1.517	1.090	3.119	2.243
Hamburg	5.655	4.153	3.131	2.310	5.861	4.331
Jokioinen	5.837	4.299	2.616	1.952	5.526	4.121
Kremsmünster	2.216	1.612	1.087	0.798	2.115	1.548
Okehampton	1.874	1.364	1.001	0.736	2.013	1.476
Piacenza	2.985	2.101	2.157	1.574	3.760	2.739
Porto	1.195	0.861	**0.700**	**0.517**	1.339	0.986
Sevilla	4.152	2.972	1.975	1.402	3.877	2.737
Thiva	6.443	4.497	3.403	2.382	6.710	4.694

Bolded values <0.75 µg/L

Cherries (apples as surrogate crop), PHI 14 days (Table 2.8.7.2-23):

- PELMO 5.5.3: in all scenarios, except for Porto at PHI 14 d (Set 1+2) and for Okehampton and Piacenza at PHI 14 d (Set 2)
- PEARL 4.4.4: all scenarios, except for Porto at PHI 14 (Set 1+2) and Okehampton (Set 2)

Table 2.8.7.2-23: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation models FOCUS PELMO and PEARL for cherries, late, PHI 14 d

Scenario	Cherries PHI 14 d Set 1; 1 x 0.07 kg a.s./ha	Cherries PHI 14 d Set 2; 1 x 0.07 kg a.s./ha	Cherries PHI 14 d Set 2; 2 x 0.07 kg a.s./ha	Cherries PHI 14 d Set 2; 2 x 0.07 kg a.s./ha
PELMO 5.5.3				
Châteaudun	1.478	1.109	2.948	2.212
Hamburg	1.622	1.221	3.207	2.410
Jokioinen	1.820	1.374	3.656	2.755
Kremsmünster	1.259	0.946	2.471	1.855
Okehampton	0.961	**0.721**	1.913	1.436

Scenario	Cherries PHI 14 d Set 1; 1 x 0.07 kg a.s./ha	Cherries PHI 14 d Set 2; 1 x 0.07 kg a.s./ha	Cherries PHI 14 d Set 2; 2 x 0.07 kg a.s./ha	Cherries PHI 14 d Set 2; 2 x 0.07 kg a.s./ha
Piacenza	0.927	**0.696**	1.634	1.227
Porto	**0.648**	**0.486**	1.249	0.940
Sevilla	4.190	3.144	8.269	6.206
Thiva	2.955	2.217	5.842	4.384
PEARL 4.4.4				
Châteaudun	1.513	1.087	3.091	2.223
Hamburg	3.095	2.291	6.042	4.468
Jokioinen	2.586	1.930	5.475	4.083
Kremsmünster	1.104	0.812	2.121	1.556
Okehampton	0.993	**0.731**	2.004	1.472
Piacenza	2.156	1.576	3.874	2.829
Porto	**0.669**	**0.491**	1.322	0.972
Sevilla	1.993	1.414	3.930	2.782
Thiva	3.410	2.379	6.731	4.709

Bolded values <0.75 µg/L

Cucumber (F+G) covering melon (G) (tomato as surrogate crop) (Table 2.8.7.2-24):

- PELMO 5.5.3: in all scenarios, except for Porto at BBCH 85/87 (Set 2)
- PEARL 4.4.4: in all scenarios, except for Porto at BBCH 85/87 (Set 2)

Table 2.8.7.2-24: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation models FOCUS PELMO and PEARL for cucumber early and late, 3 x 0.05 kg a.s./ha

Scenario	Cucumber BBCH 16/18[1] Set 1	Cucumber BBCH 16/18[1] Set 2	Cucumber BBCH 85/87[1] Set 1	Cucumber BBCH 85/87[1] Set 2
PELMO 5.5.3				
Châteaudun	5.698	4.277	2.028	1.522
Piacenza	3.200	2.402	1.270	0.953
Porto	1.785	1.340	0.804	**0.604**
Sevilla	6.530	4.901	2.486	1.866
Thiva	5.120	3.843	2.074	1.556
PEARL 4.4.4				
Châteaudun	5.343	3.826	2.182	1.535
Piacenza	4.322	2.955	2.001	1.389
Porto	2.181	1.547	0.883	**0.644**
Sevilla	8.393	5.372	3.368	2.113
Thiva	7.944	5.299	3.273	2.212

Bolded values <0.75 µg/L

Cucumber (G) (tomato as surrogate crop) (Table 2.8.7.2-25):

- PELMO 5.5.3: in all scenarios (Set 1 and 2)
- PEARL 4.4.4: in all scenarios (Set 1 and 2)

Table 2.8.7.2-25: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation models FOCUS PELMO and PEARL for cucumber early and late in greenhouse, 3 x 0.08 kg a.s./ha

Scenario	Cucumber BBCH 16/18[1] Set 1	Cucumber BBCH 16/18[1] Set 2	Cucumber BBCH 85/87[1] Set 1	Cucumber BBCH 85/87[1] Set 2
PELMO 5.5.3				
Châteaudun	9.119	6.843	3.245	2.436
Piacenza	5.121	3.844	2.031	1.525
Porto	2.856	2.143	1.287	0.966
Sevilla	10.449	7.841	3.976	2.985
Thiva	8.191	6.149	3.318	2.491
PEARL 4.4.4				
Châteaudun	8.550	6.122	3.492	2.456
Piacenza	6.916	4.728	3.202	2.223
Porto	3.489	2.475	1.413	1.030
Sevilla	13.428	8.595	5.388	3.380
Thiva	12.711	8.478	5.237	3.538

Bolded values >0.75 µg/L
Blue value >10 µg/L

Tomatoes (G+F) covering eggplants (F+G), cucumber/courgette (F+G) and melon (G) (Table 2.8.7.2-26):

- PELMO 5.5.3: in all scenarios, except for Porto at BBCH 85/87 (Set 2)
- PEARL 4.4.4: in all scenarios at BBCH 16/18 and BBCH 85/87 (Set 1 and 2)

Table 2.8.7.2-26: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation models FOCUS PELMO and PEARL for tomato covering greenhouse use, 3 x 0.06 kg a.s./ha

Scenario	Tomato BBCH 16/18[1] Set 1	Tomato BBCH 16/18[1] Set 2	Tomato BBCH 85/87[1] Set 1	Tomato BBCH 85/87[1] Set 2
PELMO 5.5.3				
Châteaudun	6.838	5.133	2.435	1.827
Piacenza	3.840	2.884	1.524	1.143
Porto	2.142	1.608	0.965	**0.724**
Sevilla	7.836	5.881	2.983	2.239
Thiva	6.144	4.610	2.489	1.868
PEARL 4.4.4				
Châteaudun	6.412	4.592	2.619	1.842
Piacenza	5.186	3.546	2.401	1.667
Porto	2.617	1.856	1.060	0.773
Sevilla	10.072	6.447	4.041	2.535
Thiva	9.533	6.358	3.928	2.654

Bolded values >0.75 µg/L

Summary of the leaching of the metabolite TFA

Applied uses and scenarios were the PECgw values for TFA are <0.1 µg/L

PECgw values for the metabolite TFA exceeded 0.1 µg/L for all the applied uses, in all FOCUS scenarios and at all BBCH stages.

Applied uses and scenarios were the PECgw values for TFA is between >0.1 µg/L and <0.75 µg/L

PECgw values for the metabolite TFA exceeded 0.1 µg/L but were below <0.75 µg/L in some of the applied uses in couple of FOCUS scenarios and in some BBCH stages. These uses, scenarios and BBCH stages are given below using both sets of input values:

Set 1 input values:

Winter cereals (2 x 0.07 kg a.s./ha): in none of the scenarios

Spring cereals (2 x 0.07 kg a.s./ha): in none of the scenarios

Apples, BBCH stages 01/07, 70, 71 (1 x 0.07 kg a.s./ha): in Porto at BBCH 70 and 71

Apples, BBCH stages 71-85/87 (2 x 0.07 kg a.s./ha) and PHI 21 d (1 and 2 x 0.07 kg a.s./ha): in Porto at PHI 21 d (1 x 0.07 kg a.s./ha)

Cherries (apples as surrogate crop), PHI 14 days: in Porto at PHI 14 d (1 x 0.07 kg a.s./ha)

Cucumber (F+G) covering melon (G) (tomato as surrogate crop) at BBCH 16/18 and BCHH 85/87 (3x 0.05 kg a.s./ha): in none of the scenarios

Cucumber (G) (tomato as surrogate crop) at BBCH 16/18 and BCHH 85/87 (3x 0.08 kg a.s./ha): in none of the scenarios

Tomatoes (G+F) covering eggplants (F+G), cucumber/courgette (F+G) and melon (G) at BBCH 16/18 and BCHH 85/87 (3x 0.06 kg a.s./ha): in none of the scenarios

Set 2 input values:

Winter cereals (2 x 0.07 kg a.s./ha): in Porto and Okehampton at BBCH 37/39 and 79

Spring cereals (2 x 0.07 kg a.s./ha): in Porto and Okehampton at BBCH 37/39 and 79

Apples, BBCH stages 01/07, 70 and 71: in Porto at BBCH 01/07, 70 and 71 (1 x 0.07 kg a.s./ha)

Apples, BBCH stages 71-85/87 (2 x 0.07 kg a.s./ha) and PHI 21 d (1 and 2 x 0.07 kg a.s./ha): in Porto at PHI 21 d (1 x 0.07 kg a.s./ha)

Cherries, PHI 14 days: in Porto and Okehampton at PHI 14 d (1 x 0.07 kg a.s./ha)

Cucumber (F+G) covering melon (G) at BBCH 16/18 and BCHH 85/87 (3x 0.05 kg a.s./ha): in Porto at BBCH 85/87

Cucumber (G) at BBCH 16/18 and BCHH 85/87 (3x 0.08 kg a.s./ha): in none of the scenarios

Tomatoes (G+F) covering eggplants (F+G), cucumber/courgette (F+G) and melon (G) at BBCH 16/18 and BCHH 85/87 (3x 0.06 kg a.s./ha): in none of the scenarios

Applied uses and scenarios were the PECgw values for TFA are >0.75 µg/L and < 10 µg/L

For most of the other applied uses, BBCH stages and scenarios, PECgw values of TFA were > 0.75 µg/L and <10 µg/L.

Applied uses and scenarios were the PECgw values for TFA are >10 µg/L

PECgw values for TFA are >10 µg/L in the following uses:

- winter cereals, early at BBCH 21, NEZ, 2 x 0.07 kg a.s./ha, Thiva: PECgw = 12.570 µg/L (PEARL)
- cucumber, early at BBCH 16/18 (IZ) in greenhouse, 3 x 0.08 kg a.s./ha, Sevilla: PECgw = 10.449 µg/L (PELMO)
- cucumber, early at BBCH 16/18 (IZ) in greenhouse 3 x 0.08 kg a.s./ha, Sevilla: PECgw = 13.428 µg/L, Thiva: PECgw = 12.711 µg/L

MACRO

Applied uses were the PECgw values for TFA are <0.1 µg/L

PECgw values for the metabolite TFA were not below <0.1 µg/L in any of the applied uses and at any BBCH stages in Châteaudun scenario.

Applied uses were the PECgw values for TFA is between >0.1 µg/L and <0.75 µg/L

PECgw values for the metabolite TFA were not below <0.75 µg/L in any of the applied uses and at any BBCH stages in Châteaudun scenario.

Applied uses were the PECgw values for TFA is between >0.75 µg/L and <10 µg/L

PECgw values for the metabolite TFA were >0.75 µg/L and <10 µg/L in all applied uses and BBCH stages in Châteaudun scenario. The highest PECgw values from different BBCH stages for each applied use is given in (Table 2.8.7.2-25). All uses resulted in PECgw values below 10 µg/L.

Table 2.8.7.2-27: PECgw at 1 m soil depth in µg/L (80th percentile) for TFA calculated with the leaching simulation model FOCUS MACRO 5.5.4 for all crops

Scenario	W cereals early 2 x 0.07 kg a.s./ha	S cereals early 2 x 0.07 kg a.s./ha	Apples late 2 x 0.07 kg a.s./ha	Cherries late 2 x 0.07 kg a.s./ha	Cucumber (F) early, 3 x 0.05 kg a.s./ha	Cucumber (G) early 3 x 0.08 kg a.s./ha	Tomato early 3 x 0.06 kg a.s./ha
Châteaudun (set 1)	7.870	4.684	8.575	8.574	4.014	6.428	4.818
Châteaudun (set 2)	5.356	3.256	6.011	6.011	2.867	4.589	3.444

In conclusion:

The 80%. annual average concentration of TFA exceeds the limit values of 0.1 µg/L in all uses and scenarios with both input value sets and 0.75 µg/L in many scenarios with the applied crops (GAP) and therefore the relevance of the metabolite TFA needs to evaluated according to the Sanco/221/2000 –rev.11, 21 October 2021: guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under regulation (EC) No 1107/2009 (see Volume 3, B.8.6.1). Uses and scenarios in which PECgw value for TFA exceeds the limit value of 10 µg/L are not acceptable.

Metabolite TFNA-OH

For the metabolite TFNA-OH, the PECgw did not exceed 0.1 µg/L, except the following crops and scenarios in FOCUS PELMO 5.5.3 and PEARL 4.4.4 (Table 2.8.7.2-26). All scenarios resulted in values below 0.75 µg/L. All

uses resulted in values below 0.001 µg/L for FOCUS MACRO 5.4.4. The maximal PECgw for the metabolite TFNA-OH in all three models was 0.449 µg/L (PELMO).

Table 2.8.7.2-28: PECgw at 1 m soil depth in µg/L (80th percentile) for TFNA-OH calculated with the leaching simulation model FOCUS PELMO 5.5.3 and PEARL 4.4.4 for all crops in which the PECgw exceeded 0.1 µg/L but were below 0.75 µg/L

Scenario	PELMO 5.5.3				PEARL 4.4.4			
	Apples PHI 21 d 1 x 0.07 kg a.s./ha	**Apples PHI 21 d 2 x 0.07 kg a.s./ha**	**Cherries PHI 14 1 x 0.07 kg a.s./ha**	**Cherries PHI 14 2 x 0.07 kg a.s./ha**	**Apples PHI 21 d 1 x 0.07 kg a.s./ha**	**Apples PHI 21 d 2 x 0.07 kg a.s./ha**	**Cherries PHI 14 1 x 0.07 kg a.s./ha**	**Cherries PHI 14 2 x 0.07 kg a.s./ha**
Jokioinen (Set 1)	**0.197**	**0.299**	**0.337**	**0.449**	**0.138**	**0.185**	**0.259**	**0.295**
Jokioinen (Set 2)	**0.136**	**0.213**	**0.288**	**0.330**	0.090	**0.118**	**0.188**	**0.207**
Hamburg (Set 1)	0.067	0.080	**0.107**	**0.126**	**0.104**	**0.170**	**0.137**	**0.219**
Hamburg (Set 1)	0.045	0.052	0.75	0.087	0.068	**0.140**	0.096	**0.136**

Bolded values >0.1 µg/L but <0.75 µg/L

In conclusion:

The 80 %. annual average concentrations of TFNA-OH exceed the limit value of 0.1 µg/L (see Table b.8.3-62) but remains below 0.75 µg/L in all the applied crops. Therefore, the relevance of the metabolite TFNA-OH needs to evaluated according to the Sanco/221/2000 –rev.11, 21 October 2021: guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under regulation (EC) No 1107/2009 (see Volume 3, B.8.6.1).

2.8.7.3 Predicted environmental concentrations in surface water and sediment (PECsw, PECsed)

The calculation of the predicted environmental concentrations of Flonicamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA in surface water and sediment was based on the recommendations provided in the Report FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC FOCUS (2003) and the FOCUS Generic Guidance for FOCUS Surface Water Scenarios FOCUS (2012, 2014, 2015) under consideration of the recommendations by EFSA (2014).

According to the residue definition Flonicamid and its metabolites TFNG AM, TFNG, TFNA, TFNA-OH, TFNA AM and TFA are considered to be of relevance for surface water and sediment exposure assessment. Predicted environmental concentrations of Flonicamid and its metabolites in surface water and sediment have been assessed with the standard FOCUS scenarios following the stepwise approach (Step 1 – Step 3) using FOCUS software: for Steps 1/2, Steps 1-2 in FOCUS Calculator and for Step 3, FOCUS SWASH 5.3, FOCUS MACRO 5.5.4, FOCUS PRZM SW 4.3.1 and FOCUS TOXSWA 5.5.3.

Input data used in PECsw modelling for flonicamid and its metabolites TFNG-AM, TFNA-OH and TFNA are given in Table 2.8.7.3-1 and TFNG-AM, TFNG, TFNA-AM and TFA in Table 2.8.7.3-2.

Notice! Two sets of input parameters were calculated concerning the studies labelled in the 4th-position of the pyridyl ring. One with the soil degradation study (CA, Vol. 3, B.8.1.1.1/01) alone and one set including additionally the metabolite studies labelled in the 4th-position (CA, Vol. 3, B.8.1.1.2/06 and B.8.1.1.2/10). **These two sets of input parameters were used for Step 1 and Step 2.**

Parameter Set 1 = parent study (CA, Vol. 3, 8.1.1.1/01) **without** metabolite studies labelled in the 4th-position of the pyridyl ring (CA, Vol. 3, B.8.1.1.2/06 and B.8.1.1.2/10).

Parameter Set 2 = parent study (CA, Vol. 3, B.8.1.1.1/01) **including** metabolite studies labelled in the 4th-position of the pyridyl ring (CA, Vol. 3, B.8.1.1.2/06 and B.8.1.1.2/10).

Table 2.8.7.3-1: Summary of input parameters of Flonicamid and its metabolites TFNA-OH and TFNA for PECsw and PECsed calculations according to FOCUS

Parameter	Flonicamid	TFNA-OH	TFNA	Reference / Remark
Entry routes into surface water	Spray drift, runoff, drainage			-
Molecular weight [g/mol]	229.2	207.1	191.1	For a.s., Vol 3, B.1.1.5
Water solubility [mg/L] (20°C)	5200	10000	10000	CA, Vol 3, B.2.5 / worst case / worst case
Vapour pressure [Pa] (20°C)	9.43×10^{-7}	0	0	Vol 3, B.2.2 / default / default
Degradation in soil				
DT_{50} soil [d]	0.59	2.14	0.71	CA, Vol 3, Table B.8.1.1.6-6 **Used for Set 1**

Parameter	Flonicamid	TFNA-OH	TFNA	Reference / Remark
	0.59	1.87	0.71	CA, Vol 3, Table B.8.1.1.6-6 **Used for Set 2**
Temperature correction function Reference temperature [°C] MACRO: [K-1] PRZM: Q10 [-]	20 0.095 2.58	Not relevant for Step 1/2	Not relevant for Step 1/2	FOCUS recommendation EFSA recommendation EFSA recommendation
Moisture correction function Reference moisture [-] PRZM / MACRO: moisture exponent [-]	pF 2 0.70	Not relevant for Step 1/2	Not relevant for Step 1/2	FOCUS recommendation
Sorption to soil				
Koc [L/kg]	14.3	2.0	1.3	Re-assessment RMS with EFSA calculator: CA, Vol 3, B.8, Table B.8.1.3.4-5
Kom [L/kg]	8.3	1.2	0.8	Kf,om = Kf,oc / 1.724
Exponent of the Freundlich Isotherm 1/n [-]	1	1	1	Default
Degradation in aquatic systems				
DT_{50} water [d]	Step 2: 39.8 Step 3: 39.8	Step 2: 39.0	Step 2: 33.5	Vol 3, study B.8.2.2.3/02
DT_{50} sediment [d]	Step 2: 39.8 Step 3: 1000	Step 2: 39.0	Step 2: 33.5	Vol 3, study B.8.2.2.3/02
DT_{50} water/sediment [d]	39.8	Step 2: 39.0	Step 2: 33.5	Vol 3, study B.8.2.2.3/02
DT_{50} crop [d]	10	Not relevant for Step 1/2	Not relevant for Step 1/2	FOCUS recommendation
Max. occurrence in soil [%]:	-	25.3	52.4	Vol 3, study B.8.1.1.1/02
Max. occurrence in water/sediment system	-	13.3	17.9	Vol 3, study B.8.2.2.3/01
Temperature correction function Reference temperature [°C] TOXSWA: activation energy [J mol-1]	20 65 400	Not relevant for Step 1/2	Not relevant for Step 1/2	FOCUS recommendation EFSA recommendation
Crop uptake factor [-]	0	Not relevant for Step 1/2	Not relevant for Step 1/2	FOCUS recommendation for non-systemic compounds
Wash off coefficient PRZM: [cm^{-1}] MACRO: [mm^{-1}]	0.5 0.05	Not relevant for Step 1/2	Not relevant for Step 1/2	FOCUS default

Table 2.8.7.3-2: Summary of input parameters of Flonicamid and its metabolites TFNG-AM, TFNG, TFNA-AM and TFA for PECsw and PECsed calculations according to FOCUS

Parameter	TFNG-AM	TFNG	TFNA-AM	TFA	Reference / Remark
Entry routes into surface water	Spray drift, runoff, drainage				-
Molecular weight [g/mol]	247.2	248.2	190.1	114.0	
Water solubility [mg/L] (20°C)	10000	10000	10000	10000	Worst case
Vapour pressure [Pa] (20°C)	0	0	0	0	Default
Degradation in soil					
DT_{50} soil [d]	0.15	0.13	1.61	765.2	CA, Vol 3, B.8, Table B.8.1.1.6-6, used for Set 1
	0.15	0.13	2.82	505.5	CA, Vol 3, B.8, Table B.8.1.1.6-6, used for Set 2
Sorption to soil					
Koc [L/kg]	7.9	1.3	4.6	0	TFNG-AM Vol 3, study B.8.1.2.2/03 TFNG Vol 3, study B.8.1.2.2/05 TFNA-AM Vol 3, study B.8.1.2.2/04 TFA – no study available
Kom [L/kg]	4.6	0.8	2.8	0	Kf,om = Kf,oc / 1.724
Exponent of the Freundlich Isotherm 1/n [-]	1	1	1	1	Default
Degradation in aquatic systems					
DT_{50} water [d]	1000	1000	1000	1000	Default
DT_{50} sediment [d]	1000	1000	1000	1000	Default
DT_{50} water/sediment [d]	1000	1000	1000	1000	Default
Max. occurrence in soil [%]:	12.6	51.3	7.6	22.5	TFNG-AM and TFNG: study B.8.1.1.1/02 TFNA-AM and TFA: study B.8.1.1.1/01
Max. occurrence in water/sediment system	0	3.8	3.0	0	Study B.8.2.2.3/01

Formulation (IKI-220 100 OD)

Predicted environmental concentrations in surface water (PECsw) and sediment (PECsed)

Step 1 and Step 2

Only PEC_{ini} values for Flonicamid and its metabolites were used in the risk assessment for aquatic organisms, hence detailed PECtwa values are not presented here. Additionally, no risk from secondary poisoning needs to be evaluated

for bird and mammals as the logPow for flonicamid is 0.1 at pH 7. PECsw and PECsed TWA values can be found in Volume 3 CP IKI-220 100 OD B.8.5.

Relevant use information and application rates for Flonicamid according to GAP is presented in Table 2.8.7.3-3. Crop interception and seasons of application timing for Step 1 to 2 calculations are presented in Table 2.8.7.3-4.

Table 2.8.7.3-3: Representative GAP for Flonicamid (IKI-220 100 OD)

FOCUS Crop(s)	Crops covered	Growth stage (BBCH)	Number of applications (Minimum interval)	Application rate per treatment [kg a.s./ha]
Field beans	Beans	BBCH 11 - 71	1	0.05
Legumes	Peas	BBCH 11 - 71	1	0.05
Winter and spring cereals	Winter and spring wheat, rye, triticale	BBCH 39 - PHI	1	0.05

At Step 1 and 2 PECsw calculations for Northern and Southern Europe and seasons selected according to the GAP were performed for field beans, peas, winter and spring cereals. Detailed information on the application windows used for the calculations in Step 1 + 2, are presented in the following table.

Table 2.8.7.3-4: Application rates, crop interception and seasons of application timing for Step 1 and Step 2 for Flonicamid (IKI-220 100 OD)

FOCUS Crop(s)	Application rate [kg a.s./ha]	Season #	Crop cover #	Interception # [%]
Northern Europe and Southern Europe				
Field beans	1 x 0.05	March-May	minimal	25
		June-Sep	minimal	25
		June-Sep	intermediate	40
		June-Sep	full canopy	70
Legumes	1 x 0.05	March-May	minimal	25
		June-Sep	intermediate	50
		June-Sep	full canopy	70
Winter and spring cereals	1 x 0.05	March-May	intermediate	20
		June-Sep	intermediate	20
		June-Sep	full canopy	70

used for Step 2 calculations

Step 1 and Step 2 – <u>Parameter Set 1</u>

The maximum predicted environmental concentration of Flonicamid and its metabolites in surface water (PECsw) and sediment (PECsed) are summarised in Table 2.8.7.3-5 for Step 1 and in Tables 2.8.7.3-6 to 2.8.7.3-12 for Step 2.

Table 2.8.7.3-5: Initial PECsw and PECsed values of Flonicamid, TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA for Step 1

FOCUS Crop	Crops covered	Application rate [kg a.s./ha]	PECsw [µg/L]	PECsed [µg/kg]
Flonicamid				
Field beans	Beans	1 x 0.05	16.815	2.339
Legumes	Peas		16.815	2.339
Spring cereals	Winter and spring wheat, rye, triticale		16.815	2.339
Winter cereals			16.815	2.339
TFNG-AM				
Field beans	Beans	1 x 0.05	2.241	0.177
Legumes	Peas		2.241	0.177
Spring cereals	Winter and spring wheat, rye, triticale		2.241	0.177
Winter cereals			2.241	0.177
TFNG				
Field beans	Beans	1 x 0.05	9.946	0.129
Legumes	Peas		9.946	0.129
Spring cereals	Winter and spring wheat, rye, triticale		9.946	0.129
Winter cereals			9.946	0.129
TFNA				
Field beans	Beans	1 x 0.05	9.821	0.127
Legumes	Peas		9.821	0.127
Spring cereals	Winter and spring wheat, rye, triticale		9.821	0.127
Winter cereals			9.821	0.127
TFNA-OH				
Field beans	Beans	1 x 0.05	5.832	0.156
Legumes	Peas		5.832	0.156
Spring cereals	Winter and spring wheat, rye, triticale		5.832	0.156
Winter cereals			5.832	0.156
TFNA-AM				
Field beans	Beans	1 x 0.05	1.467	0.071
Legumes	Peas		1.467	0.071
Spring cereals	Winter and spring wheat, rye, triticale		1.467	0.071
Winter cereals			1.467	0.071
TFA				
Field beans	Beans	1 x 0.05	1.865	< 0.001
Legumes	Peas		1.865	< 0.001
Spring cereals	Winter and spring wheat, rye, triticale		1.865	< 0.001
Winter cereals			1.865	< 0.001

Table 2.8.7.3-6: Initial PECsw and PECsed values of Flonicamid for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.460	0.062	-	-	0.468	0.065	-	-
	June-Sep	0.460	0.062	-	-	0.460	0.064	-	-
average	June-Sep	0.460	0.062	-	-	0.460	0.063	-	-
full canopy	June-Sep	0.460	0.060	-	-	0.460	0.061	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.460	0.062	-	-	0.468	0.065	-	-
average	June-Sep	0.460	0.061	-	-	0.460	0.062	-	-
full canopy	June-Sep	0.460	0.060	-	-	0.460	0.061	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.460	0.063	-	-	**0.471** [1)]	**0.066** [1)]	-	-
	June-Sep	0.460	0.063	-	-	0.460	0.064	-	-
full canopy	June-Sep	0.460	0.060	-	-	0.460	0.061	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.460	0.063	-	-	**0.471** [1)]	**0.066** [1)]	-	-
	June-Sep	0.460	0.063	-	-	0.460	0.064	-	-
full canopy	June-Sep	0.460	0.060	-	-	0.460	0.061	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CA, Volume 3, B.8.5)

Table 2.8.7.3-7: Initial PECsw and PECsed values of TFNG-AM for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 a.s g/ha									
minimal	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
average	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
full canopy	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
Legumes, 1 x 50 a.s.g/ha									
minimal	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
average	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
full canopy	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
Spring cereals, 1 x 50 a.s.g/ha									
average	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
full canopy	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
Winter cereals, 1 x 50 a.s g/ha									
average	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
full canopy	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-

Table 2.8.7.3-8: Initial PECsw and PECsed values of TFNG for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.020	< 0.001	-	-	**0.021** [1)]	**< 0.001** [1)]	-	-
	June-Sep	0.020	< 0.001	-	-	0.020	< 0.001	-	-
average	June-Sep	0.020	< 0.001	-	-	0.020	< 0.001	-	-
full canopy	June-Sep	0.019	< 0.001	-	-	0.019	< 0.001	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.020	< 0.001	-	-	**0.021** [1)]	**< 0.001** [1)]	-	-
average	June-Sep	0.020	< 0.001	-	-	0.020	< 0.001	-	-
full canopy	June-Sep	0.019	< 0.001	-	-	0.020	< 0.001	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.020	< 0.001	-	-	**0.021** [1)]	**< 0.001** [1)]	-	-
	June-Sep	0.020	< 0.001	-	-	0.021 [1)]	< 0.001	-	-
full canopy	June-Sep	0.019	< 0.001	-	-	0.020	< 0.001	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.020	< 0.001	-	-	**0.021** [1)]	**< 0.001**	-	-
	June-Sep	0.020	< 0.001	-	-	0.021[1)]	< 0.001	-	-
full canopy	June-Sep	0.019	< 0.001	-	-	0.020	< 0.001	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CA, Volume 3, B.8.5)

Table 2.8.7.3-9: Initial PECsw and PECsed values of TFNA for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.089	0.001	-	-	0.114	0.001	-	-
	June-Sep	0.088	0.001	-	-	0.101	0.001	-	-
average	June-Sep	0.083	0.001	-	-	0.094	0.001	-	-
full canopy	June-Sep	0.073	<0.001	-	-	0.078	0.001	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.089	0.001	-	-	0.114	0.001	-	-
average	June-Sep	0.080	0.001	-	-	0.089	0.001	-	-
full canopy	June-Sep	0.073	<0.001	-	-	0.078	0.001	-	-
Spring cereals, 1 x 50 g a.s./ha									

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
average	March-May	0.090	0.001	-	-	**0.117** [1)]	**0.002** [1)]	-	-
	June-Sep	0.090	0.001	-	-	0.104	0.001	-	-
full canopy	June-Sep	0.073	<0.001	-	-	0.078	0.001	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.090	0.001	-	-	**0.117** [1)]	**0.002** [1)]	-	-
	June-Sep	0.090	0.001	-	-	0.104	0.001	-	-
full canopy	June-Sep	0.073	<0.001	-	-	0.078	0.001	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CP, Volume 3, B.8.5)

Table 2.8.7.3-10: Initial PECsw and PECsed values of TFNA-OH for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.210	0.004	-	-	0.369	0.010	-	-
	June-Sep	0.210	0.004	-	-	0.290	0.006	-	-
average	June-Sep	0.178	0.004	-	-	0.242	0.005	-	-
full canopy	June-Sep	0.115	0.002	-	-	0.147	0.003	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.207	0.004	-	-	0.369	0.007	-	-
average	June-Sep	0.155	0.003	-	-	0.207	0.004	-	-
full canopy	June-Sep	0.113	0.002	-	-	0.147	0.003	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.218	0.004	-	-	**0.390** [1)]	**0.008** [1)]	-	-
	June-Sep	0.218	0.004	-	-	0.305	0.006	-	-
full canopy	June-Sep	0.113	0.002	-	-	0.147	0.003	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.218	0.004	-	-	**0.390** [1)]	**0.008** [1)]	-	-
	June-Sep	0.218	0.004	-	-	0.305	0.006	-	-
full canopy	June-Sep	0.113	0.002	-	-	0.147	0.003	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CP, Volume 3, B.8.5)

Table 2.8.7.3-11: Initial PECsw and PECsed values of TFNA-AM for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.040	0.002	-	-	0.069	0.004	-	-
	June-Sep	0.040	0.002	-	-	0.054	0.003	-	-
average	June-Sep	0.034	0.002	-	-	0.046	0.003	-	-
full canopy	June-Sep	0.023	0.001	-	-	0.029	0.002	-	-

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.040	0.002	-	-	0.068	0.004	-	-
average	June-Sep	0.030	0.002	-	-	0.040	0.002	-	-
full canopy	June-Sep	0.023	0.001	-	-	0.029	0.002	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.042	0.002	-	-	**0.072** [1)]	**0.004** [1)]	-	-
	June-Sep	0.042	0.002	-	-	0.057	0.003	-	-
full canopy	June-Sep	0.023	0.001	-	-	0.029	0.002	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.042	0.002	-	-	**0.072** [1)]	**0.004** [1)]	-	-
	June-Sep	0.042	0.002	-	-	0.057	0.003	-	-
full canopy	June-Sep	0.023	0.001	-	-	0.029	0.002	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CP, Volume 3, B.8.5)

Table 2.8.7.3-12: Initial PECsw and PECsed values of TFA for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.279	< 0.001	-	-	0.558	< 0.001	-	-
	June-Sep	0.279	< 0.001	-	-	0.418	< 0.001	-	-
average	June-Sep	0.223	< 0.001	-	-	0.335	< 0.001	-	-
full canopy	June-Sep	0.112	< 0.001	-	-	0.167	< 0.001	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.279	< 0.001	-	-	0.558	< 0.001	-	-
average	June-Sep	0.186	< 0.001	-	-	0.279	< 0.001	-	-
full canopy	June-Sep	0.112	< 0.001	-	-	0.167	< 0.001	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.297	< 0.001	-	-	**0.594** [1)]	**< 0.001** [1)]	-	-
	June-Sep	0.297	< 0.001	-	-	0.446	< 0.001	-	-
full canopy	June-Sep	0.111	< 0.001	-	-	0.167	**< 0.001** [1)]	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.297	< 0.001	-	-	**0.594** [1)]	< 0.001	-	-
	June-Sep	0.297	< 0.001	-	-	0.445	< 0.001	-	-
full canopy	June-Sep	0.111	< 0.001	-	-	0.167	< 0.001	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CP, Volume 3, B.8.5)

Step 1 and Step 2 – Parameter Set 2

The maximum predicted environmental concentration of Flonicamid and its metabolites in surface water (PECsw) and sediment (PECsed) are summarised in Table 2.8.7.3-13 for Step 1 and in Tables 2.8.7.3-14 to 2.8.7.3-20 for Step 2.

Table 2.8.7.3-13: Initial PECsw and PECsed values of Flonicamid, TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA for Step 1

FOCUS Crop	Crops covered	Application rate [kg a.s./ha]	PECsw [µg/L]	PECsed [µg/kg]
Flonicamid				
Field beans	Beans	1 x 0.05	**16.815**	**2.339**
Legumes	Peas		16.815	2.339
Spring cereals	Winter and spring wheat, rye, triticale		16.815	2.339
Winter cereals			16.815	2.339
TFNG-AM				
Field beans	Beans	1 x 0.05	2.241	0.177
Legumes	Peas		2.241	0.177
Spring cereals	Winter and spring wheat, rye, triticale		2.241	0.177
Winter cereals			2.241	0.177
TFNG				
Field beans	Beans	1 x 0.05	9.946	0.129

FOCUS Crop	Crops covered	Application rate [kg a.s./ha]	PECsw [µg/L]	PECsed [µg/kg]
Legumes	Peas		9.946	0.129
Spring cereals	Winter and spring wheat, rye, triticale		9.946	0.129
Winter cereals			9.946	0.129
TFNA				
Field beans	Beans	1 x 0.05	9.821	0.127
Legumes	Peas		9.821	0.127
Spring cereals	Winter and spring wheat, rye, triticale		9.821	0.127
Winter cereals			9.821	0.127
TFNA-OH				
Field beans	Beans	1 x 0.05	5.832	0.156
Legumes	Peas		5.832	0.156
Spring cereals	Winter and spring wheat, rye, triticale		5.832	0.156
Winter cereals			5.832	0.156
TFNA-AM				
Field beans	Beans	1 x 0.05	1.467	0.071
Legumes	Peas		1.467	0.071
Spring cereals	Winter and spring wheat, rye, triticale		1.467	0.071
Winter cereals			1.467	0.071
TFA				
Field beans	Beans	1 x 0.05	1.865	< 0.001
Legumes	Peas		1.865	< 0.001
Spring cereals	Winter and spring wheat, rye, triticale		1.865	< 0.001
Winter cereals			1.865	< 0.001

Bolded value is the highest value at Step 1

Table 2.8.7.3-14: Initial PECsw and PECsed values of Flonicamid for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.460	0.062	-	-	0.468	0.065	-	-
	June-Sep	0.460	0.062	-	-	0.460	0.064	-	-
average	June-Sep	0.460	0.062	-	-	0.460	0.063	-	-
full canopy	June-Sep	0.460	0.060	-	-	0.460	0.061	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.460	0.062	-	-	0.468	0.065	-	-
average	June-Sep	0.460	0.061	-	-	0.460	0.062	-	-
full canopy	June-Sep	0.460	0.060	-	-	0.460	0.061	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.460	0.063	-	-	**0.471** [1)]	**0.066** [1)]	-	-
	June-Sep	0.460	0.063	-	-	0.460	0.064	-	-

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
full canopy	June-Sep	0.460	0.060	-	-	0.460	0.061	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.460	0.063	-	-	**0.471** [1)]	**0.066** [1)]	-	-
	June-Sep	0.460	0.063	-	-	0.460	0.064	-	-
full canopy	June-Sep	0.460	0.060	-	-	0.460	0.061	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CA, Volume 3, B.8.5)

Table 2.8.7.3-15: Initial PECsw and PECsed values of TFNG-AM for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 a.s g/ha									
minimal	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
average	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
full canopy	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
Legumes, 1 x 50 a.s.g/ha									
minimal	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
average	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
full canopy	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
Spring cereals, 1 x 50 a.s.g/ha									
average	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
full canopy	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
Winter cereals, 1 x 50 a.s g/ha									
average	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
full canopy	June-Sep	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-

Table 2.8.7.3-16: Initial PECsw and PECsed values of TFNG for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.020	< 0.001	-	-	**0.021** [1)]	**< 0.001** [1)]	-	-
	June-Sep	0.020	< 0.001	-	-	0.020	< 0.001	-	-
average	June-Sep	0.020	< 0.001	-	-	0.020	< 0.001	-	-
full canopy	June-Sep	0.019	< 0.001	-	-	0.019	< 0.001	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.020	< 0.001	-	-	**0.021** [1)]	**<0.001** [1)]	-	-
average	June-Sep	0.020	< 0.001	-	-	0.020	<0.001	-	-
full canopy	June-Sep	0.019	< 0.001	-	-	0.019	<0.001	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.020	< 0.001	-	-	**0.021** [1)]	**<0.001** [1)]	-	-
	June-Sep	0.020	< 0.001	-	-	0.020	<0.001	-	-
full canopy	June-Sep	0.019	< 0.001	-	-	0.019	<0.001	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.020	< 0.001	-	-	**0.021** [1)]	**<0.001** [1)]	-	-
	June-Sep	0.020	< 0.001	-	-	0.020	<0.001	-	-
full canopy	June-Sep	0.019	< 0.001	-	-	0.019	<0.001	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CA, Volume 3, B.8.5)

Table 2.8.7.3-17: Initial PECsw and PECsed values of TFNA for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.089	0.001	-	-	0.114	0.001	-	-
	June-Sep	0.088	0.001	-	-	0.101	0.001	-	-
average	June-Sep	0.083	0.001	-	-	0.094	0.001	-	-
full canopy	June-Sep	0.073	<0.001	-	-	0.078	0.001	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.089	0.001	-	-	0.114	0.001	-	-
average	June-Sep	0.080	0.001	-	-	0.089	0.001	-	-
full canopy	June-Sep	0.073	<0.001	-	-	0.078	0.001	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.090	0.001	-	-	**0.117** [1)]	**0.002** [1)]	-	-
	June-Sep	0.090	0.001	-	-	0.104	0.001	-	-
full canopy	June-Sep	0.073	<0.001	-	-	0.078	0.001	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.090	0.001	-	-	**0.117** [1)]	**0.002** [1)]	-	-
	June-Sep	0.090	0.001	-	-	0.104	0.001	-	-
full canopy	June-Sep	0.073	<0.001	-	-	0.078	0.001	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CP, Volume 3, B.8.5)

Table 2.8.7.3-18: Initial PECsw and PECsed values of TFNA-OH for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.184	0.004	-	-	0.316	0.006	-	-
	June-Sep	0.184	0.004	-	-	0.250	0.005	-	-
average	June-Sep	0.157	0.003	-	-	0.210	0.004	-	-
full canopy	June-Sep	0.104	0.002	-	-	0.131	0.003	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.184	0.004	-	-	0.316	0.006	-	-
average	June-Sep	0.140	0.003	-	-	0.184	0.004	-	-
full canopy	June-Sep	0.104	0.002	-	-	0.131	0.003	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.192	0.004	-	-	**0.333** [1)]	**0.007** [1)]	-	-
	June-Sep	0.192	0.004	-	-	0.263	0.005	-	-
full canopy	June-Sep	0.104	0.002	-	-	0.131	0.003	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.192	0.004	-	-	**0.333** [1)]	**0.007** [1)]	-	-
	June-Sep	0.192	0.004	-	-	0.263	0.005	-	-
full canopy	June-Sep	0.104	0.002	-	-	0.131	0.003	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CP, Volume 3, B.8.5)

Table 2.8.7.3-19: Initial PECsw and PECsed values of TFNA-AM for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.071	0.004	-	-	0.130	0.006	-	-
	June-Sep	0.071	0.004	-	-	0.100	0.005	-	-
average	June-Sep	0.059	0.003	-	-	0.082	0.004	-	-
full canopy	June-Sep	0.035	0.002	-	-	0.047	0.002	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.071	0.004	-	-	0.130	0.006	-	-
average	June-Sep	0.051	0.003	-	-	0.071	0.004	-	-
full canopy	June-Sep	0.035	0.002	-	-	0.047	0.002	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.074	0.004	-	-	**0.138** [1)]	**0.007** [1)]	-	-
	June-Sep	0.074	0.004	-	-	0.106	0.005	-	-
full canopy	June-Sep	0.035	0.002	-	-	0.047	0.002	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.074	0.004	-	-	**0.138** [1)]	**0.007** [1)]	-	-
	June-Sep	0.074	0.004	-	-	0.106	0.005	-	-
full canopy	June-Sep	0.035	0.002	-	-	0.047	0.002	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CP, Volume 3, B.8.5)

Table 2.8.7.3-20: Initial PECsw and PECsed values of TFA for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Field beans, 1 x 50 g a.s./ha									
minimal	March-May	0.278	<0.001	-	-	0.557	<0.001	-	-
	June-Sep	0.278	<0.001	-	-	0.417	<0.001	-	-
average	June-Sep	0.223	<0.001	-	-	0.334	<0.001	-	-
full canopy	June-Sep	0.111	<0.001	-	-	0.167	<0.001	-	-
Legumes, 1 x 50 g a.s./ha									
minimal	March-May	0.278	<0.001	-	-	0.557	<0.001	-	-
average	June-Sep	0.186	<0.001	-	-	0.278	<0.001	-	-
full canopy	June-Sep	0.111	<0.001	-	-	0.167	<0.001	-	-
Spring cereals, 1 x 50 g a.s./ha									
average	March-May	0.297	<0.001	-	-	**0.594** [1)]	**<0.001** [1)]	-	-
	June-Sep	0.297	<0.001	-	-	0.445	<0.001	-	-
full canopy	June-Sep	0.111	<0.001	-	-	0.167	<0.001	-	-
Winter cereals, 1 x 50 g a.s./ha									
average	March-May	0.297	<0.001	-	-	**0.594** [1)]	**<0.001** [1)]	-	-
	June-Sep	0.297	<0.001	-	-	0.445	<0.001	-	-
full canopy	June-Sep	0.111	<0.001	-	-	0.167	<0.001	-	-

[1)] Worst case PECsw used for detailed Step 2 including actual and TWA PECsw and PECsed values (see CP, Volume 3, B.8.5)

Formulation (IKI-220 500 WG)

Predicted environmental concentrations in surface water (PECsw) and sediment (PECsed)

Step 1 and Step 2

Only PEC_{ini} values for Flonicamid and its metabolites were used in the risk assessment for aquatic organisms, hence detailed PECtwa values are not presented here. Additionally, no risk from secondary poisoning needs to be evaluated for bird and mammals as the logPow for flonicamid is 0.1 at pH 7. PECsw and PECsed TWA values can be found in Volume 3 CP IKI-220 500 WG B.8.5.

Relevant use information and application rates for Flonicamid according to GAP is presented in Table 2.8.7.3-21. Crop interception and seasons of application timing for Step 1 to 2 calculations are presented in Table 2.8.7.3-22.

Table 2.8.7.3-21: Representative GAP for Flonicamid (IKI-220 500 WG)

FOCUS Crop(s)	Crops covered	Growth stage (BBCH)	Number of applications (Minimum interval)	Application rate per treatment [kg a.s./ha]
Winter and spring cereals	Winter and spring wheat	21 - 77/79 (NEZ) 39 - 77/79 (SEZ) 37 - 77/79 (CEZ)	1 - 2 (21 d)	0.07
Pome/stone fruit early	Apples, pears, peaches/apricots, plums, cherries	01/07 - 70	1	0.07
Pome/stone fruit late	Apples, pears, peaches/apricots, plums, cherries	71 - 85/87	1 - 2 (21 d)	0.07
Vegetables fruiting	Cucumber/courgette (F, G), melons (F)	15 - 85/87	3 (7 d)	0.05
Vegetables fruiting	Cucumber/courgette (G)	16/18 - 85/87	3 (7 d)	0.08
Vegetables fruiting	Tomato/eggplant (F, G)	16/18 - 85/87	3 (7 d)	0.06

At Step 1 and 2 PECsw calculations for Northern and Southern Europe and seasons selected according to the GAP were performed for winter and spring cereals, pome and stone fruits, and fruiting vegetables. Detailed information on the application windows used for the calculations in Step 1 + 2, are presented in the following table.

Table 2.8.7.3-22: Application rates, crop interception and seasons of application timing for Step 1 and Step 2 for Flonicamid (IKI-220 500 WG)

FOCUS Crop(s)	Use(s) covered	Application rate [kg a.s./ha]	Season #	Crop cover #	Inter-ception # [%]
Northern Europe and Southern Europe					
Winter and spring cereals	Wheat (SEZ, CEZ, NEZ)	1-2 x 0.07	March-May	intermediate	20
			June-Sep	intermediate	20
			June-Sep	full canopy	70
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	March-May	no interception	0
			March-May	minimal	20
			March-May	intermediate	40
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	June-Sep	intermediate	40
			June-Sep	full canopy	65
			Oct-Feb	full canopy	65
Vegetables fruiting	Cucumber/ courgette (F, G) Tomatoes/ eggplants (F, G) Melon (F)	3 x 0.05 or 3 x 0.06 or 3 x 0.08	March-May	minimal	25
			June-Sep	intermediate	50
			June-Sep	full canopy	70

used for Step 2 calculations
* (F) = field, (G) = greenhouse

Step 1 and Step 2 – <u>Parameter Set 1</u>

The maximum predicted environmental concentration of Flonicamid and its metabolites in surface water (PECsw) and sediment (PECsed) are summarised in Table 2.8.7.3-23 for Step 1 and in Tables 2.8.7.3-24 to 2.8.7.3-30 for Step 2.

Table 2.8.7.3-23: Initial PECsw and PECsed values of Flonicamid, TFNA-OH and TFNA for Step 1

FOCUS Crop	Crops covered	Application rate [kg a.s./ha]	PECsw [µg/L]	PECsed [µg/kg]
Flonicamid				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	47.081	6.549
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	47.081	6.549
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	29.709	3.274
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ)	2 x 0.07	53.132	6.549

FOCUS Crop	Crops covered	Application rate [kg a.s./ha]	PECsw [µg/L]	PECsed [µg/kg]
	Plums (CEZ, SEZ) Cherries (CEZ, SEZ)			
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	50.444	7.016
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	80.710	11.226
Vegetables fruiting (F,G)	Tomatoes/ eggplants (F, G)	3 x 0.06	60.533	8.420
TFNG-AM				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	6.276	0.496
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	6.276	0.496
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	3.138	0.248
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	6.276	0.496
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	6.724	0.531
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	10.758	0.850
Vegetables fruiting (F,G)	Tomatoes/ eggplants (F, G)	3 x 0.06	8.069	0.637
TFNG				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	27.850	0.361
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	27.850	0.361
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	14.179	0.181
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	28.099	0.361
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	29.839	0.387
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	47.742	0.620
Vegetables fruiting (F,G)	Tomatoes/ eggplants (F, G)	3 x 0.06	35.807	0.465
TFNA				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	27.498	0.355
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	27.498	0.355
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	14.670	0.178
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	28.401	0.355
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	29.462	0.380

FOCUS Crop	Crops covered	Application rate [kg a.s./ha]	PECsw [µg/L]	PECsed [µg/kg]
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	47.140	0.609
Vegetables fruiting (F,G)	Tomatoes/ eggplants (F, G)	3 x 0.06	35.355	0.456
TFNA-OH				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	16.388	0.325
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	16.388	0.325
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	8.935	0.162
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	17.115	0.325
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	17.559	0.348
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	28.094	0.557
Vegetables fruiting (F,G)	Tomatoes/ eggplants (F, G)	3 x 0.06	21.070	0.417
TFNA-AM				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	4.108	0.200
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	4.108	0.200
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	2.208	0.100
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	4.259	0.200
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	4.402	0.214
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	7.043	0.342
Vegetables fruiting (F,G)	Tomatoes/ eggplants (F, G)	3 x 0.06	5.282	0.257
TFA				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	5.223	< 0.001
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	5.223	< 0.001
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	2.611	< 0.001
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	5.223	< 0.001
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	5.596	< 0.001
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	8.953	< 0.001
Vegetables fruiting (F,G)	Tomatoes/ eggplants (F, G)	3 x 0.06	6.715	< 0.001

Table 2.8.7.3-24: Initial PECsw and PECsed values of Flonicamid for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.644	0.088	0.959	0.129	0.660	0.092	0.959	0.133
average	June-Sep	0.644	0.088	0.959	0.129	0.644	0.090	0.959	0.131
full canopy	June-Sep	0.644	0.085	0.959	0.126	0.644	0.085	0.959	0.127
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.644	0.088	0.959	0.129	0.660	0.092	0.959	0.133
average	June-Sep	0.644	0.088	0.959	0.129	0.644	0.090	0.959	0.131
full canopy	June-Sep	0.644	0.085	0.959	0.126	0.644	0.085	0.959	0.127
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	**6.813** [1)]	**0.882** [1)]	-	-	**6.813** [1)]	**0.888** [2)]	-	-
minimal	March-May	6.813	0.881	-	-	6.813	0.886	-	-
average	March-May	6.813	0.880	-	-	6.813	0.883	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	3.669	0.476	4.769	0.620	3.669	0.477	4.769	0.622
full canopy	June-Sep	3.669	0.474	4.769	0.619	3.669	0.475	4.769	0.620
full canopy	Oct-Feb	3.669	0.477	4.769	0.622	3.669	0.476	4.769	0.621
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.460	0.062	0.893	0.119	0.468	0.065	0.893	0.122
average	June-Sep	0.460	0.061	0.893	0.118	0.460	0.062	0.893	0.119
full canopy	June-Sep	0.460	0.060	0.893	0.117	0.460	0.061	0.893	0.118
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.736	0.100	1.429	0.190	0.749	0.105	1.429	0.195
average	June-Sep	0.736	0.098	1.429	0.189	0.736	0.100	1.429	0.190
full canopy	June-Sep	0.736	0.097	1.429	0.187	0.736	0.098	1.429	0.188
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.552	0.075	1.072	0.143	0.562	0.079	1.072	0.147
average	June-Sep	0.552	0.074	1.072	0.142	0.552	0.075	1.072	0.143
full canopy	June-Sep	0.552	0.073	1.072	0.141	0.552	0.073	1.072	0.141

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-25: Initial PECsw and PECsed values of TFNG-AM for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
average	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
full canopy	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
average	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
full canopy	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
minimal	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
average	March-May	< 0.001	< 0.001	-	-	< 0.001	< 0.001	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
full canopy	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
full canopy	Oct-Feb	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
average	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
full canopy	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
average	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
full canopy	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
average	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
full canopy	June-Sep	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Table 2.8.7.3-26: Initial PECsw and PECsed values of TFNG for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.028	< 0.001	0.048	< 0.001	0.029	< 0.001	0.049	< 0.001
average	June-Sep	0.028	< 0.001	0.048	< 0.001	0.029	< 0.001	0.048	< 0.001
full canopy	June-Sep	0.027	< 0.001	0.047	< 0.001	0.027	< 0.001	0.047	< 0.001
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.028	< 0.001	0.048	< 0.001	0.029	< 0.001	0.049	< 0.001
average	June-Sep	0.028	< 0.001	0.048	< 0.001	0.029	< 0.001	0.048	< 0.001
full canopy	June-Sep	0.027	< 0.001	0.047	< 0.001	0.027	< 0.001	0.047	< 0.001
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	0.281	0.004	-	-	**0.283** [1)]	**0.004** [1)]	-	-
minimal	March-May	0.281	0.004	-	-	0.282	0.004	-	-
average	March-May	0.281	0.004	-	-	0.281	0.004	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.151	0.002	0.231	0.003	0.151	0.002	0.232	0.003
full canopy	June-Sep	0.151	0.002	0.231	0.003	0.151	0.002	0.231	0.003
full canopy	Oct-Feb	0.152	0.002	0.232	0.003	0.152	0.002	0.232	0.003
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.020	< 0.001	0.042	< 0.001	0.021	< 0.001	0.043	< 0.001
average	June-Sep	0.020	< 0.001	0.042	< 0.001	0.020	< 0.001	0.042	< 0.001
full canopy	June-Sep	0.019	< 0.001	0.042	< 0.001	0.019	< 0.001	0.042	< 0.001
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.032	< 0.001	0.068	0.001	0.034	< 0.001	0.069	0.001
average	June-Sep	0.031	< 0.001	0.067	0.001	0.032	< 0.001	0.068	0.001
full canopy	June-Sep	0.031	< 0.001	0.067	0.001	0.031	< 0.001	0.067	0.001
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.024	< 0.001	0.051	0.001	0.025	< 0.001	0.052	0.001
average	June-Sep	0.023	< 0.001	0.050	0.001	0.024	< 0.001	0.051	0.001
full canopy	June-Sep	0.023	< 0.001	0.050	0.001	0.023	< 0.001	0.050	0.001

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-27: Initial PECsw and PECsed values of TFNA for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.126	0.002	0.167	0.002	0.164	0.002	0.204	0.003
average	June-Sep	0.126	0.002	0.167	0.002	0.145	0.002	0.185	0.002
full canopy	June-Sep	0.102	0.001	0.143	0.002	0.110	0.001	0.150	0.002
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.126	0.002	0.167	0.002	0.164	0.002	0.204	0.003
average	June-Sep	0.126	0.002	0.167	0.002	0.145	0.002	0.185	0.002
full canopy	June-Sep	0.102	0.001	0.143	0.002	0.110	0.002	0.150	0.002
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	1.017	0.013	-	-	**1.030** [1)]	**0.013** [1)]	-	-
minimal	March-May	1.017	0.012	-	-	1.017	0.013	-	-
average	March-May	1.017	0.012	-	-	1.017	0.013	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.548	0.007	0.696	0.009	0.548	0.007	0.696	0.009
full canopy	June-Sep	0.548	0.007	0.696	0.008	0.548	0.007	0.696	0.009
full canopy	Oct-Feb	0.548	0.008	0.696	0.009	0.548	0.007	0.696	0.009
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.089	0.001	0.146	0.002	0.114	0.001	0.172	0.002
average	June-Sep	0.080	0.001	0.138	0.002	0.089	0.001	0.146	0.002
full canopy	June-Sep	0.073	0.001	0.132	0.002	0.078	0.001	0.136	0.002
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.142	0.002	0.234	0.003	0.182	0.002	0.275	0.004
average	June-Sep	0.128	0.002	0.221	0.003	0.142	0.002	0.234	0.003
full canopy	June-Sep	0.117	0.002	0.210	0.003	0.125	0.002	0.218	0.003
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.106	0.001	0.176	0.002	0.137	0.002	0.206	0.003
average	June-Sep	0.096	0.001	0.158	0.002	0.106	0.001	0.176	0.002
full canopy	June-Sep	0.088	0.001	0.166	0.002	0.094	0.001	0.164	0.002

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-28: Initial PECsw and PECsed values of TFNA-OH for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.309	0.006	0.345	0.007	0.546	0.011	0.582	0.011
average	June-Sep	0.309	0.006	0.345	0.007	0.428	0.008	0.241	0.005
full canopy	June-Sep	0.161	0.003	0.196	0.004	0.205	0.004	0.463	0.009
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.309	0.006	0.345	0.007	0.546	0.011	0.582	0.011
average	June-Sep	0.309	0.006	0.345	0.007	0.428	0.008	0.463	0.009
full canopy	June-Sep	0.161	0.003	0.196	0.004	0.205	0.004	0.241	0.005
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	1.058	0.021	-	-	**1.354** [1)]	**0.027** [1)]	-	-
minimal	March-May	0.998	0.020	-	-	1.235	0.024	-	-
average	March-May	0.939	0.018	-	-	1.117	0.022	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.588	0.012	0.712	0.014	0.677	0.013	0.801	0.016
full canopy	June-Sep	0.514	0.010	0.638	0.013	0.566	0.011	0.690	0.014
full canopy	Oct-Feb	0.669	0.013	0.794	0.016	0.617	0.012	0.742	0.015
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.210	0.004	0.277	0.005	0.369	0.007	0.454	0.009
average	June-Sep	0.157	0.003	0.218	0.004	0.210	0.004	0.277	0.005
full canopy	June-Sep	0.115	0.002	0.171	0.003	0.147	0.003	0.206	0.004
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.336	0.007	0.443	0.009	0.590	0.012	0.726	0.014
average	June-Sep	0.252	0.005	0.349	0.007	0.336	0.007	0.443	0.009
full canopy	June-Sep	0.184	0.004	0.274	0.005	0.235	0.005	0.330	0.007
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.252	0.005	0.332	0.007	0.443	0.009	0.544	0.011
average	June-Sep	0.189	0.004	0.262	0.005	0.252	0.005	0.332	0.007
full canopy	June-Sep	0.138	0.003	0.205	0.004	0.176	0.004	0.248	0.005

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-29: Initial PECsw and PECsed values of TFNA-AM for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.059	0.003	0.071	0.004	0.101	0.006	0.113	0.006

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
average	June-Sep	0.059	0.003	0.071	0.004	0.080	0.005	0.092	0.005
full canopy	June-Sep	0.032	0.002	0.044	0.003	0.040	0.002	0.052	0.003
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.059	0.003	0.071	0.004	0.101	0.006	0.113	0.006
average	June-Sep	0.059	0.003	0.071	0.004	0.080	0.005	0.092	0.005
full canopy	June-Sep	0.032	0.002	0.044	0.003	0.040	0.002	0.052	0.003
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	0.222	0.012	-	-	**0.275** [1)]	**0.013** [1)]	-	-
minimal	March-May	0.211	0.010	-	-	0.254	0.012	-	-
average	March-May	0.200	0.010	-	-	0.232	0.013	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.123	0.006	0.171	0.008	0.139	0.007	0.187	0.006
full canopy	June-Sep	0.109	0.005	0.158	0.008	0.119	0.006	0.167	0.005
full canopy	Oct-Feb	0.137	0.007	0.185	0.009	0.128	0.006	0.176	0.007
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.040	0.002	0.055	0.003	0.068	0.003	0.085	0.004
average	June-Sep	0.030	0.002	0.045	0.003	0.040	0.002	0.055	0.003
full canopy	June-Sep	0.023	0.001	0.037	0.002	0.029	0.001	0.043	0.002
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.064	0.003	0.088	0.004	0.110	0.005	0.136	0.007
average	June-Sep	0.049	0.002	0.072	0.004	0.064	0.003	0.088	0.004
full canopy	June-Sep	0.037	0.002	0.059	0.004	0.046	0.002	0.069	0.003
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.048	0.002	0.066	0.003	0.082	0.004	0.102	0.005
average	June-Sep	0.037	0.002	0.054	0.003	0.048	0.002	0.066	0.003
full canopy	June-Sep	0.027	0.001	0.044	0.002	0.034	0.002	0.051	0.003

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-30: Initial PECsw and PECsed values of TFA for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.416	< 0.001	0.825	< 0.001	0.833	< 0.001	1.650	< 0.001
average	June-Sep	0.416	< 0.001	0.825	< 0.001	0.624	< 0.001	1.237	< 0.001
full canopy	June-Sep	0.156	< 0.001	0.309	< 0.001	0.234	< 0.001	0.464	< 0.001
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.416	< 0.001	0.825	< 0.001	0.833	< 0.001	1.650	< 0.001
average	June-Sep	0.416	< 0.001	0.825	< 0.001	0.624	< 0.001	1.237	< 0.001
full canopy	June-Sep	0.156	< 0.001	0.309	< 0.001	0.234	< 0.001	0.464	< 0.001
Pome/stone fruit early, 1 x 70 g a.s./ha									

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
no interception	March-May	0.520	< 0.001	-	-	1.041	< 0.001	-	-
minimal	March-May	0.416	< 0.001	-	-	0.833	< 0.001	-	-
average	March-May	0.312	< 0.001	-	-	0.624	< 0.001	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.312	< 0.001	0.619	< 0.001	0.468	< 0.001	0.928	< 0.001
full canopy	June-Sep	0.182	< 0.001	0.361	< 0.001	0.273	< 0.001	0.541	< 0.001
full canopy	Oct-Feb	0.455	< 0.001	0.902	< 0.001	0.364	< 0.001	0.722	< 0.001
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.279	< 0.001	0.831	< 0.001	0.558	< 0.001	1.662	< 0.001
average	June-Sep	0.186	< 0.001	0.554	< 0.001	0.279	< 0.001	0.831	< 0.001
full canopy	June-Sep	0.112	< 0.001	0.332	< 0.001	0.167	< 0.001	0.499	< 0.001
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.446	< 0.001	1.330	< 0.001	0.892	< 0.001	**2.659** [1)]	**< 0.001** [1)]
average	June-Sep	0.297	< 0.001	0.886	< 0.001	0.446	< 0.001	1.330	< 0.001
full canopy	June-Sep	0.178	< 0.001	0.532	< 0.001	0.268	< 0.001	0.798	< 0.001
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.334	< 0.001	0.993	< 0.001	0.668	< 0.001	1.986	< 0.001
average	June-Sep	0.223	< 0.001	0.662	< 0.001	0.334	< 0.001	0.993	< 0.001
full canopy	June-Sep	0.134	< 0.001	0.397	< 0.001	0.200	< 0.001	0.596	< 0.001

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Step 1 and Step 2 – <u>Parameter Set 2</u>

The maximum predicted environmental concentration of Flonicamid and its metabolites in surface water (PECsw) and sediment (PECsed) are summarised in Table 2.8.7.3-31 for Step 1 and in Tables 2.8.7.3-32 to 2.8.7.3-38 for Step 2.

Table 2.8.7.3-31: Initial PECsw and PECsed values of Flonicamid and its metabolites for Step 1

FOCUS Crop	Crops covered	Application rate [kg a.s./ha]	PECsw [µg/L]	PECsed [µg/kg]
Flonicamid				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	47.081	6.549
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	47.081	6.549
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	29.709	3.274
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	53.132	6.549

FOCUS Crop	Crops covered	Application rate [kg a.s./ha]	PECsw [µg/L]	PECsed [µg/kg]
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	50.444	7.016
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	80.710	11.226
Vegetables fruiting (F, G)	Tomatoes/ eggplants (F, G)	3 x 0.06	60.533	8.420
TFNG-AM				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	6.276	0.496
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	6.276	0.496
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	3.138	0.248
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	6.276	0.496
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	6.724	0.531
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	10.758	0.850
Vegetables fruiting (F, G)	Tomatoes/ eggplants (F, G)	3 x 0.06	8.069	0.637
TFNG				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	27.850	0.361
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	27.850	0.361
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	14.179	0.181
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	28.099	0.361
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	29.839	0.387
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	47.742	0.620
Vegetables fruiting (F, G)	Tomatoes/ eggplants (F, G)	3 x 0.06	35.807	0.465
TFNA				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	27.498	0.355
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	27.498	0.355
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	14.670	0.178
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	28.401	0.355
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	29.462	0.380
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	47.140	0.609

FOCUS Crop	Crops covered	Application rate [kg a.s./ha]	PECsw [µg/L]	PECsed [µg/kg]
Vegetables fruiting (F, G)	Tomatoes/ eggplants (F, G)	3 x 0.06	35.355	0.456
TFNA-OH				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	16.388	0.325
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	16.388	0.325
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	8.935	0.162
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	17.115	0.325
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	17.559	0.348
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	28.094	0.557
Vegetables fruiting (F, G)	Tomatoes/ eggplants (F, G)	3 x 0.06	21.070	0.417
TFNA-AM				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	4.108	0.200
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	4.108	0.200
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	2.208	0.100
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	4.259	0.200
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	4.402	0.214
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	7.043	0.342
Vegetables fruiting (F, G)	Tomatoes/ eggplants (F, G)	3 x 0.06	5.282	0.257
TFA				
Spring cereals	Spring wheat (SEZ, CEZ, NEZ)	2 x 0.07	5.223	< 0.001
Winter cereals	Winter wheat (SEZ, CEZ, NEZ)	2 x 0.07	5.223	< 0.001
Pome/stone fruit early	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	1 x 0.07	2.611	< 0.001
Pome/stone fruit late	Apple, pears (SEZ, CEZ, NEZ) Peaches (SEZ) Peaches, apricots (CEZ) Plums (CEZ, SEZ) Cherries (CEZ, SEZ)	2 x 0.07	5.223	< 0.001
Vegetables fruiting (F, G)	Melon (F)	3 x 0.05	5.596	< 0.001
Vegetables fruiting (G)	Cucumber/ courgette (F, G)	3 x 0.08	8.953	< 0.001
Vegetables fruiting (F, G)	Tomatoes/ eggplants (F, G)	3 x 0.06	6.715	< 0.001

Table 2.8.7.3-32: **Initial PECsw and PECsed values of Flonicamid for Step 2**

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.644	0.088	0.959	0.129	0.660	0.092	0.959	0.133
average	June-Sep	0.644	0.088	0.959	0.129	0.644	0.090	0.959	0.131
full canopy	June-Sep	0.644	0.085	0.959	0.126	0.644	0.085	0.959	0.127
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.644	0.088	0.959	0.129	0.660	0.092	0.959	0.133
average	June-Sep	0.644	0.088	0.959	0.129	0.644	0.090	0.959	0.131
full canopy	June-Sep	0.644	0.085	0.959	0.126	0.644	0.085	0.959	0.127
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	**6.813** [1)]	**0.882** [1)]	-	-	**6.813** [2)]	**0.888** [2)]	-	-
minimal	March-May	6.813	0.881	-	-	6.813	0.886	-	-
average	March-May	6.813	0.880	-	-	6.813	0.883	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	3.669	0.476	4.769	0.620	3.669	0.477	4.769	0.622
full canopy	June-Sep	3.669	0.474	4.769	0.619	3.669	0.475	4.769	0.620
full canopy	Oct-Feb	3.669	0.477	4.769	0.622	3.669	0.476	4.769	0.621
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.460	0.062	0.893	0.119	0.468	0.065	0.893	0.122
average	June-Sep	0.460	0.061	0.893	0.118	0.460	0.062	0.893	0.119
full canopy	June-Sep	0.460	0.060	0.893	0.117	0.460	0.061	0.893	0.118
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.736	0.100	1.429	0.190	0.749	0.105	1.429	0.195
average	June-Sep	0.736	0.098	1.429	0.189	0.736	0.100	1.429	0.190
full canopy	June-Sep	0.736	0.097	1.429	0.187	0.736	0.098	1.429	0.188
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.552	0.075	1.072	0.143	0.562	0.079	1.072	0.147
average	June-Sep	0.552	0.074	1.072	0.142	0.552	0.075	1.072	0.143
full canopy	June-Sep	0.552	0.073	1.072	0.141	0.552	0.073	1.072	0.141

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-33: Initial PECsw and PECsed values of TFNG-AM for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
average	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
full canopy	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
average	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
full canopy	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	<0.001	<0.001	-	-	**<0.001** [1)]	**<0.001** [1)]	-	-
minimal	March-May	<0.001	<0.001	-	-	<0.001	<0.001	-	-
average	March-May	<0.001	<0.001	-	-	<0.001	<0.001	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
full canopy	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
full canopy	Oct-Feb	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
average	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
full canopy	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
average	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
full canopy	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
average	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001
full canopy	June-Sep	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001	<0.001	<0.001

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-34: Initial PECsw and PECsed values of TFNG for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.028	< 0.001	0.048	< 0.001	0.029	< 0.001	0.049	< 0.001
average	June-Sep	0.028	< 0.001	0.048	< 0.001	0.029	< 0.001	0.048	< 0.001
full canopy	June-Sep	0.027	< 0.001	0.047	< 0.001	0.027	< 0.001	0.047	< 0.001
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.028	< 0.001	0.048	< 0.001	0.029	< 0.001	0.049	< 0.001
average	June-Sep	0.028	< 0.001	0.048	< 0.001	0.029	< 0.001	0.048	< 0.001
full canopy	June-Sep	0.027	< 0.001	0.047	< 0.001	0.027	< 0.001	0.047	< 0.001
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	0.281	0.004	-	-	**0.283** [1)]	**0.004** [1)]	-	-
minimal	March-May	0.281	0.004	-	-	0.282	0.004	-	-
average	March-May	0.280	0.004	-	-	0.281	0.004	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.151	0.002	0.231	0.003	0.152	0.002	0.232	0.003
full canopy	June-Sep	0.151	0.002	0.231	0.003	0.151	0.002	0.231	0.003
full canopy	Oct-Feb	0.152	0.002	0.232	0.003	0.152	0.002	0.232	0.003
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.020	< 0.001	0.042	< 0.001	0.021	< 0.001	0.043	< 0.001
average	June-Sep	0.020	< 0.001	0.042	< 0.001	0.020	< 0.001	0.042	< 0.001
full canopy	June-Sep	0.019	< 0.001	0.042	< 0.001	0.019	< 0.001	0.042	< 0.001
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.032	0.000	0.068	0.001	0.033	0.000	0.069	0.001
average	June-Sep	0.031	0.000	0.067	0.001	0.032	0.000	0.068	0.001
full canopy	June-Sep	0.031	0.000	0.067	0.001	0.031	0.000	0.067	0.001
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.024	< 0.001	0.051	< 0.001	0.025	< 0.001	0.052	< 0.001
average	June-Sep	0.023	< 0.001	0.050	< 0.001	0.024	< 0.001	0.051	< 0.001
full canopy	June-Sep	0.023	< 0.001	0.050	< 0.001	0.023	< 0.001	0.050	< 0.001

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-35: Initial PECsw and PECsed values of TFNA for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.126	0.002	0.167	0.002	0.164	0.002	0.204	0.003
average	June-Sep	0.126	0.002	0.167	0.002	0.145	0.002	0.185	0.002
full canopy	June-Sep	0.103	0.001	0.143	0.002	0.110	0.001	0.150	0.002
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.126	0.002	0.167	0.002	0.164	0.002	0.204	0.003
average	June-Sep	0.126	0.002	0.167	0.002	0.145	0.002	0.185	0.002
full canopy	June-Sep	0.103	0.001	0.143	0.002	0.110	0.001	0.150	0.002
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	1.017	0.013	-	-	**1.030** [1)]	**0.013** [1)]	-	-
minimal	March-May	1.017	0.012	-	-	1.017	0.013	-	-
average	March-May	1.017	0.012	-	-	1.017	0.013	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.548	0.007	0.696	0.009	0.548	0.007	0.696	0.009
full canopy	June-Sep	0.548	0.007	0.696	0.008	0.548	0.007	0.696	0.009
full canopy	Oct-Feb	0.548	0.007	0.696	0.009	0.548	0.007	0.696	0.009
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.089	0.001	0.146	0.002	0.114	0.001	0.172	0.002
average	June-Sep	0.080	0.001	0.138	0.002	0.089	0.001	0.146	0.002
full canopy	June-Sep	0.073	< 0.001	0.132	0.002	0.078	0.001	0.136	0.002
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.142	0.002	0.234	0.003	0.182	0.002	0.275	0.004
average	June-Sep	0.128	0.002	0.221	0.003	0.142	0.002	0.234	0.003
full canopy	June-Sep	0.117	0.002	0.210	0.003	0.125	0.002	0.218	0.003
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.106	0.001	0.176	0.002	0.137	0.002	0.206	0.003
average	June-Sep	0.096	0.001	0.166	0.002	0.106	0.001	0.176	0.002
full canopy	June-Sep	0.088	0.001	0.158	0.002	0.094	0.001	0.164	0.002

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-36: Initial PECsw and PECsed values of TFNA-OH for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.269	0.005	0.305	0.006	0.467	0.009	0.502	0.010
average	June-Sep	0.269	0.005	0.305	0.006	0.368	0.007	0.403	0.008
full canopy	June-Sep	0.146	0.003	0.181	0.004	0.183	0.004	0.218	0.004
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.269	0.005	0.305	0.006	0.467	0.009	0.502	0.010
average	June-Sep	0.269	0.005	0.305	0.006	0.368	0.007	0.403	0.008
full canopy	June-Sep	0.146	0.003	0.181	0.004	0.183	0.004	0.218	0.004
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	1.008	0.020	-	-	**1.255** [1)]	**0.025** [1)]	-	-
minimal	March-May	0.959	0.019	-	-	1.156	0.023	-	-
average	March-May	0.909	0.018	-	-	1.057	0.021	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.558	0.011	0.682	0.013	0.632	0.012	0.756	0.015
full canopy	June-Sep	0.496	0.010	0.620	0.012	0.539	0.011	0.664	0.013
full canopy	Oct-Feb	0.626	0.012	0.750	0.015	0.583	0.011	0.707	0.014
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.184	0.004	0.243	0.005	0.316	0.006	0.385	0.008
average	June-Sep	0.140	0.003	0.195	0.004	0.184	0.004	0.243	0.005
full canopy	June-Sep	0.104	0.002	0.157	0.003	0.131	0.003	0.186	0.004
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.294	0.006	0.389	0.008	0.505	0.010	0.617	0.012
average	June-Sep	0.223	0.004	0.313	0.006	0.294	0.006	0.389	0.008
full canopy	June-Sep	0.167	0.003	0.252	0.005	0.209	0.004	0.297	0.006
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.220	0.004	0.292	0.006	0.379	0.007	0.463	0.009
average	June-Sep	0.167	0.003	0.234	0.005	0.220	0.004	0.292	0.006
full canopy	June-Sep	0.125	0.003	0.189	0.004	0.157	0.003	0.223	0.004

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-37: Initial PECsw and PECsed values of TFNA-AM for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.104	0.005	0.117	0.006	0.193	0.009	0.206	0.010
average	June-Sep	0.104	0.005	0.117	0.006	0.148	0.007	0.161	0.008
full canopy	June-Sep	0.049	0.002	0.061	0.003	0.066	0.003	0.078	0.004
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.104	0.005	0.117	0.006	0.193	0.009	0.206	0.010
average	June-Sep	0.104	0.005	0.117	0.006	0.148	0.007	0.161	0.008
full canopy	June-Sep	0.049	0.002	0.061	0.003	0.066	0.003	0.078	0.004
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	0.279	0.014	-	-	**0.389** [1)]	**0.019** [1)]	-	-
minimal	March-May	0.257	0.013	-	-	0.345	0.017	-	-
average	March-May	0.235	0.012	-	-	0.301	0.015	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.157	0.008	0.205	0.010	0.190	0.009	0.239	0.012
full canopy	June-Sep	0.129	0.006	0.178	0.009	0.149	0.007	0.197	0.010
full canopy	Oct-Feb	0.187	0.009	0.236	0.012	0.168	0.008	0.217	0.011
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.071	0.004	0.096	0.005	0.130	0.006	0.168	0.008
average	June-Sep	0.051	0.003	0.073	0.004	0.071	0.004	0.096	0.005
full canopy	June-Sep	0.035	0.002	0.054	0.003	0.047	0.002	0.068	0.003
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.113	0.006	0.154	0.008	0.207	0.010	0.269	0.013
average	June-Sep	0.081	0.004	0.116	0.006	0.113	0.006	0.154	0.008
full canopy	June-Sep	0.056	0.003	0.086	0.004	0.075	0.004	0.108	0.005
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.085	0.004	0.116	0.006	0.156	0.008	0.201	0.010
average	June-Sep	0.061	0.003	0.087	0.004	0.085	0.004	0.116	0.006
full canopy	June-Sep	0.042	0.002	0.064	0.003	0.056	0.003	0.081	0.004

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-38: Initial PECsw and PECsed values of TFA for Step 2

Crop cover	Season	Northern Europe				Southern Europe			
		single		multiple		single		multiple	
		PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]	PECsw [µg/L]	PECsed [µg/kg]
Spring cereals, 2 x 70 g a.s./ha									
average	March-May	0.416	< 0.001	0.819	< 0.001	0.831	< 0.001	1.639	< 0.001
average	June-Sep	0.416	< 0.001	0.819	< 0.001	0.623	< 0.001	1.229	< 0.001
full canopy	June-Sep	0.156	< 0.001	0.307	< 0.001	0.234	< 0.001	0.461	< 0.001
Winter cereals, 2 x 70 g a.s./ha									
average	March-May	0.416	< 0.001	0.819	< 0.001	0.831	< 0.001	1.639	< 0.001
average	June-Sep	0.416	< 0.001	0.819	< 0.001	0.623	< 0.001	1.229	< 0.001
full canopy	June-Sep	0.156	< 0.001	0.307	< 0.001	0.234	< 0.001	0.461	< 0.001
Pome/stone fruit early, 1 x 70 g a.s./ha									
no interception	March-May	0.519	< 0.001	-	-	1.039	< 0.001	-	-
minimal	March-May	0.416	< 0.001	-	-	0.831	< 0.001	-	-
average	March-May	0.312	< 0.001	-	-	0.623	< 0.001	-	-
Pome/stone fruit late, 2 x 70 g a.s./ha									
average	June-Sep	0.312	< 0.001	0.614	< 0.001	0.468	< 0.001	0.922	< 0.001
full canopy	June-Sep	0.182	< 0.001	0.358	< 0.001	0.273	< 0.001	0.538	< 0.001
full canopy	Oct-Feb	0.455	< 0.001	0.896	< 0.001	0.364	< 0.001	0.717	< 0.001
Vegetables fruiting, 3 x 50 g a.s./ha									
minimal	March-May	0.278	< 0.001	0.827	< 0.001	0.557	< 0.001	1.654	< 0.001
average	June-Sep	0.186	< 0.001	0.551	< 0.001	0.278	< 0.001	0.827	< 0.001
full canopy	June-Sep	0.111	< 0.001	0.331	< 0.001	0.167	< 0.001	0.496	< 0.001
Vegetables fruiting, 3 x 80 g a.s./ha									
minimal	March-May	0.445	< 0.001	1.323	< 0.001	0.890	< 0.001	**2.646** [1)]	**< 0.001** [1)]
average	June-Sep	0.297	< 0.001	0.882	< 0.001	0.445	< 0.001	1.323	< 0.001
full canopy	June-Sep	0.178	< 0.001	0.529	< 0.001	0.267	< 0.001	0.794	< 0.001
Vegetables fruiting, 3 x 60 g a.s./ha									
minimal	March-May	0.334	<0.001	0.992	<0.001	0.668	<0.001	1.984	<0.001
average	June-Sep	0.227	<0.001	0.661	<0.001	0.334	<0.001	0.992	<0.001
full canopy	June-Sep	0.134	<0.001	0.397	<0.001	0.200	<0.001	0.595	<0.001

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 2 are found in Table B.8.5-49

Predicted environmental concentrations in surface water (PECsw) and sediment (PECsed)

Step 3

Notice! **Step 3 modelling is not necessary for the aquatic risk assessment.**
Step 3 PECsw values were provided only for flonicamid. PECsw/sed for the parent were not re-calculated with the new two sets of input parameters used for Step 1 and 2 as parameters used previously for Step 3 represent already the worst case with respect to DT_{50} (0.61 days instead of revised 0.59 days) and Koc (5.4 mL/g instead of 14.3 mL/g) obtained with the EFSA OECD 106 Calculator.

Formulation (IKI-220 100 OD)

The calculation of the predicted environmental concentrations of Flonicamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA in surface water and sediment was based on the recommendations provided in the Report FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC FOCUS (2003) and the FOCUS Generic Guidance for FOCUS Surface Water Scenarios FOCUS (2012, 2014, 2015) under consideration of the recommendations by EFSA (2014). using FOCUS software: FOCUS SWASH 5.3, FOCUS MACRO 5.5.4, FOCUS PRZM SW 4.3.1 and FOCUS TOXSWA 5.5.3.

Relevant use information and application rates for Flonicamid according to GAP is presented in Table 2.8.7.3-39. In Step 3, scenarios representative for the uses within the EU were selected. The resulting application times reflect conservative assumptions regarding the application times as intended by the GAP (Table 2.8.7.3-40).

Table 2.8.7.3-39: Representative GAP for Flonicamid (IKI-220 100 OD)

FOCUS Crop(s)	Crops covered	Growth stage (BBCH)	Number of applications (Minimum interval)	Application rate per treatment [kg a.s./ha]
Field beans	Beans	BBCH 11 - 71	1	0.05
Legumes	Peas	BBCH 11 - 71	1	0.05
Winter and spring cereals	Winter and spring wheat, rye, triticale	BBCH 39 - PHI	1	0.05

Table 2.8.7.3-40: Crops, timings for Step 3 for Flonicamid (IKI-220 100 OD)

FOCUS Crop(s)	Use(s) covered	Details	Application rate [kg a.s./ha]
Field beans	Dry beans SEZ, CEZ	Beans early, single	1 x 0.05
		Beans late, single	
Legumes	Dry peas	Peas early, single	1 x 0.05
		Peas late, single	
Cereals	Winter cereals covering winter wheat, rye, triticale SEZ, CEZ	Winter cereals, early	1 x 0.05
		Winter cereals, late	
	Spring cereals covering spring wheat, rye, triticale SEZ, CEZ	Spring cereals, early	1 x 0.05
		Spring cereals, late	

At Step 3, the Pesticide Application Timing calculator (PAT) which is implemented in the FOCUS models was used to determine the exact application dates. The application windows were calculated according to FOCUS recommendations using the following formula: Application Window = 30 d + (number of applications - 1) x application interval. The application windows were selected to cover the growth stages as well as worst-case assumptions according to the GAP. The application period was determined for each scenario from the earliest BBCH stages upwards for early applications and from the PHI (pre-harvest interval) downwards for later applications.

For the application in peas, the start at BBCH 11 was considered 3 days after emergence. The late application at BBCH 71 was considered to be 30 d before harvest covering the late use for peas. For the application in beans, for the start of the application window with BBCH 11 emergence plus 4 days was considered. For the late applications until BBCH 71, the application window was set to end 30 days before harvest which is equivalent to BBCH 71.

For the applications in spring wheat, the early applications as BBCH 39 were considered to start 30 d after emergence and the late application window as set to end 28 days before harvest.

According to GAP, the application in winter wheat is considered between BBCH 39 and 28 d before harvest (PHI). For BBCH 39, the spring point for winter cereals taken from the FOCUS recommendations for groundwater was transferred to 3.5 months (105 d) before harvest. The late application window was set to end with the PHI of 28 d before harvest.

Application windows and the PAT selected dates for the different crops and scenarios can be found in CP, Volume B.8.5.

The initial PECsw of Flonicamid (i.e., global maximum concentration) resulting from an entry to the water bodies via spray-drift, run-off and drainage without applying mitigation measures (Step 3) are given in Tables 2.8.7.3-41 to 2.8.7.3-48. The worst case PECsw value obtained from modelled scenarios was used for calculation of actual and TWA PECsw and PECsed values. These values can be find in CP, Volume 3, B.8.5.

Table 2.8.7.3-41: FOCUS Step 3 PECsw and PECsed for <u>Flonicamid</u> following single application of IKI-220 100 OD to <u>beans, early</u> 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D2	Ditch	**0.646** [1)]	Drainage	**0.070** [1)]
D2	Stream	0.463	Drainage	0.029
D3	Ditch	0.262	Spray-drift	0.020
D4	Pond	0.011	Spray-drift	0.004
D4	Stream	0.211	Spray-drift	0.004
D6	Ditch	0.261	Spray-drift	0.016
D6	Ditch	0.257	Spray-drift	0.010
R1	Pond	0.011	Spray-drift	0.004
R1	Stream	0.181	Spray-drift	0.006
R2	Stream	0.261	Run-off	0.015
R3	Stream	0.373	Run-off	0.034
R4	Stream	0.299	Run-off	0.024

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in Table B.8.5

Table 2.8.7.3-42: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 100 OD to beans, late 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D2	Ditch	0.818	Drainage	0.315
D2	Stream	**2.787** [1)]	Drainage	**0.644** [1)]
D3	Ditch	0.263	Spray-drift	0.023
D4	Pond	0.011	Spray-drift	0.004
D4	Stream	0.236	Spray-drift	0.009
D6	Ditch	0.259	Spray-drift	0.012
D6	Ditch	0.259	Spray-drift	0.012
R1	Pond	0.060	Run-off	0.022
R1	Stream	1.315	Run-off	0.082
R2	Stream	0.244	Spray-drift	0.006
R3	Stream	0.992	Run-off	0.089
R4	Stream	0.686	Run-off	0.055

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in Table B.8.5

Table 2.8.7.3-43: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 100 OD to legumes covering peas, early 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
D3	Ditch	**0.262** [1)]	Spray-drift	**0.019** [1)]
D4	Pond	0.011	Spray-drift	0.004
D4	Stream	0.213	Spray-drift	0.004
D5	Pond	0.011	Spray-drift	0.004
D5	Stream	0.218	Spray-drift	0.003
D6	Ditch	0.262	Spray-drift	0.020
R1	Pond	0.011	Spray-drift	0.004
R1	Stream	0.181	Spray-drift	0.006
R2	Stream	0.241	Spray-drift	0.005
R3	Stream	0.257	Spray-drift	0.012
R4	Stream	0.253	Run-off	0.020

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in Table B.8.5

Table 2.8.7.3-44: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 100 OD to legumes covering peas, late 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D3	Ditch	0.262	Spray-drift	0.019
D4	Pond	0.011	Spray-drift	0.004
D4	Stream	0.217	Spray-drift	0.004
D5	Pond	0.011	Spray-drift	0.004
D5	Stream	0.248	Spray-drift	0.007
D6	Ditch	0.259	Spray-drift	0.013
R1	Pond	0.035	Run-off	0.013
R1	Stream	**1.219** [1)]	Run-off	**0.077** [1)]
R2	Stream	0.241	Spray-drift	0.006
R3	Stream	0.257	Spray-drift	0.012
R4	Stream	0.253	Run-off	0.020

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in Table B.8.5

Table 2.8.7.3-45: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 100 OD to winter cereals, early 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.339	Spray-drift	0.107
D1	Stream	0.286	Spray-drift	0.021
D2	Ditch	**5.555** [1)]	Drainage	**0.488** [1)]

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
D2	Stream	3.481	Drainage	0.259
D3	Ditch	0.317	Spray-drift	0.023
D4	Pond	0.011	Spray-drift	0.004
D4	Stream	0.264	Spray-drift	0.007
D5	Pond	0.011	Spray-drift	0.004
D5	Stream	0.253	Spray-drift	0.004
D6	Ditch	0.319	Spray-drift	0.037
R1	Pond	0.011	Spray-drift	0.005
R1	Stream	0.209	Spray-drift	0.010
R3	Stream	0.293	Spray-drift	0.012
R4	Stream	0.543	Run-off	0.039

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in Table B.8.5

Table 2.8.7.3-46 : FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 100 OD to winter cereals, late 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.331	Spray-drift	0.117
D1	Stream	0.281	Spray-drift	0.026
D2	Ditch	0.322	Spray-drift	0.117
D2	Stream	0.286	Spray-drift	0.095
D3	Ditch	0.318	Spray-drift	0.025
D4	Pond	0.011	Spray-drift	0.004
D4	Stream	0.274	Spray-drift	0.011
D5	Pond	0.011	Spray-drift	0.004
D5	Stream	0.296	Spray-drift	0.014
D6	Ditch	0.320	Spray-drift	0.062
R1	Pond	0.113	Run-off	0.039
R1	Stream	0.789	Run-off	0.067
R3	Stream	**1.376** [1)]	Run-off	**0.086** [1)]
R4	Stream	0.210	Spray-drift	0.008

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in Table B.8.5

Table 2.8.7.3-47: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 100 OD to spring cereals, early 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
D1	Ditch	0.329	Spray-drift	0.113
D1	Stream	0.281	Spray-drift	0.023
D3	Ditch	0.317	Spray-drift	0.024
D4	Pond	0.011	Spray-drift	0.004
D4	Stream	0.259	Spray-drift	0.006
D5	Pond	0.011	Spray-drift	0.004
D5	Stream	0.266	Spray-drift	0.005
R4	Stream	**0.923** [1)]	Run-off	**0.066** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in Table B.8.5

Table 2.8.7.3-48: FOCUS Step 3 PECsw and PECsed for <u>Flonicamid</u> following single application of IKI-220 100 OD to <u>spring cereals, late</u> 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	**0.322** [1)]	Spray-drift	**0.108** [1)]
D1	Stream	0.281	Spray-drift	0.022
D3	Ditch	0.318	Spray-drift	0.027
D4	Pond	0.011	Spray-drift	0.004
D4	Stream	0.273	Spray-drift	0.011
D5	Pond	0.011	Spray-drift	0.004
D5	Stream	0.295	Spray-drift	0.014
R4	Stream	0.210	Spray-drift	0.008

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in Table B.8.5

Conclusion for Step 3:

The highest initial PECsw values of Flonicamid reached 5.555 µg/L for early application to winter cereals single (D2 ditch). Highest PECsed accounted for 0.644 µg/kg in late single application in beans (D2 stream).

Predicted environmental concentrations of the Step 1/2 and Step 3 calculations are considered in the aquatic ecotoxicological risk assessment in CP, Volume 3, B.9.4.

Formulation IKI-220 500 WG

The calculation of the predicted environmental concentrations of Floncamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-OH, TFNA-AM and TFA in surface water and sediment was based on the recommendations provided in the Report FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC FOCUS (2003) and the FOCUS Generic Guidance for FOCUS Surface Water Scenarios FOCUS (2012, 2014, 2015) under consideration of the recommendations by EFSA (2014). using FOCUS software: FOCUS SWASH 5.3, FOCUS MACRO 5.5.4, FOCUS PRZM SW 4.3.1 and FOCUS TOXSWA 5.5.3.

Relevant use information and application rates for Flonicamid according to GAP is presented in Table 2.8.7.3-49. In Step 3, scenarios representative for the uses within the EU were selected. The resulting application times reflect conservative assumptions regarding the application times as intended by the GAP (Table 2.8.7.3-50).

Table 2.8.7.3-49: Representative GAP for Flonicamid (IKI-220 500 WG)

FOCUS Crop(s)	Crops covered	Growth stage (BBCH)	Number of applications (Minimum interval)	Application rate per treatment [kg a.s./ha]
Winter and spring cereals	Winter and spring wheat	21 - 77/79 (NEZ) 37 - 77/79 (CEZ) 39 - 77/79 (SEZ)	1 - 2 (21 d)	0.07
Pome/stone fruit early	Apples, pears, peaches/apricots, plums, cherries	01/07 - 70	1	0.07
Pome/stone fruit late	Apples, pears, peaches/apricots, plums, cherries	71 - 85/87	1 - 2 (21 d)	0.07
Vegetables fruiting	Cucumber/courgette (F, G), melons (F)	15 - 85/87	3 (7 d)	0.05
Vegetables fruiting	Cucumber/courgette (G)	16/18 - 85/87	3 (7 d)	0.08
Vegetables fruiting	Tomato/eggplant (F, G)	16/18 - 85/87	3 (7 d)	0.06

Table 2.8.7.3-50: Crops, timings and projects for Step 3 for Flonicamid (IKI-220 500 WG)

FOCUS Crop(s)	Use(s) covered	Details	Application rate [kg a.s./ha]	Surface water project
Winter cereals	Wheat (SEZ, CEZ, NEZ)	w-cereals_early, CEZ+SEZ, multiple	2 x 0.07	Flo_WG_1
		w-cereals_late, CEZ, SEZ, NEZ, multiple		Flo_WG_2
		w-cereals_early NEZ, multiple		Flo_WG_3
		w-cereals_early, CEZ+SEZ, single	1 x 0.07	Flo_WG_4
		w-cereals_late, CEZ, SEZ, NEZ, single		Flo_WG_5
		w-cereals_early NEZ, single		Flo_WG_6
Spring cereals	Wheat (SEZ, CEZ, NEZ)	sp-cereals_early, CEZ+SEZ, multiple	2 x 0.07	Flo_WG_7
		sp-cereals_late, CEZ, SEZ, NEZ, multiple		Flo_WG_8
		sp-cereals_early NEZ, multiple		Flo_WG_9
		sp-cereals_early, CEZ+SEZ, single	1 x 0.07	Flo_WG_10
		sp-cereals_late, CEZ, SEZ, NEZ, single		Flo_WG_11
		sp-cereals_early NEZ, single		Flo_WG_12
Pome/stone fruit early	apples, pears, plums, peaches, apricots, cherries	apples_early, at emergence	1 x 0.07	Flo_WG_13
		apples_early, BBCH 70		Flo_WG_32
Pome/stone fruit late		apples_intermediate, single	1 x 0.07	Flo_WG_14
		apples_intermediate, multiple	2 x 0.07	Flo_WG_14_ multiple
		apples_late_multiple, 21d PHI	2 x 0.07	Flo_WG_15
		apples_late, single, 21d PHI	x 0.07	Flo_WG_16
		apples_late, single, 14d PHI	1 x 0.07	Flo_WG_17
		apples_late, multiple, 14d PHI	2 x 0.07	Flo_WG_18
Vegetables fruiting	Cucumber / courgette (F, G), melon (F)	cucumber and melon, early, multiple	3x 0.05	Flo_WG_27
		cucumber and melon, late, multiple		Flo_WG_28
		cucumber and melon, early, single	1 x 0.05	Flo_WG_29
		cucumber and melon, late, single		Flo_WG_30
	Cucumber (G)	cucumber, early, multiple	3x 0.08	Flo_WG_19
		cucumber, late, multiple		Flo_WG_20
		cucumber, early, single	1 x 0.08	Flo_WG_21
		cucumber, late, single		Flo_WG_22
	Tomato / eggplant (F, G)	tomato, early, multiple	3x 0.06	Flo_WG_23
		tomato, late, multiple		Flo_WG_24
		tomato, early, single	1 x 0.06	Flo_WG_25
		tomato, late, single		Flo_WG_26

At Step 3, the Pesticide Application Timing calculator (PAT) which is implemented in the FOCUS models was used to determine the exact application dates. The application windows were calculated according to FOCUS recommendations using the following formula: Application Window = 30 d + (number of applications - 1) x application interval. The application windows were selected to cover the growth stages as well as worst-case

assumptions according to the GAP. The application period was determined for each scenario from the earliest BBCH stages upwards for early applications and from the PHI (pre-harvest interval) downwards for later applications.

For early applications to winter cereals (BBCH 39), the applications were set to 105 d before harvest which is equivalent to the FOCUS groundwater spring point which is about 3.5 months before harvest. The late applications were set to 28 days (PHI) before harvest.
For the applications in winter cereals at BBCH 21, the application at 14 d before spring point was assumed to be 115 d before harvest for all scenarios.
The early applications to spring wheat were set to 30 days after emergence for the start at BBCH 39, for the late applications the application window was set to end 28 days before harvest. For the applications starting at BBCH 21, the application window was set to start at 14 days after emergence.
For the applications in pome and stone fruit, the early applications starting at BBCH 0 are set to start with emergence, the early applications to pome and stone fruit before BBCH 70 are presented with calculations ending at 68 d after emergence as BBCH 70 should be around two and a half months after emergence minus one week. The timing for BBCH at two and a half months (75 days) after emergence was calculated with FOCUS crop pome late to cover the intermediate applications. The late applications to pome and stone fruit were set to harvest minus PHI (21 d). The application window for late applications to cherries was set to harvest minus PHI (14 d).
The early applications to cucumber and melon were calculated with an application window starting at 7 days after emergence (0.05 kg a.s./ha). The same application window was used with the respective application rates for the early uses in cucumber (0.08 kg a.s./ha) and tomatoes (0.06 kg a.s./ha). The late applications to cucumber and melon were calculated with an application window ending at 1 day before harvest. The same application window was used with the respective application rates for the late uses in cucumber (0.08 kg a.s./ha) and tomatoes (0.06 kg a.s./ha).

Application windows and the PAT selected dates in Step 3 for the different crops and scenarios can be found in CP, Volume B.8.5.

The initial PECsw of Flonicamid (i.e., global maximum concentration) resulting from an entry to the water bodies via spray drift, run-off and drainage without applying mitigation measures (Step 3) are given in Tables 2.8.7.3-51 to Table 2.8.7.3-82.

Table 2.8.7.3-51: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to winter cereals early, covering NEZ (Flo_WG_6) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.494	Spray-drift	0.161
D1	Stream	0.410	Spray-drift	0.035
D2	Ditch	**7.777** [1)]	Drainage	**0.682** [1)]
D2	Stream	4.873	Drainage	0.363
D3	Ditch	0.444	Spray-drift	0.031
D4	Pond	0.015	Spray-drift	0.006

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
D4	Stream	0.353	Spray-drift	0.007
D5	Pond	0.015	Spray-drift	0.006
D5	Stream	0.354	Spray-drift	0.005
D6	Ditch	0.450	Spray-drift	0.051
R1	Pond	0.015	Spray-drift	0.007
R1	Stream	0.292	Spray-drift	0.014
R3	Stream	0.410	Spray-drift	0.023
R4	Stream	0.292	Spray-drift	0.010

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5.

Table 2.8.7.3-52: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to winter cereals early, covering NEZ (Flo_WG_3) 2 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.550	Drainage	0.238
D1	Stream	0.384	Spray-drift	0.049
D2	Ditch	**7.777** [1)]	Drainage	**0.837** [1)]
D2	Stream	4.873	Drainage	0.377
D3	Ditch	0.388	Drainage	0.032
D4	Pond	0.021	Drainage	0.009
D4	Stream	0.320	Drainage	0.009
D5	Pond	0.021	Drainage	0.010
D5	Stream	0.358	Drainage	0.017
D6	Ditch	0.394	Spray-drift	0.053
R1	Pond	0.022	Run-off	0.011
R1	Stream	0.298	Run-off	0.018
R3	Stream	0.417	Run-off	0.040
R4	Stream	1.440	Run-off	0.104

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5.

Table 2.8.7.3-53: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to winter cereals early, covering SEZ+CEZ (Flo_WG_4) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.474	Spray-drift	0.150
D1	Stream	0.401	Spray-drift	0.029
D2	Ditch	**7.777** [1)]	Drainage	**0.683** [1)]
D2	Stream	4.873	Drainage	0.363
D3	Ditch	0.444	Spray-drift	0.033
D4	Pond	0.015	Spray-drift	0.006
D4	Stream	0.370	Spray-drift	0.010
D5	Pond	0.015	Spray-drift	0.006
D5	Stream	0.354	Spray-drift	0.005
D6	Ditch	0.446	Spray-drift	0.052
R1	Pond	0.015	Spray-drift	0.007
R1	Stream	0.292	Spray-drift	0.014
R3	Stream	0.410	Spray-drift	0.016
R4	Stream	0.761	Run-off	0.055

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5.

Table 2.8.7.3-54: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to winter cereals early, covering SEZ+CEZ (Flo_WG_1) 2 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.554	Drainage	0.243
D1	Stream	0.390	Spray-drift	0.053
D2	Ditch	**7.777** [1)]	Drainage	**0.838** [1)]
D2	Stream	4.874	Drainage	0.377
D3	Ditch	0.388	Drainage	0.034
D4	Pond	0.022	Drainage	0.009
D4	Stream	0.331	Drainage	0.014
D5	Pond	0.021	Drainage	0.010
D5	Stream	0.358	Drainage	0.017
D6	Ditch	0.392	Drainage	0.085
R1	Pond	0.035	Run-off	0.015
R1	Stream	0.897	Run-off	0.043
R3	Stream	0.357	Run-off	0.022
R4	Stream	2.665	Run-off	0.189

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-55: FOCUS Step 3 PECsw and PECsed for Flonicamide following single application of IKI-220 500 WG to winter cereals late, covering SEZ+CEZ+NEZ (Flo_WG_5) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.464	Spray-drift	0.163
D1	Stream	0.393	Spray-drift	0.036
D2	Ditch	0.450	Spray-drift	0.164
D2	Stream	0.400	Spray-drift	0.134
D3	Ditch	0.445	Spray-drift	0.035
D4	Pond	0.015	Spray-drift	0.005
D4	Stream	0.384	Spray-drift	0.016
D5	Pond	0.015	Spray-drift	0.006
D5	Stream	0.414	Spray-drift	0.019
D6	Ditch	0.448	Spray-drift	0.087
R1	Pond	0.158	Run-off	0.055
R1	Stream	1.104	Run-off	0.094
R3	Stream	**1.926** [1)]	Run-off	**0.120** [1)]
R4	Stream	0.293	Spray-drift	0.011

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-56: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to winter cereals late, covering SEZ+CEZ+NEZ (Flo_WG_2) 2 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.672	Drainage	0.274
D1	Stream	0.340	Spray-drift	0.060
D2	Ditch	1.132	Drainage	0.443
D2	Stream	0.782	Drainage	0.237
D3	Ditch	0.389	Drainage	0.035
D4	Pond	0.020	Drainage	0.009
D4	Stream	0.332	Drainage	0.014
D5	Pond	0.021	Drainage	0.009
D5	Stream	0.358	Drainage	0.018
D6	Ditch	0.393	Drainage	0.100

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
R1	Pond	0.199	Run-off	0.080
R1	Stream	1.534	Run-off	0.123
R3	Stream	**1.926** [1)]	Run-off	**0.128** [1)]
R4	Stream	1.431	Run-off	0.103

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-57: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to spring cereals early, covering NEZ (Flo_WG_12) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	**0.455** [1)]	Spray-drift	**0.155** [1)]
D1	Stream	0.393	Spray-drift	0.030
D3	Ditch	0.444	Spray-drift	0.032
D4	Pond	0.015	Spray-drift	0.006
D4	Stream	0.363	Spray-drift	0.008
D5	Pond	0.015	Spray-drift	0.006
D5	Stream	0.352	Spray-drift	0.005
R4	Stream	0.292	Spray-drift	0.010

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-58: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to spring cereals early, covering NEZ (Flo_WG_9) 2 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.669	Drainage	0.260
D1	Stream	0.340	Spray-drift	0.042
D3	Ditch	0.388	Drainage	0.032
D4	Pond	0.022	Drainage	0.009
D4	Stream	0.326	Drainage	0.011
D5	Pond	0.021	Drainage	0.009
D5	Stream	0.335	Drainage	0.007
R4	Stream	**1.303** [1)]	Run-off	**0.094** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3- 69: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to spring cereals early, covering SEZ+CEZ (Flo_WG_10) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.460	Spray-drift	0.158
D1	Stream	0.393	Spray-drift	0.032
D3	Ditch	0.444	Spray-drift	0.033
D4	Pond	0.015	Spray-drift	0.006
D4	Stream	0.363	Spray-drift	0.008
D5	Pond	0.015	Spray-drift	0.006
D5	Stream	0.373	Spray-drift	0.007
R4	Stream	**1.292** [1)]	Run-off	**0.093** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-60: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to spring cereals early, covering SEZ+CEZ (Flo_WG_7) 2 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.668	Drainage	0.259
D1	Stream	0.340	Spray-drift	0.041
D3	Ditch	0.388	Drainage	0.034
D4	Pond	0.020	Drainage	0.009
D4	Stream	0.331	Drainage	0.013
D5	Pond	0.022	Drainage	0.009
D5	Stream	0.335	Drainage	0.007
R4	Stream	**1.292** [1)]	Run-off	0.093

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-61: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to spring cereals late, covering SEZ+CEZ+NEZ (Flo_WG_11) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	**0.451** [1)]	Spray-drift	**0.151** [1)]
D1	Stream	0.393	Spray-drift	0.031
D3	Ditch	0.445	Spray-drift	0.037
D4	Pond	0.015	Spray-drift	0.005
D4	Stream	0.382	Spray-drift	0.015
D5	Pond	0.015	Spray-drift	0.006
D5	Stream	0.414	Spray-drift	0.019
R4	Stream	0.293	Spray-drift	0.011

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-62: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to spring cereals late, covering SEZ+CEZ+NEZ (Flo_WG_8) 2 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D1	Ditch	0.480	Drainage	0.212
D1	Stream	0.340	Spray-drift	0.050
D3	Ditch	0.389	Drainage	0.039
D4	Pond	0.021	Drainage	0.009
D4	Stream	0.332	Drainage	0.014
D5	Pond	0.021	Drainage	0.009
D5	Stream	0.358	Drainage	0.017
R4	Stream	**1.292** [1)]	Run-off	**0.093** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-63: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to pome/stone fruit early covering apples early, pears, plums, peaches, apricots, cherries (Flo_WG_13) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D3	Ditch	5.437	Spray-drift	0.404
D4	Pond	0.331	Spray-drift	0.132
D4	Stream	5.146	Spray-drift	0.087
D5	Pond	0.331	Spray-drift	0.134

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
D5	Stream	5.393	Spray-drift	0.079
R1	Pond	0.331	Spray-drift	0.124
R1	Stream	4.396	Spray-drift	0.142
R2	Stream	5.824	Spray-drift	0.122
R3	Stream	**6.220** [1)]	Spray-drift	**0.267** [1)]
R4	Stream	4.397	Spray-drift	0.142

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-64: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to pome/stone fruit_early at BBCH 70 covering apples early, pears, plums, peaches, apricots, cherries (Flo_WG_32) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D3	Ditch	5.446	Spray-drift	0.446
D4	Pond	0.331	Spray-drift	0.124
D4	Stream	5.543	Spray-drift	0.139
D5	Pond	0.331	Spray-drift	0.127
D5	Stream	5.909	Spray-drift	0.141
R1	Pond	0.331	Spray-drift	0.116
R1	Stream	4.423	Spray-drift	0.156
R2	Stream	5.833	Spray-drift	0.124
R3	Stream	**6.200** [1)]	Spray-drift	**0.267** [1)]
R4	Stream	4.422	Spray-drift	0.155

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-65: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to pome/stone fruit_late at BBCH 71 covering apples intermediate, pears, plums, peaches, apricots, cherries (Flo_WG_14) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D3	Ditch	2.573	Spray-drift	0.241
D4	Pond	0.115	Spray-drift	0.041
D4	Stream	2.578	Spray-drift	0.103
D5	Pond	0.115	Spray-drift	0.042
D5	Stream	**2.787** [1)]	Spray-drift	**0.131** [1)]
R1	Pond	0.115	Spray-drift	0.042
R1	Stream	1.976	Spray-drift	0.071
R2	Stream	2.643	Spray-drift	0.065

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
R3	Stream	2.785	Spray-drift	0.129
R4	Stream	1.931	Spray-drift	0.052

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-66: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to pome/stonefruit_late at BBCH 71 covering apples intermediate, pears, plums, peaches, apricots, cherries (Flo_WG_14 multiple) 2 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D3	Ditch	2.041	Drainage	0.238
D4	Pond	0.164	Drainage	0.067
D4	Stream	2.068	Drainage	0.090
D5	Pond	0.155	Drainage	0.066
D5	Stream	**2.231** [1)]	Drainage	**0.110** [1)]
R1	Pond	0.156	Run-off	0.064
R1	Stream	1.582	Spray-drift	0.057
R2	Stream	2.117	Run-off	0.059
R3	Stream	2.230	Run-off	0.107
R4	Stream	1.582	Run-off	0.109

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-67: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to pome/stone fruit_late covering apples late, pears, plums, peaches, apricots, PHI 21 d (Flo_WG_16) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D3	Ditch	2.574	Spray-drift	0.250
D4	Pond	0.115	Spray-drift	0.045
D4	Stream	2.489	Spray-drift	0.065
D5	Pond	0.115	Spray-drift	0.043
D5	Stream	**2.787** [1)]	Spray-drift	**0.131** [1)]
R1	Pond	0.115	Spray-drift	0.043
R1	Stream	1.976	Spray-drift	0.071
R2	Stream	2.648	Spray-drift	0.066
R3	Stream	2.785	Spray-drift	0.129
R4	Stream	1.975	Spray-drift	0.071

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-68: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to pome/stone fruit_late covering apples late, pears, plums, peaches, apricots, PHI 21 d (Flo_WG_15) 2 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D3	Ditch	2.046	Spray-drift	0.295
D4	Pond	0.158	Drainage	0.073
D4	Stream	2.020	Drainage	0.063
D5	Pond	0.163	Drainage	0.069
D5	Stream	**2.231** [1)]	Drainage	**0.111** [1)]
R1	Pond	0.155	Run-off	0.066
R1	Stream	1.582	Run-off	0.059
R2	Stream	2.121	Run-off	0.055
R3	Stream	2.230	Run-off	0.128
R4	Stream	1.582	Run-off	0.062

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-69: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to pome/stone fruit_late, PHI 14 d covering cherries late (Flo_WG_17) 1 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D3	Ditch	2.574	Spray-drift	0.250
D4	Pond	0.115	Spray-drift	0.047
D4	Stream	2.523	Spray-drift	0.076
D5	Pond	0.115	Spray-drift	0.043
D5	Stream	**2.787** [1)]	Spray-drift	**0.131**[1)]
R1	Pond	0.115	Spray-drift	0.043
R1	Stream	1.976	Spray-drift	0.071
R2	Stream	2.648	Spray-drift	0.066
R3	Stream	2.785	Spray-drift	0.129
R4	Stream	1.975	Spray-drift	0.071

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-70: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to pome/stone fruit_late PHI 14 d covering cherries late (Flo_WG_18) 2 x 0.07 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D3	Ditch	2.049	Spray-drift	0.330
D4	Pond	0.158	Drainage	0.073
D4	Stream	2.020	Drainage	0.063
D5	Pond	0.166	Drainage	0.071
D5	Stream	**2.231** [1)]	Drainage	**0.112** [1)]
R1	Pond	0.166	Run-off	0.072
R1	Stream	1.582	Run-off	0.060
R2	Stream	2.121	Run-off	0.054
R3	Stream	2.230	Run-off	0.112
R4	Stream	1.582	Run-off	0.062

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-71: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to vegetables fruiting early covering cucumber and melon, early, single (Flo_WG_29) 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.312	Spray-drift	0.013
R2	Stream	0.277	Spray-drift	0.012
R3	Stream	0.294	Spray-drift	0.018
R4	Stream	**0.582** [1)]	Run-off	**0.047** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-72: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to vegetables fruiting early covering cucumber and melon, early, multiple (Flo_WG_27) 3 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.230	Drainage	0.014
R2	Stream	0.528	Run-off	0.035
R3	Stream	0.520	Run-off	0.045
R4	Stream	**1.184** [1)]	Run-off	**0.092** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-73: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to vegetables fruiting late covering cucumber and melon, late, single (Flo_WG_30) 1 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.314	Spray-drift	0.015
R2	Stream	0.281	Spray-drift	0.007
R3	Stream	0.448	Run-off	0.039
R4	Stream	**1.171** [1)]	Run-off	**0.094** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-74: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to vegetables fruiting late covering cucumber and melon, late, multiple (Flo_WG_28) 3 x 0.05 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.230	Spray-drift	0.013
R2	Stream	0.204	Run-off	0.006
R3	Stream	0.458	Run-off	0.048
R4	Stream	**1.320** [1)]	Run-off	**0.126** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-75: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to vegetables fruiting early covering cucumber, early, single in greenhouse (Flo_WG_21) 1 x 0.08 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.499	Spray-drift	0.021
R2	Stream	0.443	Spray-drift	0.019
R3	Stream	0.471	Spray-drift	0.029
R4	Stream	**0.930** [1)]	Run-off	**0.075** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-76: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI - 220 500 WG to vegetables fruiting covering early cucumber, early, multiple in greenhouse (Flo_WG_19) 3 x 0.08 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.367	Drainage	0.022
R2	Stream	0.844	Run-off	0.056

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
R3	Stream	0.831	Run-off	0.072
R4	Stream	**1.896** [1)]	Run-off	**0.147** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-77: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to vegetables fruiting late covering cucumber, late, single in greenhouse (Flo_WG_22) 1 x 0.08 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.502	Spray-drift	0.024
R2	Stream	0.450	Spray-drift	0.011
R3	Stream	0.717	Run-off	0.062
R4	Stream	**1.873** [1)]	Run-off	**0.151** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-78: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to vegetables fruiting late covering cucumber, late, multiple in greenhouse (Flo_WG_20) 3 x 0.08 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.367	Spray-drift	0.021
R2	Stream	0.326	Run-off	0.009
R3	Stream	0.734	Run-off	0.077
R4	Stream	**2.113** [1)]	Run-off	**0.202** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-79: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to vegetables fruiting early covering tomato, early, single (Flo_WG_25) 1 x 0.06 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.374	Spray-drift	0.016
R2	Stream	0.332	Spray-drift	0.014
R3	Stream	0.353	Spray-drift	0.022
R4	Stream	**0.698** [1)]	Run-off	**0.056** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-80: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to vegetables fruiting early covering tomato, early, multiple (Flo_WG_23) 3 x 0.06 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.275	Drainage	0.017
R2	Stream	0.633	Run-off	0.042
R3	Stream	0.624	Run-off	0.054
R4	Stream	**1.421** [1)]	Run-off	**0.111** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-81: FOCUS Step 3 PECsw and PECsed for Flonicamid following single application of IKI-220 500 WG to vegetables fruiting late covering tomato, late, single (Flo_WG_26) 1 x 0.06 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.376	Spray-drift	0.018
R2	Stream	0.337	Spray-drift	0.008
R3	Stream	0.538	Run-off	0.047
R4	Stream	**1.406** [1)]	Run-off	**0.113** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Table 2.8.7.3-82: FOCUS Step 3 PECsw and PECsed for Flonicamid following multiple applications of IKI-220 500 WG to vegetables fruiting late covering tomato, late, multiple (Flo_WG_24) 3 x 0.06 kg a.s./ha

Scenario FOCUS	Waterbody	Max PECsw [µg/L]	Dominant entry route	Max PECsed [µg/kg]
Step 3				
D6	Ditch	0.276	Spray-drift	0.016
R2	Stream	0.245	Run-off	0.007
R3	Stream	0.550	Run-off	0.058
R4	Stream	**1.584** [1)]	Run-off	**0.152** [1)]

[1)] Actual and TWA PECsw and PECsed values for the worst-case scenario at Step 3 are found in CP, Volume 3, B.8.5

Conclusion for Step 3:

The highest initial PECsw values of Flonicamid reached 7.777 µg/L for early multiple application to winter cereals (D2 ditch). Highest PECsed accounted for 0.838 µg/kg for early multiple application to winter cereals (D2 ditch). Predicted environmental concentrations of the Step 1/2 and Step 3 calculations are considered in the aquatic ecotoxicological risk assessment below.

2.8.7.4 Predicted environmental concentrations in air (PECair)

Environmental fate studies using the two representative formulations were not conducted as data from studies with the active substance, flonicamid, are available and adequate to enable extrapolation to the behavior of the formulated product. Neither the type of plant protection products nor their ingredients and physical properties are expected to affect the volatility.

Flonicamid

The photo-oxidative degradation in air of flonicamid was estimated via the Atkinson method in the model (EPI) Suite TM v4.11 with the actual version of AOPWIN v1.92 (2010). The estimated DT_{50} in air accounted for 13.36 days (assuming an atmospheric hydroxyl radical concentration of 1.5×10^6 radicals cm^3, 12 hours a day). However, the vapour pressure of 9.43×10^{-7} Pa (20 °C) of flonicamid is below the trigger for volatilisation from plant surfaces of 1×10^{-5} Pa. (which was proposed as conservative indicator of volatilisation potential according to FOCUS Air group (SANCO/10553/2006 Rev 2, 2008)). Thus, flonicamid shows no potential to reach the air after application and there is no potential for short- and long-range transport via volatilisation from plant surfaces. The calculation of PEC values in air are therefore not deemed necessary.

TFA (trifluoroacetic acid)

TFA formed as degradation product from flonicamid was found in the soil compartment. The vapour pressure derived with EpiSuite 4.1 of 1.55×10^4 Pa (25 °C) shows a high potential of volatilisation. However, as expounded in the RAR on Flufenacet, (Volume 3 Annex B.8 (PPP) Flufenacet + Diflufenican 600 SC, August 2016, page 188), "*the determination of the Henry´s law constant for TFA* (< 2.7×10^{-10} Pa'*m^3*mol^{-1} at 20°C, current CA, Volume 3, B.2.2) *demonstrated that the compound displayed high affinity towards water, therefore atmospheric water, either in form of clouds or as fog, may be an effective sink for that compound"*. Further it is explained, that TFA formed as degradation product from active substances of plant protection products "*will be present as Trifluoroacetate – the dissociated form* (due to a pKa of 1.6, CA 2.2) *displaying very low volatility potential and as such not posing any substantial threat to the atmosphere."* The very low volatility is proven by the low vapour pressure of the sodium salt of TFA (<1.0×10^{-6} Pa at 20 °C, Vol 3, CA, B.2.2).

"The examination of the available literature data showed that the presence of the TFA in the atmosphere was not expected to be related to the degradation in that environmental compartment of the active substances of the plant protection products containing in their molecules the CF_3-functional groups, nor to the possible volatilisation from soil of TFA formed there as a result of degradation of such agrochemicals."

As TFA evolved from flonicamid only occurred in the aerobic soil degradation study and did not occur in the volatile traps during the 120 days study (B.8.1.1.1/01), a volatilisation to air from soil is very unlikely. As the substance is highly affine towards water, the substance will be associated to the soil water.

Local and global effects

Neither local nor global effects as described in the EU Regulation No. 283/2013 are expected for flonicamid due to the low vapour pressure of 9.43 x 10^{-7} Pa (20 °C). Furthermore, flonicamid does not contain unsaturated carbon-carbon bonds in the molecule and therefore an ozone depletion potential is not expected.

2.9 EFFECTS ON NON-TARGET SPECIES

2.9.1 Summary of effects on birds and other terrestrial vertebrates

Birds

Avian acute oral, short-term dietary and long-term reproduction studies have been carried out with flonicamid. The available data is summarised and evaluated by the RMS in Annex B.9 for the active ingredient. The relevant acute, short-term and long-term avian endpoints are listed in the table below.

Table 2.9.1-1 : Summary of avian toxicity endpoints for Flonicamid

Test Substance	Test Species	Endpoint	Value	Reference
Acute oral toxicity				
Flonicamid	Bobwhite quail	LD_{50}	> 2000 mg a.s./kg bw	CA 8.1.1.1/01
	Mallard duck	LD_{50}	**1591 mg a.s./kg bw** (f) 2621 mg a.s./kg bw (m)	CA 8.1.1.1/02
Dietary (short-term) toxicity				
Flonicamid	Bobwhite quail	LC_{50} (LDD_{50})	> 5000 mg a.s./kg diet (> 411 mg a.s./kg bw)	(2001), CA 8.1.1.2/01
	Mallard duck	LC_{50} (LDD_{50})	> 5000 mg a.s./kg diet **(> 301.8 mg a.s./kg bw)***	CA 8.1.1.2/02
Reproductive (long-term) toxicity				
Flonicamid	Bobwhite quail	NOED	90 mg a.s./kg bw/day	CA 8.1.1.3/02
	Mallard duck	NOED	**59 mg a.s./kg bw/day**	CA 8.1.1.3/04

m = males, f = females
values in bold are used for the quantitative risk assessment

Mammals

Mammalian acute oral toxicity and dietary long-term reproduction studies have been carried out with Flonicamid. In addition, an acute oral toxicity study on rat is available for the formulated product IKI-220 100 OD. For metabolites, acute studies are availbale. Full details of the toxicity studies are provided in Volume 3 CA B6 and CP B6. The mammalian endpoints that are used for the risk assessment are bolded in the Table below.

Table 2.9.1-2: Summary of mammalian toxicity endpoints for Flonicamid used for the risk assessment

Test Substance	Test Species	Endpoint	Value	Reference
Acute oral toxicity				
Flonicamid	Rat	LD_{50}	**884 mg a.s./kg bw** (m) 1768 mg a.s./kg bw (f)	CA 8.1.2.1/01
IKI-220 500 WG	Rat	LD_{50}	> 1000 mg a.s./kg bw	CP 10.1.2.1/01
IKI-220 100 OD	Rat	LD_{50}	> 200 mg a.s./kg bw	CP 10.1.2.1/01
Reproductive (long-term) toxicity				
Flonicamid	Rat	NOAEL *	109 mg a.s./kg bw/day	CA 8.1.2.2/01
	Rat	NOAEL **	100 mg a.s./kg bw/day	CA 8.1.2.2/02
	Rabbit	NOAEL **	**25 mg a.s./kg bw/day**	CA 8.1.2.2/03

m = males, f = females
values in bold were used for the risk assessment
* 2-generation study, NOAEL for reproductive toxicity
** developmental toxicity study

Table 2.9.1-3: Summary of mammalian toxicity endpoints for Flonicamid metabolites

Test Substance	Test Species	Endpoint	Value	Reference
Acute oral toxicity				
TFNA	Rat	LD_{50}	> 2000 mg/kg bw	CA 8.1.2.1/02
TFNA-AM	Rat	LD_{50}	> 2000 mg/kg bw	CA 8.1.2.1/03
TFNG	Rat	LD_{50}	> 2000 mg/kg bw	CA 8.1.2.1/04
TFNG-AM	Rat	LD_{50}	> 2000 mg/kg bw	CA 8.1.2.1/05

2.9.2 Summary of effects on aquatic organisms [section 11.5 of the CLH report]

2.9.2.1 Bioaccumulation [equivalent to section 11.4 of the CLH report template]

Flonicamid and its metabolites do not have potential for bioaccumulation based on octanol-water partitioning factors (Pow). The log P_{ow} of flonicamid of 0.1, and The log P_{OW} values for the metabolites TFA, TFNA, TFNG, TFNA-OH and TFNG-AM are -2.6, 0.4, -0.2, 0.6 and -0.7, respectively.

No studies on bioaccumulation are available or required.

2.9.2.1.1 Estimated bioaccumulation

Not required.

2.9.2.1.2 Measured partition coefficient and bioaccumulation test data

Not required.

2.9.2.2 Acute aquatic hazard [equivalent to section 11.5 of the CLH report template]

Test substance	Test species	Result	Key or Supportive study	Reference
Acute toxicity to fish				
Flonicamid	Rainbow trout	**96 h LC_{50} > 100 mg a.s./L (nom)**	Key	CA 8.2.1/01
Flonicamid	Bluegill sunfish	96 h LC_{50} > 100 mg a.s./L (nom)	Supportive	CA 8.2.1/02
Acute toxicity to aquatic invertebrates				
Flonicamid	*Daphnia magna*	48 h EC_{50} > 100 mg a.s./L (nom)	Supportive	CA 8.2.4.1/01
Flonicamid	*Chironomus riparius*	**48 h EC_{50} = 78 mg a.s./L (nom)**	Key	CA 8.2.4.2/02
Toxicity to green algae and additional algal species				
Flonicamid	*Raphidocelis subcapitata*	72 h E_yC_{50} > 100 mg a.s./L (nom) **72 h E_rC_{50} > 100 mg a.s./L (nom)** 72 h NOE_rC = 46 mg a.s./L (nom)	Key	CA 8.2.6.1/01; CA 8.2.6.1/02
Toxicity to aquatic macrophytes				
Flonicamid	*Lemna gibba*	**7 d EC_{50} > 119 mg a.s./L (meas.)** 7 d NOEC = 119 mg a.s./L (meas)	Key	CA 8.2.7/01

Acute toxicity to fish				
TFNA	Rainbow trout	**96 h LC_{50} > 100 mg/L (nom)**	Key	CA 8.2.1/03
TFNA-OH	Rainbow trout	**96 h LC_{50} > 100 mg/L (nom)**	Key	CA 8.2.1/04
TFNG-AM	Rainbow trout	**96 h LC_{50} > 100 mg/L (nom)**	Key	CA 8.2.1/05
TFNA-AM	Rainbow trout	**96 h LC_{50} > 100 mg/L (nom)**	Key	CA 8.2.1/06
TFA *	Zebrafish	**96 h LC_{50} > 1200 mg/L (nom)**	Key	CA 8.2.1/07
Acute toxicity to aquatic invertebrates				
TFNA	*Daphnia magna*	**48 h EC_{50} > 100 mg/L (nom)**	Key	CA 8.2.4.1/02
TFNA-OH	*Daphnia magna*	**48 h EC_{50} > 100 mg/L (nom)**	Key	CA 8.2.4.1/03
TFNG-AM	*Daphnia magna*	**48 h EC_{50} > 100 mg/L (nom)**	Key	CA 8.2.4.1/04
TFNA-AM	*Daphnia magna*	**48 h EC_{50} > 100 mg/L (nom)**	Key	CA 8.2.4.1/05
TFA *	*Daphnia magna*	**48 h EC_{50} > 1200 mg/L (nom)**	Key	CA 8.2.4.1/06
Toxicity to green algae				
TFNA	*Raphidocelis subcapitata*	72 h E_yC_{50} > 100 mg/L (nom) **72 h E_rC_{50} > 100 mg/L (nom)** 72 h NOE_rC = 100 mg/L (nom)	Key	CA 8.2.6.1/03
TFNA-OH	*Raphidocelis subcapitata*	72 h E_yC_{50} = 41.1 mg/L (nom) **72 h E_rC_{50} > 100 mg/L (nom)** 72 h NOE_rC = 4.6 mg/L (nom)	Key	CA 8.2.6.1/04

Test substance	Test species	Result	Key or Supportive study	Reference
TFNG-AM	*Raphidocelis subcapitata*	72 h E_yC_{50} > 100 mg/L (nom) **72 h E_rC_{50} > 100 mg/L (nom)** 72 h NOE_rC = 10 mg/L (nom)	Key	CA 8.2.6.1/05
TFNA-AM	*Raphidocelis subcapitata*	72 h E_yC_{50} > 100 mg/L (nom) **72 h E_rC_{50} > 100 mg/L (nom)** 72 h $NOE_rC \geq$ 100 mg/L (nom)	Key	CA 8.2.6.1/06
TFA *	*Raphidocelis subcapitata*	72 h E_yC_{50} = 4.19 mg/L (nom) 72 h NOE_yC < 0.36 mg/L (nom) **72 h E_rC_{50} = 192.48 mg/L (nom)** 72 h NOE_rC = 0.36 mg/L (nom)	Key	CA 8.2.6.1/07
IKI-220 100 OD	Rainbow trout	**96 h LC_{50} = 1.69 mg a.s./L (mm)**	Key	CP 10.2.1/01
IKI-220 100 OD	*Daphnia magna*	**48 h EC_{50} = 7.71 mg a.s./L (mm)**	Key	CP 10.2.1/02
IKI-220 100 OD blank *		48 h EC_{50} = 119 mg product/L (nom)	Supportive	CP 10.2.1/03
IKI-220 100 OD	*Raphidocelis subcapitata*	**72 h E_rC_{50} = 12.6 mg a.s./L (nom)** 72 h NOE_rC = 2.20 mg a.s./L (nom) 72 h E_yC_{50} = 2.80 mg a.s./L (nom) 72 h NOE_yC = 0.688 mg a.s./L (nom)	Key	CP 10.2.1/04
IKI-220 500 WG	Rainbow trout	96 h LC_{50} > 51 mg a.s./L (nom)	Supportive	CP 10.2.1/01
IKI-220 500 WG	*Daphnia magna*	48 h EC_{50} > 51 mg as./L (nom)	Supportive	CP 10.2.1/02
IKI-220 500 WG	*Pseudokirchneriella subcapitata*	72 h E_rC_{50} > 51 mg a.s./L (nom) 72 h E_yC_{50} = 35 mg a.s./L (nom) 72 h NOEC = 11 mg a.s./L	Supportive	CP 10.2.1/03 CP 10.2.1/04
IKI-220 500 WG	activated sludge	3 h EC_{50} > 500 mg a.s./L (nom)	Supportive	CP 10.7/01

nom = nominal concentrations
m= measure concentration at the end of exposure
* study conducted with sodium Trifluoroacetate (TFA-Na)
Values in **bold** are used in the quantitative risk assessment

2.9.2.3 Long-term aquatic hazard [equivalent to section 11.6 of the CLH report template]

Test substance	Test species	Result	Key or Supportive study	Reference
Chronic toxicity to fish				
Flonicamid	Fathead minnow	**33 d NOEC = 10 mg a.s./L (nom)**	Key	Anon. (2002)
Chronic toxicity to aquatic invertebrates				
Flonicamid	*Daphnia magna*	21 d EC_{10} = 12.9 mg a.s./L (nom) 21 d NOEC = 3.1 mg a.s./L (nom)	Supportive	CA 8.2.5.1/01
Flonicamid	*Daphnia magna*	**21 d EC_{10} = 2.82 mg a.s./L (nom)** 21 d NOEC = 6.3 mg a.s./L (nom)	Key	CA 8.2.5.1/02
Sediment dwellers				
Flonicamid	*Chironomus riparius*	**27 d NOEC = 25 mg a.s./L (nom)** 27 d NOEC = 6.6 mg a.s./kg sediment (m)	Key	CA 8.2.5.3/01

nom = nominal concentrations
m= measure concentration at the end of exposure
* study conducted with sodium Trifluoroacetate (TFA-Na)
Values in **bold** are used in the quantitative risk assessment

2.9.2.4 Comparison with the CLP criteria

Flonicamid is non-rapidly degradable and it does not have bioaccumulation potential. Adequate acute and chronic data on three trophic levels are available. Invertebrates are the most sensitive group of species. The lowest acute endpoint is EC50 = 78 mg a.s./L (*Chironomus riparius*) and the lowest chronic endpoint is EC10 = 2.82 mg a.s./L (*Daphnia magna*). The criterium for category acute 1 (LC/EC50 ≤ 1 mg/l) is thus not fulfilled. Neither are the criteria for chronic categories for non-rapidly degradable substances fulfilled (category 1: NOEC ≤ 0.1 mg/l, category 2: NOEC ≤ 1 mg/l). Thus, the classification criteria for environmental hazards according to CLP are not fulfilled.

2.9.2.5 Conclusion on classification and labelling for environmental hazards

ECHA RAC Opinion (5.6.2013) supported the proposal not to classify flonicamid for environmental toxicity. There are no new data that would change the outcome of the RAC opinion. Therefore, the conclusion not to classify flonicamid in the environmental hazard class remains.

2.9.3 Summary of effects on arthropods

Bees

A comprehensive set of laboratory, semi-field and field studies have been performed with both flonicamid and its metabolites.

Table 2.9.3-1: Endpoints and effect values for Flonicamid

Species	Substance	Exposure System	Results	Reference
Apis mellifera	Flonicamid	Acute, oral	96 h **LD_{50} > 60.5 µg a.s./bee**	CA 8.3.1.1.1/01
Apis mellifera	Flonicamid	Acute, contact	48 h **LD_{50} > 100 µg a.s./bee**	CA 8.3.1.1.1/01
Apis mellifera	Flonicamid	Acute, oral	96 h LD_{50} > 42 µg a.s./bee	CA 8.3.1.1.1/02
Apis mellifera	Flonicamid	Chronic, oral	10 d **LD_{50} = 4.5 µg a.s./bee/d** 10 d NOED = 1.1 µg a.s./bee/d	CA 8.3.1.2/01
Apis mellifera	Flonicamid	Larval toxicity acute (single) exposure	8 d ED_{50} = 63 µg a.s./larva	CA 8.3.1.3/01
Apis mellifera	Flonicamid	Larval toxicity repeated exposure	22 d ED_{10} = 47 µg a.s./larva 22 d ED_{50} = 74 µg a.s./larva 22 d **NOED = 13 µg a.s./larva**	CA 8.3.1.3/02

Values in **bold** are used in the quantitative risk assessment.

Table 2.9.3-2: Endpoints and effect values for Flonicamid metabolites

Species	Substance	Exposure System	Results	Reference
Apis mellifera	TFNG	Acute, oral	**LD_{50} > 47.4 µg/bee**	(2020), CA 8.3.1.1.1/03
		Acute, contact	**LD_{50} > 61.0 µg/bee**	
Apis mellifera	TFNA	Acute, oral	**LD_{50} > 50.8 µg/bee**	(2020), CA 8.3.1.1.1/04
		Acute, contact	**LD_{50} > 61.0 µg/bee**	
Apis mellifera	TFNG-AM	Acute, oral	**LD_{50} > 26.7 µg/bee**	(2020), CA 8.3.1.1.1/05
		Acute, contact	**LD_{50} > 53.0 µg/bee**	
Apis mellifera	TFNA-AM	Acute, oral	**LD_{50} > 28.1 µg/bee**	(2020), CA 8.3.1.1.1/06
		Acute, contact	**LD_{50} > 53.0 µg/bee**	
Apis mellifera	TFNG	Chronic, oral	**10 d LD_{50} > 8.43 µg/bee/d** 10 d NOED ≥ 8.43 µg/bee/d	(2020), CA 8.3.1.2/03
Apis mellifera	TFNA	Chronic, oral	**10 d LD_{50} > 8.72 µg/bee/d** 10 d NOED ≥ 8.72 µg/bee/d	(2020), CA 8.3.1.2/04
Apis mellifera	TFNG-AM	Chronic, oral	**10 d LD_{50} > 3.27 µg/bee/d** 10 d NOED = 0.20 µg/bee/d	(2020), CA 8.3.1.2/05
Apis mellifera	TFNA-AM	Chronic, oral	**10 d LD_{50} = 0.65 µg/bee/d** 10 d NOED = 0.08 µg/bee/d	(2020), CA 8.3.1.2/06
Apis mellifera	TFA	Chronic, oral	**10 d LD_{50} > 30.5 µg/bee/d** 10 d NOED ≥ 30.5 µg/bee/d	CA 8.3.1.2/07
Apis mellifera	TFNG	Larval toxicity	22 d ED_{50} > 50.0 µg/larva **22 d NOED ≥ 50.0 µg/larva**	CA 8.3.1.3/03
Apis mellifera	TFNA	Larval toxicity	22 d ED_{50} > 50.0 µg/larva **22 d NOED ≥ 50.0 µg/larva**	CA 8.3.1.3/04

Species	Substance	Exposure System	Results	Reference
Apis mellifera	TFNG-AM	Larval toxicity	22 d ED_{50} > 40.0 µg/larva **22 d NOED = 6.40 µg/larva**	CA 8.3.1.3/05
Apis mellifera	TFNA-AM	Larval toxicity	22 d ED_{50} > 40.0 µg/larva **22 d NOED = 1.02 µg/larva**	CA 8.3.1.3/06

Values in **bold** are used for quatitative the risk assessment

Table 2.9.3-3: Endpoints and effect values for IKI-220 500 WG relevant for the risk assessment for bees

Species	Substance	Exposure System	Results	Reference
Apis mellifera	IKI-220 500 WG	Acute, oral	96 h LD_{50} = 53.3 µg a.s./bee	CP 10.3.1.1.1/01
Bombus terrestris	IKI-220 500 WG	Acute, oral	**96 h LD_{50} = 55.4 µg a.s./bee**	CP 10.3.1.1.1/02
Apis mellifera	IKI-220 500 WG	Acute, contact	48 h LD_{50} > 51.1 µg a.s./bee	CP 10.3.1.1.1/01
Bombus terrestris	IKI-220 500 WG	Acute, contact	**96 h LD_{50} > 100 µg a.s./bee**	CP 10.3.1.1.1/02
Higher-tier studies (tunnel test, field studies)				
Apis mellifera	IKI-220 500 WG	Tunnel study, application of 70 g a.s./ha to flowering oilseed rape during bee flight	No effects on mortality, foraging activity and conditions of the colonies observed.	CP 10.3.1.5/01
Apis mellifera	IKI-220 500 WG	Tunnel study, application of 70 and 140 g a.s./ha to winter wheat during bee flight	No effects on mortality, foraging activity and conditions of the colonies observed at an application rate of 70 g a.s./ha. In the 140 g a.s/ha treated group a short-term effect on mortality of two days was observed.	CP 10.3.1.5/02
Apis mellifera	IKI-220 500 WG	Tunnel study, application of 70 g a.s./ha to flowering white mustard during bee flight	No effects on mortality, foraging activity and conditions of the colonies observed.	CP 10.3.1.5/03
Apis mellifera	IKI-220 500 WG	Tunnel study, application of 80 g a.s./ha to flowering oilseed rape during bee flight	Flonicamid applied during bee flight caused a short-term effect on mortality and foraging activity for two days. No effect on colony strength was observed.	CP 10.3.1.5/04
Apis mellifera	IKI-220 500 WG	Tunnel study, application of 80 g a.s./ha to flowering white mustard during bee flight	Flonicamid applied during bee flight caused a short-term effect on mortality and foraging activity for two days. No effect on colony strength was observed.	CP 10.3.1.5/07

Species	Substance	Exposure System	Results	Reference
Apis mellifera	IKI-220 500 WG	Tunnel study, application of 80 g a.s./ha to flowering oilseed rape during and after bee flight	Flonicamid applied during bee flight caused a short-term effect on mortality and foraging activity for two days. No effect on colony strength was observed. Flonicamid applied after bee flight caused a short-term effect on mortality for one day. No effect on foraging activity and colony strength was observed.	CP 10.3.1.5/10
Apis mellifera	IKI-220 500 WG	Tunnel study, application of 184 g a.s./ha to flowering *Phacelia* after bee flight	No effect on mortality, flight intensity, colony development, brood development in two consecutive brood cycles and food storage were observed	CP 10.3.1.5/11
Apis mellifera	IKI-220 500 WG	Tunnel study, application of 184 g a.s./ha to flowering *Phacelia* after bee flight	No effect on mortality, flight intensity, colony development, brood area and food storage were observed	CP 10.3.1.5/12
Apis mellifera	IKI-220 500 WG	Field study, application of 80 g a.s./ha to flowering *Phacelia* after bee flight	No effect on mortality, flight intensity, colony development, brood development and food storage were observed. A slight effect on egg development are not biologically relevant as there is no overall effect on honey bee brood.	CP 10.3.1.6/01
Apis mellifera	IKI-220 500 WG	Field study, application of 80 g a.s./ha to flowering *Phacelia* after bee flight	No effect on mortality, flight intensity, colony development, brood area and food storage were observed	CP 10.3.1.6/02

Table 2.9.3-4: Endpoints and effect values for IKI-220 100 OD relevant for the risk assessment for bees

Species	Substance	Exposure System	Results	Reference
Apis mellifera	IKI-220 100 OD	Acute, oral	**96 h LD_{50} = 34.8 µg a.s./bee**	CP 10.3.1.1.1/01
Bombus terrestris	IKI-220 100 OD	Acute, oral	96 h LD_{50} > 75.8 µg a.s./bee	CP 10.3.1.1.1/02
Apis mellifera	IKI-220 100 OD	Acute, contact	**96 LD_{50} = 24.1 µg a.s./bee**	CP 10.3.1.1.1/01
Bombus terrestris	IKI-220 100 OD	Acute, contact	48 h LD_{50} > 100 µg a.s./bee	CP 10.3.1.1.1/02
Apis mellifera	IKI-220 100 OD	Chronic, oral	10 d LD_{50} = 14.8 µg a.s./bee/d 10 d NOED = 2.52 µg a.s./bee/d	CP 10.3.1.2/01
Apis mellifera	IKI-220 100 OD	Larval toxicity	22 d ED_{10} = 3.54 µg a.s./larva 22 d ED_{50} = 12.2 µg a.s./larva **22 d NOED = 2.72 µg a.s./larva**	CP 10.3.1.3/01

Values in **bold** are used for the quantitative risk assessment

Non-target arthropods other than bees

Table 2.9.3-5: Endpoints and effect values for IKI-220 500 WG relevant for the risk assessment for non-target arthropods other than bees

Species	Substance	Exposure System	Results	Reference
Laboratory studies (Tier 1 – glass plate)				
Typhlodromus pyri (protonymphs)	IKI-220 500 WG	Laboratory test glass plates (2D)	LR_{50} > 273 g a.s./ha (29 % mortality) **ER_{50} > 273 g a.s./ha (**highest rate tested, 2 % reduction of reproduction)	CP 10.3.2.1/02
Aphidius rhopalosiphi (adults)	IKI-220 500 WG	Laboratory test glass plates (2D)	LR_{50} > 273 g a.s./ha (0 % mortality) NOER < 17.1 g a.s./ha (lowest rate tested, 56.6 % reduction of reproduction) **ER_{50} = 6.18 g a.s./ha** *	CP 10.3.2.1/03
Poecilus cupreus (larvae)	IKI-220 500 WG	Laboratory test sand (2D) (tox. ref. deviates from GL)	LR_{50} > 45 g a.s./ha (3.3 % mortality) ER_{50} > 45 g a.s./ha (highest rate tested, 6.02 % reduction of food consumption)	CP 10.3.2.1/04
Orius leavigatus (2^{nd} stage nymphs)	IKI-220 500 WG	Laboratory test glass plates (2D) (no tox. reference)	LR_{50} > 165 g a.s./ha (22 % mortality) ER_{50} > 165 g a.s./ha (highest rate tested, 11 % reduction of reproduction)	CP 10.3.2.1/05
Orius leavigatus	IKI-220 500 WG	Laboratory test	LR_{50} > 39.6 g a.s./ha (16	CP 10.3.2.1/06

Species	Substance	Exposure System	Results	Reference
(2nd stage nymphs)		glass plates (2D) (no tox. reference)	% mortality) ER_{50} > 39.6 g a.s./ha (highest rate tested, -10 % reduction of reproduction)	
Extended laboratory studies (Higher tier)				
Aphidius rhopalosiphi (adults)	IKI-220 500 WG	Extended laboratory test barley plants (3D) with single application at five levels (max. 185 g a.s./ha).	LR_{50} > 183 g a.s./ha (0 % mortality) **ER_{50} = 4.21 g a.s./ha**	CP 10.3.2.2/02
Typhlodromus pyri (protonymphs)	IKI-220 500 WG	Extended laboratory test bean leaves (3D) with 2 applications of 90 g a.s./ha with a 3 week interval No ring test data available for tox. ref.	LR_{50} > 90 g a.s./ha (20.2 % mortality) **ER_{50} > 90 g a.s./ha** (46.7 % reduction of reproduction)	CP 10.3.2.2/04
Chrysoperla carnea (larvae)	IKI-220 500 WG	Extended laboratory test bean leaves (2D) No ring test data available for tox. ref.	LR_{50} > 183 g a.s./ha (26.5 % mortality) **ER_{50} > 183 g a.s./ha** (highest rate tested, 2.04 % reduction of reproduction)	CP 10.3.2.2/06
Coccinella septempunctata (larvae)	IKI-220 500 WG	Extended laboratory test bean leaves (2D) Tox. reference deviated from GL.	LR_{50} > 85 g a.s./ha (6.1 % mortality) **ER_{50} > 85 g a.s./ha** (highest rate tested, 14.3 % reduction of reproduction)	CP 10.3.2.2/07
Episyrphus balteatus (larvae) **	IKI-220 500 WG	Extended laboratory test bean plants (3D) No test GL available. Supplemental information.	LR_{50} > 85 g a.s./ha (2.3 % mortality) ER_{50} > 85 g a.s./ha (highest rate tested, 30.2 % reduction of reproduction)	CP 10.3.2.2/08
Episyrphus balteatus (larvae) **	IKI-220 500 WG	Extended laboratory test bean plants (3D) No test GL available. Supplemental information.	LR_{50} > 70 g a.s./ha (5.0 % mortality) ER_{50} > 70 g a.s./ha (highest rate tested, 12.3 % reduction of reproduction)	CP 10.3.2.2/09
Orius leavigatus (2nd stage nymphs)	IKI-220 500 WG	Laboratory test bean leaves (2D) No ring test data available for tox. ref.	LR_{50} > 183 g a.s./ha (12 % mortality) **ER_{50} > 183 g a.s./ha** (highest rate tested, 12.4 % reduction of	CP 10.3.2.2/10

Species	Substance	Exposure System	Results	Reference
			reproduction)	
Modified extended laboratory studies (higher tier)				
Aphidius rhopalosiphi (adults)	IKI-220 500 WG	Extended laboratory test barley plants (3D) with 1, 2 or 3 applications of 70 g a.s./ha No ring test data available for tox. ref.	1 application: LR_{50} > 70 g a.s./ha (23.1 % mortality) ER_{50} > 70 g a.s./ha (-2.31 % reduction in reproduction) 2 applications: LR_{50} > 70 g a.s./ha (23.1 % mortality) ER_{50} > 70 g a.s./ha (5.4 % reduction in reproduction) 3 applications: LR_{50} > 70 g a.s./ha (15.4 % mortality) ER_{50} > 70 g a.s./ha (-9.1 % reduction in reproduction)	CP 10.3.2.2/11
Orius laevigatus (adults and 2nd stage nymphs)	IKI-220 500 WG	Extended laboratory test broad bean plants (3D) with 1, 2 or 3 applications of 70 g a.s./ha with 7 day intervals (BBCH > 59) No ring test data available for tox. ref.	1 application: LR_{50} > 70 g a.s./ha (mortality adults: 5.9 %, mortality nymphs: 3.3 %) ER_{50} > 70 g a.s./ha (adults: -38.2 % reduction in reproduction) 2 applications: LR_{50} > 70 g a.s./ha (mortality adults: 6.6 %, mortality nymphs: 3.4 %) ER_{50} > 70 g a.s./ha (-4.0 % reduction in reproduction) 3 applications: LR_{50} > 70 g a.s./ha (mortality adults: 0 %, mortality nymphs: 3.4 %) ER_{50} > 70 g a.s./ha (-51.1 % reduction in reproduction)	CP 10.3.2.2/12

* extrapolated endpoint
** studies were considered to be supplemental information only as no ring-tested validated guideline is available. The endpoints are not used in the risk assessment.
3D/2D: whole plants were sprayed but species were exposed on detached leaves
Values in bold are used in the quantitative the risk assessment

Table 2.9.3-6: Endpoints and effect values for IKI-220 100 OD relevant for the risk assessment for non-target arthropods other than bees

Species	Substance	Exposure System (remarks)	Results	Reference
Laboratory studies (Tier 1)				
Aphidius rhopalosiphi (adults)	IKI-220 100 OD	Laboratory test glass plates (2D)	LR_{50} = 5.78 g a.s./ha **ER_{50} < 1.95 g a.s./ha** (lowest rate tested)	CP 10.3.2.1/02
Typhlodromus pyri (protonymphs)	IKI-220 100 OD	Laboratory test glass plates (2D)	**LR_{50} = 50.2 g a.s./ha** ER_{50} > 39 g a.s./ha	CP 10.3.2.1/01
Extended laboratory studies (Higher tier)				
Aphidius rhopalosiphi (adults)	IKI-220 100 OD	Extended laboratory test barley plants (3D)	LR_{50} > 292.8 g a.s./ha ER_{50} < 18.3 g a.s./ha (lowest rate tested) (54.9 % reduction of reproduction)	CP 10.3.2.2/02
Aphidius rhopalosiphi (adults)	IKI-220 100 OD	Extended laboratory test barley plants (3D)	LR_{50} > 57.7 g a.s./ha **ER_{50} = 30.6 g a.s./ha** *	CP 10.3.2.2/03
Typhlodromus pyri (protonymphs)	IKI-220 100 OD	Extended laboratory test bean leaves (2D)	**LR_{50} = 260.7 g a.s./ha** ER_{50} > 234.2 g a.s./ha	CP 10.3.2.2/01
Chrysoperla carnea (larvae)	IKI-220 100 OD	Extended laboratory test, bean leaves (2D) (tox. ref. dosing deviates from GL)	LR_{50} > 292.8 g a.s./ha **ER_{50} > 292.8 g a.s./ha** (highest rate tested)	CP 10.3.2.2/05
Coccinella septempunctata (larvae)	IKI-220 100 OD	Extended laboratory test bean leaves (2D) (tox.ref. deviates from GL)	LR_{50} > 341.6 g a.s./ha **ER_{50} > 341.6 g a.s./ha** (highest rate tested)	CP 10.3.2.2/06
Aged residue studies (Higher tier)				
Aphidius rhopalosiphi (adults)	IKI-220 100 OD	Aged residue test sugar beet plants (3D/2D), 2 x 58.6 g a.s./ha 21 day interval	Fresh residues **: Mortality: 5.1 % Reduction of reproduction: 60.1 % (statistically significant) **14 d old residues ***: Mortality: -2.6 % Reduction of reproduction: -9.6 %** (not significant) 28 d old residues ****: Mortality: 2.5 % Reduction of reproduction: 25.5 % (not significant)	CP 10.3.2.2/04

3D/2D: whole plants were sprayed but species were exposed on detached leaves

Species	Substance	Exposure System (remarks)	Results	Reference

Values in bold are used in the quantitative risk assessment
* In the Aphidius extended laboratory study by [redacted] (2018) (CP 10.3.2.2/02), there was a 54.9% effect on reproduction at the lowest rate tested, 18.3 g a.s./ha, which thus approximates the ER_{50} though slightly exceeding the acceptability trigger of <50% effect. A second extended laboratory study was therefore conducted, with a lower range of application rates. In both studies a rather flat dose-response was apparent. In the second study [redacted] 2020) (CP 10.3.2.2/03), a definitive ER_{50} for reproduction could be calculated at 30.6 g a.s./ha. This is similar to the rate at which approximately 50% effects were seen in the study by [redacted] (2018) but is more accurately derived from a dose-response curve. The definitive ER_{50} endpoint is therefore considered to be reliable for use in the risk assessment.
** 21 days after first application; 0 days after last application
*** 14 days after the last application
**** 28 days after the last application

2.9.4 Summary of effects on non-target soil meso- and macrofauna

Earthworms

Chronic toxicity studies on earthworms are available for flonicamid, its metabolites and the representative formulations. In addition, acute studies on flonicamid and metabolites are available, and these are included for completeness's sake although the studies are not a data requirement anymore.

Table 2.9.4-1: Acute toxicity of Flonicamid and its metabolites to earthworms

Test substance	Species	Acute LC_{50} [mg/kg sdw]	Reference
Flonicamid (IKI-220)	*Eisenia fetida*	> 1000 (nom) *	CA 8.4.1/01
TFNA	*Eisenia fetida*	> 100 (nom) *	CA 8.4.1/02
TFNA-OH	*Eisenia fetida*	> 100 (nom) *	CA 8.4.1/03
TFNG-AM	*Eisenia fetida*	> 100 (nom) *	CA 8.4.1/04
TFNA-AM	*Eisenia fetida*	> 100 (nom) *	CA 8.4.1/05

Sdw = soil dry weight
* previous EU agreed endpoints

Table 2.9.4-2: Chronic endpoints and effect values for Flonicamid and its metabolites relevant for the risk assessment for earthworms

Species	Substance	Exposure System	Results for effects on reproduction	Reference
Eisenia fetida	Flonicamid	Mixed into substrate 56 d, chronic 10 % peat content	**NOEC = 250 mg a.s./kg dw** EC_{10} = 264.2 mg a.s./kg dw EC_{20} = 397.4 mg a.s./kg dw	CA 8.4.1/06
Eisenia fetida	TFNA	Mixed into substrate 56 d, chronic 10 % peat content	**NOEC ≥ 100 mg/kg sdw** EC_{10} > 100 mg/kg sdw EC_{20} > 100 mg/kg sdw	CA 8.4.1/07
Eisenia fetida	TFNA-AM	Mixed into substrate 56 d, chronic 10 % peat content	**NOEC ≥ 12.5 mg/kg sdw** EC_{10} > 12.5 mg/kg sdw EC_{20} > 12.5 mg/kg sdw	CA 8.4.1/10
Eisenia fetida	TFNA-OH	Mixed into substrate 56 d, chronic 10 % peat content	**NOEC = 25 mg/kg sdw** EC_{10} = 33.0 mg/kg sdw EC_{20} = 63.5 mg/kg sdw	CA 8.4.1/08

Species	Substance	Exposure System	Results for effects on reproduction	Reference
Eisenia fetida	TFNG-AM	Mixed into substrate 56 d, chronic 10 % peat content	**NOEC ≥ 100 mg/kg sdw** EC_{10} > 100 mg/kg sdw EC_{20} > 100 mg/kg sdw	CA 8.4.1/09
Eisenia fetida	TFA	Mixed into substrate 56 d, chronic 10 % peat content	**NOEC = 320 mg/kg sdw *** EC_{10} > 320 mg/kg sdw * EC_{20} > 320 mg/kg sdw *	CA 8.4.1/11

* endpoints for body weight were lower than for reproduction and were thus used for the risk assessment.
Values in **bold** are used in the quantitative the risk assessment

Table 2.9.4-3: Endpoints and effect values for IKI-220 500 WG relevant for the risk assessment for earthworms

Species	Substance	Exposure System	Results for effects on reproduction	Reference
Eisenia fetida	IKI-220 500 WG	Mixed into substrate 56 d, chronic 10 % peat content	NOEC ≥ 1000 mg/kg sdw EC_{10} = 767.1 mg/kg sdw (NOEC ≥ 484 mg a.s./kg sdw EC_{10} = 371.3 mg a.s./kg sdw)	CP 10.4.1.1/01

Table 2.9.4-4: Endpoints and effect values for IKI-220 100 OD relevant for the risk assessment for earthworms

Species	Substance	Exposure System	Results for effects on reproduction	Reference
Eisenia fetida	IKI-220 100 OD	Mixed into substrate 56 d, chronic 10 % peat content	NOEC ≥ 100 mg/kg sdw (NOEC ≥ 10.2 mg a.s./kg sdw) *	CP 10.4.1.1/01
Eisenia fetida	IKI-220 100 OD	Mixed into substrate 56 d, chronic 10 % peat content	NOEC ≥ 1050 mg/kg sdw (**NOEC ≥ 105 mg a.s./kg sdw**)	CP 10.4.1.1/02

Values in **bold** are used for the risk assessment
* EC_{10} not determined due to limit test design

Other non-target soil macro-organisms than earthworms

Chronic toxicity studies are available for flonicamid, its metabolites and the representative formulations.

Table 2.9.4-5: Endpoints and effect values for Flonicamid and its metabolites relevant for the risk assessment for soil non-target macro-organisms other than earthworms

Species	Substance	Exposure System	Results for effects on reproduction	Reference
Folsomia candida	Flonicamid	Mixed into substrate 28 d, chronic 5 % peat content	**NOEC ≥ 50 mg a.s./kg sdw** EC_{10} > 50 mg a.s./kg sdw EC_{20} > 50 mg a.s./kg sdw	CA 8.4.2.1/01
Folsomia candida	TFNA-AM	Mixed into substrate 28 d, chronic 5 % peat content	**NOEC ≥ 125 mg/kg sdw** EC_{10} > 125 mg/kg sdw EC_{20} > 125 mg/kg sdw	CA 8.4.2.1/03
Folsomia candida	TFA *	Mixed into substrate 28 d, chronic 5 % peat content	**NOEC ≥ 100 mg/kg sdw** EC_{10} > 100 mg a.s./kg sdw EC_{20} > 100 mg a.s./kg sdw	CA 8.4.2.1/05
Hypoaspis aculeifer	Flonicamid	Mixed into substrate 14 d, chronic 5 % peat content	**NOEC = 250 mg a.s./kg sdw** EC_{10} = 543.2 mg a.s./kg sdw EC_{20} = 896.8 mg a.s./kg sdw	CA 8.4.2.1/02
Hypoaspis aculeifer	TFNA-AM	Mixed into substrate 14 d, chronic 5 % peat content	**NOEC = 250 mg/kg sdw** EC_{10} = 250.7 mg/kg sdw EC_{20} = 363.9 mg/kg sdw	CA 8.4.2.1/04
Hypoaspis aculeifer	TFA *	Mixed into substrate 14 d, chronic 5 % peat content	**NOEC ≥ 100 mg/kg sdw** EC_{10} > 100 mg a.s./kg sdw EC_{20} > 100 mg a.s./kg sdw	CA 8.4.2.1/06

* tested as Trifluoroacetic acid sodium salt
Values in **bold** are used in the quantitative risk assessment

Table 2.9.4-6: Endpoints and effect values for IKI-220 500 WG relevant for the risk assessment for soil non-target macro-organisms other than earthworms

Species	Substance	Exposure System	Results for effects on reproduction	Reference
Hypoaspis aculeifer	IKI-220 500 WG	Mixed into substrate 14 d, chronic 5 % peat content	NOEC ≥ 1000 mg/kg dw EC_{10} > 1000 mg/kg dw (NOEC ≥ 484 mg a.s./kg dw EC_{10} > 484 mg a.s./kg dw)	CP 10.4.2.1/02
Folsomia candida	IKI-220 500 WG	Mixed into substrate 28 d, chronic 5 % peat content	NOEC = 42.7 mg/kg dw EC_{10} = 51.9 mg/kg dw (**NOEC = 20.7 mg a.s./kg dw** EC_{10} = 25.1 mg a.s./kg dw)	CP 10.4.2.1/01

Values in **bold** are used in the quantitative risk assessment

Table 2.9.4-7: Endpoints and effect values for IKI-220 100 OD relevant for the risk assessment for soil non-target macro-organisms other than earthworms

Species	Substance	Exposure System	Results for effects on reproduction	Reference
Hypoaspis aculeifer	IKI-220 100 OD	Mixed into substrate 14 d, chronic 5 % peat content	NOEC ≥ 100 mg/kg dw * (**NOEC ≥ 10.2 mg a.s./kg dw)**	CP 10.4.2.1/02
Folsomia candida	IKI-220 100 OD	Mixed into substrate 28 d, chronic 5 % peat content	NOEC ≥ 100 mg/kg dw EC_{10} > 100 mg/kg dw) ** **(NOEC ≥ 10.2 mg a.s./kg dw** EC_{10} > 10.2 mg a.s./kg dw)	CP 10.4.2.1/01

Values in **bold** are used for the risk assessment
* EC_{10} not determined due to limit test design
** estimated as no EC_{10} values were included in the study report

2.9.5 Summary of effects on soil nitrogen transformation

Studies on the effects to soil nitrogen transformation are available for the formulations IKI-220 500 WG and IKI-220 100 OD, and the metabolite TFA. Effects smaller than 25 % are considered acceptable.

Table 2.9.5-1: Endpoints and effect values for IKI-220 500 WG and the metabolite TFA relevant for the risk assessment for soil micro-organisms

Substance	Exposure System	Effects on soil nitrogen transformation at test end	Reference
IKI-220 500 WG	28 d, aerobic soil type	-6 % at **0.140** mg a.s./kg soil dw	CP 10.5/01
IKI-220 100 OD	28 d, aerobic soil type	+23.8 % at **0.792** mg a.s./kg soil dw	CP 10.5/01
TFA *	28 d, aerobic soil type	+3.1 % at 0.32 mg/kg soil dw +24.2 % at **1.60** mg/kg soil dw	CA 8.5/02

* tested as Trifluoroacetic acid sodium salt
Values in **bold** are used for the risk assessment

2.9.6 Summary of effects on terrestrial non-target higher plants

A screening study similar to OECD test guidelines 208 (seedling emergence) and OECD 227 (vegetative vigour) is available for the formulation IKI-220 500 WG. For IKI-220 100 OD an OECD 208 seedling emergency study is available.

Table 2.9.6-1: Endpoints and effect values for non-target terrestrial plants

Species	Substance	Exposure System	Results	Reference
D: (12 species): beet, cucumber, eggplant, lettuce, melon, oilseed rape, pea, pepper, soybean, turnip, kidney bean and flax M: (5 species): maize, oat, wheat, onion and barley	IKI-220 500 WG	Spray of soil with 100 and 300 g a.s./ha (seedling emergence)	No phytotoxicity ER_{50} > 300 g a.s./ha	CP 10.6.1/01
D: (8 species): beet, lettuce, melon, oilseed rape, pea, soybean, eggplant and pepper M (3 species): maize, oat and wheat	IKI-220 500 WG	Spray of seedlings with 100 and 200 g a.s./ha (vegetative vigour)	No phytotoxicity ER_{50} > 200 g a.s./ha	CP 10.6.1/01
D: Cucumber, carrot, lettuce, radish, soybean and tomato M: maize, oat, onion and perennial ryegrass	IKI-220 100 OD	Spray of soil with 117.1 g a.s./ha (seedling emergence)	No phytotoxicity ER_{50} > 117.1 g a.s./ha	CP 10.6.2/01

M: monocotyledonous; D: dicotyledonous

2.9.7 Summary of effects on other terrestrial organisms (flora and fauna)

No further data are available.

2.9.8 Summary of effects on biological methods for sewage treatment

In a respiration inhibition test IKI-220 500 WG had no significant inhibitory effect (< 15 %) on the respiration rate up to and including the highest test concentration of 1000 mg product/L. Accordingly, the 3-hour EC_{50} of IKI-220 500 WG is greater than 1000 mg product/L and the 3-hour NOEC is determined to be at least 1000 mg product/L (nominal).

2.9.9 Summary of product exposure and risk assessment

2.9.9.1 Risk assessment for birds

Full details of the risk assessment are given in the respective Vol3, B.9. The risk assessment has been performed according to "European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals on request from EFSA" (EFSA Journal 2009; 7(12):1438. doi:10.2903/j.efsa.2009.1438), referred to in the following as "EFSA GD 2009".

The TER short-term values calculated in the acute risk assessment at the screening level exceed the trigger of 10 indicating low acute risk to birds from following application of IKI-220 500 WG and IKI-220 100 OD at the proposed label rates. The TER_{LT} value calculated in the reproductive risk assessment at the Screening level exceed

the trigger of 5, indicating low long-term risk to birds following application of IKI-220 500 WG and IKI-220 100 OD at the proposed label rate.

As the ratios of effective application rate (in g/ha) to the relevant endpoint (in mg/kg bw/d) do not exceed the value of 50 for Flonicamid (Koc = 5.9 L/kg), it is not necessary to conduct a drinking water risk assessment for birds.

The log P_{OW} value of Flonicamid is 0.10, which is below the trigger value of 3. In addition, the log P_{OW} of the metabolites are also less than 3. Therefore, flonicamid and its metabolites are not expected to have potential for bioaccumulation and it is not necessary to further consider the risk from secondary poisoning.

In the plant metabolism studies, the metabolites occurring to more than 10 % TRR were TFNG, TFNG-AM and TFNA. Based on the results from a hen metabolism study, a poultry feeding study and mammalian toxicity studies, the potential risk of exposure to these metabolites in plant feed is considered to be covered by the risk assessment for the parent. In the hen metabolism study, the main metabolite was TFNA-AM (96.6 % TRR) and TFNA was mainly excreted. Although TFNG was not detected in the hen metabolism study, it had no reported adverse effects in a poultry feeding study when fed up to 25.83 mg a.s./kg feed. The metabolites TFNA-AM, TFNG-AM, TFNA and TFNG were less toxic than the parent in mammalian toxicity studies without triggering further testing. Thus, it is unlikely that metabolites could pose a risk for birds that would not be covered by the risk assessment for the parent.

IKI-220 500 WG

Table 9.9.1-2.9.9.1-1: Acute risk assessment for birds exposed to Flonicamid after application of IKI-220 500 WG (screening step) (using LD_{50} 1591 mg a.s./kg bw/d (acute) and 301.8 mg a.s./kg bw (dietary)

Crop	Indicator species	Application Rate [kg a.s./ha]	MAF (90th perc.)	Short cut value (90th perc. RUD)	Daily Dietary Dose [mg a.s./kg bw]	TER_A	TER dietary
Wheat	Small omniv. bird	0.07	1.2	158.8	13.3	119	23
Pome fruit *	Small insectiv. bird	0.07	1 [A]	46.8	3.28	486	92
			1.2 [B]		3.93	405	77
Stone fruit **	Small insectiv. bird	0.07	1 [A]	46.8	3.28	486	92
			1.2 [B]		3.93	405	77
Fruiting vegetables ***	Small omniv. bird	0.06 [C]	1.6	158.8	15.2	104	20

MAF = multiple application factor, RUD = residue unit dose, TER = toxicity exposure ratio
* comprising apple and pear
** comprising peaches, apricots, plums and cherries
*** comprising cucumber, courgette, melon, tomato and eggplant
[A] single application at BBCH 01 – 70
[B] 2 applications at BBCH 71 – 85/87
[C] field use, covering greenhouse use in non-permanent structures

Table 9.9.1-2.9.9.1-2: Reproductive risk assessment for birds exposed to Flonicamid after application of IKI-220 500 WG (screening step)(Using NOED value of 59 mg a.s./kg bw/d)

Crop	Indicator species	Application Rate [kg a.s./ha]	MAF (mean)	ftwa	Short cut value (mean RUD)	Daily Dietary Dose [mg a.s./kg bw]	TER_{LT}
Wheat	Small omniv. bird	0.07	1.23	0.53	64.8	2.96	19.9
Pome fruit *	Small insectiv. bird	0.07	1.0 [A]	0.53	18.2	0.675	87.4
			1.23 [B]			0.83	71.1
Stone fruit **		0.07	1.0 [A]	0.53	18.2	0.675	87.4
			1.23 [B]			0.83	71.1
Fruiting vegetables ***	Small omniv. bird	0.06 [C]	1.99	0.53	64.8	4.10	14.4

MAF = multiple application factor, RUD = residue unit dose, ftwa = time weighted average factor, TER = toxicity exposure ratio
* comprising apple and pear
** comprising peaches, apricots, plums and cherries
*** comprising cucumber, courgette, melon, tomato and eggplant
[A] single application at BBCH 01 – 70
[B] 2 applications at BBCH 71 – 85/87
[C] field use covering greenhouse use in non-permanent structures

Table 9.9.1-3: Acute risk assessment for birds exposed to Flonicamid after application of IKI-220 100 OD (screening step) (using LD_{50} 1591 mg a.s./kg bw/d (acute) and 301.8 mg a.s./kg bw (dietary)

Crop	Indicator species	Application Rate [kg a.s./ha]	MAF (90^{th} perc.)	Short cut value (90^{th} perc. RUD)	Daily Dietary Dose [mg a.s./kg bw]	TER_A	TER dietary
Pulses *	Small omniv. bird	0.05	1.0	158.8	7.94	200	38
Cereals **	Small omniv. bird	0.05	1.0	158.8	7.94	200	38

MAF = multiple application factor, RUD = residue unit dose, TER = toxicity exposure ratio
* comprising dry beans and peas
** comprising wheat, rye and triticale

Table 9.9.1-4: Reproductive risk assessment for birds exposed to Flonicamid after application of IKI-220 100 OD (screening step) (Using NOED value of 59 mg a.s./kg bw/d)

Crop	Indicator species	Application Rate [kg a.s./ha]	MAF (mean)	ftwa	Short cut value (mean RUD)	Daily Dietary Dose [mg a.s./kg bw]	TER_{LT}
Pulses	Small omniv. bird	0.05	1.0	0.53	64.8	1.72	34.4
Cereals	Small omniv. bird	0.05	1.0	0.53	64.8	1.72	34.4

MAF = multiple application factor, RUD = residue unit dose, ftwa = time weighted average factor, TER = toxicity exposure ratio
* comprising dry beans and peas
** comprising wheat, rye and triticale

2.9.9.2 Risk assessment for terrestrial vertebrates other than birds

Full details of the risk assessment are given in the respective Vol3, B.9. The risk assessment has been performed according to "European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals on request from EFSA" (EFSA Journal 2009; 7(12):1438. doi:10.2903/j.efsa.2009.1438), referred to in the following as "EFSA GD 2009".

The screening level TER values are above the trigger value of 10 (acute) and 5 (chronic) for the representative uses. This indicates a low acute and chronic risk to mammals from Flonicamid following application of IKI-220 500 WG and IKI-220 100 OD at all representative label rates.

Table 2.9.9.2-1: Acute risk assessment for mammals exposed to Flonicamid after application of IKI-220 500 WG (screening step)

Crop	Indicator species	Application Rate [kg a.s./ha]	MAF (90^{th} perc.)	Short cut value (90^{th} perc. RUD)	Daily Dietary Dose [mg a.s./kg bw]	TER_A
Wheat	Small herbiv mammal	0.07	1.2	118.4	9.95	88.9
Pome fruit *		0.07	1.0 [A]	136.4	9.55	92.6
			1.2 [B]		11.5	77.2

Stone fruit **		0.07	1.0 [A]	136.4	9.55	92.6
			1.2 [B]		11.5	77.2
Fruiting vegetables ***		0.06 [C]	1.6	136.4	13.1	67.5

MAF = multiple application factor, RUD = residue unit dose, TER = toxicity exposure ratio
* comprising apple and pear
** comprising peaches, apricots, plums and cherries
*** comprising cucumber, courgette, melon, tomato and eggplant
[A] single application at BBCH 01 – 70
[B] 2 applications at BBCH 71 – 85/87
[C] field use, covering greenhouse use in non-permanent structures

Table 2.9.9.2-2.9.9.2-1: Reproductive risk assessment for mammals exposed to Flonicamid after application of IKI-220 500 WG (screening step)

Crop	Indicator Species	Application Rate [kg a.s./ha]	MAF (mean)	ftwa	Short cut Value (mean RUD)	Daily Dietary Dose [mg a.s./kg bw/d]	TER_{LT}
Wheat	Small herbiv. mammal	0.07	1.23	0.53	48.3	2.20	11.4
Pome fruit *		0.07	1.0 [A]	0.53	72.3	2.68	9.32
			1.23 [B]			3.30	7.58
Stone fruit **		0.07	1.0 [A]	0.53	72.3	2.68	9.32
			1.23 [B]			3.30	7.58
Fruiting vegetables ***		0.06 [C]	1.99	0.53	72.3	4.58	5.46

MAF = multiple application factor, RUD = residue unit dose, ftwa = time weighted average factor, TER = toxicity exposure ratio
* comprising apple and pear
** comprising peaches, apricots, plums and cherries
*** comprising cucumber, courgette, melon, tomato and eggplant
[A] single application at BBCH 01 – 70
[B] 2 applications at BBCH 71 – 85/87
[C] field use, covering greenhouse use in non-permanent structures

Table 2.9.9.2-3: Acute risk assessment for mammals exposed to Flonicamid after application of IKI-220 100 OD (screening step)

Crop	Indicator species	Application Rate [kg a.s./ha]	MAF (90th perc.)	Short cut value (90th perc. RUD)	Daily Dietary Dose [mg a.s./kg bw]	TER_A
Cereals *	Small herbiv mammal	0.05	1.0	118.4	5.92	149
Pulses **		0.05	1.0	136.4	6.82	130

MAF = multiple application factor, RUD = residue unit dose, TER = toxicity exposure ratio
* comprising wheat, rye and triticale
** comprising dry beans and peas

Table 9.9.9.2-4: Reproductive risk assessment for mammals exposed to Flonicamid after application of IKI-220 100 OD (screening step)

Crop	Indicator Species	Application Rate [kg a.s./ha]	MAF (mean)	ftwa	Short cut Value (mean RUD)	Daily Dietary Dose [mg a.s./kg bw]	TER_{LT}
Cereals *	Small herbiv. mammal	0.05	1.0	0.53	48.3	1.28	19.5
Pulses **		0.05	1.0	0.53	72.3	1.92	13.0

MAF = multiple application factor, RUD = residue unit dose, ftwa = time weighted average factor, TER = toxicity exposure ratio
* comprising wheat, rye and triticale
** comprising dry beans and peas

The metabolites of Flonicamid which occurred in plants were less toxic than the parent compound in mammalian studies. All metabolites of Flonicamid which occurred in the plants also occurred in mammalian metabolism studies. Therefore, the toxicity studies with the parent are expected to cover also the toxicity of the metabolites.

As the ratios of effective application rate (in g/ha) to the relevant endpoint (in mg/kg bw/d) do not exceed the value of 50 for Flonicamid (Koc = 5.9 L/kg), it is not necessary to conduct a drinking water risk assessment for birds.

The log P_{OW} value of Flonicamid is 0.10, which is below the trigger value of 3. In addition, the log P_{OW} of the metabolites are also less than 3. Therefore, flonicamid and its metabolites are not expected to have potential for bioaccumulation and it is not necessary to further consider the risk from secondary poisoning.

2.9.9.3 Risk assessment for aquatic organisms

The risks to aquatic organisms have been assessed in accordance with the EFSA Guidance document on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters (EFSA, 2013). Full details, including Predicted Environmental Concentration (PEC) / Regulatoruy Acceptable Concentration (RAC) ratios are available in the respective Vol. 3 CP B9.3 sections.

IKI-220 500 WG

Summary of the risk assessment for Flonicamid

The relevant acute fish LC_{50} value for the rainbow trout based on toxicity studies with Flonicamid was > 100 mg a.s./L. In the chronic fish toxicity study, the 33 day NOEC was determined to be 10 mg a.s./L. In the acute toxicity study on daphnids the EC_{50} value was > 100 mg a.s./L and for *Chironomus riparius* the acute EC_{50} was 78 mg a.s./L. For daphnids the relevant endpoint is the 21 day EC_{10} of 2.82 mg a.s./L and for *Chironomus riparius* 28 day a NOEC

value of 25 mg a.s./L (concentration in overlaying water) was determined. In the toxicity studies on algae the lowest E_rC_{50} value was > 100 mg a.s./L based on the study with *Raphidocelis subcapitata*.

In the studies with the formulation IKI-220 500 WG, the acute LC_{50} value for fish, the EC_{50} value for *Daphnia magna* and the E_rC_{50} value for freshwater algae were determined to be > 51 mg a.s./L.

As all PEC/RAC ratios are less than the trigger of 1, the risk for aquatic organisms following the representative uses of IKI-220 500 WG is considered to be acceptable.

Summary of the risk assessment for Flonicamid metabolites

The relevant acute fish LC_{50} value for the rainbow trout based on toxicity studies with TFNA, TFNA-OH, TFNA-AM and TFNG-AM was > 100 mg/L. In the acute toxicity studies on daphnids the lowest EC_{50} value for TFNA, TFNA-OH, TFNA-AM and TFNG-AM was > 100 mg/L. In the toxicity studies on algae the lowest E_rC_{50} value for TFNA, TFNA-OH, TFNA-AM and TFNG-AM was > 100 mg/L.

For TFA (tested as the sodium salt), the relevant acute fish LC_{50} value for zebrafish was > 1200 mg/L. In the acute toxicity study on daphnids the EC_{50} value was > 1200 mg/L. In the toxicity study on algae the E_rC_{50} values for TFA was 192.48 mg/L. For TFNG it was assumed in the risk assessment that the toxicity is 10x higher than the parent as no data is available.

As all acute PEC/RAC ratios are less than the trigger of 1, the risk for aquatic organisms from exposure to the metabolites following the representative uses of IKI-220 500 WG is considered to be acceptable. The chronic risk for is also acceptable as $RAC_{flonicamid,\ chronic}$ > 10 x $PEC_{metabolites}$ for all scenarios.

IKI-220 100 OD

Summary of the risk assessment for Flonicamid

The relevant acute fish LC_{50} value for the rainbow trout based on toxicity studies with Flonicamid was > 100 mg a.s./L. In the chronic fish toxicity study, the 33 day NOEC was determined to be 10 mg a.s./L. In the acute toxicity study on daphnids the EC_{50} value was > 100 mg a.s./L and in the acute study with *Chironomus riparius* the EC_{50} was 78 mg a.s./L. For daphnids the relevant endpoint for the risk assessment is the 21 day EC_{10} of 2.82 mg a.s./L and for *Chironomus riparius* 28 day a NOEC value of 25 mg a.s./L (concentration in overlaying water) was determined. In the toxicity studies with Flonicamid on algae the lowest E_rC_{50} value was > 100 mg a.s./L based on the study with *Raphidocelis subcapitata*.

In the studies with the formulation IKI-220 100 OD, the acute LC_{50} value for fish, the EC_{50} value for *Daphnia magna* and the E_rC_{50} value for freshwater algae were determined to be 1.69. 7.71 and 12.6 mg a.s./L, respectively. The significantly (> 10x) higher acute toxicity of the formulated product compared to the active substance is expected to be related to co-formulants that are not expected to pose long-term exposure. Therefore, further chronic testing on the formulation is not considered necessary. In the risk assessment, the acute endpoints derived from the formulation studies are used.

As all PEC/RAC ratios are less than the trigger of 1, the risk for aquatic organisms following the representative uses of IKI-220 100 OD is considered to be acceptable.

Summary of the risk assessment for Flonicamid metabolites

The relevant acute fish LC_{50} value for the rainbow trout based on toxicity studies with TFNA, TFNA-OH, TFNA-AM and TFNG-AM was > 100 mg/L. In the acute toxicity studies on daphnids the lowest EC_{50} value for TFNA, TFNA-OH, TFNA-AM and TFNG-AM was > 100 mg/L. In the toxicity studies on algae the lowest E_rC_{50} value for TFNA, TFNA-OH, TFNA-AM and TFNG-AM was > 100 mg/L.

For TFA (tested as the sodium salt), the relevant acute fish LC_{50} value for zebrafish was > 1200 mg/L. In the acute toxicity study on daphnids the EC_{50} value was > 1200 mg/L. In the toxicity study on algae the E_rC_{50} values for TFA was 192.48 mg/L. For TFNG it was assumed in the risk assessment that the toxicity is 10x higher than the parent as no data is available.

As all acute PEC/RAC ratios are less than the trigger of 1, the risk for aquatic organisms from exposure to the metabolites following the representative uses of IKI-220 100 OD is considered to be acceptable. The chronic risk for is also acceptable as $RAC_{flonicamid,\ chronic}$ > 10 x $PEC_{metabolites}$ for all scenarios.

Overall conclusion

Based on the risk assessment for Flonicamid and its metabolites taking into account all available toxicity endpoints, it can be concluded that the acute and chronic risk for aquatic organisms is acceptable after application of IKI-220 500 WG or IKI-220 100 OD according to GAP.

2.9.9.4 Risk assessment for bees

The risk assessment was performed according to the EFSA Guidance Document on risk assessment for bees (EFSA Journal 2013;11(7):3295). Full details of the risk assessment are given in the respective Volume 3 CP, Section 9.6.1.

Screening level / Tier 1

Screening level and Tier 1 level risk assessment demonstrated acceptable risk for all assessed scenarios with the exception chronic oral risk to adult bees for the following scenarios

IKI-220 500 WG

- “weeds” when IKI-220 500 WG is applied in wheat at BBCH 10 to 29 and
- “treated crop” when IKI-220 500 WG is applied in orchards at BBCH 10 to 69 and
- “treated crop” when IKI-220 500 WG is applied in the field to fruiting vegetables at BBCH 10 to 69

IKI-220 100 OD

- “treated crop” when IKI-220 100 OD is applied in pulses at BBCH 10 to 69.

Residue decline

The risk assessment is refined taking into account decline of flonicamid in pollen and nectar. Based on residue data DT_{50} values of 1.0 d in pollen and 0.8 d in nectar were determined. Thus, there is analytical evidence of Flonicamid-specific rapid residue decline in pollen and nectar after application of the active substance under field conditions. Consequently, continuous exposure of Flonicamid, as maintained under laboratory test conditions in the chronic oral adult bee study, where bees were exposed to freshly prepared diet on a daily basis containing constant Flonicamid concentrations over ten days, is overestimating realistic exposure under field conditions. This is supported by the results of the several semi-field and field studies where an acceptable risk to honey bees is indicated when IKI-220 500 WG is applied in the evening after daily bee flight. This may be due to the rapid decline of Flonicamid residues following application.

To address residue decline quantitatively, the shortcut (SV) values used in the Tier 1 risk assessment for the oral exposure of adult bees were refined considering Flonicamid specific DT_{50} values in pollen and nectar. ETR values thus derived were below trigger values indicating acceptable risk. The risk calculation can be considered worst-case in respect to the used default TWA values (based on a default DT50 of 10 days) and the estimation for consumption of nectar (32 to 128 mg/bee/day) and pollen (12 mg/bee/day).

Higher Tier

In order to address the potential risks identified at screening / Tier 1 level, available semi-field and field studies were evaluated. Semi-field and field studies are available for IKI-220 500 WG. The results of these higher tier studies are considered applicable also for IKI-220 100 OD because acute contact and oral studies performed with IKI-220 100 OD and IKI-220 500 WG indicate comparable toxicity, i.e. the toxicity of both formulations does not differ by more than a factor of 3.

The semi-field and field studies indicate an acceptable risk to honey bees on mortality, flight intensity and brood and colony development up to and including an application rate 0.184 kg a.s./ha by showing no adverse effect or only slight and transient effects when bees are exposed to IKI-220 500 WG in the evening after daily bee flight.

The chronic oral 10-d feeding test provides the most sensitive endpoint at Tier I. Looking at the higher tier data from semi-field and field studies, increased mortality was not observed when IKI-220 500 WG is applied after bee flight. Furthermore, behavioural abnormalities observed in the laboratory were not observed in the field and did not impact the colony development as bees were not affected in their flight/forager activity, food collection and storage as well as in their brood care and nursing function.

The metabolites TFNG, TFNA, TFNG-AM, TFNA-AM and TFA were determined in pollen and nectar after application of IKI-220 500 WG to flowering *Phacelia tanacetifolia* in semi-field studies. The presence of metabolites in these semi-field studies was confirmed and therefore the potential effects on bees due to exposure to metabolites is considered to be covered by the studies. In the studies no adverse effect or only slight and transient effects were apparent when bees were exposed to IKI-220 500 WG applied in the evening after daily bee flight up to 0.184 kg a.s./ha.

In addition, ETR-values are calculated and compared with trigger values given in EFSA (2013) Guidance. For TFNA, TFNG, TFNA-AM and TFNG-AM measured ecotoxicological endpoints are used. For TFNA-OH and TFA, it is assumed that the toxicity is ten times the toxicity of the parent as no data is available. The exposure is determined based on Ftrr estimations. All ETR values for all scenarios are below the respective trigger values for acute and chronic oral toxicity and larval oral toxicity when the representative formulations (IKI-220 500 WG and IKI-220 100 OD) are applied in accordance with the GAP.

In conclusion, acceptable risk is demonstrated when the representative formulations (IKI-220 500 WG and IKI-220 100 OD) are applied at rates in accordance with the GAP.

2.9.9.5 Risk assessment for non-target arthropods other than bees

The risk assessment was performed according to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002) and the Guidance Document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods (ESCORT 2, Candolfi *et al*. 2001). Full details of the risk assessment are given in Vol. 3 CP B.9.6.2.

IKI-220 500 WG

The toxicity of IKI-220 500 WG to non-target arthropods has been investigated by carrying out Tier 1 (glass plate) and extended laboratory studies with seven species (*Typhlodromus pyri*, *Aphidius rhopalosiphi*, *Orius laevigatus*, *Episyrphus balteatus*, *Coccinella septempunctata*, *Chrysoperla carnea*, and *Poecilus cupreus*). Overall, a broad range of arthropod species, including taxa recommended as representatives for non-target arthropod fauna by the ESCORT expert panels, have been studied. *Aphidius Rhopalosiphi* was the most sensitive species. The Tier 1in-field and off-field risk assessment indicated potential risk ($HQ_{in\text{-}field} > 2$), and thus the risk assessment was refined with higher tier extended laboratory and residue studies.

Extended laboratory studies are available for *Typhlodromus pyri*, *Aphidius rhopalosiphi*, *Orius laevigatus*, *Coccinella septempunctata* and *Chrysoperla carnea*. In addition, two modified extended laboratory studies are available, one on *Aphidius rhopalosiphi*, the other on *Orius laevigatus*. The higher tier risk assessment is focussed on the most sensitive species *Aphidius rhopalosiphi* and the tested additional species *Chrysoperla carnea* and *Coccinella septempunctata.* No refined risk assessment is provided for *Typhlodromus pyri*, as an acceptable risk is already indicated based on the respective Tier 1 study.

Based on the extended studies, in-field risk for *Chrysoperla carnea* is acceptable for all representative uses. For *Coccinella septempunctata* the in-field risk is acceptable for early applications in orchards but a risk is indicated for all other uses. The higher tier in-field risk assessment for *Coccinella septempunctata* is further refined taking into account the residue decline of Flonicamid on green plant matter. Using a multiple application factor (MAF) refined with DT50 2.9 days (in plant material) acceptable in-field risk can be demonstrated (PERin-field below rate with ≤ 50 % effect in the extended study).

Based on the the extended laboratory studies, off-field risk is acceptable for *Chrysoperla carnea*, *Coccinella septempunctata* and *Orius laevigatus* for all representative uses. A risk for all representative uses is still indicated for *Aphidius rhopalosiphi*. Therefore, the off-field risk assessment is further refined by using the modified extended laboratory studies with *Aphidius rhopalosiphi.* In this study IKI-220 500 WG is applied once, twice or three times with 7-day intervals at 70 g a.s./ha under outdoor field conditions. The application rate in the study was appropriate to simulate the use pattern. No unacceptable effects (> 50 %) on mortality and reproduction of *Aphidius rhopalosiphi* on fresh dried residues were observed. Thus the study demonstrates acceptable off-field risk when when IKI-220 500 WG is applied at rates in accordance with the GAP.

A literature search revealed 37 publications with information on different non-target arthropods assessed under laboratory conditions, extended and/or aged residue laboratory conditions and under field conditions. Compared with the available data set of guideline compliant studies none of the evaluated open literature publications indicate a significantly higher sensitivity of a NTA species, or exposure routes more relevant than those already addressed in the risk assessment.

In conclusion, acceptable in-field and off-field risk is demonstrated when IKI-220 500 WG is applied at rates in accordance with the GAP.

Tier 1 assessment

Table 2.9.9.5-1: In-field risk assessment for non-target arthropods for the representative uses of IKI-220 500 WG (Tier I, based on glass plate studies)

Crop	Application rate [g a.s./ha]	ER_{50} [g a.s./ha]	MAF	$PER_{in\text{-}field}$ [g a.s./ha]	$HQ_{in\text{-}field}$ criterion: HQ ≤ 2
Typhlodromus pyri					
Wheat	70	> 273	1.7	119	< 0.436
Pome and stone fruit (single application, early)	70		1	70	< 0.256
Pome and stone fruit (two applications, late)			1.7	119	< 0.436
Fruiting vegetables *	60		2.3	138	< 0.505
Aphidius rhopalosiphi					
Wheat	70	6.18	1.7	119	**19.3**
Pome and stone fruit (single application, early)	70		1	70	**11.3**
Pome and stone fruit (two applications, late)			1.7	161	**19.3**
Fruiting vegetables *	60		2.3	138	**22.3**

MAF = multiple application factor, PER: Predicted environmental rate; HQ: Hazard quotient;
* field uses, covering greenhouse uses in non-permanent structures
Criteria values shown in bold breach the relevant trigger

Table 2.9.9.5-2: Off-field risk assessment for non-target arthropods for the representative uses of IKI-220 500 WG (Tier I, based on glass plate studies)(VDF = 5, CF =10)

Crop	Application rate [g a.s./ha]	ER_{50} [g a.s./ha]	MAF	Drift value [%]	$PER_{off\text{-}field}$ [g a.s./ha]	$HQ_{off\text{-}field}$ criterion: HQ ≤ 2
Typhlodromus pyri						
Wheat	70	> 273	1.7	2.38	5.66	< 0.021
Pome and stone fruit (single application, early)	70		1.0	29.2	40.9	< 0.150
Pome and stone fruit (two applications, late)	70		1.7	12.13	28.9	< 0.106
Fruiting vegetables *	60		2.3	2.01	5.55	< 0.020
Fruiting vegetables **	60		2.3	6.90	19.0	< 0.070
Aphidius rhopalosiphi						
Wheat	70	6.18	1.7	2.38	5.66	0.917
Pome and stone fruit (single application, early)	70		1.0	29.2	40.9	**6.62**
Pome and stone fruit (two applications, late)	70		1.7	12.13	28.9	**4.67**
Fruiting vegetables*	60		2.3	2.01	5.55	0.898
Fruiting vegetables **	60		2.3	6.90	19.0	**3.08**

MAF = multiple application factor, PER: Predicted environmental rate; HQ: Hazard quotient;
* field use, plant height < 50 cm, covering greenhouse use in non-permanent structures
** field use, plant height > 50 cm, covering greenhouse use in non-permanent structures
Criteria values shown in bold breach the relevant trigger

Higher tier

Table 2.9.9.5-3: In-field risk assessment for non-target arthropods (*Chrysoperla carnea* and *Coccinella septempunctata*) for the representative uses of IKI-220 500 WG (Higher tier - based on extended laboratory studies)

Crop	Application rate [g a.s./ha]	Rate with ≤ 50 % effect [g a.s./ha]	MAF	$PER_{in\text{-}field}$ [g a.s./ha]	$PER_{in\text{-}field}$ below rate with ≤ 50 % effect?
Chrysoperla carnea					
Wheat	70	> 183 *	1.7	119	Yes
Pome and stone fruit (single application, early)	70		1.0	70	Yes
Pome and stone fruit (two applications, late)	70		1.7	119	Yes
Fruiting vegetables **	60		2.3	138	Yes
Coccinella septempunctata					
Wheat	70	> 85 *	1.7	119	**No**
Pome and stone fruit (single application, early)	70		1.0	70	Yes
Pome and stone fruit (two applications, late)	70		1.7	119	**No**
Fruiting vegetables **	60		2.3	138	**No**

MAF = multiple application factor, PER: Predicted environmental rate; HQ: Hazard quotient;
* LR_{50}/ER_{50}
** field uses, covering the greenhouse use (non-permanent structures)
Criteria values shown in bold breach the relevant trigger

Table 2.9.9.5-4: Refined in-field risk assessment for non-target arthropods (*Coccinella septempunctata*) for the representative uses of IKI-220 500 WG (Higher tier - based on extended laboratory studies and refined MAF using DT50 2.9 days in plant material)

Crop	Application rate [g a.s./ha]	Rate with ≤ 50 % effect [g a.s./ha]	MAF	$PER_{in\text{-}field}$ [g a.s./ha]	$PER_{in\text{-}field}$ below rate with ≤ 50 % effect?
Coccinella septempunctata					
Wheat	70	> 85 *	1.0	70	Yes
Pome and stone fruit (two applications, late)	70		1.0	70	Yes
Fruiting vegetables **	60		1.3	78	Yes

MAF = multiple application factor, PER: Predicted environmental rate; HQ: Hazard quotient;
* LR_{50}/ER_{50}
** field uses, covering the greenhouse use (non-permanent structures)
Criteria values shown in bold breach the relevant trigger

Table 2.9.9.5-5: Off-field risk assessment for non-target arthropods for the representative uses of IKI-220 500 WG (Higher tier, based on extended laboratory studies)

Crop	Application rate [g a.s./ha] in GAP	Rate with ≤ 50 % effect [g a.s./ha]	MAF	Drift value [%]	$PER_{off\text{-}field}$ [g a.s./ha] [A]	$PER_{off\text{-}field}$ below rate with ≤ 50 % effect?
Aphidius rhopalosiphi						
Wheat	70	4.21 *****	1.7	2.38	14.2	**No**
Pome and stone fruit (single application, early)	70		1.0	29.2	102	**No**
Pome and stone fruit (two applications, late)	70		1.7	12.13	72.2	**No**
Fruiting vegetables *	60		2.3	2.01	13.9	**No**
Fruiting vegetables **	60		2.3	6.90	47.6	**No**
Chrysoperla carnea / Orius laevigatus						
Wheat	70	> 183 ****	1.7	2.38	2.83	Yes
Pome and stone fruit (single application, early)	70		1.0	29.2	20.44	Yes
Pome and stone fruit (two applications, late)	70		1.7	12.13	14.4	Yes
Fruiting vegetables *	60		2.3	2.01	2.77	Yes
Fruiting vegetables **	60		2.3	6.90	9.52	Yes
Coccinella septempunctata						
Wheat	70	> 85 ****	1.7	2.38	2.83	Yes
Pome and stone fruit (single application, early)	70		1.0	29.2	20.44	Yes
Pome and stone fruit (two applications, late)	70		1.7	12.13	14.4	Yes
Fruiting vegetables *	60		2.3	2.01	2.77	Yes
Fruiting vegetables **	60		2.3	6.90	9.52	Yes

MAF = multiple application factor, PER: Predicted environmental rate; HQ: Hazard quotient;
[A] PER include a vegetation distribution factor (VDF) of 5 for 2D exposure (*T. pyri*, *C. carnea* and *O. laevigatus*). In the studies with 3D design (*A. rhopalosiphi*) no VDF is used
* field use, plant height < 50 cm, covering greenhouse use in non-permanent structures
** field use, plant height > 50 cm, covering greenhouse use in non-permanent structures
**** LR_{50}/ER_{50}
***** ER_{50}
Criteria values shown in bold breach the relevant trigger

Table 2.9.9.5-6: Refined drift rates for the representative uses of IKI-220 500 WG

Crop	Crop group (ESCORT 2)	Application rate [g a.s./ha] in GAP	MAF / VDF	Correction factor	Drift value [%]	Drift rate [g a.s./ha]
Wheat	Field crops	70	1.0	3	2.77	5.8
Pome and stone fruit	Early	70	1.0	3	29.2	61.3
	Late	70	1.0	3	15.73	33.0
Fruiting vegetables	Vegetables, ornamentals, small fruits (height < 50 cm)	60 *	1.3	3	2.77	6.5
	Vegetables, ornamentals, small fruits (height > 50 cm)	60*	1.3	3	8.02	18.8

Drift rate in calculated according to Equation 4 in Escort 2.
MAF = multiple application factor, refined using DT50 2.9 days for plant material
VFD = Vegetation distribution facto (VFD = 1)
* field use, covering greenhouse uses in non-permanent structures

Table 2.9.9.5-7: Refined off-field risk assessment for *Aphidius rhopalosiphi* for the representative uses of IKI-220 500 WG based on modified extended laboratory studies

Crop	Drift rate [g a.s./ha]	Application rate in study [g a.s./ha]	Effects on mortality [%]	Effects on reproduction [%] *	Risk indicated?
Wheat	5.8	3 x 70 (7 d)	15.4	-9.1	No
Pome and stone fruit (single application, early)	61.3	3 x 70 (7 d)	15.4	-9.1	No
Pome and stone fruit (two applications, late)	33.0	3 x 70 (7 d)	15.4	-9.1	No
Fruiting vegetables, small fruits (height < 50 cm)**	6.5	3 x 70 (7 d)	15.4	-9.1	No
Fruiting vegetables, small fruits (height > 50 cm)**	18.8	3 x 70 (7 d)	15.4	-9.1	No

Drift rate is calculated according to Equation 4 in Escort 2.
* negative values indicate a better reproductive performance compared to the control
** field uses, covering the greenhouse use (non-permanent structures)

IKI-220 100 OD

The toxicity of IKI-220 100 OD to non-target arthropods was investigated by carrying out Tier 1 (glass-plate) and extended laboratory studies with four species (*Typhlodromus pyri*, *Aphidius rhopalosiphi*, *Chrysoperla carnea*, and *Coccinella septempunctata*). *Aphidius Rhopalosiphi* was the most sensitive species. The Tier 1 risk assessment indicated potential in-field and off-field risks. Therefore, the risk assessment was refined with higher tier extended and aged residue laboratory studies. Based on the extended laboratory studies the off-field risk is considered acceptable, whereas potential in-field risk is still indicated. The remaining risk is addressed by an aged residue laboratory study with *Aphidius rhopalosiphi*. In the study there were no effects > 50 % on mortality or reproduction of *Aphidius rhopalosiphi* after 14 days of residue aging when IKI-220 100 OD was applied at 2 x 58.6 g a.s./ha (21 days interval) under semi-field conditions. The study demonstrates that recovery of non-target arthropods is possible within two weeks after application of IKI-220 100 OD. Thus, the in-field risk is considered acceptable.

A literature search revealed 37 publications with information on different non-target arthropods assessed under laboratory conditions, extended and/or aged residue laboratory conditions and under field conditions. Compared with the available data set of guideline compliant studies none of the evaluated open literature publications indicate

a significantly higher sensitivity of a NTA species, or exposure routes more relevant than those already addressed in the risk assessment.

In conclusion, acceptable risk is demonstrated when IKI-220 100 OD is applied at rates in accordance with the GAP.

Tier I assessment

Table 2.9.9.5-8: In-field risk assessment for non-target arthropods for the representative uses of IKI-220 100 OD (Tier I, based on glass plate studies)

Crop	Application rate [g a.s./ha]	LR_{50} [g a.s./ha]	MAF	$PER_{in\text{-}field}$ [g a.s./ha]	$HQ_{in\text{-}field}$ criterion: HQ ≤ 2
Typhlodromus pyri					
Pulses	50	50.2	1	50	0.996
Cereals	50		1	50	0.996
Aphidius rhopalosiphi					
Pulses	50	< 1.95 *	1	50	> **25.6**
Cereals	50		1	50	> **25.6**

MAF = multiple application factor, PER: Predicted environmental rate; HQ: Hazard quotient;
* ER_{50}
Criteria values shown in bold breach the relevant trigger

Table 2.9.9.5-9: Off-field risk assessment for non-target arthropods for the representative uses of IKI-220 100 OD (Tier I, based on glass plate studies)

Crop	Application rate [g a.s./ha]	LR_{50} [g a.s./ha]	MAF	Drift value [%]	$PER_{off\text{-}field}$ [g a.s./ha]	$HQ_{off\text{-}field}$ criterion: HQ ≤ 2
Typhlodromus pyri						
Pulses	50	50.2	1	2.77	2.77	0.055
Cereals	50		1	2.77	2.77	0.055
Aphidius rhopalosiphi						
Pulses	50	< 1.95 *	1	2.77	2.77	> 1.42
Cereals	50		1	2.77	2.77	> 1.42

MAF = multiple application factor, PER: Predicted environmental rate; HQ: Hazard quotient;
* ER_{50}
Criteria values shown in bold breach the relevant trigger

Higher Tier assessment

Table 2.9.9.5-10: In-field risk assessment for non-target arthropods for the representative uses of IKI-220 500 WG (Higher Tier , based on extended laboratory studies)

Crop	Application rate [g a.s./ha]	Rate with ≤ 50 % effect [g a.s./ha]	MAF	$PER_{in-field}$ [g a.s./ha]	$PER_{in-field}$ below rate with ≤ 50 % effect?
Aphidius rhopalosiphi					
Pulses	50	30.6 **	1	50	**No**
Cereals	50		1	50	**No**
Chrysoperla carnea					
Pulses	50	> 292.8 ***	1	50	Yes
Cereals	50		1	50	Yes
Coccinella septempunctata					
Pulses	50	> 341.6 ***	1	50	Yes
Cereals	50		1	50	Yes

MAF = multiple application factor, PER: Predicted environmental rate; HQ: Hazard quotient;
* LR_{50}
** ER_{50}
*** LR_{50}/ER_{50}
Criteria values shown in bold breach the relevant trigger

Table 2.9.9.5-11: Off-field risk assessment for non-target arthropods for the representative uses of IKI-220 100 OD (Higher tier, based on extended laboratory studies)

Crop	Application rate [g a.s./ha]	Rate with ≤ 50 % effect [g a.s./ha]	MAF	Drift value [%]	$PER_{off-field}$ [g a.s./ha] [A]	$PER_{off-field}$ below rate with ≤ 50 % effect?
Aphidius rhopalosiphi						
Pulses	50	30.6 *** 3D	1	2.77	6.93	Yes
Cereals	50		1	2.77	6.93	Yes
Chrysoperla carnea						
Pulses	50	> 292.8 ***2D	1	2.77	1.39	Yes
Cereals	50		1	2.77	1.39	Yes
Coccinella septempunctata						
Pulses	50	> 341.6 ***2D	1	2.77	1.39	Yes
Cereals	50		1	2.77	1.39	Yes

MAF = multiple application factor, PER: Predicted environmental rate; HQ: Hazard quotient;
[A] PER include a risk assessment correction factor of 5 and a vegetation distribution factor (VDF) of 5 for 2D exposure (*C. carnea* and *C. septempunctata*). In the studies with 3D design (*A. rhopalosiphi*) no VDF is used
* LR_{50}
** ER_{50}
*** LR_{50}/ER_{50}
Criteria values shown in bold breach the relevant trigger

2.9.9.6 Risk assessment for non-target soil meso- and macrofauna

The risk assessment for non-target soil meso- and macrofauna follows the procedure given in the Guidance Document on Terrestrial Ecotoxicology. Full details of the risk assessment is given in the respective Vol3, B.9.

Earthworms

The exposure to earthworms was estimated by calculating the maximum initial predicted environmental concentrations in soil (PEC_{soil}) and comparing these concentrations with the toxicity endpoints. All TER values for Flonicamid and for its metabolites were greater than the required trigger for chronic toxicity. Considering the fact that the calculations represent worst-case scenarios, the risk of chronic effects on earthworms after application of representative formulations according to the GAP is considered to be low.

IKI-220 500 WG

Table 9.9.9.6-1: First-tier assessment of the chronic risk for earthworms from exposure to Flonicamid after application of IKI-220 500 WG according to the GAP

Representative use	NOEC [mg a.s./kg dw]	PEC_{soil} [mg a.s./kg dw]	TER_{LT} * (criterion TER ≥ 5)
Wheat (BBCH 21)	250	0.075	3 333
Wheat (BBCH 39)	250	0.019	13369
Pome fruit (apple, pear) and stone fruit (peach, apricot, plum, cherry)	250	0.047 / 0.033 **	5353 / 7645
Fruiting vegetables, field use (cucumber, courgette, melon)	250	0.036	6909
Fruiting vegetables, greenhouse use (cucumber, courgette)	250	0.058	4310
Fruiting vegetables, field and greenhouse use (tomato, eggplant)	250	0.043	5814

* TER values are calculated with unrounded PEC values as presented in the List of Endpoints.
** PEC values for early and late applications, respectively

IKI-220 100 OD

Table 9.9.9.6-2: First-tier assessment of the chronic risk for earthworms from exposure to Flonicamid after application of IKI-220 100 OD according to the GAP

Representative use	NOEC [mg a.s./kg dw]	PEC_{soil} [mg a.s./kg dw]	TER_{LT} * (criterion TER ≥ 5)
Beans	250 **	0.050	5000
Peas		0.043	5774
Cereals (winter and spring wheat, rye, triticale)		0.013	18797
Beans	≥ 105***	0.050	2100
Peas		0.043	2442
Cereals (winter and spring wheat, rye, triticale)		0.013	8077

* TER values are calculated with unrounded PEC values as presented in the List of Endpoints.
** endpoint from the study with the active substance
*** endpoint from the study with the formulation

Other non-target soil macro-organisms than earthworms

The exposure to other soil non-target macro-organisms was estimated by calculating the maximum initial predicted environmental concentrations in soil (PEC_{soil}) and comparing these concentrations with the toxicity endpoints.

All TER values for Flonicamid and its metabolites were greater than the required trigger for chronic toxicity. Considering the fact that the calculations represent worst-case scenarios, the risk of chronic effects on other soil non-target macro-organisms after application of the representative formulations according to the GAP is considered to be low.

IKI-220 500 WG

Table 2.9.9.6-3: Chronic risk for other soil non-target macro-organisms exposed to Flonicamid after application of IKI-220 500 WG to wheat

Species	Use	NOEC [mg a.s./kg dw]	PEC_{soil} [mg a.s./kg dw] (BBCH 21 / BBCH 39)	TER_{LT} * (criterion TER ≥ 5)
Folsomia candida	Wheat	20.7	0.075 / 0.019	276 / 1089
Hypoaspis aculeifer		250		3333 / 13 158

* TER values calculated with unrounded PEC values as presented in the List of Endpoints.

Table 2.9.9.6-4: Chronic risk for other soil non-target macro-organisms exposed to Flonicamid after application of IKI-220 500 WG to pome and stone fruit

Species	Use	NOEC [mg a.s./kg dw]	PEC_{soil} * [mg a.s./kg dw]	TER_{LT} ** (criterion TER ≥ 5)
Folsomia candida	Pome and stone fruit	20.7	0.047 / 0.033	440/627
Hypoaspis aculeifer		250		5319 / 7576

* PEC values for early / late aplications, respectively
** TER values for early / late aplications calculated with unrounded PEC values as presented in CP 9.1.3.

Table 2.9.9.6-5: Chronic risk for other soil non-target macro-organisms exposed to Flonicamid after application of IKI-220 500 WG to fruiting vegetables (field and greenhouse uses)

Species	Use	NOEC [mg a.s./kg dw]	PEC_{soil} [mg a.s./kg dw]	TER_{LT} * (criterion TER ≥ 5)
Folsomia candida	Cucumber, courgette, melon (field use)	20.7	0.036	572
Hypoaspis aculeifer		250		6944
Folsomia candida	Cucumber, courgette (greenhouse use)	20.7	0.058	357
Hypoaspis aculeifer		250		4310
Folsomia candida	Tomato, eggplant (field & greenhouse use)	20.7	0.043	481
Hypoaspis aculeifer		250		5814

* TER values calculated with unrounded PEC values as presented in the List of Endpoints.

IKI-220 100 OD

Table 2.9.9.6-6: Chronic risk for other soil non-target macro-organisms exposed to Flonicamid after application of IKI-220 100 OD to pulses (beans and peas)

Species	Use	NOEC [mg a.s./kg dw]	PEC_{soil} [mg a.s./kg dw]	TER_{LT} * (criterion TER ≥ 5)
Folsomia candida	Beans	50 **	0.050	1000
Hypoaspis aculeifer		250 **		5000
Folsomia candida	Beans	10.2 ***	0.050	204
Hypoaspis aculeifer				204
Folsomia candida	Peas	50 **	0.043	1163
Hypoaspis aculeifer		250 **		5814
Folsomia candida	Peas	10.2 ***	0.043	236
Hypoaspis aculeifer				236

* TER values calculated with unrounded PEC values as presented in CP 9.1.3.
** endpoint from active substance study
*** endpoint from formulation study

Table 2.9.9.6-7: Chronic risk for other soil non-target macro-organisms exposed to Flonicamid after application of IKI-220 100 OD to cereals (wheat, rye and triticale)

Species	Use	NOEC [mg a.s./kg dw]	PEC_{soil} [mg a.s./kg dw]	TER_{LT} * (criterion TER ≥ 5)
Folsomia candida	Cereals (wheat, rye and triticale)	50 **	0.013	3846
Hypoaspis aculeifer		250 **		19231
Folsomia candida		10.2 ***	0.013	785
Hypoaspis aculeifer				785

* TER values calculated with unrounded PEC values as presented in the List of Endpoints.
** endpoint from active substance study
*** endpoint from formulation study

2.9.9.7 Risk assessment for N-transformation in soil

The evaluation of the risk for soil nitrogen trasformation was performed following recommendations of the "Guidance Document on Terrestrial Ecotoxicology"(SANCO/10329/2002 rev 2 (final), October 17, 2002) and the OECD 216 test guideline. Full details of the risk assessment is given in the respective Vol3, B.9.

Studies on the effects to soil nitrogen transformation are available for the formulations IKI-22 500 WG, IKI-220 100 OD and the metabolite TFA. The maximum concentrations tested in the laboratory showing no effects > 25 % exceed PECsoil values for both flonicamid and TFA. The other relevant metabolites than TFA (TFNA, TFNA-AM, TFNA-OH, TFNG, TFNG) are rapidly degraded in soil (DT_{50} < 5d), and are thus considered covered by the risk assessment for the parent ,i.e. flonicamid. A low risk for soil nitrogen transformation from exposure to Flonicamid and/or its metabolites can be concluded after application of IKI 220 500 WG and IKI-220 100 OD.

IKI-220 500 WG

Table 2.9.9.7-1: Chronic risk for soil nitrogen transformation exposed to Flonicamid after application of IKI-220 500 WG

Endpoint	Representative use	NOEC * [mg a.s./kg dw]	PEC_{soil} [mg a.s./kg dw]	Risk acceptable?
Nitrogen transformation	Wheat	0.140	0.019	Yes
	Pome fruit (apple, pear) and stone fruit (peach, apricot, plum, cherry)	0.140	0.047 / 0.033	Yes
	Fruiting vegetables (cucumber, courgette, melon; field use)	0.140	0.036	Yes
	Fruiting vegetables (cucumber, courgette; greenhouse use)	0.140	0.058	Yes
	Fruiting vegetables (tomato, eggplant; field and greenhouse use)	0.140	0.043	Yes

* Maximum concentration with effects ≤ 25 %

Table 2.9.9.7-2: Chronic risk for soil nitrogen transformation exposed to TFA after application of IKI-220 500 WG

Endpoint	Use	NOEC * [mg/kg dw]	PEC_{soil} ** [mg/kg dw]	Risk acceptable?
Nitrogen transformation	Wheat	1.60	0.008	Yes
	Pome and stone fruit, early		0.023	Yes
	Pome and stone fruit, late		0.033	Yes
	Cucumber, courgette, melon (field use)		0.021	Yes
	Cucumber, courgette (greenhouse use)		0.034	Yes
	Tomato, eggplant (field and greenhouse use)		0.025	Yes

* Maximum concentration with effects ≤ 25 %
** $PEC_{accumulation}$ (sum of initial and plateau PEC)

IKI-220 100 OD

Table 2.9.9.7-3: Chronic risk for soil nitrogen tranformation exposed to Flonicamid after application of IKI-220 100 OD

Endpoint	Representative use	NOEC * [mg a.s./kg dw]	PEC_{soil} [mg a.s./kg dw]	Risk acceptable?
Nitrogen transformation	Dry beans	0.792	0.050	Yes
	Dry peas	0.792	0.043	Yes
	Cereals (wheat, rye, triticale)	0.792	0.013	Yes

* Maximum concentration with effects ≤ 25 %

Table 2.9.9.7-4: Chronic risk for soil nitrogen transformation exposed to TFA after application of IKI-220 100 OD

Endpoint	Use	NOEC * [mg/kg dw]	PEC_{soil} ** [mg/kg dw]	Risk acceptable?
Nitrogen transformation	Beans	1.60	0.011	Yes
	Peas		0.009	Yes
	Cereals		0.003	Yes

* Maximum concentration with effects ≤ 25 %
** $PEC_{accumulation}$ (sum of initial and plateau PEC)

2.9.9.8 Risk assessment for non-target plants

No phytotoxic effects are observed in the available information when the representative formulaitons (IKI 220 500 WG and IKI 220 100 OD) were applied at rates exceeding the application rates according to GAP.

Flonicamid caused no significant effects or growth inhibition in the freshwater aquatic plant *Lemna gibba* G3 after a test period of 7 days. The 7-day EC_{50}-values for the growth parameters were determined to be in excess of the highest measured concentration in the test, i.e. 119 mg a.s./L.

An adverse effect on succeeding crops is not expected since no significant residues remain in soil. The degradation of Flonicamid is rapid in soil with worst case DT_{50} of 1.92 days at 20°C under aerobic conditions. Similarly, the degradation of all soil metabolites, with the exception of TFA, is rapid. Worst case DT_{50} values ranged between 1.01 days and 4.57 days for the metabolites TFNA, TFNA-OH, TFNG, TFNG-AM and TFNA-AM. Moreover, due to degradation of flonicamid and its metabolites, it is not expected that the residues in plant materials will lead to significant residues.

Based on the available information on flonicamid containing formulations, toxicity of Flonicamid to the aquatic plant *Lemna gibba*, and efficacy studies, the RMS consideres that adverse effects on non-target plants are unlikely at the proposed application rates, and that no further testing is required.

Table 2.9.9.8-1: Tier 1 Risk assessment for terrestrial non-target plants exposed to Flonicamid after application of IKI-220 500 WG

Use	Maximum single application rate [g a.s./ha]	Rate with 50 % effects (ER_{50}) [A] [g a.s./ha]	Risk indicated?
Wheat	70	> 300	No
Pome fruit *	70		No
Stone fruit **	70		No
Fruiting vegetables ***	60		No

[A] determined in the seedling emergence study
* apple and pear
** peaches, apricots, plums and cherries
*** field use for cucumber, courgette, melon, tomato and eggplant, covering greenhouse use (non-permanent structure) for cucumber, courgette, covering tomato and eggplant

Table 2.9.9.8-2: Tier 2 Risk assessment for terrestrial non-target plants exposed to Flonicamid after application of IKI-220 100 OD

Use	Application rate [g a.s./ha]	MAF	Drift rate [%]	$PER_{off\text{-}field}$ [g a.s./ha]	ER_{50} [g a.s./ha]	TER
Pulses *	50	1	2.77	1.39	> 117.1	> 84.5
Cereals **	50	1	2.77	1.39	> 117.1	> 84.5

MAF: Multiple application factor; PER: Predicted environmental rate; TER: toxicity to exposure ratio.
* dry beans and dry peas
** winter and spring wheat, rye and triticale

2.10 ENDOCRINE DISRUPTING PROPERTIES

2.10.1 Gather all relevant information

2.10.1.1 Systemic literature review of flonicamid

A literature search for flonicamid was performed in accordance with the provisions of the EFSA Guidance "Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) 1107/2009". The objective of the literature search was the assessment of scientific peer-reviewed open literature published within the last 10 years and dealing with side-effects on health, the environment and non-target species for flonicamid and respective plant protection products. The bibliographic literature search for flonicamid was conducted via the service provider STN-International. STN is an online database service that provides global access to published research, journal literature, patents, structures, sequences, properties, and other data. The search was carried out on 23 June 2020 (calendar week 26). In a first step the CAS REGISTRY database was accessed and the CAS number was searched to retain information on identity and substance names/synonyms.

The following list of substance specific search terms generated was used as query to search the STN databases:

CAS Number: 158062-67-0
850494-91-6

Chemical names and synonyms: ARIA (INSECTICIDE)
BELEAF
CARBINE (INSECTICIDE)
F 1785-03-1
F 1785
FLONICAMID
IKI 220N-(CYANOMETHYL)-4-(TRIFLUOROMETHYL)-3-PYRIDINECARBOXAMIDE"
N-CYANOMETHYL-4-(TRIFLUOROMETHYL)NICOTINAMIDE"
TEPPEKI ULALA DF
ULALA

For identification of the most appropriate search concept the substance specific search terms were applied in a multifile search accessing following databases: AGRICOLA, BIOSIS, CABA, EMBASE, ESBIOBASE, HCAPLUS, MEDLINE, PQSCITECH, TOXCENTER. Due to the number of hits encountered a single concept search strategy (i.e. search for CAS number and the chemical names) was considered to be adequate (Table 2.10.1.1 - 1).

Table 2.10.1.1-1: Bibliographic database strategy to identify summary records on active substance flonicamid

Step	Search strategy	Number of summary records retrieved
1	ARIA (INSECTICIDE)/BI OR BELEAF/BI OR CARBINE (INSECTICIDE)/BI OR (F 1785-03-1/BI OR F 1785/BI OR FLONICAMID/BI OR IKI 220/BI OR N-(CYANOMETHYL)-4-(TRIFLUOROMETHYL)-3-PYRIDINECARBOXAMIDE/BI OR N-CYANOMETHYL-4-(TRIFLUOROMETHYL)NICOTINAMIDE/BI OR TEPPEKI/BI OR ULALA DF/BI OR ULALA/BI OR 158062-67-0/BI OR 850494-91- 6/BI	2538
2	Step 1 NOT patent/DT AND PY>2009	1236
3	Duplicates from Step 2 removed	540

In total, 540 records were retrieved from bibliographic databases and were screened by expert reviewers for relevance. Based on the evaluation of the summary records (titles/abstracts) 493 publications were assessed as obviously not relevant for the EU-data requirements related to side-effects on human health, non-target species and the environment for flonicamid. 47 full-text documents were assessed in detail. Ten of these publications did not provide relevant information for the dossier preparation or risk assessment purposes and were as well assessed as obviously not relevant for the EU-data requirements. 37 publications were selected to provide relevant information and none of these publications were relevant in the context of the assessment of endocrine disrupting properties.

2.10.1.2 *In silico* predictions (database search in accordance with Appendix D.1)

In addition to the data obtained from *in vivo* and *in vitro* mechanistic studies and the systematic literature review, *in silico* modelling was performed by the applicant to generate supporting information for endocrine modalities within a weight of evidence (WoE) approach (dRAR: B.6.8.3.2, Annex 2 to Report No. PP261-00027/5-02). The database search performed is in line with with the Appendix D.1 of the ED GD (ECHA and EFSA, 2018). For the purpose of data gathering, databases with relevance to ED were searched for information on putative estrogen, androgen, thyroid and steroidogenesis (EATS)-related endocrine activity of flonicamid. The database search was performed between September 2020 and October 2020. The databases were searched using the CAS number, the substance name or the SMILES code.

The most relevant information obtained by the database search in line with Appendix D.1 of the ED GD (ECHA and EFSA, 2018) including the Endocrine Disruptome is presented below.

US EPA CompTox Chemistry Dashboard

To obtain *in vitro* mechanistic information for potential EATS-related endocrine activity of flonicamid, the US EPA CompTox Chemistry Dashboard (https://comptox.epa.gov/dashboard, accessed on 28th September 2020) was searched and the obtained information was evaluated. None of the EATS-related *in vitro* assays listed in the EFSA instruction sheet (EFSA, 2019) provided with the ED GD (ECHA and EFSA, 2018) and no ToxCast Pathway model predictions were available for flonicamid. However, COMPARA (Consensus) and CERAPP potency level

(CONSENSUS) predictions were available (2.10.1.2-1) and stated no activity of flonicamid concerning AR and ER agonism, antagonism and binding.

Table 2.10.1.2-1: Model score values for flonicamid

Model	Receptor	Agonist	Antagonist	Binding
ToxCast Pathway Model (AUC)	Androgen	-	-	-
ToxCast Pathway Model (AUC)	Estrogen	-	-	-
COMPARA (Consensus)	Androgen	Inactive	Inactive	Inactive
CERAPP Potency Level (from Literature)	Estrogen	-	-	-
CERAPP Potency Level (Consensus)	Estrogen	Inactive (Inactive)	Inactive (Inactive)	Inactive (Inactive)

AUC: area under the curve. CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. COMPARA: Collaborative modeling project for androgen receptor activity. –: no data.

No additional relevant and reliable information, i.e. information not covered by the STN literature search, was identified in the open source databases with reference to experimental *in vivo* studies. In conclusion, the data obtained from the database search did not indicate any concern of EATS-related endocrine activity of flonicamid.

Danish Q(SAR) database

The Danish (Q)SAR database was searched (date 29th September 2020) by the CAS number 158062-67-0 for endocrine and molecular endpoints addressed by the (Q)SAR models and the prediction results are shown in Table 2.10.1.2-2.

All results for ERα binding and activation (human *in vitro*) for flonicamid, including the overall battery prediction were stated as outside of the applicability domain (AD) and are thus of very limited reliability. Leadscope reported the ER activation CERAPP data (*in vitro*) as negative (within the AD) which was is in line with CompTox Chemicals Dashboard result. For AR inhibition (human *in vitro*) all predictions including the overall battery prediction were outside the AD. However, results from COMPARA (*in vitro*) regarding AR binding (*in vitro*), inhibition (*in vitro*) and activation (*in vitro*) were stated negative (within the AD) in agreement with CompTox Dashboard results.

Both, thyroperoxidase (TPO) inhibition endpoints (QSAR1 and QSAR2, rat *in vitro*) were predicted only by one model and reported as negative within the AD (Leadscope). The predictions for TRα and TRβ binding (human *in vitro*) were all outside the AD and considered to be of very limited reliability. The predictions for the endpoint Arylhydrocarbon Receptor (AhR) activation, rational final model (human *in vitro*) and random final model (human *in vitro*), were modelled by Leadscope and the results were stated to be outside the AD. Negative predictions (within the AD) were obtained for pregnane X receptor (PXR) binding and activation (human and rat *in vitro*) for 1 out of 3 software tools, Leadscope. For the endpoint PXR binding (human *in vitro*) negative prediction within the AD was also given by SciQSAR model. CASE Ultra predictions were outside the AD. The overall battery prediction was reported as negative (within the AD). Constitutive androstane receptor (CAR) activation and inhibition endpoints

were modelled by one model (Leadscope). The results were stated as negative or inconclusive outside the AD except for the inhibition at 50 µM which was reported as negative within the AD. Prediction for cytochrome P450 (CYP) 3A4 induction (human *in vitro*), was reported as negative (within the AD) by Leadscope.

According to profiling with the OECD QSAR Toolbox v.4.2, the parent flonicamid was depicted as ER non-binder, as well as the simulated metabolites (*in vivo* rat metabolism simulator only and rat liver S9 metabolism simulator only). Furthermore, no alerts were depicted neither for parent nor for metabolites (*in vivo* rat metabolism simulator only and rat liver S9 metabolism simulator only) by the mechanistic profiling 'rtER expert system - US EPA'3 .

In conclusion, no concern was raised regarding EATS-related endocrine activity based on the results of the Danish QSAR DB search. No experimental data were available for any of the endpoints

Table 2.10.1.2-2: Prediction results of the Danish (Q)SAR Database

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		INC_OUT	NEG_OUT	NEG_OUT	NEG_OUT
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		INC_OUT	INC_OUT	POS_OUT	NEG_OUT
Estrogen Receptor α Activation (Human *in vitro*)		INC_OUT	NEG_OUT	NEG_OUT	NEG_OUT
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		INC_OUT	INC_OUT	NEG_OUT	NEG_OUT
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
mg/L			36655.47	12825.63	177.0675
µM			159955.8	55968.04	772.6806
Positive for IC50 ≤ 10 µM					
Positive for IC50 ≤ 100 µM					
Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
mg/L			0.9597073	659.3696	4956.086

µM			4.187935	2877.333	21627.19
Positive for IC50 ≤ 10 µM					
Positive for IC50 ≤ 100 µM					
Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human in vitro)		N/A	N/A	NEG_OUT	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)		NEG_IN	POS_OUT	NEG_IN	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*)		N/A	N/A	NEG_OUT	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A

Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, without OH or NH2 group
- metabolites from in vivo Rat metabolism simulator only	Non binder, non cyclic structure; Non binder, without OH or NH2 group
- metabolites from Rat liver S9 metabolism simulator only	Non binder, impaired OH or NH2 group; Non binder, non cyclic structure; Non binder, without OH or NH2 group
rtER Expert System - USEPA, alerts in:	
- parent only	No alert found
- metabolites from in vivo Rat metabolism simulator only	No alert found
- metabolites from Rat liver S9 metabolism simulator only	No alert found
OECD QSAR Toolbox v.4.2 profilers Profiler predictions are supporting information to be used together with the relevant QSAR predictions	

AhR: Arylhydrocarbon receptor. CYP: Cytochrome P450. Exp: Experimental values, from EpiSuite experimental databases or DK DTU QSAR models training sets. IC50: half-maximal inhibitory concentration. IN: Within the applicability domain. INC: inconclusive. NA: Not applicable, because training set data cannot be released for commercial models. NEG: Negative. NH2: amino group. OECD: Organisation for economic co-operation and development. OH: hydroxyl group. OUT: Outside the

applicability domain. POS: Positive. PXR: Pregnane X receptor. (Q)SAR: (Quantitative) Structure Activity Relationship. rtER: Rainbow trout estrogen receptor. S9: Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g. US EPA: United States Environmental Protection Agency.

Endocrine disruptome

In order to predict binding probabilities, the SMILES code of flonicamid was inserted on the Endocrine Disruptome webpage (http://endocrinedisruptome.ki.si, accessed on 29th September 2020). The predictions stated low probability of binding to any of the receptors listed, including the AR, ERα, ERβ, GR, PXR, TRα and TRβ, except low-intermediate probability of binding to the AR (antagonistic). Considering predictions of CoMPARA (Consensus) stating inactivity for AR agonism, antagonism and binding (see CompTox Chemicals Dashboard), the calculated low-intermediate binding probability did not raise concern towards EATS-related endocrine activity of flonicamid.

In addition to the database searches presented above also other databases were screened (September- October 2020) Endocrine Disruptor Knowledge Base (EDKB), Estrogenic Activity Database (EADB), Endocrine Active Substances Information System (EASIS), Signaling Pathways Project (SPP), COSMOS Database, (Q)SAR Data Bank and OECD QSAR Toolbox. The databases and models were described on a very general level but as a conclusion no endocrine relevant or (reliable) new information was found in these databases.

2.10.1.3 Mammalian toxicity

2.10.1.3.1 *In vivo* studies and *in vitro* mechanistic studies

Regarding mammalian toxicity, data have been collected from all relevant repeated dose toxicity studies in mammals (evaluated by the Rapporteur Member State) available in Volume 3 B.6 and the ED-relevant information gathered and analyzed in a data summary/data matrix compliant with Appendix E. A total of 17 toxicity studies were included in the assessment (plus three additional investigations on hormone levels), considering all parameters which are useful for the ED assessment (including parameters indicative of target organ toxicity as well as general adversity). Each study was given a unique identification number (Study ID (App. E)) for the identification in the data-matrix and Lines of Evidence (LoE) spreadsheets of the Appendix E excel sheet. Table 2.10.1.3.1-1 summarises the 17 toxicity studies plus the 3 additional invesigations included in the present assessment.

Table 2.10.1.3.1-1: Summary of the repeated dose *in vivo* studies included in the present assessment

Study Type	Dose levels or dietary concentrations	Study ID (App. E)
Repeated dose 28-day oral toxicity study in Wistar rats (dose range finding study)	M: 0; 3.613; 7.47; 36.45; 73.8; 353.4 mg/kg bw/d (0; 50; 100; 500; 1000 and 5000 ppm) F: 0; 8.36; 41.24; 81.9; 372.6; 642 mg/kg bw/d (0; 100; 500; 1000; 5000 and 10000 ppm)	1
Repeated dose 28-day oral toxicity study in beagle dogs	0; 2; 10; 50 mg/kg bw/d reduced to 20 mg/kg bw/d after first dose	2

Repeated dose 90-day oral toxicity study in Wistar rats	M: 0; 3.079; 12.11; 60.0; 119.4 mg/kg bw/d (0; 50; 200; 1000 and 2000 ppm) F: 0; 14.52; 72.3; 340.1 mg/kg bw/d (0; 200; 1000 and 5000 ppm)	3
Repeated dose 90-day oral toxicity study in mice (dose range finding study)	M/F: 0; 15.3/20.1;153.9/191.5; 1069/1248 mg/kg bw/d (0; 100; 1000; 7000 ppm)	4
Repeated dose 90-day oral toxicity study in beagle dogs	0; 3; 8; 20; 50 mg/kg bw/d (50 mg/kg bw/d female only)	5
Chronic toxicity (52-week in beagle dogs)	0; 3; 8; 20 mg/kg bw/d	6
Repeated dose 28-day dermal toxicity in Sprague-Dawley rats	0; 20; 150; 1000 mg/kg bw/d	7
Combined chronic toxicity/carcinogeni city study in Wistar rats	M: 0; 1.84; 3.68; 7.32; 36.5 mg/kg bw/d (0; 50; 100; 200 and 1000 ppm) F: 0; 8.92; 44.1; 219 mg/kg bw/d (0; 200; 1000 and 5000 ppm)	8
Carcinogenicity study in CD-1 mice	M/F: 0; 29/38; 88/112; 261/334 mg/kg bw/d (0; 250; 750 and 2250 ppm)	9
Carcinogenicity study in CD-1 mice	M/F: 0; 1.2/1.42; 3.14/3.67; 10.0/11.8; 30.3/36.3 mg/kg bw/d (0; 10; 25; 80 and 250 ppm)	10
One-generation reproduction toxicity study in Wistar rats (dose range inding study)	M/F: 0; 2.86/5.28; 11.49/20.8; 57.7/103.7; 114.2/214 mg/kg bw/d (0, 50, 200, 1000, or 2000 ppm)	11
Two-generation reproduction toxicity study in Wistar rats	Parental generation: M/F: 0; 3.07/4.67; 18.3/28.2; 109.1/163.8 mg/kg bw/d (0; 50; 300 or 1800 ppm) Filial generation: M/F: 0; 3.39/4.95; 20.7/30.5; 124.8/176.8 mg/kg bw/d	12
Prenatal developmental toxicity study in Wistar rats (dose range finding study)	0; 30; 100; 300; 1000 mg/kg bw/d	13
Prenatal developmental toxicity study in rabbits (dose range finding study)	0; 3; 10; 30 mg/kg bw/d	14
Prenatal developmental toxicity study in Wistar rats	0; 20; 100; 500 mg/kg bw/d	15
Prenatal developmental toxicity study in rabbits	0; 2.5; 7.5; 25 mg/kg bw/d	16
Prenatal developmental toxicity study in Sprague-Dawley rats (preliminary study)	0; 10; 100; 500 mg/kg bw/d	17
Two-generation reproduction toxicity study in Wistar rats (investigation of hormone levels)	M/F: 0; 3.39/4.95; 20.7/30.5; 124.8/176.8 mg/kg bw/d	18
28-day and 90-day repeated dose toxicity studies in Wistar rats (investigation of hormone levels)	28 days: 0; 4.3; 8.7; 26.8; 154.1 mg/kg bw/d 90 days: 0; 3.7; 7.5; 22.4; 136.0 mg/kg bw/d	19

	(0; 50; 100; 300; 1800 ppm)	
Hormonal examination in female [redacted]Wistar rats at pro-estrous	N.a. (investigation of LH, FSH, 17β-estradiol levels in non-treated female rats at pro-estrous)	N.a.

In addition to the information obtained from standard *in vivo* toxicity in mammals studies, *in vitro* mechanistic studies were performed to gain information on selected endocrine mechanism(s)/pathway(s). Table 2.10.1.3.1.-2 summarises *in vitro* mechanistic studies included in the present assessment.

Table 2.10.1.3.1-2: *In vitro* mechanistic studies included in the present assessment

Study Type	Study ID (App. E)
Thyroid peroxidase activity (TPO) (*in vitro*) No validated guideline available	25
Iodide uptake by sodium/iodide symporter (NIS) (*in vitro*) No validated guideline available. Study design was based on a modification of Waltz et al. (2010) A nonradioactive iodide uptake assay for sodiumiodide symporter function. Anal. Biochem., 396, 91-95.	26
Androgen receptor signalling No validated guideline available. Study conducted in accordance with Takeyoshi et al. (2003) Development of a high-performance reporter plasmid for detection of chemicals with androgenic activity. Arch Toxicol., 77, 274-279.	23
Aromatase inhibition using human recombinant microsomes (human CYP19 + P450 Reductase Supersomes) OPPTS 890.1200	24
Estrogen receptor signalling OECD TG 455	18
Estrogen receptor signalling OECD TG 455	23
Steroidogenesis assay - production of estradiol and testosterone in human H295R adreno-carcinoma cells	28

2.10.1.3.2 Human health and epidemiological data

Medical surveillance data on manufacturing plant personnel and monitoring studies did not reveal any data indicative of adverse effects and impact on the endocrine system. There are no epidemiological studies of flonicamid available.

2.10.1.4 Ecotoxicological studies (studies on non-target organisms other than mammals)

Standard ecotoxicological studies are available for Flonicamid. The studies are evaluated and reported Volume 3 B.9 (CA). Studies relevant for the ED assessment are listed in Table 2.10.1.4.

Table 2.10.1.4. Summary of the ecotoxicological studies relevant for the ED assessment

Study Type	Species	Test substance	Dose levels or tested concentrations	Reference	Study ID (App. E)
bird reproduction study (OECD 206)	Bobwhite quail (*Colinus virginianus*)	Batch no 9809 purity: 98.7 %	13, 33 and 90 mg/kg bw/d	KCA 8.1.1.3/02	20
bird reproduction study (OECD 206)	Mallard duck (*Anas platyrhynchos)*	Batch no 9809 purity: 98.7 %	25, 59 and 138 mg/kg bw/d	KCA 8.1.1.3/04	21
fish early life stage toxicity study (OECD 210)	Fathead minnow (*Pimephales promelas*)	Batch no 9809 purity: 98.7 %	1.3. 2.5, 5.0, 10 and 20 mg a.s./L (nominal)	KCA 8.2.2.1/01	22
Fish short term reproduction assay (OECD 229)	Medaka (*Oryzias latipes*)	Batch no 9809 purity: 99.5 %	0.100, 1.00, and 10 mg a.s./L (nominal)	KCA 8.2.3/01	27
Amphibian metamorphosis assay (OECD 231)	African clawed frog (*Xenopus laevis*)	Batch no 9809 purity: 99.6 %	9, 30, and 100 mg a.s./L (nominal)	KCA 8.2.3/02	29

2.10.2 ED assessment for humans

2.10.2.1 ED assessment for T-modality

2.10.2.1.1 Have T-mediated parameters been sufficiently investigated?

Table 2.10.2.1.1.-1: Available studies investigating T-mediated parameters

	Sufficiently investigated
T-mediated parameters	Yes based on the results of the following studies: − Repeated dose 28-day oral (capsule) toxicity study in beagle dogs, OECD TG 409 (Study ID 2) − Repeated dose 90-day oral (feeding) toxicity study in Wistar rats, OECD TG 408 (Study ID 3) − Repeated dose 90-day oral (capsule) toxicity study in beagle dogs, OECD TG 409 (Study ID 5) − Repeated dose 52-week oral (capsule) toxicity study in beagle dogs, OECD TG 409 (Study ID 6) − Repeated dose 28-day dermal toxicity study in Sprague-Dawley rats, OECD TG 410 (Study ID 7)

	− Chronic and carcinogenicity 24-month oral (feeding) toxicity study in Wistar rats, OECD TG 453 (Study ID 8) − Carcinogenicity 18-month oral (feeding) toxicity study in CD-1 mice, OECD TG 451 (Study ID 9) − Carcinogenicity 18-month oral (feeding) toxicity study in CD-1 mice, OECD TG 451 (Study ID 10) − Two-generation reproduction oral (feeding) toxicity test in Wistar rats, OECD TG 416 (Study ID 12)

Thyroid hormone levels have not been assessed in any of the studies following treatment with flonicamid. However, thyroids were histopathologically examined in all studies listed in Table 2.10.2.1.1-1 i.e. thyroid histopathology is available for rats, dogs and mice for study durations between 28 days and 24 months including two generations (rats).

2.10.2.1.2 Lines of evidence for adverse effects and endocrine activity related to T-modality and for general or target organ toxicity

According to the ED GD (ECHA and EFSA, 2018) "*the assembling of lines of evidence should take into consideration all the available evidence (positive and negative) that have been evaluated as relevant and reliable*" during the data gathering. These parameters were assessed to determine "*whether and how they contribute to the lines of evidence for adversity and/or endocrine activity*".

After assembling and assessing the lines of evidence they were integrated for the assessment of adversity and endocrine activity in respect to the modalities. The integrated lines of evidence for T-related endocrine activity and T-mediated effects are reported in Table 2.10.2.1.2-1. The data include *in silico* predictions, *in vitro* mechanistic data and data on organ weight and histopathological evaluations. All relevant parameters with regards to general or target organ toxicity are presented in the integrated lines of evidence in Table 2.10.2.1.2-2.

Table 2.10.2.1.2-1: Assessment of the integrated lines of evidence for the T-modality

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
In silico prediction	(Q)SAR prediction: Danish database	N.a	N.a	N.a	N.a	N.a	N.a	N.a	N.a	Negative predictions within the applicability domain (AD) were observed for Thyroperoxidase (TPO) inhibition in Leadscope. The predictions for TR binding were outside the AD and thus, considered not reliable.	Supporting negative evidence for TPO inhibition	Overall, negative evidence for T-related endocrine activity	T
	Endocrine Disruptome	N.a	N.a	N.a	N.a	N.a	N.a	N.a	N.a	The predictions stated low probability of binding to TRα and TRβ.	Supporting negative evidence for TR binding		T
In vitro mecha-nistic	Iodide uptake by sodium/iodide symporter (NIS) (*in vitro*)	26	Fisher Rat (FRTL 5)	7.5	Min	Uptake from the medium (*in vitro*)	(-)	µM	No effect	-	Negative evidence for T-related endocrine activity	Overall, negative evidence for T-related endocrine activity	T
	Thyroid peroxidase activity (TPO) (*in vitro*)	25	Rats Thyroid Microsomal Fraction	5	Min	Uptake from the medium (*in vitro*)	(-)	µM	No effect	-	Negative evidence for T-related endocrine activity		T
T-mediated	Thyroid weight	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for T- mediated adversity. Isolated effects on thyroid weight were observed in dogs	Overall, negative evidence for T-mediated adversity	T
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			T
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	Abs. weight: -			T

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		6	Dog	52	Weeks	Oral	20	mg/kg bw/d	Increase	Stat. significantly increased relative (to body weight) thyroid weight was observed in high dose females (47% compared with control; p<0.01). Observation considered to be related to decreased terminal body weight in high dose females (-13% compared with controls; not stat. significant). There was no effect in males. There was no histopathological correlate for the observation. No changes for abs. weight or rel. to brain weight.	(since only relative (to body weight) was affected, the finding was considered related to terminal body weight) and in high dose males of a two generation reproduction toxicity study. These findings were apparent in F_0 males only, but not in F_1 males or in F_0/F_1 females, were not accompanied by histopathological changes (a more sensitive parameter), and were not seen in rats of either sex in any other study. The weight of evidence therefore demonstrates a lack of T-mediated adversity.		T
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	Relative to brain weight			T
		12	Rat	17-18[b]	Weeks	Oral	109.1	mg/kg bw/d	Increase	F_0 generation; stat. significantly increased absolute thyroid weight was observed in high dose in males of the F_0 generation (13% compared with control; p<0.01). Stat. signicantly increased relative (to body weight) thyroid weight was observed in high dose in males of the F_0 generations (14% compared with control; p<0.01). There was no effect in females.			T

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F_1 generation; -			T
	Thyroid histopathology	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			T
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			T
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -			T
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			T
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			T
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			T
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			T
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -			T
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			T
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			T
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			T
Sensitive to, but not diagnostic of, EATS	Pituitary weight	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	No adversity on pituitary was observed. There were no organ weight changes in any study and no adverse effects in the histopathological examination of the	Overall negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS modalities.	N
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N
	Pituitary histopathogology	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -	pituitary. Observed reduced incidence of anterior pituitary adenoma is considered not to represent adversity.		N
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			N
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N
		8	Rat	104	Weeks	Oral	36.5	mg/kg bw/d	Change	Males: Reduced incidence of anterior pituitary adenoma was observed in high dose males (6/32 compared with 19/43 in control; $p<0.05$). Assessed at week 52 and week 104			N
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Change	Females: Stat. significant decreases in the incidence of anterior pituatory adenoma in females in the highest dose group. Assessed at week 52 and week 104.			N
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			N
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N

- = negative evidence. * According to column AH of template E of the ED GD (effect indicative of; ECHA and EFSA, 2018). Abs. = absolute. AD = applicability domain. F0 = Parental generation. F1 = First filial generation. FRTL-5 = Fisher Rat Thyroid Low Serum 5 % (FRTL-5). N: = Endpoints sensitive to, but not diagnostic of EATS-modalities. N.a = Not applicable/not available. NIS= Sodium-iodide symporter. (Q(SAR) = (Quantitative) Structure Activity Relationship. T= Thyroid. TPO = Thyroperoxidase. TR = Thyroid hormone receptor. a: 35 days for the low and mid dose, 28 days for the high dose after dose was reduced. b. parental animals.

Table 2.10.2.1.2-2: Assessment of the integrated lines of evidence for general and target organ toxicity

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
Target organ toxicity	Kidney weight	1	Rat	28	Days	Oral	353.4	mg/kg bw/d	Increase	Males: The high dose males showed a stat. significant increase in absolute kidney weight (12% compared with control; $p<0.05$). The high dose males showed a stat. significant increase in relative (to body weight) kidney weight (19% compared with control; $p>0.01$).	There were treatment-related histopathological alterations and kidney weight changes in rats, however the morphology of the alterations differed between the sexes (most common observation was vacuolation in the proximal tubular cell in females and in males the most common observation was increased incidence of hyaline droplet deposition in the proximal tubular cell), and changes occurred at higher doses in the females. In the male rat studies, kidney effects were consistently observed. The adverse effects on the kidneys were considered as mediated by the male rat-specific protein, α2μ-globulin, and were not regarded as relevant to humans (EFSA, 2010). As for the isolated histopathological finding in dogs (Study ID 5), observations occurred at a dose level that caused systemic toxicity (one animal
		1	Rat	28	Days	Oral	353.4	mg/kg bw/d	No effect	Females: -	
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		3	Rat	13	Weeks	Oral	60	mg/kg bw/d	Increase	Males: Stat. significantly increased absolute kidney weight was observed at the intermediate-high (10% compared with control; $p<0.05$) and high dose (15% compared with control; $p<0.01$). Stat. significantly increased relative (to body weight) kidney weight was observed at the intermediate-high (10% compared with control; $p<0.01$) and high dose (21% compared with control; $p<0.01$).	
		3	Rat	13	Weeks	Oral	340.1	mg/kg bw/d	Increase	Females: Stat. significantly increased absolute kidney weight was observed at the high dose (7% compared with control; $p>0.05$). Stat. significantly increased relative (to body weight) kidney weight was observed at the	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										high dose (13% compared with control; p<0.01).	was terminated due to adverse clinical observations) without significant effect in kidney weight. Overall, positive evidence for kidney toxicity in rats
		4	Mouse	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	
		6	Dog	52	Weeks	Oral	20	mg/kg bw/d	No effect	Absolut weight: -	
		6	Dog	52	Weeks	Oral	20	mg/kg bw/d	Increase	Relative: Stat. significantly increased relative (to body weight) kidney weight was observed at the high dose in males (13% compared with control; p<0.05). There was no stat. significant effect in females. There was no histopathological correlate for the observation.	
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males, absolute: -	
		8	Rat	104	Weeks	Oral	36.5	mg/kg bw/d	Increase	Males, relative (to body weight): Stat. significantly increased relative (to body weight) kidney weight was observed in males at week 52 at the high dose (9% compared with control; p<0.05).	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Increase	Females, absolute: Stat. significantly increased absolute kidney weight was observed in females at week 52 at the high dose (16% compared with control; p<0.01).	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Increase	Females, relative (to body weight): Stat. significantly increased relative (to body weight) kidney weight was	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										observed in females at the high dose at week 26 (11% compared with control; p<0.01), week 52 (16% compared with control; p<0.01), and week 104 (15 % compared with control; p<0.05).	
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	Absolute -	
		9	Mouse	18	Months	Oral	261	mg/kg bw/d	Decrease	Relative: Stat. significantly decreased relative (to body weight) kidney weight was observed in males at the high dose at week 78 (-8% compared with control; p<0.05). There was no histological correlate for the observation.	
		10	Mouse	18	Months	Oral	36.3	mg/kg bw/d	No effect	Absolute: Stat. significantly decreased absolute kidney weight was observed in females at week 78 at the high dose (- 8% compared with control; p<0.05). There was no effect in males. There was no histopathological correlate for the observation. No changes in relative organ weights. Changes were considered incidental to treatment.	
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	Relative -	
		11	Rat	Approx. 10	Weeks	Oral	114.2	mg/kg bw/d	Increase	F_0: Stat. significantly increased absolute kidney weight was observed at the high dose in males (20 compared with control; p<0.001). Stat. significantly increased relative (to body weight) kidney weight was observed at the high dose in males	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										(17% compared with control; p<0.001).	
		12	Rat	17-18[b]	Weeks	Oral	109.1	mg/kg bw/d	Increase	F_0 and F_1, absolute: Stat. significantly increased absolute kidney weight was observed in the F_0 generation high dose males (17% compared with control; p<0.001). Stat. significantly increased absolute kidney weight was observed in the F_1 generation high dose males (17% compared with control; p<0.01).	
		12	Rat	17-18[b]	Weeks	Oral	109.1	mg/kg bw/d	Increase	F_0, relative: Stat. significantly increased relative (to body weight) kidney weight was observed in the F_0 generation high dose males (17% compared with control; p<0.001).	
		12	Rat	17-18[b]	Weeks	Oral	20.7/176.8	mg/kg bw/d	Increase	F_1, relative: Stat. significantly increased relative (to body weight) kidney weight was observed in the F_1 generation mid dose males (4% compared with control; p<0.05).	
		15	Rat	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		17	Rat	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	-	
	Kidney histopathology	1	Rat	28	Days	Oral	7.47	mg/kg bw/d	Change	Males: Males showed increased hyaline droplet deposition in proximal tubular cells (0/6 in the control, 3/6 in the intermediate-low dose, 6/6 in the mid, intermediate-	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										high and high dose groups; p<0.01 for the mid, intermediate-high and high dose groups). Granular cast was observed in 2/6 intermediate-high dose animals and 4/6 high dose animals (p<0.05) (0/6 in the controls). Immunostaining showed that the hyaline droplets reacted strongly to α2μ-globulin antibody. In the high dose males showed pale kidney (5/6 compared with 0/6 in the controls; p<0.01). In the high dose males showed enlargement of the kidneys (3/6 compared with 0/6 in the controls).	
		1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Females: -	
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		3	Rat	13	Weeks	Oral	12.11	mg/kg bw/d	Increase	Males: Deposition of hyaline droplets containing α2μ-globulin in proximal tubules of the kidney was observed in all high (12/12; p<0.01), intermediate-high (12/12; p<0.01) and intermediate-low dose males (8/12; p<0.01) (compared with 0/12 in controls). There was increased incidence of granular casts in dilated tubules in intermediate-high (5/12 compared with 0/12 in the control; p<0.05) and high dose males (12/12 compared with 0/12 in the control; p<0.01) and basophilic change in tubular cells in intermediate-high (11/12 compared with 0/12 in the	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										control; p<0.01) and high dose males (12/12 compared with 0/12 in the control; p<0.01). Both were considered to be degenerative changes due to α2μ-globulin deposition. Gross pathology: At necropsy, pale coloured kidneys were noted in all high dose males (0/12 in controls).	
		3	Rat	13	Weeks	Oral	340.1	mg/kg bw/d	Change	Females: The observed incidence of cytoplasmic vacuolation of proximal tubular cells was increased in the high dose (12/12 compared with 0/12 in the control; p<0.01). These vacuoles were negative for PAS reaction or oil red O staining.	
		4	Mouse	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	No effects observed in the control and high dose (7000 ppm) groups that were examined.	
		5	Dog	90	Days	Oral	50	mg/kg bw/d	Change	Mild vacuolation of the tubules in the inner cortex of the kidney was noted in the female that was found dead and also in another female receiving 50 mg/kg bw/d (0/4 in the controls).	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	
		6	Dog	52	Weeks	Oral	20	mg/kg bw/d	No effect	-	
		8	Rat	104	Weeks	Oral	7.32	mg/kg bw/d	Change	Males: Increased incidence in the high dose of granular casts in dilated tubules was observed at week 26 (5/10 compared with 0/10 in controls; p<0.05). Increased incidence in the high dose of proximal tubular	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										basophilic changes was observed at week 26 (8/10 compared with 3/10 in controls; $p<0.05$) and week 52 (10/10 compared with 4/10 in controls; $p<0.01$). Increased incidence of hyaline droplet deposition was observed at week 26 in the intermediate-high (8/10 compared with 0/10 in controls; $p<0.01$) and high dose (10/10 compared with 0/10 in controls; $p<0.01$ and at week 52 in the high dose (10/10 compared with 0/10 in controls; $p<0.01$). Increased incidence in the high dose of chronic nephropathy was observed at week 104 (23/32 compared with 18/43 in controls; $p<0.01$). Hyaline droplet deposition in proximal tubular cells of the kidney in males at 200 ppm was considered treatment-related but not adverse. Gross pathology: Increased incidences of renal pelvic dilatation was observed in males at the intermediate-high (5/52 compared with 1/52 in control; not stat. significant) and high dose (7/52 compared with 1/52 in control; $p<0.05$).	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Change	Females: Increased incidence of kidney lesions which consisted of cytoplasmic vacuolation of proximal tubular cells in high dose was observed at week 26 (10/10 compared with 0/10 in controls;	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										p<0.01), week 52 (10/10 compared with 0/10 in controls; p<0.01) and week 104 (31/31 compared with 0/31 in controls; p<0.01).	
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		11	Rat	Approx. 10	Weeks	Oral	11.49	mg/kg bw/d	Change	Adult, F_0: Increased incidence of hyaline droplet deposition in the proximal tubular cell in males from the intermediate-low dose (5/8 in the intermediate-low group (p<0.05), 8/8 in the intermediate-high group (p<0.001) compared with 0/8 in the controls). Increased incidence of tubular basophilic change in males from the intermediate-high dose (8/8 in the intermediate-high group (p<0.001), 8/8 in the high group (p<0.01) compared with 0/8 in the controls). Increased incidence of granular cast in dilated tubules in males from the intermediate-high dose (1/8 in the intermediate-high group (not stat. significant), 8/8 in the high group (p<0.001) compared with 0/8 in the controls. Gross pathology: Increased incidence of pale colour in the kidney was observed in the male intermediate-high (4/8 compared with 0/8 in controls; p<0.05) and high dose (7/8 compared with 0/8 in controls; p<0.001).	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring, F_1: Although dilatation of the renal pelvis occurred only in male pups from the treated groups (2/46, 3/51, 2/44 and 3/40) and not in control male pups, an effect of treatment was not inferred because this gross lesion occurred in control male pups of both generations in the main study at incidences of up to 7.9 %	
		12	Rat	17-18[b]	Weeks	Oral	109.1/163.8	mg/kg bw/d	Change	Adult, F_0 and F_1: There were treatment-related histopathological alterations in the kidneys of both sexes in both generations, but the morphology of the alterations differed between the sexes. In F_0 males there was increased incidence of hyaline droplet deposition in the proximal tubular cell from the mid dose (23/24 in the mid group ($p<0.001$), 24/24 in the high group ($p<0.001$) compared with 0/24 in the controls). In F_0 males there was increased incidence of tubular basophilic change in the high dose (24/24 in the high group compared with 0/24 in the controls; $p<0.001$). In F_0 males there was increased incidence of granular casts in dilated tubules in the high dose (21/24 in the high group compared with 0/24 in the controls; $p<0.001$). In F_0 females there was increased incidence of vacuolation in the	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										proximal tubular cell in the high dose (22/24 in the high group compared with 0/24 in the controls; p<0.001). In F_1 males there was increased incidence of hyaline droplet deposition in the proximal tubular cell from the mid dose (24/24 in the mid group (p<0.001), 24/24 in the high group (p<0.001) compared with 0/24 in the controls). In F_1 males there was increased incidence of tubular basophilic change in the high dose (21/24 in the high group compared with 0/24 in the controls; p<0.001). In F_1 males there was increased incidence of granular casts in dilated tubules in the high dose (23/24 in the high group compared with 0/24 in the controls; p<0.001). In F_1 females there was increased incidence of vacuolation in the proximal tubular cell in the high dose (24/24 in the high group compared with 0/24 in the controls; p<0.001). Gross pathology: Pale kidneys were observed in the F0 and F1 generation parental males at the high dose, which occurred at incidences of 24/24 and 10/24, respectively, compared with zero incidences in all other treated and control groups.	
		15	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Change	Increased incidence of vacuolation of the kidney proximal tubular cells was observed in the high dose (24/24	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										compared with 0/22 in controls; p<0.001).	
		17	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Change	Increased incidence of vacuolation of the kidney proximal tubular cells was observed in the high dose (5/5 compared with 0/5 in controls; p<0.01)	
	Liver weight	1	Rat	28	Days	Oral	353.4	mg/kg bw/d	Increase	Males: The high dose males showed a stat. significant increase in absolute liver weight (12% compared with control; p<0.05). The high dose males showed a stat. significant increase in relative (to body weight) liver weight (19% compared with control; p<0.01).	Increased liver weight and centrilobular hepatocellular hypertrophy consistently observed. The liver is considered to be one of the target organs following exposure with flonicamid. Overall, positive evidence for liver toxicity in rats and mice.
		1	Rat	28	Days	Oral	372.6	mg/kg bw/d	Increase	Females: The high dose females showed a stat. significant increase in absolute liver weight (42% compared with control; p<0.01). The high dose females showed a stat. significant increase in relative (to body weight) liver weight (57% compared with control; p<0.01). The intermediate-high dose females showed a stat. significant increase in absolute liver weight (15% compared with control; p<0.01). The intermediate-high dose females showed a stat. significant increase in absolute liver weight (15 % compared with control; p<0.01).	
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		3	Rat	13	Weeks	Oral	340.1	mg/kg bw/d	Increase	Females: Stat. significantly increased absolute liver weight was observed at the high dose (13% compared with control; p<0.01). Stat. significantly increased relative (to body weight) liver weight was observed at the high dose (19% compared with control; p<0.01).	
		4	Mouse	13	Weeks	Oral	1069/1248	mg/kg bw/d	Increase	Stat. significant increase in absolute liver weight was observed in high dose males (21% compared with control; p<0.01). Stat. significant increase in relative (to body weight) liver weight was observed in high dose males (29% compared with control; p<0.01) and females (21% compared with control; p<0.01).	
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		8	Rat	104	Weeks	Oral	7.32	mg/kg bw/d	Increase	Males, absolute: Stat. significantly increased absolute liver weight was observed in males at week 26 at the intermediate-high (11% compared with control; p<0.05)) and high dose (11% compared with control; p<0.05). There was no histopathological correlate for the observation.	
		8	Rat	104	Weeks	Oral	3.68	mg/kg bw/d	Increase	Males, relative: Stat. significantly increased relative (to body weight)	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										liver weight was observed in males at week 26 at the intermediate-low (7% compared with control; p<0.05), intermediate-high (9% compared with control; p<0.01) and high dose (9% compared with control; p<0.01). There was no histopathological correlate for the observation.	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Increase	Females, absolute: Stat. significantly increased absolute liver weight was observed in females at week 52 at the high dose (23% compared with control; p<0.01).	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Increase	Females, relative: Stat. significantly increased relative (to body weight) liver weight was observed in females at weeks 26, 52 and 104 at the high dose (p<0.01).	
		9	Mouse	18	Months	Oral	261/1334	mg/kg bw/d	Increase	Stat. significantly increased absolute liver weight was observed in males at week 52 at the high dose (12% compared with control; p<0.05). Stat. significantly increased absolute liver weight was observed in females at week 78 at the high dose (11% compared with control; p<0.05). Stat. significantly increased relative (to body weight) liver weight was observed at week 26 at the high dose in males (8% compared with control; p<0.05). and females (12% compared with control; p<0.05). Stat. significantly increased relative (to body weight) liver weight was observed in females at week 78 at the	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										high dose (10% compared with control; p<0.01).	
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F_0, absolute and relative: -	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F_1, absolute: -	
		12	Rat	17-18[b]	Weeks	Oral	176.8	mg/kg bw/d	Increase	F_1, relative: Stat. significantly increased relative liver weight in females of F_1 generation. Since only relative weight in one generation was increased, it was considered not to be biologically relevant.	
		15	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Increase	Stat. significantly increased absolute liver weight was observed at the high dose (13% compared with control; p<0.01). Stat. significantly increased relative (to body weight) liver weight was observed at the high dose (12% compared with control; p<0.01).	
		17	Rat	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	Absolute: -	
		17	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Increase	Relative: Stat. significantly increased relative (to body weight) liver weight was observed at the high dose (9% compared with control; p<0.05). Considered treatment related,	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										although abs. weight was not changed.	
	Liver histopathology	1	Rat	28	Days	Oral	353.4	mg/kg bw/d	Change	Males: The high dose group all males showed slight centrilobular hepatocellular hypertrophy (6/6 compared with 0/6 in the controls; $p<0.01$). 2/6 high dose males showed enlargement and dark colour in the liver (compared with 0/6 in the controls).	
		1	Rat	28	Days	Oral	372.6	mg/kg bw/d	Change	Females: In the high dose group all females showed moderate centrilobular hepatocellular hypertrophy (6/6 compared with 0/6 in the controls; $p<0.001$). In the intermediate-high dose group females showed slight centrilobular hepatocellular hypertrophy (4/6 compared with 0/6 in the controls; $p<0.05$). In the high dose group all females showed enlargement of the liver (6/6 compared with 0/6 in the controls; $p<0.01$). In the intermediate-high dose 2/6 females showed enlargement of the liver (compared with 0/6 in the controls).	
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		3	Rat	13	Weeks	Oral	119.4	mg/kg bw/d	Change	Males: The observed incidence of centrilobular hepatocellular hypertrophy was stat. significantly increased in the high dose (12/12 compared with 0/12 in the control; $p<0.01$).	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		3	Rat	13	Weeks	Oral	340.1	mg/kg bw/d	Change	Females: The observed incidence of centrilobular hepatocellular hypertrophy was stat. significantly increased in the high dose (12/12 compared with 0/12 in the control; p<0.01).	
		4	Mouse	13	Weeks	Oral	153.9/1248	mg/kg bw/d	Change	Centrilobular hepatocellular hypertrophy occurred in all animals at the high dose (graded as minimal to moderate and correlated with the increased liver weight at this dose level, males and females 10/10, compared with 0/10 in both sexes in controls) and in 3/10 males at the mid dose (graded minimal).	
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Change	Females: Increased incidence of centrilobular hepatocyte hypertrophy was observed in high dose observed at week 26 (10/10 compared with 0/10 in controls; p<0.01), week 52 (9/10 compared with 0/10 in controls; p<0.01) and week 104 (20/31 compared with 0/31 in controls; p<0.01). Increased incidence of eosinophilic cell foci in high dose was observed at week 104 (14/31	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										compared with 5/31 in controls; p<0.05). Gross pathology: Increased incidences of dark coloration (5/52 compared with 0/52 in control; p<0.05) and accentuated lobular pattern (8/52 compared with 0/52 in control; p<0.01) in the liver observed in high dose females at week 104.	
		9	Mouse	18	Months	Oral	29/334	mg/kg bw/d	Change	Increased incidence of centrilobular hepatocyte hypertrophy was observed in high dose males at week 26 (6/10 compared with 0/10 in controls) and at week 52 (7/10 compared with 0/10 in controls). At week 78, increased incidence of centrilobular hepatocyte hypertrophy was observed in males at the low (14/60 compared with 4/60 in controls), mid (36/60 compared with 4/60 in controls) and high dose (40/60 compared with 4/60 in controls). At week 78, increased incidence of centrilobular hepatocyte hypertrophy was observed in females at the high dose (11/60 compared with 0/60 in controls).	
		10	Mouse	18	Months	Oral	36.3	mg/kg bw/d	Change	In high dose females overall (including animals found dead or killed in extremis) there was an increased incidence of centrilobular hepatocellular fatty change observed (5/50 compared with 0/50 in the controls; p<0.05). However, in animals sacrificed at the scheduled termination (after week 78) there was no stat. significant difference (0/37	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										compared with 0/44 in the controls), and therefore the observation is considered to be incidental to treatment	
		11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		15	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Change	Increased incidence of centrilobular hepatocyte hypertrophy was observed in the high dose (13/24 compared with 0/22 in controls; p<0.001).	
		17	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Change	Increased incidence of centrilobular hepatocyte hypertrophy was observed in the high dose (5/5 compared with 0/5 in controls; p<0.01).	
	Spleen weight	1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Males: -	Increased spleen weight and extramedullary haematopoiesis observed in mouse studies. The spleen as part of the haematopoietic system is considered to be one of the target organs in mice following exposure with flonicamid. Overall, positive evidence for the indication of toxicity on the haematopoietic system in mice.
		1	Rat	28	Days	Oral	642	mg/kg bw/d	Increase	Females: The high dose females showed a stat. significant increase in relative (to body weight) spleen weight (17% compared with control; p<0.01).	
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -	
		4	Mouse	13	Weeks	Oral	1069/1248	mg/kg bw/d	Increase	Stat. significant increase in absolute spleen weight was observed in high dose males (46% compared with control; p<0.05) and females (63%	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										compared with control; p<0.01). Stat. significant increase in relative (to body weight) spleen weight was observed in high dose males (59% compared with control; p<0.01) and females (74% compared with control; p<0.01).	
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	Change	Females: -	
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	Change	-	
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	Change	-	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Adult F_0: -	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Adult F_1, absolute: -	
		12	Rat	17-18[b]	Weeks	Oral	176.8	mg/kg bw/d	Increase	Adult F_1, relative: Stat. significantly increased relative (to body weight) spleen weight was observed in the F_1 generation high dose females (7% compared with control; p<0.05). There was no microscopic correlate. There was no effect in males and no effect in F_0 generation. Thus, the relative (to body weight) weight	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										change was considered not to be toxicologically relevant.	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring F_1 and F_2: -	
		17	Rat	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	-	
	Spleen histopathology	1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Females: -	
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		4	Mouse	13	Weeks	Oral	153.9/1248	mg/kg bw/d	Change	Increased incidences of minimal to moderately severe extramedullary hematopoiesis occurred in both sexes treated at the mid (5/10 males and 7/10 females) and high (10/10 males and 10/10 females) doses (compared with 2/10 males and 3/10 females controls). Increased pigment was observed in all high dose animals (10/10 in males and females, compared with 0/10 in controls both sexes). Changes were consistent with treatment related anemia and hemosiderin deposition.	
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	Change	Females: -	
		9	Mouse	18	Months	Oral	29/112	mg/kg bw/d	Change	Increased incidence of splenic extramedullary hematopoiesis was observed in high dose males at week 26 (6/10 compared with 0/10 in controls) and at week 52 (9/10 compared with 4/10 in controls). At week 78, increased incidence of splenic extramedullary hematopoiesis was observed in males at low (30/60 compared with 17/60 in controls), mid (28/60 compared with 17/60 in controls) and high dose (45/60 compared with 17/60 in controls). At week 78, increased incidence of splenic extramedullary hematopoiesis was observed in females at the mid (43/60 compared with 33/60 in controls) and high dose (46/60 compared with 33/60 in controls). At week 78, increased incidence of splenic pigment deposition was observed in males at the high dose (8/60 compared with 1/60 in controls) and high dose females (28/60 compared with 15/60 in controls).	
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		17	Rat	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	-	
Systemic toxicity	Body weight	1	Rat	28	Days	Oral	353.4	mg/kg bw/d	Decrease	Males: The high dose males showed decreased body weight throughout the treatment period and stat. significant decrease noted at weeks 1 (-6% compared with control; $p<0.01$) and 2 (-6% compared with control; $p<0.05$).	Dose-dependent decrease of body weight (gain) observed in rats, mice, rabbits and dogs
		1	Rat	28	Days	Oral	642	mg/kg bw/d	Decrease	Females: The high dose females showed decreased body weight throughout the treatment period at week 4 (-12% compared with control; $p<0.01$).	
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -	
		4	Mouse	13	Weeks	Oral	1069/1248	mg/kg bw/d	Decrease	There was a treatment-related decrease in body weight gain in both sexes treated at the high dose, with some males showing weight loss during the first 4 weeks of treatment (weeks -1 to 4 - 0.3 g in high dose males compared with gain of 4.6 g in controls ($p<0.01$) and gain of 0.9 g in high dose females compared with gain of 3.8 g in controls ($p<0.05$)). After the initial 5 weeks of treatment	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										the weight gain was similar across groups.	
		5	Dog	90	Days	Oral	20	mg/kg bw/d	Decrease	Females in the high dose exhibited stat. significant body weight loss for the first Week 1 - 9 of dosing (Week 0-9 the controls had gained 1.24 kg, compared with a loss of -0.26 kg in the high dose; $p<0.05$), and body weight gain occurred thereafter when supplemental food was provided; however, the overall body weight gain was reduced by -57% compared with that of controls. Transient and less marked body weight loss occurred in both sexes at 20 mg/kg bw/d (overall body weight gains were -28 and -52% lower than that of control males and females, respectively.	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	
		6	Dog	52	Weeks	Oral	20	mg/kg bw/d	Decrease	Body weight gain was stat. significantly reduced in females in the high dose from weeks 2 to 4 although the group mean body weight were not stat. significantly different from control values throughout the treatment period; nevertheless, the overall weight gain was -30%, compared with controls at termination, and is therefore considered related to treatment.	
		8	Rat	104	Weeks	Oral	36.5	mg/kg bw/d	Decrease	Males: A treatment-related decrease in the overall body weight gain	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										occurred in high dose males (-8% lower than the controls values) and the group mean body weight were reduced (-6% compared with control; $p<0.05$), after week 104 of treatment.	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Decrease	Females: A treatment-related decrease in the overall body weight gain occurred in high dose females (-11% lower than the controls values) and the group mean body weight were reduced (-8% compared with control; not stat. significant), after week 104 of treatment.	
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		12	Rat	17-18[b]	Weeks	Oral	109.1	mg/kg bw/d	Decrease	Adult, F_0: There was no effect of treatment on body weight at any dose level in either sex. The group mean body weight gain were significantly lower than control values (approximately 6%), during the first week of treatment only, in F_0 malesat the high dose. This change was considered likely to reflect diet palatability.	
		12	Rat	17-18[b]	Weeks	Oral	176.8	mg/kg bw/d	Decrease	Adult, F_1: There was no effect of treatment on body weight at any dose level in either sex. The group mean body weight gain were significantly	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										lower than control values (approximately 6%), during the first week of treatment only, in F_1 females at the high dose. This change was considered likely to reflect diet palatability.	
		13	Rat	GD 6 to GD 19	Days	Oral	1000	mg/kg bw/d	Decrease	Body weight loss occurred in the high dose females during GD 6 to GD 9 (-4 g compared with a gain of 7 g in the control; $p<0.01$) and during GD 6 – GD 12 (10 g compared with a gain of 22 g in the control; not stat. significant).	
		14	Rabbit	GD 6 to GD 19	Days	Oral	30	mg/kg bw/d	Decrease	Body weight loss or slightly reduced body weight gain occurred throughout the treatment period in the high dose, and group mean weight gain was stat. significantly lower than the controls during the period GD 6 to GD 24 (-157 g body weight loss in the high dose compared with a gain of 236 g in the controls; $p<0.05$).	
		15	Rat	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect		
		16	Rabbit	GD 6 to GD 19	Days	Oral	25	mg/kg bw/d	Decrease	Group mean body weight were not stat. significantly different from control values, but reduced body weight gain occurred throughout the treatment period in the high dose group (GD 6 - GD 28 body weight gain in the high dose was 39 g	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										compared with 225 g in the control; p<0.05).	
		17	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Decrease	Mean body weight was decreased in the high dose group on GD 9 (-3% compared with control; not stat. significant) and body weight gain was reduced GD 0 - GD 9 (-29% compared with control; not stat. significant).	
		19	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		19	Rat	90	Days	Oral	(-)	mg/kg bw/d	No effect	-	
	Clinical chemistry and haematology	1	Rat	28	Days	Oral	353.4	mg/kg bw/d	Change	Males: The high dose males showed a stat. significant decrease in Hct (-6% compared with control; p<0.01) and RBC (-5% compared with control; p<0.05), which may indicate anemia. The high dose males showed a stat. significant increase in total cholesterol (20% compared with control; p<0.01). Measured at termination. Urinalysis also assessed.	Changes in clinical chemistry, haematology and urinalysis parameters related to kidney, liver or spleen findings or systemic toxicity were observed in rats, mice and dogs. Some observations were considered not to be adverse as they were transient or not related to dose. Signs indicative of anemia observed in rats, mice and dogs.
		1	Rat	28	Days	Oral	372.6	mg/kg bw/d	Change	Females: The high dose females showed a stat. significant increase in platelet count (17% compared with control; p<0.01). The high dose females showed a stat. significant increase in GGT (100% compared with control; p<0.01), globulin (9% compared with control; p<0.01) and total cholesterol (72% compared with control; p<0.01). The high dose females showed a stat. significant	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										decrease in A/G ratio (-13% compared with control; p<0.01) and triglyceride (-55% compared with control; p<0.01). The intermediate-high dose females showed a stat. significant increase in total cholesterol (22% compared with control; p<0.05). Measured at termination. Urinalysis also assessed.	
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	Measured at termination. Urinalysis also assessed.	
		3	Rat	13	Weeks	Oral	119.4	mg/kg bw/d	Change	Males: At the high dose there was a stat. significant decrease in GPT (-13 % compared with control; p<0.05), CPK (- 17% compared with control; p<0.05) and TG (-20% compared with control; p<0.05).	
		3	Rat	13	Weeks	Oral	340.1	mg/kg bw/d	Change	Females: At the high dose, Hct (-3% compared with control; p<0.05) was stat. significantly decreased while MCHC was stat. significantly increased (2% compared with control; p<0.05). At the high dose, there was a stat. significant decrease in TG (-41% compared with control; p<0.01) and GPT (-12% compared with control; p<0.05). Measured at termination. Urinalysis also assessed.	
		4	Mouse	13	Weeks	Oral	1069/1248	mg/kg bw/d	Change	The hematological investigations showed a treatment-related anemia in both sexes at the high dose, significant reduction of RBC, Hb, Hct together with significant increase	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										of MCV, MCH and reticulocyte counts. Platelet counts were also slightly, but significantly lower in males at the high dose. No changes in hematological parameters were seen in either sex at lower dose levels. Stat. significant changes in clinical chemistry parameters also occurred only at the highest dose level: increased creatinine and total bilirubin concentrations in both sexes (stat. significance only for males); increased mean glucose concentrations in both sexes (stat. significance only for females); elevated sodium and chloride and reduced potassium concentrations in both sexes (stat. significance only for males).	
		5	Dog	90	Days	Oral	20	mg/kg bw/d	Change	Treatment-related hematological changes were only seen in the 50 mg/kg bw/d females which exhibited stat. significantly reduced RBC (-14% compared with controls; $p<0.01$) and stat. significantly increased reticulocyte counts (1100% compared with controls; $p<0.01$) at Week 7, but not at termination. A decrease in monocytes was observed in males at Week 7 (low dose -66% and high dose -60% compared with controls; both $p<0.05$). As these effects were transient (not observed at termination timepoint) they were not considered not to be adverse.	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										Stat. significant changes in clinical chemistry parameters were only seen in the 20 mg/kg bw/d males in which the total protein concentration was stat. significantly elevated at Week 7 (7.7% over the control value; $p<0.05$) but not at termination; such a minor and transient change without histopathological correlate is considered not to be adverse.	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	Lower plasma AST activity was observed in the male low (-23% compared with control; $p<0.05$) and high dose (-22% compared with control; $p<0.05$) but was higher in low dose females (24% compared with control; $p<0.05$). Observation was not consistent across sexes, and was not related to dose, and is therefore considered not to be related to treatment. Measured at termination.	
		6	Dog	52	Weeks	Oral	20	mg/kg bw/d	Change	After 9 and 12 months there was a suggestion of a mild anemia in both sexes at the highest dose level; males at 20 mg/kg bw/d exhibited significantly increased MCV and MCH at the 9- and 12-month time points, although individual values were within the historical control range; females at 20 mg/kg bw/d also showed reduced RBC, Hb and Hct values after 9 and 12 months of treatment; in addition, reticulocytes were increased in both sexes at 20	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										mg/kg bw/d from 6 months, with stat. significance at 12 months treatment. The female group at 8 mg/kg bw/d also showed statistically significant reduction of RBC, Hb and Hct value after 9 months, but these changes were not seen after 12 months and were not associated with increased reticulocyte counts; furthermore, RBC, Hb and Hct values in females at 8 mg/kg bw/d were significantly lower than the controls prior to the start of treatment. Therefore, they were considered to be unrelated to treatment with flonicamid.	
		8	Rat	104	Weeks	Oral	36.5	mg/kg bw/d	Change	Males: Decrease in urine specific gravity was observed in high dose males at weeks 13 and 26 and an increased urinary protein concentration at week 52. Increased platelets observed at week 52 in high dose (9% increase at week 52; $p<0.05$). Assessed at Months 3, 6 and every 6 months after that. Urinalysis also performed.	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Change	Females: Mild anemia indicated by significantly reduced Hct, reduced Hb and reduced RBC was evident in high dose females after week 104 of treatment. There was no consistent effect in these high dose females at earlier sampling intervals, and no effect at any sampling interval in females at lower dose levels. Significant changes of the clinical	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										chemistry profile were seen in the high dose females, including increased serum GGT activity and total cholesterol concentration from week 52 and reduced TG concentrations from week 13 indicative of hepatic dysfunction; such changes were not evident at lower dose levels in females or in males at any dose level or were seen at only one time point. Electrolyte and total and specific protein concentrations in high dose females also differed significantly from control values but the differences were generally inconsistent and / or minimal and / or transient in nature. Decreased urinary specific gravity was observed in high dose females at week 13. Assessed at Months 3, 6 and every 6 months after that. Urinalysis also performed.	
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	Only differential leukocyte counts.	
	Clinical signs	1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Males: -	Dose-dependent clinical signs observed in rats, rabbits and dogs.
		1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Females: -	
		2	Dog	28-35[a]	Days	10	10	mg/kg bw/d	Change	50 mg/kg bw/d caused adverse clinical observations including acute vomiting, laboured breathing, ataxia in both males and prostration and death in one male dog. Vomiting was also seen for both females on Day 1.	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										20 mg/kg bw/d caused vomiting (observed on 5 days in the male), decreased activity (observed on 2 days in the male) and excessive salivation (observed on 3 days in the male). 10 mg/kg bw/d caused vomiting in both males and one female dog on Day 1. Female dogs appeared to be less sensitive to the acute effects	
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -	
		4	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		5	Dog	90	Days	Oral	20	mg/kg bw/d	Change	Vomiting noted in high dose males (4/4) and females (3/4). Conditions in the high dose females persisted throughout the study causing decreased food consumption, inappetence, anorexia, weight loss and early termination of one female due to humane causes. One severely effected high dose female was removed from compound at Week 9 into the study and showed complete reversal from the acute effects of the compound.	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	
		6	Dog	52	Weeks	Oral	8	mg/kg bw/d	Change	Treatment-related clinical signs were confined to vomiting in several dogs at the mid and high dose levels,	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										generally during the first week of dosing.	
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Change	Females: There were stat. significantly increased incidences of red adhesive substance on the skin in females at mid (16/52 compared with 6/52 in the control; $p<0.05$) and high dose (14/52 compared with 6/52 in the control; $p<0.05$).	
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Adult, F_0: -	
		11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring, F_1: -	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Adult, F_0 and F_1: -	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring, F_1 and F_2: -	
		13	Rat	GD 6 to GD 19	Days	Oral	1000	mg/kg bw/d	Change	Vaginal hemorrhage or a white discharge in 2/8 females from the high dose group. Decreased locomotor activity observed in 3/8 high dose dams prior to death.	
		14	Rabbit	GD 6 to GD 19	Days	Oral	30	mg/kg bw/d	Change	One animal in 30 mg/kg bw/d dose group showed reddish urine on GD 23 and GD 24.	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		15	Rat	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		16	Rabbit	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		17	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Change	White material was observed on the tray for 3/5 dams (not observed in control animals). One of these animals also showed soiled fur on the perioral/perinasal/lower abdominal regions and red discharge from the vagina.	
		19	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		19	Rat	90	Days	Oral	(-)	mg/kg bw/d	No effect	-	
	Food consumption	1	Rat	28	Days	Oral	353.4	mg/kg bw/d	Decrease	Males: The high dose males showed decreased food consumption at week 1 (-14% compared with control; $p<0.01$).	Dose-dependent decrease of food consumption observed in rats, mice, rabbits and dogs
		1	Rat	28	Days	Oral	642	mg/kg bw/d	Decrease	Females: The high dose females showed decreased food consumption at weeks 1,2 and 4 (average over week 4: -28% consumed in high dose compared with control; stat. signficant on weeks 1, 2, 4).	
		2	Dog	28-35[a]	Days	10	(-)	mg/kg bw/d	No effect	-	
		3	Rat	13	Weeks	Oral	119.4	mg/kg bw/d	Decrease	Males: Food consumption in high dose males was significantly decreased at weeks 10 and 11. The	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of adminis-tration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
										average food consumption was -6% lower than the controls	
		3	Rat	13	Weeks	Oral	72.3	mg/kg bw/d	Decrease	Females: Food consumption was significantly decreased at several weeks during the treatment period in the high dose animals and the average food consumption was -11% lower than the controls. The average food consumption in the mid dose was -11 % lower than the controls.	
		4	Rat	28	Days	Oral	1069/1248	mg/kg bw/d	Decrease	Females: Food consumption was significantly decreased at several weeks during the treatment period in the high dose animals and the average food consumption was -11% lower than the controls. The average food consumption in the mid dose was -11 % lower than the controls.	
		5	Dog	90	Days	Oral	50	mg/kg bw/d	Decrease	High dose females showed a rejection of the dog chow during the first several weeks of the study and had to be supplemented with canned dog food, therefore interpretation of the data is difficult (in Week 6 food consumption was decreased in high dose females (-31% compared with controls; $p<0.01$). Partial food supplementation had to be continued with at least two animals in the group through the duration of the study.	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Decrease	Females: The food consumption of high dose females was significantly reduced during the first 48 weeks of treatment, leading to a decrease in overall food consumption throughout the treatment period (-6% compared with controls).	
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		12	Rat	17-18[b]	Weeks	Oral	163.8	mg/kg bw/d	Decrease	Adult, F_0: Treatment-related effects on food consumption were confined to slightly, but significantly reduced consumption (up to 10.9%) during the first 2 weeks of gestation and the first week of lactation in F_0 generation high dose females; there were no other effects on food consumption.	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Adult, F_1: -	
		13	Rat	GD 6 to GD 19	Days	Oral	1000	mg/kg bw/d	Decrease	The food consumption at the high dose was stat. significantly reduced on GD 6 – GD 9 (-39% compared with control; $p<0.05$) and GD 18 – GD 20 (-19% compared with control; $p<0.05$).	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		14	Rabbit	GD 6 to GD 19	Days	Oral	30	mg/kg bw/d	Decrease	The food consumption of the group treated at 30 mg/kg bw/d was consistently lower than the control group consumption from GD 12, but the effect was not statistically significant (p>0.05).	
		15	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Decrease	The mean food consumption in the high dose group was lower than that of controls on GD 6 – GD 9 (-7.3% compared with control).	
		16	Rabbit	GD 6 to GD 19	Days	Oral	25	mg/kg bw/d	Decrease	The food consumption was stat. significantly reduced in the high dose group from GD 6 - GD 21 (maximum decrease on GD 15 - GD 18, -44% decrease compared with control; p<0.001).	
		17	Rat	GD 6 to GD 19	Days	Oral	500	mg/kg bw/d	Decrease	Mean food consumption was decreased in the high dose group on GD 6 - GD 9 (-14% compared with control; not stat. significant)	
		19	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		19	Rat	90	Days	Oral	(-)	mg/kg bw/d	No effect	-	
	Mortality	1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Males: -	Dose-dependent systemic toxicity observed in rats, dogs and rabbits.
		1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Females: -	
		2	Dog	28-35[a]	Days	Oral	50	mg/kg bw/d	Increase	50 mg/kg bw/d caused acute vomiting, prostration and death in one male dog following a single dose. The animal that died had necropsy observations of congestion in the lungs and stomach.	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -	
		4	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		5	Dog	90	Days	Oral	50	mg/kg bw/d	Change	One female treated at the high dose was killed on Day 21 following severe anorexia, vomiting, ataxia, decreased activity, diarrhoea and body weight loss. Histologically, in the high dose female that was sacrificed, findings were observed consisting of mild edema of the pancreas and mild involution of the thymus. Additionally, mild vacuolation of the tubules in the inner cortex of the kidney were noted in this animal.	
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-	
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -	
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -	
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-	
		11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Adult (F_0): -	

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence
		11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring (F_1) (mortality of pups): -	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Adult (F_0+F_1):	
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring (F_1+F_2): -	
		13	Rat	GD 6 to GD 19	Days	Oral	1000	mg/kg bw/d	Increase	6/8 dams in the high dose died during GD 9 to 13 (compared with 0/8 in the controls).	
		14	Rabbit	GD 6 to GD 19	Days	Oral	30	mg/kg bw/d	Change	Two females in the high dose aborted and were killed and necropsied on GD 22 or GD 25 (one showed posterior paralysis and soiled fur on the abdomen prior to aborting and the other showed reddish coloured urine).	
		15	Rat	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		16	Rabbit	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		17	Rat	GD 6 to GD 19	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		19	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	-	
		19	Rat	90	Days	Oral	(-)	mg/kg bw/d	No effect	-	

(-) = negative evidence. *= According to column AH of template E of the ED GD (effect indicative of; ECHA and EFSA, 2018). a = 35 days for the low and mid dose, 28 days for the high dose after dose was reduced. Abs. = absolute. Approx. = approximately. . b = parental animals. bw = Body weight. F = Females. F0 = Parental generation. F1 = First filial generation. GD = Gestational Day. GPT = Glutamic pyruvic transaminase. GGPT = γ-Glutamyl transpeptidase. Hb = Haemoglobin. Hct = Haematocrit, M = Males. MCHC: Mean corpuscular haemoglobin concentration. MCV = Mean corpuscular volume. MCH = Mean corpuscular haemoglobin. RBC = Red blood cell. Stat. = Statistical(ly). TG = Triglyceride.

2.10.2.1.3 Assessment of the integrated lines of evidence and weight of evidence for T-mediated adversity and endocrine activity

Table 2.10.2.1.3-1: WoE for T-mediated adversity

• No adverse thyroid weight changes were observed in one rat study (Study ID 12) and in three dog studies (Study IDs: 2, 5, 6). No thyroid histopathological changes were observed in four rat studies (Study IDs: 3, 7, 8, 12), in two mouse studies (Study IDs 9 and 10) and in three dog studies (Study IDs: 2, 5, 6).
• The relative (to body weight) thyroid weight was statistically significantly increased in female dogs at the highest dose level of 20 mg/kg bw/d in a 52-week repeated dose toxicity study (Study ID 6). The relative weight was increased by 47% compared with controls. There was no effect in males at all, and for females absolute weight and relative (to brain weight) thyroid weight did not show any changes. Furthermore, there was no histopathological correlate. Therefore, the observation is considered to be secondary to decreased terminal body weight in high dose females (-13 % compared with controls; not statistically significant) and not as T-mediated adversity. • Males of the high dose group (treated with 1800 ppm flonicamid, equivalent to 109.1 mg/kg bw/d) of the F_0 generation showed statistically significantly increased absolute and relative (to body weight) thyroid weight (13% and 14%, respectively, compared with controls) in a two-generation reproduction toxicity study (Study ID 12). There was no significant effect in the F_1 generation, which were exposed for a longer duration. There was no significant effect in females. There was no treatment-related microscopic correlate. In summary, the observation is therefore considered not to be adverse. The isolated nature of change in thyroid weight suggests that it is coincidental and not treatment-related.

T-mediated adversity was evaluated examining thyroid histopathology and weight in the standard studies available for flonicamid. T-mediated adversity with regard to mammals was not demonstrated for flonicamid. No histopathological effects on thyroids were seen in the available dataset.

In summary, there was neither inter- nor intraspecies coherence of effects on thyroid weight and due to the absence of any histopathological change on this organ the isolated finding was considered to be of no toxicological significance.

Pituitary weight and histopathology as parameters 'sensitive to, but not diagnostic of, EATS'- modalities did not show any adverse effects following treatment of rats, dogs and mice with flonicamid.

Table 2.10.2.1.3-2:. WoE for T-mediated endocrine activity

• In the Danish (Q)SAR Database predictions for TPO inhibition were negative (within the AD) for the only available Software tool, Leadscope. Predictions for TR binding were outside the AD and thus, are considered not reliable.
• Predictions by the Endocrine Disruptome stated low probability of binding to TRα and TRβ.
• Flonicamid did not show any inhibition of thyroperoxidase activity (TPO) activity (Study ID 25).
• Flonicamid did not show any inhibition of sodium-iodide symporter (NIS) activity (Study ID 26).

AD: Applicability domain. NIS: Sodium-iodide symporter. (Q)SAR: (Quantitative) Structure Activity Relationship. TPO: Thyroperoxidase. TR: Thyroid receptor.

T-related endocrine activity in the form of specific hormone measurements was not investigated *in vivo*. However, *in silico* and *in vitro* data did not raise any concern for T-related endocrine activity and since no T-mediated adversity was observed in the available dataset, changes in hormone levels are not expected.

In a WoE approach, flonicamid is considered to cause no T-related endocrine activity.

Effects secondary to other toxicities

According to the ED GD "adverse effects that are nonspecific secondary consequences of other toxic effects shall not be considered for the identification of the substance as endocrine disruptor" (ECHA and EFSA, 2018).

Therefore, additional information on systemic general toxicity is shown in Table 8 in order to contextualize the presence of an adverse effect potentially linked to an endocrine activity and to allow the assessment of putative secondary effects.

The only changes observed for thyroid weight was a statistically significantly increased relative (to body weight) thyroid weight in female dogs at the highest dose level of 20 mg/kg bw/d in a 52-week repeated dose toxicity study (Study ID 6). There was no effect in males at all, and for females absolute weight and relative (to brain weight) thyroid weight did not show any changes. The observation is considered to be secondary to decreased terminal body weight in high dose females (-13 % compared with controls; not statistically significant) and not as T-mediated adversity.

The second thyroid weight change was observed in a two-generation reproduction toxicity study (Study ID 12). Males of the high dose group (treated with 1800 ppm flonicamid, equivalent to 109.1 mg/kg bw/d) of the F_0 generation showed statistically significantly increased absolute and relative (to body weight) thyroid weight (13% and 14%, respectively, compared with controls). There was no significant effect in the F_1 generation, which were exposed for a longer duration. There was no significant effect in females and no treatment-related microscopic correlate. In summary, the isolated nature of change in thyroid weight suggests that it is coincidental and not treatment-related. Furthermore the changes in thyroid weight appeared at a dose level where clear signs of other toxicities could be observed such as kidney toxicity in males of the high dose group (increased absolute and relative (to body weight) kidney weight in addition to histopathological findings in the kidney). Based on these findings the systemic NOAEL in males of this study was determined to be 18 mg/kg bw/d and 20.7 mg/kg bw/d for F_0 and F_1 generation, respectively, based on degenerative renal tubular lesions.

2.10.2.1.4 Initial analysis of the evidence and identification of relevant scenario for the ED assessment of T-modality

A sufficiently large number of important T-mediated parameters were covered. The data requirements of the PPP Regulation were fulfilled and studies were generally carried out in accordance with actual protocols.

T-mediated adversity was considered as sufficiently investigated (especially due to the availability of histopathological examinations of the thyroid) for a reliable assessment and the results showed no indications for T-mediated adversity as a consequence of an endocrine MoA.

T-related endocrine activity in the form of specific hormone measurements investigated *in vivo* were not available. Since T-mediated adversity is considered sufficiently investigated without showing positive evidence and since no

indication for T-related endocrine activity is given by the available *in silico* and *in vitro* data, no further investigations concerning the T-modality are required.

Overall, it can be concluded that based on sufficient investigation no T-mediated adversity was observed and therefore, "scenario 1a" applies to flonicamid, the ED criteria are not met (Table 2.10.2.1.4).

Table 2.10.2.1.4: Selection of relevant scenario

Adversity based on T-mediated parameters	**Positive mechanistic OECD CF level 2/3 test**	**Scenario**	**Next step of the assessment**	**Scenario selected**
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is no "T-mediated" adversity	X
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no "T-mediated endocrine activity" observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a /iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

2.10.2.1.5 MoA analysis for T-modality

In accordance with the selected "scenario 1a" (Table 2.10.2.1.4), no MoA analysis is required for the T-modality.

2.10.2.1.6 Conclusion on the assessment of T-modality

In summary, T-mediated adversity and T-related endocrine activity were sufficiently investigated for flonicamid and no indication for T-mediated adversity as a consequence of an endocrine MoA was evident.

Since T-mediated adversity is considered sufficiently investigated without showing positive evidence and since no indication for T-related endocrine activity is given by the available *in silico* and *in vitro* ("scenario 1a"), the ED criteria for T-modality are not met and no further investigations concerning the T-modality are required.

2.10.2.2 ED assessment for EAS-modalities

2.10.2.2.1 Have EAS-mediated parameters been sufficiently investigated?

	Sufficiently investigated
EAS-mediated parameters	Yes based on the availability of the following studies: − Repeated dose 28-day oral (feeding) toxicity study in Wistar rats, dose range finding, no guideline referred) (Study ID 1) − Repeated dose 28-day oral (capsule) toxicity study in beagle dogs, OECD TG 409 (Study ID 2) − Repeated dose 90-day oral (feeding) toxicity study in Wistar rats, OECD TG 408 (Study ID 3) − Repeated dose 90-day oral (capsule) toxicity study in beagle dogs, OECD TG 409 (Study ID 5) − Repeated dose 52-week oral (capsule) toxicity study in beagle dogs, OECD TG 409 (Study ID 6) − Repeated dose 28-day dermal toxicity study in Sprague-Dawley rats, OECD TG 410 (Study ID 7) − Chronic and carcinogenicity 24-month oral (feeding) toxicity study in Wistar rats, OECD TG 453 (Study ID 8) − Carcinogenicity 18-month oral (feeding) toxicity study in CD-1 mice, OECD TG 451 (Study ID 9) − Carcinogenicity 18-month oral (feeding) toxicity study in CD-1 mice, OECD TG 451 (Study ID 10) − Two-generation reproduction oral (feeding) toxicity test in Wistar rats, OECD TG 416 (Study ID 12) − 28-day and 90-day repeated dose toxicity studies (investigation of hormone levels, no applicable guideline) (Study ID 19)

Most relevant EAS-mediated endpoints have been assessed for flonicamid, with the exception of 'nipple development'. Due to the number of studies, in a range of species over different durations, the overall database is considered adequate for the assessment of EAS-mediated adversity.

2.10.2.2.2 Lines of evidence for adverse effects and endocrine activity related to EAS-modalities

The integrated lines of evidence for EAS-related endocrine activity and EAS-mediated effects are reported in Table 2.10.2.2.2-1. The data comprise *in silico* predictions, *in vitro* and *in vivo* mechanistic data, data on organ weight, histopathological evaluations and reproduction and developmental parameters.

All parameters with regards to general or target organ toxicity are presented in the integrated lines of evidence table, Table 2.10.2.1.2-2, as applicable.

Table 2.10.2.2.2-1: Assessment of the integrated lines of evidence for the EAS-modalities

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
***In silico* prediction**	(Q)SAR prediction: Danish database	N.a	N.a	N.a	N.a	N.a	N.a	N.a	N.a	CERAPP predictions (Consensus) stated inactivity regarding ER agonism, antagonism and binding. COMPARA predictions (Consensus) stated inactivity regarding AR agonism, antagonism and binding	Supporting negative evidence for EA-related endocrine activity	Overall, negative evidence for EAS-related endocrine activity (*in silico*)	E; A
	OECD (Q)SA R Toolbo x profilers and rtER Expert System system - US EPA	N.a	N.a	N.a	N.a	N.a	N.a	N.a	N.a	According to profiling with the OECD QSAR Toolbox v.4.2 the parent flonicamid and its simulated metabolites were depicted as ER non-binder. This was confirmed by the endpointspecific profiler 'rtER expert system - US EPA'. However, profiler predictions are supporting information to be used together with the relevant QSAR predictions.	Supporting negative evidence for E-related endocrine activity		E
	Endocrine Disruptome	N.a	N.a	N.a	N.a	N.a	N.a	N.a	N.a	The predictions stated low binding probability to any of the receptors listed, including the AR (agonistic), ERα, ERβ and GR and low-intermediate probability of binding to the AR (antagonistic)..	Supporting negative evidence for EAS-related endocrine activity		E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
***In vitro* mechanistic**	Androgen receptor signalling	23	CV-1 cells	20-24	Hours	Uptake from the medium (*in vitro*)	(-)	µM	No effect	Agonistic and antagonistic activity assessed	Supporting negative evidence for A-related endocrine activity	Isolated positive evidence was obtained from the steroidogenesis assay and the observed decrease of testosterone production. Considering the *in vivo* information on testosterone levels (Study ID 18) and the dataset for EAS-mediated adversity, in a WoE approach, negative evidence for EAS-related endocrine activity (*in vitro*) was concluded.	A
	Aromatase inhibition using human recombinant microsomes (human CYP19 + P450 Reductase Supersomes)	24	Human CYP19 + P450 Reductase Supersomes	15	Min	Uptake from the medium (*in vitro*)	(-)	µM	No effect	-	Supporting negative evidence for S-related endocrine activity		S
	Estradiol synthesis	28	Human	48	Hours	Uptake from the medium (*in vitro*)	(-)	µM	No effect	In the first experiment, the results for estradiol were slightly variable, with a stat. significant decrease in estradiol at the 5th highest concentration, 10 µM (to 0.74 fold, $p < 0.05$). As this decrease was not dose de-pendent it was considered to be anomalous. In the second experiment, there were no stat. significant changes in estradiol concentration. Overall, the results were considered as negative for estradiol, as a negative response was observed in both experiments.	Supporting negative evidence for EAS-related endocrine activity		E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
	Estrogen receptor signalling	18	Human	1	Hours	Uptake from the medium (*in vitro*)	(-)	µM	No effect	At the highest dose tested, 100 µM, ligand binding for ERα and ERβ were slightly inhibited, but not sufficient to reach an IC50 value	Supporting negative evidence for E-related endocrine activity		E
	Estrogen receptor signalling	23	hERα-HeLa-9903	20-24	Hours	Uptake from the medium (*in vitro*)	(-)	µM	No effect	Agonistic and antagonistic activity assessed	Supporting negative evidence for E-related endocrine activity		E
	Testosterone synthesis	28	Human	48	Hours	Uptake from the medium (*in vitro*)	316	µM	Decrease	In the first experiment, the test substance caused stat. significant decreases in tes-tosterone at the two highest concentrations, 1 mM and 316 µM (to 0.84 and 0.89 fold the solvent control, $p < 0.01$ and $p < 0.05$, respectively). In the second experiment, the test substance caused a stat. significant decrease in testosterone at the high-est concentration, 1 mM (to 0.84 fold the solvent con-trol, $p < 0.001$). This was the same as the result ob-served at this concentration in the first experiment. However, the second high-est concentration, 316 µM, did not produce a stat. sig-nificant decrease on this occasion. For testosterone, a positive result was ob-tained in the first experi-	Supporting positive evidence for EAS-related en-docrine activity		E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										ment as a stat. significant decrease was observed at two concentrations. However, an equivocal response was observed in the second experiment as a stat. significant decrease was observed at only one concentration. The combination of an equivocal and a positive led to an overall decision of positive.			
***In vivo* mechanistic**	Estradiol level	18	Rat	17-18[b]	Weeks	Oral	176.8	mg/kg bw/d	Decrease	17β-estradiol levels were decreased in females in the high dose group (-27% compared with controls; not stat. significant).	Slight decrease in 17β-estradiol levels could not be replicated in subsequent study. Therefore, no convincing positive evidence for EAS-related endocrine activity.	Overall, negative evidence for EAS-related endocrine activity (*in vivo*)	E; A; S
		19	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	17β-estradiol levels			E; A; S
		19	Rat	90	Days	Oral	(-)	mg/kg bw/d	No effect	17β-estradiol levels			E; A; S
	Follicle Stimulating Hormone (FSH) level	18	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			E; A; S
		18	Rat	17-18[b]	Weeks	Oral	176.8	mg/kg bw/d	Increase	Females: FSH level was stat. significantly increased in females in the high dose group (58% compared with controls; p<0.0). There was no effect in males.			E; A; S
		19	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		19	Rat	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		18	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
	Luteinizing Hormone (LH) level	18	Rat	17-18[b]	Weeks	Oral	30.5	mg/kg bw/d	Increase	Females: LH levels were stat. significantly increased in females in the mid (31% compared with controls; p<0.05) and high dose groups (50% compared with controls; p<0.01). There was no effect in males			E; A; S
		19	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		19	Rat	90		Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Progesterone	18	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -	Negative evidence for EAS-related endocrine activity		E; A; S
	Testosterone level	18	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for EAS-related endocrine activity		E; A; S
EAS-mediated	Age at balanopreputial separation	12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring (F1): -	Negative evidence for EAS-mediated adversity	*In vivo* studies with flonicamid did not provide any consistent finding or any pattern of findings indicating EAS-mediated adversity. Overall, negative evidence for EAS-mediated adversity	E; A; S
	Age at vaginal opening	12	Rat	17-18[b]	Weeks	Oral	176.8	mg/kg bw/d	Increase	F1 generation; Vaginal opening was stat. significantly delayed at the high dose by a mean of 1.5 days (34.1 days in the high dose compared with 32.6 days in the control; p<0.01).	Slight but stat. significant delay in vaginal opening observed in only one generation. Toxicological significance of the finding unclear.		E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F2 generation; Vaginal opening was, on average, 0.8 day later than the control (33.1 days in the high dose compared with			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										32.3 days in the control; not stat. significant). The study report concluded that the delay in the completion of vaginal opening was not repeated in the F2 generation			
	Anogenital distance	12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring (F2): -	Negative evidence for EAS-mediated adversity		E; A; S
	Coagulating gland histopathology	3	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for EAS-mediated adversity		E; A; S
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Epididymis weight	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for EAS-mediated adversity		E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	3	mg/kg bw/d	Increase	Increased absolute weight of epididymes only at low dose (3 mg/kg bw/d). Not considered as treatment-related as it occurred only in low dose group.			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Epididymis histopathology	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Estrus cyclicity	11	Rat	3 weeks premating to 3 weeks of lactation	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for EAS-mediated adversity		E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
	Genital abnormalities	14	Rabbit	GD6 to GD19	Days	Oral	30	mg/kg bw/d	No effect	-	Negative evidence for EAS-mediated adversity		E; A; S
		15	Rat	GD6 to GD19	Days	Oral	500	mg/kg bw/d	No effect	-			E; A; S
		16	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Mammary gland histopathology (female)	2	Dog	28-35[a]	Days	Oral	50	mg/kg bw/d	No effect	-	Isolated finding from the mammary gland histopathology was reduced incidence of mammary gland adenoma which is considered not adverse. The observation is considered to be associated with age-related tumours and may be due to normal variation in incidence at this age of the animal. Due to the effect direction (decrease of incidence) it is considered not adverse. Therefore, negative evidence for EAS-mediated adversity		E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	50	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Change	Reduced incidence of mammary gland adenoma was observed in high dose females (1/52 compared with 7/52 in control; $p<0.015$). Assessed at week 52 and week 104.			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Mammary gland histopathology (male)	7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
	Ovary weight	1	Rat	28	Days	Oral	642	mg/kg bw/d	No effect	Absolute; stat. significant decrease in absolute ovary weight was observed in high dose females (-25% compared with control; $p<0.05$).	Isolated ovary weight change in high dose group of a 28-day repeated dose toxicity study in rats, which is considered to be secondary to body weight change (-9 % compared with controls, $p<0.05$) and not a direct effect on ovaries. Furthermore, no histopathological correlate. Stat. significant ovary weight changes observed in the two-generation reproduction toxicity study were only seen in high dose group of one generation without showing a histopathological correlate. Moreover there was no obvious effect of the lower weight on the function of the ovaries. The number of		E; A; S
		1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Relative: -			E; A; S
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	163.8	mg/kg bw/d	Decrease	F_0 generation; Stat. significantly decreased absolute and relative (to body weight) ovary weight was observed in the F_0 generation high dose females (-12% compared with controls; $p<0.001$). There was no microscopic correlate.			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F1 generation; -			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
	Ovary histopathology	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	primordial follicles in the ovary of the high dose females was comparable with the controls. Therefore, the finding is considered not adverse. The isolated finding of reduced incidence of ovarian cysts may be related to the age of the animals. There were no ovarian histopathology observations noted in any other study following exposure to Flonicamid. Therefore, the isolated nature of the observation suggested that it was spurious and not treatment-related. Negative evidence for EAS-mediated adversity.		E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Change	Decreased incidence of ovarian cysts in high dose was observed at week 104 (2/31 compared with 10/31 in controls; $p<0.05$). Assessed at week 52 and week 104.			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Oviduct histopathology	12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Measured with oviduct	Negative evidence for EAS-mediated adversity.		E; A; S
	Prostate weight	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		5	Dog	90	Days	Oral	3	mg/kg bw/d	Increase	Increased absolute and relative prostate weight at 8 mg/kg bw/d, increased absolute prostate weight at 3 mg/kg bw/d.	Negative evidence for EAS-mediated adversity.		E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Prostate histopathology (with seminal vesicles and coagulating glands)	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Seminal vesicles weight	12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F_0 generation; - (weight of seminal vesicles with fluids including coagulating glands)	Isolated change in seminal vesicles weight in only one study and one generation. Only relative (to body weight) was affected which was considered		E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F_1 generation; absolute weight; - (weight of seminal vesicles with fluids including coagulating glands)			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		12	Rat	17-18[b]	Weeks	Oral	124.8	mg/kg bw/d	Increase	F_1 generation; relative (to body weight) weight; stat. significantly increased relative (to body weight) seminal vesicle weight was observed in the F1 generation high dose (9% compared with control; $p<0.05$). There was no microscopic correlate. No change in F_0 generation. (weight of seminal vesicles with fluids including coagulating glands)	secondary to body weight changes rather than a direct effect on seminal vesicles. Furthermore, there was no histopathological correlate. Negative evidence for EAS-mediated adversity		E; A; S
	Seminal vesicles histopathology	3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Sperm morphology	12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for EAS-mediated adversity.		E; A; S
	Sperm motility	12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Sperm numbers	12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Testis weight	1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	-	Isolated testis weight change was		E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	observed in the two-generation reproduction toxicity study. Absolute change in F_1 generation high dose males was seen, but no changes in relative (to body weight) testis weight or F_0 generation. Furthermore, there was no microscopic correlate. The absolute weight change was considered secondary to body weight changes and not biologically relevant. Negative evidence for EAS-mediated adversity.		E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F_0 generation; absolute and relative weight; -			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	124.8	mg/kg bw/d	Decrease	F_1 generation; absolute weight; stat. significantly decreased absolute testes weight was observed in the F_1 generation high dose males (-3 compared with control; $p<0.01$).			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F_1 generation; relative weight; -			E; A; S
	Testis histopathology	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Uterus weight (with cervix)	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-	In the two-generation reproduction toxicity study, stat. significantly decreased uterus weight was observed in the F_1 high dose weanlings. No stat. significant difference was observed in the F_2 weanlings. Histopathology was not assessed in offspring. No uterine weight changes were observed in the parental animals. All other studies did not show any uterus weight changes or findings in the histopathological		E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Adult F_1 and F_2; absolute and relative weight; measured with oviduct			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	176.8	mg/kg bw/d	Decrease	Offspring F_1; absolute and relative weight; stat. signifcantly decreased absolute and relative (to body weight) uterus weight was observed in the F_1 generation high dose group (-19% compared with controls; $p<0.05$). Histopathology was not			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										assessed in offspring. Assessed at weaning.	examination of the uterus. In the mouse carcinogenicity study changes in uterine wall thickness were observed on macroscopic examination without showing any histopathological correlate. Therefore, it is considered not adverse. Decreased gravid uterine weight was observed in high dose rabbits in a developmental toxicity study. However, this observation was considered to be related to decreased number of live fetuses and implantations at this dose level (due, in part, to a single animal with 15 corpora lutea and only one		
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring F_2; absolute and relative weight; -			E; A; S
		13	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	gravid. -			E; A; S
		14	Rabbit	GD6 to GD19	Days	Oral	30	mg/kg bw/d	Decrease	Decreased gravid uterine weight was observed in the high dose (-46% compared with control; $p<0.05$). This was due, in part, to a single animal with 15 corpora lutea and only one implantation.			E; A; S
		15	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	gravid. -			E; A; S
		16	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	gravid. -			E; A; S
		17	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	gravid. -			E; A; S
	Uterus histopathology (with cervix)	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	implantation). Maternal toxicity observed as this dose level (decreased body weight and food consumption) during treatment period. Therefore observation considered to be secondary to maternal toxicity. Moreover, it should be discussed whether gravid uterine weight is considered an EATS- mediated parameter or due to the various influences which may affect reproduction and the course of pregnancy as 'sensitive to, but diagnostic of, EATS'-modalities as the other reproductive parameters in the context of the ED GD (ECHA and EFSA, 2018). Overall, negative		E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		10	Mouse	18	Months	Oral	36.3	mg/kg bw/d	Change	Gross pathology: In the high dose females there was an increased incidence of thickened uterus wall observed (20/37 compared with 14/44 in the controls; $p<0.05$). This did not correspond to an increased incidence of any particular microscopic uterine alteration. Therefore this observation is considered not to be adverse. Assessed at week 78.			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
											evidence for EAS-mediated adversity.		
	Vagina histopathology	3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for EAS-mediated adversity.		E; A; S
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			E; A; S
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
	Vaginal smears	11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	Increase	-	Negative evidence for EAS-mediated adversity.		E; A; S
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			E; A; S
Sensitive to, but not diagnostic of, EATS	Adrenals weight	1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Males: -	Few changes in adrenal weight were observed in rats and dogs. However, these weight changes did not show a clear pattern. Effect direction was different (increase and decrease, only one sex was affected in the respective study, no consistency was observed across generations and no	*In vivo* studies with flonicamid did not provide any consistent finding or any pattern of findings indicating adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalitites. Isolated findings were noted in a	N
		1	Rat	28	Days	Oral	642	mg/kg bw/d	Decrease	Females: The high dose females showed a stat. significant decrease in absolute adrenal weight (-24% compared with control; $p<0.01$). The high dose females showed a stat. significant decrease in relative (to body weight) adrenal weight (-17% compared with control; $p<0.05$). Observation interpreted to be reflective of the lower mean final body weight (-9%			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										compared with controls, p<0.05). There was no treatment-related microscopic correlate for the lower adrenal weight. Overall, change interpreted to be secondary to the lower final body weight com pared to the control.	histopathological correlate was observed in any study. Therefore, the effects are considered secondary to other toxicities (body weight changes) and not to be adverse. Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities.	small number of studies but without any consisten pattern. Overall, negative evidence for adversity realting to parameters sensitive to, but not diagnostic of, EATS-modalitites.	
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			N
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -			N
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	Absolute weight: -			N
		5	Dog	90	Days	Oral	20	mg/kg bw/d	Increase	Relative weight; stat. significant increase in relative (to body weight) adrenal weight in high dose males observed (67% compared with control; p<0.05). There was no effect in females. There was no histopathological correlate for the observation. Observation interpreted to be reflective of the lower mean final body weight (- 10% compared with controls, p<0.05). There was no treatment-related microscopic correlate for the lower adrenal weight.			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										Systemic toxicity, adverse clinical signs leading to termination of one dog, was observed at the same dose level. Overall, change interpreted to be secondary to the lower final body weight compared to the control.			
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			N
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			N
		8	Rat	104	Weeks F1 generation; -	Oral	219	mg/kg bw/d	Decrease	Females; absolute weight; stat. significantly decreased absolute adrenal weight was observed in females at the high dose at week 52 (-16% compared with control; $p<0.05$) and at week 104 (-40% compared with control; $p<0.05$). Observation was in one sex only. There was no effect in males. There were no associated histopathological observations in this study, therefore the organ weight change is considered not to be adverse.			N
		8	Rat	104	Weeks	Oral	219	mg/kg bw/d	Decrease	Females; relative weight; stat. significantly decreased relative (to body			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										weight) adrenal weight was observed in females at the high dose at week 52 (-14% compared with control; $p<0.05$). Observation was in one sex only. There was no effect in males. There were no associated histopathological observations in this study, therefore the organ weight change is considered not to be adverse.			
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F_0 generation; absolute weight: -			N
		12	Rat	17-18[b]	Weeks	Oral	163.8	mg/kg bw/d	Decrease	F_0 generation; relative weight; stat. significantly decreased relative (to body weight) adrenal weight was observed in the F0 generation high dose in females (-8% compared with control; $p<0.05$). This observation was not repeated in the F1 generation, which were exposed for a longer duration. Observation was in one sex only. There was no effect in males. There were no associated histopathological observations in this study,			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										therefore the organ weight change is considered not to be adverse.			
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	F_1 generation; -			N
	Adrenals histopathology	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			N
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -			N
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			N
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			N
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -			N
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			N
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N
	Brain weight	1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Males: -	Isolated finding of decreased brain weight in carcinogenicity study in mice. Since only absolute weight in one sex was affected		N
		1	Rat	28	Days	Oral	(-)	mg/kg bw/d	No effect	Females: -			N
		2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -	without showing a histopathological correlate, the finding is considered not adverse. Negative evidence for adverse relating to parameters sensitive to, but not diagnostic of, EATS-modalities		N
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			N
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			N
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -			N
		9	Mouse	18	Months	Oral	261	mg/kg bw/d	Decrease	Absolute weight; stat. significantly decreased absolute brain weight was observed in males after 78 weeks at the high dose (-10% compared with control; $p<0.05$). There was no effect in females. There was no histopathological correlate for the observation.			N
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	Relative weight: -			N
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Adult (F_0+F_1): -			N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Offspring (F_1+F_2): -			N
	Brain histopathology examination	2	Dog	28-35[a]	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		3	Rat	13	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -			N
		5	Dog	90	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		7	Rat	28	Days	Dermal	(-)	mg/kg bw/d	No effect	-			N
		6	Dog	52	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Males: -			N
		8	Rat	104	Weeks	Oral	(-)	mg/kg bw/d	No effect	Females: -			N
		9	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			N
		10	Mouse	18	Months	Oral	(-)	mg/kg bw/d	No effect	-			N
	Fertility mammals	11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Fertility index: -	Decreased fertility was observed in one preliminary study, however group sizes were small in this preliminary study and the observation was not repeated at similar dose levels in the main reproduction study. Therefore, the isolated nature of this observation suggested that it was coincidental to treatment and a result of small		N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Fertility index:			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
											group sizes. Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities.		
	Fetal development	13	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	External abnormalities: -	The occurrence of the isolated finding of a skeletal variation, i.e. an increase in the incidence of cervical rib in the rat at a dose level of 500 mg/kg bw/d occurs only in 2 fetuses (from the same litter) out of 60 exhibited cervical ribs with distal cartilage, which is not significantly different compared to control animals. Furthermore, it occurs s in the absence of other treatment-related abnormalities. It is therefore considered to be related to maternal toxicity and not an		N
		14	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	External abnormalities: -			N
		15	Rat	GD6 to GD19	Days	Oral	500	mg/kg bw/d	Change	External, visceral and skeletal: An increased incidence of cervical rib was observed in the high dose group (6.5 and 34.1% in the groups treated at 0 and 500 mg/kg bw/d, respectively).			N
		16	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	External, visceral and skeletal: -			N
		17	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	External, visceral and skeletal: -			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
											indication for a teratogenic potential of flonicamid. Overall, negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities.		
	Gestation length	11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities		N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	The mean duration of gestation in F_0 generation females at the high dose was slightly, but stat. significantly longer than the control value (22.5 days at the high dose compared with 22.1 days in the control; $p<0.05$). The difference of 0.4 day is within the limits of accuracy of measurement; time of mating and time of parturition were only determined a single time each day in the F_0 generation. A more accurate deermination of the completion of parturition in F_1 females, by 3 times daily observation, did not reveal			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										an effect of treatment and therefore, the difference in the F_0 generation is considered not to be an effect of treatment.			
	Litter size	11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Mean number of pups delivered counted on LD 0: -	Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities		N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Number of pups delivered counted on LD 0: -			N
	Litter viability	11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Viability index on LD 0, 4, and 21: -	Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities.		N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Viability index on LD 0, 4, and 21: -			N
	Litter/pup weight	11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Mean body weight of male and female pups: -	Isolated effects on fetal weights were observed in rabbits which were associated with maternal toxicity. Therefore, the observations are considered to be secondary to systemic toxicity. Negative evidence for adversity relating to parameters sensitive to, but not		N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Group mean pup body weight during lactation: -			N
		13	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Fetal weights: -			N
		14	Rabbit	GD6 to GD19	Days	Oral	30	mg/kg bw/d	Decrease	Male and female fetal weights in the high dose were -11.1 and -5.9%, respectively, lower than control values. No stat. significance. Observation related, in part, to a single animal with 15 corpora lutea and only one implantation. It is			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										considered that the observations are secondary to maternal toxicity experienced by pregnant does at this dose level (GD 6 to GD 24 - 157 g body weight loss in the high dose compared with a gain of 236 g in the controls; p<0.05).	diagnostic of, EATS-modalities.		
		15	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Fetal weights: -			N
		16	Rabbit	GD6 to GD19	Days	Oral	25	mg/kg bw/d	Decrease	The fetal weights in the high dose group were lower than control (-10% in males and -10% in females compared with controls; not stat. significant). It is considered that the observations are secondary to maternal toxicity experienced by pregnant does at this dose level (GD 6 - GD 28 body weight gain in the high dose was 39 g compared with 225 g in the control; p<0.0.5).			N
		17	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Fetal weights: -			N
	Number of implantations, corpora lutea	11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	Isolated finding from a prenatal developmental dose range finding study		N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
		13	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-	in rabbits which is considered secondary to maternal toxicity. Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities.		N
		14	Rabbit	GD6 to GD19	Days	Oral	30	mg/kg bw/d	Decrease	Decreased number of implantations was observed in the high dose (5.0 compared with 9.7 in the control; no stat. significance). This was due, in part, to a single animal with 15 corpora lutea and only one implantation. It is considered that the observations are secondary to maternal toxicity experienced by pregnant does at this dose level (GD 6 to GD 24 -157 g body weight loss in the high dose compared with a gain of 236 g in the controls; $p<0.05$). Therefore, the observations are considered to be related to systemic toxicity.			N
		15	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		16	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		17	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
	Number of live births	13	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Number of live fetuses: -	Isolated finding from a prenatal developmental dose range finding study in rabbits which is considered secondary to maternal toxicity. Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities.		N
		14	Rabbit	GD6 to GD19	Days	Oral	30	mg/kg bw/d	Change	Number of live fetuses: Decreased number of live fetuses was observed in the high dose (4.8 compared with 8.8 in the control; no stat. significance). This was due, in part, to a single animal with 15 corpora lutea and only one implantation. It is considered that the observations are secondary to maternal toxicity experienced by pregnant does at this dose level (GD 6 to GD 24 -157 g body weight loss in the high dose compared with a gain of 236 g in the controls; $p<0.05$). Therefore, the observations are considered to be related to systemic toxicity.			N
		15	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	Decrease	Number of live fetuses: -			N
		16	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Number of live fetuses: -			N
		17	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	Decrease	Number of live fetuses: -			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
	Number of ovarian follicles	12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities.		N
	Numbers of embryonic or foetal deaths and viable featuses	13	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Resorptions and fetal deaths: -	Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities.		N
		14	Rabbit	GD6 to GD19	Days	Oral	30	mg/kg bw/d	No effect	Resorptions and fetal deaths: -			N
		15	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Resorptions and fetal deaths: -			N
		16	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Resorptions and fetal deaths: -			N
		17	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Resorptions and fetal deaths: -			N
	Pre implantation loss	13	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-	Isolated finding from a prenatal developmental dose range finding study in rabbits which is considered secondary to maternal toxicity. Negative evidence for adversity relating to parameters sensitive to, but not		N
		14	Rabbit	GD6 to GD19	Days	Oral	30	mg/kg bw/d	Change	Increased pre-implantation loss was observed in the high dose (52.6% compared with 25.8% in the control; no stat. significance). The high pre-implantation loss was due, in part, to a single animal with 15 corpora lutea and only one implantation. It is			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										considered that the observations are secondary to maternal toxicity experienced by pregnant does at this dose level (GD 6 to GD 24 -157 g body weight loss in the high dose compared with a gain of 236 g in the controls; $p<0.05$). Therefore, the observations are considered to be related to systemic toxicity.	diagnostic of, EATS-modalities.		
		15	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		16	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		17	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
	Reproduction	11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	Mating index; gestation index: -	In the absence of any observable fetal changes the toxicological relevance of the isolated finding of an increased placental weight in one rat study is considered questionable and secondary to maternal toxicity,		N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	Mating index; gestation index: -			N
		13	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Placental weight: -			N
		14	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Placental weight: -			N
		15	Rat	GD6 to GD19	Days	Oral	500	mg/kg bw/d	Change	The mean placental weight at 500 mg/kg bw/d was			N

Effect classification	Effect target	Study ID	Species	Duration of exposure		Route of administration	Lowest effect dose	Dose unit	Effect direction	Observed effect (positive and negative	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
										stat. significantly elevated ($p<0.01$) by 9.7%.	especially since in two other rat studies placental weights were comparable to the control values. Hence, negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities.		
		16	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Placental weight: -			N
		17	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	Placental weight, uterine contents: -			N
	Sex ratio	11	Rat	Approx. 10	Weeks	Oral	(-)	mg/kg bw/d	No effect	-	Negative evidence for adversity relating to parameters sensitive to, but not diagnostic of, EATS-modalities		N
		12	Rat	17-18[b]	Weeks	Oral	(-)	mg/kg bw/d	No effect	-			N
		13	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		14	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		15	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		16	Rabbit	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N
		17	Rat	GD6 to GD19	Days	Oral	(-)	mg/kg bw/d	No effect	-			N

- = negative evidence. * According to column AH of template E of the ED GD (effect indicative of; ECHA and EFSA, 2018). a = 35 days for the low and mid dose, 28 days for the high dose after dose was reduced. A = Androgen. Abs. = Absolute. Approx. = approximately. b = parental animals. bw = Body weight. CYP = Cytochrome P450. E = Estrogen. F = Females. F0 = Parental generation. F1 = First filial generation. F2 = = Second filial generation. FSH = Follicle stimulating hormone. GD = Gestational day. LD = Lactational

day. LH = Luteinizing hormone. M = Males. N = Endpoints potentially sensitive to, but not diagnostic of, EATS modalities. N.a. = Not applicable/not available. S = Steroidogenesis. Stat. = Statistical(ly).

2.10.2.2.3 Assessment of the integrated lines of evidence and weight of evidence for EAS-mediated adversity and endocrine activity

Table 2.10.2.2.3-1: WoE for EAS-mediated adversity

• No adversity in the following EAS-mediated parameters was observed in any of the examined species (rat, dog and/or mouse): Age at balanopreputial separation, anogenital distance, cervix histopathology, coagulating gland histopathology, epididymis weight and histopathology, estrus cyclicity, mammary gland histopathology, ovary histopathology, oviduct histopathology, prostate weight and histopathology, seminal vesicles histopathology, sperm morphology, sperm motility, sperm numbers, testis histopathology and vagina histopathology
• In a two-generation reproduction toxicity study (Study ID 12), mean age at attainment of sexual maturation (vaginal patency) by F_1 female offspring was slightly (but statistically significantly) delayed by a mean of 1.5 days (34.1 days in the high dose compared with 32.6 days in the control) by treatment at 1800 ppm equivalent to 176.8 mg/kg bw/d in F_1 females. Mean body weight at attainment of sexual maturation was also slightly higher in this group (112 g in the high dose compared with 106.7 g in the control; not statistically significant). Neither mean age nor body weight at attainment of sexual maturation was affected by treatment in F_2 female and F_1 male offspring. Absolute and relative ano-genital distance in offspring of either sex (F_2) was not affected by treatment. The toxicological significance of the delay in sexual maturation in F_1 female offspring is therefore unclear.
• Ovary weight change was found in rats of a 28-day repeated dose toxicity study (Study ID 1) and in rats of the F_0 generation of a two-generation reproduction toxicity study (Study ID 12) • In the 28-day repeated dose toxicity study (Study ID 1) absolute ovarian weight was statistically significantly reduced in female rats at the highest concentration of 10000 ppm, equivalent to 642 mg/kg bw/d by 25% compared to controls. The observation is interpreted to be reflective of the lower mean final body weight observed at this dose level (-9% compared to controls). There was no treatment-related microscopic correlate for the lower ovarian weight. There was no statistically significant effect on relative (to body weight) ovarian weight. Overall, the change is interpreted to be secondary to the lower final body weight compared to controls, and not as EAS-mediated adversity. • In the two-generation reproduction toxicity study (Study ID 12) statistically significantly decreased absolute and relative (to body weight) ovary weight was observed in the F_0 generation high dose females (1800 ppm equivalent to 163.8 mg/kg bw/d in F_0 females) (-12% and -12% decrease in absolute and relative ovarian weight, respectively, compared with controls). No statistically significant effect on ovary weight was observed in the high dose F_1 generation (159 mg/kg bw/d). There was no treatment-related microcopic correlate for the decreased ovarian weights. Moreover, there was no obvious effect on the function of the ovaries. The number of primordial follicles in the ovary of the high dose females was comparable with the controls. The toxicological significance of the reduced ovarian weight is therefore unclear. • No ovary weight changes were observed in three rat studies (Study IDs: 3, 7, 8), in one mouse study (Study ID 9) and in three dog studies (Study IDs: 2, 5, 6). • Furthermore, no adverse effects were seen in any histopathological examination of the ovaries. • A stat. significantly decreased incidence of ovarian cysts was observed in the combined chronic toxicity/carcinogenicity study in rats (Study ID 8) at Week 104 in the high dose animals treated with 219 mg/kg bw/d (2/31 compared with 10/31 in controls). The observation is considered not to be adverse and may be related to the age of the animals. No other similar effects were observed. Therefore, the isolated nature of the observation suggested that it was spurious and not treatment related.
• In the two-generation reproduction toxicity study (Study ID 12) relative (to body weight) weight of seminal vesicles with fluids (including coagulating glands) was slightly but statistically significantly higher in F_1 male rats at the highest dietary concentration of 1800 ppm, equivalent to 124.8 mg/kg bw/d. No effect was seen on absolute seminal vesicle weight and there was no effect on absolute or relative absolute seminal vesicle weights in F_0 male rats administered the same dietary concentration. No histopathological correlate was found in this study.

• Furthermore, seminal vesicles were histopathologically examined in other studies in rats and mice and no treatment-related effects were observed • The isolated finding of an increased relative (to body weight) seminal vesicle weight is therefore considered secondary to body weight effects and not as EAS-mediated adversity.
• In the two-generation reproduction toxicity study (Study ID 12) absolute testis weight was marginally (-2.9%) but statistically significantly lower in F_1 male rats at the highest dietary concentration of 1800 ppm, equivalent to 124.8 mg/kg bw/d. No effect was seen on relative (to body weight) testis weight and there was no effect on absolute or relative absolute testis weights in F0 male rats administered the same dietary concentration. No histopathological correlate was found in this study. • No treatment-related testes weight changes were observed in four rat studies (Study IDs: 1, 3, 7, 8), one mouse study (Study ID: 9) and in three dog studies (Study IDs: 2, 5, 6). • Furthermore, the histopathological examination revealed no treatment-related effects in three rat studies (Study IDs: 3, 7, 8), two mouse studies (Study IDs: 9 and 10) and in three dog studies (Study IDs: 2, 5, 6). • The isolated finding of a decreased absolute testis weight is therefore considered secondary to body weight effects and not as EAS-mediated adversity.
• In the two-generation reproduction toxicity study (Study ID 12) statistically significantly decreased absolute and relative (to body weight) uterus weight was observed in F_1 generation high dose weanlings (1800 ppm, equivalent to 176.8 mg/kg bw/d) (-19% and - 19% decrease in absolute and relative uterine weight, respectively, compared with controls). There was also a slight decrease in absolute and relative (to body weight) uterus weight in the high dose F_2 generation observed. However, this was not statistically significant (-12% and -10% decrease in absolute and relative uterine weight, respectively, compared with controls). Histopathology was not assessed in offspring. No uterine weight changes were observed in the parental animals • In the mouse carcinogenicity study (Study ID 10), changes in uterine wall thickness were observed on macroscopic examination (20/37 compared with 14/44 in the controls) in high dose females (250 ppm, equivalent to 36.3 mg/kg bw/d). The macroscopic observation did not correspond to an increased incidence of any particular microscopic uterine alteration. Therefore, this observation is considered not to be adverse. • No uterus weight changes were observed in three rat studies (Study IDs: 3, 7, 8), one mouse study (Study ID: 9) and in three dog studies (Study IDs: 2, 5, 6). • Furthermore, histopathological examination of the uterus revealed no treatment-related change in any study, i.e. in four rat studies (Study IDs: 3, 7, 8 and 12), two mouse studies (Study IDs: 9 and 10) and in three dog studies (Study IDs: 2, 5, 6). • Decreased gravid uterine weight in high dose dams (30 mg/kg bw/d) was observed in a rabbit developmental toxicity study (Study ID 14) (-46 % compared with controls). At the same dose level, decreased number of live fetuses and implantations was observed (due, in part, to a single animal with 15 corpora lutea and only one implantation). Maternal toxicity was observed at this dose level (decreased body weight (GD 6 to 24 -157 g body weight loss in the high dose compared with a gain of 236 g in the controls) and food consumption) during the treatment period. Therefore, the decreased gravid uterine weight is considered to be related to maternal toxicity observed at the same dose level, and not due to an endocrine-related MoA • Four other prenatal developmental toxicity studies in rabbits and rats (including dose range finding studies) showed no effect on gravid uterine weight (Study ID 13; Study ID 15; Study ID 16 and Study ID 17). Moreover, it should be discussed whether gravid uterine weight is considered an EATS-mediated parameter or due to the various influences which may affect reproduction and the course of pregnancy as 'sensitive to but diagnostic of EATS'-modalities as the other reproductive parameters in the context of the ED GD (ECHA and EFSA, 2018).

• In a rat carcinogenicity study (Study ID 8), a stat. significantly reduced incidence of mammary gland adenoma was observed (1/52 compared with 7/52 in controls) in the high dose females (5000 ppm equivalent to 219 mg/kg bw/d). The observation is considered to be associated with age-related tumours and may be due to normal variation in incidence at this age of the animal. Due to the effect direction (decrease of incidence) it is considered not adverse.

EAS: estrogen, androgen, steroidogenesis. GD: gestational day.

In summary, treatment with flonicamid resulted in few isolated putative EAS-mediated findings. These changes are described above in Table 2.10.2.2.3-1 and include delayed vaginal patency and organ weight changes (observed for ovaries, uterus, testis, and seminal vesicles).

None of the organ weight changes was accompanied by a histopathological correlate. Most of the organ weight changes were observed for absolute or relative (to body weight) organ weights only or the organ weight change was not observed in the filial generation for which the exposure was longer and in a more susceptible life phase compared to the parental generation. If only absolute or relative (to body weight) organ weight changes were observed, the finding was linked to lower body weights instead of to a primary EAS-mediated finding. In case of the uterine weight changes in F_1 offsprings, this organ weight change was not observed in F_2 offsprings. The same applied to delayed vaginal patency which was observed for F1 generation only, but not for F_2 generation. In case of the ovary weight changes in the F_0 generation of the two-generation toxicity study no functional impairment was seen since the number of primordial follicles in the ovary of the high dose females was comparable with the controls, i.e. it could be demonstrated that the decreased uterus weight should be considered not adverse due to the lack of impairment of functional capacity.

It must be highlighted that an effect on an EAS-mediated parameter was normally only seen in one specific study. In the view of the vast set of repeated dose toxicity studies with different durations and in different species, no consistent or coherent effects or effect pattern could be observed.

The EAS-mediated findings were only observed at the highest dose/concentration applied, at which the treated animals showed signs of an overt toxicity, see also “Effects secondary to other toxicities” below. No consistent pattern of findings was observed which would be assumed if the described findings were primarily caused by an endocrine MoA.

In a WoE approach, flonicamid is considered to cause no EAS-mediated adversity.

Table 2.10.2.2.3-2: WoE for EAS-related endocrine activity

- To investigate the potential anti-estrogenic findings (delayed vaginal opening, and reduced ovary and uterus weights) observed in the two-generation reproduction toxicity study (Study ID 12) described in Table 3-9, hormone levels (follicle stimulating hormone (FSH), luteinizing hormone (LH) and 17β-estradiol) were analysed in samples taken from 8 male and female (in proestrous) F_1 parents (samples were taken from Study ID 12 and were assessed in Study ID 18).

- FSH and LH levels were statistically significantly increased in females (FSH levels in the high dose group (176.8 mg/kg bw/d) showed an increase of 58% compared with controls; LH levels were increased by 31% in the mid dose group (30.5 mg/kg bw/d) compared with controls and by 50% in the high dose group (176.8 mg/kg bw/d) compared with controls). 17β-estradiol levels were decreased, but the difference was not statistically significant (-27% in the high dose (176.8 mg/kg bw/d) compared with controls). No effect was observed on the progesterone levels in females.

- ER binding activity was also assessed *in vitro* and ERα and ERβ binding was very low at all tested concentrations in the range between 10-2 and 10-9M (Study ID 18). These data suggest that the treatment-related findings in the two-generation reproduction toxicity study (Study ID 12) were not mediated by a receptor binding mechanism.

- FSH, LH and testosterone levels measured *in vivo* in F_1 males did not show any changes (Study ID 18).

- Based on the contention that the putative primary effect of flonicamid was a decrease in circulating 17β-estradiol concentration, raised LH concentration at 30.5 mg/kg bw/d, in the absence of reduced 17β-estradiol concentration, is considered not to be an adverse effect, since any concomitant effect on 17β-estradiol was of sufficiently small magnitude to remain within the gonadotropin-mediated compensatory capacity of homeostatic control. Consistently, the hormonal changes were considered not adverse in the EFSA conclusion (EFSA, 2010).

- The slight and not significant decrease in 17β-estradiol observed at 176.8 mg/kg bw/d is likely related to the renal findings (renal tubular vacuolation, kidneys are the target organs of Flonicamid) at this dose level, inducing higher urine volume and higher excretion of 17β-estradiol.

- The absence of an effect on male serum gonadotropin concentrations suggests that the primary effect of flonicamid in the female is one of reduction in the concentration of circulating 17β-estradiol, rather than a direct stimulation of female gonadotropin secretion. The slight increase in LH and FSH may reflect a positive feedback in response to decreased 17β-estradiol levels secondary to kidney toxicity. Besides, further studies (Inui, 2006 and Study ID 19) investigated the experimental bias from diurnal changes influencing hormonal measurements:

  In one study (Study ID 19) hormone levels (FSH, LH and 17β-estradiol) following exposure of flonicamid for 28 or 90 days were investigated and were in the normal range taking into account the fluctuations of hormone levels in untreated animals at different sampling times and the lack of variations after dietary administration of flonicamid. The other study (Hormonal examination in female [redacted] Wistar rats at pro-estrous, dRAR B 6.6.1.3) investigated circulating levels of LH in non-treated animals. The extent of diurnal hormonal changes in normal rats was shown and it was demonstrated that the measured hormone changes in the two-generation reproduction toxicity study (Study ID 12) were well within the range of basal physiological oscillation. In the two-generation reproduction toxicity study blood sampling was performed between 13h00 and 15h00 at pro-estrous and the sequence of blood sampling was: control group, low dose, middle dose and high dose groups. This means that sampling of the control animals was conducted early in the sampling time and that sampling of high dose groups was done late in the sampling time. The rats of higher dose groups were already in the early stage of LH surge, explaining the significant difference from control and very small standard deviation. It was concluded that the slightly lower hormonal levels in control and in the low dose animals were due to differences in sampling time and that they have no biological significance (Hormonal examination in female [redacted] Wistar rats at pro-estrous, dRAR: B 6.6.1.3).

- Flonicamid did not show any estrogenic or androgenic agonist or antagonist activity, in stably transfected transactivation assays (Study ID 23)

- Flonicamid was classified as a non-inhibitor in the aromatase assay (Study ID 24).

- Flonicamid affected the steroidogenesis pathway by slightly inhibiting testosterone production *in vitro* in H295R cells. There was no effect on estradiol production observed (Study ID 28).

• In the US EPA CompTox database none of the EAS-related *in vitro* assays listed in the EFSA instruction sheet (EFSA, 2019) was available for flonicamid
• CERAPP predictions (Consensus) were available for flonicamid and stated inactivity regarding ER agonism, antagonism and binding.
• COMPARA predictions (Consensus) were available for flonicamid and stated inactivity regarding AR agonism, antagonism and binding.
• According to profiling with the OECD QSAR Toolbox v.4.2 the parent Flonicamid and its simulated metabolites were depicted as ER non-binder. This was confirmed by the endpoint-specific profiler 'rtER expert system - US EPA'. However, profiler predictions are supporting information to be used together with the relevant QSAR predictions.
• The predictions by the Endocrine Disruptome stated low binding probability to any of the receptors listed, including the AR (agonistic), ERα, ERβ and GR and low-intermediate probability of binding to the AR (antagonistic).

AR: Androgen receptor. E, A, S: Estrogen, Androgen, Steroidogenesis. EFSA: European Food Safety Authority. ER: Estrogen receptor. F1 : First filial generation. F2: Second filial generation. FSH: Follicle stimulating hormone. GR: Glucocorticoid receptor. LH: Luteinizing hormone. OECD: Organisation for economic co-operation and development. P: Parental. (Q)SAR: (Quantitative) Structure Activity Relationship. rtER: rainbow trout estrogen receptor. Stat.: statistical(ly

In silico, in vitro and in vivo data obtained for EAS-related endocrine activity were negative for the test substance Flonicamid.

Initial observations showed an increase in FSH and LH in females only (Study ID 18). However, subsequent investigations demonstrated that the effects on FSH and LH were an artefact of the sampling procedure. A follow-up study (Study ID 19) confirmed the absence of effects on FSH and LH levels in female rats following exposure for 28 or 90 days at the same dietary concentrations used in the two-generation study (Study ID 12). Reduced levels of FSH and LH would be expected to reduce the synthesis of testosterone in the testes of males and reduce the synthesis of estradiol in the ovaries of females. However, there was no effect on testosterone levels in males (Study ID 18). Estradiol levels in females were shown to be slightly (not statistically significantly) reduced in this study (Study ID 18); a change that was not replicated in a follow-up study (Study ID 19). The reduced estradiol levels were considered secondary to the concomitantly observed renal findings (renal tubular vacuolation, kidneys are the target organs of flonicamid) at the respective dose level, inducing higher urine volume and higher excretion of 17β-estradiol, see also 'Effects secondary to other toxicities'..

Very low ER binding activity (Study ID 18) and a lack of AR and ER agonistic and antagonistic effects were demonstrated *in vitro* (Study ID 23).

Furthermore, flonicamid was classified as a non-inhibitor in the aromatase assay (Study ID 24).

An isolated finding of slightly decreased testosterone synthesis, beginning at a concentration of 316 µM and above, was observed in the GLP steroidogenesis assay (Study ID 28). This finding was not verified *in vivo* in the two-generation reproduction toxicity study (Study ID 12) including the subsequent determination of hormone levels (Study ID 18), although the concentrations *in vivo* in blood as well as in the adrenals were well above the determined lowest effect concentration (LOEC) *in vitro*. Based on the '*Study of the elimination and distribution of radio-label following multiple oral administrations of [12C/14C]IKI-220 to Sprague Dawley rats*' ([redacted] 2002; Doc. No. 512-004) highest concentrations in males in the two-generation reproduction toxicity study (Study ID 12) are calculated to be 114 µg/mL in blood and 159 µg/mL in the adrenal (for males treated with a dietary concentration

of 1800 ppm). The LOEC of the steroidogenesis assay was calculated to be 72 µg/mL. In case flonicamid would have an observable effect on the steroidogenesis, *in vivo* effects on testosterone levels and relevant organs and tissues showing a clear pattern would be expected. Furthermore, it should be noted that the fold-changes relative to SC for testosterone for both runs were without a clear dose-response relationship and between 0.81 and 1.03, *i.e.* the range was very small. Such differences in hormone levels can occur naturally as inter- and intraindividual variability. The biological and especially toxicological significance of the finding is considered questionable.

Worthy of note, the revision of OECD test guideline 456, which shall be used for screening and prioritisation purposes, was adopted on 30th June 2022. The 1.5-fold threshold which has al-ready been in the original validation report of the H295R steroidogenesis assay was incorpo-rated in the revised test guideline. Taking into account the 1.5 threshold as an additional crite-rion for the data interpretation, the present steroidogenesis assay performed with Flonicamid under GLP provides a negative result for estradiol as well as for testosterone synthesis, since the fold changes of the statistically different concentrations do not meet the 1.5 threshold.

It can be concluded that the statistically significant results of the steroidogenesis assay (Study ID 28) are considered to be of unclear biological and toxicological significance especially in view of no EAS-mediated adversity. In summary, the decreased *in vitro* testosterone production did not raise concern towards EAS-related endocrine activity. Furthermore, there was no effect on estradiol synthesis observed.

The available *in silico* data support that flonicamid shows no EAS-related endocrine activity.

Overall, in a WoE approach there is no indication for EAS-related endocrine activity of flonicamid in the present data set.

Effects secondary to other toxicities

The above mentioned EAS-mediated findings were observed at the highest dose/concentration of the respective study only, where animals showed concomitantly other signs of toxicity.

The findings from the two-generation reproduction toxicity study (Study ID 12) (delayed vaginal opening in F_1 females, reduced ovary weight in F_0 females and reduced uterus weights in F_1 offspring (assessed at weanling)) were observed in females of the high dose group only. The follow-up study (Study ID 18) with blood samples taken from the two-generation reproduction toxicity study revealed a slight decrease of 17β-estradiol levels in the high dose. The findings may be associated with an increased excretion via the renal system or metabolism in the liver. In the two-generation reproduction toxicity study (Study ID 12) cytoplasmic vacuolation of proximal tubular cells in the kidney occurred in high dose females of the F_0 and F_1 generation. This is in line with the EFSA conclusion where it was concluded that the short-term target organs of Flonicamid were the liver (rats, mice), the kidney (rats) and the haematopoietic system (anaemia in mice) (EFSA, 2010). As for the delay of sexual maturation in F_1 females, mean body weight at attainment of sexual maturation was also slightly higher in this group (112 g in the high dose compared with 106.7 g in the control). This difference was not statistically significant. In F2 female offspring, neither mean age nor body weight at attainment of sexual maturation was affected by treatment.

In the 28-day repeated dose toxicity study in rats (Study ID 1) decreased absolute ovary weight was observed in females of the high dose group which were treated with 10000 ppm, equivalent to 642 mg/kg bw/d. This finding was considered secondary to the lower final body weight compared to controls, and not as EAS-mediated adversity. The NOAEL of this study was considered 81.9 mg/kg bw/d in females based on liver functional changes, enlargement and hepatocellular hypertrophy.

In a rabbit developmental toxicity study (Study ID 14) decreased gravid uterine weight was observed in high dose dams (30 mg/kg bw/d). Dams of this group showed clear signs of general adversity such as body weight loss, reduced body weight gain and reduced food consumption.

2.10.2.2.4 Initial analysis of the evidence and identification of relevant scenario for the ED assessment of EAS-modalities

A sufficiently large number of important EAS-mediated parameters were covered. The data requirements of the PPP Regulation were fulfilled and studies were generally carried out in accordance with validated protocols.

Since no EAS-mediated adversity was observed in the vast set of standard toxicity studies and since no EAS-related endocrine activity was observed *in vitro* and *in vivo*, the conduct of further investigations on adversity/activity is not triggered. A reliable conclusion can be drawn without generation of further information.

Overall, with regard to the vast set of standard toxicity studies, EAS-mediated adversity and EAS-related endocrine activity was considered as sufficiently investigated for a reliable and scientifically sound assessment and in summary no indication for EAS-mediated adversity as a consequence of an endocrine MoA was evident. Therefore, "scenario 1a" applies to flonicamid, the ED criteria are not met (Table 2.10.2.2.4-1).

No EATS-mediated adversity was observed, and EATS-mediated adversity is considered sufficiently investigated. As a consequence, no further investigations are required according to the ED GD (ECHA and EFSA, 2018).

Table 2.10.2.2.4-1: Selection of relevant scenario

Adversity based on EAS-mediated parameters	Positive mechanistic OECD CF level 2/3 test	Scenario	Next step of the	Scenario selected
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is no "EASmediated" adversity	X
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no "EAS-mediated endocrine activity" observed	

No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

2.10.2.2.5 MoA analysis for EAS-modalities

In accordance with the selected "scenario 1a" (Table 2.10.2.2.4-1), no MoA analysis is required for the EAS-modalities.

2.10.2.2.6 Conlusion of the assessment of EAS-modalities

In summary, EAS-mediated adversity and EAS-related endocrine activity were sufficiently investigated for a reliable and scientifically sound assessment of flonicamid and no indication for EAS-mediated adversity as a consequence of an endocrine MoA was shown.

Therefore the conclusion the "ED criteria for EAS-modalities are not met" is applicable for flonicamid, since there was no toxicologically relevant or meaningful EAS-mediated adversity attributable to treatment with Flonicamid in the dataset of parameters evaluated ("scenario 1a").

No EATS-mediated adversity was observed, and EATS-mediated adversity is considered suf-ficiently investigated. As a consequence, no further investigations are required according to the ED GD (ECHA and EFSA, 2018).

2.10.3 Overall conclusion on the ED-assessment for humans

The EATS-mediated adversity and EATS-related endocrine activity of floncamid is considered to be sufficiently investigated based on a large data set consisting of in silico, *in vitro* and *in vivo* data and hence a reliable conclusion on ED acticity can be drawn without generation of further information.

For EATS-mediated adversity, weak evidence was seen in the two-generation reproduction toxicity study (increased thyroid weight, delayed vaginal patency, decreased ovary and uterus weight). However, in a WoE approach these findings were considered no to be linked to EATS-mediated adversity due the lack of biological plausibility, empirical support, consistency and specificity. In summary, no indication for EATS-related endocrine activity was observed in silico, *in vitro* or *in vivo*.

The evidence from the higher tier mammalian toxicity studies conducted in a range of animals also suggest that flonicamid causes no biologically significant alterations to the endocrine system and no specifically ED-related target organs were identified.

In conclusion, based on alla available data and WoE approach, flonicamid is considered as not having endocrine potential as it does not exert relevant, conclusive or consistent adverse effects as a consequence of an endocrine MoA (no EATS-mediated adversity).

2.10.4 ED assessment for non-target organisms

2.10.4.1 ED assessment for EATS-modalities

2.10.4.1.1 Have EATS-mediated parameters been sufficiently investigated?

Based on the ECHA/EFSA ED guidance (2018) section 3.4.1 EATS mediated parameters are sufficiently investigated. (It is noted, however, that hormone levels have not been assessed in any of the ecological toxicity studies following treatment with flonicamid.)

Table 2.10.4.1.1 – 1. Available studies investigating T-mediated parameters

	Sufficiently investigated?
T-mediated parameters	Yes - based on all relevant information including an Amphibian metamorphosis assay (OECD 231). There was no indication for endocrine activity in the available ecotoxicological dataset. These data are considered to be 'sensitive to, but not diagnostic of, 'T'.
EAS-mediated parameters	Yes –based on all relevant information including a Fish Early Life Satege Toxicity study (OECD 210). There was no indication for endocrine activity in the available ecotoxicological dataset. These data are considered to be 'sensitive to, but not diagnostic of, 'EAS'.

2.10.4.1.2 Lines of evidence for adverse effects and endocrine activity related to EATS-modalities

The integrated lines of evidence for EATS-mediated effects with respect to ecotoxicologial studies are reported in Table 2.10.4.1.2-1. For a complete picture of lines of evidence (including in silico predictions and mammalian toxicity) see Appendix E and/or Section 2.10.2 ED assessment for humans).

Table 2.10.4.1.2-1. Assessment of the integrated lines of evidence for the EATS-modalities

Grouping	Line(s) of evidence	Species	Duration of exposure		Route of administration	Lowest Effect dose	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
Bird reproduction studies – OECD 206 (Study ID 21)										
Sensitive to, but not diagnostic of, EATS (OECD 206)	Cracked eggs	Mallard duck	20	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	The reduced hatchability and number of 14-d survivors could potentially indicate ED-related effects, however, no 'sensitive to, but diagnostic of, EATS' parameter was affected in the northern bobwhite and no endpoint specific to the EATS modalities was assessed in either avian species. **Overall negative evidence for endocrine activity and endocrine mediated adversity in birds.**	-
	Egg production	Mallard duck	20	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Egg viability (% viable embryo of egg set)	Mallard duck	20	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Eggshell thickness	Mallard duck	20	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Hatchability	Mallard duck	20	Weeks	Oral	138 mg/kg bw/d	↓ Reduced hatchability (as % of eggs set) at highest test concentration	Likely caused by systemic toxicity (potential indication of EATS mediated effects).		-
	No of 14 day-old survivors	Mallard duck	20	Weeks	Oral	138 mg/kg bw/d	↓ Reduced number of 14-d survivors (as % of eggs set) highest test concentration	Likely caused by systemic toxicity (potential indication of EATS mediated effects).		-
	Body weight (adult)	Mallard duck	20	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Body weight (offspring)	Mallard duck	20	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Gross pathology	Mallard duck	20	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-

Grouping	Line(s) of evidence	Species	Duration of exposure		Route of administration	Lowest Effect dose	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
Systemic toxicity (OECD 206)	Mortality	Mallard duck	20	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	-	-
Bird reproduction studies – OECD 206 (Study ID 20)										
Sensitive to, but not diagnostic of, EATS (OECD 206)	Cracked eggs	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	Overall negative evidence for endocrine activity and endocrine mediated adversity	-
	Egg production	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Egg viability (% viable embryo of egg set)	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Eggshell thickness	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Hatchability	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	No of 14 day-old survivors	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Body weight (adult)	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Body weight (offspring)	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Gross pathology	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-

Grouping	Line(s) of evidence	Species	Duration of exposure		Route of administration	Lowest Effect dose	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
Systemic toxicity (OECD 206)	Mortality	Northern Bobwhite Quail	21	Weeks	Oral	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	-	-
Fish Early Life Stage Toxicity Test – OECD 210 (Study ID 22)										
Sensitive to, but not diagnostic of, EATS (OECD 210)	Body weight (fish)	*Pimephales promelas*	33	Days	Uptake from water	20 mg a.s./L	↓Slight decrease of body weight at the highest test concentration	Likely caused by systemic toxicity (potential indication of EATS mediated effects).	The high dose level in the FELS study showed slightly reduced growth compared with the control. The effect is small and is considered unlikely to be ED-related due to a lack of effect in other parameters, and more likely to reflect the start of systemic toxicity.	-
	Length (fish)	*Pimephales promelas*	33	Days	Uptake from water	20 mg a.s./L	↓ Slight decrease of body length at the highest test concentration	Likely caused by systemic toxicity (potential indication of EATS mediated effects).		-
	Survival of embryos	*Pimephales promelas*	33	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
Systemic toxicity (OECD 210)	Survival (fish)	*Pimephales promelas*	33	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	-	-
	Behaviour (fish)	*Pimephales promelas*	33	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	Overall negative evidence for endocrine activity and endocrine	-
	Embryo time-to-hatch	*Pimephales promelas*	33	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-

Grouping	Line(s) of evidence	Species	Duration of exposure		Route of administration	Lowest Effect dose	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
	Morphological abnormalities	*Pimephales promelas*	33	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	mediated adversity	-
Fish Short Term Reproduction Assay – OECD 229 (Study ID 27)										
Systemic toxicity (OECD 229)	Survival (fish)	*Oryzias latipes*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	-	-
	Behaviour (fish)	*Oryzias latipes*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	-	-
Sensitive to, but not diagnostic of, EATS (OECD 229)	Fertility (number of spawned eggs and number of spawned eggs/day)	*Oryzias latipes*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	Overall negative evidence for endocrine activity and endocrine mediated adversity	-
	Fertilisation rate	*Oryzias latipes*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Body weight (fish)	*Oryzias latipes*	21	Days	Uptake from water	No effect	↓Slight decrease of body weight in females at 1 mg/L	Not biologically relevant due to lack of dose-response relationship. Furthermore, the mean body weight of the females at 1 mg/L (0.316 ± 0.017 g) is within the range of the historical control data (0.315 ± 0.041 to 0.471 ± 0.040 g).		-
	Length (fish)	*Oryzias latipes*	21	Days	Uptake from water	No effect	↓Slight decrease of length in females at all test concentrations	Not biologically relevant due to lack of dose-response relationship. Furthermore, the mean length of the females at 0.1, 1 and 10 mg/L (3.19 ± 0.10 cm, 3.12 ± 0.05 cm and		-

Grouping	Line(s) of evidence	Species	Duration of exposure		Route of administration	Lowest Effect dose	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
								3.17 ± 0.10 cm) is within the range of the historical control data (3.01± 0.10 to 3.41 ± 0.040 cm).		
Endpoint for EAS mediated activity (OECD 229)	Hepatic vitellogenin concentration in males and females	*Oryzias latipes*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
	Secondary sex characteristics in males	*Oryzias latipes*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
Endpoint for A-mediated activity (OECD 229)	Secondary sex characteristics in females	*Oryzias latipes*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
Amphibian Metamorphosis Assay – OECD 231 (Study ID 29)										
Systemic toxicity (OECD 231)	Mortality (amphibian)	*Xenopus laevis*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	-	-
Sensitive to, but not diagnostic of, EATS (OECD 231)	Behaviour (amphibian)	*Xenopus laevis*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	-	-
	Body weight (amphibian)	*Xenopus laevis*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.	Overall negative evidence for endocrine activity and endocrine mediated adversity	-
	Snout-vent length/growth	*Xenopus laevis*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-
Endpoint for EATS mediated	Developmental stage	*Xenopus laevis*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-

Grouping	Line(s) of evidence	Species	Duration of exposure		Route of administration	Lowest Effect dose	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
activity (OECD 231)	Hind limb length	*Xenopus laevis*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		
	Thyroid histopathology (amphibian)	*Xenopus laevis*	21	Days	Uptake from water	No effect	No effect	No evidence for endocrine activity and endocrine mediated adversity.		-

- = negative evidence.

2.10.4.1.3 Assessment of the integrated lines of evidence and weight of evidence for EATS-mediated adversity and endocrine activity

Two bird reproduction studies, two fish studies and an Amphibian metamorphosis study are available for Flonicamid. The tests are evaluated and reported in Volume 3 B.9 CA.

The available reproductive toxicity studies with birds showed slight differences in the sensitivity of the test species. The study with bobwhite quail (Study ID 20) did not show any treatment related effects for systemic toxicity or reproductive parameters up to and including the highest dose tested of 90 mg Flonicamid/kg bw/d (corresponding to NOEL). At the same concentration, the study with mallard duck (Study ID 21 in Appendix E) reported effects on reproductive parameters such as number of hatchlings (expressed as % of eggs set) and number of 14-day-old survivors (expressed as % of eggs set). The observed effects in the highest test concentration are likely to be related to overall systemic toxicity of Flonicamid. This is additionally supported since no equivalent effects have been observed in the study with bobwhite quail which is to be expected if an avian endocrine pathway would have been influenced by Flonicamid. The observed difference between species is likely explained by varying sensitivity towards systemic toxicity, with mallard duck being more sensitive than bobwhite quail. Therefore, these valid bird reproduction studies, although 'not diagnostic of EAS', add weight of evidence for the likely lack of EAS-mediated adverse effects in birds.

The available fish ELS study with Fathead minnow (Study ID 22 in Appendix E) did not show effects on any parameter up to a concentration of 10 mg a.s./L (corresponding to NOEC). At the concentration of 20 mg a.s./L (highest concentration tested) a slight reduction of growth (length) and body weight was observed. No other effects occurred in the test. At a concentration of 20 mg a.s./L observed effects of any kind are very likely related to overall systemic toxicity of Flonicamid but without further information an action via endocrine mediated pathways cannot be completely excluded. Therefore, this fish ELS study with Fathead minnow, although 'not diagnostic of EAS', adds weight of evidence for the likely lack of EAS-mediated adverse effects in fish but further data should be generated to support this conclusion.

The available fish short term reproduction assay (FSTRA) with medaka (Study ID 27 in Appendix E) did not show effects on any parameter up to and including a concentration of 10 mg a.s./L (corresponding to NOEC). Slight reductions of growth (length and body weight) were observed in female fish but this observation was considered to be not biologically relevant due to a lacking concentration-response relationship. No other effects occurred in the test. Therefore, this study adds weight of evidence for the likely lack of EAS-mediated activity in fish.

In the Amphibian metamorphosis study no treatment related effects on survival, developmental stage, wet weight, snout-to-vent length or normalized hind-limb length were observed. The thyroid gland histopathology found no histological findings in any of the test item treatment groups compared to the control. There was no indication to associate Flonicamid with thyroid activity up to and including a concentration of 100 mg a.s./L

No relevant indications for EATS-activity or EATS-mediated adversity were observed in the available studies.

2.10.4.1.4 Initial analysis of the evidence and identification of relevant scenario for the ED assessment of EAS-modalities

The data set is considered sufficent for EATS-related endocrine activity to support a conclusion on absence of EATS-related endocirine activity (ED guidance 3.4.2). No EATS related adversity nor endocrine activity was observed. Therefore, scenario 1a is consider approriate and no MoAs need to be postulated. In accordance with EFSA GD it can be conluded that ED criteria are not met.

Table 2.10.4.1.4-1. Selection of relevant scenario

Adversity based on EATS-mediated parameters	**Positive mechanistic OECD CF level 2/3 test**	**Scenario**	**Next step of the assessment**	**Scenario selected**
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is no "**EATS-mediated**" adversity	X
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no "**EATS-mediated endocrine activity**" observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

2.10.4.1.5 MoA analysis for EAS-modalities

In accordance with the selected "scenario 1a", no MoA analysis is required for EATS-modalities.

2.10.5 Overall conlusion of the ED assessment

With regards to human health, information on mammalian toxicity according to the OECD conceptual frame-work (CF) level 1 and level 2 was available for flonicamid and showed no concern regarding EATS–modalities considering the available *in vivo* information. A few isolated findings with regard to EATS-mediated parameters (increased thyroid weight, delayed vaginal patency, decreased ovary and uterus weight) and few affected parameters in the sense of 'sensitive to, but not diagnostic of, EATS'-modalities without inter- and intra-species coherence and consistency in the available toxicological dataset was observed.

Based on all the information obtained from the mammalian toxicity studies no relevant, consistent or conclusive indication for EATS-mediated adversity (sufficiently investigated for a reliable and scientifically sound assessment) or for EATS-related endocrine activity (sufficiently investigated for a reliable and scientifically sound assessment) was shown.

As a conclusion, the evidence from all higher tier mammalian toxicity studies conducted in a range of animals suggests that flonicamid causes no biologically significant alterations to the endocrine system and no specifically ED-related target organ was identified.

With regard to non-target organism, the data set comprises of OECD CF level 2/3 studies an is considered sufficient. Key studies for the ED assessment are the OECD 229 Fish Short-term Reproduction study and the OECD 231 Amphibibian Metamorphosis Assay. No EATS related adversity nor endocrine activity was observed.

Scenario 1a" applies to flonicamid for the T- and EAS-modalities based on the (eco)toxicological dataset. No mode of action (MoA) needed to be developed.

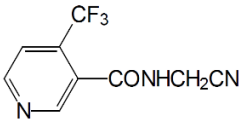
No EATS-mediated adversity was observed, and EATS-mediated adversity is considered sufficiently investigated. As a consequence, no further investigations are required.

2.11 PROPOSED HARMONISED CLASSIFICATION AND LABELLING ACCORDING TO THE CLP CRITERIA *[SECTIONS 1-6 OF THE CLH REPORT]*

2.11.1 Identity of the substance [section 1 of the CLH report]

2.11.1.1 Name and other identifiers of the substance

Table 74: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	N-cyanomethyl-4-(trifluoromethyl)nicotinamide
Other names (usual name, trade name, abbreviation)	*N*-(cyanomethyl)-4-(trifluoromethyl)-3-pyridinecarboxamide
ISO common name (if available and appropriate)	Flonicamid
EC number (if available and appropriate)	No EC-number available*
CAS number (if available)	158062-67-0
Other identity code (if available)	CIPAC number: 763
Molecular formula	$C_9H_6F_3N_3O$
Structural formula	
SMILES notation (if available)	C1=CN=CC(=C1C(F)(F)F)C(=O)NCC#N
Molecular weight or molecular weight range	229.16 g/mol

* A list number is provided: 605-127-0

2.11.1.2 Composition of the substance

Table 75: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**

Table 76: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**

Table 77: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**

Table 78: Test substances (non-confidential information)

Identification of test substance	**Purity**	**Impurities and additives (identity, %, classification if available)**	**Other information**	**The study(ies) in which the test substance is used**

2.11.2 Proposed harmonized classification and labelling

2.11.2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 79: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	616-216-00-9	flonicamid (ISO); *N*-(cyanomethyl)-4(trifluoromethyl)pyridine-3-carboxamide	N/A	158062-67-0	Acute Tox. 4	H302	GHS07 Wng	H302			
Dossier submitters proposal	616-216-00-9	flonicamid (ISO);*N*-(cyanomethyl)-4-(trifluoromethyl)pyridine-3-carboxamide	N/A	158062-67-0	**Retain** Acute Tox. 4	**Retain** H302	**Retain** GHS07 Wng	**Retain** H302		oral: ATE = 884 mg/kg bw	
Resulting Annex VI entry if agreed by RAC and COM	616-216-00-9	flonicamid (ISO);*N*-(cyanomethyl)-4-(trifluoromethyl)pyridine-3-carboxamide	N/A	158062-67-0	Acute Tox. 4	H302	GHS07 Wng	H302		oral: ATE = 884 mg/kg bw	

2.11.2.2 Additional hazard statements / labelling

Table 80: Reason for not proposing harmonised classification and status under CLH public consultation

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Explosives	Data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Hazard class not applicable	No
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Hazard class not applicable	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Data conclusive but not sufficient for classification	No
Self-reactive substances	Data conclusive but not sufficient for classification	No
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Data conclusive but not sufficient for classification	No
Self-heating substances	Data inconclusive	No
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	No
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Data conclusive but not sufficient for classification	No
Organic peroxides	Hazard class not applicable	No
Corrosive to metals	Data conclusive but not sufficient for classification	No
Acute toxicity via oral route	No change into current harmonised classification Acute Tox. 4; H302 is proposed. (No new data compared to the ECHA RAC Opinion 5 June 2013).	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Skin corrosion/irritation	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Serious eye damage/eye irritation	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Respiratory sensitisation	Data lacking (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Skin sensitisation	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Germ cell mutagenicity	Data conclusive but not sufficient for classification (New acceptable *in vitro* micronucleus test with negative result was submitted).	No
Carcinogenicity	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Reproductive toxicity	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Specific target organ toxicity-single exposure	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Specific target organ toxicity-repeated exposure	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Aspiration hazard	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013).	No
Hazardous to the aquatic environment	Data conclusive but not sufficient for classification (No new data compared to the ECHA RAC Opinion 5 June 2013. RAC opinion supported the proposal not to classify flonicamid for environmental toxicity.)	No
Hazardous to the ozone layer		No

2.11.3 History of the previous classification and labelling

The data on active substance flonicamid were evaluated during the first Annex I review of flonicamid and were presented in the monograph (Vol.3, Annex B, Section B.6 Toxicology and metabolism, February 2005) and in the Final addenum (June 2007). Proposal for Harmonised Classification and Labelling (CLH report, version number 2, March 2012) was submitted to ECHA and the proposal was based mainly on the information presented in this assessment of flonicamid.

A harmonised classification and labelling for flonicamid has been adopted by the ECHA Committee for Risk Assessment (RAC) on 5 June 2013 (ECHA/RAC/CLH-O-0000002561-80-03/F). The resulting classification is available in COMMISSION REGULATION (EU) 2015/1221 of 24 July 2015 (7th adaptation to technical and scientific progress of Regulation (EC) No 1272/2008) and the classification for human health is the following:

Acute Tox. 4; H302

Based on re-evaluation of all old and new studies, no change to the current harmonised classification is proposed by the RMS and the previous classification is still considered valid.

2.11.4 Identified uses

Only used as insecticide in agriculture.

2.11.5 Data sources

Please see RAC opinion (5 June 2013 (ECHA/RAC/CLH-O-0000002561-80-03/F) and dRAR Vol 3, B.6.2.1, dRAR Vol 3, B8 and B9 and sections 2.8.2 and 2.9.2.

2.12 RELEVANCE OF METABOLITES IN GROUNDWATER

The relevance of flonicamid metabolites is assessed following SANCO/221/2000 rev. 11 guidance.

2.12.1 STEP 1: Exclusion of degradation products of no concern

Accoding to SANCO/221/2000 rev. 11 guidance, if condition a), b) or c) is met, the degradation product is considered to be a degradation product of no concern and no additional data are required :

a) it is CO2 or an inorganic compound, not containing a heavy metal; or,
b) it is an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern.
c) it is a substance, which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment.

None of the flonicamid metabolites TFNG-AM, TFNG, TFNA, TFNA-AM, TFNA-OH or TFA fulfil any of the above mentioned conditions. Therefore, the metabolites are further assessed in step 2.

2.12.2 STEP 2: Quantification of potential groundwater contamination

Formulation IKI-220 100 OD

Based on modelling with PELMO 5.5.3, PEARL 4.4.4 and MACRO 5.5.4 all PECgw values for flonicamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-AM and TFNA-OH are below the legal drinking water limit of 0.1 µg/L.

- PECgw values for the metabolite **TFA** exceeded 0.1 µg/L for almost all uses and all scenarios. Only in beans, late (Porto) and winter and spring cereals, late (Okehampton and Porto the PECgw concentration

for TFA were <0.1 µg/L with triennial application using input Parameter Set 2. The maximal PECgw for the metabolite TFA in all three models was 3.103 µg/L (PEARL) in Jokioinen scenario (peas early, BBCH 11, 1 x 0.05 kg a.s./ha).

Formulation IKI-220 500 WG

Based on modelling with PELMO 5.5.3, PEARL 4.4.4 and MACRO 5.5.4 all PECgw values for flonicamid and its metabolites TFNG-AM, TFNG, TFNA and TFNA-AM are below the legal drinking water limit of 0.1 µg/L.

- PECgw values for the metabolite **TFA** exceeded 0.1 µg/L for all uses and all scenarios. The maximal PECgw for the metabolite TFA in all three models was 13.428 µg/L (PEARL) in greenhouse use in Sevilla scenario (cucumber, BBCH 16/18, 3 x 0.08 kg a.s./ha) and 12.570 µg/L in field use in winter cereals, early in Thiva scenario using input Parameter Set 1. Highest PECgw value of TFA that was below 10 µg/L was 9.533 µg/L in tomato use in Thiva scenario.
- PECgw values for the metabolite **TFNA-OH** exceeded 0.1 µg/L in pome and stone fruit in Jokioinen and Hamburg scenarios. The maximal PECgw for the metabolite TFNA-OH in all three models was 0.449 µg/L (PEARL) in Jokioinen scenario (cherries, PHI 14 days, 2 x 0.07 kg a.s./ha).

2.12.3 STEP 3: Hazard assessment – identification of relevant metabolites

Metabolites TFNA-OH and TFA are further assessed in STEP 3.

2.12.3.1 STEP 3, Stage 1: screening for biological activity

The goal of this stage is to identify metabolites, which have a comparable target activity as the parent active ingredient, and to deal with cases where the parent molecule is a precursor of the active substance. Flonicamid belongs to the class of nicotinoid insecticides. It exhibits systemic and translaminar activity and inhibits feeding. It is used as a foliar application to specifically control aphids.

According to SANCO/221/2000 rev. 11, it should be sufficient to demonstrate that the biological activity of a metabolite is clearly less than 50% of the activity of the parent molecule. Otherwise the biological activity should be considered as “comparable”. From a regulatory perspective, metabolites with a comparable or higher biological activity than the parent are considered as relevant and must, therefore, not exceed a level of 0.1 µg/L in groundwater as determined according to Step 2. All other products passing this stage should be further screened in Stage 2.

Based on available ecotoxicity data on insects (Tabes 2.12.2-1 and 2.12.3-2), the applicant concluded in their assessment that the metobolites TFNA-OH and TFA do not show insecticidal activity. In addition, data on the toxicity of TFNA-OH, TFA and the parent flonicamid to *Daphnia magna* are available (Table 2.1.3-3).

Based on the available data on arthropods, it is considered that TFA and TFNA-OH show less than 50% of the activity of the parent molecule. Thus the metabolites pass this stage and are further screened in Stage 2.

Table 2.12.3-1. Chronic toxicity of Flonicamid and its metabolites to aphid larvae.

Test substance	µg/mL	Mortality [%]					Reference
		TSM		SBP	GPA	CC	
		Adults	Eggs	Larvae	Larvae	Larvae	
Flonicamid	500	0	0	0	100	0	[redacted] 2004, Doc. No.: 834-008, N4, 3.3.1//01
	100	0	0	0	100	0	
TFNA-OH	500	0	0	0	0	0	
	100	0	0	0	0	0	

TSM Two-spotted spider mite (*Tetranychus urticae*)
SBP Small Brown plant hopper (*Laodelphax striatellus*)
GPA Green peach aphid (*Myzus persicae*)
CC Common cutworm (*Spodoptera liture*)

Table 2.1.3-2. Chronic toxicity of Flonicamid and its metabolites to honey bees.

Test substance	NOED [bee/d]	LD_{10} [µg/bee/d]	LD_{20} [µg/bee/d]	LD_{50} [µg/bee/d]	Reference
Flonicamid	1.1	1.5	2.5	4.5	[redacted] 2020, Doc. No.: 832-005, CA 8.3.1.2/01
TFA	≥ 30.5	> 30.5	> 30.5	> 30.5	[redacted] 2020, Doc. No.: 832-040, CA 8.3.1.2/07

Table 2.1.3-3. Acute toxicity to Flonicamid and its metabolites to *Daphnia magna*.

Flonicamid	*Daphnia magna*	48 h EC_{50} > 100 mg a.s./L (nom)	[redacted] 2001), CA 8.2.4.1/01
TFNA-OH	*Daphnia magna*	48 h EC_{50} > 100 mg/L (nom)	[redacted] (2002), CA 8.2.4.1/03
TFA *	*Daphnia magna*	48 h EC_{50} > 1200 mg/L (nom)	[redacted] (1992), CA 8.2.4.1/06

2.12.3.2 STEP 3, Stage 2: screening for genotoxicity

TFNA-OH

Ames test: Negative

In vitro mammalian cell gene mutation test (mouse lymphoma L5178Y $TK^{+/-}$ cells): Negative

In vitro chromosome aberration test (Chinese hamster lung CHL/IU cells): Negative

In vitro micronucleus test (TK6 human lymphoblastoid cells): Negative

TFA

Ames test: Negative

In vitro mammalian cell gene mutation test (mouse lymphoma L5178Y $TK^{+/-}$ cells): Negative

In vitro chromosome aberration test (human blood lymphocytes): Negative; Supplementary information

In vitro micronucleus test (TK6 human lymphoblastoid cells): Negative

2.12.3.3 STEP 3, Stage 3: screening for toxicity

TFNA-OH

Acute oral toxicity study (rat): LD_{50} > 2000 mg/kg bw

90-day dietary study (rat): NOAEL 346 mg/kg bw/day (males) / 400 mg/kg bw/day (females); Mild decrease of body weight gain (statistically not significant) in male rats at 703 mg/kg bw/day. Subchronic toxicity of TFNA-OH is lower than subchronic toxicity of flonicamid.

In silico analyses: Metabolite TFNA-OH unlikely poses a risk for carcinogenicity, reproductive toxicity or developmental toxicity.

TFA

Acute oral toxicity study (rat): LD_{50} > 2000 mg/kg bw

90-day dietary study (rat): NOAEL 9.9 mg/kg bw/day (males) / 12.2 mg/kg bw/day (females); Increased absolute and relative liver weights with increased incidence of hypertrophy, reduced glucose and bilirubin concentrations in blood, increased ketone levels in urine at 98/123 mg/kg bw/day.

Developmental toxicity study (rat): NOAEL for maternal toxicity 75 mg/kg bw/day (increased relative liver and kidney weights at 150 mg/kg bw/day); NOAEL for foetal toxicity > 150 mg/kg bw/day); Range-finding study.

Developmental toxicity study (rat): NOAEL for maternal toxicity 75 mg/kg bw/day (slightly increased absolute liver and kidney weights at 150 mg/kg bw/day); NOAEL for foetal toxicity > 150 mg/kg bw/day); Supplementary information.

Notification under Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful or unacceptable effects of TFA was submitted on 7 January 2021 to EFSA, the European Commission and Member States by the notifier Bayer of the REACH registration dossier on TFA and the REACH lead registrant and producer of TFA under Regulation (EC) No 1907/2006. According to this data in questioon, ECHA's post-check to dossier evaluation conclusion was: "Recommended for CLH for **Repr. 1B for development** based on clear malformations and other effects seen in the rabbit PNDT study."

Based on the data provided in the dossier of flonicamid, it is not possible to conclude the non-relevance of TFA.

In conclusion: The maximum acceptable concentration of TFA in groundwater is 0.1 µg/L.

2.12.4 STEP 4: Exposure assessment – threshold of concern approach

TFNA-OH

Metabolite TFNA-OH may occur in groundwater up to concentration of 0.449 µg/L. Based on the toxicological data provided, it is possible to use the reference values of flonicamid to TFNA-OH. However, TFNA-OH was not proposed to be included in the risk assessment residue definition for food in the present RAR. As the concentrations of TFNA-OH in groundwater were below 0.75 µg/L in all applied uses, and as no significant consumer exposure is expected, TFNA-OH is concluded to pass step 4.

2.12.5 STEP 5: Refined risk assessment

Not relevant for the applied uses.

2.12.6 Overall conclusion

TFNA-OH

Based on the toxicological data submitted, it can be concluded that toxicity of TFNA-OH is likely less or at the same level as toxicity of flonicamid. *In silico* analyses indicated that TFNA-OH unlikely poses a risk for carcinogenicity, reproductive toxicity or developmental toxicity. Therefore, it is possible to apply the reference values of flonicamid to the risk assessment of TFNA-OH.

According to the modelling data, TFNA-OH can occur in groundwater up to the concentration of 0.449 µg/L. TFNA-OH was not suggested to be included in the residue definitions for food commodities in the present RAR, and thus, exposure via food sources is not expected to exceed 0.02 µg/kg bw/ day as set in SANCO/221/2000 for groundwater metabolite.

TFA

TFA is a known breakdown product of numerous pesticides. It is also a breakdown product of many industrial chemicals. Notification under Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful or unacceptable effects of TFA was submitted on 7 January 2021 to EFSA, the European Commission and Member States by the notifier Bayer of the REACH registration dossier on TFA and the REACH lead registrant and producer of TFA under Regulation (EC) No 1907/2006. According to this data in question, ECHA's post-check to dossier evaluation conclusion was: "Recommended for CLH for Repr. 1B for development based on clear malformations and other effects seen in the rabbit PNDT study." Based on this data showing toxicological relevance of TFA, The maximum acceptable concentration of TFA in groundwater is 0.1 µg/L.

Due to the high leaching potential of soil metabolite TFA to groundwater, flonicamid can only be renewed to a very limited number of the applied field uses and renewal requires specific conditions for greenhouse use. Flonocamid can only be renewed

- for field use for beans (Porto) and winter and spring cereals (Okehampton and Porto), both only for late BBCH stages with triennial application (input Parameter Set 2) (IKI-220 100 OD)
- for greenhouse use for tomato, aubergine, cucumber/courgette and melon in high-tech greenhouses having concrete floors to prevent the leaching of the soil metabolite to groundwater (IKI-220 500 WG).

2.13 CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.13.1 Identity and physical chemical properties

Due to the structural formula of Flonicamid, isomeric compositions are not relevant for the risk assessments.

2.13.2 Methods of analysis

Due to the structural formula of Flonicamid, isomeric compositions are not relevant for the risk assessments.

2.13.3 Mammalian toxicity

Due to the structural formula of Flonicamid, isomeric compositions are not relevant for the risk assessments.

2.13.4 Operator, Worker, Bystander and Resident exposure

Due to the structural formula of Flonicamid, isomeric compositions are not relevant for the risk assessments.

2.13.5 Residues and Consumer risk assessment

Due to the structural formula of Flonicamid, isomeric compositions are not relevant for the risk assessments.

2.13.6 Environmental fate

Due to the structural formula of Flonicamid, isomeric compositions are not relevant for the risk assessments.

2.13.7 Ecotoxicology

Due to the structural formula of Flonicamid, isomeric compositions are not relevant for the risk assessments.

2.14 RESIDUE DEFINITIONS

2.14.1 Definition of residues for exposure/risk assessment

Food of plant origin:

The sum of flonicamid, TFNG and TFNA, expressed as flonicamid (primary crops);

Separately for succeeding crops: TFA, expressed as TFA

Food of animal origin:

The sum of flonicamid and TFNA-AM (free and bound), expressed as flonicamid

Soil:

Flonicamid and metabolites TFNA, TFNA-OH, TFNG-AM, TFNG, TFNA-AM and TFA

Groundwater:

Flonicamid and metabolites TFNA, TFNA-OH, TFNG-AM, TFNG, TFNA-AM and TFA

Surface water:

Flonicamid and metabolites TFNA, TFNA-OH + soil metabolites TFNG-AM, TFNG, TFNA-AM and TFA

Sediment:

Flonicamid and metabolites TFNA, TFNA-OH. It should be noted that the water/sediment study provided was performed with flonicamid labelled at 3rd carbon of pyridyl ring and therefore formation of TFA (attached to 4th carbon of pyridyl ring) in sediment or adsorption to sediment cannot be ruled out in sediment.

Air:

Currently no guideline for definition of residue in air is given. However, due to the low vapour pressure of flonicamid it is concluded that it is unlikely that significant residues will occur in the air.

2.14.2 Definition of residues for monitoring

Food of plant origin:

The sum of flonicamid, TFNG and TFNA, expressed as flonicamid

Food of animal origin:

The sum of flonicamid and TFNA-AM, expressed as flonicamid

Soil:

Flonicamid

Groundwater:

Flonicamid, TFA, TFNA-OH

Surface water:

Flonicamid

Sediment:

Flonicamid

Air:

Flonicamid

Level 3

FLONICAMID

3 PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1 BACKGROUND TO THE PROPOSED DECISION

3.1.1 Proposal on acceptability against the decision making criteria – Article 4 and annex II of regulation (EC) No 1107/2009

3.1.1.1 Article 4

		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.		N	Currently flonicamid can be renewed under Regulation (EC) No 1107/2009 only with the conditions specified in 3.2, or if the data gaps identified in point 3.1.4. are addressed.

3.1.1.2 Submission of further information

		Yes	No	
i)	It is considered that a complete dossier has been submitted	Y		
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.			

3.1.1.3 Restrictions on approval

		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.	Y		The minimum degree of purity of the active substance is 960 g/kg. According to the current specification, Flonicamid technical can contain the relevant impurity toluene at levels of up to 3 g/kg, but in the renewal the notifier proposes to increase the value to 4 g/kg while RMS FI would like to keep the level at 3 g/kg.

3.1.1.4 Criteria for the approval of an active substance

Dossier

		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	Y		
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.		N	Risk assessment could not be finalised for soil metabolite TFA in succeeding crops, livestock commodities (via succeeding feed crops) and drinking water. Significant residue levels of TFA may be present in rotationally grown crops via all non-permanent representative uses. Calculated livestock exposure exceeded trigger value of 0.004 mg/kg bw/day for all livestock species. Metabolism or feeding studies on TFA are not available for the current review. Concentration of TFA in ground water exceeds 0.1 µg/L in almost all field use scenarios, except in triennial application using input Parameter Set 2 few in (beans, late (Porto); winter and spring cereals, late in (Okehampton and Porto).
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.	Y		
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	Y		Sufficient information on efficacy of flonicamid was provided by applicant. For details please see Level 2, Section 2.3.
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.		N	TFA: Adverse developmental toxicity data is available in the frame of article 56 of regulation (EC) 1107/2009 but has not been evaluated in the present RAR. The data is currently being evaluated under REACH. The CLH substance classification proposal by DE is expected to be submitted to ECHA during spring 2024.
Composition				

		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.		N	According to the current specification, Flonicamid technical can contain the relevant impurity toluene at levels of up to 3 g/kg, but in the renewal the notifier proposes to increase the value to 4 g/kg while RMS FI would like to keep the level at 3 g/kg.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.			Not available
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted			There is no FAO specification for flonicamid.
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	Y		Technical active substance: HPLC-UV Impurities: HPLC-UV; GC-FID (toluene)
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	Y		
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	Y		
Impact on human health				
Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	Y		The proposed ADI and AOEL of flonicamid is 0.073 mg/kg bw/d, based on the NOAEL of 7.32 mg/kg bw/d from the combined toxicity and carcinogenicity study in Wistar rats by applying a safety factor of 100.

				ARfD and an acute acceptable operator exposure level (AAOEL) of flonicamid is proposed at 0.075 mg/kg bw, based on the NOAEL of 7.5 mg/kg bw/d from the teratogenicity study in rabbits and a safety factor of 100.
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		N	
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**		N	Based on the available data, flonicamid does not require classification for carcinogenicity in accordance with Regulation (EC) No. 1272/2008 and this conclusion is still valid based on the Committee for Risk Assessment (RAC) opinion of flonicamid (5 June 2013; CLH-O-0000002561-80-03/F).
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not applicable.
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by		N	Based on the available data, no classification of flonicamid for sexual function and fertility, developmental toxicity or effects on or via lactation is proposed in accordance with Regulation (EC) No. 1272/2008.

	the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**			
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not applicable.
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE identified as having endocrine disrupting properties** in accordance with the provisions of point 3.6.5 in Annex II of Regulation (EC) No 1107/2009		N	With regards to human health, information on mammalian toxicity according to the OECD conceptual frame-work (CF) level 1 and level 2 was available for flonicamid and showed no concern regarding EATS–modalities considering the available in vivo information. Based on all the information obtained from the mammalian toxicity studies no relevant, consistent or conclusive indication for EATS-mediated adversity (sufficiently investigated for a reliable and scientifically sound assessment) or for EATS-related endocrine activity (sufficiently investigated for a reliable and scientifically sound assessment) was shown. As a conclusion, the evidence from all higher tier mammalian toxicity studies conducted in a range of animals suggests that flonicamid causes no biologically significant alterations to the endocrine system and no specifically ED-related target organ was identified.
ii)	Linked to above identification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food			Not applicable.

	and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Fate and behaviour in the environment				
Persistent organic pollutant (POP)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		N	- The half-life in soil (geom. 0.6 days) does not exceed the criterion for persistence in soil. - The dissipation half-life in water (worst case 27.9 days) or sediment (worst case 67.5 days) or the degradation half-life in total system (worst case 44.6 days) does not exceed the criterion for persistence in water and sediment. - The photochemical degradation half-life in air (13.7 days) based on the Atkinson method exceeds the criterion for long-range transport in air. The POP criteria of DT50 in air of 2 days is set for active substances that is known or expected to have a potential for long-range environmental transport through air. However, the vapour pressure of 9.43×10^{-7} Pa (20 °C) and water solubility 5.2 g/L of flonicamid indicate that no long-range transport would occur. Hence, RMS considers that flonicamid does not fulfil the POP criteria for long-range transport. - The B criterion (BCF > 2000) is not fulfilled, as the screening criterion for B (logPow < 4.5) is not fulfilled. The log Pow of flonicamid (0.1) does not indicate potential for bioaccumulation. Thus the B criterion (BCF 2000) is not fulfilled based on the screening criterion logPow < 4.5. - The T criterion is not fulfilled as, - the long-term no-observed effect concentration (NOEC) or EC10 for marine or freshwater organisms are above 0,01 mg/l; - classification criteria for carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B, or 2) or (STOT RE category 1 or 2) are not met. **Therefore, flonicamid does not fulfill the POP criteria.**

Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		N	- The half-life in soil (geom. 0.6 days) does not exceed the criterion for persistence in soil. - The dissipation half-life in water (worst case 27.9 days) or sediment (worst case 67.5 days) or the degradation half-life in total system (worst case 44.6 days) does not exceed the criterion for persistence in water and sediment. The B criterion (BCF > 2000) is not fulfilled, as the screening criterion for B (logPow < 4.5) is not fulfilled. The log P_{ow} of flonicamid (0.1) does not indicate potential for bioaccumulation. Thus the B criterion (BCF 2000) is not fulfilled based on the screening criterion logPow < 4.5. The T criterion is not fulfilled as, - the long-term no-observed effect concentration (NOEC) or EC10 for marine or freshwater organisms are above 0,01 mg/l; - classification criteria for carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B, or 2) or (STOT RE category 1 or 2) are not met. **Therefore, flonicamid does not fulfill the PBT criteria.**
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		N	**vPvB criterion is not fulfilled (see above).**
Ecotoxicology				
		Yes	No	
i	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the	Y		No unacceptable risks were identified for birds and mammals. No unacceptable risks were identified for aquatic organisms. No unacceptable risks were identified for non-target arthropods. No unacceptable risks were identified for earthworms or other macro soil dwelling organisms. No unacceptable risks were identified for soil micro-organisms.

	severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.			No unacceptable risks were identified for other non-target plants.
ii	It is considered that, the substance **SHOULD BE identified as having endocrine disrupting properties** that may cause adverse effects on non-target organisms in accordance with the provisions of point 3.8.2 in Annex II of Regulation (EC) No 1107/2009.		N	With regard to non-target organism, the data set comprises of OECD CF level 2/3 studies an is considered sufficient. Scenario 1a" applies to flonicamid for the T- and EAS-modalities based on the (eco)toxicological dataset. No mode of action (MoA) needed to be developed. No EATS-mediated adversity was observed, and EATS-mediated adversity is considered sufficiently investigated. As a consequence, no further investigations are required.
iii	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.			Not applicable.
iv	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	Y		No unacceptable risks have been identified regarding - acute or chronic effects on adult honey bees, - oral and acute contact effects on adult bumble bees, - acute or chronic effects on colony survival or development of honey bees due to Flonicamid and its metabolites under the proposed conditions of use of the representative plant protection products.(For details see section 2.9.9.3).
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.		N	Residue definition for risk assessment in livestock commodities and honey is pending the data on TFA (exposure via rotational crops).
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites,	Y		Applicant has used two input parameter sets for PECgw modelling (mainly affecting the PECgw values for the mobile metabolite TFA). Two sets of input parameters were calculated concerning the studies labelled in the 4th-position of the pyridyl ring. One with the parent soil degradation study alone and one

	degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.			set including additionally metabolite studies labelled in the 4th-position provided late in the evaluation period (March 2023). Use of the additional metabolite studies resulted in lower DT_{50} value for TFA. **Formulation IKI-220 100 OD:** **Triennial application**: All PECgw values for flonicamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-AM and TFNA-OH. PELMO and PEARL **PECgw values for the metabolite TFA were <0.1 µg/L in few scenarios and few BBCH stages** (beans, late (Porto); winter and spring cereals, late (Okehampton and Porto). **Annual application**: PELMO, PEARL and MACRO: All PECgw values for flonicamid and its metabolites TFNG-AM, TFNG, TFNA, TFNA-AM and TFNA-OH are below the legal drinking water limit of 0.1 µg/L for all applied uses. PELMO and PEARL: **PECgw values for the metabolite TFA exceeded 0.1 µg/L for all uses and all scenarios** but was <0.75 µg/L in both models: **Input set 1:** Peas, BBCH 11 (1 x 0.05 kg a.s./ha) - in none of the scenarios Peas, BBCH 71 (1 x 0.05 kg a.s./ha) - in all scenarios Beans, BBCH 11 (1 x 0.05 kg a.s./ha) - in none of the scenarios Beans, BBCH 71 (1 x 0.05 kg a.s./ha) - in Porto, Jokioinen and Okehampton at BBCH 11 Winter cereals, BBCH 39 (1 x 0.05 kg a.s./ha) - in Hamburg, Kremsmünster, Okehampton, Piacenza and Porto at BBCH 39 Winter cereals, PHI (1 x 0.05 kg a.s./ha) - in Hamburg, Kremsmünster, Okehampton, Piacenza and Porto at PHI Spring cereals, BBCH 39 (1 x 0.05 kg a.s./ha)

				- in Kremsmünster, Okehampton and Porto at BBCH 39 Spring cereals, PHI (1 x 0.05 kg a.s./ha) - in Kremsmünster, Okehampton and Porto at PHI **Input set 2:** Peas, BBCH 11 (1 x 0.05 kg a.s./ha) - in none of the scenarios Peas, BBCH 71 (1 x 0.05 kg a.s./ha) - in all scenarios Beans, BBCH 11 (1 x 0.05 kg a.s./ha) - in Porto at BBCH 11 Beans, BBCH 71 (1 x 0.05 kg a.s./ha) - in all scenarios Winter cereals, BBCH 39 (1 x 0.05 kg a.s./ha) - in all scenarios, except Thiva Winter cereals, PHI (1 x 0.05 kg a.s./ha) - in all scenarios, except Thiva Spring cereals, BBCH 39 (1 x 0.05 kg a.s./ha) - in all scenarios Spring cereals, PHI (1 x 0.05 kg a.s./ha) - in all scenarios Rest of the PECgw values for TFA were below 10 µg/L with both Parameter Sets. Highest PECgw value of TFA was below 10 µg/L 3.103 in peas, early in Jokioinen scenario. MACRO, All crops PECgw values exceeded 0.1 µg/L for all uses in Châteaudun scenario and 0.75 µg/L in peas early, and winter cereals, early and late, but remained below 10 µg/L. **Formulation IKI-220 500 WG:** PELMO and PEARL:

				All PECgw values for flonicamid and its metabolites TFNG-AM, TFNG, TFNA and TFNA-AM are below the legal drinking water limit of 0.1 µg/L for all the applied uses. **TFNA-OH** PECgw values for the **metabolite TFNA-OH** exceeded the limit 0.1 µg/L in either only Jokioinen or in both Jokioinen and Hamburg scenarios in apples (PHI 21 d) and cherries (PHI 14 d) (both at 1x and 2 x 70 g a.s./ha), but remained below 0.75 µg/L (max PECgw 0.449 µg/L in Jokioinen scenario, cherries) (see Table 2.8.7.2-26). **TFA** PELMO and PEARL: PECgw values for the **metabolite TFA** exceeded 0.1 µg/L for all uses and all scenarios but was <0.75 µg/L in both models: **Input set 1:** Winter cereals, BBCH 21, 37/39 and 79 (2 x 0.07 kg a.s./ha) - in none of the scenarios Spring cereals, BBCH 21, 37/39 and 79 (2 x 0.07 kg a.s./ha) - in none of the scenarios at BBCH 21 Apples, BBCH stages 01/07, 70, 71 (1 x 0.07 kg a.s./ha) - in Porto at BBCH 70 and 71 Apples, BBCH stages 71-85/87 (2 x 0.07 kg a.s./ha) and PHI 21 d (1 and 2 x 0.07 kg a.s./ha) - in Porto at PHI 21 d (1 x 0.07 kg a.s./ha) Cherries (apples as surrogate crop), PHI 14 days - in Porto at PHI 14 d (1 x 0.07 kg a.s./ha) Cucumber (F+G) covering melon (G) (tomato as surrogate crop) at BBCH 16/18 and BCHH 85/87 (3x 0.05 kg a.s./ha) - in none of the scenarios Cucumber (G) (tomato as surrogate crop) at BBCH 16/18 and BCHH 85/87 (3x 0.08 kg a.s./ha) - in none of the scenarios Tomatoes (G+F) covering eggplants (F+G), cucumber/courgette (F+G) and melon (G) at BBCH 16/18 and BCHH 85/87 (3x 0.06 kg a.s./ha)

				- in none of the scenarios **Input set 2:** Winter cereals, BBCH 21, 37/39 and 79 (2 x 0.07 kg a.s./ha) - in Porto and Okehampton at BBCH 37/39 and 79 Spring cereals, BBCH 21, 37/39 and 79 (2 x 0.07 kg a.s./ha) - in Porto and Okehampton at BBCH 37/39 and 79 Apples, BBCH stages 01/07, 70 and 71 (1 x 0.07 kg a.s./ha) - in Porto at BBCH 01/07, 70 and 71 Apples, BBCH stages 71-85/87 (2 x 0.07 kg a.s./ha) and PHI 21 d (1 and 2 x 0.07 kg a.s./ha) - in Porto at PHI 21 d (1 x 0.07 kg a.s./ha) Cherries, PHI 14 days - in Porto and Okehampton at PHI 14 d (1 x 0.07 kg a.s./ha) Cucumber (F+G) covering melon (G) at BBCH 16/18 and BCHH 85/87 (3x 0.05 kg a.s./ha) - in Porto at BBCH 85/87 Cucumber (G) at BBCH 16/18 and BCHH 85/87 (3x 0.08 kg a.s./ha) - in none of the scenarios Tomatoes (G+F) covering eggplants (F+G), cucumber/courgette (F+G) and melon (G) at BBCH 16/18 and BCHH 85/87 (3x 0.06 kg a.s./ha) - in none of the scenarios **Input set 1:** In other uses PECgw values of TFA were > 0.75 µg/L and <10 µg/L, except >10 µg/L in the following uses: - winter cereals, early at BBCH 21, NEZ, 2 x 0.07 kg a.s./ha, Thiva: PECgw = 12.570 µg/L (PEARL) - cucumber, early at BBCH 16/18 (IZ) in greenhouse, 3 x 0.08 kg a.s./ha, Sevilla: PECgw = 10.449 µg/L (PELMO) - cucumber, early at BBCH 16/18 (IZ) in greenhouse 3 x 0.08 kg a.s./ha, Sevilla: PECgw = 13.428 µg/L, Thiva: PECgw = 12.711 µg/L (PEARL) Highest PECgw value of TFA that was below 10 µg/L was 9.533 µg/L in tomato use in Thiva scenario.

				MACRO: PECgw values exceeded 0.75 µg/L for all uses in Châteaudun scenario but remained below 10 µg/L.

3.1.2 Proposal – Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution		N	

3.1.3 Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** If the active substance is not a micro-organism, in particular it is considered that: (a) the substance **should NOT be classified or proposed for classification** in accordance to Regulation (EC) No 1272/2008 as any of the following: — carcinogenic category 1A, 1B or 2, — mutagenic category 1A, 1B or 2, — toxic to reproduction category 1A, 1B or 2, — skin sensitiser category 1, — serious damage to eye category 1, — respiratory sensitiser category 1, — acute toxicity category 1, 2 or 3, — specific Target Organ Toxicant, category 1 or 2, — toxic to aquatic life of acute and chronic category 1 on the basis of appropriate standard tests, — explosive, — skin corrosive, category 1A, 1B or 1C;		N	

	(b) it has **not been identified as priority substance under Directive 2000/60/EC**; (c) it is **not deemed to be an endocrine disruptor** in accordance to Annex II of Regulation (EC) No 1107/2009; (d) it **has no neurotoxic or immunotoxic effects**; (e) it **is not persistent** (half-life in soil is more than 60 days) or its **bio-concentration factor is lower than 100**. (f) it is a **semiochemical** and verifies points (a) to (d). Paragraph (e) doesn't apply to naturally occurring active substances. If the active substance is a micro-organism, in particular it is considered that at strain level the micro-organism has not demonstrated multiple resistance to anti-microbials used in human or veterinary medicine. If the active substance is a baculovirus, in particular it has not demonstrated adverse effects on non-target insects.			

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

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1 Identity of the active substance or formulation				
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
3.1.4.3 Data on uses and efficacy				
3.1.4.4 Data on handling, storage, transport, packaging and labelling				
3.1.4.5 Methods of analysis				
none				
3.1.4.6 Toxicology and metabolism				
Soil and ground water metabolite TFA: developmental toxicity study missing	relevant for all outdoor uses (Art. 56 of (EC) 1107/2009)	x		The developmental toxicity data is currently being evaluated under REACH. The CLH substance classification proposal by DE is expected to be submitted

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
				to ECHA during spring 2024.
3.1.4.7 Residue data				
Storage stability of TFA in all relevant succeeding crop matrices	Non-permanent crops. Necessary only if outdoor uses can be accepted	x		
Metabolism studies of TFA in livestock.	Non-permanent crops. Necessary only if outdoor uses can be accepted	x		
Nature and magnitude of TFA residues in processed commodities	Non-permanent crops. Necessary only if outdoor uses can be accepted	x		Nature of residue study may be available according to the applicant
Residues of TFA in rotationally grown melliferous crops	Non-permanent crops. Necessary only if outdoor uses can be accepted	x		
Sufficient number of residue decline trials on apples to complete 50% of trials.	Relevant for uses on apple in all zones. Necessary only if outdoor uses can be accepted.	x		
Sufficient number of residue decline trials on peaches and nectarines to complete 50% of trials.	Relevant for uses on peaches and nectarines in the SEU zone. Necessary only if outdoor uses can be accepted.	x		
3.1.4.8 Environmental fate and behaviour				
A water/sediment study with flonicamid labelled in 4th carbon of pyridyl enabling the	relevant for all uses	x		

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
analysis of TFA in the study. However, a default of 1000 days has been used in water, sediment and total system in PECsw modelling.				
3.1.4.9 Ecotoxicology				
none				

3.1.5 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, as laid out in Commission Regulation (EU) No 546/2011, 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).

Area of the risk assessment that could not be finalised on the basis of the available data	**Relevance in relation to representative use(s)**
Developmental toxicity of soil and groundwater metabolite TFA	TFA exceeds 0.1 µg/L (and 0.75 µg/L) in groundwater in majority of outdoor scenarios. The non-relevance of TFA has not been shown. The toxicity of the metabolite trifluoroacetic acid (TFA) was the subject of a notification falling under Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful or unacceptable effects, submitted on 7 January 2021 to EFSA, the European Commission and Member States by the notifier Bayer of the REACH registration dossier on TFA and the REACH lead registrant and producer of TFA under Regulation (EC) No 1907/2006. According to the data, ECHA's post-check to dossier evaluation conclusion was: "Recommended for CLH for Repr. 1B for development based on clear malformations and other effects seen in the rabbit PNDT study." As at the time of conducting the peer review process on the renewal of approval of flonicamid, the follow-up investigations and preparation of the harmonised classification proposal for TFA were still ongoing at MS and ECHA level.

3.1.6 Critical areas of concern

An issue is listed as a critical area of concern:
(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, 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.

Critical area of concern identified	**Relevance in relation to representative use(s)**
Developmental toxicity of TFA	Critical for all uses.

3.1.7 Overview table 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 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)
All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		**Teppeki IKI-220 500 WG (all uses)** (X^1)	**Shoori IKI-220 100 OD (all uses)** (X^1)
Operator risk	Risk identified		
	Assessment not finalised	X	X
Worker risk	Risk identified		
	Assessment not finalised	X	X
Bystander risk	Risk identified		
	Assessment not finalised	X	X
Consumer risk	Risk identified		
	Assessment not finalised	X	X
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		
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached	X (TFA)	X (TFA)
	Parametric value of 10µg/L[(a)] breached	X (TFA)	
	Assessment not finalised	X (TFA)	X (TFA)
Comments/Remarks			

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.
(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 11, European Commission, 2021

3.1.8 Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	Justification

3.1.9 Critical issues on which the Co RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	Opinion of Co-RMS	Opinion of RMS

3.2 PROPOSED DECISION

It is proposed that:

[redacted]

3.3 RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPROVAL OR AUTHORISATION(S), AS APPROPRIATE

3.3.1 Particular conditions proposed to be taken into account to manage the risks identified

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)

3.4 APPENDICES

3.4.1 Guidance documents and other references used in this assessment

Guidance at place at the moment of submission of the supplementary dossiers.

General

European Food Safety Authority, 2019. Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances, EFSA supporting publication 2019:EN-1612. 49 pp. doi:10.2903/sp.efsa.2019.EN-1612

SANCO/12580/2012– rev. 4 22 March 2019 Guidance document on preparing lists of test and study reports according to article 60 of Regulation (EC) No 1107/2001

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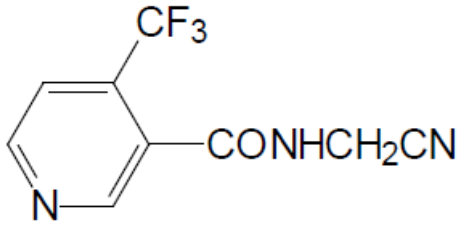
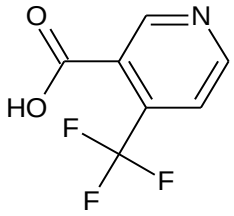
3.4.2 Substances and metabolites; structures, codes, synonyms

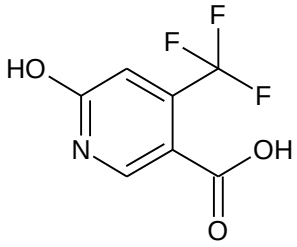
Substances and metabolites; structures, codes, synonyms

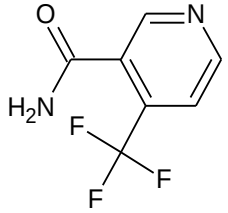
RMS note: any changes made by the RMS on the applicant's text are highlighted as ~~strikethrough~~ and/or *italic text*.

Code Number (Synonyms) That indicated in bold was used in the summary dossier	**IUPAC name /SMILES notation /InChiKey**	**Structural formula**	**Compound found in…**
IKI-220 (Flonicamid)	N-cyanomethyl-4-(trifluoromethyl)nicotinamide		**Rat:** - Faeces: 0.52 (females) – 0.56 % (males) of orally applied low dose (2 mg/kg bw), 0.79 (females)– 1.22 % (males) of orally applied high dose (400 mg/kg bw), - Urine (single dose): 51.58 (males)– 60.38 % (females) of orally applied low dose (2 mg/kg bw), 63.41 (males) - 71.99 % (females) of orally applied high dose (400 mg/kg bw), - Urine (repeated dose): 45.72 (males)– 53.61 % (females) of orally applied low dose (2 mg/kg bw), - Bile: 2.48 (females) – 2.67 % (males) of orally applied low dose (2 mg/kg bw), 2.80 (males)- 3.32 % (females) of orally applied high dose (400 mg/kg bw) Bile duct cannulated rats: - Faeces: 0.32 (males) – 2.04 % (females) of orally applied low dose (2 mg/kg bw), 0.89 % (males) - 0.92 (female) of orally applied high dose (400 mg/kg bw) - Urine: 61.01(male) - 66.27 % (female) of orally applied low dose (2 mg/kg bw), 59.74 % (males) - 70.40 % (female) of orally applied high dose (400 mg/kg bw) **Crop:** <u>Primary plant metabolism:</u>

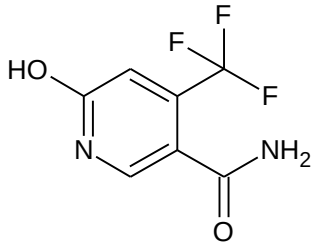
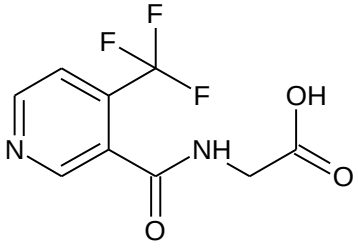
Code Number (Synonyms) That indicated in bold was used in the summary dossier	IUPAC name /SMILES notation /InChiKey	Structural formula	Compound found in…
			- Wheat: Straw (50.2 %), chaff (46.9 %), grain (29.9 %), forage (42.8 %), hay (21.7 %) - Potato: Tuber (19.3 %), foliage (92.3 %) - Peach: Fruit (60.6 %), foliage (64.9 %) - Bell pepper: Leaves (74.3 %), fruit (91.4 %) **Rotational crop metabolism:** - Lettuce: Immature lettuce (8.9 %), mature lettuce (5.7 %) - Carrot: Immature carrot (4.7 %), mature root (2.3 %), mature top (5.2 %) - Wheat: Grain (12.9 %), chaff (5.9 %), straw (4.5 %), forage (10.5 %) **Livestock:** - Poultry: Egg white (2.5 %), egg yolk (3.8 %), whole egg (2.8 %), liver (0.3 %), kidney (0.4 %), muscle (0.6 %), skin (0.4 %), fat (0.7 %), excreta (7.5 %) Lactating ruminants: Milk (1.2 %), liver (0.6 %), kidney (1.6 %), fat (5.5 %), muscle (2.0 %), urine (2.4 %) **Hydrolysis study (simulated processing):** - Pasteurisation (100.28 %), baking, brewing, boiling (96.87 %), sterilisation (96.58 %)

TFNA 4-(Trifluoromethyl)nicotinic acid	IUPAC name: 4-(Trifluoromethyl)pyridine-3-carboxylic acid SMILES: C1=CN=CC(=C1C(F)(F)F)C(=O)O InChIKey: LMRJHNFECNKDKH-UHFFFAOYSA-N CAS: 158063-66-2 EC number: 623-902-1		**Rat:** - Not present in faeces (< 0.5 % of the applied low and high dose for both sexes) - Not present in urine (< 0.5 % of the applied low and high dose for both sexes), Bile duct cannulated rats: - Not present in bile (none detected of the applied low and high dose for both sexes) **Crop:** <u>Primary plant metabolism:</u> - Wheat: Straw (3.8 %), chaff (5.7 %), grain (8.1 %), forage (6.5 %), hay (3.8 %) Potato: Tuber (69.4 %), foliage (17.3 %) Peach: Fruit (49.2 %), foliage (15.8 %) Bell pepper: Leaves (2.4 %), fruit (3.7 %) <u>Rotational Crop metabolism:</u> - Lettuce: Immature lettuce (8.2 %), mature lettuce (1.8 %) - Carrot: Immature carrot (4.6 %), mature root (1.0 %), mature top (4.0 %) - Wheat: Grain (19.6 %), chaff (9.4 %), straw (2.5 %), forage (11.4 %) **Livestock:** - Poultry: Kidney (1.4 %), muscle (0.1 %), excreta (11.3 %) - Lactating ruminants: Liver (0.7 %), kidney (5.6 %), fat (6.5 %), urine (1.8 %), faeces (86.0 %) **Hydrolysis study (simulated processing):** - Pasteurisation (97.5 %), baking, brewing, boiling (99.5 %), sterilisation (98.5 %) **Soil:** <u>Aerobic soil degradation study</u>

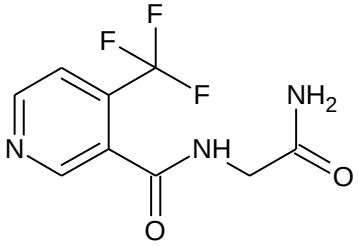
Code Number (Synonyms) **That indicated in bold was used in the summary dossier**	**IUPAC name /SMILES notation /InChiKey**	**Structural formula**	**Compound found in…**
			- 36.4 % at day 5 (n= 4) [^{14}C-3rd position of the pyridyl]-label - ~~52.9~~ *52.4* % at day 2 (n= 4) [^{14}C-4th position of the pyridyl ring]-label **Water-sediment** Water-sediment study 17.9 % at day 30 *in total system*
TFNA-OH 6-hydroxy-4-trifluoromethyl)nicotinic acid	IUPAC name: 6-Hydroxy-4-(trifluoromethyl)pyridine-3-carboxylic acid SMILES: FC(F)(F)c1cc(O)ncc1C(=O)O InChIKey: WCUKVMMGYGOCGJ-UHFFFAOYAJ CAS: 849020-87-7 EC number: 674-226-9		**Crop:** Rotational Crop metabolism: - Lettuce: Immature lettuce (4.9 %), mature lettuce (2.0 %) - Carrot: Immature carrot (4.0 %), mature root (1.9 %), mature top (2.2 %) - Wheat: Grain (4.7 %), chaff (9.1 %), straw (9.6 %), forage (37.8 %) - **Soil:** Aerobic soil degradation study - 21.3 % at day 3 (n=4) [^{14}C-3rd position of the pyridyl]-label - 25.3 % at day 5 (n= 4) [^{14}C-4th position of the pyridyl ring]-label - **Water-sediment** Water-sediment study ~~13.2~~ *13.3* % at day 42

Code Number (Synonyms) **That indicated in bold was used in the summary dossier**	**IUPAC name /SMILES notation /InChiKey**	**Structural formula**	**Compound found in…**
TFNA-AM 4-(Trifluoromethyl)nicotinamide	IUPAC name: 4-(Trifluoromethyl)pyridine-3-carboxamide SMILES: C1=CN=CC(=C1C(F)(F)F)C(=O)N InChIKey: JUIWZYBJXUPIKF-UHFFFAOYSA-N CAS: 158062-71-6 EC number: 674-262-5		**Rat:** - Faeces: 0.71 (females) – 0.80 % (males) of orally applied low dose (2 mg/kg bw), 0.51 (females) – 1.02 % (males) of orally applied high dose (400 mg/kg bw), - Urine (single dose): 21.19 (females) - 24.99 % (males) of orally applied low dose (2 mg/kg bw), 17.77 (females) - 23.07 % (males) of orally applied high dose (400 mg/kg bw), - Urine (repeated dose): 20.87 (females) - 27.34 % (males) of orally applied low dose (2 mg/kg bw), Bile duct cannulated rats: - Bile: 1.02 (females) – 1.13 % (males) of orally applied low dose (2 mg/kg bw), 0.63 (females) - 0.79 %(males) of orally applied high dose (400 mg/kg bw) - Faeces: 0.71 % (females) - 0.78 % (males) of orally applied high dose (400 mg/kg bw) - Urine: 16.49 % (females) - 19.86 (male) of orally applied low dose (2 mg/kg bw), 15.77 % (females) - 20.13 % (males) of orally applied high dose (400 mg/kg bw)

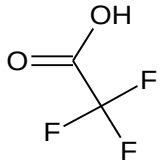
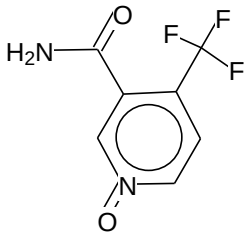
			Crop: <u>Primary plant metabolism:</u> - Wheat: Straw (2.4 %), chaff (3.8 %), grain (9.5 %), forage (0.3 %), hay (1.1 %) Potato: Tuber (1.4 %), foliage (7.9 %) Peach: Fruit (2.8 %), foliage (4.1 %) Bell pepper: Leaves (1.1 %) <u>Rotational crop metabolism:</u> - Lettuce: Immature lettuce (4.4 %), mature lettuce (3.7 %) - Carrot: Immature carrot (7.1 %), mature root (15.4 %), mature top (10.8 %) - Wheat: Grain (3.0 %), chaff (8.2 %), straw (10.7 %), forage (8.0 %) **Livestock:** - Poultry: Egg white (96.0 %), egg yolk (94.7 %), whole egg (95.7 %), liver (92.9 %), kidney (76.4 %), muscle (96.8 %), skin (96.4 %), fat (94.7 %), excreta (76.6 %) - Lactating ruminants: Milk (97.4 %), liver (29.4 %), kidney (41.1 %), fat (74.1 %), muscle (50.2 %), urine (29.4 %), faeces (5.9 %) **Soil:** <u>Aerobic soil degradation study</u> - ~~10.2~~ *7.6* % at day 2 (n=4) [^{14}C-3rd position of the pyridyl]-label - ~~12.6~~ *4.8* % at day 0.17 (n=4) [^{14}C-4th position of the pyridyl ring]-label **Hydrolysis:** 2.9 % at day 30 (pH 9, 25 °C) **Water-sediment** <u>Water-sediment study</u>

Code Number (Synonyms) **That indicated in bold was used in the summary dossier**	**IUPAC name /SMILES notation /InChiKey**	**Structural formula**	**Compound found in…**
			- % at day 111
OH-TFNA-AM	IUPAC name: 6-Hydroxy-4-(trifluoromethyl)-pyridine-3-carboxamide SMILES: FC(F)(F)c1cc(O)ncc1C(N)=O InChIKey: JZASIHOQMPWGMF-UHFFFAOYAC CAS: not available EC number: Not available		**Rat:** - Not present in faeces (None detected of the applied low and high dose for both sexes) - Not present in urine (< 0.7 %) of the applied low and high dose for both sexes in single and repeated dose studies), Bile duct cannulated rats: Not present in bile (none detected of the applied low and high dose for both sexes) **Livestock:** - Poultry: Liver (0.1 %), kidney (2.4 %), muscle (1.3 %), skin (0.3 %), fat (0.5 %), excreta (1.8 %) - Lactating ruminants: Liver (6.4 %), kidney (6.3 %), fat (1.4 %), muscle (0.5 %), urine (7.0 %), faeces (1.1 %)
TFNG *N*-{[4-(trifluoromethyl)pyridin-3-yl]carbonyl}glycine	IUPAC name: 2-[[4-(Trifluoromethyl)pyridine-3-carbonyl]amino]acetic acid SMILES: C1=CN=CC(=C1C(F)(F)F)C(=O)NCC(=O)O InChIKey: AXMBYGGSBXWTEY-UHFFFAOYSA-N CAS: 207502-65-6		**Rat:** - Not present in faeces (none detected of the applied low and high dose for both sexes) - Not present in urine (none detected of the applied low and high dose for both sexes), Bile duct cannulated rats: - Not present in bile (none detected of the applied low and high dose for both sexes)

Code Number (Synonyms) **That indicated in bold was used in the summary dossier**	**IUPAC name /SMILES notation /InChiKey**	**Structural formula**	**Compound found in…**
	EC number: Not available		**Crop:** Primary plant metabolism: - Wheat: Straw (21.3 %), chaff (18.9 %), grain (44.1 %), forage (32.7 %), hay (52.6 %) - Potato: Tuber (39.3 %), foliage (36.4 %) - Peach: Fruit (6 %), foliage (19.3 %) - Bell pepper: Leaves (28.2 %), fruit (7.8 %) Rotational crop metabolism: - Lettuce: Immature lettuce (10.0 %), mature lettuce (2.7 %) - Carrot: Immature carrot (11.0 %), mature root (4.9 %), mature top (7.9 %) - Wheat: Grain (36.3 %), chaff (18.3 %), straw (15.4 %), forage (20.9 %) **Hydrolysis study (simulated processing):** - Pasteurisation (99.0 %), baking, brewing, boiling (98.5 %), sterilisation (101.5 %) **Soil:** Aerobic soil degradation study - 3.9 % at day 7 (n=4) [^{14}C-3rd position of the pyridyl]-label - 51.9 % at day 1 (n=4) [^{14}C-4th position of the pyridyl ring]-label **Hydrolysis:** 2.0 % at day 120 (pH 9, 25 °C) **Water-sediment** Water-sediment study ~~3.8~~ *2.7* % at day 30

Code Number (Synonyms) **That indicated in bold was used in the summary dossier**	**IUPAC name /SMILES notation /InChiKey**	**Structural formula**	**Compound found in…**
TFNG-AM N-(4-Trifluoromethylnicotinoyl)glycinamide	IUPAC name: *N*-(2-Amino-2-oxoethyl)-4-(trifluoromethyl)pyridine-3-carboxamide SMILES: C1=CN=CC(=C1C(F)(F)F)C(=O)NCC(=O)N InChIKey: FZAQQBPOTJCLJM-UHFFFAOYSA-N CAS: 158062-96-5 EC number: Not available		**Rat:** - Not present in faeces (< 0.5 % of the applied low and high dose for both sexes) - Urine (single dose): 0.76 (males)– 0.86 % (females) of orally applied low dose (2 mg/kg bw), not present in urine of orally applied high dose (400 mg/kg bw), - Urine (repeated dose): 0.89 % (females) of orally applied low dose (2 mg/kg bw), Bile duct cannulated rats: - Not present in bile (< 0.5 % of the applied low and high dose for both sexes) - Urine: 0.99 % (males) of orally applied high dose (400 mg/kg bw)

Code Number (Synonyms) That indicated in bold was used in the summary dossier	IUPAC name /SMILES notation /InChiKey	Structural formula	Compound found in…
			Crop: Primary plant metabolism: - Wheat: Straw (5.6 %), chaff (5.4 %), grain (5.7 %), forage (11.0 %), hay (13.1 %) Potato: Tuber (1.2 %), foliage (4.0 %) Peach: Fruit (3.1 %), foliage (3.4 %) Rotational crop metabolism: - Lettuce: Immature lettuce (9.0 %), mature lettuce (20.2 %) - Carrot: Immature carrot (16.8 %), mature root (23.2 %), mature top (25.8 %) - Wheat: Grain (5.4 %), chaff (17.7 %), straw (25.0 %), forage (19.9 %) **Livestock:** - Poultry: Kidney (0.1 %), muscle (0.1 %), skin (0.1 %), fat (0.1 %) **Soil:** Aerobic soil degradation study - 10.2 % at day 2 (n= 4) [^{14}C-3rd position of the pyridyl]-label - ~~12.6~~ *12.5* % at day 0.17 (n= 4) [^{14}C-4th position of the pyridyl ring]-label **Hydrolysis:** 30.5 % at day 120 (pH 9, 25 °C)

Code Number (Synonyms) **That indicated in bold was used in the summary dossier**	**IUPAC name /SMILES notation /InChiKey**	**Structural formula**	**Compound found in…**
TFA Trifluoroacetic acid Perfluoroacetic acid	IUPAC name: 2,2,2-Trifluoroacetic acid SMILES: C(=O)(C(F)(F)F)O InChIKey: DTQVDTLACAAQTR-UHFFFAOYSA-N CAS: 76-05-1 EC number: 200-929-3		**Soil:** <u>Aerobic soil degradation study</u> - 22.5 % at day 14 (n=4) [^{14}C-4th position of the pyridyl ring]-label ***Succeeding crops :*** *- Lettuce immature 96.7 %; mature 97 %,* *- Carrot root immature 93 %; mature 93.3 %* *- Wheat forage 89.9 %, grain 73 %, hay 88.5 %, straw 95.5 %*
N-oxide of TFNA-AM	IUPAC name: 1-oxo-4-(trifluoromethyl)-1λ5-pyridine-3-carboxamide SMILES: NC(=O)c1cn(=O)ccc1C(F)(F)F		**Rat:** - Not present in faeces (< 0.5 % of the applied low and high dose for both sexes) - Urine (single dose): 2.29 (females) – 3.11 % (males) of orally applied low dose (2 mg/kg bw), 1.42 (males) - 1.10 %(females) of orally applied high dose (400 mg/kg bw), - Urine (repeated dose): 3.70 (males)– 2.04 % (females) of orally applied low dose (2 mg/kg bw), Bile duct cannulated rats: - Not present in bile (none detected of the applied low and high dose for both sexes) - Urine: 0.80 (females) – 1.05 % (males) of orally applied low dose (2 mg/kg bw),

Code Number (Synonyms) **That indicated in bold was used in the summary dossier**	**IUPAC name /SMILES notation /InChiKey**	**Structural formula**	**Compound found in…**
			Crop: <u>Primary plant metabolism:</u> - Wheat: Grain (6.1 %)

3.5 REFERENCE LIST

Section identity, physical chemical and analytical methods

No additional references used for Volume 1.

Section data on application and efficacy

No additional references used for Volume 1.

Section toxicology

No additional references used for Volume 1.

Section residue and consumer risk assessment

EFSA (European Food Safety Authority), 2014. Reasoned opinion on the review of the existing maximum residue levels (MRLs) for flonicamid according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal 2014; 12(6):3740, 49 pp. doi:10.2903/j.efsa.2014.3740

Section fate and behavior in environment

No additional references used for Volume 1.

Section ecotoxicology

No additional references used for Volume 1.