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HSE

Draft Assessment Report

Evaluation of Active Substance

Plant Protection Products

Prepared according to **Regulation (EC) No 1107/2009** as it applies in Great Britain

Flonicamid

Volume 1

GB Article 7 Amendment

Great Britain

August 2023

Version History

When	What
August 2023	HSE Initial Assessment

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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

Flonicamid was first approved in the European Union (EU) on 01 September 2010 under Commission Directive 2010/29/EU. Upon the introduction of Regulation (EC) No 1107/2009, it was added to the Annex to Regulation (EU) No 540/2011. This approval was later adopted directly into Great Britain (GB) law as a result the UK withdrawal from the EU. At this point the expiry date for flonicamid in GB was administratively extended by a further three years. Details of the GB approval can be found in the GB Approvals Register on HSE's website.

This application was submitted by the producer ISK Biosciences Europe N.V. The company are seeking to amend the Acute Reference Dose (ARfD). This request is supported with the submission of toxicology information and a reasoned case relating to a more recent opinion from the EU Committee for Risk Assessment (RAC).

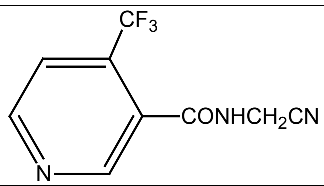
APPLICANT INFORMATION

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

Address : ISK Biosciences Europe N.V.
Pegasus Park
De Kleetlaan 12B – Box 9
B-1831 Diegem - Belgium

Contact person : [redacted]

IDENTITY OF THE ACTIVE SUBSTANCE

1.1.2. Common name proposed or ISO-accepted and synonyms	Flonicamid (approved ISO)
1.1.3. Chemical name (IUPAC and CA nomenclature)	
IUPAC	N-cyanomethyl-4-trifluoromethylnicotinamide [IUPAC]
CAS	N-(cyanomethyl)-4-(trifluoromethyl)-3-pyridinecarboxamide
1.1.4. Producer's development code number	IKI-220
1.1.5. CAS, EEC and CIPAC numbers	
CAS	158062-67-0
EEC	not available
CIPAC	not available
1.1.6. Molecular and structural formula, molecular mass	
Molecular formula	$C_9H_6F_3N_3O$
Structural formula	
Molecular mass	229.16 g/mol
1.1.7. Method of manufacture (synthesis pathway) of the active substance	This application to amend the ARFD does not require re-assessment of the representative product so these details are unchanged from the DAR dated February 2005 and final addenda to that DAR dated October 2009.
1.1.8. Specification of purity of the active substance in g/kg	The minimum content of IKI-220 (Flonicamid) technical is 960 g/kg.
1.1.9. Identity and content of additives (such as stabilisers) and impurities	
1.1.9.1. Additives	No additives are present in the active substance as manufactured
1.1.9.2. Significant impurities	Unchanged from DAR February 2005 and final addenda to that DAR dated October 2009
1.1.9.3. Relevant impurities	Unchanged from DAR February 2005 and final addenda to that DAR dated October 2009
1.1.10. Analytical profile of batches	Unchanged from DAR February 2005 and final addenda to that DAR dated October 2009

INFORMATION ON THE PLANT PROTECTION PRODUCT

1.1.11. Applicant	ISK Biosciences Europe N.V.
1.1.12. Producer of the plant protection product	Confidential data see Volume 4 DAR February 2005
1.1.13. Trade name or proposed trade name and producer's development code number of the plant protection product	**Teppeki M20213** **IKI-220** **(additional tradenames: 'Hinode' and 'Afinto')**
1.1.14. Detailed quantitative and qualitative information on the composition of the plant protection product	
1.1.14.1. Composition of the plant protection product	Confidential data see Volume 4 DAR February 2005
1.1.14.2. Information on the active substances	Confidential data see Volume 4 DAR February 2005
1.1.14.3. Information on safeners, synergists and co-formulants	Confidential data see Volume 4 DAR February 2005
1.1.15. Type and code of the plant protection product	Water dispersible granule (WG)
1.1.16. Function	Professional insecticide
1.1.17. Field of use envisaged	Agriculture
1.1.18. Effects on harmful organisms	Insecticidal, by antifeeding activity Flonicamid 50% WG (trade name Teppeki®) is a systemic insecticide for the control of aphids in multiple agricultural crops, for example potatoes, cereals and orchards (i.e. apple/pear and peach). The active ingredient flonicamid exhibits systemic and translaminar activity. The product needs to be applied in the initial/early development phase of the population. Up to maximum 2-3 treatments per year can be done on the same crop (depending on crop type and aphid pressure) in all crops at a maximum individual application rate per spray of 70-80 g as./ha at a 21-day interval.

DETAILED USES OF THE PLANT PROTECTION PRODUCT

Crop and/or situation (a)	Member State	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc of a.i. g/kg (i)	Method kind (f-h)	Growth stage and season (j)	Number min max (k)	Interval between applications (min)	Kg a.i./hL min max (g/hl)	Water l/ha min max	Lk a.i./ha min max (*) (g/ha)		
Potatoes	all EU countries	Teppeki	F	Aphids	50 WG	500 g/kg	foliar application	maturation of tubers (j) late spring till early september	2	21 days	0.040 – 0.016	200-500	80	14	
Wheat	all EU countries	Teppeki	F	Aphids	50 WG	500 g/kg	foliar application	Ears stage (j) Late spring till early september	2	21 days	0.035 – 0.014	200-500	70	28	
Apples/ pears	all EU countries	Teppeki	F	Aphids	50 WG	500 g/kg	foliar application	Maturation of fruits (j) Early spring till early summer	3	21 days	0.035 – 0.007 (0.0047)	200-1000 (1500 excep.)	70	21	
Peaches	all EU countries	Teppeki	F	Aphids	50 WG	500 g/kg	foliar application	Maturation of fruits (j) Very early spring till early summer	2	21 days	0.035 – 0.007 (0.0047)	200-1000 (1500 excep.)	70	14	

* For uses where the column „Remarks“ in marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).
(a) For crops, the EU and Codex classification (both) should be taken into account ; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes – GIFAP Technical Monograph N° 2, 1989
(f) All abbreviations used must be explained: WG (water-dispersible granules)
(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) Concentration in g ai/kg of g ai/L.
(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 synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: extent of use / economic importance / restrictions

Level 2

Flonicamid

2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

2.1. IDENTITY

Flonicamid (IKI-220) is an insecticide (aphicide) showing a rapid systemic activity.

2.2. PHYSICAL AND CHEMICAL PROPERTIES

For this Article 7 amendment application, data on application and efficacy is unchanged from the assessment in the existing DAR dated February 2005 and final addenda to that DAR dated October 2009.

2.3. DATA ON APPLICATION AND EFFICACY

For this Article 7 amendment application, data on application and efficacy is unchanged from the assessment in the existing DAR dated February 2005 and final addenda to that DAR dated October 2009.

2.4. FURTHER INFORMATION

For this Article 7 amendment application, further information is unchanged from the assessment in the existing DAR dated February 2005 and final addenda to that DAR dated October 2009.

2.5. METHODS OF ANALYSIS

For this Article 7 amendment application, methods of analysis is unchanged from the assessment in the existing DAR dated February 2005 and final addenda to that DAR dated October 2009.

2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

Flonicamid is an insecticide active substance evaluated in the EU according to Directive 91/414/EEC and approved by way of Commission Directive 2010/29/EU of 27 April 2010. It was included in the Annex to Commission Implementing Regulation (EU) No 540/2011 with an entry into force date of 25 May 2011. Following UK withdrawal from the EU, the substance is considered approved in GB with an expiry date of 31 August 2026.

The EU rapporteur Member State (RMS) France made the draft assessment report (DAR) of its initial evaluation of the dossier on flonicamid available on 24 May 2005.

The European Food Safety Agency (EFSA) published their conclusion on the peer review of the DAR[1]. A Harmonised Classification & Labelling (CLH) report was submitted to European Chemicals Agency (ECHA) by France in June 2012. The EU Committee for Risk Assessment (RAC) adopted an Opinion (at EU level) in June 2013.

Toxicological reference values for flonicamid were established in the EFSA Conclusion. The agreed acceptable daily intake (ADI), acceptable operator exposure level (AOEL) and acute reference dose (ARfD) are 0.025 mg/kg bw/d. A standard safety factor of 100 was applied to the No Observed Adverse Effect Level (NOAEL) for developmental toxicity (malformations at the Lowest Observed Adverse Effect Level (LOAEL) of 7.5 mg/kg bw/d) in the rabbit study of 2.5 mg/kg bw/d to derive these values. The DAR summary of the rabbit developmental toxicity study is available in Appendix 1.

Considering additional information, RAC concluded that there was no developmental toxicity in the rabbit leading to a developmental NOAEL of 25 mg.kg bw/d, the highest dose tested. Following the RAC Opinion, the applicant has claimed that the rationale used to derive the EU ARfD is no longer supported. The applicant has therefore submitted an Art 7 application to amend the ARfD in GB to support a future request for amended Maximum Residue Levels (MRLs) for potatoes under Regulation (EC) No 396/2005. The applicant proposes to use the maternal NOAEL of 7.5 mg/kg bw/d from the rabbit teratogenicity study as the basis for the ARfD.

HSE has reconsidered the ARfD for flonicamid within this Art 7 amendment application. In addition to considering the rabbit developmental study used to derive the current ARfD, early effects seen in studies in the total data package which may be applicable for setting an ARfD, have also been considered.

Study evaluations from the DAR and CLH report, and outcomes from the EFSA Conclusion and RAC Opinion have been considered.

This draft assessment report contains all the information related to an application for amendment of the ARfD of flonicamid in GB. This assessment complements the DAR that supported the first inclusion of flonicamid in Annex I of Directive 91/414, dated February 2005 and final addenda to that DAR dated October 2009. This addendum only updates those parts of the DAR impacted by the amendment of the ARfD, all other sections are unaffected and remain unchanged.

2.6.1. B.6.1.0.4. Acute reference dose (ARfD)

EFSA/EU evaluation of developmental toxicity and current ARfD

In 2010, EFSA published their conclusion on the peer review of the pesticide risk assessment of flonicamid. The experts agreed to use the rabbit prenatal

[1] 2010 (EFSA Journal 2010; 8(5):1445).

developmental toxicity study to derive the ARfD. A safety factor of 100 was applied to the NOAEL (2.5 mg/kg bw/d) for developmental toxicity (malformations at the LOAEL of 7.5 mg/kg bw/d) from the rabbit study. The currently agreed ARfD is 0.025 mg/kg bw/d. This is also the ARfD that currently applies in GB.

Rabbit developmental toxicity study

In the rabbit teratology study ([redacted] 2002d), the maternal NOAEL proposed by the EU RMS was 7.5 mg/kg bw/d, based on reduced body weight gain at 25 mg/kg bw/d. EFSA/EU agreed with this NOAEL. The DAR summary of the rabbit developmental toxicity study is available in Appendix 1.

The EU RMS concluded that there was no developmental toxicity up to the highest dose tested. However, during the peer review process, the experts agreed that there were some indications of foetotoxicity (foetuses with one or more visceral malformations, table 1) at a dose level (7.5 mg/kg bw/d) without maternal toxicity. The resulting developmental NOAEL was 2.5 mg/kg bw/d.

Table 1: Summary incidences of external, visceral and skeletal findings from DAR B6 (Table 6.6.2.4-3)

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	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	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	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	7 (4.0)	1* (0.6)	10 (6.4)	7 (4.1)
Foetuses with skeletal	55 (31.8)	59 (35.3)	43 (27.6)	65 (38.2)

*p < 0.05

[a] one foetus with malpositioned testis

[b] two 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 stemebrae, 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

Rat developmental toxicity study

In the rat teratology study, the developmental NOAEL was 100 mg/kg bw/d, related to an increased incidence of skeletal variations (table 2), namely extra cervical ribs at the top dose of 500 mg/kg bw/d. The EFSA/EU experts discussed the significance of this finding in light of the length of the rib. Taking into account the available data from the study, this effect was considered adverse, despite occurring in the presence of slight maternal toxicity (the maternal NOAEL was 100 mg/kg bw/d, based on effects observed in the kidneys and liver at the top dose of 500 mg/kg bw/d).

Table 2: Summary incidences of external, visceral and skeletal / cartilaginous tissue findings taken from DAR B6 (Table 6.6.2.3-3)

Parameter	**No. and (%) foetuses at (mg/kg bw/d):**			
	0	20	100	500
No. litters evaluated (external)	22	24	23	24
No. foetuses evaluated	298	337	302	341
External abnormalities	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)
No. litters evaluated (visceral)	22	24	23	24
No. foetuses evaluated (visceral)	143	160	146	165
Abnormal foetuses (visceral)	0 (0.0)	2[a] (1.3)	0 (0.0)	1[b] (0.6)
No. litters evaluated (skeletal)	22	24	23	24
No. foetuses evaluated (skeletal)	155	177	156	176
Abnormal foetuses (skeletal)	2[c] (1.3)	1[d] (0.6)	1[e] (0.6)	1[f] (0.6)
Total abnormal foetuses	2 (0.7)	3 (0.9)	1 (0.3)	2 (0.6)
Total abnormal litters	2 (9.1)	1 (4.2)	1 (4.3)	2 (8.3)
Foetuses with visceral variations	2 (1.4)	3 (1.9)	4 (2.7)	6 (3.6)
Foetuses with skeletal variations	18 (11.6)	8* (4.5)	8* (5.1)	70***

* $p < 0.05$; *** $p < 0.001$
[a] one foetus with retroesophageal subclavian aortic arch, one foetus with right-sided aortic arch;
[b] one foetus with malpositioned ovary;
[c] 2 foetuses with fused and/or absent ribs, fused rib cartilage, absent and/or fused thoracic arches and centra, dumbbell-shaped cartilage and abnormalities of the thoracic and lumbar centra;
[d] one foetus with hemicentric thoracic centrum:
[e] one foetus with dumbbell-shaped cartilage of the thoracic centrum;
[f] one foetus with fused rib cartilage

Classification for reproductive toxicity

Based on the findings of foetotoxicity observed in both species the EFSA/EU experts agreed to propose a classification of Repr. Cat.3 (R63, Possible risk of harm to the unborn child – equivalent to Repro Cat.2, H361d when translated to the new CLP Regulation 1272/2008/EC). This classification proposal was then considered by ECHA RAC.

RAC evaluation of developmental toxicity

Based on the findings of foetotoxicity observed in both species, EFSA and the EU experts proposed classification for reprotoxicity (Repr. Cat.3, R63, equivalent to Repro Cat.2, H361d when translated to the new CLP Regulation 1272/2008/EC). The substance was therefore considered by RAC for harmonised classification.

In addition to the data available in the DAR, RAC considered supplementary information and data provided by the dossier submitter in the response to comments submitted during public consultation.

Incidence of extra-cervical ribs in rats

EFSA/EU considered the occurrence of cervical ribs in rats in the light of the length of the rib to be an adverse effect.

RAC considered the findings of extra-cervical ribs at a dose level of 500 mg/kg bw/d in rats as minor defects. Only 2 foetuses (from the same litter) out of 60 exhibited (extra) cervical ribs with distal cartilage, which was not significant compared to control animals. Other cervical ribs were completely ossified and rudimentary (or small) and were adjacent to the 7th cervical vertebra uni- or bilaterally. The majority of the supernumerary ribs showed no distal cartilage and they are transient variations which disappear postnatally and should hence not be regarded as a relevant effect. In addition, the extra cervical ribs were seen at doses which caused toxicity in the dams (liver hypertrophy, vacuolation of renal tubular cells and increased placental weight). Overall, the developmental findings in the rat were considered insufficient for classification by RAC.

Visceral malformations in rabbits

EFSA/EU considered the indications of foetotoxicity (foetuses with one or more visceral malformations) at a dose level without maternal toxicity (7.5 mg/kg bw/d) as an adverse effect.

Additional information was provided following submission of the CLH report, including summaries of more detailed data of the visceral malformations seen in the rabbit developmental toxicity study ([redacted] 2002d) and historical control values in the same laboratory (HCV IET) and in the survey of JPMA literature (HCV JPMA; Nakatsuka et al. 1997[2]):

- Abnormal lung lobation: 2 foetuses (1.28%) at a dose of 7.5 mg/kg bw/d, 2 foetuses (1.18%) at a dose of 25 mg/kg bw/d. (HCV IET = 0–0.69%, HCV JPMA = 0–32.59%)

[2] Nakatsuka et al., Japan pharmaceutical manufacturers association (JPMA) survey on background control data of developmental and reproductive toxicity studies in rats, rabbits and mice. Cong Anom, 37:47-138, 1997

- Absent lungs: 1 foetus (0.59%) at a dose 25 mg/kg bw/d. (HCV IET = 0–0.55%, HCV JPMA = 0–3.1%)
- Small lungs: 1 foetus (0.64%) at a dose 7.5 mg/kg bw/d. (HCV IET = 0–0.67%, HCV JPMA = 0–1.81%)
- Various other visceral malformations such as membranous ventricular septum defect, interrupted aortic arch, narrowed pulmonary trunk, retroesophageal subclavian artery, absent kidney, small bladder and absent ureter occurred in 1 single foetus either in the group of 7.5 mg/kg bw/d or in the group of 25 mg/kg bw/d. (HCV IET = 0–1.32%, HCV JPMA = 0–5.0%)
- Undescended testis was found in 1 control foetus (0.57%), 1 foetus at 7.5 mg/kg bw/d (0.64%), 2 foetuses at 2.5 mg/kg bw/d (1.19%) and in no foetuses at 25 mg/kg bw/d. (HCV IET = 0–1.28%, HCV JPMA = 0–4.4)

The number of foetuses having one or more visceral malformations regardless of the type of malformation was increased in the 7.5 and 25 mg/kg bw/d groups, with a statistically significant difference from the control group at 7.5 mg/kg bw/d.

No significant trend was detected for incidences of foetuses having visceral malformations, abnormal lung lobation, absent kidney and absent ureter, respectively. Moreover, the type of malformations varied widely among foetuses and though exceeding the incidence in the historical control values reported at the [redacted] testing facility, no statistically significant difference was observed between the control and treated groups when the incidence of each malformation, which was as low as 0/173 – 2/156, was analysed.

Absent kidney and ureter was found in 2 foetuses that had multiple malformations at the middle and high dose; the accompanying malformations were totally different in these 2 foetuses, suggesting that the malformations occurred independently and were incidental. Though the incidence of absent kidney exceeds the background control incidence at the [redacted] testing facility, it is slightly under the upper limit of the range (0 – 0.69) reported by Nakatsuka et al. (1997).

Abnormal lung lobation was observed in the middle and high dose groups. However, the feature of this malformation was not the same among individuals: fusion of the lobes occurred in the right lung of the 2 middle-dose foetuses, and in the left lung in the 2 high-dose foetuses. The background control incidence of abnormal lung lobation has been reported in the literature by Nakatsuka et al. (1997) as combined incidence (0 to 32.59%) and as individual incidences at each testing facility (0-1.30; 0-23.31; 13.27-20.99; 0-2.33; 0-3.14; 0-0.80; 0-2.94; 0-2.44; 0-32.59; 0-2.59; 0-1.92; 0-1.70%). These data indicate that the incidence of this anomaly in most testing facilities is almost similar to that of the [redacted] laboratory, although the values in 3 facilities are higher. Furthermore, the incidence of this anomaly in the 7.5 and 25 mg/kg bw/d groups falls in the range of control data from all facilities except one and is well within the range of 0 to 32.59%.

The rabbit developmental NOAEL was therefore set at 25 mg/kg bw/d.

<u>RAC Assessment and comparison with the classification criteria</u>

RAC's analysis of the developmental toxicity studies indicates that flonicamid is not foetotoxic and it does not have intrinsic properties to induce malformations in rabbits or in rats. The observed malformations in rabbits were spontaneous developmental anomalies not related to exposure to flonicamid. The frequency of anomalies did not significantly increase with dose, even though the dose of 25 mg/kg bw/d induced maternal toxicity. Additionally, the frequency of all observed visceral malformations seen was within the historical control values and they occurred spontaneously with varying incidence in the same testing laboratory, and were within the historical control values reported in the survey of the JPMA literature (HCV JPMA; Nakatsuka et al. 1997).

Taking into account the weight of evidence analysis, it was concluded by RAC that the results obtained in the analysed studies did not meet the criteria for classification for reproductive toxicity (development).

Applicant proposal for the ARfD

EFSA/EU agreed an ARfD of 0.025 mg/kg bw/d. The applicant suggests that based on the conclusions in the RAC Opinion (flonicamid is not foetotoxic and it does not have intrinsic properties to induce malformations in rabbits or in rats), the lowest relevant NOAEL for developmental effects is 25 mg/kg bw/d, established in the rabbit. The original rationale used to derive the current ARfD is no longer supported, and the ARfD agreed by EFSA/EU should be revoked.

The applicant's proposal for the revised ARfD is quoted below:

"The calculation of an acute reference dose (ARfD) is usually based on the acute toxicity effects observed in the first few days / first week of dosing where clinical signs and body weight changes might be evident. In rabbits, the maternal NOAEL was 7.5 mg/kg bw/d, based on reduced body weight gain and the developmental NOAEL was 25 mg/kg bw/d. In rabbits, 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 (RAC Opinion June 2013).

Since there are no specific uncertainties relating to human risk assessment without mechanism-based NOAEL values, a safety factor of 100 is proposed. The proposed ARfD is 0.075 mg/kg bw/d."

HSE derived ARfD

Flonicamid is acutely toxic by the oral route (LD50 884 and 1768 mg/kg for males and females respectively) meeting the classification criteria for Acute Tox. 4 – H302 (Harmful if swallowed). It is not a neurotoxicant. HSE agrees with RAC that flonicamid is not a developmental toxicant: in rabbits, a number of external, skeletal and visceral anomalies were observed; however, they were spontaneous, not dose-related, and they fell within the historical control data and can thus be considered as incidental.

The totality of the database has been checked for early effects relevant to the derivation of the ARfD (Table 3). The studies showing toxicological effects potentially relevant for the derivation of an ARfD include the rabbit developmental study and the 12-month oral toxicity dog study. Other studies have been checked and no effects were observed at the beginning of the study treatment.

Table 3: Repeat dose studies checked for early adverse effects that may be relevant for setting ARfD taken from DAR B6 (table 6.10.3-1):

Species	Study	NOAEL in M / F (mg/kg bw/d)
Rat	4-w dietary toxicity (range-finding)	73.8[a] / 81.9
Dog	28-d oral toxicity	8/8
Dog	**52-w oral toxicity**	**8/8**
Rat	13-w dietary toxicity	60.0[b] / 72.3
Mouse	13-w dietary toxicity (range-finding)	15.3 / 20.1
Dog	13-w oral toxicity	20 / 20
Rat	Developmental toxicity	NA / 100
Rabbit	**Developmental toxicity**	**NA / 7.5**

[a] NOAEL relevant for human risk assessment. NOEL and LOEL of 3.6 and 7.5mg/kg bw/day, respectively, were established on the basis of male rat-specific a2p.globulin-mediated renal toxicity;
[b] NOAEL relevant for human risk assessment. NOEL and LOEL of 3.1 and 12.1mg/kg bw/day, respectively, were established on the basis of male rat-specific a2p.globulin-mediated renal toxicity

In the rabbit gavage developmental study, a decrease in maternal body weight gain was seen at the beginning of the dosing period (first 3-6 days) at the top dose of 25 mg/kg bw/d. This effect is considered to be a potentially acute effect appropriate for the derivation of the ARfD. A NOAEL of 7.5 mg/kg bw/d (for maternal toxicity) was identified from the study ([redacted] 2002d) for this effect at the LOAEL of 25 mg/kg bw/d. The effects driving this NOAEL could be partly due to the method of administration (gavage) of flonicamid in the study: initial administration via gavage dosing can affect body weight and food intake, particularly in rabbits. Such effects may not be relevant to the derivation of the ARfD. However, the effects cannot be excluded as being solely related to administration by the gavage route and are therefore considered appropriate for the derivation of the ARfD. The DAR summary of the rabbit developmental toxicity study is available in Appendix 1.

Table 4: Rabbit developmental toxicity study summary of cumulative group mean body weight gain and food consumption taken from DAR B6 (Table 6.6.2.4-1)

Parameter	Group mean value at (mg/kg bw/d):			
	0	**2.5**	**7.5**	**25**
Bw gain (kg) on days:				
6 - 9	-10 ± 55	-32 ± 68	-10 ± 38	-48 ± 55
6 - 12	21 + 70	-8 ± 86	3 ± 59	-64 ± 89**
6 - 15	72 ± 95	46 ± 114	37 ± 105	-50 ± 131**
6 - 18	104 ± 113	48 ± 145	23 ± 154	-90 ± 189***
6 - 21	130 ± 124	58 ± 142	14 + 204	-85 ± 221**
6 - 24	174 ± 134	82 ± 149	81 ± 201	-50 ± 238**
6 - 28	225 ± 126	126 ± 202	124 ± 258	39 ± 243*
Gravid uterus weight	418 ± 114	398 ± 172	405 ± 88	384 ± 114

Adjusted bw (kg) on	3.63 ± 0.28	3.56 ± 0.25	3.54 ± 0.33	3.49 ± 0.25
Food cons.(g/day) on				
0 - 3	179 ± 36	181 ± 33	181 ± 28	182 ± 25
3 -6	187 ± 34	181 ±29	185 ± 29	184 ± 21
6 - 9	174 ± 34	164 ± 37	175 ± 26	148 ± 29
9 - 12	159 ± 37	159 ± 33	156 ± 25	129 ± 38*
12 - 15	145 ± 46	140 ± 43	126 ± 49	93 ± 34**
15 - 18	161 ± 43	134 ± 58	121 ± 55	90 ± 62***
18 - 21	153 ± 46	136 ± 51	120 ± 55	97 ± 61*
21 -24	137 ± 47	121 ±55	116 ± 51	102 ± 51
24 - 27	110 ± 39	106 ± 51	99 ± 42	106 ± 45
27 - 28	109 ± 38	102 ± 47	101 ±44	103 ± 47
* p < 0.05; ** p < 0.01; *** p < 0.001				

In the 12-month dog study a NOAEL of 8 mg/kg bw/d was identified ([redacted] 2003b). Haematological changes suggestive of mild anaemia were seen in both sexes at 20 mg/kg bw/d, however this was not seen before the month 9 investigations and is not relevant for setting the ARfD. Body weight gain was significantly reduced in females at 20 mg/kg bw/d in w2, w3 and w4, but not at the beginning of the dosing period and is therefore unlikely to be an acute effect relevant to the derivation of the ARfD. The DAR summary of the 12- month dog toxicity study is available in Appendix 1.

Table 5: 12-month dog study summary of group mean bw gain (kg) taken from DAR (Table 6.3.7-1)

	Males				**Females**			
(mg/kg/ day)	0	3	8	20	0	3	8	20
wl	-0.02± 0.10	-0.07 ±0.16	-0.04 ± 0.20	-0.08 ± 0.14	0.02 ± 0.07	-0.07±0.14	-0.11 ± 0.20	-0.08 ± 0.10
w4	0.61 ± 0.23	0.80 ± 0.24	0.71 + 0.25	0.63 ± 0.37	0.78 + 0.14	0.68 + 0.20	0.46 ± 0.39	0.37 ±0.24*
w20	3.48 ± 0.68	3.65 ± 0.58	3.55 ± 0.61	3.92 ± 0.56	3.18 + 0.78	3.08 + 0.43	2.83 ± 0.75	2.28 ± 0.65
w30	4.43 ± 0.96	4.56 ± 0.45	4.69 + 0.92	4.90 ± 0.84	4.29 ± 1.02	4.43 + 1.10	3.75 ± 0.63	3.18 ± 0.51
w40	4.53 ± 0.99	4.63 ± 0.59	4.88 ± 1.01	5.03 ± 1.03	4.43 ± 1.27	4.75 ± 1.63	3.61 ± 0.75	3.05 ± 0.77
w52	4.68 ± 1.18	4.66 ± 0.70	5.13 ± 0.96	5.48 ± 1.19	4.90 ± 1.62	5.43 + 1.90	3.92 ± 0.91	3.41 ± 0.80

Overall, the NOAEL of 7.5 mg/kg bw/d for maternal toxicity from the rabbit developmental toxicity study is an appropriate starting point for the derivation of the ARfD. By applying a standard assessment factor of 100 (there is no evidence to suggest that it is necessary to deviate from this default), an ARfD value of 0.075 mg/kg bw/d is derived.

2.7. RESIDUE

Consumer intake calculations have been performed using the UK acute dietary exposure model and EFSA PRIMo. The chronic risk assessment is not required as this evaluation concerns the amendment of the ARfD only. The acute risk assessments have only been estimated for the representative uses of flonicamid considered at approval.

UK NESTIs
UK NESTIs have been calculated for ten consumer groups using the acute model (v 1.2) with the following assumptions:

- For the NESTIs, upper range of normal (97.5th percentile) consumption of each individual crop which may have been treated.
- All produce eaten which may have been treated has been treated and contains residues at the levels given in Table 1-1.
- There is no loss of residue during transport, storage or processing of foods prior to consumption.

The inputs used in the original DAR are no longer relevant to the current residue definitions. Values appropriate to the current residue definition for risk assessment (Sum of flonicamid, TFNA and TFNG, expressed as flonicamid) were calculated and have been used as inputs in this case.

With regard to products of animal origin (POAO), no inputs have been included within this assessment to remain consistent with the original DAR. The approval recommended MRLs for POAO be set at the LOQ, and as the inputs are not changing for any risk assessment codes (RACs), there is no need to recalculate these inputs by amending the dietary burden in this case. Furthermore, as any recent recalculations of the dietary burden following MRL reviews have used the lower ARfD, no consumer risk concerns are anticipated from POAO.

PRIMo

The PRIMo IESTIs for the active substance and commodities listed in Table 1-2 have been calculated using PRIMo revision 3.1 – Pesticide Residues Intake Model.

The following assumptions have been made:

- All produce eaten which may have been treated, has been treated and contains residues at the levels as given in Table 1-2.
- There is no loss of residue during transport, storage or processing of foods prior to consumption.

As with the NESTI model it is noted that the inputs used in the original DAR are no longer relevant to the current residue definitions. Values appropriate to the current residue definition for risk assessment (Sum of flonicamid, TFNA and TFNG, expressed as flonicamid) were calculated and have been used as inputs in this case. Similarly, with regard to products of animal origin (POAO), no inputs have been included within this assessment to remain consistent with the original DAR. The approval recommended MRLs for POAO be set at the LOQ, and as the inputs are not changing for any RACs, there is no need to recalculate these inputs by amending the dietary burden in this case. Furthermore, as any recent recalculations of the dietary burden following MRL reviews have used the lower ARfD, no consumer risk concerns are anticipated from POAO.

Conclusions

The highest UK NESTI was 24.2% of the ARfD (apples/infant). The highest PRIMo IESTI was 38% of the ARfD (children/peaches). Therefore, no health effects due to acute exposure are expected from the consumption of commodities treated with flonicamid.

2.8 Fate and behaviour in the environment

For this Article 7 amendment application, methods of analysis is unchanged from the assessment in the original DAR dated February 2005 and final addenda to that DAR dated October 2009.

2.9 Effects on non-target species

For this Article 7 amendment application, methods of analysis is unchanged from the assessment in the original DAR dated February 2005 and final addenda to that DAR dated October 2009.

2.10 Classification and labelling

For this Article 7 amendment application, the classification and labelling is unchanged from the assessment in the original DAR dated February 2005 and final addenda to that DAR dated October 2009.

2.11 Relevance of metabolites in groundwater

For this Article 7 amendment application, the classification and labelling is unchanged from the assessment in the original DAR dated February 2005 and final addenda to that DAR dated October 2009.

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

This application to amend ARFD does not require re-assessment of the representative product. The approval criteria are met.

- It is considered that Article 4 of Retained Regulation (EC) No 1107/2009 is complied with as the data considered supports the proposed amended ARfD.
- It is considered that the approval of the active substance may be amended. There is no need to reassess elements of the approval that were not affected.
- It is considered that in line with Article 6 of retained Regulation (EC) No 1107/2009, approval should be subject to conditions and restrictions and these are unchanged from the current approval.
- It is considered the dossier contains the information needed in order to amend the Acute Reference Dose (ARfD).
- 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. Data supports revised ARfD of 0.075 mg/kg

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

There are no studies which are still to be generated or on-going in relation to this Article 7 amendment application.

3.1.3. 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)

None.	

3.1.4. 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 Retained 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)
None.	

3.1.5. Overview table of the concerns identified for each representative use considered

None.

3.1.6. 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
None.	

3.2 PROPOSED DECISION

It is proposed that:

The approval of Flonicamid can be amended under retained Regulation (EC) No 1107/2009 in relation to the ARfD. The specific provisions of the approval will be unaltered.

3.4 APPENDICES

Appendix 1: Studies considered for derivation of the ARfD

Developmental rabbit study summary

The following study summary has been taken directly from the DAR produced by the RMS France, applicable to GB.

[redacted] (2002d): IKI-220 technical: teratogenicity study in rabbits; [redacted] unpublished report n° [redacted] 00-0025 (February 19, 2002) and amended report (November 28, 2002).

Materials and Methods

- Test methods: OECD 414; US-EPA 870.3700; JMAFF 12 NouSan n° 8147
- GLP standards: Yes
- Deviations: none
- Test system:

Groups of 25 artificially inseminated female Japanese White rabbits (Kbl:JW strain; 18 w old at mating; bw = 3.26 - 4.19 kg) were administered, by gavage, 0; 2.5; 7.5 and 25 mg/kg bw/d of IKI-220 technical (batch 9809 ; purity = 98.7%) suspended in 1% aqueous carboxymethylcellulose from d6 through d27 of gestation (dose volume = 5mL/kg bw)

Dose levels were selected from the results of the preliminary study in pregnant rabbits at dose levels of 0, 3, 10 and 30mg/kg bw/d ([redacted]2002c, report n° [redacted] 00-0024, see B.6.6.2.2.), in which the dose levels 100mg/kg bw/d clearly exceeded the maternal maximum tolerated dose level and the NOAEL for maternal animals and foetuses was 10mg/kg bw/day.

The stability at ca. 5°C for 14 days of suspensions containing 1 or 200mg/mL IKI-220 technical was confirmed by analysis in previous studies ([redacted]2002a, report [redacted] 00-0022; [redacted] 2002b, report [redacted] 00-0024; see B.6.6.21 & B.6.6.2.2.) and therefore dosing suspension were prepared weekly. The homogeneity of suspensions containing 0.5 or 5 mg/mL, the stability of the 0.5 mg/mL suspension and the achieved concentrations of all formulations were confirmed by analysis

The females were observed at least once daily for mortality and clinical signs and a detailed physical examination was performed at weighing intervals. Females found dead were immediately necropsied on discovery; females showing signs of abortion were killed and subjected to necropsy. Bw were recorded on d0; d6; d9; d12; d15; d18; d21; d24; d27 and d28 of gestation and food consumption was determined on d0-3; d3-6; d69; d9-12; d12-15; d15-18; d18-21; d21-24; d24-27 and d27-28 of gestation. All surviving rabbits were killed on d28 of gestation and subjected to necropsy and *post mortem* examination of major organs and tissues. Gross lesions were recorded but no organs were retained. The ovaries and uterine contents of pregnant animals were examined and the apparently non-gravid uteri were stained with ammonium sulfide solution to detect early resorptions. The gravid uterus weight, the numbers of corpora lutea and implantation sites, the numbers of live and dead foetuses were recorded. Resorbed embryos or dead foetuses were classified as early resorptions (implantation sites or placental remnants) or late resorptions (macerated foetuses including dead foetuses at term). Live foetuses were sexed by examination of the internal reproductive organs and the weights of individual placentae and live foetuses were recorded. The thoracic and abdominal viscera of all foetuses were examined fresh by dissection. The eyes of 50% of the foetuses/litter were also examined after removal of the palpebral skin and the brain was examined by making a transverse razor section through the coronal suture of the skull. The heads of the remaining foetuses were preserved in Bouin's fluid and the eyes, brain, nasal passages and tongue examined by Wilson's razor sectioning technique. All carcasses were stained with alizarin red S for examination of the ossified skeleton for abnormalities and variations.

Results

- Test diet analysis: The 0.5 mg/mL formulation was shown to be stable at 5°C for 14 days, at which time 101% of starting concentration remained. The 0.5 and 5 mg/mL formulations were found to be homogeneous, with coefficients of variation of 0.5 and 0.3%, respectively, for 3 samples/concentration. Achieved concentrations of all formulations were in the range 97 - 101% nominal concentration.

- Maternal findings:

Mortality, clinical signs, bw and food consumption (Table 6.6.2.4-1): There were no treatment related deaths or treatment-related clinical signs in maternal animals at any dose level, but 1 female from the 2.5 mg/kg bw/d group was found dead on gestation d9 (death was attributed to a mechanical intubation damage because of findings such as rhinorrhagia, subcutaneous hemorrhage in the brachial and axillary regions, hydrothorax, atelectasis, bone fracture in the humerus...) and 1 female in each of the 2.5; 7.5 and 25 mg/kg bw/d groups were killed on d23; d24 and d26 of gestation, respectively because of abortion without other clinical abnormalities (these females stopped eating before abortion; no gross changes were found in these females at necropsy and abortion were not likely to be related to treatment because of the absence of a dose response relationship). Group mean bw were not significantly different from control values, but reduced bw gain occurred throughout the treatment period in the 25mg/kg bw/d group (achieving statistically significance on d12-28 of gestation); bw gains at 2.5 or 7.5mg/kg bw/d were lower than control group bw gains but did not achieve statistical significance. The food consumption was significantly reduced from d9 through d21 of gestation in the 25 mg/kg bw/d group only.

Table 6.6.2.4-1: Summary of cumulative group mean body weight gain and food consumption

Parameter	Group mean value at (mg/kg bw/d):			
	0	**2.5**	**7.5**	**25**
Bw gain (kg) on days:				
6 - 9	-10 ± 55	-32 ± 68	-10 ± 38	-48 ± 55
6 - 12	21 + 70	-8 ± 86	3 ± 59	-64 ± 89**
6 - 15	72 ± 95	46 ± 114	37 ± 105	-50 ± 131**
6 - 18	104 ± 113	48 ± 145	23 ± 154	-90 ± 189***
6 - 21	130 ± 124	58 ± 142	14 + 204	-85 ± 221**
6 - 24	174 ± 134	82 ± 149	81 ± 201	-50 ± 238**
6 - 28	225 ± 126	126 ± 202	124 ± 258	39 ± 243*
Gravid uterus weight	418 ± 114	398 ± 172	405 ± 88	384 ± 114
Adjusted bw (kg) on	3.63 ± 0.28	3.56 ± 0.25	3.54 ± 0.33	3.49 ± 0.25
Food cons.(g/day) on				
0 - 3	179 ± 36	181 ± 33	181 ± 28	182 ± 25
3 -6	187 ± 34	181 ±29	185 ± 29	184 ± 21
6 - 9	174 ± 34	164 ± 37	175 ± 26	148 ± 29
9 - 12	159 ± 37	159 ± 33	156 ± 25	129 ± 38*
12 - 15	145 ± 46	140 ± 43	126 ± 49	93 ± 34**
15 - 18	161 ± 43	134 ± 58	121 ± 55	90 ± 62***
18 - 21	153 ± 46	136 ± 51	120 ± 55	97 ± 61*
21 -24	137 ± 47	121 ±55	116 ± 51	102 ± 51
24 - 27	110 ± 39	106 ± 51	99 ± 42	106 ± 45
27 - 28	109 ± 38	102 ± 47	101 ±44	103 ± 47
* p < 0.05; ** p < 0.01; *** p < 0.001				

- Necropsy findings

Gross lesions: There were no treatment-related gross findings at necropsy in maternal animals killed on gestation d 28.

Reproductive parameters: The pregnancy incidence in all groups was uniformly high and 23; 22; 21 and 23 females treated at 0; 2.5; 7.5 and 25mg/kg bw/d, respectively, had viable young on d28. 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 fetal death (Table 6.6.2.4-2).

Table 6.6.2.4-2: Group mean reproductive and fetal data

Parameter	Group mean value at (mg/kg bw/d):			
	0	**2.5**	**7.5**	**25**
No. pregnant / no. mated	24 / 25	25 / 25	25 / 25	24 / 25
No. females with resorptions	1	1	3	0
No. with live foetuses on day	23	22[a]	21[b]	23[b]
Gravid uterus weight (g)	418 ± 114	398 ± 172	405 ± 88	384 ± 114
Number corpora lutea	10.1 ± 1.9	10.5 ± 2.1	10.0 ± 1.5	10.3 ± 1.9
Number implantations	8.1 ± 2.7	8.3 ± 4.0	8.0 ± 2.2	8.2 ± 2.8
Pre-implantation loss (%)	20.4	25.4	19.1	20.7
Number live foetuses	7.5 ± 2.6	7.6 ± 3.9	7.4 ± 2.0	7.4 ± 2.5
Total no. dead foetuses	6	7	6	5
Post-implantation loss (%)	6.9	8.1	7.0	8.7
Male fetal weight (g)	39.2 ± 5.7	36.7 ± 7.7	38.0 ± 6.2	35.4 ± 5.5
Female fetal weight (g)	38.6 ± 5.6	37.3 ± 7.6	36.7 ± 6.7	34.9 ± 5.3
Placental weight (g)	5.30 ±0.92	5.37 ± 1.09	5.14 ± 0.83	5.27 ± 0.86
Sex ratio (% males)	48.0	51.5	55.8	49.4
a one female died and one female aborted; [b] one female aborted; * $p < 0.05$				

- Foetus examinations:

The fetal weights in treated groups were not statistically reduced, although they were 9.7 and 9.6% lower than control in both sexes. There were no treatment-related effects on mean placental weight and sex ratio at any dose level (Table 6.6.2.4-2).

Higher incidences of abnormal foetuses occurred in all treated groups, but the total fetal and litter incidences of abnormal foetuses in the groups treated at 2.5 or 25 mg/kg bw/d were not significantly different from control values. The incidence of foetuses with visceral abnormalities and the overall litter incidence of abnormalities at 7.5mg/kg bw/d were significantly higher than the control values: the nature of the observed abnormalities (malpositioned innominate; malpositioned subclavian branch; thymic remnant in the neck...) in all treatment groups was diverse and all individual abnormalities occurred at very low frequencies of 1 or 2 foetuses only ; therefore, no statistically significant differences at any dose level in the incidence of individual abnormalities was found and these findings should be considered as incidental. There were no treatment-related effects at any dose level on the incidences of visceral and skeletal variations. There were no statistically significant differences between control and treated groups in the incidences of skeletal variations, but the incidence of visceral variations at 2.5mg/kg bw/d was significantly lower than the controls, due to a lower incidence of thymic remnant (Table 6.6.2.4-3).

Table 6.6.2.4-3: Summary incidences of external, visceral and skeletal findings

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	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	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	173	167	156	170
Abnormal foetuses (skeletal)	0 (0.0)	3 (1.8)	3 (1.9)	3 (1.8)
Total abnormal foetuses	l[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	7 (4.0)	1* (0.6)	10 (6.4)	7 (4.1)
Foetuses with skeletal	55 (31.8)	59 (35.3)	43 (27.6)	65 (38.2)

* p < 0.05

b 2 foetuses with malpositioned testis, one foetus with anal atresia, one foetus stemebrae, one foetus with absent cervical vertebral arch
one foetus with local edema, one foetus with omphalocele, one foetus with multiple subclavian aortic arch, absent kidney and ureter, fused rib and supernumerary 2 foetuses with abnormal lung lobation, one foetus with narrowed pulmonary trunk foetus with malpositioned testis, one foetus with fused stemebrae, one foetus with vertebral centrum, one foetus with supernumerary thoracic vertebral arch
d one foetus with amelia, short tail and gastroschisis, one foetus with arch, one foetus with fused stemebrae, one foetus with absent lung, 2 foetuses with with absent kidney and ureter with small bladder, one foetus with fused caudal multiple vertebral and long-bone abnormalities

Conclusion

The GB assessment matches the key points from the French assessment. IKI-220 is not teratogenic in the rabbit. The NOEL in maternal rabbits was 7.5mg/kg bw/d, based on the occurrence of reduced bw gain and food consumption at 25mg/kg bw/d. The NOEL in the foetus was > 25mg/kg bw/d, based on the absence of developmental toxicity at the highest dose level employed

Oral 12 months dog study summary

The following study summary has been taken directly from the DAR produced by the RMS France

[redacted] (2003b): A 52-week oral toxicity study in dogs with IKI-220 technical; [redacted] unpublished report n° 012075-1 (November 15, 2002) as amended by unpublished report n° 012075-1-1 (January 02, 2003).

Materials and Methods

- Test methods: OECD 452; US-EPA OPPTS 870.3150.
- GLP standards: Yes
- Deviations: none
- Test system

Groups of 6/sex beagle dogs (6 months old at start of dosing; bw at start = 4.5 - 7.5 kg) were administered orally, by capsules, 0; 3; 8 and 20 mg/kg bw/d of IKI-220 technical (batch no 9809, purity = 98.7%) for at least 52w. Capsules were prepared weekly and stored under refrigerated conditions.

Dose levels were selected from the results of the 90 days study ([redacted] 2001a, report n° 011509-1; see B.6.3.5) in which the dose level of 50mg/kg bw/d to females clearly exceeded the maximum tolerated dose level; the NOEL in this study was 8mg/kg bw/d for both sexes.

All dogs were examined twice daily for morbidity/mortality; clinical signs were checked once daily at lh after dosing and a detailed clinical examination was performed pre-test and weekly throughout the treatment period.

An ophthalmoscopic examination was performed on all dogs pre-test and in w 52. Bw were recorded twice pre-dose, weekly throughout the study and at necropsy. Food consumption was recorded daily.

Hematology (Ht, Hb, RBC, total and differential leukocyte counts, Ptl, MCV, MCH, MCHC, reticulocyte count), blood chemistry (BUN, creatinin, ALP, ALT, AST, total bilirubin, total protein, albumin, globulins, A/G ratio, glucose, sodium, potassium, chloride, calcium, inorganic phosphorous, CPK, total cholesterol, GGT) and urinalysis (volume, specific gravity, occult blood, protein, pH, bilirubin, ketones, glucose, nitrite, urobilinogen, color and appearance, microscopic examination of the sediment) were performed on all animals pre-test, at 3-month intervals throughout the treatment period and prior to termination.

All surviving animals were subjected to necropsy and detailed post *mortem* examination of major organs and tissues. Selected organs were weighed and samples of major organs and tissues and all gross lesions were preserved from all animals. A female decedent was subjected to necropsy within 2 h of death and a full tissue list was examined microscopically. Preserved tissues from the animals treated at 0 or 20mg/kg bw/d, and gross lesions from all animals, were examined by light microscopy.

Results

- Mortality and clinical examinations

One female treated at 3 mg/kg bw/d died during the first week of treatment; this death was not considered as related to treatment because necropsy showed findings suggestive of severe pneumonia. All other animals survived the scheduled treatment period. Treatment-related clinical signs were confined to vomiting in several dogs at the 8 and 20 mg/kg bw/d dose levels, generally during the first w of dosing only. One animal of each sex at 20 mg/kg bw/d exhibited occasional decreased activity and an isolated occurrence of ataxia, but these findings were likely related to general debility following episodes of vomiting. There were no abnormal ophthalmological findings at any dose level after 52 w.

- Bw and food consumption

Bw gain was significantly reduced in females at 20mg/kg bw/d in w2, w3 and w4, although the group mean bw were not significantly different from control values throughout the treatment period; nevertheless, the overall weight gain decrement was 30.4% at termination and should therefore be considered as related to treatment. Overall bw gain was also reduced in females at 8mg/kg bw/d, but differences in weekly bw and bw gains were not statistically significant. There were no treatment-related effects on the bw gain of females at 3 mg/kg bw/d, or in males at any dose level. There were no treatment-related effects on the food consumption of either sex at any dose level (Table 6.3.7.1).

Table 6.3.7-1: Summary of group mean bw and bw gain (kg)

	Males				Females			
(mg/kg/ day)	0	3	8	20	0	3	8	20
Bw (kg)								
Pretest	6.48 ± 0.68	6.48 ± 0.81	6.11 ± 0.37	6.00 ± 0.47	5.35 ± 0.53	5.09 ± 0.54	5.22 ± 0.22	5.52 ± 0.47
wl	6.46 ± 0.63	6.41 ± 0.68	6.07 + 0.29	5.92 ± 0.47	5.37 + 0.55	5.03 + 0.49	5.11 ± 0.21	5.44 ± 0.52
w4	7.08 ± 0.71	7.28 ± 0.62	6.82 + 0.46	6.63 ± 0.56	6.13 ± 0.61	5.82 + 0.58	5.68 ± 0.35	5.88 ± 0.51
w20	9.95 ± 1.15	10.13 ±0.85	9.66 ± 0.50	9.92 ± 0.38	8.53 ± 0.92	8.22 ± 0.89	8.04 ± 0.76	7.80 ± 0.91
w30	10.91 ±1.36	11.03 ±1.01	10.80 ±0.76	10.90 ±0,54	9.64 ± 1.22	9.57 ± 1.52	8.97 ± 0.71	8.70 ± 1.16
w40	11.01 ±1.36	11.11 ±1.19	10.98 ±0.87	11.03 ±0,77	9.78 ± 1.43	9.89 ± 2.00	8.83 ± 0.84	8.57 ± 0.97
w52	11.16 ±1.48	11.13 ±1.18	11.24 ±0.76	11.48 ±0.86	10.25 ±1.79	10.57 ±2.18	9.13 ± 1.02	8.93 ± 1.06
Bw gain (kg)								
wl	-0.02± 0.10	-0.07 ±0.16	-0.04 ± 0.20	-0.08 ± 0.14	0.02 ± 0.07	- 0.07±0 .14	-0.11 ± 0.20	-0.08 ± 0.10
w4	0.61 ± 0.23	0.80 ± 0.24	0.71 + 0.25	0.63 ± 0.37	0.78 + 0.14	0.68 + 0.20	0.46 ± 0.39	0.37 ±0.24*
w20	3.48 ± 0.68	3.65 ± 0.58	3.55 ± 0.61	3.92 ± 0.56	3.18 + 0.78	3.08 + 0.43	2.83 ± 0.75	2.28 ± 0.65

w30	4.43 ± 0.96	4.56 ± 0.45	4.69 + 0.92	4.90 ± 0.84	4.29 ± 1.02	4.43 + 1.10	3.75 ± 0.63	3.18 ± 0.51
w40	4.53 ± 0.99	4.63 ± 0.59	4.88 ± 1.01	5.03 ± 1.03	4.43 ± 1.27	4.75 ± 1.63	3.61 ± 0.75	3.05 ± 0.77
w52	4.68 ± 1.18	4.66 ± 0.70	5.13 ± 0.96	5.48 ± 1.19	4.90 ± 1.62	5.43 + 1.90	3.92 ± 0.91	3.41 ± 0.80

Laboratory investigations:

- Hematological profile

There were no treatment-related effects on the hematological profile after 3 or 6 months of treatment, but after 9 and 12 months there was a suggestion of a mild anemia in both sexes at the highest dose level; males at 20mg/kg bw/d exhibited significantly increased MCV and MCH at the 9 and 12 months 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 20mg/kg bw/d from 6 months, with statistical significance at 12 months treatment. The female group at 8 mg/kg bw/d also showed statistically significant reduction of RBC, Hb and Ht 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 8mg/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 IIU-220 technical. There were no other treatment-related effects on the hematological profile at any dose level (Table 6.3.7-2).

- Clinical chemistry and urinalysis parameters

There were no consistent treatment-related effects at any dose level or sampling interval on the plasma clinical chemistry and urinalysis profiles.

- Necropsy, organ weights and histopathological examinations

There were no treatment-related gross necropsy fmdings and organ weight changes at any dose level. There were no histopathological alterations in any of the tissues and organs examined in animals treated at 20mg/kg bw/d. Specifically, there were no treatment-related histopathological alterations in the tissues of the hematopoietic system. All histopathological alterations detected occurred at comparable incidences in the treated and control groups and were considered to be incidental to treatment.

Table 6.3.7-2: Selected group mean hematological parameters

Parameter (units)	Study	**Group mean values**							
	month	**Males**				**Females**			
Doses (mg/kg bw/d)		**0**	**3**	**8**	**20**	**0**	**3**	**8**	**20**

RBC ($10^6/mm^3$)	Pretest	5.73	5.66	5.67	5.07**	5.75	5.82	5.17*	5.47
	3	5.85	6.09	5.95	5.55	6.17	6.09	5.51	5.59
	6	6.33	6.31	6.04	6.24	6.36	6.45	5.71	5.84
	9	6.92	7.23	6.50	6.37	7.04	7.00	5.89**	6.01**
	12	6.68	6.62	6.39	6.57	6.80	6.61	6.49	5.90
Hb (g/dL)	P	13.9	13.8	13.9	12.8*	14.1	14.3	12.8*	13.8
	3	13.7	14.6	14.1	13.4	14.6	15.0	13.7	13.9
	6	15.0	15.7	14.9	15.6	15.7	16.2	14.7	15.2
	9	16.6	16.9	16.2	16.5	17.5	18.1	15.8*	15.6*
	12	15.6	15.8	15.4	16.4	16.4	16.2	16.4	15.2
Hct (%)	P	40.1	39.9	39.8	36.8*	40.4	41.4	37.1*	39.2
	3	40.7	43.3	42.2	39.6	43.2	44.2	40.1	40.7
	6	44.4	45.8	43.6	45.8	45.9	47.7	42.8	43.8
	9	48.8	52.5	47.2	47.7	51.3	52.5	45.1*	45.6*
	12	45.6	46.4	44.7	47.4	47.4	47.1	46.6	43.1
MCV (fL)	P	69.9	70.6	70.1	72.5	70.4	71.3	71.8	71.7
	3	69.6	71.3	71.0	71.4	70.2	72.6	73.0	72.9
	6	70.2	72.6	72.2	73.4	72.3	74.0	75.1	75.2
	9	70.6	72.6	72.6	74.9**	73.0	75.0	76.5*	76.0
	12	68.2	70.1	69.9	72.1**	69.9	71.4	71.9	73.1
MCH (pg)	P	24.4	24.5	24.5	25.2	24.5	24.6	24.7	25.3
	3	23.5	24.0	23.8	24.2	23.7	24.7	24.8	25.0
	6	23.7	24.9	24.7	25.0*	24.7	25.1	25.8	26.0
	9	24.1	23.6	25.0	25.9*	24.9	25.9	26.7**	26.0
	12	23.4	23.9	24.1	24.9**	24.2	24.7	25.3	25.7*

Retics (%)	3	0.6	0.5	0.4	0.8	0.1	0.1	0.3	0.4
	6	0.6	0.8	0.4	1.1	0.2	0.2	0.3	0.6
	9	0.6	0.5	0.5	1.1	0.4	0.4	0.5	1.1
	12	0.5	0.6	0.8	1.9**	0.3	0.3	0.4	1.0*
* p < 0.05; ** p < 0.01									

Conclusion

No specific target organs were identified. The NOAEL was 8 mg/kg bw/d in both sexes, based on the occurrence of hematological changes suggestive of mild anemia in both sexes, and reduced bw gain in females, at 20 mg/kg bw/d.

Appendix 2: Models used

Residues Models

Flonicamid EFSA PRIMo rev 3.1

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 for all crops

Unprocessed commodities

Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI new
Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI new
Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI				IESTI				IESTI new				IESTI new			
Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
38%	Peaches	0 / 0.3	28	8%	Pears	0 / 0.19	5.7								
34%	Pears	0 / 0.19	26	7%	Peaches	0 / 0.3	5.6								
27%	Apples	0 / 0.19	20	7%	Apples	0 / 0.19	5.2								
11%	Potatoes	0 / 0.06	8.6	3%	Wheat	0 / 0.31	2.6								
6%	Wheat	0 / 0.31	4.5	2%	Potatoes	0 / 0.06	1.7								

Expand/collapse list

Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)

Total number of commodities found exceeding the ARfD/ADI in children and adult diets (IESTI new calculation)

Processed commodities

Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI new): ---

Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI new): ---

IESTI				IESTI				IESTI new				IESTI new			
Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
10%	Peaches / canned	0 / 0.3	7.7	3%	Peaches / canned	0 / 0.3	2.4	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!
7%	Potatoes / fried	0 / 0.06	5.2	2%	Wheat / bread/pizza	0 / 0.31	1.4	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!
5%	Wheat / milling (flour)	0 / 0.31	3.7	2%	Wheat / pasta	0 / 0.31	1.2	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!
2%	Wheat / milling (wholeme:	0 / 0.31	1.7	1%	Wheat / bread	0 / 0.31	1.1	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!
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#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!
#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!	#NUM!

Expand/collapse list

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.

Acute consumer models

Results intake

Acute Intakes (97.5th percentiles) — Goto Inputs

			adult		infant		toddler		4-6 year old child		7-10 year old child	
commodity	HR	P	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
Apples	0.19		0.00277	3.7	0.01812	24.2	0.01333	17.8	0.01031	13.8	0.00760	10.1
Pears	0.19		0.00327	4.4	0.01340	17.9	0.01570	20.9	0.01113	14.8	0.00739	9.9
Peaches	0.30		0.00365	4.9	0.01026	13.7	0.01640	21.9	0.01144	15.3	0.00765	10.2
Potatoes	0.06		0.00135	1.8	0.00861	11.5	0.00595	7.9	0.00448	6.0	0.00308	4.1
Wheat	0.31		0.00187	2.5	0.00399	5.3	0.00409	5.5	0.00448	6.0	0.00339	4.5

			11-14 year old child		15-18 year old child		vegetarian		Elderly - own home		Elderly - residential	
commodity	HR	P	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
Apples	0.19		0.00477	6.4	0.00391	5.2	0.00327	4.4	0.00246	3.3	0.00245	3.3
Pears	0.19		0.00486	6.5	0.00372	5.0	0.00367	4.9	0.00342	4.6	0.00336	4.5
Peaches	0.30		0.00552	7.4	0.00402	5.4	0.00379	5.1	0.00347	4.6	0.00341	4.6
Potatoes	0.06		0.00218	2.9	0.00163	2.2	0.00167	2.2	0.00133	1.8	0.00145	1.9
Wheat	0.31		0.00275	3.7	0.00260	3.5	0.00243	3.2	0.00142	1.9	0.00141	1.9

Pesticide	Flonicamid
ARfD	0.075 mg/Kg bw/day
Source	Art 7

* 0.00000 corresponds to <0.000005 mg/kg bw/day (any value ≥0.000005 is rounded to 0.00001

Consumption

Acute Consumption (97.5th percentiles) — Goto Inputs

	adult			infant			toddler			4-6 year old child			7-10 year old child		
commodity	F in kg/day	F min (95% CI)	Fmax (95% CI)	F in kg/day	F min (95% CI)	Fmax (95% CI)	F in kg/day	F min (95% CI)	Fmax (95% CI)	F in kg/day	F min (95% CI)	Fmax (95% CI)	F in kg/day	F min (95% CI)	Fmax (95% CI)
Apples	0.464	0.398	0.555	0.180	0.150	0.238	0.373	0.321	0.421	0.471	0.406	0.696	0.598	0.452	0.780
Pears	0.322	0.284	0.370	0.090	0.080	0.120	0.211	0.186	0.289	0.213	0.180	0.260	0.215	0.180	0.410
Peaches	0.272	0.248	0.554	0.043	0.031	0.084	0.138	0.110	0.197	0.127	0.093	0.130	0.133	0.126	0.151
Potatoes	0.531	0.513	0.550	0.191	0.170	0.216	0.246	0.234	0.262	0.346	0.327	0.456	0.405	0.394	0.497
Wheat	0.459	0.433	0.484	0.112	0.102	0.140	0.191	0.180	0.196	0.296	0.269	0.357	0.338	0.324	0.365

	11-14 year old child			15-18 year old child			vegetarian			Elderly - own home			Elderly - residential		
commodity	F in kg/day	F min (95% CI)	Fmax (95% CI)	F in kg/day	F min (95% CI)	Fmax (95% CI)	F in kg/day	F min (95% CI)	Fmax (95% CI)	F in kg/day	F min (95% CI)	Fmax (95% CI)	F in kg/day	F min (95% CI)	Fmax (95% CI)
Apples	0.566	0.452	0.646	0.677	0.520	1.050	0.509	0.397	0.722	0.271	0.250	0.307	0.143	0.111	0.299
Pears	0.241	0.202	0.333	0.263	0.185	0.267	0.302	0.247	0.334	0.288	0.214	0.340	0.160	0.150	0.240
Peaches	0.229	0.139	0.444	0.201	0.111	0.226	0.188	0.136	0.375	0.164	0.143	0.327	0.101	0.090	0.114
Potatoes	0.573	0.473	0.612	0.559	0.524	0.799	0.694	0.552	0.868	0.386	0.358	0.406	0.304	0.282	0.381
Wheat	0.426	0.389	0.480	0.536	0.454	0.588	0.522	0.455	0.591	0.325	0.313	0.355	0.281	0.248	0.296

Please note that values specified as 0.000 in the table are in the range of 0.1g/day to 0.4g/day. Values between 0.4g/day and 0.14g/day will be rounded to 0.1g/day [0.001 in the table].

Worst intakes

Acute Intakes (97.5th percentiles) Goto Inputs

commodity	HR	P	Consumer group 1	NESTI	%ARfD	Consumer group 2	NESTI	%ARfD	Consumer group 3	NESTI	%ARfD
Apples	0.19		infant	0.01812	24.2	toddler	0.01333	17.8	4-6 year old child	0.01031	13.8
Pears	0.19		toddler	0.01570	20.9	infant	0.01340	17.9	4-6 year old child	0.01113	14.8
Peaches	0.30		toddler	0.01640	21.9	4-6 year old child	0.01144	15.3	infant	0.01026	13.7
Potatoes	0.06		infant	0.00861	11.5	toddler	0.00595	7.9	4-6 year old child	0.00448	6.0
Wheat	0.31		4-6 year old child	0.00448	6.0	toddler	0.00409	5.5	infant	0.00399	5.3

Pesticide	Flonicamid	
ARfD	0.075	mg/Kg bw/day
Source	Art 7	

* 0.00000 corresponds to <0.000005 mg/kg bw/day (any value ≥0.000005 is rounded to 0.00001

Worst-consumption

Acute Consumption (97.5th percentiles) Goto Inputs

commodity	Consumer group 1	F in kg/day	F min (95% CI)	Fmax (95% CI)	Consumer group 2	F in kg/day	F min (95% CI)	Fmax (95% CI)	Consumer group 3	F in kg/day	F min (95% CI)	Fmax (95% CI)
Apples	infant	0.180	0.150	0.238	toddler	0.373	0.321	0.421	4-6 year old child	0.471	0.406	0.696
Pears	toddler	0.211	0.186	0.289	infant	0.090	0.080	0.120	4-6 year old child	0.213	0.180	0.260
Peaches	toddler	0.138	0.110	0.197	4-6 year old child	0.127	0.093	0.130	infant	0.043	0.031	0.084
Potatoes	infant	0.191	0.170	0.216	toddler	0.246	0.234	0.262	4-6 year old child	0.346	0.327	0.456
Wheat	4-6 year old child	0.296	0.269	0.357	toddler	0.191	0.180	0.196	infant	0.112	0.102	0.140

Please note that values specified as 0.000 in the table are in the range of 0.1g/day to 0.4g/day. Values between 0.4g/day and 0.14g/day will be rounded to 0.1g/day [0.001 in the table].

Appendix 3: Guidance documents used in this assessment

Section Toxicology

EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665

Guidance of EFSA: Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009: EFSA Journal 2011;9(2):2092.

Guidance on the application of the CLP criteria; guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 4.0 June 2015.

European Commission, 2011. Guidance Document on the Assessment of the Equivalence of Technical Materials of Substances Regulated under Regulation (EC) No 1107/2009. SANCO/10597/2003 – rev. 9, 17 June 2011.

Section Residues

EC (European Commission), 1996. Appendix G. Livestock Feeding Studies. 7031/VI/95 rev.4

EC (European Commission), 1997a. Appendix A. Metabolism and distribution in plants. 7028/IV/95-rev.3.

EC (European Commission), 1997b. Appendix B. General recommendations for the design, preparation and realization of residue trials. Annex 2. Classification of (minor) crops not listed in the Appendix of Council Directive 90/642/EEC. 7029/VI/95-rev.6.

EC (European Commission), 1997c. Appendix C. Testing of plant protection products in rotational crops. 7524/VI/95-rev.2.

EC (European Commission), 1997d. Appendix E. Processing studies. 7035/VI/95-rev.5.

EC (European Commission), 1997e. Appendix F. Metabolism and distribution in domestic animals. 7030/VI/95-rev.3

EC (European Commission), 1997f. Appendix H. Storage stability of residue samples. 7032/VI/95-rev.5.

EC (European Commission), 1997g. Appendix I. Calculation of maximum residue level and safety intervals. 7039/VI/95. As amended by the document: classes to be used for the setting of EU pesticide maximum residue levels (MRLs). SANCO 10634/2010.

EC (European Commission), 2000. Residue analytical methods. For pre-registration data requirement for Annex II (part A, section 4) and Annex III (part A, section 5 of Directive 91/414. SANCO/3029/99-rev.4.

EC (European Commission), 2004. Residue analytical methods. For post-registration control. SANCO/825/00-rev.7.

EC (European Commission), 2010. Classes to be used for the setting of EU pesticide Maximum Residue Levels (MRLs). SANCO 10634/2010 Rev. 0, finalized in the Standing Committee on the Food Chain and Animal Health at its meeting of 23-24 March 2010.

EC (European Commission), 2011. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. 7525/VI/95-rev.9.