



Draft Assessment Report

Evaluation of Active Substances

Plant Protection Products

Prepared according to **assimilated Regulation No 1107/2009**
as it applies in Great Britain

Inpyrfluxam

Volume 1

Great Britain

March 2026

Version History

When	What
November 2025	Initial DAR
March 2026	Updates made after ECP

Contents

1. Statement of the Subject Matter and Purpose for Which this Report has been Prepared and Background Information on the Application	5
1.1. Context in Which this Draft Assessment Report was Prepared	5
1.2. Applicant Information	6
1.3. Identity of the Active Substance	7
1.4. Information on the Plant Protection Product	9
1.5. Detailed Uses of the Plant Protection Product	11
2. Summary of Active Substance Hazard and of Product Risk Assessment	16
2.1. Identity	16
2.2. Physical and Chemical Properties	16
2.3. Data on Application and Efficacy	17
2.4. Further Information	19
2.5. Methods of Analysis	22
2.6. Effects on Human and Animal Health	26
2.7. Residue	84
2.8. Fate and Behaviour in the Environment	274
2.9. Effects on Non-target Species	288
2.10. Classification and Labelling	318
2.11. Relevance of Metabolites in Groundwater	322
2.12. Consideration of Isomeric Composition in the Risk Assessment	324
2.13. Residue Definitions	329
3. Proposed Decision with Respect to the Application	333
3.1. Background to the proposed decision	333
3.2. Proposed Decision	368
3.3. Rationale for the conditions and restrictions to be associated with the approval or authorisation(s), as appropriate	369
3.4. Appendices	370
3.5. Reference List	385
Further information	386

Level 1

INPYRFLUXAM

1. Statement of the 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 draft assessment report has been prepared to evaluate the dossier for the new, pesticidal active substance inpyrfluxam and its formulated product “S-2399 60 g/L EC”. This dossier was submitted by Sumitomo Chemical Agro Europe S.A.S. (“Sumitomo”) for the first approval of this substance in Great Britain (GB) under assimilated Regulation No 1107 with the evaluation performed by the Chemicals Regulation Division of the Health and Safety Executive. Sumitomo chemical also have an ongoing application for the approval of inpyrfluxam as a new active substance in the EU, with the evaluation being performed by the Netherlands as Rapporteur Member State (RMS) and France as Co-Rapporteur Member State (Co-RMS).

Inpyrfluxam is a new active substance in the context of assimilated Regulation 1107/2009 and belongs to succinate dehydrogenase inhibitor (SDHI) family of fungicides. It is intended for use as foliar application to control a range of fungal pests in outdoor crops such as barley and wheat.

Data have been generated on the active substance and representative formulation pursuant to the requirements laid out in the Annexes to Regulations 283/2013 and 284/2013, and in accordance with the test guidelines defined under the associated communications (2013/C 95/01 and 2013/C 95/02 respectively).

Sumitomo state that the application is made for approval of this new active substance in accordance with Article 4 and Article 5 of Regulation 1107/2009, and the submitted dossier is considered to demonstrate compliance with all of the relevant criteria set out therein.

Sumitomo Chemical Agro Europe S.A.S. are the sole applicant in support of the active substance and are the sole owner of the supporting data package.

Currently, inpyrfluxam does not have an entry under Annex VI of Regulation (EC) No 1272/2008. However, a mandatory classification and labelling report has been prepared

under GB CLP by HSE, with HSE acting as the Agency. This will be submitted to the Secretary of State, with consent from the devolved administrations to follow the aligned evaluation process.

1.1.2. Regulatory history for use in Plant Protection Products

Not relevant for the purpose of this submission as inpyrfluxam is a new active substance and products containing it have not previously been authorised in Great Britain.

1.1.3. Evaluations carried out under other regulatory contexts

Inpyrfluxam is a new fungicidal active substance developed by the applicant (Sumitomo). Sumitomo provided a dossier in support of their application for first approval of this pesticide in Great Britain in accordance with assimilated Regulation No. 1107. No registrations or authorisations of inpyrfluxam-containing plant protection products currently exist in GB or EU Member States.

There is also an ongoing application for the approval of inpyrfluxam as a new active substance in the EU, with the evaluation being performed by the Netherlands as Rapporteur Member State (RMS) and France as co-Rapporteur Member State (Co-RMS).

Inpyrfluxam has approval in other non-EU countries such as the United States (US), Japan and Canada.

1.2. Applicant Information

1.2.1. Names and addresses of applicant(s) for approval of the active substance

Name	Sumitomo Chemical Agro Europe S.A.S
Central Address	Parc D’Affaires de Crécy 10A rue de la Voie Lactée 69370 Saint-Didier-au-Mont-D’Or France
Telephone	[REDACTED]
Facsimile	[REDACTED]
Contact	[REDACTED]

1.2.2. Producer or producers of the active substance

Name	[REDACTED]
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Address



Telephone



Facsimile



Email



Contact

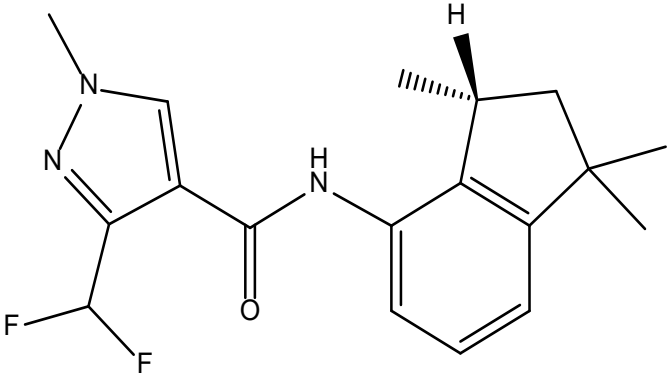


1.2.3. Information relating to the collective provision of dossiers

The dossier is submitted for the purpose of approval of inpyrfluxam, as a new active substance, with Sumitomo as the sole applicant. Therefore, a joint dossier is not relevant to this active substance.

1.3. Identity of the Active Substance

1.3.1. Common name proposed or ISO-accepted and synonyms	Inpyrfluxam
1.3.2. Chemical name (IUPAC and CA nomenclature)	
IUPAC	3-(Difluoromethyl)-1-methyl-N-[(3R)-1,1,3-trimethyl-2,3-dihydro-1H-inden-4-yl]-1H-pyrazole-4-carboxamide
CA	3-(Difluoromethyl)-N-[(3R)-2,3-dihydro-1,1,3-trimethyl-1H- inden-4-yl]-1-methyl-1H-pyrazole-4-carboxamide
1.3.3. Producer's development code number	S-2399
1.3.4. CAS, EEC and CIPAC numbers	
CAS	1352994-67-2
EEC	875-886-2

CIPAC	1005
1.3.5. Molecular and structural formula, molecular mass	
Molecular formula	$C_{18}H_{21}F_2N_3O$
Structural formula	 <p>The chemical structure of Inpyrfluxam consists of a 4-methyl-1H-imidazole ring substituted at the 2-position with a difluoromethyl group (-CHF₂) and at the 5-position with a carbonyl group (-C(=O)-). This carbonyl group is part of an amide linkage (-NH-) connecting to a bicyclic system. The bicyclic system is a 6,6-fused ring system where the six-membered ring is a benzene ring, and the five-membered ring is a cyclopentene ring with a gem-dimethyl group and a hydrogen atom at the bridgehead position. The hydrogen atom is shown with a wedge bond, indicating stereochemistry.</p>
Molecular mass	333.38 g/mol

1.3.6. Method of manufacture (synthesis pathway) of the active substance	Confidential information. Please refer to the Volume 4 (Confidential information) section of the DAR.
1.3.7. Specification of purity of the active substance in g/kg	940 g/kg
1.3.8. Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1. Additives	Confidential information. Please refer to the Volume 4 (Confidential information) section of the DAR.
1.3.8.2. Significant impurities	Confidential information. Please refer to the Volume 4 (Confidential information) section of the DAR.
1.3.8.3. Relevant impurities	None.
1.3.9. Analytical profile of batches	Confidential information. Please refer to the Volume 4 (Confidential information) section of the DAR.

1.4. Information on the Plant Protection Product

The information under point 1.4.1 – 1.4.8 should be provided for all Plant Protection Products in an overview table.

1.4.1. Applicant	Sumitomo Chemical Agro Europe S.A.S Parc D’Affaires de Crécy 10A rue de la Voie Lactée 69370 Saint-Didier-au-Mont-D’Or France
1.4.2. Producer of the Plant Protection Product	Confidential Information. Please refer to the Volume 4 (Confidential Information) section of the DAR.
1.4.3. Trade name or proposed trade name and producer’s development code number of the plant protection product	Trade name: S-2399 60 g/L EC Code number: S-2399 6EC
1.4.4. Detailed quantitative and qualitative information on the composition of the plant protection product	
1.4.4.1. Composition of the plant protection product	Confidential Information. Please refer to the Volume 4 (Confidential Information) section of the DAR.
1.4.4.2. Information on the active substances	Confidential Information. Please refer to the Volume 4 (Confidential Information) section of the DAR.
1.4.4.3. Information on the safeners, synergists and co-formulants	Confidential Information. Please refer to the Volume 4 (Confidential Information) section of the DAR.
1.4.5. Type and code of the plant protection product	Emulsifiable concentrate [Code : EC]
1.4.6. Function	Fungicide
1.4.7. Field of use envisaged	For the control of foliar diseases in winter and spring wheat, winter and spring barley, and durum wheat.

1.4.8. Effects on harmful organisms	<p>Inpyrfluxam is a broad spectrum fungicide. The new active substance coded S-2399 (inpyrfluxam) is a SDHI (Succinate-dehydrogenase inhibitors) fungicide, acting at complex II in the mitochondrial respiration chain and involving the inhibition of mitochondrial respiration.</p> <p>The target enzyme of SDH inhibitors is succinate dehydrogenase (SDH), which is a functional part of the tricarboxylic cycle and linked to the mitochondrial electron transport chain.</p> <p>As a succinate dehydrogenase inhibitor (SDHI) S-2399 interrupts the normal action of the enzyme complex succinate dehydrogenase. This specifically disrupts the Krebs cycle preventing the oxidation of succinate into fumarate.</p>
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1.5. Detailed Uses of the Plant Protection Product

1.5.1. Details of representative uses

Crop and/or situation (a)	GB or country For IT	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.i. (i)	method kind (f-h)	Timing/ Growth Stages & season (j)	number min-max (k)	Interval between application (min)	L/ha min-max (l)	Water Volume L/ha min-max	g a.s./ha min-max (l) a) max rate per appl b) max total rate per crop/season		
Winter wheat (TRZA W), Spring wheat (TRZAS), Durum wheat (TRZDU)	GB	S-2399 60 g/L EC	F	<i>Puccinia recondita</i> (PUCCRE) <i>Puccinia striiformis</i> (PUCCSI)	EC	60 g/L	Foliar spray	GS 30-71 Spring	1	N/A	1.5	75-300	90	35	-
Winter barley (HORV W), Spring barley (HORV S)	GB	S-2399 60 g/L EC	F	<i>Puccinia hordei</i> (PUCCHD)	EC	60 g/L	Foliar spray	GS 30-71 Spring	1	N/A	1.5	75-300	90	35	-

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

(b) State if the use is outdoor, field use (F) or glass house (G) or indoor use (I).

(c) e.g. biting and sucking insects, soil borne insects, foliar fungi, weeds

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

(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 stages 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

(e) CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide	(k) Indicate the minimum and maximum number of applications possible under practical conditions of use
(f) All abbreviations used must be explained	(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)
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench	(m) PHI - minimum pre-harvest interval
(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated	

1.5.2. Further information on representative uses

Method of application

S-2399 60 g/L EC is applied as a foliar spray using a hydraulic boom sprayer in a water volume of 75-300 L/ha. See table 1.5.1 above for the application rates applied to each crop.

Number and timing of applications and duration of protection

See section 1.5.1. above for details. Inpyrfluxam is recommended to be applied at the onset of disease development.

Necessary waiting periods or other precautions to avoid phytotoxic effects on succeeding crops

Inpyrfluxam poses a low risk of phytotoxic effects in succeeding crops and no waiting periods or restrictions are likely to be necessary. A full risk assessment on succeeding crops will be conducted at the product authorisation stage.

Proposed instructions for use

Inpyrfluxam is intended to be used as an agricultural fungicide for the control of foliar diseases in winter and spring wheat, winter and spring barley, and durum wheat. See section 1.5.1. above for further details. Specific instructions for use, including the product label, will be considered in full at the product authorisation stage.

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

MRLs have been proposed based on GB uses (Table 1.5.1) of barley and wheat. MRLs are not required to cover any residues expected in rotational crops, livestock or honey and so the proposed default MRLs apply for these other commodities – see Volume 1, Section 2.7.12.

HSE will cover MRLs assessment for any further crops or uses that need to be considered outside of this assessment for the representative intended uses on wheat and barley.

1.5.4. Overview on authorisations in EU Member States

Whilst inpyrfluxam is not yet approved in the EU, an application is currently undergoing consideration for the approval of inpyrfluxam as a new active substance (NAS) within the EU (the Netherlands are RMS and France Co-RMS). Therefore there are currently no authorisations for the use of plant protection products containing inpyrfluxam within EU Member States.

Level 2

INPYRFLUXAM

2. Summary of Active Substance Hazard and of Product Risk Assessment

2.1. Identity

Acceptable data and information have been submitted to support the manufacturing process of inpyrfluxam, and the proposed specification is considered supported by the available data, based on pilot scale manufacturing at one site.

None of the impurities identified in technical inpyrfluxam are considered of toxicological or ecotoxicological relevance.

Following scale-up from pilot to full scale manufacture, data to confirm the commercial scale technical specification must be submitted. In addition, the toxicological significance of any changes in the impurity profile must be addressed.

2.2. Physical and Chemical Properties

2.2.1. Summary of physical and chemical properties of the active substance

Inpyrfluxam is a beige solid in the form of granules, with a melting point of 104 °C (pure) and a decomposition temperature of 250 °C (pure). Inpyrfluxam is not classified as flammable or oxidising, and is not a self-heating substance. The pure active substance is slightly soluble in pure water (1.64×10^{-2} g/L at pH 5.5 to 5.8). It has a n-octanol/water coefficient log Pow of 3.65 at pH ~7.2 at 25 °C, indicating it does not have the potential to bioaccumulate. UV/VIS, IR, NMR, and MS spectra are available for the active substance and are consistent with its structure.

Explosive properties data is expected November 2025 which will confirm explosive classification.

Data was provided to demonstrate the explosive properties of inpyrfluxam. Inpyrfluxam is not classified as explosive.

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

The formulation 'S-2399 60 g/L EC' is an emulsifiable concentrate (EC) formulation containing 60 g/L inpyrfluxam with proposed in-use concentrations of 0.5 – 2.0 %v/v.

The appearance of the product is that of a clear yellow liquid. It is considered not to have explosive and oxidising properties and is not classified as flammable. It has an auto-ignition temperature of 302 °C, which indicates the formulation is not self-heating. When diluted with 1 % deionised water the pH value is 5.43. The kinematic viscosity is <20.5 mm²/s and when considered together with the composition of the formulation, a Category 1 aspiration hazard classification is required and the product label should carry the hazard statement H304. The surface tension at the highest in-use concentration of the product is 28.1 mN/m indicating that the product is surface active. Its technical characteristics are acceptable for an EC formulation.

Following both 7 days at 0 °C and 14 days at 54 °C, neither the active substance content nor the physical, chemical, and technical properties were significantly changed, indicating acceptable stability at low and high temperatures. Due to separation of the preparation being observed after low temperature storage, label instructions recommending 'protect from frost' and 'shake well before use' should be included on the product label. Data to support a shelf life of 2 years at ambient temperature when stored in HDPE/PA bottles was also submitted demonstrating acceptable stability of both the active substance content and the physical, chemical, and technical properties. Due to a layer of cream observed on the surface of the product that readily homogenised upon mixing, a label instruction recommending contiguous agitation during spraying should be included on the product label.

Tank mixing is proposed but a tank mixing study has not been provided. A tank mixing study is to be submitted in November 2025 to address tank mixing compatibility.

Sufficient data was provided to demonstrate the compatibility of 'S-2399 60 g/L EC' with other products during tank mixing.

2.3. Data on Application and Efficacy

2.3.1. Summary of effectiveness

The applicant has provided sufficient data to establish the appropriateness of the GAP and the effectiveness of the proposed formulation. A biological assessment dossier and associated individual trials reports will be fully evaluated at the product authorisation stage. Overall, the data provided are sufficient to confirm that inpyrfluxam and the associated representative formulation (S-2399 60 g/L EC) are sufficiently effective, and the proposed GAP is realistic and fulfils the needs of a risk envelope. For further details see Volume 3CP B3.

2.3.2. Summary of information on the development of resistance

Inpyrfluxam belongs to the chemical group of pyrazole-4-carboxamides, which is within the SDHI fungicide group (FRAC Code 7 – target site C2). It has a broad-spectrum foliar fungicide action interrupting the normal action of the enzyme complex succinate dehydrogenase, disrupting the Krebs cycle and preventing the oxidation of succinate into fumarate.

There are existing target site mutations conferring reduced resistance to SDHIs; however, different target site mutations confer varying levels of reduced sensitivity to SDHIs. Various mutations are present in field populations and as a result SDHI fungicides provide variable levels of efficacy depending on the type of strains present and the frequency of these strains in the field.

SDHI fungicides are currently classified as having a medium to high resistance risk by FRAC and inpyrfluxam is expected to have the same risk. SDHIs do not show cross resistance with other chemical classes such as strobilurins, benzimidazoles, anilinopyrimidines or demethylation inhibitors. Therefore, no cross resistance to fungicides from different mode of action groups is expected. However, within the SDHI group, cross-resistance is expected and has been shown for multiple strains.

To manage the resistance risk, a resistance management strategy has been proposed for the representative product of inpyrfluxam, which includes the following guidance:

- Apply SDHI fungicides always in mixtures. The mixture partner should provide satisfactory disease control when used alone on the target disease and must have a different mode of action.
- Apply a maximum of 2 SDHI fungicide containing sprays per cereal crop.
- Apply the SDHI fungicide preventatively or as early as possible in the disease cycle. Do not rely only on the curative potential of SDHI fungicides.

The exact management strategy for S-2399 60 g/L EC and other products containing inpyrfluxam will be considered in full at the product authorisation stage.

2.3.3. Summary of adverse effects on treated crops

The applicant has provided sufficient data to examine the effects of the active substance and representative formulation on the treated crops, when applied in accordance with the proposed GAP. No phytotoxic effects were observed from the proposed uses of S-2399 60 g/L EC in any trials. No negative effects on yield, quality, germination or transformation processes were observed. For further details see Volume 3CP B3.

Overall, the proposed GAP is realistic in terms of its crop safety in the proposed crops. A detailed evaluation of all potential adverse effects on the treated crops, including

phytotoxicity, yield quantity and quality, effects on plant parts for propagation and transformation processes, must be conducted at the product authorisation stage.

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

Based on the data provided, a low risk is expected for succeeding crops, adjacent crops and crops treated with the same equipment that previously applied inpyrfluxam.

A detailed evaluation of all potential undesirable or unintended side-effects, including the impact on succeeding crops, other plants such as adjacent crops, tank cleaning, and beneficial and non-target organisms will be conducted at the product authorisation stage.

2.4. Further Information

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

Handling

The applicant has provided the following guidance on handling:

Precautions for safe handling: For its agricultural use as a fungicide, the usual precautions for handling chemicals should be observed. First look for precautions and protection measures on the officially approved label on the packaging or for other official guidance in force. If these are lacking, please refer to section B.4.1. 'Exposure controls/personal protection'. Avoid breathing dust. Wear protective gloves (nitrile), safety goggles or face shield, and suitable protective clothing. Remove ignition sources. Launder clothes before reuse. Do not allow escape into sewage system or water courses. Collect all waste material and remains from cleaning equipment, etc., and dispose of as hazardous waste. See section B.4.2. 'Disposal considerations' for disposal considerations.

Exposure controls/personal protection

The applicant has provided the following guidance on controlling exposure and personal protection:

Control parameters: TLV/ACGIH(2009) - not listed.

Exposure controls: Use appropriate engineering controls. Use general and/or local exhaust ventilation to control dust. Provide safety showers and eye wash.

Personal protective equipment: Eye protection: Use safety goggles or face shield.

Personal protective equipment: Skin protection: Wear suitable working clothes, gloves and boots.

Personal protective equipment: Hand protection: Wear protective gloves of nitrile.

Personal protective equipment: Respiratory protection: In case of dust formation, use dust mask.

Storage

The applicant has provided the following guidance on storage:

Conditions for safe storage: Store in a cool, dry place. Keep container in a well-ventilated place. Keep away from food, drink and animal feeding stuffs. Do not drink, eat or smoke in work areas. Do not mix with water (except for the normal preparations).

Specific end use(s): Fungicide for agricultural use.

Transport

The applicant has provided the following guidance on transport:

Land Transport (RID/ADR):

UN number: 3082

UN proper shipping name: Pesticide, solid, toxic, n.o.s. (Inpyrfluxam)

Transport hazard class(es): 9

Packaging group: III

Environmental hazards: Marine pollutant

Sea Transport (IMDG):

UN number: 3082

UN proper shipping name: Pesticide, solid, toxic, n.o.s. (Inpyrfluxam)

Transport hazard class(es): 9

Packaging group: III

Environmental hazards: Marine pollutant

Air Transport (ICAO/IATA-DGR):

UN number: 3082

UN proper shipping name: Pesticide, solid, toxic, n.o.s. (Inpyrfluxam)

Transport hazard class(es): 9

Packaging group: III

Environmental hazards: Marine pollutant

Fire

The applicant has provided the following guidance on firefighting measures:

Extinguishing media: Dry chemical powder, carbon dioxide, foam, water and sand. No known unsuitable extinguishing media.

Specific hazards arising from the substance or mixture: May emit toxic and irritant vapours under fire conditions (carbon monoxide (CO), carbon dioxide (CO₂), hydrocarbon (C_xH_y) and nitrous gases (NO_x)).

Advice for firefighters: Wear self-contained breathing apparatus. Wear suitable protective clothing and eye/face protection. Water used to extinguish a fire should not be allowed to enter the drainage system or water course.

Further details are available in the Material Data Safety Sheet (MSDS) document.

2.4.2. Summary of procedures for destruction or decontamination

Disposal considerations

The applicant has provided the following guidance on methods of disposal:

Waste treatment methods: According to local regulations. For further advice contact manufacturer.

Decontamination

The applicant has provided the following guidance on measures to deal with accidental release:

Personal precautions, protective equipment and emergency procedures: Do not breathe dust. Wear protective gloves (nitrile), safety goggles or face shield, and suitable protective clothing. Remove of ignition sources. Evacuate the danger area or consult an expert.

Environmental precautions: Do not allow to escape into sewage system or water courses. Do not wash residues into drains or other waterways.

Methods and materials for containment and clean up: Do not allow to escape into sewage system or water courses. Clean up spills immediately. Sweep up and place into sealable containers. Dig up heavily contaminated soil and place into drums. Use a damp cloth to

clean floors and other objects, and also place in sealable container. Dispose of all waste and contaminated clothing in the same manner as waste chemicals (i.e. via an authorized disposal facility). Do not wash residues into drains or other waterways.

2.4.3. Summary of emergency measures in case of an accident

The applicant has provided the following guidance on first aid measures:

General: In all cases of doubt, seek medical attention.

Inhalation: Move to fresh air. If symptoms persist, seek medical advice.

Skin contact: Remove contaminated clothing. Wash skin immediately with water.

Eye contact: Rinse thoroughly with plenty of water. Eyelids should be held away from the eyeball to ensure thorough rinsing. Seek medical advice if irritation develops.

Ingestion: Rinse mouth. Never induce vomiting in unconscious or confused persons. Seek medical advice.

Most important symptoms and effects, both are acute and delayed: Toxic if swallowed; Dust may be irritating to the respiratory tract and cause symptoms of bronchitis.

Immediate medical attention and specific treatment method: No specific recommendations.

2.5. Methods of Analysis

2.5.1. Methods used for the generation of pre-authorisation data

Acceptable methods have been submitted for the determination of the active substance and all significant impurities in the technical material as manufactured.

Acceptable methods have been submitted for the determination of the active substance in the representative plant protection product. There are no relevant impurities in inpyrfluxam technical material therefore methods to determine relevant impurities in the product are not required.

Acceptable methods have been submitted for the determination of inpyrfluxam and selected metabolites in various studies used in support of the environmental fate, toxicology, residues, ecotoxicology, and physical chemical properties areas of the risk assessment.

Extraction efficiency of the methods used to determine residues for data generation is sufficiently proven for high acid commodities, high oil commodities, high water commodities and dry commodities (high protein/high starch), and for products of animal origin with the exception of eggs. However, as residues are shown to be <0.01 mg/kg TRR

from the poultry metabolism study (Section 2.7.6), the lack of data on extraction efficiency for eggs has no impact on the overall evaluation. Should the dietary burden increase resulting in residues of >0.01 mg/kg TRR in eggs then further data may be required.

2.5.2. Methods for post control and monitoring purposes

Methods have been submitted for the determination of inpyrfluxam and selected metabolites in various matrices for use in post-approval monitoring and control. These methods are considered acceptable with the following exceptions:

The following data are required:

~~Stability of extract and standard solutions data is required to address the monitoring method for body tissue. Applicant has not indicated a timeline for when data will be available yet.~~

Acceptable data was provided to address the stability of extracts and standard solutions for the monitoring method for body tissue. Therefore, the monitoring method for body tissue is acceptably validated in accordance with SANTE 2020/12830 rev.1.

A summary of the available methods is given below.

Matrix/Crop group	Analytes(s)	Method	LOQ	ILV?	Fully validated
High water High acid High oil Dry	Inpyrfluxam	LC-MS/MS [QuEChERS method]	0.01 mg/kg	Yes	Yes The proposed residues definition for monitoring is: Inpyrfluxam
Egg Fat Liver Milk Meat Blood	Inpyrfluxam	LC-MS/MS [QuEChERS method]	0.01 mg/kg	Yes	Yes The proposed residues definition for monitoring is: Inpyrfluxam
Honey	n/a	n/a	n/a	n/a	Not required.

Matrix/Crop group	Analytes(s)	Method	LOQ	ILV?	Fully validated
					Residues in honey not expected therefore no analytical method is required.
Soil	Inpyrfluxam 1'-COOH-S-2840 (sum of isomers)	LC-MS/MS	0.002 mg/kg (0.001 mg/kg for 1'-COOH-S-2840 A and 0.001 mg/kg 1'-COOH-S-2840 B)	n/a	Yes LOQ < 0.05 mg/kg (the relevant ecotoxicological concentration (ER50, LC50, NOEC) for the most sensitive terrestrial non-target organism is higher than 0.05 mg/kg for both Inpyrfluxam and 1'-COOH-S-2840 (sum of isomers). The proposed residues definition for monitoring is: Inpyrfluxam, 1'-COOH-S-2840 (sum of isomers)
Sediment	n/a	n/a	n/a	n/a	Not required. No residue definition has been set as there are no ecotoxicologically relevant compounds. Therefore no analytical method is required for monitoring.
Surface water	Inpyrfluxam	LC-MS/MS	0.03 µg/L	Yes	Yes LOQ < RAC (0.66 µg/L) The proposed residues definition for monitoring is: Inpyrfluxam.
Ground water	Inpyrfluxam	LC-MS/MS	0.03 µg/L	Yes	Yes

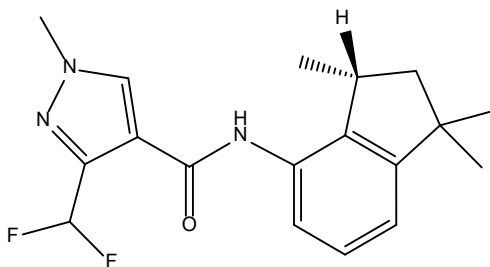
Matrix/Crop group	Analytes(s)	Method	LOQ	ILV?	Fully validated
					LOQ < 0.1 µg/L. The proposed residues definition for monitoring is: Inpyrfluxam.
Air	Inpyrfluxam	LC-MS/MS	0.83 µg/m ³	n/a	Yes LOQ < “c” (12 µg/m ³ based on AOEL of 0.04 mg/kg bw/day) The proposed residues definition for monitoring is: Inpyrfluxam
Body fluid (Urine)	1'-COOH-S-2840 (sum of isomers)	LC-MS/MS	0.01 mg/L	n/a	Yes The proposed residues definition for monitoring is: 1'-COOH-S-2840 (sum of isomers) LOQ ≤ 0.01 mg/L for body fluids.
Body tissues	1'-COOH-S-2840 (sum of isomers)	LC-MS/MS	0.01 mg/kg (0.005 mg/kg 1'-COOH-S2840A and 0.005 mg/kg 1'-COOH-S2840B).	n/a	To be confirmed upon submission of data. Yes The proposed residues definition for monitoring is: 1'-COOH-S-2840 (sum of isomers) LOQ ≤ 0.01 mg/kg for body tissue.

Sufficient data has been submitted to demonstrate the extraction efficiency for QuEChERS monitoring methods validated for the monitoring of inpyrfluxam residues from high water, high oil, high acid and dry commodities. Extraction efficiency is also sufficiently addressed for products of animal origin.

2.6. Effects on Human and Animal Health

Inpyrfluxam, also known as S-2399, is a new fungicidal active substance, developed by Sumitomo Chemical Agro Europe S.A.S. It is intended to control various foliar diseases from *Puccinia sp.* on winter and spring cereals (wheat and barley).

The structure of inpyrfluxam is presented below:



Inpyrfluxam belongs to the succinate dehydrogenase inhibitor (SDHI) family of fungicides. Its mode of action is by inhibiting the activity of the enzyme succinate dehydrogenase (SDH), which is a key component of both the Krebs cycle (tricarboxylic acid cycle) and the mitochondrial electron transport chain (Complex II). Inhibition of SDH disrupts the Krebs cycle, preventing normal cellular respiration and energy (ATP) production, and the mitochondrial electron transport, leading to energy deficiency and eventually cell death in the fungal pathogen.

The representative product for inpyrfluxam is S-2399 60 g/L EC which is an emulsifiable concentrate containing 60 g /L of inpyrfluxam.

This document uses the term 'inpyrfluxam' when referring to the active substance. However, the development code S-2399 has been used by the applicant within the individual study reports. The batches of inpyrfluxam used in the toxicology studies are considered representative of the technical specification (see Vol 4 for more details). All of the methods of analysis for the active substance in different matrices (diet, air, gavage solutions or plasma) used in the in vivo toxicological studies are either validated or fit for regulatory purposes (see document CA B5 and B6 for further details).

The classification of inpyrfluxam for human health effects has been addressed in an aligned MCL (Mandatory Classification and Labelling) report produced by HSE.

The toxicological data requirements of assimilated Regulation (EC) 1107/2009 and assimilated Regulation (EU) 283/2013 have been met and HSE concludes that there are no data gaps.

2.6.1. Summary of absorption, distribution and excretion in mammals

The ADME (absorption, distribution, metabolism, excretion) properties of inpyrfluxam have been investigated via oral (gavage) dosing in rats. The data set consists of 2 studies using [pyrazolyl-4-¹⁴C] and [phenyl-¹⁴C] radiolabelled inpyrfluxam, the first following single exposure and the second following repeated exposure for 14 days. Two in vitro metabolism studies are also available, the first employing human and rat liver microsomes and the second using dog liver microsomes only. The main findings of these studies are summarised in table 6.1.6-1 below.

Table 2.6.1-1 Summary of available ADME studies

Data point/ Study Acceptability	Species / Strain/ sex	Doses	Summary
KCA 5.1.1/01 <i>Metabolism of S-2399 in rats</i> - GLP <i>Acceptable</i>	Rat/ Wistar Hannover rats/M &F	Males and Females: 1 and 150 mg/kg bw Single oral (gavage) dose <u>Radiolabel positions:</u> ([pyrazolyl-4- ¹⁴ C] inpyrfluxam) and ([phenyl- ¹⁴ C] inpyrfluxam)	12 metabolites were identified and characterised in excreta. The two major metabolites in urine were 1'-COOH-S-2840 and N-des-Me-1'-COOH-S-2840 The major metabolite in the bile was glucuronide of 1'-CH₂OH-S-2840 Elimination was predominantly via urine and bile. Evidence of enterohepatic recirculation.
KCA 5.1.1/02 <i>Metabolism of S-2399 in rats (Repeated Oral Administration)</i> - GLP <i>Acceptable</i>	Rat/ Wistar Hannover rats/M &F	Males and Females: 1 mg/kg bw repeated oral (gavage) dose for 14 days <u>Radiolabel position:</u> ([pyrazolyl-4- ¹⁴ C] inpyrfluxam)	12 metabolites were identified and characterised in excreta. No major (>10%) metabolites detected. Elimination was predominantly via urine and faeces. No accumulation
KCA 5.1.1/03 <i>Comparative in vitro metabolism study of [pyrazolyl-4-¹⁴C]S-2399 in rat and human liver microsomes</i>	Human (mix genders) and rat (male and female) liver microsomes	10 µM for 15 minutes	6 metabolites were identified and characterised. No unique human metabolite

Data point/ Study Acceptability	Species / Strain/ sex	Doses	Summary
- GLP <i>Acceptable</i> KCA 5.1.1/04			
<i>In vitro metabolism study of [pyrazolyl-4-¹⁴C]S-2399 in dog liver microsomes</i> - GLP <i>Acceptable</i>	Dog (male and female) liver microsomes	10 µM for 15 minutes	6 metabolites were identified and characterised.

Absorption

In the single oral dose study in rats, absorption of inpyrfluxam from the GI (gastro-intestinal) tract was more rapid at 1 mg/kg bw (plasma T_{max} of radioactivity reached at 1 h) than at 150 mg/kg bw (plasma T_{max} of radioactivity reached at 8 h). The C_{max} and AUC increased with the dose in a linear manner.

From the bile-duct experiment, it was clear that inpyrfluxam was almost completely absorbed (96%) by the oral route at the low dose of 1 mg/kg bw. An **oral absorption value of 100%** is considered appropriate at the low dose of 1 mg/kg bw. No saturation in absorption and no bioaccumulation were noted at the high dose of 150 mg/kg bw.

In the repeated dose study in rats, absorption of inpyrfluxam from the GI tract was also rapid at 1 mg/kg bw, with the plasma T_{max} reached at 1 h and 2 h after administration in males and females respectively.

No data is available on inpyrfluxam with regards to **inhalation absorption**. Therefore, a default value of **100%** is proposed for inpyrfluxam. The dermal absorption of inpyrfluxam from the representative product S-2399 60 g/L EC was determined from an in vitro study in accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873). **Dermal absorption values of 8.8% and 20%** were established for the concentrate and dilution respectively. For more detail, please refer to volume 3CP B6.

Post hepatic systemic availability was estimated as 60% (difference between the 96% oral absorption value and the mean level of radioactivity excreted in bile during the first 6 hours (35%) and considered not to be systemically available).

Distribution

Inpyrfluxam and/or its metabolites were widely distributed, with higher levels found in blood, plasma, liver, kidney, adrenal and heart.

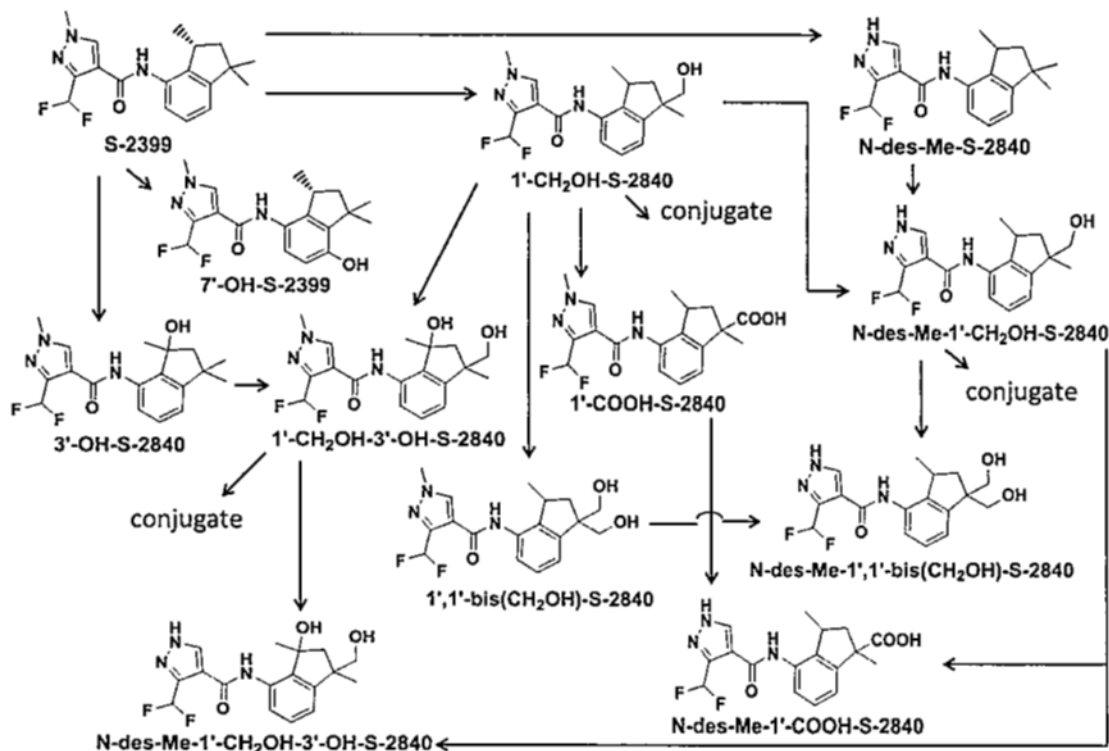
In the single oral dose study, at the low dose of 1 mg/kg bw, the plasma T_{max} of radioactivity was reached at 1 h after dosing with a C_{max} of 1.77 $\mu\text{g equivalents/g}\cdot\text{h}$ in males and 1.63 $\mu\text{g equivalents/g}\cdot\text{h}$ in females. At the high dose of 150 mg/kg bw, the plasma T_{max} of radioactivity was reached at 8 h after dosing with a C_{max} of 270 $\mu\text{g equivalents/g}\cdot\text{h}$ in males and 382 $\mu\text{g equivalents/g}\cdot\text{h}$ in females. Within 72 hours, the level of radioactivity in plasma had declined to extremely low levels, indicating that there was no retention of inpyrfluxam and/or its metabolites at the doses tested. The half-life of radioactivity remained comparable between sexes and ranged from 12 to 17 hours.

At 1 and 150 mg/kg bw, the tissue T_{max} of radioactivity was reached at 0.25 - 1 h and 1 - 8 h after dosing respectively except for the gastrointestinal tract or its content. At the low and high dose, the mean elimination half-lives of radioactivity were 2 - 8 h and 7 - 48 h after dosing respectively, in the examined tissues, except for the gastrointestinal tract or its content. At 168 h after administration of both doses, the total radioactive residue in the carcass was 0.1- 0.2% AD (administered dose). No remarkable sex-related difference was observed in the tissue C_{max} values at either dose, although the C_{max} and half-lives were higher at the high dose.

In the repeated oral dose study, at 1 mg/kg bw, the plasma T_{max} of radioactivity was reached at 1 h and 2 h after dosing in males and females respectively. The radioactivity concentrations in the tissues were generally low in both males and females after 7 days from the end of dosing. The highest radioactivity concentrations were noted in the liver and GI tract. The total percentages of radioactivity in tissues 7 days after 14 consecutive administrations were 0.2% AD in males, and 0.1% AD in females. There was no evidence of bioaccumulation. In addition, no remarkable sex-related differences in distribution in organs or tissues were noted.

Metabolism

Inpyrfluxam was extensively metabolized, and in addition to the parent, a total of 12 metabolites, including two conjugates, were identified, and quantified in both single and repeat dose studies in rats. 1'-COOH-S-2840 and N-des-Me-1'-COOH-S-2840 were the major metabolites in urine and the glucuronide of 1'-CH₂OH-S-2840 was a major metabolite in bile. From the in vitro metabolism studies using liver microsomes, no unique human metabolite was identified. A metabolic pathway for inpyrfluxam was proposed by the applicant with N-demethylation, oxidation of the 1',1'-dimethylgroup of the indane ring followed by further oxidation to carboxylic acid and glucuronide conjugation along with minor metabolic reactions such as 3' and 7'-hydroxylation of the indane ring.



Elimination

In the single dose study, elimination was rapid, with >67% AD excreted within 24 hours of dosing and was essentially complete (>90% AD) within 2-3 days. Elimination was predominantly via urine (49.2% – 61% AD) and bile (46.9 – 68.9% AD). Faecal excretion of radioactivity was between 39.4% and 47.9% AD, at 168 hours, of which a significant proportion was excreted via bile. There was evidence of entero-hepatic re-circulation.

In the repeated dose study, elimination was rapid and was essentially complete, with >90% AD excreted within 24 hours after the end of dosing. Elimination was predominantly via urine (33 – 51.6% AD) and faeces (44.8 – 61.5% AD).

Overall conclusion

Overall, the following conclusions regarding the toxicokinetic properties of inpyrfluxam can be made:

- Absorption of inpyrfluxam from the GI tract was rapid and practically complete.
- An overall **oral absorption value of 100%** was established. However, the **post hepatic systemic availability** was estimated **at 60%**. With regard to **inhalation absorption**, a default value of **100%** was proposed. **Dermal absorption values**

of 8.8 and 20% were established for inpyrfluxam in the representative product for the concentrate and dilution respectively.

- Radioactivity was widely distributed throughout the body and plasma levels rapidly declined once peak plasma concentrations were reached.
- Inpyrfluxam was extensively metabolized. Up to 12 metabolites were identified and characterised in the excreta of rats, suggesting that when the parent substance is metabolised, numerous reactions take place.
- No significant bioaccumulation of radioactivity was noted in the plasma or tissue during repeat dose testing with inpyrfluxam.
- No unique human metabolites were observed in the in vitro comparative metabolism study.
- The residue definition for body fluid from a toxicological point of view, should be 1'-COOH-S-2840 in urine.
- The residue definition for tissues from a toxicological point of view should be 1'-COOH-S-2840 in liver/kidney.

2.6.2. Summary of acute toxicity

The acute toxicity of inpyrfluxam was investigated in multiple in vivo studies conducted via the oral, dermal and inhalation routes. In addition, an in vivo study assessing skin sensitisation, as well as in vitro studies evaluating the skin and eye irritation potential of inpyrfluxam, and phototoxicity were also available. In vivo skin and eye irritation studies were submitted; however, these were not relied upon as valid in vitro alternatives were available.

Based on the results of these studies, inpyrfluxam is acutely toxic via the oral route (LD50 of 180 mg/kg) and meets the criteria for classification under Reg. (EC) No. 1272/2008 as it applies in GB for acute oral toxicity in category 3 (H301) but has low acute toxicity when administered dermally (LD50 > 2000 mg/kg) and via inhalation (4-hr-LC50 > 2.61 mg/L; analytically determined) to rats. It is not a skin or eye irritant, nor a skin sensitiser, and is not phototoxic. No conclusion could be reached on the phototoxicity potential of inpyrfluxam.

The table below provides an overview of the available acute toxicity studies:

Table 2.6.2-1: Summary of acute toxicity studies for inpyrfluxam

Data point/ Study	Species/ Strain/Tissue	Sex	Acceptable	Result	Classification according to Reg. (EC) No. 1272/2008 as it applies in GB
KCA 5.2.1/01 Acute Oral (OECD 423; <i>in vivo</i>)	Rat/ RccHan:WIST	F	Acceptable Relied upon	50 < LD ₅₀ < 300 mg/kg	Cat. 3 (H301)
KCA 5.2.1/02 Acute Oral (OECD 425; <i>in vivo</i>)	Rat/ RccHan:WIST	F	Acceptable Relied upon	LD ₅₀ 180 mg/kg	Cat. 3 (H301)
KCA 5.2.2/01 Acute Dermal (OECD 402; <i>in vivo</i>)	Rat/ RccHan:WIST	M&F	Acceptable Relied upon	LD ₅₀ >2000 mg/kg	Not classified
KCA 5.2.3/01 Acute Inhalation (OECD 403; <i>in vivo</i>)	Rat/ RccHan:WIST	M&F	Acceptable Relied upon	LC ₅₀ > 2.61 mg/L analytically determined (maximal attainable concentration)	Not classified
KCA 5.2.4/02 Skin irritation (OECD 439; <i>in vitro</i>)	EpiDerm™	-	Acceptable	Not irritating	Not classified
KCA 5.2.5/02 Eye irritation (OECD 492; <i>in vitro</i>)	EpiOcular™	-	Acceptable	Not irritating	Not classified

Data point/ Study	Species/ Strain/Tissue	Sex	Acceptable	Result	Classification according to Reg. (EC) No. 1272/2008 as it applies in GB
KCA 5.2.6/01 Skin sensitisation (GPMT) (OECD 406; <i>in vivo</i>)	Guinea pig/ Hartley	F	Acceptable Relied upon	Not sensitising	Not classified
KCA 5.2.7/01 <i>In vitro</i> phototoxicity (OECD 432)	Balb/3T3 clone A31 cells/ NA	NA	Not acceptable Not relied upon	Not phototoxic Inconclusive	N/A

M: Male

F: Female

NA: not applicable

2.6.3. Summary of short-term toxicity

The short-term toxicity of inpyrfluxam has been investigated via the oral route of exposure in a preliminary 28-day (range-finding) study performed in rats, 90-day studies performed in rats, mice, and dogs and 1-year study performed in dogs. A 28-day dermal exposure study in rats is also available.

With the exception of the 28-day range-finding oral study in rats, all the remaining studies were conducted in compliance with GLP and OECD test guidelines. The main findings are summarised in table below.

Table 2.6.3-1: Summary of short-term toxicity studies for inpyrfluxam

Data point/ Study <i>Acceptability</i>	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
KCA 5.3.1/01	Rat/ Wistar Hanover	0, 500, 1000, 3000 and 5000 ppm	Not set as range- finding study	Not set as range- finding study	3000 ppm: ↓ bw (10.7%* in M & 8.3%** in F) ↑ total cholesterol (50%* in M & 100% in F), phospholipid (30.6% in M & 70.8%

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
<p><i>One-month Oral Toxicity</i></p> <p>- not GLP or OECD compliant</p> <p>- Range finding study</p> <p><i>Acceptable as a range-finding study</i></p>	rats/ M&F	<p><u>Mean substance intakes</u></p> <p>Males: 0, 44.4, 85.9, 246.4 and 406.5 mg/kg bw/day</p> <p>Females: 0, 47.4, 91.4, 263.0 and 377.8 mg/kg bw/day</p>			<p>in F), γ-glutamyl transpeptidase (650%* in M and 300%* in F), triglyceride (217.6%** in F)</p> <p>↑ relative liver weight (16.3%** in M & 25.1%** in F), absolute liver weight (14.7%** in F),</p> <p>↓ absolute kidney weight (11.9%** in F), absolute thymus weight (33.3%** in M), relative thymus weight (25%** in M), absolute ovary weight (19.2%* in F)</p> <p><u>Histopathological findings</u></p> <p>Liver: ↑ hepatocellular hypertrophy (3/6 in M & 6/6** in F)</p> <p>Kidney: ↑ tubular hyaline droplets in 1/6 in M - not relevant to humans</p> <p>Thyroid: ↑ follicular cell hypertrophy (4/6 in M & 5/6* in F)</p> <p>Adrenal gland: glomerular fine vacuolation (5/6** in M)</p> <p>Bone marrow: fatty infiltration (5/6* in F)</p>

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
					<p>Ovary: Vacuolation of the interstitial gland (2/6 in F)</p> <p>Uterus: Slight atrophy (2/6 in F)</p>
<p>KCA 5.3.2/01</p> <p>90-Day Oral Toxicity</p> <p>OECD TG 408 (1998)</p> <p>Acceptable</p>	<p>Rat/</p> <p>Wistar Han- over/ M&F</p>	<p>0, 150, 500, 2000, or 4000 ppm</p> <p><u>Mean substance intakes</u></p> <p>Males: 0, 9.72, 31.7, 123 and 255 mg/kg bw/day</p> <p>Females: and 11.5, 37.5, 144 and 292 mg/kg bw/day</p>	<p>500 ppm</p> <p>31.7 mg/kg bw/day</p>	<p>2000 ppm</p> <p>123 mg/kg bw/day</p>	<p>↓ bw (10%** in F)</p> <p>↓ bw gain (21%** in F)</p> <p>↓ food consumption (17%** in F)</p> <p>↑ γ-glutamyl transpeptidase (114%** in M and 238%** in F), Alkaline phosphatase (34%** in F)</p> <p>↑ relative liver weight (11%** in M & 19%** in F)</p> <p><u>Histopathological findings</u></p> <p>Liver: ↑ diffuse hepatocellular hypertrophy (4/10** in M & 7/10** in F)</p> <p>Kidney: ↑ tubular hyaline droplets in 2/10 in M - not relevant to humans</p> <p>Thyroid: ↑ follicular cell hypertrophy (4/10 in F)</p>

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
					Adrenal gland: ↑ cortical cell vacuolation (3/10 in F) Ovary: ↑ vacuolation of the interstitial gland (7/10* in F)
KCA 5.3.2/02 90-Day Oral Toxicity OECD TG 408 (1998) <i>Acceptable</i>	Mice/ [redacted]:C D [redacted] [redacted]) / M&F	0, 200, 800, 3500, or 7000 ppm <u>Mean substance intakes</u> Males: 0, 27.2, 111, 491, 973 mg/kg bw/day Females: and 0, 31.7, 130, 559 and 1097 mg/kg bw/day	800 ppm 111 mg/kg bw/day	3500 ppm 491 mg/kg bw/day	↑ globulin (10%* in M & 10% in F) ↓ albumin (8%** in F), albumin/globulin ratio (9% in M & 15%** in F) ↑ relative liver weight (18%** in M & 11%** in F), absolute liver weight (16%** in M & 7% in F) <u>Histopathological findings</u> Liver: ↑ diffuse hepatocellular hypertrophy (4/10 in F), Centrilobular hepatocyte hypertrophy (8/10** in M), Centrilobular hepatocyte fatty change (3/10 in M)
KCA 5.3.2/03 90-Day Oral Toxicity	Dogs/ Beagle / M&F	0, 40, 160 or 700/500 mg/kg bw/day	40 mg/kg bw/day	160 mg/kg bw/day	↓ reticulocyte count (25%) in M&F, albumin (21%** in M & F), globulin (19%* in M) albumin/globulin ratio (13% in M & 20%** in F) ↑ alkaline phosphatase (ALP) (261%** in M & 247%** in F) and γ-glutamyl

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
OECD TG 409 (1998) <i>Acceptable</i>		(Due to severe toxicity at 700 mg/kg bw/day at week 2, the animals were not treated at week 3. At week 4 (week 1 for this group), the high dose was reduced to 500 mg/kg bw/day)			<p>transpeptidase (GGTP) (87%** in M & 90%** in F) and in alanine aminotransferase (ALT) (103% in M & 51% in M), total cholesterol (31% in M & 16% in F)</p> <p>Enlarged liver in M (3/4) & F (2/4), biliary sludge in gall bladder (1/4 in M)</p> <p>↑ relative liver weight (49%** in M & 38%** in F), absolute liver weight (53%** in M and 41%** in F)</p> <p><u>Histopathological findings</u></p> <p>Liver: ↑ diffuse hepatocellular hypertrophy (3/4 in M and 4/4* in F), cytoplasmic eosinophilic inclusion bodies (/4 in F), Brown pigment deposition in the Kupffer cells (1/4 in M)</p> <p>Gall bladder: calculi (1/4 in M)</p> <p>Kidney: hypertrophy (3/4 in M) and cytoplasmic eosinophilic inclusion body (1/4 in M) in the proximal tubular cells</p> <p>Thyroid: Follicular cell hypertrophy (1/4 in F)</p>

Data point/ Study <i>Acceptability</i>	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
					Adrenal gland: zona fasciculata cell vacuolation (2/4 in M) Eye: optic nerve fibre degeneration (1/4 in F)
KCA 5.3.2/04 <i>One-year Oral Toxicity</i> OECD TG 452 (2009) <i>Acceptable</i>	Dogs/ Beagle / M&F	0, 2, 6, 30 or 160 mg/kg bw/day	6 mg/kg bw/day	30 mg/kg bw/day	<p>↑ ALP (by >60%) and GGTP (by >50%) in M</p> <p>↓ Albumin/globulin ratio (44%) in M</p> <p>↑ absolute (32%*) and relative (24%*) liver weights in M</p> <p><u>Histopathological findings</u></p> <p>Liver: ↑ diffuse hepatocellular hypertrophy (1/4 in M),</p> <p>Adrenal gland: zona fasciculata cell vacuolation (2/4 in M & 1/4 in F)</p> <p>Eye: optic nerve fibre degeneration (1/4 in F)</p>
KCA 5.3.3/01 28-day dermal toxicity	Rats/ Sprague Dawley	0, 100, 300 or 1000 mg/kg bw/day	1000 mg/kg bw/day	Not established	No adverse effects

Data point/ Study	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
OECD TG 410 (1981)	█ / M&F				
<i>Acceptable</i>					

* and **: $p \leq 0.05$ and $p \leq 0.01$ (Fisher's exact probability test)

Rat

In rats, the main target organs of toxicity were the liver, adrenal glands, thyroid, and ovary.

Adverse ($\geq 15\%$) increased liver weights with hypertrophy were seen from 123 mg/kg bw/day in the 90-day study. These effects were associated with alterations in coagulation (eg. prothrombin time) and clinical-chemistry parameters (eg. increased total cholesterol, γ -glutamyl transpeptidase etc) indicative of liver damage.

Increased cortical cell vacuolation in the adrenal gland of females was seen from 144 mg/kg bw/day in the 90-day study. Increased thyroid follicular hypertrophy was noted in females from 144 mg/kg bw/day in the 90-day study.

In addition to a decrease in weight, vacuolation of the interstitial gland was noted in the ovaries of females from 144 mg/kg bw/day in the 90-day study.

In addition to toxic effects in these organs, decreases in body weight and/or body weight gain and food consumption were also observed from around 123 mg/kg bw/day in the 90-day study.

Mouse

In mice, the main target organs of toxicity were the liver and thyroid.

Adverse ($\geq 15\%$) increased liver weights with hypertrophy and fatty changes were seen from 491 mg/kg bw/day in the 90-day study. These effects were associated with alterations in albumin/globulin ratio.

In addition, follicular cell hypertrophy of the thyroid was observed at the top dose of 973 mg/kg bw/day in the 90-day study.

Dog

In dogs, the main target organs of toxicity were the liver, gall bladder, kidney, adrenal glands, thyroid and the optic nerve.

Adverse ($\geq 15\%$) increased liver weights with hypertrophy, eosinophilic inclusion bodies and brown pigmentation of Kupffer cells (the latter only in the 90-day study) were seen from 160 mg/kg bw/day in the 90-day study and from 30 mg/kg bw/day in the one-year study. These effects were associated with alterations in clinical-chemistry parameters indicative of liver damage (eg. increased total cholesterol, γ -glutamyl transpeptidase etc).

Calculi in the gallbladder were seen from 160 mg/kg bw/day in males and at 700/500 mg/kg bw/day in females in the 90-day study.

In the 90-day study, proximal tubular hypertrophy and cytoplasmic eosinophilic inclusion bodies were seen in the kidneys of males from 160 mg/kg bw/day. In addition, proximal tubular cell vacuolation was observed at the top dose of 700/500 mg/kg bw/day in both sexes.

In the adrenal gland, zona fasciculata cell vacuolation was seen in males from 160 mg/kg bw/day in the 90-day study and from 30 mg/kg bw/day in both sexes in the one-year study.

Thyroid follicular cell hypertrophy was observed in one female at 160 mg/kg bw/day and one male at 700/500 mg/kg bw/day in the 90-day study.

In females, increased incidence of degeneration of the optic nerve was noted from 160 mg/kg bw/day in the 90-day study and at the top dose of 160 mg/kg bw/day in the one-year study.

In addition to these effects, vomiting was reported from 160 mg/kg bw/day in the 90-day study and from 30 mg/kg bw/day in the one-year study and signs of anaemia were seen from 160 mg/kg bw/day in the 90-day study. The most sensitive NOAEL for the short-term toxicity of inpyrfluxam was 6 mg/kg bw/day (with a respective LOAEL of 30 mg/kg bw/day) taken from the 12-month dog study. At the LOAEL, there were adverse ($>15\%$) increases in liver weights with hypertrophy, effects on clinical chemistry parameters indicative of liver damage (ALP, GGTP, A/G ratio) and zona fasciculata cell vacuolation of the adrenal gland in both sexes.

Overall conclusion

Overall, therefore, repeated-dose toxicity has been adequately investigated in studies in rats, mice and dogs. The critical target organs were the liver and thyroid in all three species, with the adrenal gland affected in rats and dogs, the ovary in rats and the gall bladder, kidney, and optic nerve in dogs. **The most sensitive species appears to be the dog, followed by the rat.** The mouse was the least sensitive species to the short-term

toxicity of inpyrfluxam. Potential classification for STOT-RE according to Regulation 1272/2008 as it applies in GB is addressed in the aligned MCL report.

2.6.4. Summary of genotoxicity

Inpyrfluxam was evaluated for its mutagenic potential in vitro using the bacterial reverse mutation test, mammalian gene mutation test, and the chromosomal aberration test. An in vivo mouse micronucleus test was also performed to investigate clastogenicity and aneugenicity. In these valid GLP and guideline studies, there was no evidence of genotoxicity, and it is concluded that inpyrfluxam is not genotoxic. Therefore, inpyrfluxam does not meet the criteria for classification for germ cell mutagenicity according to Regulation 1272/2008 as it applies in GB (see aligned MCL report for further details).

Table 2.6.4-1: Summary of genotoxicity studies for inpyrfluxam

Data point/Type of study and Acceptability	Organism/ Cells	Dose range tested	Result	Reference
In vitro studies				
KCA 5.4.1/01 Reverse mutation (OECD TG 471) <i>Acceptable</i>	<i>Salmonella typhimurium</i> (strains TA100, TA1535, TA98 and TA1537) and <i>Escherichia coli</i> (WP2uvrA)	1.5 to 5000 µg/plate	Negative	██████████ (2014a/2017) TPT-0004
KCA 5.4.1/02 <i>In vitro</i> chromosomal aberration test (OECD TG 473) <i>Acceptable</i>	Chinese hamster lung cells (CHL/IU)	32.5-130 µg/mL (short-term treatment, -S9 Mix) 42.5-170 µg/mL (short-term treatment, +S9 Mix) 0.188-1.5 µg/mL (long-term treatment, -S9 Mix)	Negative	██████████ (2014b) TPT-0005

KCA 5.4.1/03 Mammalian cell gene mutation (OECD TG 476) <i>Acceptable</i>	V79 cells – HPRT locus	6.5 to 39.0 µg/mL (4 h treatment - S9 Mix) 6.5 to 78.0 µg/mL (4 h treatment +S9 Mix) 13.0 to 78.0 µg/mL (24 h treatment -S9 Mix)	Negative	██████ (2014) TPT-0002
<i>In vivo studies</i>				
KCA 5.4.2/01 Mouse micronucleus (OECD TG 474) <i>Acceptable</i>	CD-1 mice	200, 400 or 800 mg/kg bw (24 h sampling) 800 mg/kg bw (48 h sampling)	Negative	██████ (2015) TPT-0021

2.6.5. Summary of long-term toxicity and carcinogenicity

The long-term toxicity and carcinogenicity of inpyrfluxam have been investigated via the oral route of exposure in rats and mice. Both studies were conducted in compliance with GLP and OECD test guidelines. The main findings are summarised in the table below.

Table 2.6.5-1: Summary of long term and carcinogenicity studies for inpyrfluxam

Data point/ Study <i>Acceptability</i>	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
KCA 5.5/01 : <i>Combined Chronic Toxicity and Carcinogenicity Study in Rats</i>	Rat/ Wistar Hannover rats/ M&F	Males: 0,150, 500, and 2000 ppm	<u>Chronic toxicity:</u> 500 ppm (19.4 mg/kg bw/day)	<u>Chronic toxicity:</u> 1500/1000 ppm (65.8 mg/kg bw/day)	<u>Systemic chronic toxicity</u> <u>Chronic toxicity phase:</u>

Data point/ Study	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
OECD 453 (2009)		Females: 0, 150, 500, and 1000/1500 ppm	<u>Carcinoge nicity:</u> 1500/100 0 ppm (65.8 mg/kg bw/day) - top dose	<u>Carcinoge nicity:</u> N/A	↓ bw (6% in M & 14%** in F)
GLP		<u>Mean substance intakes</u>			↓ bw gain (8%* in M & 37%** in F)
Acceptable		<i>Males (chronic toxicity phase):</i> 0, 6.77, 22.8 and 95.9 mg/kg bw/day			↓ food consumption (M&F)
		<i>(carcinogenicity phase):</i> 0, 5.85, 19.4 and 78.4 mg/kg bw/day			↓ neutrophil (41% in F), monocyte (40% in F)
		<i>Females: (chronic toxicity phase):</i> 0, 8.84, 30.1 and 86.4 mg/kg bw/day			↑ γ-glutamyl transpeptidase (157%* in M and 125%* in F at week 14), ↑ albumin/globulin ratio (16%** in F at week 14 and 26)
		<i>(carcinogenicity phase):</i> 0, 7.47, 25.5, and 65.8 mg/kg bw/day			↓ globulin (13% in F at week 26)
					↑ relative liver weight (11%** in M)
					<u>Carcinogenicity phase:</u>
					↓ bw (19%** in M & 13%** in F)
					↓ bw gain (18%** in M & 27%** in F)
					↓ food consumption (M&F)
					↓ neutrophil (20% in M & 35% in F), monocytes (19% in M and 28% in F),

44

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
		(<i>carcinogenicity phase</i>): 0, 69.3, 210, and 701 mg/kg bw/day			<p>↓ bw gain (37%** in M & 24%** in F)</p> <p>centrilobular hepatocellular hypertrophy in M</p> <p>amyloid nephropathy in M&F</p> <p>amyloidosis in cervical lymph nodes, glandular stomach in F</p> <p><u>Carcinogenicity</u></p> <p>Inpyrfluxam is not carcinogenic in mice</p>

Rat

In rats, inpyrfluxam was not carcinogenic up to the top dose of 1500/1000 ppm at which generalised and target organ toxicity occurred. The carcinogenicity NOAEL in the rat is therefore 1500/1000 ppm (65.8 mg/kg bw/day).

With regard to chronic toxicity, the main target organ was the liver. Increased liver weight with associated findings in clinical-chemistry (eg. increased γ -glutamyl transpeptidase, albumin/globulin ratio) and haematological (differential leukocyte count) parameters was seen at the top dose of 1500/1000 ppm (65.8 mg/kg bw/day) in the chronic toxicity phase. Adverse effects on differential leukocyte count were also noted in the carcinogenicity phase. In addition to the toxic effects in the liver, decreases in body weight, body weight gain and food consumption were also observed at 65.8 mg/kg bw/day in both the chronic and carcinogenicity phase. The NOAEL for chronic toxicity in the rat is 500 ppm (19.4 mg/kg bw/day).

Mouse

In mice, inpyrfluxam was not carcinogenic up to the top dose of 7000/5000 ppm at which generalised and target organ toxicity occurred. The carcinogenicity NOAEL in the mice is therefore 7000/5000 ppm (701 mg/kg bw/day).

With regard to chronic toxicity, the main target organs were the liver and kidney. Increased liver and kidney weights were seen from the mid-dose of 2000 ppm (210 mg/kg bw/day) in the satellite group. These changes were associated with centrilobular hepatocellular hypertrophy, coarse surface of the kidney and diffuse luminal dilatation and hypertrophy of the proximal renal tubules. Increases in centrilobular hepatocellular hypertrophy of the liver, amyloid nephropathy and amyloidosis in cervical lymph node and glandular stomach were also noted from 210 mg/kg bw/day in the carcinogenicity groups. In addition, decreases in body weight and body weight gain were observed from 210 mg/kg bw/day in both the satellite and carcinogenicity group. The NOAEL for chronic toxicity in the mouse is 700 ppm (69.3 mg/kg bw/day).

Overall conclusion

Overall, therefore, long term toxicity and carcinogenicity have been adequately investigated in studies in rats and mice. The substance is not carcinogenic in rats or mice. With regard to chronic toxicity, the critical target organ was the liver in both species with the kidney, cervical lymph nodes and stomach affected in mice. The most sensitive species to the long-term toxicity of inpyrfluxam is the rat, with a NOAEL of 19.4 mg/kg bw/day.

In addition, the following conclusions can be drawn:

- No classification for carcinogenicity is required (see aligned MCL report).
- The data requirements of assimilated Regulation 283/2013 have been met.

2.6.6. Summary of reproductive toxicity

The reproductive toxicity of inpyrfluxam has been investigated via the oral route of exposure. There were two generational toxicity studies (a preliminary one generation range finding study and a definitive two generation study in rats) and seven developmental toxicity studies (two dose finding and two definitive developmental toxicity studies in rats; and two range finding and a definitive developmental toxicity study in rabbits). All the definitive studies were conducted in compliance with GLP and OECD test guidelines. The main findings are summarised in the table below.

Table 2.6.6-1: Summary of reproductive toxicity studies for inpyrfluxam

Data point/ Study <i>Acceptability</i>	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
Reproduction toxicity					
<p>KCA 5.6.1/01</p> <p><i>Dose Range- Finding One- generation Reproduction Toxicity Study in Rats</i></p> <p>- not GLP or OECD compliant</p> <p>- Range finding study</p> <p><i>Acceptable as a range-finding study</i></p>	<p>Rat/</p> <p>Wistar Hannov er rats/M &F</p>	<p>Males and Females: 0, 300,1000,2000, and 4000 ppm</p> <p><u>Mean substance intakes</u></p> <p><i>Males:</i> 15.1, 50.4, 105 or 203 mg/kg bw/day</p> <p><i>Females:</i> 20.4, 68, 132 or 254 mg/kg bw/day</p>	<p>Not set as range- finding study</p>	<p>Not set as range- finding study</p>	<p><u>2000 ppm:</u></p> <p><u>Reproductive toxicity</u></p> <p><u>No adverse effects up to top dose.</u></p> <p><u>Parental toxicity (F0)</u></p> <p>↓ bw in F (on gestation day 20 and lactation days 0, 4, 7, and 14)</p> <p>↓ bw gain in F (during gestation days 0-20)</p> <p>↓ food consumption (F)</p> <p>↑ relative liver weight (16%) in M)</p> <p>↓ absolute ovary weight (18% in F)</p> <p><u>Offspring toxicity (F1)</u></p> <p>↓ bw in M & F (from lactation day 4)</p>

					<p>enlargement of the eye associated with synechia and cataract</p> <p>↓ absolute thymus and brain weight (in M and F)</p> <p>↓ absolute uterus weight in F</p>
<p>KCA 5.6.1/02</p> <p><i>Definitive Two-generation Reproduction Toxicity Study in Rats</i></p> <p>- GLP</p> <p>-OECD 416 (2001)</p> <p><i>Acceptable</i></p>	<p>Rat/</p> <p>Wistar Hannover rats/M&F</p>	<p>Males: 0, 150,500, and 2000 ppm</p> <p>Females: 0, 150,500, and 1250 ppm</p> <p><u>Mean substance intakes</u></p> <p>Males: 0, 8.34, 27.8 or 113 mg/kg bw/day</p> <p>Females: 0, 10.9, 35.5 or 86 mg/kg bw/day</p>	<p><u>Reproductive toxicity</u></p> <p>1250/2000 ppm (86 mg/kg bw/day)</p> <p><u>Parental and offspring toxicity</u></p> <p>500 ppm (27.8 mg/kg bw/day)</p>	<p><u>Reproductive toxicity</u></p> <p>N/A</p> <p><u>Parental and offspring toxicity</u></p> <p>1250/2000 ppm (86 mg/kg bw/day)</p>	<p><u>Reproductive toxicity</u></p> <p><u>No adverse effects up to the top dose</u></p> <p><u>Parental toxicity</u></p> <p><u>F0</u></p> <p>↓ bw in M & F</p> <p>↓ bw gain in M & F</p> <p>↓ food consumption in M & F</p> <p>↑ absolute and relative liver weights in F</p> <p>↓ absolute and relative thyroid weight in F</p> <p>↑ Thyroid follicular hypertrophy in F</p> <p><u>F1</u></p>

					<p>↓ bw in M & F</p> <p>↓ bw gain in M & F</p> <p>↓ food consumption in F</p> <p>↑ absolute and relative liver weights in F</p> <p>↓ absolute and relative thyroid weight in F</p> <p>↑ Thyroid follicular hypertrophy in F</p> <p><u>Offspring toxicity</u></p> <p>↓ bw in M & F</p>
Developmental toxicity					
<p>KCA 5.6.2/07</p> <p><i>Preliminary prenatal developmental toxicity study in rats</i></p> <p>- not GLP or OECD compliant</p> <p>- Range finding study</p>	<p>Rat/</p> <p>Wistar Hannover rats/F</p>	<p>0, 12.5, 25, 50 or 100 mg/kg bw/day</p>	<p>Not set as range-finding study</p>	<p>Not set as range-finding study</p>	<p><u>100 mg/kg bw/day</u></p> <p><u>Maternal toxicity</u></p> <p>Mortality</p> <p>Clinical signs of toxicity (stains all over the body, clonic convulsion and irregular respiration)</p> <p>↓ bw and bw gain</p>

Acceptable as a range-finding study					<p>retention of foamy fluid in trachea</p> <p><u>Developmental toxicity</u></p> <p>↓ mean number of live foetuses per</p> <p>↓ foetal weight</p>
<p>KCA 5.6.2/01</p> <p><i>Dose Range-Finding Teratogenicity Study in Rats</i></p> <p>- not GLP or OECD compliant</p> <p>- Range finding study</p> <p>Acceptable as a range-finding study</p>	<p>Rat/</p> <p>Wistar Hannover rats/F</p>	0, 20, 40 or 80 mg/kg bw/day	Not set as range-finding study	Not set as range-finding study	<p><u>80 mg/kg bw/day</u></p> <p><u>Maternal toxicity</u></p> <p>↓ bw and bw gain</p> <p>↓ food consumption</p> <p><u>Developmental toxicity</u></p> <p>↓ foetal weight</p>
<p>KCA 5.6.2/02</p> <p><i>Definitive Teratogenicity Study in Rats</i></p> <p>- GLP</p> <p>-OECD 414 (2001)</p>	<p>Rat/</p> <p>Wistar Hannover rats/F</p>	0, 10, 25 or 80 mg/kg bw/day	<p><u>Maternal toxicity</u></p> <p>25 mg/kg bw/day</p> <p><u>Developmental toxicity</u></p>	<p><u>Maternal toxicity</u></p> <p>80 mg/kg bw/day</p> <p><u>Developmental toxicity</u></p>	<p><u>Maternal toxicity</u></p> <p>↓ bw and bw gain</p> <p>↓ food consumption</p> <p><u>Developmental toxicity</u></p> <p>↓ foetal weight</p>

<i>Acceptable</i>			25 mg/kg bw/day	80 mg/kg bw/day	Cyclopia (n=1)
KCA 5.6.2/03 <i>Investigative Teratogenicity Study in Rats</i> - GLP -OECD 414 <i>Acceptable as additional study</i>	Rat/ Wistar Hannov er rats/F	0 or 90 mg/kg bw/day	<u>Maternal toxicity</u> N/A <u>Developm ental toxicity</u> N/A	<u>Maternal toxicity</u> N/A <u>Developm ental toxicity</u> N/A	<u>90 mg/kg bw/day</u> <u>Maternal toxicity</u> ↓ bw and bw gain ↓ food consumption ↓ mean gravid uterine weight <u>Developmental toxicity</u> ↓ foetal weight
KCA 5.6.2/04 <i>Dose Range- Finding Teratogenicity Study in Rabbits</i> - not GLP or OECD compliant - Range finding study <i>Acceptable as a range-finding study</i>	Rabbit/ Japanes e White /F	0, 15, 50 or 150 mg/kg bw/day	Not set as range- finding study	Not set as range- finding study	<u>150 mg/kg bw/day</u> <u>Maternal toxicity</u> None <u>Developmental toxicity</u> None

<p>KCA 5.6.2/05</p> <p><i>Additional Dose Range-Finding Teratogenicity Study in Rabbits</i></p> <p>- not GLP or OECD compliant</p> <p>- Range finding study</p> <p><i>Acceptable as a range-finding study</i></p>	<p>Rabbit/ Japanese White /F</p>	<p>0, 300, 500, or 1000 mg/kg bw/day</p>	<p>Not set as range-finding study</p>	<p>Not set as range-finding study</p>	<p>300 mg/kg bw/day</p> <p><u>Maternal toxicity</u></p> <p>Clinical signs of toxicity (lateral and prone position, decreased spontaneous motor activity, abnormal behaviour (convulsion), bradypnoea, abortion)</p> <p>↓ bw and bw gain</p> <p>↓ food consumption</p> <p>Gross pathological changes in stomach and large intestine</p> <p><u>Developmental toxicity</u></p> <p>None</p>
<p>KCA 5.6.2/06</p> <p><i>Definitive Teratogenicity Study in Rabbits</i></p> <p>- GLP</p> <p>-OECD 414 (2001)</p>	<p>Rabbit/ Japanese White /F</p>	<p>0, 20, 60, or 200 mg/kg bw/day</p>	<p><u>Maternal toxicity</u></p> <p>60 mg/kg bw/day</p> <p><u>Developmental toxicity</u></p>	<p><u>Maternal toxicity</u></p> <p>200 mg/kg bw/day</p>	<p><u>Maternal toxicity</u></p> <p>Clinical signs of toxicity (red discharge in the tray and abortions)</p> <p>↓ bw gain</p> <p>↓ food consumption</p>

Acceptable			200 mg/kg bw/day	<u>Developmental toxicity</u> N/A	<u>Developmental toxicity</u> None
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Effects on fertility and reproductive performance

The potential effects of inpyrfluxam on fertility and reproductive performance have been investigated in the rat via the oral (dietary) route of exposure in a guideline 2-generation study.

Administration of inpyrfluxam at concentrations of 0, 150, 500 or 1250/2000 ppm (females/males) (0, 8.34, 27.8 or 113 mg/kg bw/day in males and 0, 10.9, 35.5 or 86 mg/kg bw/day in females) for two successive generations caused no effects on fertility and reproductive performance. Therefore, a NOAEL of 1250/2000 ppm (86 mg/kg bw/day) can be established for reproductive toxicity. Parental toxicity was noted at the top dose in F0 and F1 animals and consisted of reductions in body weights, body weight gains and food consumption, increased liver weight with associated hypertrophy and increased thyroid weight with associated follicular hypertrophy, mainly in females. Offspring toxicity was also noted at the top dose with decreased body weights in both F1 and F2 weanlings. A NOAEL of 500 ppm (27.8 mg/kg bw/day) is therefore established for both parental and offspring toxicity.

Additional information on the potential effects of inpyrfluxam on reproductive organs from the repeated dose toxicity studies in rats, mice and dogs has been taken into account. In the 28-day oral (dietary) toxicity study in rats, at 3000 ppm (246.4 mg/kg bw/day), there were decreases in ovary and uterus weight along with associated histopathological findings (section B.6.3.1, ██████████ 2014). In the 90-day studies in rats, histopathological findings were noted in the ovary at 2000 ppm (123 mg/kg bw/day) and 4000 ppm (255 mg/kg bw/day) (section B.6.3.2, ██████████ 2016). Similar effects were not seen in the multigeneration study (although lower doses were employed). Therefore, it is most likely these were high dose effects occurring in the excess of the MTD – maximum tolerated dose (significant effects on body weights, body weight gains, liver toxicity, adrenal toxicity and histopathology of other organs) and hence of limited relevance at realistic exposure levels.

Developmental toxicity

The developmental toxicity of inpyrfluxam has been investigated via the oral (gavage) route of exposure in rats and rabbits in guideline studies.

Rats

Administration of inpyrfluxam via oral gavage to rats at doses of 0, 10, 25 or 80 mg/kg bw/day caused developmental toxicity (decreased foetal weight) and maternal toxicity (reduced body weights, body weight gains and food consumption) at the top dose of 80 mg/kg bw/day. On this basis, a NOAEL of 25 mg/kg bw/day was identified for both maternal and developmental toxicity. It is most likely that the foetal effects are the secondary unspecific consequence of maternal toxicity. An additional developmental toxicity study was performed in rats (using 40 dams) at the high dose of 90 mg/kg bw/day to investigate whether a single occurrence of cyclopia observed in the main study at 80 mg/kg bw/day was related to treatment with inpyrfluxam. There was no evidence of cyclopia, confirming that inpyrfluxam **does not** cause cyclopia.

It should be noted that although cyclopia in rats and optic nerve fibre degeneration in dogs are effects on the eye, they are completely unrelated.

Rabbits

Administration of inpyrfluxam via oral gavage to rabbits at doses of 0, 20, 60 or 200 mg/kg bw/day did not cause developmental toxicity. However, maternal toxicity (clinical signs of toxicity and reduced body weight gain and food consumption) was observed at the top dose of 200 mg/kg bw/day. On this basis the NOAEL for developmental toxicity is 200 mg/kg bw/day, the highest dose tested and the NOAEL for maternal toxicity is 60 mg/kg bw/day.

Overall conclusion

Overall, therefore, reproduction and developmental toxicity have been adequately investigated in studies in rats and rabbits. The substance does not affect fertility in rats and is not a specific developmental toxicant in rats or rabbits. The reproductive toxicity NOAEL from the two-generation study is 86 mg/kg bw/day. The lowest developmental toxicity NOAEL is 25 mg/kg bw/day from the rat developmental toxicity study.

In addition, the following conclusions can be drawn:

- No classification for reproductive toxicity is required (see aligned MCL report).
- The data requirements of assimilated Regulation 283/2013 have been met.

2.6.7. Summary of neurotoxicity

The neurotoxicity of inpyrfluxam was investigated via the oral (gavage or dietary) route of exposure. There were two acute neurotoxicity studies (a preliminary dose range finding and a definitive study) and a sub-chronic neurotoxicity study in rats. All the studies were conducted in compliance with GLP and OECD test guidelines. The main findings of these studies are summarised in table 6.1.6-1 below.

Table 2.6.7-1 Summary of available neurotoxicity studies

Data point/ Study <i>Acceptability</i>	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
KCA 5.7.1/02 <i>Acute Oral Neuro toxicity</i> - OECD TG 424 (1997) <i>Acceptable</i>	Rat/ Wistar Han- ver rats/ M&F	0, 30, 100, and 200 mg/kg bw	<u>Systemic toxicity</u> 30 mg/kg bw <u>Neurotox icity</u> 200 mg/kg bw	<u>Systemic toxicity</u> 200 mg/kg bw (highest tested dose) <u>Neurotoxic ity</u> -	<u>Systemic toxicity</u> ↓ motor activity ↓ body temperature <u>Neurotoxicity</u> None
KCA 5.7.1/03 <i>Oral Neuro toxicity- Repeat dose</i> - OECD TG 424 (1997)	Rat/ Wistar Han- ver rats/ M&F	<u>Males</u> 0, 500, 2000 and 4000 ppm (mean substance intakes: 30, 118.9 and 240 mg/kg bw/day) <u>Females</u> 0, 500, 1000, 2000 ppm (mean substance intakes: 0, 35.2, 68	<u>Systemic toxicity</u> 35.2 mg/kg bw/day <u>Neurotox icity</u>	<u>Systemic toxicity</u> 133 mg/kg bw/day (highest tested dose) <u>Neurotoxic ity</u>	<u>Systemic toxicity</u> ↓ Body weight ↓ Food consumption <u>Neurotoxicity</u> None

Acceptable		and 133 mg/kg bw/day)	133 mg/kg bw	-	
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In the acute neurotoxicity study in rats, systemic toxicity related decreases in body temperature and motor activity were noted from 100 mg/kg bw in both sexes. Therefore, a **NOAEL of 30 mg/kg bw** was established for **systemic toxicity**. Inpyrfluxam did not induce any neurotoxicity up to the highest tested dose of 200 mg/kg bw. Therefore, a **NOAEL of 200 mg/kg bw** was established for **neurotoxicity**.

In the 90-day repeat dose neurotoxicity study in rats, decreases in body weight and food consumption were observed from around 1000 ppm (68 mg/kg bw/day). Therefore, a **NOAEL of 500 ppm (35.2 mg/kg bw/day)** was established for **systemic toxicity**. Inpyrfluxam did not induce any neurotoxicity up to the highest tested dose of 2000 ppm (133 mg/kg bw/day). Therefore, A **NOAEL of 2000 ppm (133 mg/kg bw/day)** was established for **neurotoxicity**. Overall, inpyrfluxam is not neurotoxic.

Inpyrfluxam has neither a structural relationship to any chemical class that causes delayed neurotoxicity, nor did repeat-dose studies show any indications of delayed neurotoxicity. Therefore, a specific study for delayed neurotoxicity of inpyrfluxam is not required.

Additional information on the potential effects of inpyrfluxam on the nervous system from the short and long-term toxicity studies in rats that included neuro behavioural evaluation (FOB and motor activity) has been taken into account. There were no adverse effects on neurobehavioral parameters, brain weight or neuropathology in these studies.

However, In the 90-day repeat dose study in dogs, optic nerve fibre degeneration was noted at the top dose (700/500 mg/kg bw/day) in males and from the mid dose (160 mg/kg bw/day) in females (██████████ 2016; section B.6.3.2). However, significant systemic toxicity was noted at and above 160 mg/kg bw/day including vomiting, signs of anaemia, changes in clinical-chemistry parameters indicative of liver **damage changes**, increased liver weight and histopathological findings in the liver, gall bladder, kidney, thyroid and adrenal. The top dose of 700/500 mg/kg bw/day was highly toxic with additional signs of toxicity, such as mortality, clinical signs of toxicity, effects on body weight and food consumption, changes in urinalysis parameters and additional effects on other organs.

In the one-year repeat dose study in dogs, degeneration of the optic nerve was noted at 160 mg/kg bw/day in females (██████████ 2017; section B.6.3.3). However, significant systemic toxicity was noted at and above 30 mg/kg bw/day (vomiting, clinical chemistry parameters indicative of liver **damage changes**, increased liver weights, and histopathological findings of the liver) with the MTD being reached at 30 mg/kg bw/day already.

Overall, the increased incidence in optic nerve degeneration in dogs occurred above the MTD and therefore this effect does not represent specific neurotoxicity. although significant systemic toxicity occurred at the same doses at which the optic nerve fibre degeneration was observed, it is unclear whether the degeneration was specific or secondary. Therefore, in the absence of any further information, it was concluded that inpyrfluxam was neurotoxic in dogs at highly toxic doses (at and above 160 mg/kg bw/day).

2.6.8. Summary of further toxicological studies on the active substance

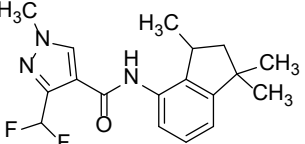
2.6.8.1. Summary of toxicological characterisation of plant and livestock metabolites for the purposes of the residue definition (RD) for risk assessment

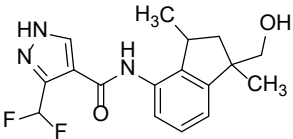
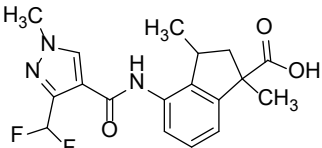
All of the plant and livestock metabolites of inpyrfluxam have been assigned the parent's dietary reference values, because either they are major rat metabolites covered by parent (1'-COOH-S-2840, N-des-Me-1'-COOH-S-2840, 1'-CH₂OH-S-2840 glucuronide and 1'-CH₂OH-S-2840), or are no more toxic than parent based on experimental data (1'-COOH-S-2840, 3'-OH-S-2840, DFPA, N-des-Me-DFPA and DFPA-CONH₂) or a comparative QSAR analysis and read-across approach (Gly-1'-CH₂OH-S-2840, 1',1'-bis-(CH₂OH)-S-2840, N-des-Me-S-2840, Glc-NDM-S-2399A and Glc-NDM-S-2399B).

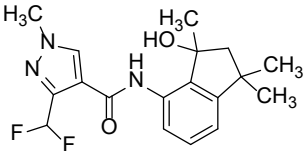
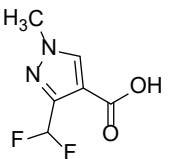
No toxicological information is available for a postulated low-level metabolite in wheat and barley grain processed products, dehydrate of 3'-OH-S-2840. Therefore, currently no toxicological reference values (TRVs) can be established for this metabolite.

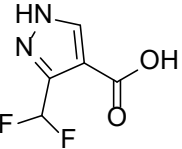
A summary table of the toxicological characterisation of the plant/livestock metabolites of inpyrfluxam is presented below.

Table 2.6.8.1-1: Summary table of the toxicological characterisation of plant/livestock metabolites of inpyrfluxam for the purposes of the RD for risk assessment

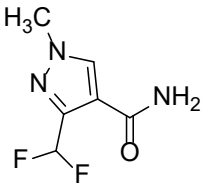
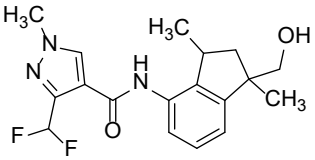
Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
<p>Parent</p> <p>Inpyrfluxam</p> <p>--</p> <p><chem>O=C(NC1=CC=CC2=C1C(CC2(C)C)C)C3=CN(C)N=C3C(F)F</chem></p>		Parent	<p>Non-genotoxic</p> <p><u>Full genotoxicity data package</u></p> <p>Ames test (negative)</p> <p>Mammalian cells gene mutation assay (negative)</p> <p>Chromosome aberration assay (negative)</p> <p><i>In vivo</i> micronucleus assay (negative)</p>	<p>Classification</p> <p>Acute tox Cat 3, H301: Toxic if swallowed</p> <p><u>Full data package</u></p> <p>No evidence of carcinogenicity, reproductive and developmental toxicity, or neurotoxicity.</p> <p>Repeat dose exposure resulted in liver changes in all test species with secondary thyroid findings in rats, mice and dogs; in adrenal gland changes in rats and dogs; and in ovary changes in rats.</p>	<p>ADI = 0.06 mg/kg/day</p> <p>ARfD = 0.3 mg/kg bw</p>

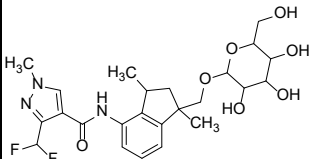
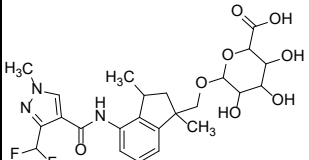
Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
N-des-Me-1'-CH₂OH-S-2840 -- <chem>O=C(NC1=CC=CC2=C1C(CC2(C)CO)C)C3=CN=C3C(F)F</chem>		Yes	Non-genotoxic Covered by parent (major rat metabolite)	Covered by parent (major rat metabolite)	Parent's TRVs
1'-COOH-S-2840 -- <chem>O=C(NC1=CC=CC2=C1C(CC2(C(O)=O)C)C)C3=CN(C)N=C3C(F)F</chem>		Yes (>10 % of the AD, urine, both sexes)	Non-genotoxic Covered by parent (major rat metabolite) + Negative adequate genotoxicity package	Covered by parent (major rat metabolite) ± <u>Data</u> Acute oral study: LD ₅₀ > 2000 mg/kg bw	Parent's TRVs

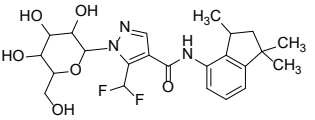
Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
3'-OH-S-2840 -- <chem>O=C(NC1=CC=CC2=C1C(C)(O)CC2(C)C)C3=CN(C)N=C3C(F)F</chem>		No	Non-genotoxic <u>Negative adequate genotoxicity package</u>	Not more toxic than parent <u>Data</u> Acute oral study: LD ₅₀ > 2000 mg/kg bw 90-day dietary toxicity study in rat: NOAEL = 500 ppm (37.9 mg/kg/day) based on histopathological findings in the liver and ovary	Parent's TRVs
DFPA -- <chem>O=C(O)C1=CN(C)N=C1C(F)F</chem>		No	Non-genotoxic <u>Negative genotoxicity package</u> Ames test (negative)	Not more toxic than parent <u>Data</u> Acute oral study: LD ₅₀ > 2000 mg/kg bw	Parent's TRVs

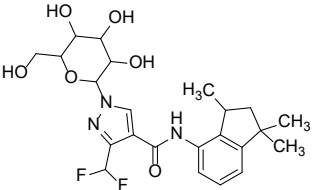
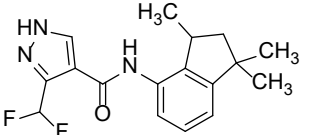
Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
			<p>Mammalian cells gene mutation assay (negative)</p> <p>Chromosome aberration assay (negative)</p> <p>+ negative QSAR prediction for in vivo micronucleus</p>	<p>90-day dietary toxicity study in rat: NOAEL = 1000 mg/kg bw/day (no effect at the highest dose)</p> <p>Pre-natal developmental toxicity in rabbit: NOAEL (maternal and developmental) = 250 mg/kg bw/day (highest dose; severe maternal toxicity at ≥ 500 mg/kg/day in range-finding study)</p>	
<p>N-des-Me-DFPA</p> <p>--</p> <p><chem>O=C(O)C1=CN=C(C(F)F)C1</chem></p>		No	<p>Non-genotoxic</p> <p><u>Negative genotoxicity package</u></p>	<p>Not more toxic than parent</p> <p><u>Data</u></p>	Parent's TRVs

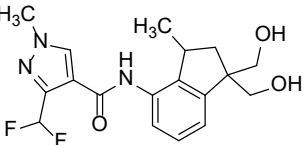
Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
			<p>Ames test (negative)</p> <p>Mammalian cells gene mutation assay (negative)</p> <p>Chromosome aberration assay (negative)</p> <p>+ negative QSAR prediction for in vivo micronucleus</p>	<p>Acute oral study: LD₅₀ > 2000 mg/kg bw</p> <p>28-day dietary toxicity study in rat: NOAEL = 1018 mg/kg bw/day (no effect at the limit dose)</p> <p>90-day dietary toxicity study in rat: NOAEL = 1000 mg/kg bw/day (no effect at the limit dose)</p> <p>Pre-natal developmental toxicity in rabbit: NOAEL (maternal) = 300 mg/kg bw/day (reduction of body weight gain and food consumption)</p> <p>NOAEL (developmental) =</p>	

Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
				1000 mg/kg bw/day (no effect at the limit dose)	
DFPA-CONH₂ -- <chem>O=C(N)C1=CN(C)N=C1C(F)F</chem>		No	Non-genotoxic <u>Negative adequate genotoxicity package</u> Ames test (negative) Mammalian cells gene mutation assay (negative) Chromosome aberration assay (positive) <i>In vivo</i> micronucleus assay (negative)	Not more toxic than parent <u>Data</u> Acute oral study: LD ₅₀ > 500 and < 2000 mg/kg bw 28-day dietary toxicity study in rat: NOAEL = 37.4 mg/kg bw/day (based on lower body weight, body weight gain and food consumption)	Parent's TRVs
1'-CH₂OH-S-2840 -- <chem>O=C(NC1=CC=CC2=C1C(CC2(C)CO)C)C3=CN(C)N=C3C(F)F</chem>		Yes (its direct downstream glucuronide conjugate, Glu-1'-CH ₂ OH-S-	Non-genotoxic Covered by parent	Covered by parent (major rat metabolite)	Parent's TRVs

Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
		2840 is a major rat metabolite)	(major rat metabolite)		
Gly-1'-CH₂OH-S-2840 (sugar conjugate of 1'-CH₂OH-S-2840 -- <chem>O=C(NC1=CC=CC2=C1C(CC2(C)COC(C(C(O)C3O)O)OC3CO)C)C4=CN(N=C4C(F)F)C</chem>		No	Non-genotoxic As the sugar conjugate of 1'-CH ₂ OH-S-2840, a predicted major rat metabolite, covered by parent – the sugar will be cleaved in the GI tract releasing the predicted major rat metabolite	Covered by parent As the sugar conjugate of 1'-CH ₂ OH-S-2840, a predicted major rat metabolite, covered by parent – the sugar will be cleaved in the GI tract releasing the predicted major rat metabolite	Parent's TRVs
Glu-1'-CH₂OH-S-2840 (Glucuronide of 1'-CH₂OH-S-2840) -- <chem>O=C(NC1=CC=CC2=C1C(CC2(C)COC(C(C(O)C3O)O)OC3CO)C)C4=CN(N=C4C(F)F)C</chem>		Yes (>10% of the AD, urine + bile)	Non-genotoxic Covered by parent (major rat metabolite)	Covered by parent (major rat metabolite)	Parent's TRVs

Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
<chem>C(O)=O)C)C4=CN(N=C4C(F)F)C</chem>					
Glc-NDM-S-2399B -- <chem>O=C(NC1=CC=CC2=C1C(CC2(C)C)C)C3=C(N(N=C3)C4C(C(O)C(O)C(CO)O4)O)C(F)F</chem>		No	Non-genotoxic Aas the conjugated form of the metabolite <i>N</i> -des-Me-S-2840, the toxicity profile of this metabolite is expected to be comparable / less severe compared to its aglycon form <i>N</i> -des-Me-S-2840; no concern for genotoxicity was identified in the comparative QSAR analysis of <i>N</i> -des-Me-S-2840 compared to inpyrfluxam	Not more toxic than parent Aas the conjugated form of the metabolite <i>N</i> -des-Me-S-2840, the toxicity profile of this metabolite is expected to be comparable / less severe compared to its aglycon form <i>N</i> -des-Me-S-2840; no additional relevant alert for general toxicity was identified in the comparative QSAR analysis of <i>N</i> -des-Me-S-2840 compared to inpyrfluxam	Parent's TRVs

Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
Glc-NDM-S-2399A -- <chem>O=C(NC1=CC=CC2=C1C(CC2(C)C)C)C3=CN(N=C3C(F)F)C4OC(CO)C(O)C(O)C4O</chem>		No	Non-genotoxic As the conjugated form of the metabolite <i>N</i> -des-Me-S-2840, the toxicity profile of this metabolite is expected to be comparable / less severe compared to its aglycon form <i>N</i> -des-Me-S-2840; no concern for genotoxicity was identified in the comparative QSAR analysis of <i>N</i> -des-Me-S-2840 compared to inpyrfluxam	Not more toxic than parent As the conjugated form of the metabolite <i>N</i> -des-Me-S-2840, the toxicity profile of this metabolite is expected to be comparable / less severe compared to its aglycon form <i>N</i> -des-Me-S-2840; no additional relevant alert for general toxicity was identified in the comparative QSAR analysis of <i>N</i> -des-Me-S-2840 compared to inpyrfluxam	Parent's TRVs
<i>N</i>-des-Me-S-2840 -- <chem>O=C(NC1=CC=CC2=C1C(CC2(C)C)C)C3=CN=C3C(F)F</chem>		No	Non-genotoxic No concern for genotoxicity was identified in the comparative QSAR	Not more toxic than parent No additional relevant alert for general toxicity was identified in the	Parent's TRVs

Name, code, and smiles	Structure	Major rat metabolite (%)?	Genotoxicity conclusion and basis	General toxicity conclusion and basis	Reference values for dietary risk assessment
			analysis compared to inpyrfluxam	comparative QSAR analysis compared to inpyrfluxam	
1',1'-bis-(CH₂OH)-S-2840 -- <chem>O=C(NC1=CC=CC2=C1C(CC2(CO)CO)C3=CN(C)N=C3C(F)F</chem>		No	Non-genotoxic No concern for genotoxicity was identified in the comparative QSAR analysis compared to the predicted major rat metabolite 1'-CH ₂ OH-S-2840	Not more toxic than parent No additional relevant alert for general toxicity was identified in the comparative QSAR analysis compared to the predicted major rat metabolite 1'-CH ₂ OH-S-2840	Parent's TRVs

2.6.8.2. Summary of endocrine disruption

The endocrine disruption (ED) potential of inpyrfluxam has been assessed according to the ECHA/EFSA guidance for the identification of endocrine disruptors in the context of Regulations (EU) 528/2012 and (EC) No 1107/2009 (EFSA Journal 2018;16(6):5311) and it considers the EATS (Estrogen, Androgen, Thyroid, Steroidogenesis) modalities.

EAS modalities

EAS-mediated adversity has been sufficiently investigated, based on the available repeated dose toxicity studies and in particular a modern 2-generation study.

In all species investigated (rat, mouse, dog) there were no specific adverse effects on reproductive organs and other endocrine organs related to the EAS modalities following repeated exposure to inpyrfluxam. In addition, there were no specific adverse effects on reproduction in the rat and on development in the rat and rabbit. Overall, there was no clear and specific pattern of adversity for the EAS modalities. In addition, there was no evidence of EAS activity in a steroidogenesis assay and in a hER α or hAR transactivation test. In conclusion, inpyrfluxam does not meet the ED criteria for the EAS modalities in relation to human health and these modalities have been sufficiently investigated.

T modality

T-mediated adversity (thyroid weight and histopathology) has been sufficiently investigated in short-term and long-term toxicity studies and reproductive toxicity studies.

In all species investigated (rat, mouse, dog), adverse effects (weight increase and follicular cell hypertrophy) were observed in the thyroid. However, these occurred at or above the MTD/limit dose and therefore they do not raise concerns regarding endocrine disruption. In addition, whilst such effects occurred in the short-term studies, they were not replicated in the long-term studies up to doses causing significant toxicity. Overall, therefore, inpyrfluxam does not present a clear and specific pattern of adversity for the T modality. In addition, mechanistic information suggests that the thyroid effects might be secondary to liver effects (UGT induction) and that inpyrfluxam does not have any effect on hTR α - mediated transactivation and TPO activity. In conclusion, inpyrfluxam does not meet the ED criteria for the T modality in relation to human health and this modality have been sufficiently investigated.

2.6.8.3. Summary of immunotoxicity

No specific immunotoxicity studies conducted with inpyrfluxam are available. However, an assessment of the immunotoxicity potential of inpyrfluxam has been performed by considering the available repeated dose toxicity, carcinogenicity and reproductive toxicity studies. These standard regulatory studies have assessed its potential impact on several immune-related endpoints, including haematological parameters such as total and differential white blood cell counts, spleen and thymus weights, and histopathology of the

spleen, thymus, lymph nodes and bone marrow. Overall, the investigations on all immune-related endpoints in repeated dose studies (in the rat, mouse, dog and rabbit) and generational studies (in rats) did not find evidence of any consistent immune-specific effects caused by inpyrfluxam. Therefore, it can be concluded that inpyrfluxam does not show immunotoxic potential.

2.6.9. Summary of medical data and information


According to the statement from the manufacturer, Sumitomo Chemical Co., Ltd. inpyrfluxam has not been commercially manufactured or marketed. It has only been synthesized in the laboratory and/or at a pilot plant at the facility of Sumitomo Chemical Co. Ltd for research and development purposes.

Health checks are routinely conducted on staff involved in the synthesis or research and development of inpyrfluxam. Sumitomo has confirmed that no inpyrfluxam-related health issues have been identified by or reported to medical personnel.

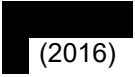
2.6.10. Overview of studies and points of departure relevant to reference value derivation

Table 2.6.10-1 gives an overview of all the available studies relevant to reference value setting.




Table 2.6.10-1: Overview of all the available studies relevant to reference value setting


Data point/ Study <i>Acceptability</i>	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
90-Day, dietary OECD TG 408 (1998)  (2016) <i>Acceptable</i>	Rat/ Wistar Hanover/ M&F	0, 150, 500, 2000, or 4000 ppm <u>Mean substance intakes</u> Males: 0, 9.72, 31.7, 123 and 255 mg/kg bw/day	500 ppm 31.7 mg/kg bw/day	2000 ppm 123 mg/kg bw/day	↓ bw (10%** in F) ↓ bw gain (21%** in F) ↓ food consumption (17%** in F) ↑ γ-glutamyl transpeptidase (114%** in M and 238%** in F), Alkaline phosphatase (34%** in F)

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
		Females: and 11.5, 37.5, 144 and 292 mg/kg bw/day			<p>↑ relative liver weight (11%** in M & 19%** in F)</p> <p><i>Histopathological findings</i></p> <p>Liver: ↑ diffuse hepatocellular hypertrophy (4/10** in M & 7/10** in F)</p> <p>Kidney: ↑ tubular hyaline droplets in 2/10 in M - not relevant to humans</p> <p>Thyroid: ↑ follicular cell hypertrophy (4/10 in F)</p> <p>Adrenal gland: ↑ cortical cell vacuolation (3/10 in F)</p> <p>Ovary: ↑ vacuolation of the interstitial gland (7/10* in F)</p>
<p>90-Day, dietary</p> <p>OECD TG 408 (1998)</p> <p>█ (2016a)</p>	<p>Mice/█ █ / M&F</p>	<p>0, 200, 800, 3500, or 7000 ppm</p> <p><u>Mean substance intakes</u></p> <p>Males: 0, 27.2, 111, 491, 973 mg/kg bw/day</p>	<p>800 ppm</p> <p>111 mg/kg bw/day</p>	<p>3500 ppm</p> <p>491 mg/kg bw/day</p>	<p>↑ globulin (10%* in M & 10% in F)</p> <p>↓ albumin (8%** in F), albumin/globulin ratio (9% in M & 15%** in F)</p> <p>↑ relative liver weight (18%** in M & 11%** in F), absolute liver weight (16%** in M & 7% in F)</p>

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
<i>Acceptable</i>		Females: and 0, 31.7, 130, 559 and 1097 mg/kg bw/day			<i>Histopathological findings</i> Liver: ↑ diffuse hepatocellular hypertrophy (4/10 in F), Centrilobular hepatocyte hypertrophy (8/10** in M), Centrilobular hepatocyte fatty change (3/10 in M)
90-Day, gelatin capsule OECD TG 409 (1998)  (2016) <i>Acceptable</i>	Dogs/ Beagle / M&F	0, 40, 160 or 700/500 mg/kg bw/day (Due to severe toxicity at 700 mg/kg bw/day at week 2, the animals were not treated at week 3. At week 4 (week 1 for this group), the high dose was reduced to 500 mg/kg bw/day)	40 mg/kg bw/day	160 mg/kg bw/day	↓ reticulocyte count (25%) in M&F, albumin (21%** in M & F), globulin (19%* in M) albumin/globulin ratio (13% in M & 20%** in F) ↑ alkaline phosphatase (ALP) (261%** in M& 247%** in F) and γ-glutamyl transpeptidase (GGTP) (87%** in M& 90%** in F) and in alanine aminotransferase (ALT) (103% in M & 51% in M), total cholesterol (31% in M & 16% in F) Enlarged liver in M (3/4) & F (2/4), biliary

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
					<p>sludge in gall bladder (1/4 in M)</p> <p>↑ relative liver weight (49%** in M & 38%** in F), absolute liver weight (53%** in M and 41%** in F)</p> <p><i>Histopathological findings</i></p> <p>Liver: ↑ diffuse hepatocellular hypertrophy (3/4 in M and 4/4**in F), cytoplasmic eosinophilic inclusion bodies (/4 in F), Brown pigment deposition in the Kupffer cells (1/4 in M)</p> <p>Gall bladder: calculi (1/4 in M)</p> <p>Kidney: hypertrophy (3/4 in M) and cytoplasmic eosinophilic inclusion body (1/4 in M) in the proximal tubular cells</p> <p>Adrenal gland: zona fasciculata cell vacuolation (2/4 in M)</p> <p>Eye: optic nerve fibre degeneration (1/4 in F)</p>

Data point/ Study <i>Acceptability</i>	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
One-year, dietary (gelatin capsule) OECD TG 452 (2009)  (2017) <i>Acceptable</i>	Dogs/ Beagle / M&F	0, 2, 6, 30 or 160 mg/kg bw/day	6 mg/kg bw/day	30 mg/kg bw/day	↑ ALP (by >60%) and GGTP (by >50%) in M ↓ Albumin/globulin ratio (44%) in M ↑ absolute (32%*) and relative (24%*) liver weights in M <i>Histopathological findings</i> Liver: ↑ diffuse hepatocellular hypertrophy (1/4 in M), Adrenal gland: zona fasciculata cell vacuolation (2/4 in M & 1/4 in F) Eye: optic nerve fibre degeneration (1/4 in F)
28-day, dermal OECD TG 410 (1981)  (2015) <i>Acceptable</i>	Rats/ Sprague Dawley  / M&F	0, 100, 300 or 1000 mg/kg bw/day	1000 mg/kg bw/day	Not established	No adverse effects

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
Combined Chronic Toxicity and Carcinogen icity OECD 453 (2009)  (2017) Acceptable	Rat/ Wistar Han- no- ver rats/ M&F	<p>Males: 0, 150, 500, and 2000 ppm</p> <p>Females: 0, 150, 500, and 1000/1500 ppm</p> <p><u>Mean substance intakes</u></p> <p>Males (chronic toxicity phase): 0, 6.77, 22.8 and 95.9 mg/kg bw/day</p> <p>(carcinogenicity phase): 0, 5.85, 19.4 and 78.4 mg/kg bw/day</p> <p>Females: (chronic toxicity phase): 0, 8.84, 30.1 and 86.4 mg/kg bw/day</p> <p>(carcinogenicity phase): 0, 7.47, 25.5, and 65.8 mg/kg bw/day</p>	<p><u>Chronic toxicity:</u> 500 ppm (19.4 mg/kg bw/day)</p> <p><u>Carcinogenicity:</u> 1500/1000 ppm (65.8 mg/kg bw/day) - top dose</p>	<p><u>Chronic toxicity:</u> 1500/1000 ppm (65.8 mg/kg bw/day)</p> <p><u>Carcinogenicity:</u> N/A</p>	<p><u>Systemic chronic toxicity</u></p> <p><u>Chronic toxicity phase:</u></p> <p>↓ bw (6% in M & 14%** in F)</p> <p>↓ bw gain (8%* in M & 37%** in F)</p> <p>↓ food consumption (M&F)</p> <p>↓ neutrophil (41% in F), monocyte (40% in F)</p> <p>↑ γ-glutamyl transpeptidase (157%* in M and 125%* in F at week 14), ↑ albumin/globulin ratio (16%** in F at week 14 and 26)</p> <p>↓ globulin (13% in F at week 26)</p> <p>↑ relative liver weight (11%** in M)</p> <p><u>Carcinogenicity phase:</u></p> <p>↓ bw (19%** in M & 13%** in F)</p> <p>↓ bw gain (18%** in M & 27%** in F)</p>

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
					<p>↓ food consumption (M&F)</p> <p>↓ neutrophil (20% in M & 35% in F), monocytes (19% in M and 28% in F), white blood cell count (23% in F)</p> <p><u>Carcinogenicity</u></p> <p>Inpyrfluxam is not carcinogenic in rats</p>
<p>Carcinogenicity,</p> <p>OECD 451 (2009)</p> <p>(2017)</p> <p>Acceptable</p>	<p>Mice</p> <p>/</p> <p>M&F</p>	<p>0, 700, 2000 and 7000/5000 ppm</p> <p><u>Mean substance intakes</u></p> <p>Males (satellite group): 0, 77.1, 240 and 826 mg/kg bw/day</p> <p>(carcinogenicity group): 0, 77, 224, and 775 mg/kg bw/day</p> <p>Females: (chronic toxicity phase): 0,</p>	<p><u>Chronic toxicity:</u> 700 ppm (69.3 mg/kg bw/day)</p> <p><u>Carcinogenicity:</u> 7000/5000 ppm (701 mg/kg bw/day) - top dose</p>	<p><u>Chronic toxicity:</u> 2000 ppm (210 mg/kg bw/day)</p> <p><u>Carcinogenicity:</u> N/A</p>	<p><u>Systemic chronic toxicity</u></p> <p><u>Satellite group:</u></p> <p>↓ bw (6% in M & 20%** in F)</p> <p>↓ bw gain (23% in M & 35%** in F)</p> <p>coarse surface of the kidney in F</p> <p>centrilobular hepatocellular hypertrophy, diffuse luminal dilatation of proximal renal tubules in M</p> <p><u>Carcinogenicity group:</u></p>

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
		72.9, 222, and 790 mg/kg bw/day (carcinogenicity phase): 0, 69.3, 210, and 701 mg/kg bw/day			↓ bw (13%** in M & 11%** in F) ↓ bw gain (37%** in M & 24%** in F) centrilobular hepatocellular hypertrophy in M amyloid nephropathy in M&F amyloidosis in cervical lymph nodes, glandular stomach in F <u>Carcinogenicity</u> Inpyrfluxam is not carcinogenic in mice
Two- generation, dietary OECD 416 (2001) ██████ (2017) <i>Acceptable</i>	Rat/ Wistar Han- over rats/M & F	Males: 0, 150,500, and 2000 ppm Females: 0, 150,500, and 1250 ppm <u>Mean substance intakes</u> Males: 0, 8.34, 27.8 or 113 mg/kg bw/day	<u>Reproduc tive toxicity</u> 1250/200 0 ppm (86 mg/kg bw/day) <u>Parental and offspring toxicity</u>	<u>Reproducti ve toxicity</u> N/A <u>Parental and offspring toxicity</u>	<u>Reproductive toxicity</u> No adverse effects up to the top dose <u>Parental toxicity</u> <u>F0</u> ↓ bw in M & F ↓ bw gain in M & F

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
		Females: 0, 10.9, 35.5 or 86 mg/kg bw/day	500 ppm (27.8 mg/kg bw/day)	1250/2000 ppm (86 mg/kg bw/day)	<p>↓ food consumption in M & F</p> <p>↑ absolute and relative liver weights in F</p> <p>↓ absolute and relative thyroid weight in F</p> <p>↑ Thyroid follicular hypertrophy in F</p> <p><u>F1</u></p> <p>↓ bw in M & F</p> <p>↓ bw gain in M & F</p> <p>↓ food consumption in F</p> <p>↑ absolute and relative liver weights in F</p> <p>↓ absolute and relative thyroid weight in F</p> <p>↑ Thyroid follicular hypertrophy in F</p> <p><u>Offspring toxicity</u></p> <p>↓ bw in M & F</p>

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
Prenatal development, gavage OECD 414 (2001) [REDACTED] (2017a) <i>Acceptable</i>	Rat/ Wistar Hanover rats/F	0, 10, 25 or 80 mg/kg bw/day	<u>Maternal toxicity</u> 25 mg/kg bw/day <u>Developmental toxicity</u> 25 mg/kg bw/day	<u>Maternal toxicity</u> 80 mg/kg bw/day <u>Developmental toxicity</u> 80 mg/kg bw/day	<u>Maternal toxicity</u> ↓ bw and bw gain ↓ food consumption <u>Developmental toxicity</u> ↓ foetal weight Cyclopia (n=1)
Prenatal development, gavage OECD 414 (2001) [REDACTED] (2017c) <i>Acceptable</i>	Rabbit/ Japanese White /F	0, 20, 60, or 200 mg/kg bw/day	<u>Maternal toxicity</u> 60 mg/kg bw/day <u>Developmental toxicity</u> 200 mg/kg bw/day	<u>Maternal toxicity</u> 200 mg/kg bw/day <u>Developmental toxicity</u> N/A	<u>Maternal toxicity</u> Clinical signs of toxicity (red discharge in the tray and abortions) ↓ bw gain ↓ food consumption <u>Developmental toxicity</u> None

Data point/ Study Acceptability	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
<p>Acute neurotoxicity, gavage</p> <p>OECD TG 424 (1997)</p> <p>██████████ (2016b)</p> <p>Acceptable</p>	<p>Rat/ Wistar Han over rats/ M&F</p>	<p>0, 30, 100, and 200 mg/kg bw</p>	<p><u>Acute systemic toxicity</u></p> <p>30 mg/kg bw</p> <p><u>Neurotoxicity</u></p> <p>200 mg/kg bw</p>	<p><u>Acute systemic toxicity</u></p> <p>200 mg/kg bw (highest tested dose)</p> <p><u>Neurotoxicity</u> ✓ -</p>	<p><u>Acute systemic toxicity</u></p> <p>↓ motor activity ↓ body temperature</p> <p><u>Neurotoxicity</u></p> <p>None</p>
<p>Repeat dose neurotoxicity, dietary</p> <p>OECD TG 424 (1997)</p> <p>██████████ (2016)</p>	<p>Rat/ Wistar Han over rats/ M&F</p>	<p><u>Males</u></p> <p>0, 500, 2000 and 4000 ppm (mean substance intakes: 30, 118.9 and 240 mg/kg bw/day)</p> <p><u>Females</u></p> <p>0, 500, 1000, 2000 ppm (mean substance intakes: 0, 35.2, 68 and 133 mg/kg bw/day)</p>	<p><u>Systemic toxicity</u></p> <p>35.2 mg/kg bw/day</p>	<p><u>Systemic toxicity</u></p> <p>133 mg/kg bw/day (highest tested dose)</p> <p><u>Neurotoxicity</u> ✓ -</p>	<p><u>Systemic toxicity</u></p> <p>↓ Body weight ↓ Food consumption</p> <p><u>Neurotoxicity</u></p> <p>None</p>

Data point/ Study	Species / Strain/ sex	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Adverse effects at LOAEL
Acceptability			<u>Neurotoxicity</u> 133 mg/kg bw		

2.6.11. Toxicological end point for assessment of risk following long-term dietary exposure – ADI

The most suitable studies for the derivation of the ADI (Acceptable Daily Intake) are chronic studies or the study providing the lowest point of departure (PoD).

The lowest NOAEL from the totality of the dataset is 6 mg/kg bw/day identified from the one-year toxicity study in dogs (██████████ 2017), with a LOAEL of 30 mg/kg bw/day for increased incidence and frequency of vomiting, changes in clinical chemistry indicative of liver damage changes (ALP by >60%, GGTP by >50%), increased liver weights (>10%) (>15%), and histopathological findings of the liver (diffuse hepatocyte hypertrophy) and adrenal gland (zona fasciculata cell vacuolation). These effects seen in the dogs are considered relevant to humans.

By applying a standard assessment factor of 100 (there is no evidence to suggest that deviation from this default is necessary), an **ADI of 0.06 mg/kg bw/day** is derived.

2.6.12. Toxicological end point assessment of the risk following acute dietary exposure – ArfD (acute reference dose)

An Acute Reference Dose (ARfD) is usually derived from acute and short-term toxicity studies.

Inpyrfluxam is acutely toxic via the oral route and is classified for Acute Tox. 3 (H301). Therefore, setting of an ARfD is required.

In the rat acute neurotoxicity study (██████████ 2016b), a NOAEL of 30 mg/kg bw was identified for systemic effects (reduced motor activity and body temperature) at the LOAEL of 200 mg/kg bw. This 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 deviation from this default is necessary), an **ARfD of 0.3 mg/kg bw** is derived.

2.6.13. Toxicological end point for assessment of occupational, bystander and residents risks – AOEL

The systemic AOEL (Acceptable Operator Exposure Level) is usually derived from medium-term studies.

For inpyrfluxam, the lowest NOAEL from such studies is 6 mg/kg bw/day identified from the 1-year dog study (██████████ 2017), with a LOAEL of 30 mg/kg bw/day for increased incidence and frequency of vomiting, changes in clinical chemistry indicative of liver damage changes (ALP by >60%, GGTP by >50%), increased liver weights (>10%) (>15%), and histopathological findings of the liver (diffuse hepatocyte hypertrophy) and adrenal gland (zona fasciculata cell vacuolation).

Since the AOEL is an internal (systemic) dose, it should be adjusted according to the extent of systemic bioavailability. An oral absorption value of 100% and a post-hepatic systemic bioavailability value of 60% (Section 2.6.1) have been established for inpyrfluxam. Since the adverse effects at the LOAEL in the 1-year dog study were not just specific liver effects, the NOAEL should be adjusted to account for the post-hepatic systemic bioavailability. By applying the post-hepatic systemic bioavailability value of 60% and a standard assessment factor of 100 (there is no evidence to suggest that deviation from this default is necessary), an **AOEL of 0.04 mg/kg bw/day** (rounded value of $(6/100) \times 60\%$) is derived.

2.6.14. Toxicological end point for the assessment of occupational, bystander and residents risk – AAOEL

The ARfD was based on a NOAEL of 30 mg/kg bw for systemic effects (reduced motor activity and body temperature) at the LOAEL of 200 mg/kg bw from the acute neurotoxicity study in the rat (██████████ 2016b). The effects driving this NOAEL may be partly due to the method of administration (gavage) of inpyrfluxam during the study. However, the effects cannot be excluded as being solely related to the method of administration and therefore are considered appropriate for the derivation of the AAOEL (Acute Acceptable Operator Exposure Level). Therefore, the NOAEL of 30 mg/kg bw from the rat acute neurotoxicity study is a suitable starting point for derivation of the AAOEL.

An oral absorption value of 100% and a post hepatic systemic bioavailability value of 60% (Section 2.6.1) have been established for inpyrfluxam. In this case it is considered appropriate to adjust the NOAEL based on the post-hepatic systemic bioavailability value of 60% as the adverse effects observed at the LOAEL were due to systemic toxicity and not a specific liver effect. By adjusting the NOAEL using the post-hepatic systemic bioavailability and by applying a standard assessment factor of 100 (there is no evidence to suggest that deviation from this default is necessary) an **AAOEL of 0.2 mg/kg bw** (rounded value of $(30/100) \times 60\%$) is derived.

2.6.15. Summary of the product exposure and risk assessment

Estimates of operator, worker, bystander and resident exposure have been conducted in line with the 2014 EFSA exposure guidance¹ and the respective calculator (hereafter referred to as the EFSA Calculator).

At the time of the active substance evaluation, the 2022 EFSA exposure guidance² and corresponding online model (hereafter referred to as the online EFSA OPEX Model) have since been implemented in GB. Therefore, to ensure consistency in future product assessments and authorisations, estimates of operator, worker, bystander and resident exposure have also been conducted in line with the 2022 EFSA exposure guidance.

The two versions of the EFSA exposure guidance use different terminology for the non-dietary exposure assessment. Both versions of the guidance require an acute exposure assessment for substances that have the potential to induce an adverse health effect after a single exposure event (on one day). The estimates of acute exposure are then compared to the acute acceptable operator exposure level (AAOEL). An exposure assessment is also required where adverse effects may be caused by longer periods of contact, ranging from weeks to months. The 2014 EFSA exposure guidance refers to this as 'longer term' exposure, whilst the 2022 EFSA exposure guidance refers to this as 'short term exposure'. These estimates are then compared to the acceptable operator exposure level (AOEL). For consistency, the 2022 EFSA guidance terminology ('short term exposure') has been used throughout for the non-dietary exposure assessment of inpyrfluxam.

Operator Exposure

Estimates of operator exposure according to the EFSA 2014 and the EFSA 2022 exposure guidance predict that the proposed uses of 'S-2399 60 g/L EC' on cereals will result in acceptable short term and acute systemic exposure to inpyrfluxam for operators without PPE.

The estimated short term exposure for application via vehicle mounted boom sprayer according to the EFSA Calculator (version 30 March 2015) is calculated to be equivalent to 64% of the AOEL of inpyrfluxam and according to the EFSA OPEX Model (version 1.1.2) is calculated to be equivalent to 85.7% of AOEL of inpyrfluxam.

The estimated acute exposure for application via vehicle mounted boom sprayer according to the EFSA Calculator (Version: 30th March 2015) is calculated to be equivalent to 55.5%

¹ European Food Safety Authority (2014). 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.

² European Food Safety Authority (2022). Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products, EFSA Journal 2022;20(1):7032.

of the AAOEL of inpyrfluxam and according to EFSA OPEX Model (version 1.1.2) is calculated to be equivalent to 72.2% of the AAOEL of inpyrfluxam.

There are no PPE requirements for operators based on the systemic exposure estimates from the EFSA Calculator and the EFSA OPEX Model. However, the product 'S-2399 60 g/L EC' is classified for human health effects. Based on the classification of the product the use of suitable protective clothing (coveralls), suitable protective gloves and face protection (faceshield) is required for operators when handling the concentrate.

Bystander and Resident Exposure

Resident exposure

Estimates of child and adult resident exposure according to the EFSA 2014 and the EFSA 2022 exposure guidance predict the proposed uses of 'S-2399 60 g/L EC' on cereal crops will result in acceptable short term systemic exposure to inpyrfluxam for all exposure pathways.

The estimated exposure according to the EFSA Calculator (version 30 March 2015) for the (mean) sum of all pathways is calculated to be equivalent to 18.3% of the AOEL of inpyrfluxam for a child resident, and 6% of the AOEL of inpyrfluxam for an adult resident.

The estimated exposure according to the EFSA OPEX Model (version 1.1.2) for the (mean) sum of all pathways is calculated to be equivalent to 15.6% of the AOEL of inpyrfluxam for a child resident, and 5.4% of the AOEL of inpyrfluxam for an adult resident.

The estimated short term exposure to residents is also considered to cover the short term exposure to bystanders.

Bystander exposure

Estimates of child and adult bystander exposure according to the EFSA 2014 and the EFSA 2022 exposure guidance predict that the proposed uses of 'S-2399 60 g/L EC' on cereal crops will result in acceptable acute systemic exposure to inpyrfluxam for the spray drift, vapour, surface deposits, and re-entry in treated crops pathways. The estimated acute exposure to bystanders is also considered to cover acute exposure to residents.

Worker Exposure

Estimates of worker exposure according to the EFSA 2014 and the EFSA 2022 exposure guidance predict that the proposed uses of 'S-2399 60 g/L EC' on cereal crops will result in acceptable short term systemic exposure to inpyrfluxam for workers undertaking inspection/irrigation activities wearing workwear (arms, body and legs covered). The estimated exposure according to the EFSA Calculator (version 30 March 2015) and also

the EFSA OPEX Model (version 1.1.2) is calculated to be equivalent to 6.3% of the AOEL of inpyrfluxam.

2.7. Residue

2.7.1. Summary of storage stability of residues

Plant matrices

As samples in the residue studies on primary crops (wheat and barley), rotational crops (carrot, lettuce, barley and wheat) and processed commodities (wheat and barley) were routinely stored frozen prior to their analysis, the effects of frozen storage on the residue levels have been investigated.

The studies conducted reflect homogenate plant materials that have been fortified with known amounts of the analytes to determine their levels over time in the process of storing the samples frozen over the long term.

The studies evaluated in Vol 3 are considered to demonstrate that the analytes are stable in matrices studied for the periods tested in the stability studies. There is no evidence to suggest that any marked instability has been observed.

Inpyrfluxam contains a chiral centre and therefore exists as both R- and S-isomers. The active substance is identified as the R-isomer. Some of the metabolites contain a chiral centre and are also present as R and S isomers, these are referred to as 'A' and 'B'. For the metabolites which are also isomers, the A and B isomers were fortified in the same samples in the study and are therefore listed together below.

The use of mixed spiking solutions is not recommended in OECD 506 as it can mask potential transformations from one compound to another. However, as there is very minimal degradation observed in the studies, this approach is considered acceptable.

The following analytes can be considered stable in all matrices tested for at least 22 months under frozen conditions ($\leq -18^{\circ}\text{C}$):

- Inpyrfluxam
- N-des-Me-DFPA
- DFPA
- 3'-OH-S-2840
- DFPA-CONH₂

- 1'-COOH-S-2840A & 1'-COOH-S-2840B
- 1'-CH₂OH-S-2840A & 1'-CH₂OH-S-2840B

The following analytes can be considered stable in all matrices tested for at least 12 months:

- *N*-des-Me-S-2840
- *N*-des-Me-1'-CH₂OH-S-2840-A & *N*-des-Me-1'-CH₂OH-S-2840-B

The storage stability studies are summarised in Table 2.7.1-1.

Table 2.7.1-1: Supported storage stability lengths of inpyrfluxam and its metabolites *N*-des-Me-S-2840, *N*-des-Me-1'-CH₂OH-S-2840-A, *N*-des-Me-1'-CH₂OH-S-2840-B, *N*-des-Me-DFPA, DFPA, 3'-OH-S-2840, DFPA-CONH₂, 1'-CH₂OH-S-2840A, 1'-CH₂OH-S-2840B, 1'-COOH-S-2840A and 1'-COOH-S-2840B in plant samples

Sample material		Frozen storage stability (months)
Commodity group	Crop matrix	
Analyte: Inpyrfluxam		
High water content	Cucumber	22
	Apples	16
High acid content	Grape	22
High oil content	Soyabean seed	22
Dry / High starch content	Wheat grain	22
	Potatoes	20
	Maize/corn Grain	20
Dry / High protein content	Field bean	22
Analytes: N-des-Me-S-2840, N-des-Me-1'-CH ₂ OH-S-2840-A & N-des-Me-1'-CH ₂ OH-S-2840-B		
High water content	Cucumber	12
High acid content	Grape	12

High oil content	Soyabean seed	12
High starch content	Wheat grain	12
High protein content	Field bean	12
Analytes: N-des-Me-DFPA & DFPA		
High water content	Cucumber	22
High acid content	Grape	22
High oil content	Soyabean seed	22
High starch content	Wheat grain	22
High protein content	Field bean	22
Analytes: 3'-OH-S-2840 & DFPA-CONH₂		
High water content	Cucumber	22
	Apples	16
	Maize/corn Forage	19
High acid content	Grape	22
High oil content	Soyabean seed	22
High starch content	Wheat grain	22
	Potatoes	20
	Maize/corn Grain	20
High protein content	Field bean	22
Analytes: 1'-CH₂OH-S-2840A & 1'-CH₂OH-S-2840B		
High water content	Cucumber	22
	Apples	16
	Maize/corn Forage	19

High acid content	Grape	22
High oil content	Soyabean seed	22
Dry / High starch content	Wheat grain	22
	Potatoes	20
	Maize/corn Grain	20
Dry / High protein content	Field bean	22
Analytes: 1'-COOH-S-2840A & 1'-COOH-S-2840B		
High water content	Cucumber	22
	Maize/corn Forage	19
High acid content	Grape	22
High oil content	Soyabean seed	22
High starch content	Wheat grain	22
	Potatoes	20
	Maize/corn Grain	20
High protein content	Field bean	22

In accordance with OECD 506, as there is no observed decline of residues in the raw agricultural commodities (RAC) from the five commodity categories above, freezer storage stability data for processed foods is not required. Therefore, stability of the analytes in processed commodities can be assumed for the periods tested for RACs in the stability studies i.e., for at least 22 months.

Some of the storage stability studies tested stability in various processed commodities (of potatoes, wheat, maize, soyabean, rice, peanuts and sugar beet); these studies demonstrated stability across the periods tested in the studies (between 2 and 19 months of frozen storage, see Vol 3. CA B7). These provide supporting evidence of stability of the tested analytes in processed commodities.

The longest periods of frozen storage of samples from plant residue studies (field residue, processing, or rotational crop trials) are shown in the table below.

Table 2.7.1-2: Supported storage stability lengths compared to residue data

Residue trials					Supporting storage stability data
Crop	Matrix	Analytes	Maximum storage period (days)	Reference	
Primary crop residues trials					
Wheat	High starch	Inpyrfluxam 3'-OH-S-2840 DFPA-CONH ₂	503 (16.5 months)	TPR-0076 TPR-0074	All 7 analytes considered to be stable in wheat grain for 22 months
Barley	High starch	N-des-Me-DFPA DFPA 1'-COOH-S-2840 ^(a) 1'-CH ₂ OH-S-2840 ^(a)	398 (13 months)	TPR-0071 TPR-0073	
Rotational crop field study					
Barley	High starch	Inpyrfluxam 3'-OH-S-2840	369 (12 months)	TPR-0080	All 8 analytes considered stable for at least 12 months across all crop matrices
Lettuce	High water	DFPA-CONH ₂			
Carrot	High starch	N-des-Me-S-2840 DFPA			
Wheat	High starch	1'-COOH-S-2840 ^(a) 1'-CH ₂ OH-S-2840 ^(a) N-des-Me-1'CH ₂ OH-S-2840 ^(b)			
Processed commodities					
Wheat processed commodities	High starch	Inpyrfluxam 3'-OH-S-2840	519 (17 months)	TPR-0081	All 7 analytes considered to be stable in the RAC wheat grain for 22

Barley processed commodities	High starch	DFPA-CONH ₂ <i>N</i> -des-Me-DFPA DFPA 1'-COOH-S-2840 ^(a) 1'-CH ₂ OH-S-2840 ^(a)	375 (12 months)	TPR-0082	months. The same can be concluded for stability in processed grain.
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(a) 1'-COOH-S-2840 A + 1'-COOH-S-2840 B; 1'-CH₂OH-S-2840 A + 1'-CH₂OH-S-2840 B

(b) *N*-des-Me-1'-CH₂OH-S-2840 A + *N*-des-Me-1'-CH₂OH-S-2840 B

Animal matrices

As samples in the animal feeding studies were stored frozen prior to their analysis, the effects of frozen storage on the residue levels have been investigated.

These studies on storage stability conducted reflect homogenate animal matrices that have been fortified with known amounts of the analytes to determine their levels over time. In the magnitude of residues studies (feeding studies, see section Vol 1 2.7.7 and Vol 3 B.7.4), the samples matched this as samples were frozen, homogenised with dry ice before shipping and then stored frozen prior to their extraction and analysis.

The studies evaluated in Vol 3. are considered to demonstrate that the analytes are stable in matrices studied for the periods tested in the stability studies. There is no evidence to suggest that any marked instability has been observed.

In poultry matrices, inpyrfluxam, 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1'-CH₂OH-S-2840A and 1'-CH₂OH-S-2840B have been demonstrated to be stable for at least 90 days in eggs, 40 days in muscle and liver and 49 days in fat under frozen conditions (<0°C).

In ruminant matrices, inpyrfluxam, 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1'-CH₂OH-S-2840A and 1'-CH₂OH-S-2840B have been demonstrated to be stable for at least 75 days in milk, 29 days in muscle, liver and kidney and 31 days in fat under frozen conditions (<0°C).

This accommodates the periods that the samples were stored in the supporting feeding studies (see Volume 3, Section 7.4).

Stability of extracts

Samples in the magnitude of residues (MOR) work were not always analysed very quickly after extraction of the samples. When stored prior to analysis they were typically kept between 1 and 10 °C:

- In the barley primary crop trials, the extracts were stored for a maximum of 33 days prior to analysis.
- In the wheat primary crop trials, the extracts were stored for a maximum of 14 days prior to analysis.
- Processing study (wheat and barley studies), extracts were analysed within 14 days (wheat) and 18 days (barley).
- In the rotational crops trials study, the extracts were stored for a maximum of 14 days (crops) and soil (relatively quickly, within 2 days)
- In the feeding studies, ruminant extracts were analysed within 22 days. Hen extracts were analysed quickly apart from eggs, analysed after 22 days of storage of the extracts.

The following indented text is noted from the evaluation in the methods of analysis (section B.5) where stability of extracts has been considered within the various method validation studies.

Regarding the method of analysis for inpyrfluxam and metabolites for crop samples S16-03371: It is concluded that stability of extracts stored between 1 and 10°C is confirmed for at least 15 days for inpyrfluxam, 3'-OH-S-2840, DFPA-CONH₂, *N*-des-Me-DFPA, DFPA, 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1'-CH₂OH-S-2840A, and 1'-CH₂OH-S-2840B in grapes, potato (tubers), wheat (whole plant), wheat (grain) and soybean (seeds).

Regarding the method of analysis for inpyrfluxam for soil samples S16-05522: Stability of inpyrfluxam was tested after storage in the dark at 1 – 10 °C for at least 8 days. The recoveries of the fortified samples were measured against freshly prepared standards. Stability in sample extracts was sufficiently demonstrated after storage in the dark at 1 – 10 °C for at least 8 days.

Within the assessment of the soil methods of analysis study it states "Inpyrfluxam and 3'-OH-S-2840 standards and stock solutions was demonstrated to be stable for 62 days in methanol when stored in the dark between 1 and 10 °C as the peak areas of the stored then diluted stock solutions were within ±20% of the peak areas of the freshly prepared standards.

1'-COOH-S-2840A and 1'-COOH-S-2840B standards and stock solutions was demonstrated to be stable for 46 days in methanol when stored in the dark between 1 and 10 °C as the peak areas of the stored then diluted stock solutions were within ±20% of the peak areas of the freshly prepared standards".

It has been concluded in B.5.1.2 that stability of residues in sample extracts (hen and bovine) has been satisfactorily addressed in the feeding study, as procedural recovery samples were extracted and stored for the same length of time as the test sample extracts. The recoveries were within the acceptable range of 70 – 120%.

The magnitude of the residues study reports propose that extract stability is not an issue where the extracts have been stored for long periods prior to analysis. The applicant considers that stability of residues in sample extracts has been satisfactorily addressed as the matrix-matched standards used for quantification were always prepared on the same day (using control untreated sample fortified with solvent standards) as the production of the sample extracts for residues analysis; these matrix matched standards were also stored at 1 to 10°C. The procedural recoveries were handled and stored in the same way and for the same time period as the sample extracts that were prepared within the same analytical set.

However, HSE notes that matrix matching, whilst a valuable approach in residues analysis, brings the compounds into close contact with the matrix in the matrix matched standards, that (in these studies) were also stored, rather than being freshly prepared on the day of analysis. HSE notes that to support all the magnitude of residues studies there is a body of evidence of procedural recoveries demonstrating typically very good performance of the methods of analysis.

Taken together, there is evidence from the above mentioned method validation studies (from section B.5), including stability of compounds in standards and stock solutions, procedural recoveries in the magnitude of residues studies, and re-analysis of extracts in metabolism studies showing no major changes. This suggests that the quantitative data generated in the overall residues assessment for magnitude of residues (parent and metabolites) in crops and livestock (and parent in soil in the rotational crops study) is valid.

2.7.2. Summary of metabolism, distribution and expression of residues in plants

Prior to the overview of the metabolism studies, HSE is providing some introductory text on isomers, storage stability of residues and location of plant metabolism studies, as this provides useful context.

Isomers – Parent (Inpyrfluxam)

In some of the primary crop plant metabolism studies, where detectable residues were analysed and residues of parent inpyrfluxam were extracted, these were analysed using chiral methodology to determine whether the residues were found as R-isomer (inpyrfluxam) or whether any S-isomer was found. These reports showed that only R-isomer was present (apple rinse, apple peels, apple pulp, rice forage and straw (in the granular study), rice foliage, straw, hulls and grain (in the rice foliar study) and in soya bean matrices (forage, hay, edamame pods, and mature pods)). In the radiolabelled

hydrolysis study (see section on the nature of the residues over processing. Vol. 3 CA B.7.5.1) the solutions at time 0 and termination of the study were analysed and shown not to contain any S-isomer. This potential for conversion from R-isomer (inpyrfluxam) to S-isomer was not assessed in the rotational crop metabolism samples (section Vol. 3 CA B.7.6.1). The evidence taken together indicates that R-isomer of inpyrfluxam is stable and does not convert to S-isomer, either in terms of high temperature hydrolysis conditions or during **plant** metabolism.

In animal metabolism samples (hen fat - hexane extracts and goat liver- hexane extracts) chiral methodology was used to confirm the stability of the R-isomer. Again, there was no marked conversion from the R-isomer. The hen fat extracts were mainly R-isomer (3-4% S-isomer). The goat liver extracts were 100% R-isomer.

Therefore, for consumer risk assessment purposes, no conversion factor needs to be applied to either products of plant or animal origin to account for the potential of isomer conversion of inpyrfluxam in plants or animals.

Isomers - Metabolites

In the metabolism studies (and nature of hydrolysis studies) some metabolites were specifically analysed as the 'A' and 'B' isomers of the various metabolites. Commonly whilst these were specifically determined as 'A' and 'B' they were often summed for the purpose of summary of residues results.

The applicant has explained that (N5 document) "For metabolites substituted on the 1-methyl groups of the indane (1'-CH₂OH-S-2840, 1'-COOH-S-2840), a second chiral centre was introduced, and this is expected to be racemic. Two diastereomer pairs could be separated on standard RP-HPLC columns, resulting in "A" and "B" compounds. These were summed together to ensure the total racemic mixture was quantified for risk assessment purposes".

As examples, please see section B.7.5.1 for pictorial depictions of the 4 isomers of 1'-CH₂OH-S-2840, comprising 1'-CH₂OH-S-2840A (an isomer pair) and 1'-CH₂OH-S-2840B (an isomer pair). Likewise for 1'-COOH-S-2840A and 1'-COOH-S-2840B.

Considering the prevalence of 'A' and 'B' forms for both 1'-COOH-S2480 and 1'-CH₂OH-S2480 there are variable results in the metabolism data, but both feature (in plants and animals). There is no evidence that there is just a shift in only one direction in terms of formation in the metabolism studies.

Additionally in the magnitude of residues trials on wheat and barley, the 'A' and the 'B' isomer pairs for 1'-COOH-S-2840 and 1'-COOH-S-2840 were reported separately (see section 2.7.4), and the amounts in wheat and barley grain and straw are similar across the 'A' and the 'B' forms.

Storage stability of residues in a metabolism context

Some of the metabolism studies were completed within a period of six months. OECD test guidelines on primary crop, rotational crop and livestock metabolism state that “Storage stability data are not normally necessary for samples analysed within 6 months of collection, provided evidence is given that attempts were made to limit degradation of residues by appropriate storage of matrices and extracts during the analytical portion of the study”.

All the residues metabolism studies describe appropriate care of samples and extracts such as samples being frozen within 24 hours, transfer to analytical laboratory on dry ice, and keeping samples and extracts frozen that are still to be worked on.

Some of the studies required a longer work up and analysis which meant the samples exceeded 6 months from collection/harvest to analysis therefore, these studies have included data to address storage stability in a metabolism context. For example, in the potato metabolism study there was re-extraction of samples after the storage period and comparative HPLC analysis, using the same analytical system, to compare the initially extracted and latterly extracted samples. Similar approaches were taken in other studies. In the foliar rice metabolism, stability of extracts (initial extracts re-analysed later in the study) as well as re-extraction of stored samples and re-analysis was reported. There were no marked changes in analytical profile.

In the rotational crop metabolism study, residues samples were stored for a minimum of 85 days (3 months) and maximum 418 days (13 months) before extraction. All sample extracts were then analysed within 18 days. 17 – 21 months after the initial extraction, representative freezer-stored crop samples (30 DAT mature lettuce, mature radish tops, mature radish roots, sorghum stover and sorghum grain from both phenyl and pyrazolyl labels) were re-extracted and re-analysed to determine the storage stability of the samples. The overall recoveries of total residue and metabolite compositions of 30 DAT samples analysed were approximately similar in both extractions (pre- and post-storage of the samples). These metabolite compositions in the rotational crops storage stability work are reported by way of comparative TLC plate pictures in the study reports showing the position and ‘strength’ of the metabolite spots. This storage stability work indicates that the major inpyrfluxam metabolites in the rotational crop samples were likely stable for the period between the initial extractions (for some sample extractions these ‘initial’ extractions were done a year after harvest) and later re-extraction of the samples. This provides some support for the argument that the sample analysis results in this study are relevant for the assessment of nature of rotational crop residues for consumer risk assessment, since the nature of the residues hasn’t markedly changed in a long period (17 to 21 months).

HSE notes that the non-radiolabelled residue storage stability studies (see section 2.7.1 for full details) have tested a broad range of analytes (parent and 11 key metabolites

(covering examples of 'A' and 'B' isomers for metabolites)). The supported stability of these residues in all commodity types for the periods tested included the initial one year period (noting above that some of the rotational crop samples were stored frozen for just over a year before extraction and initial characterisation of the residues). This non-radiolabelled stability work is a good set of residues stability data (parent plus 11 metabolites with no instability seen) to support the view that the samples in plant metabolism studies stored prior to extraction would not be expected to have residues that are degraded.

In animal metabolism studies, the hen metabolism study was completed within a year of sacrifice (11 months) and the ruminant study was completed within 15 months of sacrifice. Initial characterisation (analysis) of the all the tissue extracts was undertaken within 2 months (60 days for ruminants and 40 days for poultry). In the goat metabolism study, liver and kidney samples were re-extracted at the end of the study (431 days after the initial extraction) and compared to chromatographic profiles investigated at the time of initial extraction. In the hen metabolism study, hen liver extracts were reanalysed (chromatographic profiles of extracts were compared to extracts that had been stored in a freezer for at least 286 days). These chromatographic profile comparisons in the livestock metabolism studies show broad comparability and do not indicate concerns for stability of the residues. The ruminant and poultry feeding studies were also supported by non-radiolabelled study freezer storage stability of residues investigations, in line with the principles of OECD 506, and are reported in section 2.7.1. In these studies inpyrfluxam, 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1'-CH₂OH-S-2840A and 1'-CH₂OH-S-2840B were all shown to be stable during freezer storage in the livestock matrices samples tested (various times tested from 29 to 90 days).

These aspects to do with storage stability in a metabolism context, needed to validate a metabolism study, are reported in the Vol 3 B.7 evaluation of each of the metabolism studies.

Taking the information from both the storage stability of residues samples studies (section 2.7.1) where samples stored and assessed using studies in accordance with OECD 506 test guideline, and considering the data from across the metabolism studies, there is reassurance that the metabolism studies can be used to derive the all required knowledge on nature of the residues assessment of these studies, supporting the consumer risk assessment. There are no concerns regarding storage stability of residues in either the samples or the extracts that would impact the assessment of these studies for consumer risk assessment.

Extraction Efficiency

Extraction efficiency of incurred residues in food crops has been addressed in Vol. 1, section 2.5.1 and 2.5.2 and in section B.5.1.2 KCA 4.1.2/19 and KCA 4.1.2/20. Acceptable

conclusions were derived on the basis that the methods of analysis evaluation (in section B.5) concluded that solvents used in these studies are similar to the solvents used in the metabolism studies that were effective in releasing the residues of interest. These metabolism studies were used to derive the residue definition for dietary risk assessment (RD-RA) and residue definition for enforcement (RD-Enf).

Overview of metabolism studies

Metabolism in primary crops was investigated using pyrazole and phenyl labelled inpyrfluxam. Studies were performed on seven plant species: apple (fruit crop group), maize/corn, sorghum, rice (cereal crop group), soyabean, rapeseed/canola (pulses and oilseed crop group) and potato (root and tuber crop group). Radiolabelled inpyrfluxam was applied as a post emergence foliar spray to apple, soyabean and rice and applied as a seed treatment to potato, maize/corn, sorghum and rapeseed/canola. Radiolabelled inpyrfluxam was applied as a granular soil treatment for rice also. Considering the representative uses are cereals, the metabolism studies performed on rice (and soyabean, from the oilseeds and pulses crop group) are within $\pm 25\%$ compared to the cGAP in terms of application rate. A consistent pattern of metabolism was observed, and the metabolism studies are considered relevant to the consideration of the residue definition for the uses being assessed. A summary of the available primary crop metabolism studies is presented below in Table 2.7.2-1.

All plant metabolism studies (including rotational crops) were conducted outdoors in USA, California. It is noted that the conclusion of the fate and behaviour evaluation is that photodegradation is not expected to be a major degradation process in soil (Vol 3 CA B.8.1) for inpyrfluxam and direct aqueous photolysis of inpyrfluxam was considered to be negligible (List of Endpoints). Any differences in light levels for the metabolism studies conducted in USA, California compared to UK outdoor conditions are not expected to impact an understanding of nature of residues relevant to the current consumer risk assessment.

Table 2.7.2-1: Summary of plant metabolism studies

Group	Crop	Label	Application and sampling details			
			Method, F or G ^(a)	Application rate	BBCH growth stage at application	Sampling (DAT)
Fruits and fruiting vegetables	Apple	[phenyl-U- ¹⁴ C] & [pyrazolyl- ¹⁴ C]	Foliar spray, F	3 x ~220 g a.s./ha	77 – 79, 79 – 81 & 81 – 83	14

		4- ¹⁴ C] inpyrfluxam				
Cereals	Maize/ Corn	[phenyl-U- ¹⁴ C] & [pyrazolyl- 4- ¹⁴ C] inpyrfluxam	Seed treatment, F	~6.6 g a.s./100 kg seed	00	At maturity
	Sorghum	[phenyl-U- ¹⁴ C] & [pyrazolyl- 4- ¹⁴ C] inpyrfluxam	Seed treatment, F	~6.3 g a.s./100 kg seed	00	At maturity
	Rice	[phenyl-U- ¹⁴ C] & [pyrazolyl- 4- ¹⁴ C] inpyrfluxam	Foliar spray, F	1 x ~100 g a.s./ha	77	14 (immature plants) 28 (grain, straw, hulls)
			Soil application, F	1 x 391 or 357 g a.s./ha	13 – 14	30 (immature plants) 132 (grain, straw, hulls)
Pulses and oilseeds	Soyabean	[phenyl-U- ¹⁴ C] & [pyrazolyl- 4- ¹⁴ C] inpyrfluxam	Foliar spray, F	2 x ~110 g a.s./ha	60 & 75	53 & 89
	Rapeseed /Canola	[phenyl-U- ¹⁴ C] & [pyrazolyl- 4- ¹⁴ C] inpyrfluxam	Seed treatment, F	1 x ~5.0 g a.s./100 kg seed	00	at maturity
Root and tuber vegetable s	Potato	[phenyl-U- ¹⁴ C] & [pyrazolyl- 4- ¹⁴ C] inpyrfluxam	Seed treatment, F	1 x ~5.0 g a.s./100 kg seed	00	at maturity

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(a) Field or Glasshouse

The major identified component of the residue was parent inpyrfluxam for apple, soyabean and rice (foliar treated) for both radiolabels and for [phenyl-U-¹⁴C] treated potato. The metabolite 1'-COOH-S-2840 was the major identified component for [pyrazolyl-4-¹⁴C] treated potato. For rice treated with soil application, the major identified component varied between crop portions and radiolabel. No residues were detected in seed treated maize/corn, sorghum and rapeseed/canola.

Overall, 14 metabolites were identified and characterised:

- 3'-OH-S-2840
- 3'-OH-S-2840 conjugate
- 1'-CH₂OH-S-2840
- 1'-CH₂OH-S-2840 conjugate
- 1'-COOH-S-2840
- 1'-COOH-S-2840 conjugate
- DFPA
- DFAP conjugate
- *N*-des-Me-S-2840
- *N*-des-Me-DFPA
- *N*-des-Me-DFPA conjugate
- Glc-NDM-S-2399
- Gly-1'-CH₂OH-S-2840
- DFPA-CONH₂

Of these metabolites, 3'-OH-S-2840, *N*-des-Me-DFPA, 1'-CH₂OH-S-2840, Gly-1'-CH₂OH-S-2840, 1'-COOH-S-2840 and DFPA-CONH₂ exceeded 10% of the TRR in at least one crop matrix investigated. The highest absolute amount of individual metabolite was

identified in rice forage (pyrazolyl-4-¹⁴C treated) (soil application) Gly-1'-CH₂OH-S-2840 at 1.010 mg eq./kg (26 % TRR).

Apple

See the overview of metabolism in apple in Table 2.7.3-1 in section 2.7.3.

The metabolism of inpyrfluxam was investigated in apple after three spray applications at circa 200 g inpyrfluxam/ha. The applications were performed at the growth stage BBCH 77-79, BBCH 79-81 and BBCH 81-83.

After spray application of [phenyl-U-¹⁴C] and [pyrazolyl-4-¹⁴C] inpyrfluxam to apple, residue levels determined were broadly similar across the two radiolabels. The initial total radioactive residues (TRRs), determined by combustion, in whole apple fruit were 0.300 mg eq./kg and 0.249 mg eq./kg for the phenyl and pyrazolyl labels respectively.

The majority of the radioactive residues were detected in the surface rinse for both [phenyl-U-¹⁴C] and [pyrazolyl-4-¹⁴C] inpyrfluxam treated apples, with residues of 0.192 mg eq./kg (64.0% of TRR) and 0.145 mg eq./kg (58.3% of TRR), respectively. The TRR in apple peel contained 0.094 mg eq./kg (31.3% TRR) for [pyrazolyl-4-¹⁴C] inpyrfluxam treated apple and 0.093 mg eq./kg (37.3% TRR) for [phenyl-U-¹⁴C] inpyrfluxam. The TRR in apple pulp contained 0.014 mg eq./kg (4.7% TRR) for [pyrazolyl-4-¹⁴C] inpyrfluxam treated apple and 0.011 mg eq./kg (4.4% TRR) for [phenyl-U-¹⁴C] inpyrfluxam.

Following extraction with acetonitrile: water (1:1, v/v) x 2 and then acetonitrile, extraction of radioactivity was high and amounted to 89% (0.084 mg eq./kg) of the TRR for peel and 93% (0.013 mg eq./kg) of the TRR for pulp in [pyrazolyl-4-¹⁴C] inpyrfluxam treated apple. For [phenyl-U-¹⁴C] inpyrfluxam treated apple, the extraction rates were also high and amounted to 90% (0.084 mg eq./kg) of the TRR for peel and 91% (0.010 mg eq./kg) of the TRR for pulp.

The residues present in the solids after extraction (PES) represented 3 to 4%TRR (0.01 mg eq./kg) of the TRR for peel and 0.3 to 0.4% (0.001 mg eq./kg) for pulp. Due to the low levels no further extraction was undertaken.

Overall, identification rates were sufficient. In relation to overall TRR amounts (across rinse, peel, and pulp), the primary component of the residues in both radiolabels was parent inpyrfluxam, (78 – 79% of TRR). There were two other metabolites detected, 3'-OH-S-2840 present at circa 11% of TRR and 1'-CH₂OH-S-2840 present at 5 – 6% of TRR. In the pulp the individual residues (metabolites or parent) were present only at up to 0.004 mg eq./kg. The maximum amount of an individual metabolite in peel was 0.015 mg eq./kg (3'-OH-S-2840).

Rice (foliar treated)

See the overview of metabolism in rice in Table 2.7.3-3 in section 2.7.3.

A foliar application was made to rice at 1 x ~100 g a.s./ha. This metabolism study is the one that is most relevant to the currently intended uses on wheat and barley, by way of application rate. For the current intended GAPs on these crops the application rates corresponds to circa 1.1N or 1.2N. The rice plants were grown in flooded plots to mimic normal application to paddy rice. Although this practice does not reflect agricultural practice for cereal crops in the UK, the study represents an acceptable cereal metabolism study.

Samples of immature rice plants were taken 14 days after application. Mature rice plants were sampled 28 days after application and separated into straw, grain and hulls.

The initially determined TRRs, by combustion, were similar across the two different radiolabels: immature rice plants was 0.32 – 0.39 mg eq./kg, straw was 0.81 to 0.85 mg eq./kg, rice grain was 0.04 – 0.05 mg eq./kg, and hulls was 1.4 to 1.6 mg eq./kg.

Following extraction with acetonitrile: water (1:1, v/v) x 2 and then acetonitrile, extraction of radioactivity was high, in the range of 81.5 to 95.9% across all the sample types and both radiolabels.

The amounts remaining in the post extraction solids (PES) after the initial solvent extraction were:

- For immature rice plants, pyrazolyl label - 10.2% (0.029 mg eq./kg) TRR and phenol phenyl label - 12.9% (0.049 mg eq./kg) TRR
- For rice straw, pyrazolyl label - 14% (0.119 mg eq./kg) TRR and phenol phenyl label - 18.6% (0.172 mg eq./kg) TRR
- For rice hulls, pyrazolyl label - 14.5% (0.221 mg eq./kg) TRR and phenol phenyl label - 17% (0.285 mg eq./kg) TR.
- For rice grain, pyrazolyl label - 4.7% (0.003 mg eq./kg) TRR and phenol phenyl label - 4.1% (0.002 mg eq./kg) TRR.

Solids remaining after the solvent extraction (the PES) of rice matrices were then sequentially extracted using acidified acetonitrile (0.1 M HCl in acetonitrile), followed by 50 mM ethylene glycol bis-(2-aminoethyl ester ether)-N,N,N',N'-tetraacetic acid (EGTA), shaken in DMSO for 66 hours, DMSO for 1 hour at 80°C, strong base (24% KOH) and finally strong acid (6M H₂SO₄). The applicant postulated that this work up possibly characterised the residues as a mixture of pectin, lignin, hemicelluloses and cellulose fractions.

The final remaining solid (after the further characterisation of radioactivity work done on the PES) was combusted to determine the remaining residual radiocarbon levels (comprising 0.6 to 3.2% TRR, maximum 0.054 mg eq./kg in rice hulls).

The amounts identified were taken from the total amounts determined from residues present in the solvent extracts plus the 0.1 M HCL extract. The amounts released by 0.1 M HCL were low.

The parent substance inpyrfluxam represented the most prominent residue component in all matrices for labels, comprising 42 to 87% TRR. Parent comprised 60.6% (0.039 mg eq./kg) of the TRR in grain for [pyrazolyl-4-¹⁴C] inpyrfluxam and 78.6% (0.038 mg eq./kg) of the TRR in grain for [phenyl-U-¹⁴C] inpyrfluxam.

The next prevalent constituents, the metabolites, were 3'OH-S-2840 at 5 to 12% TRR and 1'-CH₂OH-S-2840A and 1'-CH₂OH-S-2840B. Together with postulated conjugated material of 1'-CH₂OH-S-2840 as 'Gly-1'-CH₂OH-S-2840', 1'-CH₂OH-S-2840 was found in low amounts in straw, grain and immature plants, and large amounts in rice hulls especially (combined 39% TRR in the pyrazolyl labelled study in rice hulls); the latter 'Gly-1'-CH₂OH-S-2840' was proposed as an undifferentiated peak region consisting of multiple sugar conjugates of 1'-CH₂OH-S-2840. Profiles of the rice matrices showed some major differences across the individual matrices. *N*-des-Me-S-2840 was found in only trace amounts (max 0.005 mg eq./kg). A pyrazolyl specific metabolite was found in rice straw: DFPA-CONH₂ at up to 5%TRR (0.039 mg eq./kg).

Overall, the identification from the study was sufficient and represented a good characterisation of the metabolism for cereals.

Rice (soil granular application)

See the overview of metabolism in rice in Table 2.7.3-4 in section 2.7.3.

A granular application was made to soil planted with rice at 1 x 391 or 357 g a.s./ha. Whilst this study represents an acceptable cereal metabolism study, the study on foliar treated rice crops (above) is more relevant to the current intended uses on wheat and barley in terms of application rate and type.

Samples of immature rice plants were taken 30 days after application. Mature rice plants were sampled 132 days after application and separated into straw, grain and hulls.

The initially determined TRRs, by combustion, were similar across the two different radiolabels: immature rice plants was 1.9 to 3.8 mg eq./kg, straw was 1.1 to 1.5 mg eq./kg, rice grain was 0.010 to 0.015 mg eq./kg, and hulls was 0.16 to 0.17 mg eq./kg.

Following extraction with acetonitrile: water (1:1, v/v) x 2 and then acetonitrile, extraction of radioactivity was in the range of 33 to 64% across all the sample types and both radiolabels.

The amounts remaining in the post extraction solids (PES) after the initial solvent extraction were:

- For immature rice plants, pyrazolyl label - 48.7% (1.895 mg eq./kg) TRR and phenyl label - 41.5% (0.783 mg eq./kg) TRR
- For rice straw, pyrazolyl label - 36.0% (0.569 mg eq./kg) TRR and phenyl label - 37.6% (0.403 mg eq./kg) TRR
- For rice hulls, pyrazolyl label - 37.1% (0.065 mg eq./kg) TRR and phenyl label - 39.7% (0.062 mg eq./kg) TRR.
- For rice grain, pyrazolyl label - 44.4% (0.004 mg eq./kg) TRR and phenyl label - 66.7% (0.010 mg eq./kg) TRR.

Solids remaining after the solvent extraction (the PES) of rice matrices were sequentially extracted with acidified acetonitrile (0.1 M HCl in acetonitrile), followed by 50 mM ethylene glycol bis-(2-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), shaken in DMSO for 48-72 hours, DMSO for 1 hour at 80°C, strong base (24% KOH) and finally strong acid (72% H₂SO₄). The applicant postulated that this work up possibly characterised the residues as a mixture of pectin, lignin, hemicelluloses and cellulose fractions.

The final remaining solid (after the further characterisation of radioactivity work done on the PES) was combusted to determine the remaining residual radiocarbon levels. No radioactive residues remained for immature rice plants and straw. Rice hulls had remaining radioactive levels of 6.9 to 9.6% TRR, maximum 0.015 mg eq./kg. Rice grain had remaining radioactive levels for phenyl labelled inpyrfluxam at 60% TRR (0.009 mg eq./kg) and 44%TRR (0.004 mg eq./kg representing 44%TRR). These grain samples, however, were only subjected to the 0.1M HCl treatment and not the follow on more extensive treatments due to the low level of remaining residues involved.

In the immature rice plants, parent inpyrfluxam was a major metabolite for both labels (20.3 and 38.4% TRR, 0.788 and 0.724 mg eq./kg). Inpyrfluxam also accounted for 2.0 and 2.8% (0.032 and 0.031 mg eq./kg) of the TRR in straw for both labels.

The metabolite Gly-1'-CH₂OH-S-2840 was a major component in immature rice plants and rice straw for both labels (16.7 – 38.0% of the TRR, 0.315 – 1.010 mg eq./kg). The metabolite 1'-CH₂OH-S-2840 was a major component in straw and rice hulls for both labels (23.2 – 53.9% of the TRR, 0.070 – 0.365 mg eq./kg) and for phenyl radiolabelled

rice grain (6.8%). It was also 6.3 – 7.2% of the TRR (0.118 and 0.279 mg eq./kg) in immature rice plants for both labels.

Profiles of the rice matrices showed some differences across the individual matrices. The pyrazolyl specific metabolites DFPA-CONH₂ was found in rice hulls (17.5% TRR, 0.031 mg eq./kg) and *N*-des-Me-DFPA was found in rice grain (23.1% TRR, 0.002 mg eq./kg). The latter metabolite was the most prominent residue component in rice grain, noting that smaller proportions of the radioactivity were extracted in grain as outlined above.

Overall, the identification from the study was sufficient and represented a good characterisation of the metabolism for cereals.

Canola/oilseed rape, corn and sorghum (seed treatment)

See the overview of metabolism in canola/oilseed rape, corn (maize) and sorghum in Table 2.7.3.4 and Table 2.7.3.5 in section 2.7.3.

Applications were made to these crops as seed treatments prior to the planting of the crops. The rates of application were ~5 g a.s./100 kg seed (canola/OSR), ~6.6 g a.s./100 kg seed (maize) and ~6.3 g a.s./100 kg seed (sorghum).

Samples of mature canola/oilseed rape seeds were harvested at maturity (BBCH 97 – 99).

For maize/corn, maize/corn forage was harvested at late dough/early dent stage. Maize/corn kernels plus cob with husks removed were harvested at the milk/succulent stage to represent sweet corn. The remaining crop was harvested at maturity. Matured dried stalks were separated from grain. The cob was included with the stalks to produce corn stover.

For sorghum, sorghum forage was harvested at soft dough to hard dough stage. The remaining crop was harvested at maturity and separated into sorghum grain and sorghum stover (mature stalks from which the grain has been removed).

Due to the very low TRR levels (<0.005 mg eq./kg) in all the sampled plant parts no extraction and characterisation or identification of the residues work was performed.

Potato (seed treatment)

See the overview of metabolism in potato in Table 2.7.3-5 in section 2.7.3.

The applications of either [pyrazolyl-4-¹⁴C] inpyrfluxam and [phenyl-U-¹⁴C] inpyrfluxam were made after seed treatment at a rate of ~5 g a.s./100 kg of seed potato.

Samples of mature tuber were harvested at BBCH 49. Initially determined TRRs, by combustion, were 0.040 mg eq./kg for the pyrazolyl treatment and 0.012 mg eq./kg for the

phenyl treatment. Potato foliage samples were collected at growth stage of BBCH 48 and only used to determine report initial TRR levels which were 0.385 mg eq./kg for pyrazolyl treatment and 0.151 mg eq./kg for phenyl treatment.

Samples of potato tuber were extracted with acetone (x 2) producing the 'acetone extract'. The remaining residue was further extracted twice by acetone and water (60:40, v/v), producing the 'aqueous extract'.

Residues in the 'aqueous extract' and the remaining post-extraction solids (PES) were very low for both labels, up to 0.003 mg eq./kg.

The extractability in the 'acetone extract' was high at 85.5% (pyrazolyl) and 80.3% (phenyl). Extraction rates based on 'acetone' and 'aqueous' extracts were higher; solvent extraction levels were 93.4% (pyrazolyl) and 87.9% (phenyl).

Further extractions were performed on residues in the 'acetone extract' to assist with further characterisation and identification of the residues in this extract. Some proposed polar material was found which did not resolve well in HPLC. Acid hydrolysis of the residues (2 M HCl at 100 degrees C for 2 hrs) and analysis of the hydrolysates enabled better identification of the residues, and to propose that some of the metabolites were considered to be conjugates.

Overall, the following metabolites were identified: 3'-OH-S-2840 (free and conjugated), 1'-CH₂OH-S-2840 (free and conjugated), 1'-COOH-S2840 (free and conjugated), DFPA (free and conjugated) and *N*-des-Me-DFPA (free and conjugated).

For [pyrazolyl-4-¹⁴C] inpyrfluxam, the metabolite 1'-COOH-S2840 (conjugated) was the major component in potato (18.5% of the TRR, amounting to 0.008 mg eq./kg). The parent substance inpyrfluxam accounted for 5.8% (0.002 mg eq./kg) of the TRR.

For [phenyl-U-¹⁴C] inpyrfluxam, the parent compound was the major component in potato (15.0% of the TRR, amounting to 0.002 mg eq./kg).

Other low level metabolites were identified: 3'-OH-S-2840 (free and conjugated) up to 0.001 mg eq./kg, 1'-CH₂OH-S-2840 (free and conjugated) up to 0.001 mg eq./kg, 1'-COOH-S2840 (free and conjugated) up to 0.009 mg eq./kg, DFPA (free and conjugated) up to 0.004 mg eq./kg and *N*-des-Me-DFPA (free and conjugated) up to 0.004 mg eq./kg. The 'DFPA metabolites' were only found in the pyrazolyl label.

Soyabean

See the overview of metabolism in soyabean in Table 2.7.3-2 in section 2.7.3. Two foliar applications were made to soyabean at 2 x ~110 g a.s./ha.

Samples of soyabean forage were harvested 20 days after the first application (16 days before the second application) (BBCH 65). Soyabean hay was harvested 33 days after the first application (3 days before the second application) (BBCH 75). Immature soyabean (edamame) pods and seeds were harvested 11 days after the second application (47 days after the first application) (BBCH 77). Mature soyabeans were harvested 53 days after the second application (89 days after the first application) (BBCH 89).

The initially determined TRRs, by combustion, were similar across the two different radiolabels, except for mature seeds and pods where residues were lower in the phenyl label: soyabean forage was 1.65 – 1.88 mg eq./kg, hay was 1.94 – 2.09 mg eq./kg, immature (edamame) seeds was 0.02 – 0.12 mg eq./kg, immature (edamame) pods was 0.70 – 0.72 mg eq./kg, mature seeds was 0.04 – 0.21 mg eq./kg and mature pods (total (rinse + post-rinse)) was 0.71 – 1.19 mg eq./kg.

Following extraction with acetonitrile: water (1:1, v/v) x 2 and then acetonitrile, extraction of radioactivity was variable, in the range of 58 – 96% across all the sample types and both radiolabels. Extraction rates were higher for forage and edamame pods. Extraction rates were lower in hay and mature seeds and pods (especially for the phenyl label where the extraction rates were 58% in mature seeds and 59% in mature pods - in the pods a further 5 – 7% TRR was released in the rinse for both labels, circa 0.06 mg/kg).

The amounts remaining in the post extraction solids (PES) after the initial solvent extraction were:

- For soyabean forage, pyrazolyl label – 15.3% (0.213 mg eq./kg) TRR and phenyl label – 15.7% (0.244 mg eq./kg) TRR.
- For soyabean hay, pyrazolyl label – 36.5% (0.867 mg eq./kg) TRR and phenyl label – 40.4% (0.906 mg eq./kg) TRR.
- For immature (edamame) seed, pyrazolyl label – 3.7% (0.004 mg eq./kg) TRR and phenyl label – 27.3% (0.006 mg eq./kg) TRR.
- For immature (edamame) pods, pyrazolyl label – 16.9% (0.120 mg eq./kg) TRR and phenyl label – 15.3% (0.097 mg eq./kg) TRR.
- For mature seed, pyrazolyl label – 11.0% (0.024 mg eq./kg) TRR and phenyl label – 42.1% (0.016 mg eq./kg) TRR.
- For mature pods, pyrazolyl label – 26.7% (0.321 mg eq./kg) TRR and phenyl label – 33.8% (0.251 mg eq./kg) TRR.

Solids remaining after solvent extraction (PES) of soyabean matrices (solids with TRR > 10%) were then sequentially extracted using acidified acetonitrile (0.1 M HCl in

acetonitrile), followed by 50 mM ethylene glycol bis-(2- aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), shaken in DMSO for 48 hours, DMSO for 1 hour at 80°C, strong base (24% KOH) and finally strong acid (72% H₂SO₄). The applicant postulated that this work up possibly characterised the residues as a mixture of pectin, lignin, hemicelluloses and cellulose fractions. The strong base extracts containing > 10% TRR were partitioned a further three times with ethyl acetate.

The final remaining solid (after the further characterisation of radioactivity work done on the PES) was combusted to determine the remaining residual radiocarbon levels (comprising 4.1 to 36.8% TRR, 0.009 to 0.014 mg eq./kg in mature seeds). The larger degree of radioactivity in the PES2 for mature seeds (phenyl 36.8%) reflects that due to low radioactive residues the seeds were not worked on through all of the above mentioned steps for assessment of the PES1.

The parent substance inpyrfluxam represented the most prominent residue component in all matrices for [pyrazolyl-4-¹⁴C] inpyrfluxam (6.9 – 40.3% TRR), except for immature (edamame) seeds and mature seeds in which the most prominent residue component was N-des-Me-DFPA conjugate (Uk 24) (9.0% and 17.5% TRR, respectively).

The parent substance inpyrfluxam represented the most prominent residue component in all matrices for [phenyl-U-¹⁴C] inpyrfluxam (9.8 – 65.2 % TRR), except for mature seeds in which the most prominent residue component was 1'-CH₂OH-S-2840 (5.2% TRR).

The next prevalent metabolite was 3'-OH-S-2840 with a maximum content of 22.1% TRR (maximum amount 0.349 mg eq./kg).

Furthermore, trace amounts of Glc-NDM-S-2399 (only up to 5% TRR in hay (0.11 mg eq./kg) and 1.6% TRR in mature seeds (≤0.001 mg eq./kg), when considering the sum of the 'A' and 'B' forms), and not detected in other sample types). ~~This is the only plant metabolism study with any reports of finding parent inpyrfluxam as a conjugate, showing some (limited level) conjugation of parent with glucose.~~

Overall, identification rates were reasonably sufficient (14 to 85%, with the lowest levels being seen in the matrices with the lowest TRR levels). The study provides a good characterisation of the metabolism for pulses and oilseeds.

Summary

Metabolism of inpyrfluxam in each of the foliar treated crops was broadly similar and followed the same initial metabolic pathway: oxidation of inpyrfluxam forming hydroxylation products. Foliar treated rice also showed de-methylation of inpyrfluxam. Foliar treated soyabean included likely hydrolysis of the amide bond and rapid conjugation of the pyrazolyl moiety with sugar (the phenyl moiety likely rapidly decomposed). Rice treated with soil application showed phase II transformation pathways forming multiple glycoside

conjugates which were potentially further transformed into plant constituents associated with pectin, lignin, hemicellulose and cellulose. Seed treated potato demonstrated a similar metabolic pathway with the addition of further transformation through *N*-methylation.

Across each of the primary crop metabolism studies, the degree of identification of residues was acceptable.

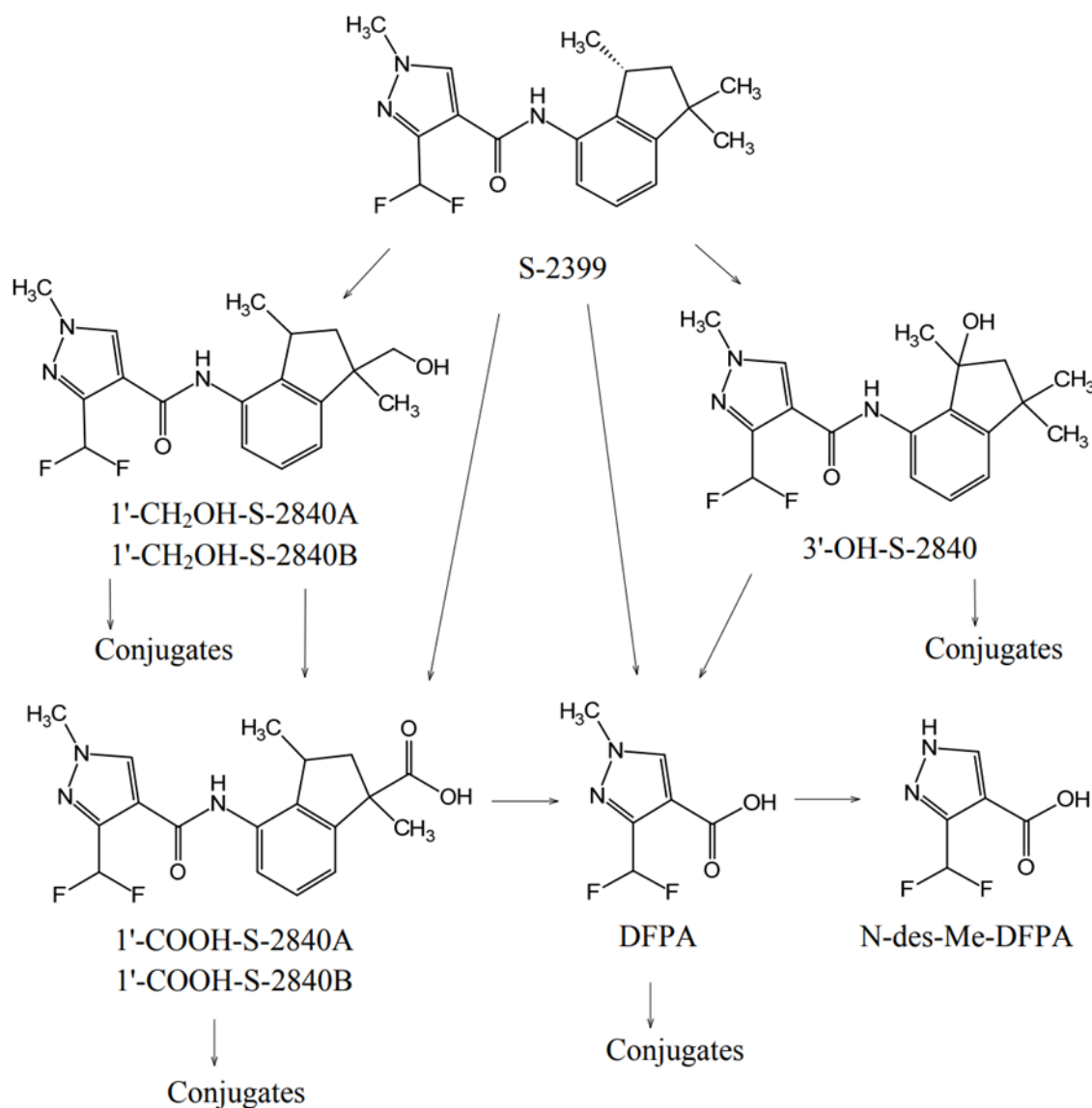
Please refer to the section on residue definition (section 2.7.3) which also considers a justification for the proposal for primary crops. ~~The current assessment includes the current primary crop representative uses (cereals) and import tolerance requests (cereals). The available data are suitable to cover the import tolerance requests.~~

Metabolic pathway

A mainly consistent picture of inpyrfluxam metabolism is observed for both phenyl and pyrazolyl labels and across the different crop groups (cereals, pulses and oilseeds, fruit and fruiting vegetables and root and tuber vegetables).

In plants, the biotransformations observed were:

- Oxidation of inpyrfluxam forming hydroxylation products 3'-OH-S-2840, 1'-CH₂OH-S-2840 and 1'-COOH-S-2840
- In some plants, more extensive metabolism was observed, with the following biotransformations:
- De-methylation of inpyrfluxam forming *N*-des-Me-S-2840 (rice and soyabean)
- Hydroxylated metabolites may form conjugates (foliar treated rice, potato seed treatment)
- The 1'-CH₂OH-S-2840 metabolite appears to undergo phase II transformation forming multiple glycoside conjugates which might be becoming associated with plant macromolecular constituents such as with pectin, lignin, hemicellulose and cellulose (foliar and granular treated rice)
- Cleavage of amide bond and subsequent loss of indenyl moiety of inpyrfluxam, 3'-OH-S-2840, 1'-CH₂OH-S-2840 or 1'-COOH-S-2840 forming DFPA (seed treated potato)
- DFPA can undergo further transformation by *N*-methylation on the pyrazolyl ring forming *N*-des-Me-S-2840 (seed treated potato, rice granular and foliar treated soyabean)

Figure 2.7.2-1: Proposed metabolic pathway in primary crops

It should be noted that the above metabolic pathway is specifically related to potato but is considered applicable to all crops as metabolic pathways are similar. The potato pathway encapsulates all the metabolites included in the residue definitions. Whilst some crop matrices include other metabolites, these are at low levels and have not been included in the residue definitions (see Vol 3 B7).

2.7.3. Definition of the residue for plants

Primary crop metabolism following foliar spray was studied in apple (fruit crop group), soyabean (pulses/oilseeds crop group) and rice (cereal/grass crop group) and following seed treatment of maize and sorghum (cereal/grass crop group), canola/oilseed rape (pulses/oilseeds crop group) and potatoes (root and tuber crop group). Granular application to rice was also studied.

The most relevant metabolism data for the intended uses is the foliar study on rice, which is reflective of the GAP in terms of proposed application rates and broadly in terms of timings of application. Whilst rice is not grown in the UK, it is in the same metabolism group as wheat and barley (cereal/grass). All of the metabolism studies that showed residues >0.005 mg eq./kg were used when considering the residue definitions for plants.

Based on all the metabolism studies, the applicant selected the following residue analytes for study in all the GAP compliant field trials:

- Inpyrfluxam
- 3'-OH-S-2840
- DFPA-CONH₂
- *N*-des-Me-DFPA
- DFPA
- 1'-COOH-S-2840A
- 1'-COOH-S-2840B
- 1'-CH₂OH-S-2840A
- 1'-CH₂OH-S-2840B

Therefore, there is comprehensive quantitative information available on parent and these metabolites in the crops for the representative uses. This information is valuable in considering the residue definition proposals, especially for the suitability to the currently intended crops of wheat and barley.

Whilst residue trials are only available on the current crops under consideration, because the residues found in these trials reflect metabolites found across all the crop metabolism groups, a universal 'all crops' residue definition has also been considered in this section on residue definition. The summaries of metabolism across crops where the understanding of the nature of residues was elucidated are provided in the tables below.

Table 2.7.3-1: Overview of metabolism in apple in terms of % TRR

	Apple (fruit)	
Study reference	KCA 6.2.1/01 - 2507W (TPM-0013)	
Outdoor/Indoor	outdoor	
Type of application	foliar spray	
Number treatments	3	3
Timing of treatments (dd/mm/yyyy)	16.08.2013 27.08.2013 06.09.2013	16.08.2013 27.08.2013 06.09.2013
g a.s./ha/treatment	214, 214, 221	220, 218, 220
Crop growth stage at last application (BBCH GS)	BBCH 81-83	BBCH 81-83
Total seasonal application rate (g a.s./ha)	649	658
PHI (days)	14	14
¹⁴C labelling	[pyrazolyl-4-¹⁴C] inpyrfluxam	[phenyl-U-¹⁴C] inpyrfluxam

Plant part	Surface rinse	Peel	Pulp	Whole fruit	Surface rinse	Peel	Pulp	Whole fruit
TRR (mg eq./kg)	0.192	0.094	0.014	0.300	0.145	0.093	0.011	0.249
Surface wash extract (% TRR)	64.0	--	--	64.0	58.2	--	--	58.2
Total extracted residues (% TRR)	--	28.0	4.3	32.3	--	33.7	4.0	37.7
Parent compound (free)	57.2	20.4	1.5	79.1	53.5	23.3	1.0	77.8
3'-OH-S-2840	6.8	4.4	0.3	11.5	4.7	6.1	0.2	11.0
3'-OH-S-2840 conjugate								
1'-CH ₂ OH-S-2840		3.2	1.4	4.6		4.3	1.3	5.6
1'-CH ₂ OH-S-2840 conjugate								
1'-COOH-S-2840								
1'-COOH-S-2840 conjugate								
DFPA								

DFPA conjugate								
<i>N</i>-des-Me-S-2840								
<i>N</i>-des-Me-DFPA								
<i>N</i>-des-Me-DFPA conjugate								
Glc-NDM-S-2399B								
Glc-NDM-S-2399A								
Gly-1'-CH₂OH-S-2840								
DFPA-CONH₂								
Total identified (% TRR)	64.0	28.0	3.2	95.2	58.2	33.7	2.5	94.4
Organosoluble fractions		72.8	32.2			68.5	30.0	
Aqueous soluble fractions		27.3	67.8			31.5	70.0	
Neutral fraction								
Acidic fraction								
Polar fraction								

Total characterised (% TRR)								
Unknown 1								
Unknown 2								
Others			1.1	1.1			1.5	1.5
Polar compounds (un-retained in HPLC)								
Not analysed fractions								
Unresolved								
Unextracted radioactive residues (% TRR)		3.3	0.3	3.6		3.6	0.4	4.0
Acid/base hydrolysis								
Enzymatic hydrolysis								
DMSO, EGTA^(a)								
PES (% TRR)		3.3	0.3	3.6		3.6	0.4	4.0

Sum of radioactive residues (% TRR)	--	--	--	99.9	--	--	--	99.9
--	----	----	----	------	----	----	----	------

(a) Ethylene glycol bis-(2-aminoethyl ether)-N,N,N',N'-tetraacetic acid

Table key:

> 10 % TRR < 0.01 mg/kg

> 10 % TRR > 0.01 mg/kg

Table 2.7.3-1 continued: Overview of metabolism in apple in terms of mg eq./kg

	Apple							
	[pyrazolyl-4-¹⁴C] inpyrfluxam				[phenyl-U-¹⁴C] inpyrfluxam			
	Surface rinse	Peel	Pulp	Whole fruit	Surface rinse	Peel	Pulp	Whole fruit
Parent compound (free)	0.171	0.061	0.004	0.236	0.133	0.058	0.002	0.193
3'-OH-S-2840	0.021	0.013	0.001	0.035	0.012	0.015	0.001	0.028
3'-OH-S-2840 conjugate								

1'-CH₂OH-S-2840		0.010	0.004	0.014		0.011	0.003	0.014
1'-CH₂OH-S-2840 conjugate								
1'-COOH-S-2840								
1'-COOH-S-2840 conjugate								
DFPA								
DFPA conjugate								
N-des-Me-S-2840								
N-des-Me-DFPA								
N-des-Me-DFPA conjugate								
Glc-NDM-S-2399B								
Glc-NDM-S-2399A								
Gly-1'-CH₂OH-S-2840								
DFPA-CONH₂								
Total identified (mg eq./kg)	0.192	0.084	0.009	0.285	0.145	0.084	0.006	0.235

Organosoluble fractions		0.068	0.005			0.064	0.003	
Aqueous soluble fractions		0.026	0.009			0.029	0.008	
Neutral fraction								
Acidic fraction								
Polar fraction								
Total characterised (mg eq./kg)								
Unknown 1								
Unknown 2								
Others			0.003	0.003			0.004	0.004
Polar compounds (un-retained in HPLC)								
Not analysed fractions								
Unresolved								

Table 2.7.3-2: Overview of metabolism in soyabeans in terms of % TRR

	Soyabeans (pulses/oilseeds)			
Study reference	KCA 6.2.1/02 - 2506W (TPM-0015)			
Outdoor/Indoor	outdoor			
Type of application	foliar spray			
Number treatments	2		2	
Timing of treatments (dd/mm/yyyy)	01/08/2013	06/09/2013	01/08/2013	06/09/2013
g a.s./ha/treatment	108	113	107	111
Crop growth stage at last application (BBCH GS)	BBCH 60	BBCH 75	BBCH 60	BBCH 75
Total seasonal application rate (g a.s./ha)	221		218	

PHI (days)	20	33	11	11	53	53	20	33	11	11	53	53
¹⁴C labelling	[pyrazolyl-4-¹⁴C] inpyrfluxam						[phenyl-U-¹⁴C] inpyrfluxam					
Plant part	Forage	Hay	Immat ure Seeds	Immat ure Pods	Mature Seeds	Mature Pods	Forag e	Hay	Immat ure Seeds	Immat ure Pods	Mature Seeds	Mature Pods
TRR (mg eq./kg)	1.391	2.378	0.109	0.710	0.219	1.201	1.557	2.241	0.022	0.635	0.038	0.742
Surface wash extract (% TRR)						5.4						7.4
Total extracted residues (% TRR)	84.7	63.5	96.3	83.1	89.0	67.9	84.3	59.6	72.7	84.7	57.9	58.8
Parent compound (free)	40.3	17.8	3.0	34.0	0.0	10.9	50.5	22.1	9.8	65.2	2.0	29.2
3'-OH-S-2840	22.1	14.7	0.0	9.2	0.0	3.5	15.3	14.3	0.0	9.0	0.8	12.7
3'-OH-S-2840 conjugate												
1'-CH₂OH-S-2840	3.6	3.7	0.0	0.0	0.0	0.0	3.7	0.0	0.0	4.0	5.2	2.8
1'-CH₂OH-S-2840 conjugate												

1'-COOH-S-2840												
1'-COOH-S-2840 conjugate												
DFPA												
DFPA conjugate												
<i>N</i>-des-Me-S-2840	2.3	2.3	0.0	4.6	0.0	2.1	2.8	2.4	4.6	6.6	0.0	3.9
<i>N</i>-des-Me-DFPA												
<i>N</i>-des-Me-DFPA conjugate	0.0	0.0	9.0	0.0	17.5	1.8						
Glc-NDM-S-2399B							0.0	1.3	0.0	0.0	0.0	0.0
Glc-NDM-S-2399A							0.0	3.8	0.0	0.0	1.6	0.0
Gly-1'-CH₂OH-S-2840												
DFPA-CONH₂												
Total identified (% TRR)	68.3	38.5	12.0	47.8	17.5	18.3	72.3	43.9	14.4	84.8	9.6	48.6

Organosoluble fractions	68.5	24.9		41.0		17.4	62.5	39.5		67.3		25.3
Aqueous soluble fractions	31.5	75.1		59.0		82.6	37.5	60.5		32.7		74.7
Neutral fraction												
Acidic fraction												
Polar fraction												
Total characterised (% TRR)												
Unknown 1												
Unknown 2												
Others	16.5	25.1	22.7	8.5	7.8	6.2	12.1	15.9	58.3	0.0	36.7	17.7
Polar compounds (un-retained in HPLC)	0.0	0.0	61.6	26.8	63.8	48.9	0.0	0.0	0.0	0.0	11.7	0.0
Not analysed fractions												
Unresolved												

Unextracted radioactive residues (% TRR)	15.3	36.5	3.7	16.9	11.0	26.7	15.7	40.4	27.3	15.3	42.1	33.8
Acid/base hydrolysis	11.7	27.7		14.6	3.7	22.2	12.2	30.4		11.3	5.3	29.6
Enzymatic hydrolysis												
DMSO, EGTA^(a)	3.5	8.8		2.6	2.8	4.4	3.5	10.0		4.3	2.6	4.1
PES (% TRR)			3.7		4.1				27.3		36.8	
Sum of radioactive residues (% TRR)	100.0	100.1	100.0	100.3	99.7	100.0	100.1	100.2	100.0	100.4	102.7	100.0

(a) — Parent in the top row of identified metabolites (underneath the row representing total radioactive residues) is to reflect free inpyrfluxam. In soyabean a low level of conjugated material (glucose conjugate) was found—see the row entries for Glc-NDM-S-2399A and Glc-NDM-S-2399B in hay and mature seeds

(a) Ethylene glycol bis-(2-aminoethyl ether)-N,N,N',N'-tetraacetic acid

Table key:

> 10 % TRR < 0.01 mg/kg

> 10 % TRR > 0.01 mg/kg

Table 2.7.3-2 continued: Overview of metabolism in soyabeans in terms of mg eq./kg

	Soyabeans (pulses/oilseeds)											
	[pyrazolyl-4-¹⁴C] inpyrfluxam						[phenyl-U-¹⁴C] inpyrfluxam					
	Forage	Hay	Immat ure Seeds	Immat ure Pods	Mature Seeds	Mature Pods	Forage	Hay	Immat ure Seeds	Immat ure Pods	Mature Seeds	Mature Pods
Parent compound (free)	0.561	0.424	0.003	0.241	0	0.130	0.786	0.495	0.002	0.414	< 0.001	0.216
3'-OH-S-2840	0.308	0.349	0	0.065	0	0.042	0.238	0.321	0	0.057	< 0.001	0.094
3'-OH-S-2840 conjugate												
1'-CH₂OH-S-2840	0.050	0.087	0	0	0	0	0.058	0	0	0.026	0.002	0.021
1'-CH₂OH-S-2840 conjugate												
1'-COOH-S-2840												
1'-COOH-S-2840 conjugate												

DFPA												
DFPA conjugate												
<i>N</i>-des-Me-S-2840	0.032	0.054	0	0.032	0	0.025	0.044	0.053	< 0.001	0.042	0	0.029
<i>N</i>-des-Me-DFPA												
<i>N</i>-des-Me-DFPA conjugate	0	0	0.010	0	0.038	0.022						
Glc-NDM-S-2399B							0	0.028	0	0	0	0
Glc-NDM-S-2399A							0	0.085	0	0	<0.001	0
Gly-1'-CH₂OH-S-2840												
DFPA-CONH₂												
Total identified (mg eq./kg)	0.951	0.914	0.013	0.338	0.038	0.219	1.126	0.982	0.003	0.539	0.005	0.360
Organosoluble fractions	0.953	0.592		0.291		0.209	0.973	0.885		0.427		0.188
Aqueous soluble fractions	0.438	1.786		0.419		0.992	0.584	1.356		0.208		0.554

Neutral fraction												
Acidic fraction												
Polar fraction												
Total characterised (% TRR)												
Unknown 1												
Unknown 2												
Others	0.226	0.596	0.025	0.060	0.016	0.075	0.188	0.354	0.013		0.014	0.130
Polar compounds (un-retained in HPLC)	0	0	0.067	0.191	0.140	0.588	0	0	0	0	0.004	0
Not analysed fractions												
Unresolved												

Table 2.7.3-3: Overview of metabolism in rice (foliar application) in terms of % TRR

	Rice (cereals/grass crops)							
Study reference	KCA 6.2.1/04 - 2508W (TPM-0014)							
Outdoor/Indoor	outdoor							
Type of application	foliar spray							
Number treatments	1				1			
Timing of treatments (dd/mm/yyyy)	18/09/2013				18/09/2013			
g a.s./ha/treatment	95				108.1			
Crop growth stage at last application (BBCH GS)	28 days before BBCH 77				28 days before BBCH 77			
Total seasonal application rate (g a.s./ha)	95				108.1			
PHI (days)	14	28	28	28	14	28	28	28
N rate	1.1				1.2			
¹⁴C labelling	[pyrazolyl-4-¹⁴C] inpyrfluxam				[phenyl-U-¹⁴C] inpyrfluxam			

Plant part	Forage	Straw	Hulls	Grain	Forage	Straw	Hulls	Grain
TRR (mg eq./kg)	0.285	0.851	1.527	0.064	0.379	0.927	1.680	0.049
Surface wash extract (% TRR)								
Total extracted residues (% TRR)	89.8	86.0	85.5	95.3	87.1	81.5	83.0	95.9
Parent compound (free)	86.7	67.7	41.8	60.6	81.2	77.8	52.5	78.6
3'-OH-S-2840	5.6	12.0	5.8	5.9	7.1	6.0	5.6	7.0
3'-OH-S-2840 conjugate								
1'-CH ₂ OH-S-2840	0.2	0.7	33.9	0.0	3.0	1.5	18.0	0.0
1'-CH ₂ OH-S-2840 conjugate								
1'-COOH-S-2840								
1'-COOH-S-2840 conjugate								
DFPA								
DFPA conjugate								

N-des-Me-S-2840	0.2	0.4	0.0	0.0	0.5	0.5	0.0	0.0
N-des-Me-DFPA								
N-des-Me-DFPA conjugate								
Glc-NDM-S-2399B								
Glc-NDM-S-2399A								
Gly-1'-CH₂OH-S-2840	0.0	5.2	7.2	16.0	0.0	0.0	7.1	3.1
DFPA-CONH₂	0.0	4.6	0.0	0.0				
Total identified (% TRR)	92.7	90.6	88.7	82.5	91.8	85.8	83.2	88.7
Organosoluble fractions	71.5	70.6	74.1	75.1	75.6	75.8	74.0	75.5
Aqueous soluble fractions	28.5	29.4	25.9	24.9	24.4	24.2	26.0	24.5
Neutral fraction								
Acidic fraction								
Polar fraction								
Total characterised (% TRR)								

Unknown 1								
Unknown 2								
Others	1.4	5.8	5.6	11.4	0.3	0.5	4.5	4.3
Polar compounds (un-retained in HPLC)								
Not analysed fractions								
Unresolved								
Unextracted radioactive residues (% TRR)	10.2	14.0	14.5	4.7	12.9	18.6	17.0	4.1
Acid/base hydrolysis	6.4	8.8	8.6		7.9	9.4	9.1	
Enzymatic hydrolysis								
DMSO, EGTA^(a)	3.5	4.5	3.9		4.3	6.3	4.8	
PES (% TRR)	0.7	0.6	2.0	4.7	0.8	2.8	3.2	4.1
Sum of radioactive residues (% TRR)	104.7	110.3	108.8	98.6	105.1	104.8	104.8	97.1

(a) Ethylene glycol bis-(2-aminoethyl ether)-N,N,N',N'-tetraacetic acid

Table key:

> 10 % TRR < 0.01 mg/kg

> 10 % TRR > 0.01 mg/kg

Table 2.7.3-3 continued: Overview of metabolism in rice (foliar application) in terms of mg eq./kg

	Rice (cereals/grass crops)							
	[pyrazolyl-4- ¹⁴ C] inpyrfluxam				[phenyl-U- ¹⁴ C] inpyrfluxam			
	Forage	Straw	Hulls	Grain	Forage	Straw	Hulls	Grain
Parent compound (free)	0.247	0.576	0.639	0.039	0.308	0.721	0.881	0.038
3'-OH-S-2840	0.016	0.102	0.088	0.004	0.027	0.055	0.087	0.003
3'-OH-S-2840 conjugate								
1'-CH ₂ OH-S-2840	≤0.001	0.006	0.517	0	0.011	0.014	0.277	0
1'-CH ₂ OH-S-2840 conjugate								

1'-COOH-S-2840								
1'-COOH-S-2840 conjugate								
DFPA								
DFPA conjugate								
<i>N</i>-des-Me-S-2840	≤0.001	0.003	0	0	0.002	0.005	0	0
<i>N</i>-des-Me-DFPA								
<i>N</i>-des-Me-DFPA conjugate								
Glc-NDM-S-2399B								
Glc-NDM-S-2399A								
Gly-1'-CH₂OH-S-2840	0	0.040	0.110	0.010	0	0	0.118	0.002
DFPA-CONH₂	0	0.039	0	0				
Total identified (mg eq./kg)	0.263	0.766	1.354	0.053	0.348	0.795	1.363	0.043
Organosoluble fractions	0.204	0.601	1.132	0.048	0.287	0.703	1.243	0.037
Aqueous soluble fractions	0.081	0.250	0.395	0.016	0.092	0.224	0.437	0.012

Neutral fraction								
Acidic fraction								
Polar fraction								
Total characterised (% TRR)								
Unknown 1								
Unknown 2								
Others	0.006	0.056	0.120	0.007	0.001	0.005	0.076	0.002
Polar compounds (un-retained in HPLC)								
Not analysed fractions								
Unresolved								

Table 2.7.3-4: Overview of metabolism in rice (granular application) in terms of % TRR

	Rice (cereals/grass crops)
Study reference	KCA 6.2.1/05 - 2509W (TPM-0016)

Outdoor/Indoor	outdoor							
Type of application	nursery box granular application							
Number treatments	1				1			
Timing of treatments (dd/mm/yyyy)	27/06/2013				27/06/2013			
g a.s./ha/treatment	391				357			
Crop growth stage at last application (BBCH GS)	BBCH 13-14				BBCH 13-14			
Total seasonal application rate (g a.s./ha)	391				357			
PHI (days)	30	132	132	132	30	132	132	132
¹⁴C labelling	[pyrazolyl-4-¹⁴C] inpyrfluxam				[phenyl-U-¹⁴C] inpyrfluxam			
Plant part	Forage	Straw	Hulls	Grain	Forage	Straw	Hulls	Grain
TRR (mg eq./kg)	3.888	1.582	0.175	0.009	1.887	1.072	0.156	0.015
Surface wash extract (% TRR)								

Total extracted residues (% TRR)	51.3	64.0	62.9	55.6	58.5	62.4	60.3	33.3
Parent compound (free)	20.3	2.0	0.0	0.0	38.4	2.8	0.0	0.0
3'-OH-S-2840	3.6	0.6	0.0	0.0	1.2	0.1	0.0	0.0
3'-OH-S-2840 conjugate								
1'-CH₂OH-S-2840	7.2	23.2	40.1	4.7	6.3	25.7	53.2	6.8
1'-CH₂OH-S-2840 conjugate								
1'-COOH-S-2840								
1'-COOH-S-2840 conjugate								
DFPA								
DFPA conjugate								
N-des-Me-S-2840								
N-des-Me-DFPA	0.0	1.6	5.3	23.1				
N-des-Me-DFPA conjugate								
Glc-NDM-S-2399B								

Glc-NDM-S-2399A								
Gly-1'-CH₂OH-S-2840	26.0	31.7	0.0	0.0	16.7	38.0	9.4	0.0
DFPA-CONH₂	2.2	2.1	17.5	1.5				
Total identified (% TRR)	59.3	61.2	62.9	29.3	62.6	66.6	62.6	6.8
Organosoluble fractions	33.7	6.8			38.4	7.3		
Aqueous soluble fractions	66.4	93.3			61.6	92.8		
Neutral fraction								
Acidic fraction								
Polar fraction								
Total characterised (% TRR)								
Unknown 1								
Unknown 2								
Others	0.9	6.7		26.3			3.4	26.5

Polar compounds (un-retained in HPLC)								
Not analysed fractions								
Unresolved								
Unextracted radioactive residues (% TRR)	48.7	36.0	37.1	44.4	41.5	37.6	39.7	66.7
Acid/base hydrolysis	42.3	28.5	22.3		26.7	28.2	24.4	6.7
Enzymatic hydrolysis								
DMSO, EGTA^(a)	6.6	7.5	7.9		14.8	9.4	6.5	
PES (% TRR)			6.9	44.4			9.6	60.0
Sum of radioactive residues (% TRR)	109.1	103.9	100.0	100.0	104.1	104.2	106.5	100.0

(a) Ethylene glycol bis-(2-aminoethyl ether)-N,N,N',N'-tetraacetic acid

Table key:

> 10 % TRR < 0.01 mg/kg

> 10 % TRR > 0.01 mg/kg

Table 2.7.3-4 continued: Overview of metabolism in rice (granular application) in terms of mg eq./kg

	Rice (cereals/grass crops)							
	[pyrazolyl-4- ¹⁴ C] inpyrfluxam				[phenyl-U- ¹⁴ C] inpyrfluxam			
	Forage	Straw	Hulls	Grain	Forage	Straw	Hulls	Grain
Parent compound (free)	0.788	0.032	0.000	0.000	0.724	0.031		
3'-OH-S-2840	0.142	0.009	0.000	0.000	0.023	<0.001		
3'-OH-S-2840 conjugate								
1'-CH ₂ OH-S-2840	0.279	0.365	0.070	<0.001	0.118	0.276	0.084	<0.001
1'-CH ₂ OH-S-2840 conjugate								
1'-COOH-S-2840								
1'-COOH-S-2840 conjugate								
DFPA								
DFPA conjugate								

N-des-Me-S-2840								
N-des-Me-DFPA	0.000	0.025	0.009	0.002				
N-des-Me-DFPA conjugate								
Glc-NDM-S-2399B								
Glc-NDM-S-2399A								
Gly-1'-CH₂OH-S-2840	1.010	0.498	0.000	0.000	0.315	0.407	0.015	
DFPA-CONH₂	0.086	0.034	0.031	<0.001				
Total identified (mg eq./kg)	2.305	0.963	0.110	0.002	1.180	0.714	0.099	0.000
Organosoluble fractions	1.308	0.107						
Aqueous soluble fractions	2.580	1.475						
Neutral fraction								
Acidic fraction								
Polar fraction								
Total characterised (% TRR)								

Unknown 1								
Unknown 2								
Others	0.034	0.106		0.002			0.005	0.003
Polar compounds (un-retained in HPLC)								
Not analysed fractions								
Unresolved								

Table 2.7.3-5: Overview of metabolism in potato in terms of % TRR

	Potato (root crops)	
Study reference	KCA 6.2.1/07 - VP-38692 (TPM-0042)	
Outdoor/Indoor	outdoor	
Type of application	seed treatment	
Number treatments	1	1
Timing of treatments (dd/mm/yyyy)	19/03/2014	19/03/2014

g a.s./ha/treatment	4.99 g ai/100 kg tubers	4.92 g ai/100 kg tubers
Crop growth stage at last application (BBCH GS)	N/A	N/A
Total seasonal application rate (g a.s./ha)	N/A	N/A
PHI (days)	84	84
¹⁴C labelling	[pyrazolyl-4- ¹⁴ C] inpyrfluxam	[phenyl-U- ¹⁴ C] inpyrfluxam
Plant part	Tubers	Tubers
TRR (mg eq./kg)	0.041	0.012
Surface wash extract (% TRR)		
Total extracted residues (% TRR)	93.4	87.9
Parent compound (free)	5.8	15.0
3'-OH-S-2840	1.6	3.6
3'-OH-S-2840 conjugate	0	2.4
1'-CH₂OH-S-2840	0.9	1.8

1'-CH₂OH-S-2840 conjugate	2.6	1.0
1'-COOH-S-2840	3.7	5.3
1'-COOH-S-2840 conjugate	18.5	9.2
DFPA	4.7	
DFPA conjugate	4.5	
<i>N</i>-des-Me-S-2840		
<i>N</i>-des-Me-DFPA	10.1	
<i>N</i>-des-Me-DFPA conjugate	0.1	
Glc-NDM-S-2399B		
Glc-NDM-S-2399A		
Gly-1'-CH₂OH-S-2840		
DFPA-CONH₂		
Total identified (% TRR)	52.7	38.2
Organosoluble fractions		

Aqueous soluble fractions		
Neutral fraction		
Acidic fraction		
Polar fraction		
Total characterised (% TRR)		
Unknown 1		
Unknown 2		
Others	40.8	49.7
Polar compounds (un-retained in HPLC)		
Not analysed fractions		
Unresolved		
Unextracted radioactive residues (% TRR)	6.6	12.1
Acid/base hydrolysis		
Enzymatic hydrolysis		

DMSO, EGTA^(a)		
PES (% TRR)		
Sum of radioactive residues (% TRR)	100.1	100.0

(a) Ethylene glycol bis-(2-aminoethyl ether)-N,N,N',N'-tetraacetic acid

Table key:

> 10 % TRR < 0.01 mg/kg

> 10 % TRR > 0.01 mg/kg

Table 2.7.3-5 continued: Overview of metabolism in potato in terms of mg eq./kg

	Potato (root crops)	
	[pyrazolyl-4-¹⁴C] inpyrfluxam	[phenyl-U-¹⁴C] inpyrfluxam
	Tubers	Tubers
Parent compound (free)	0.002	0.002
3'-OH-S-2840	0.001	<0.001

3'-OH-S-2840 conjugate	0	<0.001
1'-CH₂OH-S-2840	<0.001	<0.001
1'-CH₂OH-S-2840 conjugate	0.001	<0.001
1'-COOH-S-2840	0.002	0.001
1'-COOH-S-2840 conjugate	0.008	0.001
DFPA	0.002	
DFPA conjugate	0.002	
<i>N</i>-des-Me-S-2840		
<i>N</i>-des-Me-DFPA	0.004	
<i>N</i>-des-Me-DFPA conjugate	<0.001	
Glc-NDM-S-2399B		
Glc-NDM-S-2399A		
Gly-1'-CH₂OH-S-2840		
DFPA-CONH₂		

Total identified (% TRR)	0.022	0.004
Organosoluble fractions		
Aqueous soluble fractions		
Neutral fraction		
Acidic fraction		
Polar fraction		
Total characterised (% TRR)		
Unknown 1		
Unknown 2		
Others	0.017	0.006
Polar compounds (un-retained in HPLC)		
Not analysed fractions		
Unresolved		

Prevalence of residue constituents in primary crop metabolism data

Based on the available metabolism studies, the parent compound was the major component in each of the crops studied. Inpyrfluxam was identified above 10% TRR in apple peel and surface rinse (21 – 57% TRR or 0.058 – 0.171 mg eq./kg across both radiolabels), in soyabean forage, hay and immature and mature pods (11 – 65% TRR or 0.13 – 0.786 mg eq./kg across both radiolabels), in all rice matrices treated with a foliar spray (42 – 87% TRR or 0.038 – 0.881 mg eq./kg across both radiolabels), in granular-treated rice forage (20 and 38 %TRR or 0.788 and 0.724 mg eq./kg across both radiolabels) and in phenyl labelled potato tubers (15% TRR, 0.002 mg eq./kg). It was also found at 0.031 and 0.032 mg eq./kg in granular-treated rice straw, but this was not > 10% TRR.

The results of the A and B isomers of 1'-CH₂OH-S-2840 and 1'-COOH-S-2840 were summed in the metabolism study and are discussed together below. According to Toxicology (section 2.6.8.1 of Vol 1), the 'A' and 'B' isomers of the metabolite can be summed, as there is no toxicological information to suggest that one isomer is more toxic than the other and the isomeric forms were therefore considered together in the toxicological evaluation (see also section Volume 1 on isomer composition 2.12.3 (toxicology) and 2.12.4 (residues) and also the explanation of isomers in plant metabolism studies in section Volume 1 2.7.2 (summary of metabolism)).

The levels of free and conjugate 3'-OH-S-2840, 1'-CH₂OH-S-2840, 1'-COOH-S-2840, DFPA and *N*-des-Me-DFPA were reported. The specific glycoside conjugate of 1'-CH₂OH-S-2840 (A and B) was also reported. The only conjugates to feature at >10% TRR was for *N*-des-Me-DFPA, 1'-COOH-S-2840 (A and B) and the glycoside conjugate of 1'-CH₂OH-S-2840 (A and B).

1'-CH₂OH-S-2840 A and B were identified above 10% TRR in rice hulls treated with a foliar spray (18 and 34% TRR, 0.517 and 0.277 mg eq./kg across both radiolabels) and granular-treated rice straw and hulls (23 – 54% TRR, 0.07 – 0.365 mg eq./kg). They were also found in apple peel (phenyl label), soyabean forage (both labels), soyabean hay (pyrazolyl label only), immature and mature soyabean pods (phenyl label) and granular-treated rice forage (both labels) at levels > 0.01 mg eq./kg, but these were not > 10% TRR.

3'-OH-S-2840 was identified above 10% TRR in whole fruit for apple (i.e., summed surface rinse, peel and pulp, 11.0% TRR or 0.014 mg eq./kg for both radiolabels), in soyabean forage and hay (14 – 22% TRR or 0.238 – 0.349 mg eq./kg across both radiolabels), in mature soyabean pods (13% TRR or 0.094 mg eq./kg, phenyl label only) and in foliar spray rice straw (12% TRR or 0.102 mg eq./kg, pyrazolyl label only). It was also found in immature soyabean pods (both labels), mature soyabean pods (pyrazolyl label only), foliar spray rice forage and rice hulls (both labels) and granular-treated rice forage (both labels) at levels > 0.01 mg eq./kg, but these were not > 10% TRR.

1'-COOH-S-2840A and B were identified above 10% TRR in the pyrazolyl labelled potato tubers in its conjugated form (18.5% TRR, 0.008 mg eq./kg). For the phenyl label, the conjugated metabolite was found at 9% TRR and the non-conjugated metabolite was found at 4% and 5% TRR for the two radiolabels; if the conjugated and non-conjugated metabolite are summed, the %TRR for both radiolabels would be > 10%, but still < 0.01 mg eq./kg.

N-des-Me-S-2840 was found in soyabean matrices at up to 6.6%TRR in immature pods (0.042 mg eq./kg) and up to 4.6%TRR in immature seeds (at very low levels <0.001 mg eq./kg). It was found at up to 3.9% TRR in mature pods (0.028 mg eq./kg).

N-des-Me-DFPA and its conjugates was the only major metabolite found in rice grain (23% TRR or 0.002 mg eq./kg, pyrazolyl radiolabel only) and was another major metabolite in potato tubers (10.1% TRR or 0.004 mg eq./kg, pyrazolyl radiolabel only). It was also found in rice straw at 0.025 mg eq./kg and soyabean mature seeds and pods at 0.038 and 0.022 mg eq./kg, but this was < 10% TRR. DFPA and its conjugates were found in potato tubers at 4 – 5% TRR, which when combined is 10.2% TRR. This equated to 0.002 mg eq./kg each. It was not found in any other matrix.

DFPA-CONH₂ was found at 17.5% TRR in rice hulls (0.031 mg eq./kg) for the pyrazolyl radiolabel. It was < 10% TRR in all other matrices but was between 0.034 – 0.086 mg eq./kg in rice forage and straw. **Prevalence of residue constituents in primary crop trials**

In the GAP compliant wheat and barley trials the applicant analysed for inpyrfluxam, 3'-OH-S-2840, DFPA-CONH₂, N-des-Me-DFPA, DFPA, 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1'-CH₂OH-S-2840A and 1'-CH₂OH-S-2840B. This is considered an effective consideration of potential for any residues in wheat and barley grain and straw, based on all available metabolism data.

The respective methods of analysis determined DFPA, 1'-COOH-S-2840A and B and 1'-CH₂OH-S-2840A and B after an acid hydrolysis step, so the reported residue levels will also include conjugates. Conjugates of inpyrfluxam and 3'-OH-S-2840 are not expected to feature. The only conjugated 3'-OH-2840 was in the potato seed treatment study, potato tuber at 2.4%, and < 0.001 mg eq./kg, and none of the parent has been reported as conjugated in the studies. Any conjugated material of 3'-OH-2840 would not have been released by the respective methods used to determine residue levels of these analytes in the trials, but based on expected absence in cereals this is acceptable. Based on the metabolism studies, the only conjugates to feature at > 10% TRR was for N-des-Me-DFPA, 1'-COOH-S-2840 (A and B) and the glycoside conjugate of 1'-CH₂OH-S-2840 (A and B). Only 1'-COOH-S-2840 (A and B) and 1'-CH₂OH-S-2840 (A and B) have been considered further for the residue definition for risk assessment based on their prevalence in the residue trials.

Table 2.7.3-6 Results of parent and metabolites from the residue trials, scaled to the current GAP

Crop	Range of scaled residues (mg/kg) expressed on a metabolite basis								
	Inpyr- fluxam	3'-OH- S- 2840	DFPA- CONH₂	N-des- Me- DFPA	DFPA	1'- COOH- S-2840A	1'- COOH- S-2840B	1'- CH₂OH- S- 2840A	1'- CH₂OH- S- 2840B
Barley grain	<0.01 – 0.204	<0.01 – 0.020	<0.01	<0.01	<0.01 – 0.057	<0.005 – 0.011	<0.005 – 0.015	0.008 – 0.048	0.008 – 0.062
Barley straw	0.062 – 3.13	<0.01 – 0.308	<0.01	<0.01 – 0.013	<0.01 – 0.214	<0.005 – 0.153	<0.005 – 0.144	0.018 – 0.194	0.011 – 0.661
Wheat grain	<0.01 – 0.02	<0.01	<0.01	<0.01	<0.01	<0.005 – 0.009	<0.005 – 0.010	<0.005	<0.005 – 0.017
Wheat straw	0.026 – 2.95	<0.01 – 0.755	<0.01	<0.01	0.013 – 0.147	<0.005 – 0.455	<0.005 – 0.633	<0.005 – 0.261	<0.005 – 0.495

With reference to these main metabolites, the following conclusions are made on the toxicology (section 2.6.8.1 of Vol 1):

Table 2.7.3-7: Summary table of the toxicological characterisation of plant/livestock metabolites of inpyrfluxam for the purposes of the RD for risk assessment

Name, code, and smiles	General toxicity conclusion and basis	Reference values for dietary risk assessment
Parent Inpyrfluxam	Classification Acute tox Cat 3, H301: Toxic if swallowed <u>Full data package</u> No evidence of carcinogenicity, reproductive and developmental toxicity, or neurotoxicity. Repeat dose exposure resulted in liver changes in all test species with secondary thyroid findings in rats, mice and dogs; in adrenal gland changes in rats and dogs; and in ovary changes in rats.	ADI = 0.06 mg/kg/day ARfD = 0.3 mg/kg bw
1'-COOH-S-2840	Covered by parent	Parent's TRVs
3'-OH-S-2840	Not more toxic than parent	Parent's TRVs
DFPA	Not more toxic than parent (DFPA can be considered "significantly less toxic than parent" (Vol 3 B.6.8.1).)	Parent's TRVs

Name, code, and smiles	General toxicity conclusion and basis	Reference values for dietary risk assessment
N-des-Me-DFPA	Not more toxic than parent	Parent's TRVs
DFPA-CONH₂	Not more toxic than parent	Parent's TRVs
1'-CH₂OH-S-2840	Covered by parent	Parent's TRVs

Toxicologically it is concluded that the risk assessment for these metabolites are covered by the TRVs for parent. It has been confirmed by toxicology that DFPA can be considered “significantly less toxic than parent” (Vol 3 B.6.8.1).

The highest residue observed in grain and straw for wheat and barley for the individual metabolites in the GAP compliant residue trials have been expressed as parent (using molecular weight adjustment) in table 2.7.3-8 below. The overall % contribution of parent and each metabolite (as parent) found at a detectable level has also been calculated. Inpyrfluxam contributed 37.3 – 63.3% to the overall level of residues in each crop matrices. 3'-OH-S-2840 contributed >10% in wheat straw, and 4.1 and 5.9% in barley grain and straw respectively. DFPA contributed 23.6% in barley grain and 8.2 and 4.9% in barley and wheat straw. 1'-COOH-S-2840A and B contributed 2.2 – 3.0% to the total residues in both barley matrices, but 15.4 – 17.2 in wheat grain and 7.4 – 10.3% in wheat straw. 1'-CH₂OH-S-2840B contributed >10% in all barley matrices and in wheat grain (30.1%). 1'-CH₂OH-S-2840A was 9.9% in barley grain. If the isomers are summed for this metabolite, they also contribute > 10% in wheat straw so overall contribute > 10% in all matrices.

Table 2.7.3-8 Results of parent and metabolites (expressed as parent) from the residue trials, based on highest residues observed, when scaled to the current GAP and the % contribution of each component (to the total sum for that matrix, when summing detectable residues only)

Crop	Range of scaled residues (mg/kg)								
	Inpyrfluxam	3'-OH-S-2840 expressed as parent	DFPA- CONH₂ expressed as parent	N-des-Me- DFPA expressed as parent	DFPA expressed as parent	1'-COOH-S- 2840A expressed as parent	1'-COOH-S- 2840B expressed as parent	1'-CH₂OH- S-2840A expressed as parent	1'-CH₂OH- S-2840B expressed as parent
Molecular weight (g/mol)	333.4	349.4	175.1	162.1	175.1	363.4	363.4	349.4	349.4
MW conversion to parent	-	0.95	1.90	2.06	1.90	0.92	0.92	0.95	0.95
Barley grain (mg/kg)	0.204	0.019	-	-	0.108	0.010	0.014	0.046	0.059
% contribution	44.4	4.1	-	-	23.6	2.2	3.0	9.9	12.8
Barley straw (mg/kg)	3.13	0.293	-	0.027	0.407	0.141	0.132	0.184	0.628
% contribution	63.3	5.9	-	0.5	8.2	2.8	2.7	3.7	12.7

Wheat grain (mg/kg)	0.02	-	-	-	-	0.0083	0.0092	-	0.0162
% contribution	37.3	-	-	-	-	15.4	17.2	-	30.1
Wheat straw (mg/kg)	2.95	0.717	-	-	0.279	0.419	0.582	0.248	0.470
% contribution	52.1	12.7	-	-	4.9	7.4	10.3	4.4	8.3

Table key:

> 0 - < 10 % contribution to total residues

> 10 % contribution to total residues

Conclusion on primary crops

Residue Definition for enforcement (RD-Enf)

Based on the available primary crop metabolism studies, parent inpyrfluxam is present at significant levels in at least one matrix in all crop categories and hence would be appropriate as a marker compound. The parent compound has been shown to remain stable when exposed to conditions representative of major industrial processes, so the RD-Enf is also considered to apply to processed commodities. In the rotational crop metabolism study, inpyrfluxam was most prevalent in most of the rotational matrices, and as significant residues are not expected in rotational crops (other than some animal feed items – see below) based on the currently proposed uses, it is considered appropriate for the RD-Enf to be the parent compound only

HSE proposal for RD-Enf: inpyrfluxam only

Residue Definition for Dietary risk assessment (RD-RA)

As discussed above, inpyrfluxam is present at significant levels in at least one matrix in all crop categories in the primary crop metabolism studies and was found at levels > 0.01 mg eq./kg in all straw samples and some grain samples in the GAP compliant residue field trials on wheat and barley.

1'-CH₂OH-S-2840 and 3'-OH-S-2840 are proposed for inclusion in the plant residue definition given their occurrence both in the metabolism studies and in the residue trials. After parent, they were the analytes found most frequently > 10% TRR and > 0.01 mg eq./kg. When expressed as parent, the summed isomers of 1'-CH₂OH-S-2840 contributed > 10% to the total residues in all matrices (23 or 30% in grain), and 3'-OH-S-2840 was found > 10% in wheat straw and 4.1 and 5.9% in barley matrices. Taking inpyrfluxam and these two metabolites together, at least ~70% of residues in the trials are accounted for.

When expressed as parent, DFPA contributed 23.6% to the total residues in barley grain, which was the highest contribution after parent. However, the molecular weight of this metabolite is low and the conversion factor is therefore higher than a number of the other metabolites; the levels of DFPA expressed as itself was <0.01 – 0.057 in barley grain, with most results at or below 0.01 mg eq./kg. All results were < 0.01 mg eq./kg in wheat grain so it was not consistently seen across edible crop matrices. It has been confirmed by toxicology that DFPA can be considered “significantly less toxic than parent” (Vol 3 B.6.8.1) so HSE proposes not to include DFPA in the RD-RA. In terms of relative toxicity, inpyrfluxam, 1'-CH₂OH-S-2840 and 3'-OH-S-2840 then accounts for much more than 70% of the total residues in the trials.

1'-COOH-S-2840A and B contributed > 10% to the total residues in both wheat grain and straw when summed, but each contributed a low mg/kg in wheat grain, each < 0.01 mg

eq./kg for each of 1'-COOH-S-2840A and B. When summed they comprised ~5% in both barley matrices (0.024 mg eq./kg in barley grain). Whilst this metabolite was present at comparable amounts to 3'-OH-S-2840 in the residue trials, it was not seen as widely across the metabolism studies. The summed metabolites of 1'-COOH-S-2840A and B were identified above 10% TRR in the pyrazolyl labelled potato tubers (in the seed treatment metabolism) in their conjugated form (18.5% TRR, 0.008 mg eq./kg). It was therefore not considered necessary for inclusion in the universal RD-RA at this time. **HSE advises that future crop trials (either for seed treatment or foliar use) on root and tuber vegetables, including potatoes and bulb vegetables should analyse for 1'-COOH-S-2840 (to include free and conjugated residues); see also note below regarding N-des-Me-DFPA.**

N-des-Me-DFPA (pyrazolyl only) and its conjugates were also considered for inclusion in the RD-RA, as it was found in rice grain (23.1% TRR or 0.002 mg eq./kg) and was another metabolite in potato tubers (found slightly above 10%, 10.1% TRR or 0.004 mg eq./kg in the seed treatment potato metabolism study). It was also found (as the conjugated form) in soyabean mature seeds and pods at 0.038 mg eq./kg (17.5%TRR) and 0.022 mg eq./kg (2%TRR). This metabolite was analysed for in the GAP compliant residue field trials on wheat and barley, but only a few positive residues in straw were seen, and no positive residues in grain were observed. Overall it was not considered necessary for inclusion in the RD-RA at this time. **HSE advises that future crop trials on pulses/oilseeds, including legumes, should analyse for N-des-Me-DFPA, free and conjugated (and also it might also be beneficial to analyse this component in root and tuber vegetables, including potatoes and bulb vegetables as well).**

DFPA-CONH₂ was sought but not found in the wheat and barley residues trials. In the metabolism studies, it was only found at a relatively high %TRR (above 10%TRR) at 17.5%TRR (0.031 mg eq./kg) in the rice hulls from the soil applied granular treatment to rice. The total radioactive residues in rice hulls were higher for the foliar treatment than the soil applied granular application. Aside from rice hulls, in the soil applied granular study on rice it was present at <5%TRR and <0.1 mg eq./kg in feed items. Therefore, this component is not proposed for inclusion in the residue definition.

N des Me-S-2840 was found in soyabean samples at up to 6.6%TRR in immature pods, 0.042 mg eq./kg and up to 4.6%TRR in immature seeds (very low mg eq./kg, <0.001 mg eq./kg). It was found at up to 3.9 %TRR in mature pods (0.029 mg eq./kg). Although consistently <10%TRR, the levels found suggest that residues of N des Me-S-2840 could be found in (human) foods, such as legumes. **HSE advises that future crop trials on pulses/oilseeds, including legumes, should analyse for N des Me-S-2840.**

In terms of conjugates, of the proposed residues for inclusion in the residue definition for risk assessment, only conjugates of 1'-CH₂OH-S-2840 are included in the definition. The glycoside conjugate of 1'-CH₂OH-S-2840 featured > 10% TRR in the metabolism studies for rice grain (foliar and granular application) and the method of analysis in the residue trials included a hydrolysis step, so the measured levels of 1'-CH₂OH-S-2840A and B in the cereal trials include the free and conjugate forms. In terms of parent, there was mainly only free inpyrfluxam found across the metabolism studies, except for soyabean. In soyabean, low level/trace amounts of glucose conjugate of parent, Glc-NDM-S-2399 were found (only up to 5% TRR in hay and 0.1% TRR in mature seeds, when considering the sum of the 'A' and 'B' forms), and not detected in other sample types). This is the only plant metabolism study with any reports of finding parent inpyrfluxam as a conjugate, showing some (limited level) conjugation of parent with glucose. Only a trace amount of conjugated 3'-OH-S-2840 was identified in a metabolism study (potato seed treatment at 2.4 TRR% and < 0.001 mg eq./kg only), and the method of analysis used in the cereal residue trials covered free inpyrfluxam and 3'-OH-S-2840 only. This is acceptable.

Overall, HSE considers that the proposed RD-RA as suitable for the intended uses on wheat and barley, could also be suitable as a universal residue definition for all crops. HSE considers, that if in the future, a wider range of crop uses are proposed, then (as discussed in this section on RD-RA) then some additional specified plant metabolites in specific crop matrices should be analysed in the future crop field trials to reconfirm the applicability of this residue definition to 'all crops'. If the new data generated provided information on some metabolites being found at higher levels, then the universal RD-RA might need to be reconsidered.

HSE proposal for RD-RA: Sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam.

HSE advises that future crop trials should analyse the following to reconfirm (or to reconsider if needed) the proposed universal residue definition for plants:

at least for *N*-des-Me-DFPA (free and conjugated)* for members of the oilseeds and pulses metabolism grouping, including legumes; and

at least for *N*-des-Me-S-2840 for members of the oilseeds and pulses metabolism grouping, including legumes; and

at least for 1'-COOH-S-2840 (free and conjugated) for members of the root and tuber vegetables metabolism grouping, including potatoes and bulb vegetables. to reconfirm the proposed universal residue definition for plants).

*It might also be advisable to include *N*-des-Me-DFPA in trials set up for members of the root and tuber vegetables metabolism grouping, including potatoes and bulb vegetables, although 1'-COOH-S-2840 (free and conjugated) might be an adequate marker to

determine whether residues are found/not found in root, tuber and bulb vegetable crops, including potatoes.

Rotational crop consideration

Significant residues are not expected in rotational crops based on the current proposed uses on wheat and barley. A separate RD-RA for rotational crops is not required at this time. **If a higher soil exposure is expected for a future GAP such that residues would be expected to be found, the RD-RA for rotational crops should be considered further at that time.**

The following (tabular) overview of the nature of residues in rotational crops is included for completeness at this time. The metabolism of radio-labelled inpyrfluxam in rotational crops (lettuce, sorghum and radish) was investigated after spray application of the test item at a nominal rate of 235 g a.s./ha to bare soil. Crops were sown at intervals of 30, 120 and 365 days after treatment (DAT), with crops being harvested at maturity.

Table 2.7.3-9: Overview of rotational crop metabolism in lettuce

Study reference	KCA 6.6.1/01 - VP-38482 (TPM-0047)											
Outdoor/Indoor	Outdoor											
Bare soil application: Y/N	Y											
Dose of application (g a.s./ha)	233 - 236											
Ploughing at 20 cm depth: Y/N	N											
¹⁴ C labelling	[pyrazolyl-4- ¹⁴ C] inpyrfluxam						[phenyl-U- ¹⁴ C] inpyrfluxam					
Crop	Lettuce											
Plant back intervals (days) ^(a)	30	120	365	30	120	365	30	120	365	30	120	365
Plant part	Immature leaves			Mature leaves			Immature leaves			Mature leaves		
TRR (mg eq./kg)	0.076	0.100	0.037	0.075	0.087	0.023	0.042	0.052	0.021	0.100	0.064	0.010
Total extracted residues (% TRR)	94.9	93.4	93.4	89.1	87.0	87.5	95.0	95.6	93.7	93.4	93.2	93.8

Parent compound (free) and/or conjugated)	27.4	28.9	8.3	12.2	11.4	0.5	46.2	41.8	26.4	26.9	17.4	27.2
3'-OH-S-2840 (free)	2.8	5.2	2.3	2.8	3.7		8.5	10.9	10.5	7.5	11.7	7.7
3'-OH-S-2840 (conj)	0.9	3.7		0.9	1.6		3.1	4.2		2.9	5.9	
N-des-Me-S-2840 (free)	0.7		5.9		0.6		1.0	0.6			0.8	1.3
N-des-Me-S-2840 (conj)	2.0			2.2			2.6			2.8		
1'-CH₂OH-S-2840 (free)	1.4	0.8		3.3			2.6	2.2	5.6	3.6	9.0	2.4
1'-CH₂OH-S-2840 (conj)	14.0	7.6		13.5	11.3		15.7	13.3		21.2	14.8	
1'-COOH-S-2840 (free)	0.7	1.2		1.9	1.9		1.2	2.9	4.3	1.5	6.0	3.1
1'-COOH-S-2840 (conj)	2.8	3.0		7.3	8.1		4.2	3.9		7.9	8.6	

<i>N</i>-des-Me-1'-CH₂OH-S-2840 (free)												
<i>N</i>-des-Me-1'-CH₂OH-S-2840 (conj)										0.9		
DFPA (free)	19.1	22.4	9.9	13.0	11.7	15.6						
DFPA (conj)	5.9	6.4		12.5	16.6							
<i>N</i>-des-Me-DFPA (free)	7.6	6.8	18.5	8.4	8.1	28.0						
<i>N</i>-des-Me-DFPA (conj)				1.2								
DFPA-CONH₂ (free)	3.3	2.7	4.5	3.2	2.5	3.1						
DFPA-CONH₂ (conj)												
Total identified (% TRR)	88.7	88.7	49.4	82.2	77.4	52.2	85.3	79.9	46.8	75.3	74.1	42.8
Organosoluble fractions												

Aqueous soluble fractions												
Neutral fraction												
Acidic fraction												
Polar fraction												
Total Characterized (%TRR)												
Unknown 1												
Unknown 2												
Others	6.2	4.8	44.0	6.9	9.6	35.2	9.8	15.7	46.8	18.1	19.1	51.0
Not analysed fractions												
Unresolved												
Unextracted radioactive residues(% TRR)												

Acid/base hydrolysis												
Enzymatic hydrolysis												
PES(% TRR)	5.1	6.6	6.6	10.9	13.0	12.5	5.0	4.4	6.3	6.6	6.8	6.2
Accountability (% TRR)	100	100.1	100	100	100	99.9	100.1	100	99.9	100	100	100

(a) Time from harvest to extraction; first value in days, second value in months

Table key:

> 10 % TRR < 0.01 mg/kg

> 10 % TRR > 0.01 mg/kg

Table 2.7.3-9 continued: Overview of rotational crop metabolism in lettuce in terms of mg eq./kg

	[pyrazolyl-4- ¹⁴ C] inpyrfluxam						[phenyl-U- ¹⁴ C] inpyrfluxam					
	Lettuce											
	30	120	365	30	120	365	30	120	365	30	120	365

	Immature leaves			Mature leaves			Immature leaves			Mature leaves		
Parent compound (free) and/or conjugated)	0.021	0.029	0.003	0.009	0.010	0.001	0.019	0.022	0.005	0.027	0.011	0.003
3'-OH-S-2840 (free)	0.002	0.005	0.001	0.002	0.003		0.004	0.006	0.002	0.008	0.008	0.001
3'-OH-S-2840 (conj)	0.001	0.004		0.001	0.001		0.001	0.002		0.003	0.004	
N-des-Me-S-2840 (free)	0.001		0.002		0.001		<0.001	<0.001			<0.001	<0.001
N-des-Me-S-2840 (conj)	0.002			0.002			0.001			0.003		
1'-CH₂OH-S-2840 (free)	0.002	0.001		0.003			0.002	0.001	0.001	0.003	0.006	<0.001
1'-CH₂OH-S-2840 (conj)	0.010	0.008		0.010	0.010		0.007	0.007		0.021	0.010	
1'-COOH-S-2840 (free)	<0.001	0.001		0.002	0.002		<0.001	0.002	0.001	0.002	0.004	<0.001

1'-COOH-S-2840 (conj)	0.003	0.003		0.005	0.007		0.002	0.002		0.008	0.005	
N-des-Me-1'-CH₂OH-S-2840 (free)												
N-des-Me-1'-CH₂OH-S-2840 (conj)												
DFPA (free)	0.014	0.022	0.004	0.010	0.010	0.004						
DFPA (conj)	0.004	0.006		0.009	0.014							
N-des-Me-DFPA (free)	0.006	0.007	0.007	0.006	0.007	0.006						
N-des-Me-DFPA (conj)				0.001								
DFPA-CONH₂ (free)	0.002	0.003	0.002	0.002	0.002	0.001						
DFPA-CONH₂ (conj)												
Total identified (% TRR)												
Organosoluble fractions												
Aqueous soluble fractions												
Neutral												

Acidic												
Polar												
Total Characterized (%TRR)												
Unknown 1												
Unknown 2												
Others	0.005	0.005	0.016	0.005	0.008	0.008	0.004	0.008	0.01 0	0.01 8	0.012	0.005
Not analysed fractions												
Unresolved												

Table 2.7.3-10: Overview of rotational crop metabolism in sorghum

Study reference	KCA 6.6.1/01 - VP-38482 (TPM-0047)
Outdoor/Indoor	Outdoor

Formulation type	Suspension Concentrate (40 SC)																	
Bare soil application: Y/N	Y																	
Dose of application (g a.s./ha)	233 - 236																	
Ploughing at 20 cm depth: Y/N	N																	
¹⁴ C labelling	[pyrazolyl-4- ¹⁴ C] inpyrfluxam									[phenyl-U- ¹⁴ C] inpyrfluxam								
Crop	Sorghum																	
Plant back intervals (days) ^(a)	30	120	365	30	120	365	30	120	365	30	120	365	30	120	365	30	120	365
Plant part	Forage			Grain			Straw			Forage			Grain			Straw		
TRR (mg eq./kg)	0.200	0.187	0.047	0.049	0.062	0.017	0.752	1.107	0.210	0.094	0.118	0.036	0.012	0.010	0.014	0.684	1.252	0.136

Total extracted residues (% TRR)	85.9	77.9	77.4	59.9	49.8	47.4	76.7	78.8	78.7	82.6	84.5	80.3	49.9	51.7	52.4	76.6	81.9	77.6
Parent compound (free) and/or conjugated)	3.4	1.7	0.5				1.0	1.8	1.0	3.6	4.1					0.8	0.9	1.3
3'-OH-S-2840 (free)	3.1	3.8	1.4				1.2	1.6	2.1	2.7	4.4	1.4				1.1	2.6	3.5
3'-OH-S-2840 (conj)	0.5		3.6				4.3	3.4	5.5	3.1		3.6				5.5	7.8	8.6
N-des-Me-S-2840 (free)	0.4	0.3					0.1		1.6	0.3						<0.1		2.1
N-des-Me-S-2840 (conj)																		
1'-CH₂OH-S-2840 (free)							0.7	0.3								0.4	2.2	
1'-CH₂OH-S-2840 (conj)	7.8	3.5	7.8				10.3	7.2	3.1	13.8	13.0	9.7				13.5	13.3	3.7

1'-COOH-S-2840 (free)																		
1'-COOH-S-2840 (conj)	1.7	0.6	3.9				2.4	3.4	2.2	4.4	1.6	4.6				3.7	3.8	4.5
N-des-Me-1'-CH₂OH-S-2840 (free)			3.8				0.4									0.3	0.5	
N-des-Me-1'-CH₂OH-S-2840 (conj)	7.5	3.9	2.5				4.5	4.2	2.3	9.0	12.3	10.1				7.6	8.9	3.9
DFPA (free)	1.8	2.2	0.7				0.7	0.3										
DFPA (conj)	9.3	11.1	9.8	22.6			11.0	11.6	6.1									
N-des-Me-DFPA (free)	0.7	1.4					0.3	0.2										
N-des-Me-DFPA (conj)	7.6	7.1	5.8	8.6			4.8	4.5	3.8									
DFPA-CONH₂ (free)	1.8	2.9	1.8				0.3	1.4	1.4									

DFPA-CONH₂ (conj)																		
Total identified (% TRR)	45.5	38.6	41.7	31.2	0.0	0.0	43.0	39.9	28.9	36.9	35.4	29.3	0.0	0.0	0.0	33.1	39.8	27.7
Organosoluble fractions																		
Aqueous soluble fractions																		
Neutral fraction																		
Acidic fraction																		
Polar fraction																		
Total Characterized (%TRR)																		
Unknown 1																		

Unknown 2																		
Others	40.4	39.3	35.8	28.7	49.8	47.4	33.7	38.9	49.7	45.7	49.1	51.0	49.9	51.7	52.4	43.5	42.1	49.9
Not analysed fractions																		
Unresolved																		
Unextracted radioactive residues(% TRR)																		
Acid/base hydrolysis																		
Enzymatic hydrolysis																		
PES(% TRR)	14.1	22.1	22.6	40.1	50.2	52.6	23.3	21.3	21.3	17.4	15.5	19.7	50.1	48.3	47.6	23.4	18.0	22.4
Accountability (% TRR)	100	100	100.1	100	100	100	100	100.1	99.9	100	100	100	100	100	100	100	99.9	100

(a) Time interval between treatment/ageing of the soil with the pesticide and planting of the rotational crops (days)

Table key:

> 10 % TRR < 0.01 mg/kg

> 10 % TRR > 0.01 mg/kg

Table 2.7.3-10 continued: Overview of rotational crop metabolism in sorghum in terms of mg eq./kg

	[pyrazolyl-4- ¹⁴ C] inpyrfluxam									[phenyl-U- ¹⁴ C] inpyrfluxam								
	Sorghum																	
	30	120	365	30	120	365	30	120	365	30	120	365	30	120	365	30	120	365
	Forage			Grain			Straw			Forage			Grain			Straw		
Parent compound (free) and/or conjugated)	0.007	0.003	<0.001				0.008	0.020	0.002	0.003	0.005	-				0.006	0.011	0.002
3'-OH-S-2840 (free)	0.006	0.007	0.001				0.009	0.017	0.004	0.003	0.005	0.001				0.008	0.033	0.005
3'-OH-S-2840 (conj)	0.001		0.002				0.032	0.038	0.012	0.003		0.001				0.038	0.098	0.012
N-des-Me-S-2840 (free)	0.001	0.001					<0.001		0.003	<0.001						<0.001		0.003

<i>N</i>-des-Me-S-2840 (conj)																		
1'-CH₂OH-S-2840 (free)							0.004	0.003								0.003	0.027	
1'-CH₂OH-S-2840 (conj)	0.016	0.006	0.003				0.078	0.080	0.006	0.013	0.015	0.003				0.092	0.167	0.005
1'-COOH-S-2840 (free)																		
1'-COOH-S-2840 (conj)	0.003	0.002	0.002				0.018	0.038	0.005	0.004	0.002	0.002				0.025	0.048	0.006
<i>N</i>-des-Me-1'-CH₂OH-S-2840 (free)			0.002				0.003									0.002	0.006	
<i>N</i>-des-Me-1'-CH₂OH-S-2840 (conj)	0.015	0.007	0.001				0.041	0.046	0.005	0.009	0.015	0.004				0.051	0.111	0.005
DFPA (free)	0.004	0.004	<0.001				0.005	0.004										
DFPA (conj)	0.019	0.021	0.005	0.011			0.083	0.129	0.013									

<i>N</i>-des-Me-DFPA (free)	0.001	0.003					0.003	0.002										
<i>N</i>-des-Me-DFPA (conj)	0.015	0.013	0.003	0.004			0.036	0.059	0.008									
DFPA-CONH₂ (free)	0.004	0.006	0.001				0.002	0.016	0.003									
DFPA-CONH₂ (conj)																		
Total identified (% TRR)																		
Organosoluble fractions																		
Aqueous soluble fractions																		
Neutral																		
Acidic																		

Polar																		
Total Characterized (%TRR)																		
Unknown 1																		
Unknown 2																		
Others	0.081	0.073	0.017	0.014	0.031	0.008	0.253	0.430	0.104	0.043	0.058	0.018	0.006	0.005	0.007	0.297	0.528	0.068
Not analysed fractions																		
Unresolved																		

Table 2.7.3-11: Overview of rotational crop metabolism in pyrazolyl radiolabelled radish

Study reference	KCA 6.6.1/01 - VP-38482 (TPM-0047)
Outdoor/Indoor	Outdoor
Formulation type	Suspension Concentrate (40 SC)

Bare soil application: Y/N	Y											
Dose of application (g a.s./ha)	233 - 236											
Ploughing at 20 cm depth: Y/N	N											
¹⁴C labelling	[pyrazolyl-4- ¹⁴ C] inpyrfluxam											
Crop	Radish											
Plant back intervals (days)^(a)	30	120	365	30	120	365	30	120	365	30	120	365
Plant part	Immature roots			Mature roots			Immature tops			Mature tops		
TRR (mg eq./kg)	0.042	0.059	0.022	0.066	0.108	0.021	0.133	0.213	0.095	0.226	0.370	0.072
Total extracted residues (% TRR)	95.7	95.8	96.8	96.0	96.1	94.3	94.6	94.8	93.8	93.1	89.5	94.0
Parent compound (free) and/or conjugated	52.1	46.7	28.2	57.3	41.2	33.0	14.0	7.9	6.5	6.1	6.9	7.6

3'-OH-S-2840 (free)	5.1	6.6	4.4	4.8	4.0	4.5	1.8	1.2		0.8	1.4	
3'-OH-S-2840 (conj)					0.2		0.3	2.0	0.3	1.0	2.7	2.0
N-des-Me-S-2840 (free)	1.0	1.6	2.1	1.8	7.6	1.8	11.3	12.6	7.4	10.3	10.2	12.8
N-des-Me-S-2840 (conj)							1.4			2.5		
1'-CH₂OH-S-2840 (free)	2.0	3.0		2.2	3.5		0.9				1.7	
1'-CH₂OH-S-2840 (conj)					4.5		2.9	6.5	4.6	7.9	8.3	6.4
1'-COOH-S-2840 (free)	8.7	6.2	14.3	3.1	6.3	4.6	1.8	0.9		0.7	1.9	2.7
1'-COOH-S-2840 (conj)					7.1		1.0	3.2	12.0	5.5	5.3	8.1
N-des-Me-1'-CH₂OH-S-2840 (free)		0.8			0.5		2.5	2.1			2.6	
N-des-Me-1'-CH₂OH-S-2840 (conj)					0.3		6.2	12.3	5.1	13.0	12.4	5.4

DFPA (free)	11.0	11.2	23.6	4.2	6.1	13.7	3.5	3.0	6.7	2.0	3.3	4.7
DFPA (conj)					6.5		10.2	3.7	8.4	8.3	6.2	8.7
<i>N</i>-des-Me-DFPA (free)	3.3	3.2		1.1	1.2		1.8	1.5	6.3	1.7		6.6
<i>N</i>-des-Me-DFPA (conj)					0.6		3.0	2.9	1.3	4.7	3.4	2.7
DFPA-CONH₂ (free)		3.2			1.4		18.5	17.1	14.3	10.3	7.2	9.9
DFPA-CONH₂ (conj)							0.5					
Total identified (% TRR)	83.3	79.4	72.6	74.4	91.0	57.6	81.5	77.0	72.9	74.8	73.5	77.6
Organosoluble fractions												
Aqueous soluble fractions												
Neutral fraction												
Acidic fraction												

Polar fraction												
Total Characterized (%TRR)												
Unknown 1												
Unknown 2												
Others	12.4	16.4	24.2	21.7	5.1	36.7	13.1	17.8	20.9	18.3	16.0	16.4
Not analysed fractions												
Unresolved												
Unextracted radioactive residues(% TRR)												
Acid/base hydrolysis												
Enzymatic hydrolysis												
PES(% TRR)	4.3	4.2	3.2	4.0	3.9	5.7	5.4	5.2	6.4	6.9	10.5	5.8

Accountability (% TRR)	100	100	100	100.1	100	100	100	100	100.2	100	100	99.8
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(a) Time interval between treatment/ageing of the soil with the pesticide and planting of the rotational crops (days)

Table key:

> 10 % TRR < 0.01 mg/kg

> 10 % TRR > 0.01 mg/kg

Table 2.7.3-11: Overview of rotational crop metabolism in pyrazolyl radiolabelled radish in terms of mg eq./kg

	[pyrazolyl-4-¹⁴C] inpyrfluxam											
	Radish											
	30	120	365	30	120	365	30	120	365	30	120	365
	Immature roots			Mature roots			Immature tops			Mature tops		
Parent compound (free)-and/or conjugated)	0.022	0.027	0.006	0.038	0.045	0.007	0.019	0.017	0.006	0.014	0.025	0.005
3'-OH-S-2840 (free)	0.002	0.004	0.001	0.003	0.004	0.001	0.002	0.003		0.002	0.005	
3'-OH-S-2840 (conj)					<0.001		<0.001	0.004	<0.001	0.002	0.010	0.001

<i>N</i>-des-Me-S-2840 (free)	<0.001	0.001	<0.001	0.001	0.008	<0.001	0.015	0.027	0.007	0.023	0.038	0.009
<i>N</i>-des-Me-S-2840 (conj)							0.002			0.006		
1'-CH₂OH-S-2840 (free)	0.001	0.002		0.001	0.004		0.001				0.006	
1'-CH₂OH-S-2840 (conj)					0.005		0.004	0.013	0.005	0.018	0.030	0.005
1'-COOH-S-2840 (free)	0.004	0.004	0.003	0.003	0.007	0.001	0.002	0.002		0.002	0.006	0.002
1'-COOH-S-2840 (conj)					0.008		0.002	0.007	0.011	0.012	0.020	0.006
<i>N</i>-des-Me-1'-CH₂OH-S-2840 (free)		<0.001			0.001		0.003	0.004			0.010	
<i>N</i>-des-Me-1'-CH₂OH-S-2840 (conj)					<0.001		0.008	0.026	0.005	0.029	0.046	0.004
DFPA (free)	0.005	0.007	0.005	0.003	0.007	0.003	0.005	0.006	0.006	0.005	0.012	0.003
DFPA (conj)					0.007		0.014	0.008	0.008	0.019	0.023	0.006
<i>N</i>-des-Me-DFPA (free)	0.001	0.002		0.001	0.001		0.002	0.003	0.014	0.004		0.005
<i>N</i>-des-Me-DFPA (conj)					0.001		0.004	0.006	0.001	0.011	0.012	0.002
DFPA-CONH₂ (free)		0.002			0.001		0.025	0.037	0.013	0.023	0.027	0.007

DFPA-CONH₂ (conj)							0.001					
Total identified (% TRR)												
Organosoluble fractions												
Aqueous soluble fractions												
Neutral												
Acidic												
Polar												
Total Characterized (%TRR)												
Unknown 1												
Unknown 2												
Others	0.005	0.010	0.005	0.014	0.006	0.008	0.017	0.038	0.020	0.041	0.059	0.012
Not analysed fractions												
Unresolved												

Table 2.7.3-12: Overview of rotational crop metabolism in phenyl radiolabelled radish

Study reference	KCA 6.6.1/01 - VP-38482 (TPM-0047)											
Outdoor/Indoor	Outdoor											
Formulation type	Suspension Concentrate (40 SC)											
Bare soil application: Y/N	Y											
Dose of application (g a.s./ha)	233 - 236											
Ploughing at 20 cm depth: Y/N	N											
¹⁴C labelling	[phenyl-U-¹⁴C] inpyrfluxam											
Crop	Radish											
Plant back intervals (days)^(a)	30	120	365	30	120	365	30	120	365	30	120	365
Plant part	Immature roots			Mature roots			Immature tops			Mature tops		
TRR (mg eq./kg)	0.032	0.027	0.022	0.047	0.030	0.024	0.115	0.101	0.084	0.129	0.103	0.085

Total extracted residues (% TRR)	93.4	89.8	95.6	94.6	93.4	96.7	90.3	93.5	95.0	90.3	92.4	94.9
Parent compound (free) and/or conjugated)	58.9	43.1	40.2	54.8	34.9	48.7	15.0	9.9	6.4	12.3	8.3	10.5
3'-OH-S-2840 (free)	9.8	11.9	11.0	8.7	9.9	11.1	3.4	3.6	3.5	3.1	3.6	3.6
3'-OH-S-2840 (conj)							0.7	6.5	-	10.2	2.5	6.4
N-des-Me-S-2840 (free)	1.9	1.1		2.0	1.6		14.3	12.4	10.2	10.7	10.9	13.6
N-des-Me-S-2840 (conj)							0.8			0.7		
1'-CH₂OH-S-2840 (free)	2.6	2.3		2.7	2.3						1.0	
1'-CH₂OH-S-2840 (conj)							6.2	3.8	7.7	7.9	5.4	8.4
1'-COOH-S-2840 (free)	5.8	11.7	25.7	9.8	15.7	19.1	1.3	1.0	4.0	1.8	2.5	

1'-COOH-S-2840 (conj)							2.5	7.0	25.6	5.5	13.4	22.1
<i>N</i>-des-Me-1'-CH₂OH-S-2840 (free)	1.6	0.6					1.7	2.2		1.4	2.4	
<i>N</i>-des-Me-1'-CH₂OH-S-2840 (conj)							13.0	8.2	7.6	9.8	11.5	7.9
DFPA (free)												
DFPA (conj)												
<i>N</i>-des-Me-DFPA (free)												
<i>N</i>-des-Me-DFPA (conj)												
DFPA-CONH₂ (free)												
DFPA-CONH₂ (conj)												
Total identified (% TRR)	80.5	70.7	77.0	77.8	64.3	78.9	58.9	54.6	61.0	63.3	61.5	72.5

Organosoluble fractions												
Aqueous soluble fractions												
Neutral fraction												
Acidic fraction												
Polar fraction												
Total Characterized (%TRR)												
Unknown 1												
Unknown 2												
Others	12.9	19.1	18.7	16.8	29.1	17.8	31.4	38.9	34.0	27.0	30.9	22.4
Not analysed fractions												
Unresolved												

Unextracted radioactive residues(% TRR)												
Acid/base hydrolysis												
Enzymatic hydrolysis												
PES(% TRR)	6.6	10.2	4.3	5.4	6.6	3.3	9.7	6.5	4.9	9.7	7.6	5.1
Accountability (% TRR)	100	100	100	100	100	100	100	100	99.9	100	100	100

(a) Time interval between treatment/ageing of the soil with the pesticide and planting of the rotational crops (days)

Table key:

> 10 % TRR < 0.01 mg/kg

> 10 % TRR > 0.01 mg/kg

Table 2.7.3-12 continued: Overview of rotational crop metabolism in phenyl radiolabelled radish in terms of mg eq./kg

	[phenyl-U-¹⁴C] inpyrfluxam											
	Radish											
	30	120	365	30	120	365	30	120	365	30	120	365
	Immature roots			Mature roots			Immature tops			Mature tops		
Parent compound (free) and/or conjugated)	0.019	0.012	0.009	0.026	0.010	0.012	0.017	0.010	0.005	0.016	0.009	0.009
3'-OH-S-2840 (free)	0.003	0.003	0.002	0.004	0.003	0.003	0.004	0.004	0.003	0.004	0.004	0.003
3'-OH-S-2840 (conj)							0.001	0.007		0.013	0.003	0.005
N-des-Me-S-2840 (free)	0.001	<0.001		0.001	<0.001		0.016	0.013	0.009	0.014	0.011	0.012
N-des-Me-S-2840 (conj)							0.001			0.001		
1'-CH₂OH-S-2840 (free)	0.001	0.001		0.001	0.001						0.001	
1'-CH₂OH-S-2840 (conj)							0.007	0.004	0.007	0.010	0.005	0.007
1'-COOH-S-2840 (free)	0.002	0.003	0.006	0.005	0.005	0.005	0.001	0.001	0.003	0.002	0.003	

1'-COOH-S-2840 (conj)							0.002	0.008	0.021	0.007	0.014	0.019
<i>N</i>-des-Me-1'-CH₂OH-S-2840 (free)	0.001	<0.001					0.002	0.002		0.002	0.002	
<i>N</i>-des-Me-1'-CH₂OH-S-2840 (conj)							0.015	0.008	0.007	0.012	0.012	0.007
DFPA (free)												
DFPA (conj)												
<i>N</i>-des-Me-DFPA (free)												
<i>N</i>-des-Me-DFPA (conj)												
DFPA-CONH₂ (free)												
DFPA-CONH₂ (conj)												
Total identified (% TRR)												
Organosoluble fractions												
Aqueous soluble fractions												
Neutral												

Acidic												
Polar												
Total Characterized (%TRR)												
Unknown 1												
Unknown 2												
Others	0.004	0.005	0.004	0.008	0.009	0.004	0.036	0.039	0.029	0.035	0.032	0.019
Not analysed fractions												
Unresolved												

The rotational crop metabolism showed a similar profile to the primary crop metabolism. Inpyrfluxam was a major metabolite in lettuce, immature and mature radish roots, and in some radish top samples. The metabolite 3'-OH-S-2840 was found > 10% TRR in phenyl radiolabelled lettuce and radish roots at residue levels mostly < 0.01 mg eq./kg. 1'-CH₂OH-S-2840 was also found in lettuce at > 10% TRR, and in some straw and forage PBIs; these >10% TRR findings were also often >0.01 mg eq./kg in magnitude. 1'-COOH-S-2849 was only found in radish samples at >10% TRR, but it was found at a range of PBIs and in both tops and roots. *N*-des-Me-1'-CH₂OH-S-2840 was found in sorghum forage and radish tops >10% TRR and at > 0.01 mg eq./kg in a number of sorghum straw samples. DFPA was found in pyrazolyl labelled lettuce, and in all immature and one mature radish root sample for the same radiolabel. This metabolite was the only metabolite > 10% TRR to be found in sorghum grain, but only at the earliest PBI (30 days). *N*-des-Me-DFPA was found > 10% TRR in some pyrazolyl labelled lettuce samples only.

Rotational crop field trials are available which analysed for inpyrfluxam, 3'-OH-S-2840, DFPA-CONH₂, *N*-des-Me-S-2840, DFPA, 1'-COOH-S-2840 (A and B), 1'-CH₂OH-S-2840 (A and B) and *N*-des-Me-1'-CH₂OH-S-2840.

Inpyrfluxam (considered very persistent) and the soil metabolites 3'-OH-S-2840 and 1'-COOH-S-2840 are very persistent and can accumulate in soil from year-on-year use. The application rate in this study was ~240 g/ha, which is 1.69N compared to the expected A_{total} of 141.7 g/ha, to account for accumulation, based on the current GAP, with a predicted crop interception of 80% to account for the presence of the wheat or barley cereals as a primary crop, except for the final year before treatment (no interception assumed in the final year to account for the potential for crop failure) (See section 2.7.9 Vol 1 for details).

In the rotational crop magnitude of residue trial samples (results for the overdosed trials 1.69N), residues of inpyrfluxam and its metabolites were all < 0.01 mg/kg except for in some straw samples from the 1st rotation (~ 30 day PBI). In the German trial, 3'-OH-S-2840 was found at 0.01 mg/kg, DFPA at 0.09 mg/kg, 1'-COOH-S-2840 (sum of isomers) at 0.019 mg/kg and 1'-CH₂OH-S-2840 (sum of isomers) at 0.023 mg/kg. In the Italian trial DFPA was found at 0.1 mg/kg, 1'-COOH-S-2840 (sum of isomers) at 0.017 mg/kg, 1'-CH₂OH-S-2840 (sum of isomers) at 0.023 mg/kg and *N*-des-Me-1'-CH₂OH-S-2840 (sum of isomers) at 0.019 mg/kg.

No residues > 0.01 mg/kg were observed in (human) food items in the overdosed rotational crop trials.

When the results from the trials are scaled to the expected GAP, the only residues expected to be > 0.05 mg/kg in straw (i.e., a feed item) is DFPA at 0.053 – 0.059 mg/kg. Given that it is concluded that DFPA is of a significantly lower toxicity compared to parent inpyrfluxam and that DFPA is therefore not proposed for inclusion in the primary crop RD-RA despite it being found in primary crop cereal

straw samples at up to 0.22 mg/kg, the level of the rotational crop findings of DFPA in straw will not result in significant residues in the diets of livestock.

It is noted that for future uses with higher application rates, the potential A_{total} may need to be refined upwards which could result in potential residues expected in rotational crops. It is not considered necessary at this time to set MRLs above the LOQ for rotational crops, and a separate RD-RA for rotational crops is not required at this time. **If a higher soil exposure is expected for a future GAP leading to residues being found in rotational crops, the RD-RA for rotational crops should be considered further.**

Processed commodities consideration

Inpyrfluxam, 1'-CH₂OH-S-2840, and 1'-COOH-S-2849 were all observed to be stable under standard hydrolysis conditions in the studies provided. Under simulated conditions of pasteurization (pH 4, 90°C, 20 mins), baking, brewing and boiling (pH 5, 100°C, 60 mins), some degradation of 3'-OH-S-2840 was observed to form 3'-OH-S-2840 dehydrate and a small number of minor unidentified degradation products. Under the condition of sterilisation (pH 6, 120°C, 20 mins) there was no significant degradation and 3'-OH-S-2840 can be considered hydrolytically stable **under these conditions**. It seems to be under the more acidic conditions that 3'-OH-S-2840 has converted to the 3'-OH-S-2840 dehydrate.

There is no available toxicity data on the 3'-OH-S-2840 dehydrate (as per Vol 1 section 2.6.8.1). The risk assessment for 3'-OH-S-2840 is covered by the risk assessment for inpyrfluxam (section 2.6.8.1 of Vol 1). For the intended wheat and barley uses, due to the low levels of 3'-OH-S-2840 in cereal grains (expressed as parent < 0.01 mg eq./kg for wheat grain and up to 0.02 mg eq./kg for barley grain), there is only a small uncertainty in the risk assessment through not having analysed 3'-OH-S-2840 dehydrate in the MOR processing studies for cereals and through toxicological data not being available for the 3'-OH-S-2840 dehydrate. The RD-RA for processed cereal foods, does not need to include 3'-OH-S-2840 dehydrate as an additional component currently. However, for future intended uses and crops where the levels of residues in the raw agricultural commodities could be higher, HSE recommends that **the MOR processing studies should also include analysis of 3'-OH-S-2840 dehydrate as well as the other components of the RD-RA for products of plant origin**. This would enable the RD-RA for processed foods to be reconsidered, if needs be.

Therefore for the current uses, the processing of inpyrfluxam, 1'-CH₂OH-S-2840, 3'-OH-S-2840 and 1'-COOH-S-2849 is not expected to significantly modify the nature of the residues.

Therefore, the HSE proposed residue definitions for plants are:

Residue definition for enforcement (RD-Enf): inpyrfluxam

Residue definition for dietary risk assessment (RD-RA): Sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam.

HSE advises that future crop trials should analyse the following to reconfirm (or to reconsider if needed) the proposed universal residue definition for plants:

at least for *N*-des-Me-DFPA (free and conjugated)* for members of the oilseeds and pulses metabolism grouping, including legumes; and

at least for *N*-des-Me-S-2840 for members of the oilseeds and pulses metabolism grouping, including legumes; and

at least for 1'-COOH-S-2840 (free and conjugated) for members of the root and tuber vegetables metabolism grouping, including potatoes and bulb vegetables..

*It might also be advisable to include *N*-des-Me-DFPA in trials set up for members of the root and tuber vegetables metabolism grouping, including potatoes and bulb vegetables, although 1'-COOH-S-2840 (free and conjugated) might be an adequate marker to determine whether residues are found/not found in root, tuber and bulb vegetable crops, including potatoes

(HSE advises that future crop trials should analyse at least for *N*-des-Me-DFPA* in oilseeds and pulses and for 1'-COOH-S-2840 (free and conjugated) in root and tuber vegetables, including potatoes to reconfirm the proposed universal residue definition for plants).

*It might also be advisable to include *N*-des-Me-DFPA in trials set up on root and tuber vegetables, including potatoes, although 1'-COOH-S-2840 (free and conjugated) might be an adequate marker to determine whether residues are found/not found in root and tuber crops, including potatoes.

2.7.4. Summary of residue trails in plants and identification of critical GAP

The representative uses are for cereal crops (wheat, triticale and barley).

The requested GAPs are presented in Table 2.7.4-1 below.

Table 2.7.4-1 Requested GAPs

Crop	Application				PHI (days)
	Method/ kind	Growth stage of crop	Number of applications	Rate per application (g a.s./ha)	
Barley	Foliar spray	BBCH 30-71	1	90	35
Wheat	Foliar spray	BBCH 30-71	1	90	35

Barley

Fourteen independent GLP trials were conducted on barley in northern Europe (considered climatically comparable to the UK for residues trials purposes) in 2016 and 2019. In these trials, two different formulation were tested. Barley was treated with one application of 90, 120 or 200 g inpyrfluxam/ha formulated as either an SC or EC at the latest growth stage of BBCH 83. The trials at 120 g as/ha were side by side plots in the other trials, and they did not need to be relied upon. The available trials are summarised in the table below:

Table 2.7.4-2: Overview of residue trials conducted on barley relevant to the UK

Crop	Region	No. of independent trials ^(a) (application rate)			Report No (Formulation)	Document Number	Reference
		Year		Total			
		2016	2019				
Barley	NEU	9 (200 g a.s./ha)	5 (90 g a.s./ha)	14	380-2019 (S-2399 60 g/L EC) 258-2016 (S-2399 40 SC)	TPR-0139 TPR-0073	KCA 6.3.4/01 KCA 6.3.5/01

S-2399 60 g/L EC: Containing 60 g/L inpyrfluxam applied at 90 g a.s./ha and 120 g a.s./ha

S-2399 40 SC: Containing 400 g/L inpyrfluxam applied at 200 g a.s./ha

(a) In some cases, S-2399 60 g/L EC formulation was tested in side-by-side plots at the same location using different application rates; where this is the case the trials are not considered as independent and the residue data from the application rate relevant to the GB cGAP (90 g a.s./ha) has been used to support the GB use.

The samples from all trials were analysed for the parent compound and the metabolites 3'-OH-S-2840, DFPA-CONH₂, *N*-des-Me-DFPA, DFPA, 1'-CH₂OH-S-2840A, 1'-CH₂OH-S-2840B, 1'-COOH-S-2840A and 1'-COOH-S-2840B using the analytical method S16-03371 (validated in accordance with SANTE/2020/12830 rev.1 (see Section B.5.1.2.5)). The LOQ of the method is 0.01 mg/kg for parent inpyrfluxam, 3'-OH-S-2840, DFPA-CONH₂, *N*-des-Me-DFPA and DFPA, and 0.005 mg/kg for 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1'-CH₂OH-S-2840A and 1'-CH₂OH-S-2840B each expressed as respective compound.

Sufficient storage stability data is available to support the maximum storage periods of samples (370 days) (see Section B.7.1). Storage stability of sample extracts was addressed as matrix-matched procedural recovery samples were extracted and stored from the same length of time and under the same conditions as the test sample extracts (see also the discussion on extracts stability at the end of section 2.7.1 of volume 1).

As highlighted above, a number of the residue trials were overdosed compared to the representative GAP. These trials were conducted at approximately 200 g a.s./ha. As this application rate represents approximately 2.2 N compared to the GAP, and all other trial parameters were the same as the GAP, the proportionality principle can be applied. The scaling factor for the overdosed trials is approximately 0.45, but varied based on the specific application rate used in the trials (see the table below for individual scaling factors).

In all cases where, for example, LOQ value of < 0.01 mg/kg, were scaled down (in accordance with EFSA, 2018, guidance on the proportionality principle), the numeric values based on the scaled residues were used for the sum of the RD-RA, e.g. for trial AU08 (single application of inpyrfluxam at 214.6 g as/ha), the residue of 3'-OH-S-2840 was determined as < 0.01 mg/kg (expressed on a metabolite equivalent basis). However, after scaling (applying a down-scaling factor of x 0.42) and expressed on a parent basis, the down-scaled residue results for this trial was < 0.0040 mg/kg. While this is represented as < LOQ (i.e., 0.01 mg/kg) in the summary below, the numeric value of 0.0040 mg/kg for this metabolite was the value taken forward into the summed residue (expressed as parent) in the RD-RA. Residues of parent are given individually so the exact figure as used in the sum of the RD-RA is presented below. The same was done for residues in wheat.

The submitted dossier also includes trials data from southern Europe. These trials do not reflect the agronomic and climatic conditions of the UK and were therefore not used in support of the representative use for approval.

Summary

Table 2.7.4-3: Residues of inpyrfluxam in barley in accordance with the GAP

Crop	Trial	Unscaled residues (mg/kg)	Application rate used in trial (g a.s./ha)	Scaling factor	Scaled residues (mg/kg)	Range of scaled residues (mg/kg)
Barley grain	HU01	0.02	93.9	0.958	0.019	0.004 – 0.204
	PL02	0.20	88.2	1.02	0.204	
	GE03	<0.01	89.7	1.00	<0.010	
	FR04	<0.01	94.4	0.953	<0.0095	
	DK05	0.06	93.9	0.958	0.058	
	UK01	0.13	213.5	0.422	0.055	
	FR02	0.26	204.3	0.441	0.115	
	PL03	0.12	210.7	0.427	0.051	
	DK05	0.03	215.5	0.418	0.013	
	BE06	0.02	211.8	0.425	0.0085	
	HU07	0.07	211.4	0.426	0.030	
	AU08	<0.01	214.6	0.419	<0.0042	
	NL09	0.06	203.8	0.442	0.026	
	SW10	0.02	202.1	0.445	0.0089	

Barley straw	HU01	0.18	93.9	0.958	0.173	0.062 – 3.13
	PL02	1.70	88.2	1.02	1.73	
	GE03	0.09	89.7	1.00	0.09	
	FR04	0.28	94.4	0.953	0.267	
	DK05	0.09	93.9	0.958	0.086	
	UK01	0.80	213.5	0.422	0.337	
	FR02	7.10	204.3	0.441	3.13	
	PL03	0.65	210.7	0.427	0.278	
	DK05	0.25	215.5	0.418	0.104	
	BE06	0.50	211.8	0.425	0.212	
	HU07	0.67	211.4	0.426	0.285	
	AU08	0.50	214.6	0.419	0.210	
	NL09	0.18	203.8	0.442	0.079	
	SW10	0.14	202.1	0.445	0.062	

Table 2.7.4-4: Residues of the metabolites of inpyrfluxam in barley in accordance with the GAP

Crop	Metabolite	Scaled residues (mg/kg) (expressed as parent)
Barley grain	3'-OH-S-2840	12 x <0.010, 0.013, 0.019
	DFPA-CONH ₂	14 x <0.019
	N-des-Me-DFPA	13 x <0.021, 0.021

	DFPA	12 x <0.019, 0.019, 0.109
	1'-COOH-S-2840A	13 x <0.005, 0.010
	1'-COOH-S-2840B	13 x <0.005, 0.014
	1'-CH ₂ OH-S-2840A	0.007, 0.011, 0.012, 0.014, 0.019, 0.021, 0.024, 0.025, 2 x 0.031, 0.034, 0.037, 0.040, 0.046
	1'-CH ₂ OH-S-2840B	0.007, 0.008, 0.012, 2 x 0.015, 0.022, 0.023, 2 x 0.026, 0.027, 0.029, 0.032, 2 x 0.059
Barley straw	3'-OH-S-2840	4 x <0.010, 0.020, 0.028, 0.029, 0.037, 0.045, 0.053, 0.055, 0.060, 2 x 0.29
	DFPA-CONH ₂	14 x <0.019
	<i>N</i> -des-Me-DFPA	13 x <0.021, 0.026
	DFPA	3 x <0.019, 3 x 0.032, 0.033, 0.048, 0.073, 0.076, 2 x 0.11, 0.25, 0.41
	1'-COOH-S-2840A	2 x 0.004, 0.005, 4 x 0.006, 2 x 0.011, 0.012, 0.013, 0.017, 0.033, 0.14
	1'-COOH-S-2840B	5 x <0.005, 2 x 0.005, 0.007, 2 x 0.009, 2 x 0.010, 0.015, 0.13
	1'-CH ₂ OH-S-2840A	0.017, 0.026, 0.027, 0.034, 0.035, 0.084, 0.096, 0.10, 0.11, 2 x 0.12, 0.15, 0.18, 0.31

	1'-CH ₂ OH-S-2840B	0.010, 2 x 0.033, 0.049, 0.091, 0.10, 2 x 0.12, 0.13, 0.15, 0.17, 0.19, 0.20, 0.63
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Table 2.7.4-5: Summary of residues in barley accordance with the residue definitions for enforcement and risk assessment

Crop	Analyte	Scaled residues (mg/kg) (expressed as parent)	STMR (mg/kg)	HR (mg/kg)	MRL (OECD Calculator) (mg/kg)
Barley grain	RD-Enf: inpyrfluxam	3 x <0.01, 2 x 0.01, 0.013, 0.019, 0.026, 0.030, 0.051, 0.055, 0.058, 0.11, 0.20	0.023	0.20	0.3 (rounded) (unrounded 0.257)
	RD-RA: Sum of inpyrfluxam and its metabolites 1'-CH ₂ OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam	2 x 0.028, 0.039, 0.042, 0.071, 0.085, 0.087, 0.088, 0.094, 0.11, 0.12, 0.13, 0.22, 0.30	0.088	0.30	-

Barley straw	RD-Enf: inpyrfluxam	0.062, 0.079, 0.086, 0.090, 0.10, 0.17, 2 x 0.21, 0.27, 0.28, 0.29, 0.34, 1.73, 3.13	0.21	3.13	MRLs not currently set for animal feed items
	RD-RA: Sum of inpyrfluxam and its metabolites 1'-CH ₂ OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam	0.12, 0.14, 0.24, 0.28, 2 x 0.37, 0.39, 0.44, 0.51, 0.55, 0.59, 0.68, 2.40, 4.36	0.415	4.36	-

Wheat

Fifteen independent GLP trials were conducted on wheat in northern Europe (considered climatically comparable to the UK for residues trials purposes). In these trials, two different formulations were tested. Wheat was treated with one application of 90, 120 or 200 g inpyrfluxam/ha formulated as either an SC or EC at the latest growth stage of BBCH 83. The trials at 120 g as/ha were side by side plots in the other trials, and they did not need to be relied upon. The available trials are summarised in the table below:

Table 2.7.4-6: Overview of residue trials conducted on wheat relevant to the UK

Crop	Region	No. of independent trials ^(a) (application rate)			Report No (Formulation)	Document Number	Reference
		Veget. Period		Total			
		2016	2019				
Wheat	NEU	10 (200 g a.s./ha)	5 (90 g a.s./ha)	15	376-2019 (S-2399 60 g/L EC)	TPR-0137	KCA 6.3.1/01
					256-2016 (S-2399 40 SC)	TPR-0076	KCA 6.3.2/01

S-2399 60 g/L EC: Containing 60 g/L inpyrfluxam applied at 90 g a.s./ha and 120 g a.s./ha

S-2399 40 SC: Containing 400 g/L inpyrfluxam applied at 200 g a.s./ha

(a) In some cases, S-2399 60 g/L EC formulation was tested in side-by-side plots at the same location using different application rates; where this is the case the trials are not considered as independent and the residue data from the application rate relevant to the GB cGAP (90 g a.s./ha) has been used.

The MRL for wheat applies to triticale.

The samples from all trials were analysed for the parent compound and the metabolites 3'-OH-S-2840, DFPA-CONH₂, *N*-des-Me-DFPA, DFPA, 1'-CH₂OH-S-2840A, 1'-CH₂OH-S-2840B, 1'-COOH-S-2840A and 1'-COOH-S-2840B using the analytical method S16-03371 (validated in accordance with SANTE/2020/12830 rev.1 (see Section B.5.1.2.5)). The LOQ of the method is 0.01 mg/kg for parent inpyrfluxam, 3'-OH-S-2840, DFPA-CONH₂, *N*-des-Me-DFPA and DFPA, and 0.005 mg/kg for 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1'-CH₂OH-S-2840A and 1'-CH₂OH-S-2840B each expressed as respective compound.

Sufficient storage stability data is available to support the maximum storage periods of samples (455 days) (see Section B.7.1). Storage stability of sample extracts was addressed as matrix-matched procedural recovery samples were extracted and stored from the same length of time and under the same conditions as the test sample extracts (see also the discussion on extracts stability at the end of section 2.7.1 of volume 1).

As highlighted above, a number of the residue trials were overdosed compared to the GAP. These trials were conducted at approximately 200 g a.s./ha. As this application rate represents approximately 2.2 N compared to the GAP, and all other

trial parameters were the same as the GAP, the proportionality principle can be applied. The scaling factor for the overdosed trials is approximately 0.45, but varied based on the specific application rate used in the trials (see the table below for individual scaling factors).

The submitted dossier also includes trials data from southern Europe. These trials do not reflect the agronomic and climatic conditions of the UK and were therefore not used in support of the representative use for approval.

Summary

Table 2.7.4-7: Residues of inpyrfluxam in wheat in accordance with the GAP

Crop	Trial	Unscaled residues (mg/kg)	Application rate used in trial (g a.s./ha)	Scaling factor	Scaled residues (mg/kg)	Range of scaled residues
Wheat grain	HU01	<0.01	91.0	n/a	<0.0099	<0.0043 – 0.0196
	PL02	0.02	91.8	0.980	0.0196	
	GE03	<0.01	91.8	n/a	<0.0098	
	FR04	0.02	95.3	0.944	0.0189	
	DK05	<0.01	86.2	n/a	<0.0104	
	UK01	<0.01	204.2	n/a	<0.0044	
	FR02	<0.01	206.3	n/a	<0.0044	
	PL03	0.02	207.3	0.434	0.0087	
	GE04	0.02	207.3	0.434	0.0087	
	DK05	<0.01	200.0	n/a	<0.0045	
	BE06	<0.01	211.0	n/a	<0.0043	
	HU07	<0.01	207.3	n/a	<0.0043	

	AU08	<0.01	207.3	n/a	<0.0043	
	NL09	<0.01	200.4	n/a	<0.0045	
	SW10	<0.01	208.3	n/a	<0.0043	
Wheat straw	HU01	0.23	91.0	0.989	0.227	0.026 – 2.94
	PL02	3.0	91.8	0.980	2.94	
	GE03	2.8	91.8	0.980	2.75	
	FR04	2.4	95.3	0.944	2.27	
	DK05	0.96	86.2	1.044	1.00	
	UK01	2.1	204.2	0.441	0.926	
	FR02	0.2	206.3	0.436	0.087	
	PL03	0.57	207.3	0.434	0.247	
	GE04	0.5	207.3	0.434	0.217	
	DK05	0.37	200.0	0.450	0.167	
	BE06	3.3	211.0	0.427	1.41	
	HU07	0.25	207.3	0.434	0.109	
	AU08	0.06	207.3	0.434	0.026	
	NL09	0.17	200.4	0.449	0.076	
	SW10	0.2	208.3	0.432	0.086	

Table 2.7.4-8: Residues of the metabolites of inpyrfluxam in wheat in accordance with the GAP

Crop	Metabolite	Scaled residues (mg/kg) (expressed as parent)
Wheat grain	3'-OH-S-2840	15 x <0.010
	DFPA-CONH ₂	15 x <0.019
	<i>N</i> -des-Me-DFPA	15 x <0.021
	DFPA	15 x <0.019
	1'-COOH-S-2840A	13 x <0.005, 0.005, 0.008
	1'-COOH-S-2840B	13 x <0.005, 0.007, 0.009
	1'-CH ₂ OH-S-2840A	14 x <0.005, 0.005
	1'-CH ₂ OH-S-2840B	14 x <0.005, 0.017
Wheat straw	3'-OH-S-2840	2 x 0.008, 0.016, 0.017, 0.029, 0.046, 0.047, 0.050, 0.075, 0.16, 0.20, 0.21, 0.43, 0.45, 0.72
	DFPA-CONH ₂	15 x <0.019
	<i>N</i> -des-Me-DFPA	15 x <0.021
	DFPA	2 x 0.025, 2 x 0.033, 0.034, 0.058, 0.099, 0.13, 0.16, 0.18, 0.21, 0.26, 2 x 0.27, 0.28
	1'-COOH-S-2840A	4 x <0.005, 0.005, 0.006, 0.008, 0.018, 0.019, 0.029, 0.12, 0.21, 0.33, 0.37, 0.42

	1'-COOH-S-2840B	5 x <0.005, 0.006, 0.008, 0.022, 0.025, 0.029, 0.35, 2 x 0.37, 0.40, 0.58
	1'-CH ₂ OH-S-2840A	2 x <0.005, 0.006, 0.013, 0.016, 0.019, 0.021, 0.041, 0.046, 0.054, 0.070, 0.077, 0.079, 0.23, 0.25
	1'-CH ₂ OH-S-2840B	1 x <0.005, 0.005, 0.006, 2 x 0.010, 0.037, 0.042, 0.054, 0.078, 0.083, 0.090, 0.11, 0.31, 0.37, 0.47

Table 2.7.4-9: Summary of residues in wheat accordance with the residue definitions for enforcement and risk assessment

Crop	Analyte	Scaled residues (mg/kg) (expressed as parent)	STMR (mg/kg)	HR (mg/kg)	MRL (OECD Calculator) (mg/kg)
Wheat grain	RD-Enf: inpyrfluxam	10 x <0.01, 3 x 0.01, 0.019, 0.020	0.010	0.020	0.03 (rounded) (unrounded 0.025)
	RD-RA: Sum of inpyrfluxam and its metabolites 1'-CH ₂ OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-	0.012, 6 x 0.013, 0.014, 0.019 2 x 0.029, 0.030, 0.034, 0.037, 0.038	0.014	0.038	-

	2840, expressed as inpyrfluxam				
Wheat straw	RD-Enf: inpyrfluxam	0.026, 0.076, 0.086, 0.087, 0.11, 0.17, 0.22, 0.23, 0.25, 0.93, 1.00, 1.41, 2.27, 2.75, 2.94	0.23	2.94	MRLs not currently set for animal feed items
	RD-RA: Sum of inpyrfluxam and its metabolites 1'-CH ₂ OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam	0.15, 0.16, 0.20, 0.23, 0.24, 0.33, 0.45, 0.64, 0.94, 1.22, 2 x 1.74, 2.73, 3.19, 3.67	0.64	3.67	-

Conversion factors

The data indicate a median conversion factor (CF) of 1.9 from RD-Enf (parent inpyrfluxam) to RD-RA (inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam) for barley grain.

For wheat grain a robust conversion factor could not be calculated as residues of parent (inpyrfluxam) or metabolites (1'-CH₂OH-S-2840, 3'-OH-S-2840) were not all > LOQ in any of the available trials. The OECD Guidance on Crop Field Trials (2016, ENV/JM/MONO(2011)50/REV1) states "For the calculation of CFs residue trials resulting in residue levels below the LOQ should not be taken into account".

For barley grain, this calculation has been done accounting only for the trials where residues of parent and metabolites were all > LOQ in line with the OECD 2016 Crop Field Trial guidance. In total there were 5 trials that were suitable for calculation of the conversion factor.

The CF for barley could be considered suitable for other cereal grains.

Conversion factors have not been calculated for wheat or barley straw as these are feed commodities and MRLs are not set. Therefore, a conversion factor from RD-Enf to RD-RA is not required for these commodities.

Table 2.7.4-10: Summary of the residue trial results used to calculate the individual CFs and derive the median CF for barley grain

Trial number	Residue in compliance with the residue definition for enforcement ^(a)	Residue in compliance with the residue definition for risk assessment ^(b)	Individual CFs
1	0.20	0.30	1.5
2	0.055	0.12	2.2
3	0.12	0.22	1.9
4	0.051	0.094	1.8
5	0.030	0.085	2.9
Median value of individual CFs: 1.9			

(a) inpyrfluxam

(b) sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam

2.7.5. Summary of metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish

Livestock metabolism

The metabolism of inpyrfluxam in livestock has been studied in laying hens and lactating goats after oral administration of either phenyl or pyrazole pyrazolyl labelled inpyrfluxam. A summary of the available studies is below.

Table 2.7.5-1: Summary of the animal metabolism studies

Animal	Dose (mg/kg bw/d)	Duration (days)	N rate/Comment
Laying hen	Pyrazolyl-4- ¹⁴ C 12.44mg a.s./kg feed (0.86 mg a.s./kg bw/d) (14.12 mg / kg DM / day)	7	25N
	Phenyl-U- ¹⁴ C 13.13mg a.s./kg feed (0.83 mg a.s./kg bw/d) (14.90 mg / kg DM / day)		24N
Lactating goat	Pyrazolyl-4- ¹⁴ C 13.74 mg a.s./kg feed/day (0.51 mg a.s./kg bw/d)	5	4N
	Phenyl-U- ¹⁴ C 15.74 mg a.s./kg feed/day (0.64 mg a.s./kg bw/d)		5N

As noted in section 2.7.6, the test substance used in the livestock metabolism (and feeding studies) should be representative of the residues of feedstuffs. Dosing in the

metabolism and feeding studies involved inpyrfluxam only. Parent inpyrfluxam represents a large component of the residue in plants, including feed items. The main metabolites found in plants were also detected in livestock and rats (3'-OH-S-2840 was minor in the rat, and 1'-COOH-S-2840 and 1'-CH₂OH-S-2840 are major metabolites in the rat, Vol 3 section B.6.1.1). Therefore there are no unique plant metabolites that might need further consideration in the livestock assessment. The available livestock metabolism studies indicate that animals, when dosed with inpyrfluxam, will also be 'exposed' to the anticipated feed item metabolites. Specific livestock metabolism studies on plant metabolites would not be justified.

Laying hen metabolism

Inpyrfluxam was administered orally to twenty hens in two radiolabelled forms; [Phenyl-U-¹⁴C] inpyrfluxam and [Pyrazolyl-4-¹⁴C] inpyrfluxam for 7 consecutive days at the actual dose rate of 12.44 mg a.s/kg feed for [Pyrazolyl-4-¹⁴C] inpyrfluxam and 13.13 mg a.s/kg feed for [Phenyl-U-¹⁴C] inpyrfluxam dosed hens. Based on the daily feed consumption and body weight of the birds, the dose level corresponds to 14.12 mg a.s./kg dry matter for birds dosed with [Pyrazolyl-4-¹⁴C] inpyrfluxam and 14.90 mg a.s./kg dry matter for birds dosed with [Phenyl-U-¹⁴C] inpyrfluxam.

The overall post dose recovery was 82.68% in the [Pyrazolyl-4-¹⁴C] inpyrfluxam labelled study and 84.63% in the [Phenyl-U-¹⁴C] inpyrfluxam study. The largest % of the dose was detected in the excreta accounting for approximately 80.25% ([Pyrazolyl-4-¹⁴C] inpyrfluxam) and 81.70% ([Phenyl-U-¹⁴C] inpyrfluxam). Radioactive residues recovered in cage wash and rinse accounted for up to 1.33% in the [Pyrazolyl-4-¹⁴C] inpyrfluxam label and 1.57% in the [Phenyl-U-¹⁴C] inpyrfluxam label. Radioactive residues in the edible portions (egg and tissue) accounted for up to 0.22% of the total dose in [Pyrazolyl-4-¹⁴C] inpyrfluxam and 0.11% in [Phenyl-U-¹⁴C] inpyrfluxam dosed hens. No explanation was provided for the 15.4 – 17.4 % of the dose which was not recovered.

Residue levels in eggs were monitored for 7 consecutive days and accounted for 0.06% of the total dose in both labels. The residue level followed an approximately linear increase over the 7 day dosing period, reaching a maximum of 0.033 mg eq./kg in both radiolabels. In edible matrices the highest TRR was found in the liver (0.268-0.526 mg eq./kg).

Muscle, liver and composite samples of egg were extracted twice with acetonitrile/water (1:1, v/v) and then with acetonitrile. Fat samples were extracted once with hexane/acetone (4:1, v/v) and then with acetone. > 90% of the [¹⁴C] inpyrfluxam residues in all tissue, egg and excreta samples were extracted with only up to 10% of the TRR remaining in the post extraction solids. The only exception was muscle samples from hens dosed with [Phenyl-U-¹⁴C] inpyrfluxam which only had an extraction efficacy of 80% of the TRR with 20% of the total TRR remaining in the post extraction solids. However, this equated to < 0.003 mg eq./kg of residues

which is below the 0.05 mg/kg trigger in the OECD guidance so no further characterisation was required.

Parent compound and metabolites were identified based on HPLC retention times; quantification was performed using reverse phase HPLC. Identities of the components were confirmed by TLC using comparison of R_f values to standards which were analysed with the sample by LC-MS.

Parent compound was detected in egg, thigh and fat samples in both [Pyrazolyl-4-¹⁴C] inpyrfluxam and [Phenyl-U-¹⁴C] inpyrfluxam dosed hens. Inpyrfluxam was also detected in breast from [Pyrazolyl-4-¹⁴C] inpyrfluxam dosed hens. Metabolites 1'-COOH-S-2840 (sum of isomers), sulphate conjugates of 1'-CH₂OH-S-2840 termed sulphate 37 and 39, 1'-CH₂OH-S-2840 (sum of isomers), 3'-OH-S-2840 and *N*-des-Me-S-2840 were detected in several tissues from both labels. The label specific metabolite DFPA-CONH₂ was detected in samples from [Pyrazolyl-4-¹⁴C] inpyrfluxam dosed hens only. A total of seven metabolites were detected in samples from laying hens, see table 2.7.6-1 in the residue definition section % TRR found in each matrix from both studies.

Lactating goat metabolism

Inpyrfluxam was administered orally to two lactating goats in two radiolabelled forms [Pyrazolyl-4-¹⁴C] inpyrfluxam and [Phenyl-U-¹⁴C] inpyrfluxam for 5 consecutive days at the actual dose rate 13.74 mg/kg feed/day for [Pyrazolyl-4-¹⁴C] inpyrfluxam and 15.74 mg/kg feed/day for [Phenyl-U-¹⁴C] inpyrfluxam dosed goats. This equates to 0.51 and 0.63 mg/kg body weight/day for the goat treated with [pyrazolyl-4-¹⁴C] inpyrfluxam and [phenyl-U-¹⁴C] inpyrfluxam respectively.

The overall post dose recovery was 96.97% TRR in the [Pyrazolyl-4-¹⁴C] inpyrfluxam label study and 97.11% in the [Phenyl-U-¹⁴C] inpyrfluxam label. The largest % of the dose was detected in excreta accounting for approximately 76% in the [Pyrazolyl-4-¹⁴C] inpyrfluxam label and 78% in the [Phenyl-U-¹⁴C] inpyrfluxam label. The amounts remaining in the GI tracts at sacrifice were > 18.61% of the initial dose. Radioactive residues recovered in cage wash and rinse accounted for < 0.1% in both labels. Radioactive residues in the edible portions accounted for < 1 % of the total TRR.

Residue levels in milk were monitored for five days and accounted for maximum of 0.40 mg eq./kg in whole milk for both radiolabelled test substances. No definitive plateau was reached over the five day period, residues were quick to reduce between AM and PM samples showing that residues do not accumulate. In edible matrices the highest TRR was found in the liver (0.334 – 0.350 mg eq./kg).

Muscle, liver, kidney and faeces samples were extracted with acetonitrile:water (1:1, v/v) and then acetonitrile. Milk fat, omental, subcutaneous and renal fat portions were extracted with hexane:acetone (4:1, v/v) and acetone. Skimmed milk was

extracted with acetone:water and then acetone. Urine samples were analysed directly by chromatographic methods. In all matrices, > 90 % of the [^{14}C] Inpyrfluxam residues were extracted, excluding omental, subcutaneous and renal fat for the pyrazolyl label where 83.33, 83.33 and 71.43% TRR were extracted respectively. For these fat matrices, PES were < 30% TRR, however the absolute residues were very low (≤ 0.002 mg eq./kg) so no further characterisation was needed.

Radiolabelled residues were characterised by linear gradient reverse phase HPLC using co-chromatography with reference standards. The identity of residues was assigned based on the HPLC retention times. Identity of components was confirmed by TLC using comparison of R_f values to standards analysed with the sample by LC-MS.

Parent compound was detected in liver and subcutaneous fat samples in both labels. Inpyrfluxam was also detected in omental fat, renal fat and milk fat in the [Phenyl- ^{14}C] inpyrfluxam label. Metabolites of 1'-COOH-S-2840 (sum of isomers), 1'-CH₂OH-S-2840, 3'-OH-S-2840, Glu-1'-CH₂OH-S-2840 were detected in several matrices. DFPA-CONH₂ and '1'-bis(CH₂OH)-S-2840B were label specific residues detected in the [Pyrazolyl-4- ^{14}C] inpyrfluxam dosed goats only. A total of eight metabolites were detected in lactating goats. See table 2.7.6-2 in the residue definition section for the %TRR found in each matrix from both studies.

Summary

The metabolism in hens (poultry) and goat (ruminants) is similar with minor variations. The metabolism in both hens and ruminants following oral administration of inpyrfluxam proceeds via oxidation to form the hydroxylated component 1'-CH₂OH-S-2840A and 1'-CH₂OH-S-2840B. This metabolite is further transformed by oxidation to the carboxylic acid metabolite 1'-COOH-S-2840A and 1'-COOH-S-2840B. N-demethylation of inpyrfluxam forms the metabolite N-des-Me-S-2840. Cleavage of the amide bond in inpyrfluxam forms DFPA-CONH₂. In poultry the sulphate conjugate of 1'-CH₂OH-S-2840 is formed from the primary alcohol. N-demethylation on the pyrazolyl ring of inpyrfluxam forms the metabolite N-des-Me-S-2840. In ruminants a minor pathway is observed with formation of 1'-1'-bis-(CH₂OH)-S-2840 by oxidation of the 1'-CH₂OH-S-2840 metabolite.

Inpyrfluxam and its metabolites 1'-CH₂OH-S-2840A, 1'-CH₂OH-S-2840B, 1'-COOH-S-2840A and 1'-COOH-S-2840B were individually determined in milk, egg and tissues. These common metabolites were included for analysis in the livestock feeding studies.

A RD-RA for inpyrfluxam has not been proposed at this time (See 2.7.6 Vol 1) therefore only the fat solubility of **this inpyrfluxam** needs consideration. Parent inpyrfluxam has an octanol-water partition coefficient of 3.65, suggesting potential accumulation in fat. Inpyrfluxam residues were predominantly found in liver and

kidney commodities. In goats, concentrations between fat and muscle were close to the LOQ without clear tendency for accumulation in the fat. In poultry metabolism studies, fat contained approximately 30x higher residue concentrations compared to muscle. However, no accumulation was observed in milk fat or egg yolk. In the feeding studies, residues were generally < LOQ, not allowing estimation of ratios between fatty and non-fatty tissues. Overall it is considered that inpyrfluxam is not fat-soluble.

The proposed metabolic pathway in poultry and ruminants is shown in figures 2.7.5-1 and 2 below. The metabolic pathway is similar to that observed in rats (Vol 3 CA B6, Section 6.1).

Figure 2.7.5-1: Proposed metabolic pathway in poultry

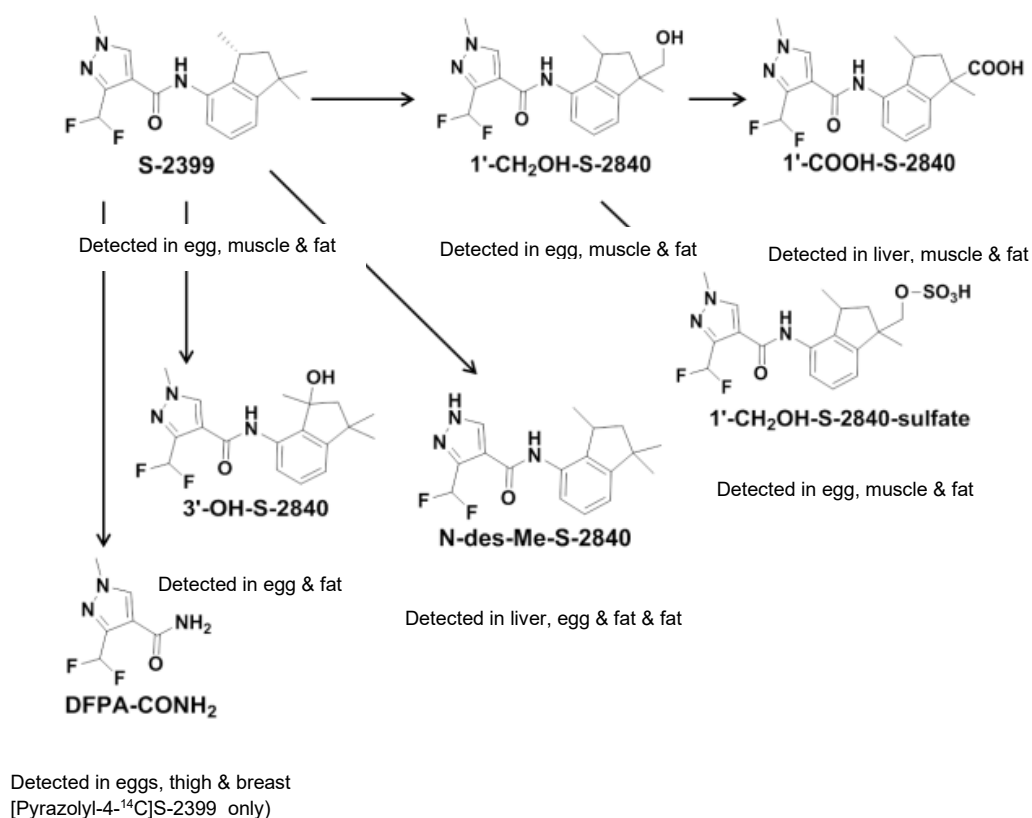
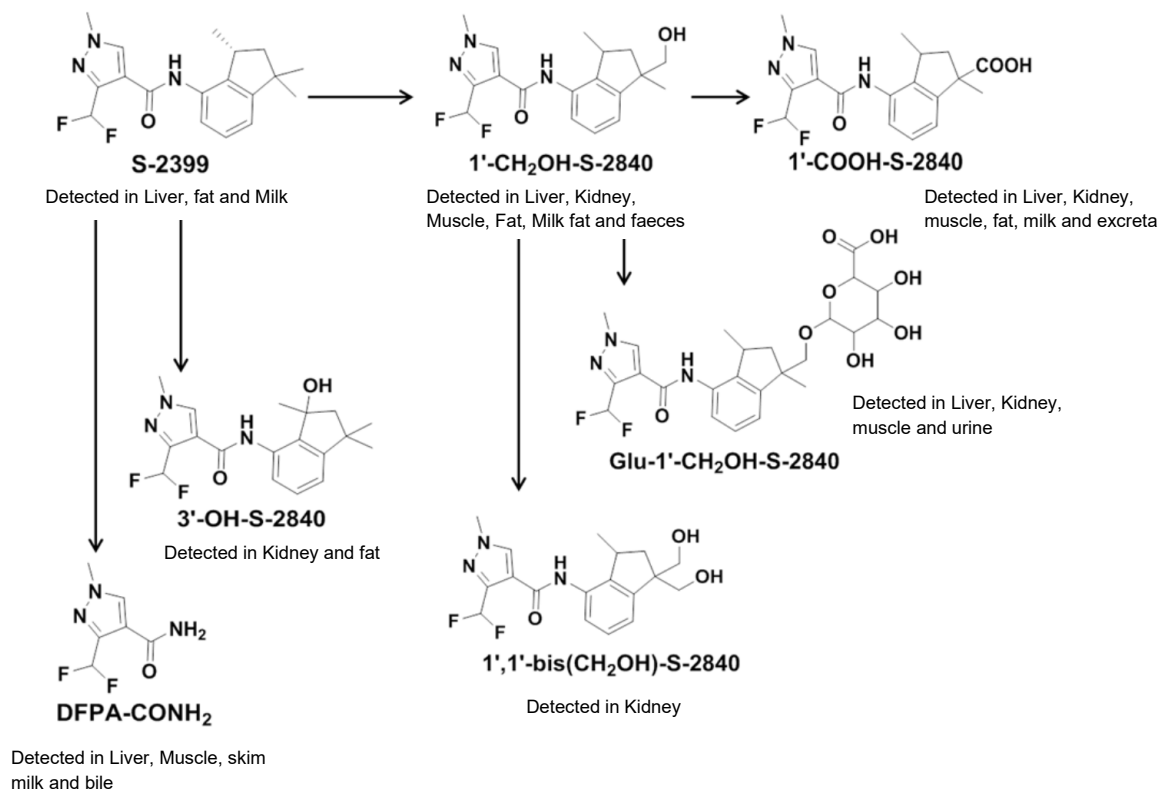


Figure 2.7.5-2: Proposed metabolic pathway in ruminants

The metabolic pathway of inpyrfluxam in laying hen and lactating goat is evaluated to be sufficiently similar since in general the same metabolic steps are involved and a number of the same metabolites are found.

Fish

At present there is no agreed guidance on how to conduct fish metabolism studies to determine the residue definition for risk assessment and enforcement and there are no agreed guidance documents on how then to conduct a fish feeding study.

Guidance on residues in fish (metabolism studies and feeding studies) has been under development in the EU. The OECD programme on residue guidelines has not yet considered guidelines applicable to fish.

Since no agreed guidance is available at this time, it is considered that the residue requirements for fish do not need to be addressed in the current evaluation.

Depending on the residues in crops, further information to address this data requirement (nature of residues in fish [metabolism], and if needed, magnitude of the residues in fish [feeding studies]) will be required when guidance becomes available.

Pigs

As the metabolic pathway observed in hens and goats is similar to the metabolism observed in rats (Vol 3 CA B6, Section 6.1), an assessment of the metabolism in pigs is not required.

2.7.6. Definition of the residue in products of animal origin

Based on the intakes for the current GAP on wheat and barley, the dietary burden trigger of 0.004 mg/kg bw per day is exceeded for all relevant groups, except swine. Metabolism of inpyrfluxam in laying hens and lactating goats was therefore submitted. The metabolism studies indicated that at 1N, residues above the LOQ could be expected in ruminants so feeding studies were required. Based on the current GAP, residues in poultry matrices are not expected above the LOQ based on the metabolism study **at (assuming 1N rate)**. However, a feeding study on both poultry and ruminants have been submitted and evaluated.

The test substance used in the livestock metabolism and feeding studies should be representative of the residues of feedstuffs. Dosing in the metabolism and feeding studies involved inpyrfluxam only. Parent inpyrfluxam represents a large component of the residue in plants, including feed items. The main metabolites found in plants were also detected in livestock and rats (3'-OH-S-2840 was minor in the rat, and 1'-COOH-S-2840 and 1'-CH₂OH-S-2840 are major metabolites in the rat, Vol 3 section B.6.1.1). Therefore there are no unique plant metabolites that might need further consideration in the livestock assessment. The available livestock metabolism studies indicate that animals, when dosed with inpyrfluxam, will also experience 'exposure' to the anticipated feed item metabolites).

An overview of the results from the livestock metabolism studies is presented in the following tables.

Table 2.7.6-1: Overview of metabolism in poultry in terms of % TRR

Study reference	KCA 6.2.2/01 - 2453W (TPM-0025)												
Animal	Poultry (Laying Hens)												
Number of animals	20 (10 per radio label)												
number of applications	Once a day on 7 consecutive days												
mg/kg bw/day	0.855						0.835						
mg/kg DM basis	14.12						14.90						
Number dosing days	7						7						
Time of sacrifice after the final dose (hours)	6						6						
Plateau reached in eggs and milk (days)	Not reached						Not reached						
Storage: sampling to extraction/analysis (days/months)¹⁾	35 / 43	28 / 42	28 / 327	28 / 327	28 / 329	33 / 39	40 / 43	28 / 36	28 / 328	28 / 328	28 / 329	33 / 40	
¹⁴C labelling	[pyrazolyl-4-¹⁴C] inpyrfluxam						[phenyl-U-¹⁴C] inpyrfluxam						
Matrix	Muscle		Fat		Liver	Egg	Muscle		Fat		Liver	Egg	

	thigh	breast	abdominal	subcutan.			thigh	breast	abdominal	subcutan.		
TRR (mg eq./kg)	0.013	0.012	0.064	0.102	0.317	0.023	0.015	0.023	0.094	0.081	0.255	0.020
Total extracted residues (% TRR)	92.3	91.7	98.4	99.0	94.3	91.3	80.0	91.3	96.8	97.5	91.4	90.0
Parent compound (free and/or conjugated)	4.9	2.9	69.9	73.7	0.0	10.5	2.2	0.0	55.0	80.7	0.0	10.9
3'-OH-S-2840	0.0	0.0	2.7	2.2	0.0	1.9	0.0	0.0	1.5	0.0	0.0	2.5
N-des-Me-S-2840	0.0	0.0	3.3	3.2	4.6	5.0	0.0	0.0	2.5	0.0	9.5	5.6
1'-CH₂OH-S-2840A	0.0	0.0	0.0	0.0	0.0	6.6	5.2	0.0	0.0	0.0	0.0	6.1
1'-CH₂OH-S-2840B	11.1	5.6	2.7	2.6	0.0	25.0	5.6	3.4	2.3	0.0	0.0	23.7
Sulphate 37 (sulphate conjugate of 1'-CH₂OH-S-2840)	4.4	4.5	1.1	0.0	22.2	1.7	11.6	12.3	2.7	16.9	27.6	3.1
Sulphate 39 (sulphate conjugates of 1'-CH₂OH-S-2840)	6.9	5.7	0.0	3.2	29.5	3.4	13.6	35.3	5.7	0.0	16.5	6.1
Glu-1'-CH₂OH-S-2840 (sum of isomers)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

1'-COOH-S-2840A	4.3	4.9	0.0	0.0	3.3	0.0	5.2	2.8	0.0	0.0	4.4	2.2
1'-COOH-S-2840B	5.5	6.1	1.2	0.0	3.2	0.0	11.2	7.8	3.2	0.0	6.6	2.5
DFPA	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DFPA-CONH₂	14.5	11.8	0.0	0.0	0.0	5.0	0.0	0.0	0.0	0.0	0.0	0.0
1',1'-bis-(CH₂OH)-S-2840	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total identified (% TRR)	51.6	41.5	80.7	84.8	62.8	59.2	54.6	61.6	72.9	97.5	64.5	62.6
Organosoluble fractions												
Aqueous soluble fractions												
Neutral fraction												
Acidic fraction												
Polar fraction												
Total characterised (% TRR)												
Unknown 1												
Unknown 2												
Others	40.7	50.2	17.7	14.3	31.5	32.1	25.4	29.7	23.9		26.9	27.4

Not analysed fractions												
Unresolved												
Unextracted radioactive residues (% TRR)												
Acid/base hydrolysis												
Enzymatic hydrolysis												
PES (% TRR)	7.7	8.3	1.6	1.0	5.7	8.7	20.0	8.7	3.2	2.5	8.6	10.0
Sum of radioactive residues (% TRR)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table key:

> 10 % TRR < 0.01 mg eq./kg

> 10 % TRR > 0.01 mg eq./kg

Table 2.7.6-1 continued: Overview of metabolism in poultry in terms of mg eq./kg

Study reference	KCA 6.2.2/01 - 2453W (TPM-0025)
Animal	Poultry (Laying Hens)
Number of animals	20 (10 per radio label)

number of applications	Once a day on 7 consecutive days												
mg/kg bw/day	0.855						0.835						
mg/kg DM basis	14.12						14.90						
Number dosing days	7						7						
Time of sacrifice after the final dose (hours)	6						6						
Plateau reached in eggs and milk (days)	Not reached						Not reached						
Storage: sampling to extraction/analysis (days/months) ¹⁾	35 / 43	28 / 42	28 / 327	28 / 327	28 / 329	33 / 39	40 / 43	28 / 36	28 / 328	28 / 328	28 / 329	33 / 40	
¹⁴ C labelling	[pyrazolyl-4- ¹⁴ C] inpyrfluxam						[phenyl-U- ¹⁴ C] inpyrfluxam						
Matrix	Muscle		Fat		Liver	Egg	Muscle		Fat		Liver	Egg	
	thigh	breast	abdominal	subcutan.			thigh	breast	abdominal	subcutan.			
TRR (mg eq./kg)	0.013	0.012	0.064	0.102	0.317	0.023	0.015	0.023	0.094	0.081	0.255	0.020	
Total extracted residues (% TRR)	92.3	91.7	98.4	99.0	94.3	91.3	80.0	91.3	96.8	97.5	91.4	90.0	

Parent compound (free and/or conjugated)	0.001	≤0.001	0.045	0.075	0.000	0.002	≤0.001	0.000	0.052	0.065	0.000	0.002
3'-OH-S-2840	0.000	0.000	0.002	0.002	0.000	≤0.001	0.000	0.000	0.001	0.000	0.000	≤0.001
N-des-Me-S-2840	0.000	0.000	0.002	0.003	0.015	0.001	0.000	0.000	0.002	0.000	0.024	0.001
1'-CH₂OH-S-2840A	0.001	0.000	0.000	0.000	0.000	0.002	0.001	0.000	0.000	0.000	0.000	0.001
1'-CH₂OH-S-2840B	0.000	0.001	0.002	0.003	0.000	0.006	0.001	0.001	0.002	0.000	0.000	0.005
Sulphate 37 (sulphate conjugate of 1'-CH₂OH-S-2840)	0.001	0.001	0.001	0.000	0.070	≤0.001	0.002	0.003	0.003	0.014	0.070	≤0.001
Sulphate 39 (sulphate conjugate of 1'-CH₂OH-S-2840)	0.001	0.001	0.000	0.003	0.094	0.001	0.002	0.008	0.005	0.000	0.042	0.001
Glu-1'-CH₂OH-S-2840 (sum of isomers)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1'-COOH-S-2840A	0.001	0.001	0.000	0.000	0.010	0.000	0.001	0.001	0.000	0.000	0.011	≤0.001
1'-COOH-S-2840B	0.001	0.001	0.001	0.000	0.010	0.000	0.002	0.002	0.003	0.000	0.017	≤0.001
DFPA	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DFPA-CONH₂	0.002	0.001	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000

1',1'-bis-(CH₂OH)-S-2840	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Total identified (% TRR)	0.008	0.006	0.053	0.086	0.199	0.013	0.009	0.015	0.068	0.079	0.164	0.010
Organosoluble fractions												
Aqueous soluble fractions												
Neutral fraction												
Acidic fraction												
Polar fraction												
Total characterised (% TRR)												
Unknown 1												
Unknown 2												
Others	0.005	0.006	0.011	0.015	0.100	0.007	0.004	0.007	0.022		0.068	0.005
Not analysed fractions												
Unresolved												

Table 2.7.6-2: Overview of metabolism in ruminants in terms of % TRR – pyrazolyl only

Study reference	KCA 6.2.3/01 - 2452W (TPM-0024)								
Animal	Ruminants (Lactating Goat)								
Number of animals	2 (1 per radio label)								
number of applications	Once a day on 5 consecutive days								
mg/kg bw/day	0.51								
mg/kg DM basis	13.74								
Number dosing days	5								
Time of sacrifice after the final dose (hours)	6-8								
Plateau reached in eggs and milk (days)	Not reached								
Storage: sampling to extraction/analysis (days/months)¹⁾	23 /	23 /	24	24 / 43 / 50 / 100	24	22 / 408	22 / 36	37 / 50	34 / 55

¹⁴ C labelling	[pyrazolyl-4- ¹⁴ C] inpyrfluxam								
Matrix	Muscle		Fat			Liver	Kidney	Milk	
	flank	loin	omental	subcutaneous	renal			skim	fat
TRR (mg eq./kg)	0.014	0.012	0.006	0.012	0.007	0.313	0.162	0.034	0.029
Total extracted residues (% TRR)	100.0	91.7	83.3	83.3	71.4	91.1	98.2	100.0	100.0
Parent compound (free) and/or conjugated)	0.0	0.0	not analysed	3.1	not analysed	5.9	0.0	0.0	0.0
3'-OH-S-2840	0.0	0.0		<1.00		0.0	3.1	0.0	0.0
N-des-Me-S-2840	0.0	0.0		0.0		0.0	0.0	0.0	0.0
1'-CH ₂ OH-S-2840A	8.4	5.6		6.2		4.9	0.0	0.0	0.0
1'-CH ₂ OH-S-2840B	0.0	0.0		6.1		0.0	0.0	0.0	0.0
Sulphate 37 (sulphate conjugate of 1'-CH ₂ OH-S-2840)	0.0	0.0		0.0		0.0	0.0	0.0	0.0
Sulphate 39 (sulphate conjugate	0.0	0.0		0.0		0.0	0.0	0.0	0.0

of 1'-CH ₂ OH-S-2840)									
Glu-1'-CH₂OH-S-2840 (sum of isomers)	22.1	16.0		0.0		15.9	24.5	0.0	0.0
1'-COOH-S-2840A	20.2	18.9		27.2		31.7	39.1	12.1	8.8
1'-COOH-S-2840B	23.6	14.7		1.7		10.4	10.6	0.0	0.0
DFPA	0.0	0.0		0.0		0.0	0.0	0.0	0.0
DFPA-CONH₂	11.2	0.0		0.0		2.5	0.0	2.1	0.0
1',1'-bis-(CH₂OH)-S-2840	0.0	0.0		0.0		0.0	1.1	0.0	0.0
Total identified (% TRR)	85.4	55.2		44.2		71.4	78.4	14.2	8.8
Organosoluble fractions									
Aqueous soluble fractions									
Neutral fraction									
Acidic fraction									

Polar fraction									
Total characterised (% TRR)									
Unknown 1									
Unknown 2									
Others	14.6	36.5		39.2		19.7	19.7	85.8	91.2
Not analysed fractions									
Unresolved									
Unextracted radioactive residues (% TRR)									
Acid/base hydrolysis									
Enzymatic hydrolysis									
PES (% TRR)	0.0	8.3	16.7	16.7	28.6	9.0	1.9	0.0	0.0
Sum of radioactive residues (% TRR)	100.0	100.0	100.0	100.0	100.0	100.0	99.9	100.0	100.0

Table key:

> 10 % TRR < 0.01 mg eq./kg

> 10 % TRR > 0.01 mg eq./kg

Table 2.7.6-2 continued: Overview of metabolism in ruminants in terms of mg eq./kg – pyrazolyl only

Study reference	KCA 6.2.3/01 - 2452W (TPM-0024)									
Animal	Ruminants (Lactating Goat)									
Number of animals	2 (1 per radio label)									
number of applications	Once a day on 5 consecutive days									
mg/kg bw/day	0.51									
mg/kg DM basis	13.74									
Number dosing days	5									
Time of sacrifice after the final dose (hours)	6-8									
Plateau reached in eggs and milk (days)	Not reached									
Storage: sampling to extraction/analysis (days/months)¹⁾	23 /	23 /	24	24 / 43 / 50 / 100	24	22 / 408	22 / 36	37 / 50	34 / 55	
¹⁴C labelling	[pyrazolyl-4-¹⁴C] inpyrfluxam									

Matrix	Muscle		Fat			Liver	Kidney	Milk	
	flank	loin	oment al	subcutan .	renal			skim	fat
TRR (mg eq./kg)	0.014	0.012	0.006	0.012	0.007	0.313	0.162	0.034	0.029
Total extracted residues (% TRR)	100.0	91.7	83.3	83.3	71.4	91.1	98.2	100.0	100.0
Parent compound (free) and/or conjugated)	0.000	0.000	--	≤0.001	--	0.019	0.000	0.000	0.000
3'-OH-S-2840	0.000	0.000	--	≤0.001	--	0.000	0.005	0.000	0.000
N-des-Me-S-2840	0.000	0.000	--	0.000	--	0.000	0.000	0.000	0.000
1'-CH ₂ OH-S-2840A	0.001	0.001	--	0.001	--	0.015	0.000	0.000	0.000
1'-CH ₂ OH-S-2840B	0.000	0.000	--	0.001	--	0.000	0.000	0.000	0.000
Sulphate 37 (sulphate conjugate of 1'-CH ₂ OH-S-2840)	0.000	0.000	--	0.000	--	0.000	0.000	0.000	0.000
Sulphate 39 (sulphate conjugate of 1'-CH ₂ OH-S-2840)	0.000	0.000	--	0.000	--	0.000	0.000	0.000	0.000
Glu-1'-CH ₂ OH-S-2840 (sum of isomers)	0.003	0.002	--	0.000	--	0.050	0.040	0.000	0.000
1'-COOH-S-2840A	0.003	0.002	--	0.003	--	0.099	0.063	0.004	0.003
1'-COOH-S-2840B	0.003	0.002	--	≤0.001	--	0.033	0.017	0.000	0.000

DFPA	0.000	0.000	--	0.000	--	0.000	0.000	0.000	0.000
DFPA-CONH₂	0.002	0.000	--	0.000	--	0.008	0.000	0.001	0.000
1',1'-bis-(CH₂OH)-S-2840	0.000	0.000	--	0.000	--	0.000	0.002	0.000	0.000
Total identified (% TRR)	0.012	0.007	--	0.005	--	0.224	0.127	0.005	0.003
Organosoluble fractions									
Aqueous soluble fractions									
Neutral fraction									
Acidic fraction									
Polar fraction									
Total characterised (% TRR)									
Unknown 1									
Unknown 2									
Others	0.002	0.003	--	0.005	--	0.063	0.032	0.029	0.026
Not analysed fractions									
Unresolved									

Table 2.7.6-3: Overview of metabolism in ruminants in terms of % TRR – phenyl only

Study reference	KCA 6.2.3/01 - 2452W (TPM-0024)								
Animal	Ruminants (Lactating Goat)								
Number of animals	2 (1 per radio label)								
number of applications	Once a day on 5 consecutive days								
mg/kg bw/day	0.64								
mg/kg DM basis	15.74								
Number dosing days	5								
Time of sacrifice after the final dose (hours)	6-8								
Plateau reached in eggs and milk (days)	Not reached								
Storage: sampling to extraction/analysis (days/months)¹⁾	23 / 38	23 / 38	24 / 50	24 / 43 / 51 / 100	24	22 / 36	22 / 38	37 / 50	34 / 55
¹⁴C labelling	[phenyl-U-¹⁴C] inpyrfluxam								
Matrix	Muscle		Fat			Liver	Kidney	Milk	
	flank	loin	omental	subcutan.	renal			skim	fat

TRR (mg eq./kg)	0.021	0.015	0.024	0.029	0.041	0.344	0.170	0.040	0.018
Total extracted residues (% TRR)	95.2	93.3	87.5	96.6	90.2	90.4	97.7	100.0	94.4
Parent compound (free) and/or conjugated)	0.0	0.0	15.8	6.4	8.2	4.9	0.0	0.0	9.1
3'-OH-S-2840	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	0.0
N-des-Me-S-2840	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1'-CH₂OH-S-2840A	7.8	6.6	8.6	10.4	0.0	6.3	3.4	0.0	3.0
1'-CH₂OH-S-2840B	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Sulphate 37 (sulphate conjugate of 1'-CH₂OH-S-2840)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Sulphate 39 (sulphate conjugate of 1'-CH₂OH-S-2840)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Glu-1'-CH₂OH-S-2840 (sum of isomers)	24.4	28.6	0.0	0.0	0.0	19.2	33.5	0.0	0.0
1'-COOH-S-2840A	17.8	17.1	29.4	32.3	36.1	30.2	34.4	9.9	5.5
1'-COOH-S-2840B	28.7	10.0	4.4	0.0	3.6	5.1	10.9	5.9	0.0

DFPA	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DFPA-CONH₂	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1',1'-bis-(CH₂OH)-S-2840	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total identified (% TRR)	78.7	62.6	58.2	49.1	47.9	65.7	84.0	15.9	17.6
Organosoluble fractions									
Aqueous soluble fractions									
Neutral fraction									
Acidic fraction									
Polar fraction									
Total characterised (% TRR)									
Unknown 1									
Unknown 2									
Others	16.6	30.7	29.3	47.5	42.3	24.7	13.6	84.1	76.9
Not analysed fractions									
Unresolved									

Unextracted radioactive residues (% TRR)									
Acid/base hydrolysis									
Enzymatic hydrolysis									
PES (% TRR)	4.8	6.7	12.5	3.5	9.8	9.6	2.4	0.0	5.6
Sum of radioactive residues (% TRR)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table key:

> 10 % TRR < 0.01 mg eq./kg

> 10 % TRR > 0.01 mg eq./kg

Table 2.7.6-3 continued: Overview of metabolism in ruminants in terms of mg eq./kg – phenyl only

Study reference	KCA 6.2.3/01 - 2452W (TPM-0024)
Animal	Ruminants (Lactating Goat)
Number of animals	2 (1 per radio label)
number of applications	Once a day on 5 consecutive days
mg/kg bw/day	0.64

mg/kg DM basis	15.74								
Number dosing days	5								
Time of sacrifice after the final dose (hours)	6-8								
Plateau reached in eggs and milk (days)	Not reached								
Storage: sampling to extraction/analysis (days/months)¹⁾	23 / 38	23 / 38	24 / 50	24 / 43 / 51 / 100	24	22 / 36	22 / 38	37 / 50	34 / 55
¹⁴C labelling	[phenyl-U-¹⁴C] inpyrfluxam								
Matrix	Muscle		Fat			Liver	Kidney	Milk	
	flank	loin	oment al	subcut an.	renal			skim	fat
TRR (mg eq./kg)	0.021	0.015	0.024	0.029	0.041	0.344	0.170	0.040	0.018
Total extracted residues (% TRR)	95.2	93.3	87.5	96.6	90.2	90.4	97.7	100.0	94.4
Parent compound (free) and/or conjugated)	0.000	0.000	0.004	0.002	0.004	0.017	0.000	0.000	0.002
3'-OH-S-2840	0.000	0.000	0.000	0.000	0.000	0.000	0.003	0.000	0.000
N-des-Me-S-2840	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1'-CH₂OH-S-2840A	0.002	0.001	0.002	0.003	0.000	0.022	0.006	0.000	0.001

1'-CH₂OH-S-2840B	0.000	<0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Sulphate 37 (sulphate conjugate of 1'-CH ₂ OH-S-2840)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Sulphate 39 (sulphate conjugate of 1'-CH ₂ OH-S-2840)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Glu-1'-CH₂OH-S-2840 (sum of isomers)	0.005	0.004	0.000	0.000	0.000	0.066	0.057	0.000	0.000
1'-COOH-S-2840A	0.004	0.003	0.007	0.009	0.016	0.104	0.059	0.004	0.001
1'-COOH-S-2840B	0.006	0.001	0.001	0.000	0.002	0.018	0.019	0.002	0.000
DFPA	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DFPA-CONH₂	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1',1'-bis-(CH₂OH)-S-2840	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Total identified (% TRR)	0.017	0.009	0.014	0.014	0.022	0.227	0.144	0.006	0.004
Organosoluble fractions									
Aqueous soluble fractions									
Neutral fraction									
Acidic fraction									
Polar fraction									

Total characterised (% TRR)									
Unknown 1									
Unknown 2									
Others	0.003	0.005	0.007	0.014	0.015	0.084	0.022	0.034	0.013
Not analysed fractions									
Unresolved									

Based on the metabolism study, parent inpyrfluxam was the major metabolite in poultry fat and eggs for both radiolabels. In ruminants it was detected in lower amounts.

1'-CH₂OH-S-2840 (sum of isomers) and its conjugates (sulphate conjugate in poultry and glucuronide conjugate in ruminant) was also prevalent in several matrices, and was present at > 10 % of the TRR.

1'-COOH-S-2840A and B were found in most ruminant matrices at > 10% TRR, with some >0.01 mg eq./kg results. It was also found at > 0.01 mg eq./kg in some poultry matrices, although these all equated to < 10% TRR.

The label specific metabolite DFPA-CONH₂ was detected > 10% TRR in both poultry and ruminant muscle but was < 0.01 mg eq./kg in all matrices.

The results of the feeding studies were also considered. For poultry, 1'-CH₂OH-S-2840 isomer B was found > LOQ of 0.005 mg/kg (0.00524 – 0.014 mg/kg) in egg and liver at the high-dose rate and parent was found at 0.017 mg/kg (LOQ = 0.01 mg/kg) in fat in the high-dose group. Based on the dietary burden for the current GAP, for poultry the high-dose group represents 18N.

For ruminants, 1'-CH₂OH-S-2840 isomer B was found > LOQ of 0.005 mg/kg (0.0061 – 0.0215) in liver and kidney in the mid- and high-dose groups. For ruminants, based on the dietary burden for the current GAP, the mid- and high-dose groups represent 1.6 and 5N respectively.

Based on the results of the feeding studies, for both poultry and ruminants, residues are expected to be < LOQ in all matrices at 1N.

Residue Definition for enforcement (RD-Enf)

Based on the metabolism studies, there is no clear marker compound common to all animal matrices. Parent was the major metabolite in poultry fat and eggs for both radiolabels, and in one fat sample for ruminants (phenyl label only).

Found at > 10% TRR more widely in the studies was both isomers (A and B) of 1'-CH₂OH-S-2840 and their sulphate and glucuronide conjugates. The unconjugated metabolite was only found in poultry thighs and eggs and ruminant subcutaneous fat (both radiolabels for all), so in order for it to be a good marker compound the conjugates would need to be included in the residue definition for enforcement. In order to release the metabolite from its conjugates a hydrolysis step is required; this makes it more difficult to analyse in an enforcement setting. The free and conjugated metabolite are only > 0.01 mg eq./kg in some matrices.

All results for all compounds at 1N in the feeding study are expected to be < 0.01 mg/kg. As significant residues of either parent or 1'-CH₂OH-S-2840 in animal commodities are not anticipated based on the currently proposed use, parent only is proposed.

This definition is considered provisional only and may require further consideration if the dietary burden of livestock increases on consideration of additional uses or a more critical GAP. If exposure is increased, parent may not be the best marker compound in all commodities, and the residue definition should be reconsidered.

HSE proposal for RD-Enf: Inpyrfluxam only

Residue Definition for Dietary risk assessment (RD-RA)

All results for all compounds at 1N in the feeding studies are expected to be < 0.01 mg/kg. Based on the current exposure and low contribution of residues in animal matrices to the overall risk assessment, a residue definition for dietary risk assessment in livestock products is not proposed at this time.

This definition is considered provisional only and may require further consideration if the dietary burden of livestock increases on consideration of additional uses or a more critical GAP.

HSE proposal for RD-RA: A residue definition for dietary risk assessment for inpyrfluxam in livestock products is not proposed at this time.

2.7.7. Summary of feeding studies in poultry, ruminants, pigs and fish

Dietary burden calculation

The dietary burden calculation has been undertaken using the OECD **feeding** tables (OECD guidance document on overview of residue chemistry studies Series 64/32 **and OECD guidance document on residues in livestock, Series 73**) and the EFSA Animal Model 2017.

The following assumptions have been made:

- The highest likely inclusion rate of all crops which may have been treated has been used with the proviso that the aggregate does not exceed 100% diet.
- All produce eaten which may have been treated, has been treated and contains residues at the STMR/HR found in the trials considered to support the GAP.
- There is no loss of residue during transport, storage, preparation of feed prior to consumption.

- Default processing factors as set out in the EFSA Animal Model 2017 have been used unless other specific processing factors are available or residues <LOQ are expected.

The dietary burden considered the components of the RD-RA for plant matrices (Sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam) considering the primary crops for the representative uses of the inpyrfluxam.

Input values are summarised in Table 2.7.7-1 and the estimated animal intakes are summarised in Table 2.7.7-2.

Table 2.7.7-1: Inputs for animal dietary burden according to the GB cGAP

Feed commodity	Median dietary burden		Maximum dietary burden	
	Input (mg/kg)	Comment	Input (mg/kg)	Comment
Risk assessment residue definition: Sum of inpyrfluxam and its metabolites 1'-CH ₂ OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam				
Barley straw	0.415	Barley straw STMR	4.36	Barley straw HR
Triticale straw	0.64	Wheat straw STMR	3.67	Wheat straw HR
Wheat straw	0.64	Wheat straw STMR	3.67	Wheat straw HR
Barley grain	0.088	Barley grain STMR	0.088	Barley grain STMR – The proposed use is not a post-harvest use.
Triticale grain	0.014	Wheat grain STMR	0.014	Wheat grain STMR – The proposed use is not a post-harvest use.
Wheat grain	0.014	Wheat grain STMR	0.014	Wheat grain STMR – The proposed use is not a post-harvest use.

Feed commodity	Median dietary burden		Maximum dietary burden	
	Input (mg/kg)	Comment	Input (mg/kg)	Comment
Risk assessment residue definition: Sum of inpyrfluxam and its metabolites 1'-CH ₂ OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam				
Brewer's grain, dried	0.061	Barley grain STMR (0.088) x PF 0.69	0.061	Barley grain STMR (0.088) x PF 0.69
Distillers grain, dried	0.046	Wheat grain STMR (0.014) x Default PF 3.3	0.046	Wheat grain STMR (0.014) x Default PF 3.3
Wheat gluten meal	0.004	Wheat grain STMR (0.014) x PF 0.28	0.004	Wheat grain STMR (0.014) x PF 0.28
Wheat milled-by-pdts	0.014	Wheat grain STMR (0.014) x PF 0.97	0.014	Wheat grain STMR (0.014) x PF 0.97

Table 2.7.7-2: Median and maximum dietary burden in livestock according to the GB cGAP

Relevant groups	Dietary burden expressed in				Most critical diet (a)	Most critical commodity (b)		Trigger exceeded (Yes/No)
	mg/kg bw per day		mg/kg DM					0.004
	Median	Maximum	Median	Maximum				mg/kg bw
Cattle (all diets)	0.008	0.058	0.22	1.54	Dairy cattle	Barley	straw	Yes
Cattle (dairy only)	0.008	0.058	0.20	1.52	Dairy cattle	Barley	straw	Yes
Sheep (all diets)	0.015	0.127	0.35	2.98	Lamb	Barley	straw	Yes
Sheep (ewe only)	0.011	0.099	0.34	2.98	Ram/Ewe	Barley	straw	Yes
Swine (all diets)	0.003	0.003	0.09	0.09	Swine (finishing)	Barley	grain	No
Poultry (all diets)	0.011	0.035	0.16	0.51	Poultry layer	Wheat	straw	Yes
Poultry (layer only)	0.011	0.035	0.16	0.51	Poultry layer	Wheat	straw	Yes

(a) When several diets are relevant (e.g. cattle, sheep and poultry "all diets"), the most critical diet is identified from the maximum dietary burdens expressed as "mg/kg bw per day"

(b) The most critical commodity is the major contributor identified from the maximum dietary burden expressed as "mg/kg bw per day"

Based on the proposed uses, the estimated livestock dietary burden is ≥ 0.004 mg/kg bw/day for all animal groups except swine and the livestock metabolism studies indicate residues in some products of animal origin may be at or above 0.01 mg/kg at a 1N dose. As such, consideration of feeding studies is required.

Feeding studies for ruminants (lactating goats) and poultry (laying hens) have been submitted. An overview of these studies is presented below. The detailed evaluation of these studies is in Vol 3 B7.4.

Based on the animal dietary burdens the following N rates for the livestock metabolism and feeding studies are estimated below. These have been estimated based on mg/kg bw/d.

Table 2.7.7-3: Comparison of the livestock studies and expected dietary burden

Study	Livestock	Actual dosing rates (mg/kg bw/d)	Maximum dietary burden (relevant group) (mg/kg bw/d)	N rate of study
Metabolism	Lactating goats: [pyrazolyl-4- ¹⁴ C]Inpyrfluxam	0.51	0.127	4N
	Lactating goats: [Phenyl-U- ¹⁴ C]Inpyrfluxam	0.64	0.127	5N
	Laying hens: [pyrazolyl-4- ¹⁴ C]Inpyrfluxam	0.86	0.035	25N
	Laying hens: [Phenyl-U- ¹⁴ C]Inpyrfluxam	0.83	0.035	24N
Feeding	Laying hen (Low-dose)	0.063	0.035	1.8N
	Laying hen	0.19	0.035	5N

	(Mid-dose)			
	Laying hen (High-dose)	0.63	0.035	18N
	Lactating cattle (Low-dose)	0.07	0.127	0.006N
	Lactating cattle (Mid-dose)	0.20	0.127	1.6N
	Lactating cattle (High-dose)	0.61	0.127	5N

Poultry

The feeding study was conducted with Inpyrfluxam on poultry to determine the levels of relevant residues in poultry tissues and in eggs.

Inpyrfluxam was administered orally (via gelatine capsules) to laying hens for 28 consecutive days at average dose rates of 0mg (Control), 1 mg (low-dose), 3 mg (mid-dose) and 10 mg (high-dose) Inpyrfluxam/kg diet (dry weight basis). This equates to 0.063 mg/kg bw/day (1.8N), 0.19 mg/kg bw/day (5N) and 0.63 mg/kg bw/day (18N).

Feed consumption, body weights and egg production were not adversely affected and post-mortem examinations did not reveal any significant tissue abnormalities.

Eggs and tissues were analysed for the residues of Inpyrfluxam, 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1-CH₂OH-S-2840A and 1-CH₂OH-S-2840B.

Residues in eggs (composite white and yolk samples) were found to be <LOQ for Inpyrfluxam, 1'-COOH-S-2840A, 1'-COOH-S-2840B and 1-CH₂OH-S-2840A at all dosage rates and time points. 1-CH₂OH-S-2840B was detected in the high-dose group from day 7 onwards but quickly depreciated to <LOQ during the depuration stage.

Residues in egg white and yolk were found < LOQ for Inpyrfluxam, 1'-COOH-S-2840A, 1'-COOH-S-2840B and 1-CH₂OH-S-2840A at all dosage rates and time points. Residues of 1-CH₂OH-S-2840B were detected in the high-dose group at Day 14.

Residues in fat were all < LOQ, except Inpyrfluxam which was detected above LOQ in the high-dose group.

Residues in muscle were all < LOQ.

Residues in liver were all <LOQ except for 1'-COOH-S-2840B which was found in the mid-dose group and 1'-CH₂OH-S-2840B which was found in the mid- and high-dose group.

After the depuration phase of 3, 7 and 14 days all measured residues of Inpyrfluxam and its metabolites were below LOQ in eggs and tissues.

Given the high dosage rate of the feeding studies (at least 1.8N) it is not expected that in any poultry matrices residues > LOQ will be detected.

Ruminant

The feeding study was conducted with Inpyrfluxam on ruminants to determine the levels of relevant residues in ruminant's milk and tissues.

Inpyrfluxam was administered orally to cows for 28 consecutive days at the dose rates of 0 mg (Group 1 – control group), 2 mg (Group 2 – Low-dose), 6mg (Group 3 – Mid-dose) and 20 mg (Group 4 – High-dose) Inpyrfluxam/kg diet (dry weight basis). This equates to an average dose rate of 0.07 mg/kg bw/day (0.006N), 0.20 mg/kg bw/day (1.6N) and 0.61 mg/kg bw/day (5N).

Feed consumption, body weight and milk production were monitored throughout and no adverse effects were noted.

Milk and tissues were analysed for residues of Inpyrfluxam, 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1-CH₂OH-S-2840A and 1-CH₂OH-S-2840B.

No quantifiable residues (> LOQ) were detected of 1'-COOH-S-2840A, 1'-COOH-S-2840B, 1-CH₂OH-S-2840A in any samples at any time point. Residues of 1-CH₂OH-S-2840B were detected in samples of liver and kidney from the mid- and high-dose groups in the day 28 samples. A plateau in milk could not be determined as residues were < LOQ at all time points.

After the depuration phase of 31, 35 and 42 days all measured residues of Inpyrfluxam and its metabolites were below LOQ in tissue and milk sample.

Given the high dosage rate of the feeding studies (up to 5N) it is not expected that residues in ruminant matrices > LOQ will be detected.

Feeding studies have been used to determine STMR, HR and MRL values for products of animal origin using the EFSA (OECD feed tables) animal model, 2015-2017. The results of the calculations are reported in Table 2.7.7-4.

Table 2.7.7-4: MRL, STMR and HR proposals derived from the livestock feeding studies

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) :	0.07	mg/kg bw	1.2	N Dairy cattle (highest diet)				
Muscle	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Fat	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Liver	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Kidney	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Cattle (dairy only)								
Closest feeding level ^(a) :	0.07	mg/kg bw	1.2	N Dairy cattle				
Milk ^(b)	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Sheep (all diets)								
Closest feeding level ^(a) :	0.07	mg/kg bw	0.6	N Lamb (highest diet)				
Muscle	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Fat	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Liver	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01

Kidney	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Sheep (dairy only) Closest feeding level ^(a) : 0.07 mg/kg bw 0.7 N Ewe								
Milk ^(b)	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Swine Closest feeding level ^(a) : 0.07 mg/kg bw 25.9 N Finishing (highest diet)								
Muscle	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Fat	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Liver	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Kidney	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Poultry (all diets) Closest feeding level ^(a) : 0.063 mg/kg bw 1.8 N Layer (highest diet)								
Muscle	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Fat	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Liver	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01
Poultry (layer only) Closest feeding level ^(a) : 0.063 mg/kg bw 1.8 N Layer								
Eggs ^(c)	0.01	0.01	0.01	0.01	0.01*	n.c.	0.01	0.01

- (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).

2.7.8. Summary of effects of processing

Nature of the residues after processing

Four studies have been submitted to address the nature of residues over conditions representative of high temperature hydrolysis in accordance with OECD guidelines 507.

These have addressed all components of the proposed RD-RA for products of plant origin: parent inpyrfluxam, 1'-CH₂OH-S-2840 and 3'-OH-S-2840 (and additionally, 1'-COOH-S-2840).

Inpyrfluxam

The parent compound was stable under all test conditions. The mean % applied recovery of radioactivity was 97.6 – 97.9%, and no degradation products were detected.

1'-CH₂OH-S-2840

The metabolite 1'-CH₂OH-S-2840 was found to be stable under the simulation conditions of pasteurisation, baking, brewing and boiling and sterilisation. No degradation products were formed. The overall % applied recoveries of radioactivity ranged from 95.1 – 107.7%. The study had involved using a test material that was a mix of isomers 1'-CH₂OH-2840A and 1'-CH₂OH-S-2840B. There were no marked isomer changes over the course of the study.

1'-COOH-S-2840

The metabolite 1'-COOH-S-2840 can be considered hydrolytically stable under the simulated conditions. No degradation occurred. In addition, no isomerisation between the two isomer pairs which were tested separately was detected in any of the samples (1'-COOH-2840A and 1'-COOH-S-2840B). The overall recovery of the applied recovery of radioactivity was between 92.6 – 106.7%.

3'-OH-S-2840

The overall % applied recoveries of radioactivity in all the test solutions were between 91.7 – 93.2%, however this did not include test vessel washings which accounted for a further up to 7% applied radioactivity.

Under the simulated conditions of pasteurisation, baking brewing and boiling degradation of 3'-OH-S-2840 was observed to form 3'-OH-S-2840 dehydrate and up to eight other minor unidentified degradation products. The amount of the 3'-OH-S-2840 dehydrate formed under conditions of pasteurisation (pH 4, 90°C, 20 mins) was 13%TRR (when normalising the radioactivity in the samples to 100%); and the amount of the 3'-OH-S-2840 dehydrate formed under conditions of baking brewing and boiling (pH 5, 100°C, 60 mins) was 9%TRR (when normalising the radioactivity in the samples to 100%);

Under the condition of sterilisation (pH 6, 120°C, 20 mins), no significant degradation was observed, and the metabolite can be considered hydrolytically stable **under these conditions**.

The degradation of 3'-OH-S-2840 **was observed** to form 3'-OH-S-2840 dehydrate seems to occur under more acidic conditions.

A proposed degradation pathway is shown in in figure 2.7.8-1 below.

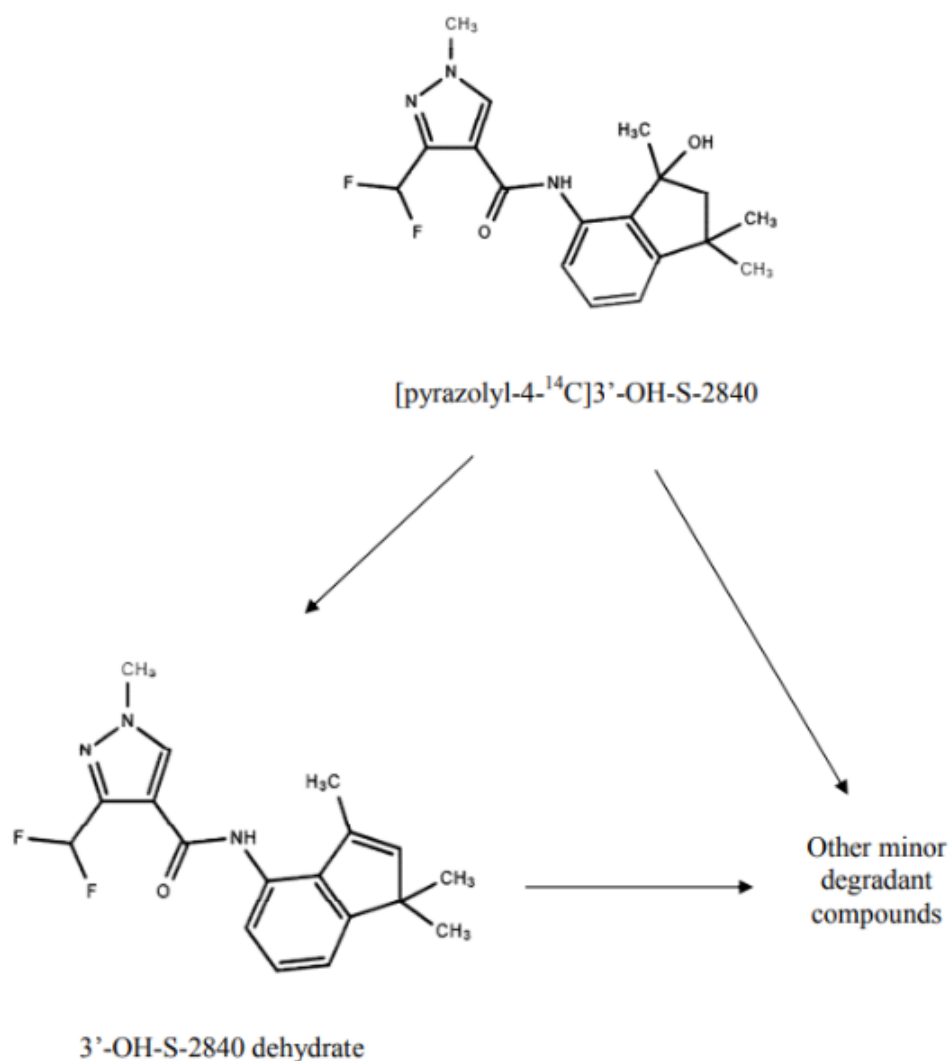
The 3'-OH-S-2840 dehydrate metabolite was not sought in the processing magnitude of residues (MOR) studies (see below).

The range of residues of metabolite 3'-OH-S-2840 in the grain raw agricultural commodity (RAC) in GAP compliant primary crop residues trials was:

- barley grain - < 0.01 to 0.02 mg/kg (residue expressed as parent inpyrfluxam) with only two positive residues across 14 barley trials.
- wheat grain, the residues were all < 0.01 mg/kg (residue expressed as parent inpyrfluxam) across all the wheat trials.

Since metabolite 3'-OH-S-2840 is only found infrequently (at low levels) in the raw agricultural commodity when inpyrfluxam is used in accordance with the proposed GAP, the absolute amount of 3'-OH-S-2840 dehydrate formed in the cereal processed commodities would be minimal. Whilst 13% was the maximum yield of formation for the 3'-OH-S-2840 dehydrate in the processing hydrolysis studies, this was for pasteurisation. Under conditions suitable for brewing (relevant to barley), the rate of formation was lower (9%).

See section 2.7.3 on the residue definition for processed commodities.

Figure 2.7.8-1 – Proposed degradation pathway of 3'-OH-S-2840

Magnitude of the residues after processing

Studies on the magnitude of residues after processing have been submitted and evaluated for wheat and barley, each based on RAC residue data from 2 independent field trials. Harvested samples of RAC were processed under simulated industrial conditions. For barley, the process procedures for the production of pearled (pot) barley, malt and beer were simulated. For wheat, the process procedures for the production of flour (type 550 and wholemeal), whole-grain bread, wheat germs, starch and gluten were simulated.

The processing factor is calculated as shown below:

$$\text{Processing factor} = \frac{\text{Residue found in processed commodity (e. g. in mg/kg)}}{\text{Mean residue found before processing (e. g. in mg/kg)}}$$

Sufficient storage stability data is available to support the storage period of the RAC, processed commodities and extracts during the studies. Inpyrfluxam and its metabolites were quantified using analytical method S16-03371. Acceptable additional validation data sets were provided for barley beer, wheat flour and wheat- whole grain bread, concurrently to the processing studies. The work was supported by generally acceptable procedural recoveries for all of the matrices and analyte combinations studied (typically conducted at LOQ and 10x LOQ); some minor deviations from this were noted on a very small number of occasions and these slight uncertainties are not considered to impact the overall derivation of the processing factors.

The processing factors presented below have been calculated for the RD-Enf (for enforcement purposes, namely inpyrfluxam only) and separately for the RD-RA (residue definition for dietary risk assessment, which comprises the sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam).

Barley

Table 2.7.8-1 Summary of barley processing factors

Crop (RAC)/Processed product	Number of studies	MRL processing factor (Pf)- inpyrfluxam		Risk assessment processing factor (Pf)^(a)	
		Individual Pf	Mean Pf^(b)	Individual Pf	Mean Pf^(b)
Barley/Grain, stored	2	0.88, 0.65	0.76	0.88, 0.78	0.83
Barley/Malt sprouts	2	0.67, 0.53	0.60	0.74, 0.80	0.77
Barley/Brewer's malt	2	0.67, 0.35	0.51	0.74, 0.51	0.63
Barley/Brewer's grain (fresh)	2	0.52, 0.35	0.44	0.29, 0.18	0.23
Barley/Brewer's grain (dried)	2	1.45, 0.71 ^(c)	1.08	0.94, 0.43 ^(c)	0.69
Barley/Flocs (hops draff)	2	0.74, 0.35 ^(c)	0.55	0.51, 0.29	0.40

Barley/Brewer's yeast	2	0.19, 0.18	0.18	0.17, 0.16	0.17
Barley/Beer	2	0.02, 0.06	0.04 ^(d)	0.08, 0.09	0.08
Barley/Grain, stored 2	2	1.05, 0.82	0.94	0.95, 0.87	0.91
Barley/Pearled (pot)	2	0.17, 0.18	0.17	0.16, 0.21	0.18
Barley/Bran	2	7.14, 4.76	5.95	6.25, 4.30	5.28
Barley/Flour	2	5.95, 3.76	4.86	4.61, 3.28	3.94

(a) RD-RA = Sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam

(b) Pfs derived from the mean of two processing studies

(c) The individual Pfs differ by only slightly >50% (Brewer's grain (dried): 51% (RD-Enf) and 54% (RD-RA); Flocs (hops draff): 53%) therefore they are considered sufficiently similar to remove the need for a third trial

(d) Note that the difference between the two individual Pfs is >50%, however, they both demonstrate a significant dilution upon processing. A third trial is not considered necessary.

The results of the processing study on barley indicate that generally residues of parent inpyrfluxam are diluted by the brewing process, other than in brewer's grain (dried) which results in slightly concentrated residues. For the pearled (pot) barley process, generally residues of parent inpyrfluxam are concentrated in bran and flour but are diluted in pearl (pot) barley.

Considering the processing factors based on the residue definition for dietary risk assessment, generally a dilution of residues is indicated from the studies for the brewing process. For the pearled (pot) barley process, generally residues are concentrated in bran and flour but are diluted in pearl (pot) barley.

Wheat**Table 2.7.8-2 Summary of wheat processing factors**

Crop (RAC)/Processed product	Number of studies	MRL processing factor (Pf) inpyrfluxam		Risk assessment processing factor (Pf)^(a)	
		Individual Pf	Mean Pf^(b)	Individual Pf	Mean Pf^(b)
Wheat/Aspirated grain	2	7.00, 1.74 ^(e)	4.37	6.62, 1.73 ^(e)	4.18
Wheat/Bran	2	3.82, 4.81	4.32	3.67, 4.73	4.20
Wheat/Middlings	2	2.09, 1.48	1.79	2.14, 1.44	1.79
Wheat/Short	2	4.09, 2.67	3.38	4.03, 2.88	3.46
Wheat/Flour	2	0.18, 0.19	0.18	0.17, 0.20	0.18
Wheat/Wholemeal flour	2	0.73, 1.00	0.86	0.75, 0.96	0.86
Wheat/Wholegrain bread	2	0.64, 0.59	0.61	0.61, 0.59	0.60
Wheat/Germ	2	0.73, 0.44	0.59	0.64, 0.44	0.54
Wheat/Milled bypds	2	0.91, 1.04	0.97	0.94, 1.00	0.97
Wheat/Starch	2	<0.09, <0.04 ^(c)	<0.06	<0.12, 0.08	<0.10
Wheat/Gluten	2	0.18, 0.56 ^(d)	0.37	0.42, 0.50	0.46
Wheat/Gluten feed meal	2	0.18, 0.44 ^(c)	0.31	0.16, 0.39 ^(d)	0.28

(a) RD-RA = Sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam

(b) Pfs derived from the mean of two processing studies

(c) The individual Pfs differ by only slightly >50% (Starch: 56%, Gluten feed meal: 59%) therefore they are considered sufficiently similar to remove the need for a third trial. The Pfs for starch are all based on <LOQ results in the processed commodity, therefore, there is a small level of uncertainty in the values.

(d) Note that the difference between the two individual Pfs is >50%, however, they both demonstrate a dilution upon processing. A third trial is not considered necessary.

(e) Note that the difference between the two individual Pfs is >50%, however, as it is for aspirated wheat, a third trial is not considered necessary for risk assessment purposes.

The results of the study indicate that generally residues of parent inpyrfluxam are concentrated in aspirated grain fractions. In the flour production process, generally residues of parent inpyrfluxam are concentrated in bran, middlings and shorts but diluted in the final products of flour and whole-meal flour. Generally, residues of parent inpyrfluxam are diluted in whole-grain bread. Likewise for the production of wheat germ and gluten, generally the residues of parent inpyrfluxam are diluted.

For risk assessment residues (considering Pfs based on the RD-RA), the study indicates that residues are generally concentrated in aspirated grain fractions. In the flour production process, generally risk assessment residues are concentrated in bran, middlings and shorts but diluted in the final products of flour and whole-meal flour. Generally, risk assessment residues are diluted in whole-grain bread. Likewise for the production of wheat germ and gluten, generally the risk assessment residues are diluted.

2.7.9. Summary of residues in rotational crops

Soil exposures

The representative uses on wheat and barley can be grown in rotation, and field soil degradation studies indicate that the DT₉₀ and DT₅₀ values for inpyrfluxam are > 1000 days and 383 days (Volume 3 CP B.8.2). The (geometric mean from laboratory studies) DT₅₀s for the metabolites 3'-OH-S-2840 and 1'-COOH-S-2840 are 314 and 229 days respectively (Volume 3 CP B.8.2 and Table B.8.2-8),

Inpyrfluxam is regarded as very persistent in soils, see section 2.8.1. Therefore, a consideration of residues in rotational crops is therefore required. In this evaluation both rotational crop metabolism and rotational crop magnitude of residues studies are available.

Furthermore, considering the potential for residues to accumulate in soil from year-on-year use of inpyrfluxam, there is a need to consider the plateau of soil residues that could develop and contribute to the annually applied amount of active substance.

The potential for a soil plateau level to be considered in the context of addressing potential and levels of residues taken up into rotational crops occurs when DT₉₀ values > 500 days

or DT₅₀ values > 150 days (OECD, 2018). Therefore accumulation of inpyrfluxam and the metabolites 3'-OH-S-2840 and 1'-COOH-S-2840 should be considered.

The fate and behaviour evaluation has concluded (see List of end-points) that the plateau concentration of 0.069 mg/kg (inpyrfluxam) would be reached after 18 years (based on calculation). In the field accumulation study, modelling approaches indicate parent inpyrfluxam concentrations would plateau after 8 years (beyond the term of the study).

The fate and behaviour evaluation (Vol 3 CP B.8) has used accumulation calculations to derive an A_{total} for both parent and the metabolites – an active ingredient equivalent application rate corresponding to total soil residues from long term use and crop failure for parent, and a maximum relevant parent equivalent rate for the metabolites. This latter value can be considered the maximum rate that the parent could be applied at that would result in the highest metabolite levels expected. The residues studies determining the potential levels of rotational crop residues should cover these application rates for both parent and metabolites.

The table below (taken from the fate assessment CP.B.8.2) summarises these calculations, with the most critical (parent) used as the maximum. A crop interception rate of 80% has been used to determine these values, which considers application to the intended use wheat/barley crops from around BBCH 30 (GS 30).

Note, that in the Guidance Document on residues in Rotational crops (OECD, 2018) it is suggested that assuming zero interception could aid an evaluation suitable for all potential future uses of an active substance. However in the current case (fate calculations in Vol 3 CP B.8) with zero interception there might be higher rotational crop residue levels anticipated and there is a potential that label replant restrictions to limit rotational crop residues would be needed. Therefore in the current assessment, the 80% interception refinement was applied. This is a valid approach, OECD, 2018 also states "Crop interception is only valid for applications made directly onto a primary crop and may be used to calculate the effective application rate to the soil if an application to a primary crop occurs at leaf development growth stage or later".

Table 2.7.9-1: parent and metabolite application rates from rotational crops with 80 % crop interception

Use pattern	Result	Inpyrfluxam	3'-OH-S-2840	1'-COOH-S-2840
90 g a.s./ha	Application rate corresponding to total soil residues from long term use and crop failure (g a.s./ha)	141.7	Not applicable	Not applicable

(BBCH 30 to 71)	Relevant parent application rate (g a.s./ha)	Not applicable	71.9	60.9
	Day of metabolite maximum in first year	Not applicable	>365	>365

Note, interception has not been applied for the seasonal application occurring in the year of crop failure and the planting of the rotational crop, i.e. the final application before planting of the rotational crops.

An A_{total} of 141.7 g/ha is covered by the application rate in the below evaluated magnitude of residues studies in rotational crops which were conducted at 240 g as/ha, application to a preceding primary crop which was destroyed and incorporated into the soil to mimic crop failure). Furthermore the A_{total} of 141.7 g/ha is also covered in the below confined rotational crop (metabolism) study (235 g/ha).

Nature of the residue

The metabolism of radio-labelled inpyrfluxam in rotational crops was investigated after spray application of the test item at a nominal rate of 235 g a.s./ha to bare soil. Crops were sown at intervals of 30, 120 and 365 days after treatment (DAT), with crops being harvested at maturity.

The application rate of 235 g as/ha corresponds to 2.6 N, regarding comparison to the maximum seasonal dosage for the GB assessed uses. An exaggerated rate of study is useful for considering the potential for uptake of residues in rotational crops following year to year use and accumulation that add to soil exposure levels (see above soil exposures) and for potential future extensions of uses. Even when considering the potential for soil accumulation of residues the derived the A_{total} in this evaluation of 141.7 g/ha is below the application rate in this confined rotational crop (metabolism) study (235 g/ha).

The total radioactive residues (TRR) were calculated by combining the extracted residues (ERR) and the non-extracted residues (RRR) as well as determining the residues by combustion. The values of the TRR from ERR and RRR were similar to the residues measured by combustion (86 – 118% of the combustion TRR). Generally, there was a considerable decrease in the TRR values between the first and second and third rotations and this decreased further for the third rotation. The highest concentration of residues was found in the forage matrices; at up to 1.074 mg eq./kg in sorghum stover and 0.37 mg eq./kg in radish tops. In the human food matrices of lettuce, radish root and sorghum grain, immature lettuce contained the highest concentration at 0.103 mg eq./kg (0.094 mg eq./kg in mature lettuce).

Matrices were extracted with acetonitrile and then water, with the main radioactive portions found in the acetonitrile extracts (except for sorghum stover and grain). At 30 DAT,

extractability was 76.6 – 96.0% TRR for all matrices except sorghum grain for both labels, while sorghum grain was 49.9 – 59.9% TRR. At 120 and 365 DAT, similar extractability was seen at 76.6 – 96.7% TRR for all other matrices and 47.4 – 52.4% TRR for sorghum grain.

The study further analysed a major HPLC peak (present in all crops studied) further which was characterised as polar material during the chromatography. Acid hydrolysis was used to release metabolites (as free exocons) from the **proposed** conjugated residues (in the isolated peak fraction). A scheme of further analysis was applied (acid and base treatments) to characterise the nature of the material that remained in post extraction solids, especially the case for sorghum stover.

The metabolites identified by HPLC-MS analysis were: Parent compound inpyrfluxam, 3'-OH-S-2840 (free and/or conjugated), *N*-des-Me-S-2840 (free and/or conjugated), 1'-CH₂OH-S-2840 (free and/or conjugated), 1'-COOH-S-2840 (free and/or conjugated), *N*-des-Me-1'-CH₂OH-S-2840 (free and/or conjugated), DFPA (free and/or conjugated), *N*-des-Me-DFPA (free and/or conjugated) and DFPA-CONH₂ (free and/or conjugated). Levels of parent inpyrfluxam above 10% TRR were only found in lettuce, radish tops and radish roots. Other prominent residues (> 10% TRR) in these matrices include 1'-CH₂OH-S-2840 (conjugate), 3'-OH-S-2840 (free), 1'-COOH-S-2840 (free and conjugate), DFPA (free and conjugate), *N*-des-Me-DFPA (free), *N*-des-Me-S-2840 (free), DFPA-CONH₂ (free) and *N*-des-Me-1'-CH₂OH-S-2840 (conjugate). In sorghum matrices, residues of 1'-CH₂OH-S-2840 (conjugate), *N*-des-Me-1'-CH₂OH-S-2840 (conjugate) and DFPA (conjugate) were found, with grain found to only contain DFPA (conjugate).

The qualitative and quantitative nature of the radioactive residues observed in this study indicated that inpyrfluxam was extensively metabolised into a large number of metabolites, many of which formed complex conjugates with indigenous compounds, and became potentially incorporated as 'bound' residues in various plant constituents. The parent inpyrfluxam underwent a number of transformation processes including oxidation, demethylation, amide bond cleavage, conjugation as well as combinations of these processes.

- The primary oxidation products of inpyrfluxam were:
3'-OH-S-2840, in which the site of oxidation was the 3'-position in the fused cyclopentenyl ring
- 1'-CH₂OH-S-2840, in which one of the two CH₃ groups attached to the 1'-position of the same ring was oxidized to CH₂OH
- 1'-COOH-S-2840, in which one of the CH₃ groups attached to the 1'-position of this ring was oxidized to COOH. The amide bond cleavage of the parent Inpyrfluxam and its metabolites produced DFPA and DFPA-CONH₂. The metabolites, *N*-des-Me-S-2840, *N*-des-Me-1'-CH₂OH-S-2840, and *N*-des-Me-DFPA were produced as a result of the loss of the *N*-methyl group in the pyrazolyl ring of the parent inpyrfluxam, its oxidation products and the cleavage product, respectively.

The metabolites of inpyrfluxam and their degradation products combined with various endogenous compounds to form the major polar fraction and proposed 'bound' residues in crop plants. Analysis of unextracted residues in PES samples of sorghum, lettuce and radish samples showed that a number of metabolites including 1'-COOH-S-2840, 1'-CH₂OH-S-2840, *N*-des-Me-S-2840, DFPA and *N*-des-Me-DFPA, formed acid hydrolysable covalent bonds with the solids remaining after extraction. The metabolite residues might have degraded further into simpler compounds, and became incorporated into starch, protein, lignin, cellulose and other natural components of plants. A significant part of the unextracted residue in sorghum grain which the applicant proposed might be a 'bound' residue was present in the acid hydrolysate (in further work up of the unextracted material) fraction which the applicant proposed could be hydrolysed starch, indicating that metabolites in grain might have essentially degraded and incorporated into starch.

In conclusion, inpyrfluxam is extensively metabolised in rotational crops, yielding several major metabolites, and several minor metabolites, the proposed pathway of this metabolism is displayed in Figure 2.7.9-1 below.

The diagram illustrates the chemical structures and metabolic pathways of S-2840 and its derivatives. The central molecule is S-2399, which can be converted to 3'-OH-S-2840 or N-des-Me-S-2840. 3'-OH-S-2840 can be converted to 3'-OH-S-2840-dehydrate or N-des-Me-S-2840. N-des-Me-S-2840 can be converted to N-des-Me-1'-CH₂OH-S-2840 or N-des-Me-1'-COOH-S-2840. N-des-Me-1'-CH₂OH-S-2840 can be converted to 1'-CH₂OH-S-2840 or 1'-COOH-S-2840. 1'-CH₂OH-S-2840 can be converted to 1'-COOH-S-2840. The scheme also shows the conversion of 3'-OH-S-2840-dehydrate to N-des-Me-DFPA, which can be converted to DFPA. DFPA can be converted to Conjugates. The scheme also shows the conversion of 3'-OH-S-2840 to Conjugates. The scheme also shows the conversion of N-des-Me-S-2840 to Conjugates. The scheme also shows the conversion of N-des-Me-1'-CH₂OH-S-2840 to Conjugates. The scheme also shows the conversion of 1'-CH₂OH-S-2840 to Conjugates. The scheme also shows the conversion of 1'-COOH-S-2840 to Conjugates.

Residue data was obtained from two independent field trials (one in Northern Europe and one in Southern Europe) conducted with the rotational crops lettuce, carrot, barley and wheat. One application was made to a preceding crop of winter barley (at BBCH 30 – 65) at a rate of 240 g a.s./ha. Within two weeks of application, this crop was destroyed to simulate a crop failure and incorporated in the soil while preparing the soil for the later planting of the rotational crops. These crops were planted at plant back intervals of 30, 120 and 350 days after the application to the preceding crop.

254

for the persistence and subsequent accumulation of parent and the soil metabolites 3'-OH-S-2840 and 1'-COOH-S-2840. The highest A_{total} based on the current use is for parent inpyrfluxam, 141.7 g a.s./ha. The respective A_{totals} for 3'-OH-S-2840 and 1'-COOH-S-2840 are 71.9 and 60.9 g a.s./ha and are therefore covered by the A_{total} for parent. This magnitude of residues in rotational crops study can be considered to be around 1.7N times overdosed.

Residues of the metabolite in rotational crops were very low, with only the 30 day PBI demonstrating any residues above LOQ (0.01 mg/kg) in mature crop samples. Parent was not found in any samples at any PBIs. Residues were only found at the 30 day PBI in spring wheat straw. These were DFPA at 0.09 – 0.1 mg/kg, 1'-CH₂OH-S-2840 (sum of isomers) at 0.023 mg/kg, 1'-COOH-S-2840 (sum of isomers) at 0.017 – 0.019 mg/kg, *N*-des-Me-1'CH₂OH-S-2840 (sum of isomers) at 0.019 mg/kg and 3'-OH-S-2840 at 0.01 mg/kg.

Considering the 1.7N application rate of the confined studies, no residues > 0.01 mg/kg are expected in (human) food items. At 1N, the only residues expected to be > 0.05 mg/kg in straw (i.e., a feed item) is DFPA estimated at 0.053 – 0.059 mg/kg (following scaling). Given that it is concluded that DFPA is of a significantly lower toxicity compared to parent inpyrfluxam and that DFPA is therefore not proposed for inclusion in the primary crop RD-RA despite it being found in primary crop cereal straw samples at up to 0.22 mg/kg, the level of the rotational crop findings of DFPA in straw will not result in significant residues in the diets of livestock. It is noted that for future uses with higher application rates, the potential A_{total} may need to be refined upwards which could result in potential residues expected in rotational crops. However, it is not considered necessary at this time to set MRLs above the LOQ for rotational crops.

2.7.10. Summary of other studies

Effect on the residue level in pollen and bee products

No studies on residue levels in pollen and bee products have been evaluated. Residues in honey are not expected as the representative uses are on non-melliferous crops and significant residues in rotational crops are not expected.

Literature review

The literature search undertaken by the applicant is considered suitable to determine whether there were any published papers that would need to be considered in this residues regulatory evaluation. There were no papers that needed to be considered further on the topic of residues. The search is acceptable in terms of databases searched and the search criteria applied. The timespan of the literature review is acceptable when a later 'top up' January 2025 report is taken account of alongside the original September 2018 report on the literature review. Both literature reports are suitable for considering parent inpyrfluxam and metabolites that could be of interest to the residues assessment. The

search did not reveal any references for evaluation and inclusion in this residues evaluation and consumer risk assessment.

2.7.11. Estimation of the potential and actual exposure through diet and other sources

In order to evaluate the potential chronic and acute exposures to inpyrfluxam residues through the diet, calculations were conducted using the UK chronic model (version 1.2) and the UK acute model (revision 1.1) and PRIMo (version 3.1).

The residue definitions for risk assessment are:

- RD-RA plants: Sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam
- RD-RA livestock: Inpyrfluxam

The relevant toxicological reference values are:

- ADI of 0.06 mg/kg bw/day
- ARfD of 0.3 mg/kg bw

Chronic (long term) UK dietary intake estimates – UK NEDIs and NTMDIs

The UK NEDIs for the active and commodities listed below have been calculated for ten consumer groups as detailed in the Regulatory Update 21/2005. The following assumptions have been made:

- 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 median residue (STMR) (NEDI) found in the trials to support the GAP, as given below.
- There is no loss of residue during transport or storage, or processing of foods prior to consumption.
- The STMR values used in the NEDI estimation are based on RD-RA. The NTMDI has used the MRL (RD-Enf).

Table 2.7.11-1: Chronic (long term) UK inputs – NEDI

Commodity	STMR (mg/kg)	Comments
Barley	0.088	STMR based on primary crop data

Commodity	STMR (mg/kg)	Comments
Wheat	0.014	STMR based on primary crop data
Poultry	0.01	Expected STMR for the current GAP, based on feeding studies (See section 2.7.7 Vol 1)
Meat fat	0.01	
Meat excl. poultry & offal	0.01	
All types of kidney	0.01	
All types of Liver	0.01	
Other types of offal	0.01	
Eggs	0.01	
Milk	0.01	

Table 2.7.11-2: Chronic (long term) UK inputs – NTMDI

Commodity	MRL (mg/kg)	Comments
Barley	0.3	MRL (See section 2.7.4 for further details)
Wheat	0.03	
All other commodities	Default MRL at LOQ	-

Chronic intakes for all consumer groups are below the ADI. The highest UK NEDI was estimated at 2% of the ADI (all components of the residue definition are covered by parent's TRV - see section 2.7.3 Vol 1), with infants being the critical consumer group. Therefore, no chronic health effects are expected.

The highest UK NTMDI was estimated at 3% of the ADI for all consumer groups, with infants being the critical consumer group. Therefore, no chronic health effects are expected.

The relevant intakes are presented in Tables 2.7.11-3 and 2.7.11-4.

Table 2.7.11-3: UK NEDI for 10 consumer groups (calculated using chronic consumer version 1.1)

Active substance: Inpyrfluxam ADI: 0.06 ^{mg/kg} _{bw/day} Source: DAR

	TOTAL INTAKE based on 97.5th percentile									
	ADULT	INFANT	TODDLER	4-6 YEARS	7-10 YEARS	11-14 YEARS	15-18 YEARS	VEGETARIAN	ELDERLY (OWN HOME)	ELDERLY (RESIDENTIAL)
mg/kg bw/day	0.00015	0.00108	0.00071	0.00045	0.00030	0.00020	0.00017	0.00016	0.00015	0.00018
% of ADI	<1%	2%	1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%

STMR		P	COMMODITY INTAKES									
Commodity	(mg/kg)		(mg/kg bw/day)									
Barley	0.088		0.00002	L/C	0.00003	0.00003	0.00007	0.00002	0.00002	0.00002	0.00002	0.00001
Wheat	0.014		0.00005	0.00004	0.00012	0.00012	0.00009	0.00007	0.00006	0.00006	0.00005	0.00005
Poultry	0.01		0.00002	0.00002	0.00003	0.00003	0.00002	0.00002	0.00002	0.00002	0.00002	0.00001
Meat fat	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Meat excl. poultry & offal	0.01		0.00002	0.00004	0.00004	0.00003	0.00003	0.00002	0.00002	0.00000	0.00002	0.00002
All types of kidney	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	L/C	0.00000	0.00000
All types of Liver	0.01		0.00000	0.00002	0.00002	0.00000	0.00000	0.00001	0.00000	L/C	0.00001	0.00000
Other types of offal	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001
Eggs	0.01		0.00001	0.00005	0.00003	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001
Milk	0.01		0.00008	0.00098	0.00056	0.00029	0.00018	0.00012	0.00009	0.00010	0.00009	0.00012

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

L/C Low consumption (<0.1 g/day) or low number of consumers (<4)

Table 2.7.11-4: UK NTMDI for 10 consumer groups (calculated using chronic consumer version 1.1)

Active substance: Inpyrfluxam ADI: 0.06 ^{mg/kg}_{bw/day} Source: DAR

	TOTAL INTAKE based on 97.5th percentile									
	ADULT	INFANT	TODDLER	4-6 YEARS	7-10 YEARS	11-14 YEARS	15-18 YEARS	VEGETARIAN	ELDERLY (OWN HOME)	ELDERLY (RESIDENTIAL)
mg/kg bw/day	0.00038	0.00158	0.00143	0.00096	0.00088	0.00050	0.00044	0.00039	0.00031	0.00039
% of ADI	<1%	3%	2%	2%	1%	<1%	<1%	<1%	<1%	<1%

Commodity	STMR	P	COMMODITY INTAKES									
	(mg/kg)		(mg/kg bw/day)									
Grapefruit	0.01		0.00002	0.00002	0.00006	0.00005	0.00012	0.00002	0.00001	0.00002	0.00002	0.00002
Lemons	0.01		0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Limes	0.01		0.00000	L/C	0.00002	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001
Mandarins	0.01		0.00001	L/C	0.00006	0.00004	0.00003	0.00002	0.00002	0.00001	0.00002	0.00001
Oranges	0.01		0.00004	0.00011	0.00016	0.00011	0.00008	0.00008	0.00007	0.00005	0.00004	0.00003
Almonds	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Brazil nuts	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
Cashew nuts	0.01		0.00000	L/C	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Chestnuts	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	0.00000	0.00000	0.00000	L/C
Coconuts	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Hazelnuts	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Pecan nuts	0.01		0.00000	L/C	0.00000	L/C	0.00000	0.00000	L/C	0.00000	0.00000	L/C
Pistachios	0.01		0.00000	L/C	0.00000	L/C	0.00000	L/C	L/C	0.00000	L/C	L/C
Walnuts	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Peanuts	0.01		0.00000	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000
Apples	0.01		0.00003	0.00008	0.00015	0.00009	0.00008	0.00004	0.00004	0.00003	0.00002	0.00001
Pears	0.01		0.00001	0.00003	0.00007	0.00004	0.00002	0.00002	0.00001	0.00002	0.00002	0.00001

Apricots	0.01		0.00000	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Peaches	0.01		0.00001	0.00001	0.00003	0.00002	0.00001	0.00001	0.00000	0.00001	0.00001	0.00000
Plums	0.01		0.00001	0.00000	0.00002	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Cherries	0.01		0.00000	0.00001	0.00001	0.00002	0.00001	0.00001	0.00001	0.00001	0.00000	0.00000
Table grapes	0.01		0.00001	0.00002	0.00005	0.00002	0.00003	0.00001	0.00001	0.00002	0.00001	0.00000
Wine grapes	0.01		0.00010	0.00001	0.00001	0.00001	0.00000	0.00001	0.00004	0.00010	0.00007	0.00001
Strawberries	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Blackberries	0.01		0.00000	L/C	0.00002	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Loganberries	0.01		0.00000	0.00001	0.00001	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000
Raspberries	0.01		0.00000	L/C	0.00002	0.00001	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000
Gooseberries	0.01		0.00000	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	0.00001	0.00000
Blackcurrants	0.01		0.00001	0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00000	0.00001	0.00000
Red currants	0.01		0.00000	L/C	0.00001	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
White currants	0.01		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Avocados	0.01		0.00001	L/C	0.00001	L/C	L/C	L/C	0.00000	0.00001	0.00001	L/C
Bananas	0.01		0.00002	0.00007	0.00007	0.00004	0.00003	0.00002	0.00001	0.00002	0.00002	0.00002
Dates	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	L/C	0.00000	0.00001	0.00000
Figs	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Kiwi fruit	0.01		0.00001	L/C	0.00002	0.00002	0.00001	0.00001	0.00002	0.00001	0.00001	0.00000
Lychees	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Mangoes	0.01		0.00001	L/C	0.00002	0.00001	0.00002	0.00001	0.00004	0.00001	0.00000	L/C
Olives	0.01		0.00000	L/C	0.00001	0.00001	L/C	0.00000	L/C	0.00000	0.00000	L/C
Passion fruit	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C	L/C
Pineapples	0.01		0.00001	0.00005	0.00005	0.00007	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001
Pomegranates	0.01		0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00000	0.00001	0.00001	0.00001
Beetroot	0.01		0.00000	L/C	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Carrots	0.01		0.00001	0.00004	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Celeriac	0.01		0.00000	L/C	L/C	0.00000	0.00000	L/C	L/C	L/C	L/C	L/C
Horseradish	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C

Jerusalem artichokes	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Parsnips	0.01		0.00000	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000
Radishes	0.01		0.00000	L/C	0.00001	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Salsify	0.01		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Swedes	0.01		0.00000	0.00003	0.00002	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00000
Turnips	0.01		0.00000	L/C	0.00001	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00000
Yam	0.01		0.00003	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Garlic	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
Onions	0.01		0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
Spring onions	0.01		0.00000	L/C	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Tomatoes	0.01		0.00001	0.00002	0.00003	0.00002	0.00002	0.00001	0.00001	0.00002	0.00001	0.00001
Peppers	0.01		0.00000	L/C	0.00001	0.00000	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Aubergines	0.01		0.00000	L/C	0.00002	0.00001	0.00000	0.00001	0.00000	0.00001	0.00000	L/C
Marrows	0.01		0.00001	L/C	0.00002	0.00000	0.00001	0.00001	0.00000	0.00001	0.00001	0.00001
Cucumbers	0.01		0.00000	0.00000	0.00002	0.00002	0.00001	0.00001	0.00000	0.00001	0.00000	0.00000
Gourd	0.01		0.00001	L/C	L/C	L/C	L/C	0.00000	L/C	0.00000	L/C	L/C
Courgettes	0.01		0.00000	0.00001	0.00002	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Melons	0.01		0.00002	0.00003	0.00005	0.00004	0.00003	0.00002	0.00003	0.00003	0.00003	0.00001
Sweet corn	0.01		0.00001	0.00001	0.00002	0.00001	0.00001	0.00000	0.00001	0.00001	0.00001	0.00000
Broccoli	0.01		0.00001	0.00001	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
Cauliflower	0.01		0.00001	0.00003	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Brussels sprouts	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
Head cabbage	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Chinese cabbage	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00001	0.00000	L/C
Kohl Rabi	0.01		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Cress	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Lettuce	0.01		0.00001	0.00000	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Spinach	0.01		0.00001	0.00001	0.00002	0.00001	0.00001	0.00001	0.00000	0.00001	0.00001	0.00000
Watercress	0.01		0.00000	L/C	L/C	0.00000	0.00000	0.00000	L/C	0.00000	0.00000	L/C

Chicory	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C	L/C
Parsley	0.02		0.00000	L/C	0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001
Beans with pods	0.01		0.00001	0.00001	0.00002	0.00001	0.00001	0.00000	0.00001	0.00000	0.00001	0.00000
Runner Beans	0.01		0.00001	L/C	0.00001	0.00000	0.00001	0.00001	0.00000	0.00002	0.00001	0.00001
Beans without pods	0.01		0.00000	0.00001	0.00002	0.00000	0.00001	0.00000	0.00000	0.00001	0.00001	0.00001
Peas with pods	0.01		0.00000	L/C	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	L/C
Peas without pods	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Beansprouts	0.01		0.00000	L/C	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000
Asparagus	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	0.00000	0.00001	0.00000	L/C
Bamboo shoots	0.01		0.00000	L/C	0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
Celery	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Fennel	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Globe artichokes	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C	L/C
Leeks	0.01		0.00000	L/C	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000
Rhubarb	0.01		0.00000	0.00001	0.00001	0.00000	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000
Cultivated mushrooms	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Beans	0.01		0.00002	0.00006	0.00005	0.00003	0.00003	0.00002	0.00002	0.00002	0.00001	0.00001
Lentils	0.01		0.00001	0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
dried Peas	0.01		0.00001	L/C	0.00002	0.00000	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Oilseeds	0.01		0.00003	0.00006	0.00007	0.00007	0.00006	0.00004	0.00004	0.00005	0.00003	0.00004
Potatoes	0.01		0.00003	0.00011	0.00009	0.00008	0.00007	0.00005	0.00005	0.00004	0.00003	0.00003
Oats	0.01		0.00000	0.00002	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001	0.00001	0.00001
Barley	0.3		0.00007	L/C	0.00010	0.00010	0.00024	0.00006	0.00007	0.00008	0.00008	0.00004
Millet	0.01		L/C	L/C	0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Buckwheat	0.01		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Cornmeal & Cornflour	0.01		0.00000	0.00003	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Maize	0.01		0.00000	0.00005	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Wheat	0.03		0.00011	0.00008	0.00025	0.00027	0.00020	0.00015	0.00012	0.00013	0.00010	0.00010
Rice	0.01		0.00002	0.00003	0.00005	0.00004	0.00005	0.00004	0.00003	0.00002	0.00001	0.00000

Rye	0.01		0.00001	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Poultry	0.01		0.00002	0.00002	0.00003	0.00003	0.00002	0.00002	0.00002	0.00002	0.00002	0.00001
Meat fat	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Meat excl. poultry & offal	0.01		0.00002	0.00004	0.00004	0.00003	0.00003	0.00002	0.00002	0.00000	0.00002	0.00002
All types of kidney	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	L/C	0.00000	0.00000
All types of Liver	0.01		0.00000	0.00002	0.00002	0.00000	0.00000	0.00001	0.00000	L/C	0.00001	0.00000
Other types of offal	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001
Eggs	0.01		0.00001	0.00005	0.00003	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001
Milk	0.01		0.00008	0.00098	0.00056	0.00029	0.00018	0.00012	0.00009	0.00010	0.00009	0.00012
Sugar beet	0.01		0.00014	0.00033	0.00056	0.00034	0.00031	0.00020	0.00019	0.00012	0.00011	0.00015

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

L/C Low consumption (<0.1 g/day) or low number of consumers (<4)

Acute (short term) UK dietary intake estimates – UK NESTIs

The UK NESTIs for the active and commodities listed below have been calculated for ten consumer groups as detailed in the Regulatory Update 21/2005. The following assumptions have been made:

- 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 highest residue (based on RD-RA) found in the trials considered to support GAP, as given below.
- There is no loss of residue during transport or storage, or processing of foods prior to consumption.

Table 2.7.11-5: Acute (short term) UK inputs

Commodity	Tentative HR (mg/kg)	Comments
Barley	0.088	STMR based on primary crop data – cereals are well mixed commodities
Wheat	0.014	STMR based on primary crop data
Poultry	0.01	Expected HR for the current GAP, based on feeding studies (See section 2.7.7 Vol 1)
Meat fat	0.01	
Meat excl. poultry & offal	0.01	
All types of kidney	0.01	
All types of Liver	0.01	
Other types of offal	0.01	
Eggs	0.01	
Milk	0.01	Expected STMR for the current GAP, based on feeding studies

The highest acute exposure was estimated at 0.4% of the ARfD for all consumer groups, with infants consuming milk leading to the highest intake. Therefore, no acute health effects are expected.

The relevant intakes are presented in Tables 2.7.11-6.

Table 2.7.11-6: UK NESTI for 10 consumer groups (calculated using acute consumer version 1.2)

commodity	HR	P	adult		infant		toddler		4-6 year old child		7-10 year old child	
			NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
Barley	0.09		0.00006	0.0	0.00000	0.0	0.00006	0.0	0.00016	0.1	0.00049	0.2
Wheat	0.01		0.00008	0.0	0.00018	0.1	0.00018	0.1	0.00020	0.1	0.00015	0.1
Poultry	0.01		0.00006	0.0	0.00007	0.0	0.00009	0.0	0.00009	0.0	0.00007	0.0
Meat fat	0.01		0.00001	0.0	0.00002	0.0	0.00002	0.0	0.00002	0.0	0.00001	0.0
Meat excl.poultry & offal	0.01		0.00005	0.0	0.00012	0.0	0.00010	0.0	0.00009	0.0	0.00008	0.0
All types of kidney	0.01		0.00002	0.0	0.00002	0.0	0.00004	0.0	0.00002	0.0	0.00002	0.0
All types of liver	0.01		0.00003	0.0	0.00008	0.0	0.00007	0.0	0.00002	0.0	0.00003	0.0
Other types of offal	0.01		0.00003	0.0	0.00007	0.0	0.00007	0.0	0.00006	0.0	0.00005	0.0
Eggs	0.01		0.00003	0.0	0.00012	0.0	0.00008	0.0	0.00007	0.0	0.00005	0.0
Milk	0.01		0.00013	0.0	0.00124	0.4	0.00073	0.2	0.00047	0.2	0.00030	0.1

commodity	HR	P	11-14 year old child		15-18 year old child		vegetarian		Elderly - own home		Elderly - residential	
			NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
Barley	0.09		0.00004	0.0	0.00005	0.0	0.00007	0.0	0.00004	0.0	0.00003	0.0
Wheat	0.01		0.00012	0.0	0.00012	0.0	0.00011	0.0	0.00006	0.0	0.00006	0.0
Poultry	0.01		0.00006	0.0	0.00005	0.0	0.00012	0.0	0.00005	0.0	0.00003	0.0
Meat fat	0.01		0.00001	0.0	0.00001	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Meat excl.poultry & offal	0.01		0.00006	0.0	0.00006	0.0	0.00003	0.0	0.00004	0.0	0.00003	0.0
All types of kidney	0.01		0.00001	0.0	0.00002	0.0	0.00000	0.0	0.00002	0.0	0.00001	0.0
All types of liver	0.01		0.00004	0.0	0.00002	0.0	0.00000	0.0	0.00002	0.0	0.00002	0.0
Other types of offal	0.01		0.00005	0.0	0.00002	0.0	0.00001	0.0	0.00002	0.0	0.00002	0.0
Eggs	0.01		0.00004	0.0	0.00003	0.0	0.00004	0.0	0.00002	0.0	0.00002	0.0
Milk	0.01		0.00021	0.1	0.00018	0.1	0.00015	0.0	0.00011	0.0	0.00014	0.0

Pesticide Inpyrfluxam

ARfD 0.300 mg/Kg bw/day

Source DAR

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

Acute and chronic EU dietary intake estimates

The PRIMo IEDIs and PRIMo IESTIs for the active and commodities listed below have been calculated using PRIMo – Pesticide Residues Intake Model (revision 3.1).

The following assumptions have been made:

- a) All produce eaten which may have been treated, has been treated and contains residues at the STMR (IEDI) or HR (IESTI), as given below:
- b) For most commodities there is here is no loss of residue during transport or storage, or processing of foods prior to consumption. However some PFs have been used where there are relevant data (see section 2.7.6). These are also as outlined below.
- c) There is no loss of residue during transport or storage, or processing of foods prior to consumption.

Table 2.7.11-7: Chronic (long term) PRIMo inputs - IEDI

Commodity	Tentative STMR (mg/kg)	Comments
Barley	0.088	STMR based on primary crop data
Wheat	0.014	STMR based on primary crop data
Bovine, Sheep, Goat, Equine and other farmed animals: Muscle/meat, Fat tissue, Liver, Kidney, Edible offals (other than liver and kidney), Other products	0.01	Expected STMR for the current GAP, based on feeding studies (See section 2.7.7 Vol 1) (default level of 0.01 mg/kg for consumer risk assessment, in view of RD-RA not being proposed for livestock commodities at this time)
Milk	0.01	
Poultry: Poultry: Muscle/meat, Fat tissue, Liver, Kidney, Edible offals (other than liver and kidney), Other products	0.01	
Birds eggs	0.01	

Table 2.7.11-8: Chronic (long term) PRIMo inputs – TMDI

Commodity	Tentative STMR (mg/kg)	Comments
Barley	0.3	MRL (See section 2.7.4 for further details)
Wheat	0.03	STMR based on primary crop data
All other commodities	Default MRL at LOQ	-

Table 2.7.11-9: Acute (short term) PRIMo inputs

Commodity	Tentative HR (mg/kg)	Comments
Barley	0.088	STMR based on primary crop data
Wheat	0.014	STMR based on primary crop data
Bovine, Sheep, Goat, Equine and other farmed animals: Muscle/meat, Fat tissue, Liver, Kidney, Edible offals (other than liver and kidney), Other products	0.01	Expected HR for the current GAP, based on feeding studies (See section 2.7.7 Vol 1) (default level of 0.01 mg/kg for consumer risk assessment, in view of RD-RA not being proposed for livestock commodities at this time)
Poultry: Poultry: Muscle/meat, Fat tissue, Liver, Kidney, Edible offals (other than liver and kidney), Other products	0.01	
Birds eggs	0.01	

Commodity	Tentative HR (mg/kg)	Comments
Milk	0.01	Expected STMR for the current GAP, based on feeding studies (default level of 0.01 mg/kg for consumer risk assessment, in view of RD-RA not being proposed for livestock commodities at this time)

A full description of PRIMo and the underlying assumptions is in the document: 'Use of EFSA pesticide residues intake model (EFSA PRIMo revision 3.1)' available at the following link:

<http://www.efsa.europa.eu/en/applications/pesticides/tools>

Information is also included in the PRIMo model in the tab 'Background information'.

The relevant residue level inputs for the IEDI are presented in Table 2.7.11-7, TMDI in Table 2.7.11-8 and the IESTI in Table 2.7.11-9.


Chronic intakes for all consumer groups are below the ADI. The critical consumer group are NL toddler with intakes estimated as up to 1% of the ADI. Therefore, no chronic health effects are expected.

The highest TMDI was estimated at 2% of the ADI, with infants being the critical consumer group. Therefore, no chronic health effects are expected.

Acute intakes for all consumer groups are below the ARfD. The highest acute exposure was estimated at 0.4% of the ARfD, with infants consuming milk leading to the highest intake. Therefore, no acute health effects are expected.

Relevant intakes are presented in Tables 2.7.11-10, -11 and -12.

Table 2.7.11-10: EFSA model (PRIMo) IEDI for chronic risk assessment – rev. 3.1



European Food Safety Authority

EFSA PRIMo revision 3.1; 2019/03/19

Inpyrfluxam

LOQs (mg/kg) range from: _____ to: _____

Toxicological reference values

ADI (mg/kg bw/day): **0.06** ARID (mg/kg bw): **0.3**

Source of ADI: _____ Source of ARID: _____

Year of evaluation: _____ Year of evaluation: _____

Input values

Details - chronic risk assessment

Supplementary results - chronic risk assessment

Details - acute risk assessment/children

Details - acute risk assessment/adults

Comments: _____

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

				No of diets exceeding the ADI: ---				Exposure resulting from			
	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	MRLs set at the LOQ (in % of ADI)	commodities not under assessment (in % of ADI)
TMDI/NED/IEDI calculation (based on average food consumption)	1%	NL toddler	0.69	1.0%	Milk: Cattle	0.1%	Wheat	0.0%	Barley		
	0.8%	UK infant	0.46	0.6%	Milk: Cattle	0.1%	Wheat	0.0%	Eggs: Chicken		
	0.6%	FR toddler 2-3 yr	0.37	0.5%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat		
	0.6%	FR child 3-15 yr	0.33	0.4%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat		
	0.5%	NL child	0.33	0.4%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat		
	0.5%	UK toddler	0.29	0.3%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat		
	0.5%	DE child	0.28	0.3%	Milk: Cattle	0.1%	Wheat	0.0%	Eggs: Chicken		
	0.4%	ES child	0.22	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat		
	0.4%	SE general	0.22	0.2%	Milk: Cattle	0.1%	Wheat	0.1%	Bovine: Muscle/meat		
	0.4%	GEMS/Food G15	0.22	0.1%	Milk: Cattle	0.1%	Barley	0.1%	Wheat		
	0.4%	DK child	0.22	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat		
	0.4%	GEMS/Food G11	0.22	0.1%	Milk: Cattle	0.1%	Barley	0.1%	Wheat		
	0.3%	GEMS/Food G08	0.21	0.1%	Barley	0.1%	Wheat	0.1%	Milk: Cattle		
	0.3%	DE general	0.21	0.2%	Milk: Cattle	0.1%	Barley	0.0%	Wheat		
	0.3%	RO general	0.21	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Poultry: Muscle/meat		
	0.3%	GEMS/Food G07	0.20	0.1%	Milk: Cattle	0.1%	Wheat	0.1%	Barley		
	0.3%	GEMS/Food G10	0.19	0.1%	Wheat	0.1%	Milk: Cattle	0.1%	Barley		
	0.3%	FR infant	0.19	0.3%	Milk: Cattle	0.0%	Wheat	0.0%	Bovine: Muscle/meat		
	0.3%	DE women 14-50 yr	0.18	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Barley		
	0.3%	NL general	0.15	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Barley		
	0.2%	GEMS/Food G06	0.15	0.2%	Wheat	0.0%	Milk: Cattle	0.0%	Barley		
	0.2%	ES adult	0.15	0.1%	Milk: Cattle	0.1%	Barley	0.1%	Wheat		
	0.2%	IE adult	0.10	0.1%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat		
	0.2%	IT toddler	0.09	0.2%	Wheat	0.0%	Barley	0.0%	Bovine: Muscle/meat		
	0.2%	FR adult	0.09	0.1%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat		
	0.1%	DK adult	0.08	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Bovine: Muscle/meat		
	0.1%	UK adult	0.07	0.0%	Milk: Cattle	0.0%	Wheat	0.0%	Bovine: Muscle/meat		
	0.1%	LT adult	0.07	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Barley		
	0.1%	UK vegetarian	0.07	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Eggs: Chicken		
	0.1%	IT adult	0.06	0.1%	Wheat	0.0%	Barley	0.0%			
	0.1%	PT general	0.06	0.1%	Wheat	0.0%	Barley	0.0%			
	0.1%	IE child	0.06	0.1%	Milk: Cattle	0.0%	Wheat	0.0%	Eggs: Chicken		
0.0%	FI 3 yr	0.02	0.0%	Wheat	0.0%	Barley	0.0%	Honey and other apiculture products			
0.0%	FI 6 yr	0.02	0.0%	Wheat	0.0%	Barley	0.0%	Honey and other apiculture products			
0.0%	FI adult	0.01	0.0%	Wheat	0.0%	Barley	0.0%				
	Column 7				Grapefruits		Grapefruits				

Conclusion:
 The estimated long-term dietary intake (TMDI/NED/IEDI) was below the ADI.
 The long-term intake of residues of Inpyrfluxam is unlikely to present a public health concern.

Table 2.7.11-11: EFSA model (PRIMo) TMDI for chronic risk assessment – rev. 3.1


 European Food Safety Authority EFSA PRIMo revision 3.1; 2019/03/19		Inpyrfluxam				Input values					
		LOQs (mg/kg) range from: 0.01 to: 0.05				Details - chronic risk assessment		Supplementary results - chronic risk assessment			
		Toxicological reference values				Details - acute risk assessment/children		Details - acute risk assessment/adults			
		ADI (mg/kg bw/day): 0.06		ARID (mg/kg bw): 0.3							
Source of ADI:		Source of ARID:		Year of evaluation:		Year of evaluation:					
Year of evaluation:											
Comments:											
Normal 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	MRLs set at the LOQ (in % of ADI)	commodities not under assessment (in % of ADI)
TMDI(NED/IEDI) calculation (based on average food consumption)	2%	NL toddler	1.37	1.0%	Milk: Cattle	0.2%	Wheat	0.2%	Apples	2%	
	1%	NL child	0.75	0.4%	Milk: Cattle	0.2%	Wheat	0.1%	Sugar beet roots	1%	
	1%	DE child	0.72	0.3%	Milk: Cattle	0.2%	Wheat	0.2%	Apples	1.0%	
	1%	GEMS/Food G08	0.72	0.4%	Barley	0.2%	Wheat	0.1%	Milk: Cattle	0.5%	
	1%	GEMS/Food G11	0.71	0.4%	Barley	0.2%	Wheat	0.1%	Milk: Cattle	0.6%	
	1%	GEMS/Food G15	0.70	0.4%	Barley	0.2%	Wheat	0.1%	Milk: Cattle	0.5%	
	1%	UK infant	0.66	0.6%	Milk: Cattle	0.1%	Wheat	0.1%	Potatoes	1.0%	
	1%	FR child 3 15 yr	0.65	0.4%	Milk: Cattle	0.2%	Wheat	0.1%	Sugar beet roots	0.8%	
	1%	GEMS/Food G07	0.64	0.3%	Barley	0.2%	Wheat	0.1%	Milk: Cattle	0.6%	
	1%	FR toddler 2 3 yr	0.62	0.5%	Milk: Cattle	0.2%	Wheat	0.1%	Apples	0.9%	
	1%	GEMS/Food G10	0.62	0.3%	Barley	0.2%	Wheat	0.1%	Milk: Cattle	0.5%	
	0.9%	DE general	0.55	0.3%	Barley	0.2%	Milk: Cattle	0.1%	Wheat	0.6%	
	0.9%	GEMS/Food G06	0.55	0.4%	Wheat	0.1%	Tomatoes	0.0%	Milk: Cattle	0.5%	
	0.9%	UK toddler	0.53	0.3%	Milk: Cattle	0.2%	Wheat	0.1%	Potatoes	0.7%	
	0.8%	DK child	0.50	0.2%	Wheat	0.2%	Milk: Cattle	0.1%	Rye	0.6%	
	0.8%	RO general	0.48	0.3%	Wheat	0.2%	Milk: Cattle	0.1%	Potatoes	0.5%	
	0.8%	DE women 14-50 yr	0.47	0.2%	Milk: Cattle	0.1%	Wheat	0.1%	Barley	0.6%	
	0.8%	ES child	0.47	0.2%	Wheat	0.2%	Milk: Cattle	0.0%	Cocoa beans	0.6%	
	0.7%	SE general	0.44	0.2%	Milk: Cattle	0.2%	Wheat	0.1%	Bovine: Muscle/meat	0.6%	
	0.7%	NL general	0.42	0.1%	Barley	0.1%	Milk: Cattle	0.1%	Wheat	0.5%	
	0.7%	ES adult	0.40	0.2%	Barley	0.1%	Wheat	0.1%	Milk: Cattle	0.3%	
	0.6%	IE adult	0.38	0.1%	Wheat	0.1%	Milk: Cattle	0.1%	Sweet potatoes	0.5%	
	0.6%	FI adult	0.36	0.5%	Coffee beans	0.0%	Potatoes	0.0%	Wheat	0.6%	
	0.5%	FR infant	0.31	0.3%	Milk: Cattle	0.0%	Wheat	0.0%	Potatoes	0.5%	
	0.5%	IT toddler	0.30	0.3%	Wheat	0.0%	Other cereals	0.0%	Tomatoes	0.2%	
	0.5%	PT general	0.30	0.2%	Wheat	0.1%	Potatoes	0.0%	Wine grapes	0.3%	
	0.4%	FR adult	0.26	0.1%	Wheat	0.1%	Milk: Cattle	0.0%	Wine grapes	0.3%	
	0.4%	FI 3 yr	0.22	0.1%	Potatoes	0.1%	Wheat	0.0%	Barley	0.3%	
	0.3%	IT adult	0.21	0.2%	Wheat	0.0%	Tomatoes	0.0%	Apples	0.1%	
	0.3%	LT adult	0.20	0.1%	Milk: Cattle	0.1%	Potatoes	0.1%	Wheat	0.3%	
	0.3%	UK vegetarian	0.19	0.1%	Wheat	0.1%	Milk: Cattle	0.0%	Potatoes	0.2%	
	0.3%	DK adult	0.19	0.1%	Milk: Cattle	0.1%	Wheat	0.0%	Potatoes	0.3%	
	0.3%	FI 6 yr	0.18	0.1%	Potatoes	0.0%	Wheat	0.0%	Barley	0.2%	
	0.3%	UK adult	0.18	0.1%	Wheat	0.0%	Milk: Cattle	0.0%	Potatoes	0.2%	
	0.2%	IE child	0.10	0.1%	Milk: Cattle	0.1%	Wheat	0.0%	Potatoes	0.1%	
	0.2%	PL general	0.10	0.1%	Potatoes	0.0%	Apples	0.0%	Tomatoes	0.2%	
Conclusion: The estimated long-term dietary intake (TMDI/NED/IEDI) was below the ADI. The long-term intake of residues of Inpyrfluxam is unlikely to present a public health concern.											

Table 2.7.11-12: EFSA model (PRIMo) IESTI for acute risk assessment – rev. 3.1

Acute risk assessment /children					Acute risk assessment / adults / general population					
Details - acute risk assessment /children					Details - acute risk assessment/adults					
The acute risk assessment is based on the ARfD. The calculation is based on the large portion of the most critical consumer group.										
Show results for all crops										
Unprocessed commodities	Results for children					Results for adults				
	No. of commodities for which ARfD/ADI is exceeded (IESTI):					No. of commodities for which ARfD/ADI is exceeded (IESTI):				
	---					---				
	IESTI					IESTI				
	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)		
	0.4%	Milk: Cattle	0 / 0.01	1.2	0.1%	Barley	0 / 0.09	0.43		
	0.2%	Barley	0 / 0.09	0.49	0.1%	Milk: Cattle	0 / 0.01	0.39		
	0.08%	Milk: Goat	0 / 0.01	0.24	0.06%	Milk: Goat	0 / 0.01	0.18		
	0.07%	Wheat	0 / 0.01	0.20	0.05%	Milk: Sheep	0 / 0.01	0.15		
	0.06%	Poultry: Muscle/meat	0 / 0.01	0.17	0.04%	Wheat	0 / 0.01	0.12		
	0.04%	Eggs: Chicken	0 / 0.01	0.12	0.04%	Poultry: Muscle	0 / 0.01	0.12		
	0.03%	Bovine: Liver	0 / 0.01	0.08	0.02%	Bovine: Muscle	0 / 0.01	0.06		
	0.02%	Bovine: Edible offals	0 / 0.01	0.07	0.02%	Other farmed animals:	0 / 0.01	0.06		
	0.02%	Bovine: Muscle/meat	0 / 0.01	0.07	0.02%	Equine: Muscle/meat	0 / 0.01	0.05		
	Expand/collapse list					Expand/collapse list				
Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)					Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)					
Processed commodities	Results for children					Results for adults				
	No of processed commodities for which ARfD/ADI is exceeded (IESTI):					No of processed commodities for which ARfD/ADI is exceeded (IESTI):				
	---					---				
	IESTI					IESTI				
	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)		
	0.1%	Barley / cooked	0 / 0.09	0.32	0.2%	Barley / beer	0 / 0.02	0.63		
	0.1%	Wheat / milling (flour)	0 / 0.01	0.17	0.02%	Wheat / bread/pizza	0 / 0.01	0.06		
	0.1%	Barley / milling (flour)	0 / 0.09	0.16	0.02%	Wheat / pasta	0 / 0.01	0.05		
	0.0%	Wheat / milling (wholemea	0 / 0.01	0.08	0.02%	Wheat / bread	0 / 0.01	0.05		
	#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!		
	Expand/collapse list					Expand/collapse list				

Drinking water exposure

A drinking water assessment for 1'-COOH-S-2840 was conducted (See section 2.11, Vol 1). Estimated intakes of 1'-COOH-S-2840 from drinking water were up to 0.7 % of the ADI for inpyrfluxam.

2.7.12. Proposed MRLs and compliance with existing MRLs

Plant matrices

The proposed residue definition for setting MRL values in plants in the in GB is inpyrfluxam parent only. MRLs are calculated and proposed based on the available residue data in support of the representative uses of inpyrfluxam on barley and wheat.

Calculations of MRLs were carried out using the OECD MRL calculator.

Barley

An MRL of 0.3 mg inpyrfluxam /kg is proposed for barley, based on all NEU residue data.

Wheat

An MRL of 0.03 mg inpyrfluxam /kg is proposed for wheat, based on all NEU residue data.

Other crops

Residues of parent compound in rotational crops are expected to be <0.01 mg/kg. Thus, for all other crops, an MRL of 0.01* mg/kg (at the LOQ level of the enforcement method) is proposed.

Animal matrices

The proposed residue definition for setting MRL values in animal commodities is inpyrfluxam.

Based on the metabolism studies and feeding studies, residues of inpyrfluxam in ruminants and poultry are expected to be <0.01 mg/kg in muscle, liver, kidney and fat. Hence no MRLs above the LOQ level are considered necessary.

Honey matrices

Residues of inpyrfluxam above LOQ are not expected in honey. Hence, the default honey MRL of 0.05* mg/kg should apply.

Table 2.7.12-1 Proposed MRLs for inpyrfluxam

Code number	Commodity	Proposed MRL (mg/kg)
0500010	Barley	0.3
0500090	Wheat	0.03

Code number	Commodity	Proposed MRL (mg/kg)
1011000	Swine	0.01*
1012000	Bovine	
1013000	Sheep	
1014000	Goat	
1015000	Equine	
1017000	Other farmed terrestrial animals	
1020000	Milk	
1016000	Poultry matrices	
1030000	Birds eggs	
1040000	Honey and other apiculture products	0.05*
All other commodities	Default MRL at LOQ	-

2.8. Fate and Behaviour in the Environment

Inpyrfluxam, code name S-2399, is an SDHI fungicide. Single spray applications to winter and spring wheat, winter and spring barley and durum wheat at a rate of up to 1.5 L product/ha (90 g a.s./ha) are proposed for a spring application window of BBCH 30-71.

Two different radiolabels were used in the environmental fate and behaviour studies: [pyrazolyl-4-¹⁴C] inpyrfluxam and [phenyl-¹⁴C] inpyrfluxam. These radiolabel positions are sufficient to define the route of degradation.

Inpyrfluxam has two main metabolites, 3'-OH-S-2840 and 1'-COOH-S-2840, which have been included in the environmental exposure assessment. Inpyrfluxam contains a chiral centre and exists as both R- and S-isomers. The enantiomeric ratio of parent and 1'-COOH-S-2840 (and, where appropriate, chiral minor metabolites) were monitored throughout the studies via chiral HPLC analysis. The active substance is present predominantly as the R-isomer and the ratio of the two isomers did not change during the studies. Inpyrfluxam degrades via two main mechanisms, forming 3'-OH-S 2840 via one route of degradation, with 1'-COOH-S-2840 (and associated minor metabolites) forming

via the other route. Conclusions regarding chirality for 3'-OH-S-2840, are the same as for the parent. Metabolites formed via the second route also contain an additional chiral carbon, leading to two pairs of isomers and adding further complexity to stereoisomer considerations.

Proposed pathways of degradation are given in Figure 2.8-1 for aerobic soil and Figure 2.8-2 for aerobic water.

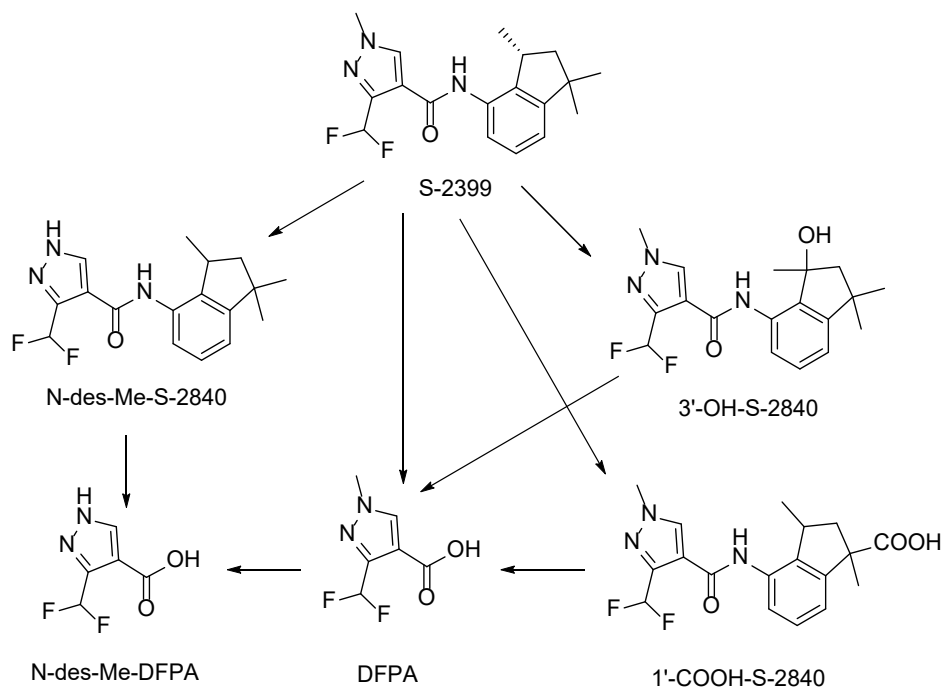


Figure 2.8-1: Proposed degradation pathway of inpyrfluxam in soil

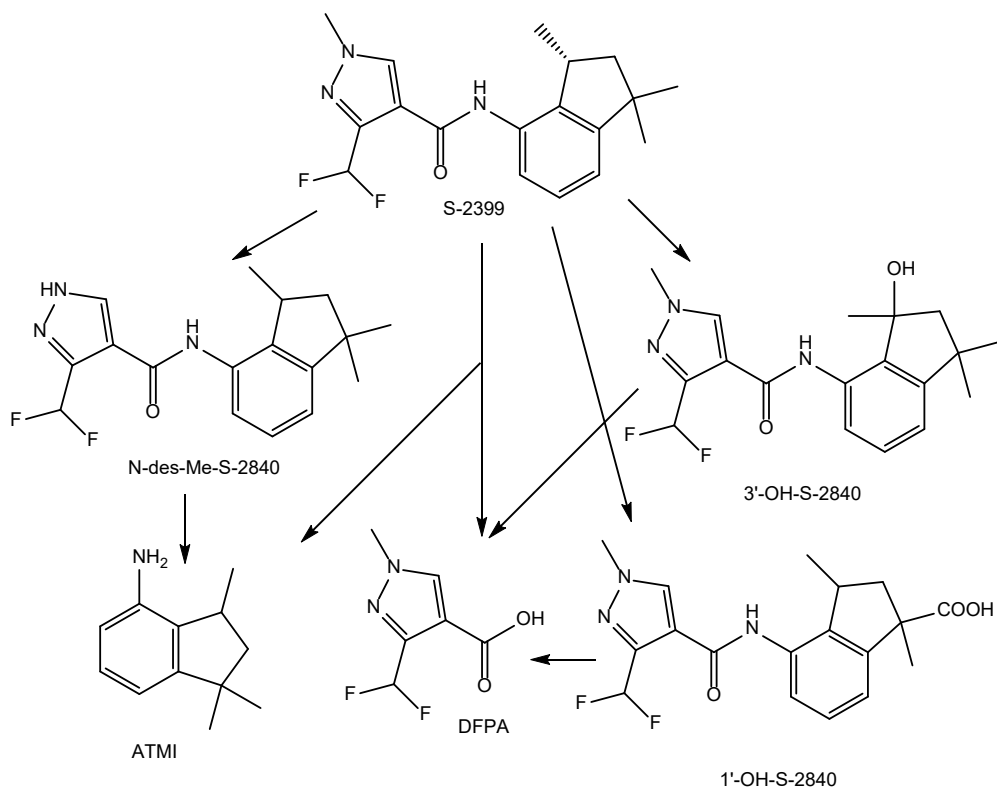


Figure 2.8-2: Proposed degradation pathway of inpyrfluxam in water-sediment systems

Inpyrfluxam contains a fluorinated methyl group but it does not meet the definition of a PFAS according to the OECD criteria.

2.8.1. Summary of fate and behaviour in soil

It can be concluded that inpyrfluxam is slowly degraded under aerobic soil conditions. In parent applied route and rate of degradation studies, minimal mineralisation of inpyrfluxam and its metabolites to CO₂ occurred (maximum 0.8 % applied radioactivity (AR) detected). Bound residues were also formed in parallel to mineralisation (maximum of 12.2 % AR).

In addition to parent residues and carbon dioxide, six metabolites were observed in soil extracts. The principle degradation routes in soil metabolism studies under aerobic conditions were oxidation of the 1' methyl group and the 3-carbon on the indenyl ring to form 1'-COOH-S-2840 (max. 30.1 % AR) and 3'-OH-S-2840 (max. 20.7 % AR), as well as hydrolysis of the central amide linkage or dealkylation of the N-methyl group on the pyrazolyl ring to yield DFPA, DFPA-CONH₂ and N-des-Me-DFPA or N-des-Me-S-2840 in minor amounts (all <5 % AR). The degradation of the major metabolites 1'-COOH-S-2840 and 3'-OH-S-2840 was also investigated in metabolite applied studies. A further metabolite, 1'-keto-S-2840, was observed in the 1'-COOH-S-2840 applied study, reaching a maximum of 21.7 % AR. Based on the maximum level of 1'-COOH-S-2840 formed in the parent applied study, metabolite 1'-keto-S-2840 could be expected to form at a

maximum of 6.5 % of applied inpyrfluxam; nevertheless 1'-keto-S-2840 was not observed in the parent applied study. Although the applicant did not submit any studies to address the degradation or adsorption parameters of 1'-keto-S-2840, this metabolite was not observed in field studies. It was concluded that the exposure of groundwater for this metabolite is covered by the exposure of 1'-COOH-S-2840 and 3'-OH-S-2840. It was therefore deemed unnecessary to request a full exposure assessment for this metabolite.

In anaerobic soil, only four of the metabolites observed in aerobic soil were present. Metabolites DFPA and N-des-Me-DFPA were both present at <5 % AR, while metabolites 1'-COOH-S-2840 and 3'-OH-S-2840 reached maximums of 11.2 and 9.5 % AR respectively and were thus within the levels observed in the aerobic soil study. Photodegradation in soil was slow with a DT50 value at 50 °N of 591 to 616 days and photodegradation is not therefore considered to be an important process in soil.

The maximum observed levels of both major metabolites are summarised in Table 2.8.1-1 below.

Table 2.8.1-1: Summary of maximum occurrences of the major metabolites 1'-COOH-S-2840 and 3'-OH-S-2840 and carbon dioxide and non-extracted residues in soil (in % AR)

Compound	Soil metabolism, aerobic [%]	Soil metabolism, anaerobic [%]	Soil photolysis [%]
1'-COOH-S-2840	30.1	23.4	-
3'-OH-S-2840	20.7	9.4	-
Carbon dioxide	0.8	0.5	0.5
Unextracted residues	12.2	7.7	2.0

The degradation of inpyrfluxam, 1'-COOH-S-2840 and 3'-OH-S-2840 under aerobic conditions was studied under both laboratory and field conditions. Non-normalised and normalised endpoints were derived for both laboratory studies and field studies (5 sites considered to be relevant to European conditions). A summary of the results is presented in table 2.7.5-2.

A normalised geometric mean field DT₅₀ of 121.4 days has been calculated by HSE for inpyrfluxam in soil for use in PEC_{gw} calculations. For PEC_{soil} and persistence calculations, a worst case non-normalised field SFO DT₅₀ of 383 days was calculated for

exposure calculations for a single growing season, alongside a DFOP DT₅₀ of 254 days for PECsoil accumulation over several growing seasons. Inpyrfluxam therefore meets the Persistent and very Persistent criteria under Regulation 1107/2009.

A field geometric mean DT₅₀ value of 74.7 days has been calculated by HSE for 1'-COOH-S-2840, and a field geometric mean DT₅₀ value of 131 days for 3'-OH-S-2840.

No pH dependent degradation was observed for parent or any major metabolite.

Table 2.8.1-2: Summary of DT50 values of inpyrfluxam and its major metabolites 1'-COOH-S-2840 and 3'-OH-S-2840

Compound	Soil metabolism, aerobic non normalised worst case field [days]	Soil metabolism, aerobic normalised, field geometric mean [days] ^	Soil photolysis at 50 °N [days]	Soil metabolism anaerobic [days]	Formation fraction
Inpyrfluxam	383* 254**	121.4	615	>10,000	-
1'-COOH-S-2840	840	74.7	-	-	0.53
3'-OH-S-2840	369	131	-	-	0.23

^ field values only following EFSA (2014 guidance)

* SFO (worst case for applications within a single growing season)

** DFOP (worst case for accumulation in soil over several growing seasons)

Persistence (P) or very persistent (vP) criteria are defined according to Section 3.7.2.1 and 3.7.3.1, respectively, of Annex II of EC Regulation 1107/2009 as follows:

An active substance, safener or synergist fulfils the persistence criterion where:

- *The half-life in soil is higher than 120 days.*

An active substance, safener or synergist fulfils the ‘very persistent’ criterion where:

- *The half-life in soil is higher than 180 days.*

Based on these criteria inpyrfluxam is classified as ‘very persistent’ in soil.

Adsorption of inpyrfluxam and metabolites 1'-COOH-S-2840 and 3'-OH-S-2840

The soil adsorption properties of inpyrfluxam and metabolites 1'-COOH-S-2840 and 3'-OH-S-2840 have been assessed. There was no pH dependence observed for parent or either metabolite.

For inpyrfluxam, adsorption was studied in seven soils. One soil was a volcanic soil; following the HSE assessment this soil was excluded from adsorption calculations as it is not considered to be representative of GB agricultural conditions. The K_{foc} values for the remaining soils ranged between 500 and 891 mL/g, with a geometric mean value of 647 mL/g used in groundwater modelling. The $1/n$ values for the six remaining soils ranged between 0.932 and 0.996 with an arithmetic mean value of 0.960 for use in the exposure modelling.

The adsorption behaviour of metabolite 3'-OH-S-2840 was assessed in three soils. HSE considered all soils to be acceptable for use in the assessment. The K_{foc} values ranged between 349 and 492 mL/g, while the $1/n$ values ranged between 0.879 and 0.973. A geometric mean K_{foc} value of 410 mL/g and an arithmetic mean $1/n$ of 0.936 were used in groundwater modelling.

The adsorption parameters of the A and B diastereomers of metabolite 1'-COOH-S-2840 were determined separately in the same five soils. HSE accepted all the proposed soils for use in the assessment. For 1'-COOH-S-2840A, the K_{foc} values ranged between 11 and 35 mL/g, with $1/n$ values ranging between 0.937 and 0.966. The corresponding geometric mean K_{foc} value was 20.8 mL/g and the arithmetic mean $1/n$ value was 0.950. For 1'-COOH-S-2840B, K_{foc} values ranged between 16 and 45 mL/g, with a geometric mean value of 28.6 mL/g and $1/n$ values ranged between 0.923 and 0.972 with an arithmetic mean value of 0.942.

The need for including both diastereomers separately or using mean values of the adsorption parameters of 1'-COOH-S-2840A and B in the exposure assessment has been considered in line with both EFSA and GB guidance on stereoisomers. In line with the GB guidance, the susceptibility of the compound to leaching based on the K_{foc} values, degradation rate and the overall leaching potential have been considered. As 1'-COOH-S-2840 is of very high mobility, small differences in the sorption parameters can have a large influence on the behaviour of the substance in leaching simulations. The environmental exposure assessments were therefore conducted for both worst case parameters and with

mean values for the diastereomers combined to determine the impact of combining the diastereomer data on modelling outcomes.

The applicant did not submit lysimeter or column leaching studies as the data requirement was fully addressed by the OECD 106 studies.

2.8.2. Summary of fate and behaviour in water and sediment

Eight metabolites were observed in aquatic system studies, two of which were defined as major metabolites, according to the appropriate guidelines and have therefore been included in the exposure assessment. Six additional metabolites were identified at low levels (< 5%). These are N-des-Me-S-2840, N-des-Me-DFPA, DFPA, DFPA-CONH₂, ATMI and 1' CH₂OH-S-2840. Table 2.8.2-1 summarises the major metabolites identified in the aquatic degradation studies.

Table 2.8.2-1: Major metabolites identified in aquatic degradation studies

Metabolite identity	Relevant studies	Peak formation (% AR)
1'-COOH-S-2840 isomers A and B combined	Water-sediment	13.1 % whole system ^a 10.0 % water ^b / 4.8 % sediment ^a
3'-OH-S-2840	Indirect photolysis Water-sediment	8.6 % water ^a 6.8 % whole system ^b 2.9 % water ^b / 6.0 % sediment ^b

^a – phenyl label

^b – pyrazolyl label

Route and rate of chemical and photochemical degradation in aquatic systems

Hydrolytic degradation

Inpyrfluxam was hydrolytically stable at pH 4, 7 and 9 over 5 days at 50 °C and no *R* to *S* isomerisation occurred. As inpyrfluxam did not exhibit a decline phase, no reliable persistence endpoints could be obtained. Consequently, hydrolysis is not considered to be a significant route of degradation.

Photochemical degradation

The aqueous photolysis of inpyrfluxam was investigated in two separate studies - one in sterile aqueous buffer using pyrazolyl-labelled test substance ([pyrazolyl-4-¹⁴C] inpyrfluxam), and the other in sterilised natural water using both pyrazolyl- and phenyl- ([phenyl-U-¹⁴C] inpyrfluxam) labelled inpyrfluxam.

Pyrazolyl-labelled inpyrfluxam was stable in sterile aqueous buffer after continuous artificial irradiation for 15 days at pH 7 (equivalent to 42 days of natural sunlight at 40°N) and in dark controls. 3'-OH-S-2840 was detected at 3.1% in at the start of the study, suggesting it may be a minor impurity rather than a degradation product, and represented up to 5.9% AR during the study period. No DT₅₀ values for inpyrfluxam could be determined due to the lack of significant degradation.

In sterilised natural water irradiated continuously for 16 days (equivalent to 34 days of natural sunlight at 40°N), pyrazolyl- and phenyl-labelled inpyrfluxam degraded slowly remaining close to 100% AR with [pyrazolyl-4-¹⁴C] inpyrfluxam, and declining to a mean of 92.6 % AR with [phenyl-U-¹⁴C] inpyrfluxam. The metabolite 3'-OH-S-2840 was observed at a maximum of 8.6% at study end while minor metabolites DFPA-CONH₂ and DFPA which reached maxima of 3.4% (at 16 DAT) and 4.7 % (14 DAT) respectively.

The DT₅₀ values ranged from 80 to 179 days in natural sunlight for [pyrazolyl-4-¹⁴C] inpyrfluxam and [phenyl-U-¹⁴C] inpyrfluxam, respectively (OECD 30 – 50 °N values, corrected for dark control). The observed degradation rates indicate that photolysis contributes to the overall degradation of inpyrfluxam to some extent; however, its overall significance will be limited by other removal processes. As the occurrence of 3'-OH-S-2840 in aqueous indirect photolysis reached a maximum of 8.6 % with an increasing trend at study end, it represents a worst-case formation in surface water. This is in comparison to the water phase of the water-sediment studies, where the maximum formation of 3'-OH-S-2840 was 2.9% with a decreasing trend. Therefore, the maximum % occurrence of this metabolite used in the exposure assessment is based on the indirect photolysis study.

Ready biodegradability

Using the OECD 301 B carbon dioxide evolution test, inpyrfluxam was not readily biodegradable as it did not reach 60% CO₂ evolution within a 10-day window by day 28 and showed no inhibition of microbial activity.

Aerobic mineralisation

The aerobic mineralisation of inpyrfluxam was evaluated using pyrazolyl and phenyl-labelled inpyrfluxam in a pelagic (pure water) system under dark aerobic conditions at 10 and 100 µg/L for 61 days.

Inpyrfluxam was very slowly degraded, with 96.5 % AR ([pyrazolyl-4-¹⁴C] inpyrfluxam) and 92.1 % AR ([phenyl-U-¹⁴C] inpyrfluxam) remaining at study end at the low concentration, and 90.4 % AR and 90.6 % AR remaining at the high concentration. The metabolite observed at the highest concentration was not identified as it only reached a maximum of 3.9 % AR. Mineralisation was low and volatiles peaked at 0.4 % AR. Only the *R*-isomer was present in both the application solution and at 61 days after application, indicating no isomerisation to the *S*-isomer. DT₅₀ values of 1,540 to 23,600 days were calculated; these values are extrapolated beyond the study duration and are therefore subject to uncertainty.

Water sediment studies

The route and rate of degradation in water/sediment of inpyrfluxam was investigated in five water sediment systems of contrasting physicochemical characteristics (pH 5.7-7.9, OC 0.9-3.7%, loamy sand to clay) under dark, aerobic conditions. Two radiolabelled positions (pyrazolyl- and phenyl-label) were used for two systems while the other 3 systems were radiolabelled with the [pyrazolyl-4-¹⁴C] inpyrfluxam label only.

Across the five water-sediment systems, inpyrfluxam degraded slowly, with 69.8 - 90.2 % AR of the dose remaining unchanged at study end. The maximum bound residues were 12.6% AR at study end, which was subject to further extraction and analysis. Mineralisation to CO₂ was insignificant, with a maximum of 0.5% AR.

The major metabolites identified were 1'-COOH-S-2840 isomers A and B with a maximum of 13.1% AR (Golden Lake whole system, 112 DAT), and 3'-OH-S-2840 with a maximum of 6.8% AR (Taunton River whole system, 30 DAT). These metabolites trigger inclusion in the exposure assessment. Additional metabolites were detected at low levels (≤2.6%), including N-des-Me-S-2840, DFPA, N-des-Me-DFPA, DFPA-CONH₂, 1'-CH₂OH-S-2840 and ATMI. Minor amounts of DFPA were observed (<2 %) resulting from hydrolysis of the central amide bond and/ or dealkylation of the N-methyl group on the pyrazolyl ring. Overall, the test substance degraded slowly across all systems, with DT₅₀ values ranging from 212 to >10,000 days (based on persistence endpoints using whole system values). No isomerisation of [¹⁴C] inpyrfluxam occurred. The proposed aerobic degradation pathway for inpyrfluxam in aerobic aquatic systems is shown in Figure 2.7-2 above.

Inpyrfluxam partitioned from the water phase into the sediment phase. As such, the sediment compartment was considered to be the relevant compartment against which to assess inpyrfluxam persistence criteria. According to the criteria in Regulation (EC) No 1107/2009, inpyrfluxam triggers classification as very persistent in freshwater sediment as the DT₅₀ values were > 180 days in all five systems.

Water-treatment processes

Inpyrfluxam possesses three nitrogen atoms – two within a pyrazole ring and the third as part of an amide group. The major metabolites 1'-COOH-S-2840 and 3'-OH-S-2840

contain the same structure in respect of the nitrogen atoms. As these are considered to be stable, it is unlikely that inpyrfluxam or its major metabolites would form nitrosamines during water treatment.

It is noted that while ozonation had been addressed, chlorination and other potential processes have not. Confirmatory data will be required to address this when the relevant GB guidance is noted, as there is currently a lack of agreed guidance in this area.

Endpoints for use in exposure assessment

Table 2.8.2-2 provides a summary of the compounds considered in the exposure assessment along with the endpoints derived from aquatic studies.

Table 2.8.2-2: Compounds and endpoints in the exposure assessment

Compound	Compartment	Longest non-normalised DissT ₅₀ (d)	Model	Maximum occurrence in compartment (%)
Inpyrfluxam	Water	34.28 (maximum, n = 5)	DFOP	- ^a
	Sediment	1000	Default ^b	84.6 (water-sediment study, Taunton River PY label, DAT 112)
1'-COOH-S-2840 A & B	Water	1000	Default ^b	10.0 (water-sediment study, Golden Lake PY label, DAT 112)
	Sediment	1000	Default ^b	4.8 (water-sediment study, Golden Lake PH label, DAT 63)
3'-OH-S-2840	Water	1000	Default ^b	8.6 (indirect photolysis, Lake Tuckahoe water, PH label)

	Sediment	1000	Default ^b	6.0 (water-sediment study, Taunton River PY label, 30 DAT)
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^a Not relevant for parent compound in the exposure assessment

^b No significant decline was noted. Use of 1000 day default DissT₅₀ is suggested.

2.8.3. Summary of fate and behaviour in air

Inpyrfluxam has a vapour pressure below the FOCUSair trigger of 1×10^{-5} pa at 20°C (3.81×10^{-8} pa at 20°C) and therefore does not require assessment for short range transport due to its low volatility. Photochemical oxidative degradation of inpyrfluxam by atmospheric hydroxyl radicals was calculated using the AOPWIN v.1.92 quantitative structure-activity relationship (QSAR) model and OH (12h) concentration of 1.5×10^6 radicals/cm³ as recommended in FOCUS Air guidance document. The atmospheric half-life of inpyrfluxam was calculated to be 2.80 hours. Based on this, it was concluded that inpyrfluxam is not persistent in air there is a low risk of long range transport.

2.8.4. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

Inpyrfluxam is a new active substance and so no monitoring data are available.

2.8.5. Definition of the residues in the environment requiring further assessment

The following was identified as the residue definition for risk assessment.

Compartment	Residue definition for risk assessment
Soil	Inpyrfluxam, 3'-OH-S-2840, 1'-COOH-S-2840 (A + B combined)
Groundwater	Inpyrfluxam, 3'-OH-S-2840, 1'-COOH-S-2840 (A + B combined)
Surface water	Inpyrfluxam, 1'-COOH-S-2840 (A + B combined), 3'-OH-S-2840
Sediment	Inpyrfluxam, 3'-OH-S-2840
Air	Inpyrfluxam

2.8.6. Summary of exposure calculations and product assessment

PECsoil, cereals, 1 application of 90 g/ha

PECsoil modelling for the formulation, inpyrfluxam and its 2 major metabolites 3' OH S 2840 and 1' COOH S 2840 is presented in section B.8.2. of the CP. Modelling was conducted using the PECsoil spreadsheet calculator version 2.1.1 for the sole application scheme in the GAP (1 x 90 g a.s/ha application to cereals at BBCH 30 71, 80 % crop interception).

The fitted endpoint values from the worst case DT₅₀ in soil were used to calculate the maximum PEC in soil for a single year. As inpyrfluxam has a DT₉₀ > 1 year, PECsoil(accumulation) was also calculated for inpyrfluxam. For this, the fitted endpoint values from the soil with the worst case DT₉₀ were used to calculate soil accumulation as a conservative assessment. The two kinetic models used are given below.

- An SFO DT₅₀ of 383 days ($k = 0.00181$) was used to calculate PECsoil within a single growing season.
- A DFOP DT₅₀ of 254 days and DT₉₀ of > 1,000 days ($k_1 = 0.00861$, $k_2 = 0.000693$, $g = 0.465$) was used to calculate PECsoil(accumulation) across multiple growing seasons.

All assessments were made assuming bulk density of 1.5 g/cm³ and a 5 cm incorporation depth for annual applications; this is to reflect an assessment of potential accumulation in soil under minimum/shallow tillage practice. As parent accumulation was calculated, PECsoil(accumulation) for metabolites were calculated to include degrading inpyrfluxam already present within the soil as a simple worst case approach.

PECsoil for the formulated product was also calculated, assuming the density of the product was 0.9273 g/mL and the application rate of 1.5 L/ha. The produced a formulation application rate of 1391 g/ha.

PECgw, cereals, 1 application of 90 g/ha

PECgw values were calculated for inpyrfluxam and metabolites 3'-OH-S-2840 and 1'-COOH-S-2840 for the sole representative use of 1 x 90 g a.s/ha on cereals at BBCH 30-71 using the FOCUS PEARL v5.5.5., PELMO v6.6.4., and MACRO v5.5.4. groundwater models. Application was modelled for early (BBCH 30) & late (BBCH 71) treatment, on both winter & spring cereals at all GB relevant scenarios. A tier 1 approach was used for the groundwater assessment. Further details are provided in section CP.B.8.3 of Volume 3CP.

Metabolite 1'-COOH-S-2840 is formed as an enantiomeric pair, with differing sorption parameters for the diastereomers (1'-COOH-S-2840A and 1'-COOH-S-2840B). Modelling

was therefore initially conducted using mean sorption parameters (K_{oc} 24.4, $1/n$ 0.946) and conservative sorption parameters (K_{oc} 20.8, $1/n$ 0.950). Exceedances of $>0.1 \mu\text{g/L}$ were determined in all modelled scenarios using both sets of sorption endpoints. It was decided that the use of PEC_{gw} values determined from conservative or mean parameters did not have an impact on subsequent areas of the risk assessment, as both sets of endpoints lead to the same regulatory outcome (see CP section B.8). To ensure simplicity and consistency for future products, HSE recommends that it will not be required to conduct modelling with both sets of parameters, but modelling can just be based on average substance parameters. As such, only groundwater modelling results determined from mean parameters are presented here.

Metabolite 1'-COOH-S-2840 is calculated to exceed the $0.1 \mu\text{g/L}$ trigger value in all scenarios reaching a maximum of $1.802 \mu\text{g/L}$ (spring cereals, late, Hamburg scenario), and therefore requires a relevance assessment; this is presented in Section 2.11. The 80th percentile PEC_{gw} values for inpyrfluxam (maximum $0.004 \mu\text{g/L}$, spring cereals, late, Hamburg) and metabolite 3'-OH-S-2840 (maximum $0.010 \mu\text{g/L}$, spring cereals, late, Hamburg) were all $<0.1 \mu\text{g/L}$ and thus no relevance assessment is required for 3'-OH-S-2840. The worst case results were all determined from late application to spring cereals, in the Hamburg scenario, using the PEARL groundwater model. Exceedances of the $0.1 \mu\text{g/L}$ limit value are shown in bold in the table below.

Table 2.8.6-1 Worst case PEC_{gw} for PEARL v5.5.5, spring cereals, late

Scenario	Parent ($\mu\text{g/L}$)	Metabolites ($\mu\text{g/L}$)	
		3'-OH-S-2840	1'-COOH-S-2840
Hamburg	0.004	0.010	1.802

PEC_{sw} surface water and sediment, cereals, 1 application of 90 g/ha

PEC_{sw} and PEC_{sed} values were calculated for both the spray drift and drainflow exposure routes using the HSE PEC Surface Water and Sediment Calculator version 2.0.1. The GAP proposes that a single 90 g/ha application can be made to spring and winter cereals between BBCH 30-71, with 1st tier drainflow calculations based on applications at BBCH 30 and 80% crop interception within the drainflow window as a worst case.

Exposure from spraydrift was calculated for buffer zones of 1 and 5 m using Rautmann spraydrift values of 2.77 % and 0.57 % respectively for a single application. Further details and PEC values are provided in section CP.B.8.5 of Volume 3CP.

Due to the lack of a decline phase observed in the sediment phase of the water/ sediment studies, the PEC_{sed} accumulation via spray drift was calculated for the parent using a worst-case default DT₅₀ value of 1000 days.

Only PEC_{sw} values via drift and drainflow have been calculated for the 1'-COOH-S-2840 and 3'-OH-S-2840. The PEC_{sed} values metabolites were not calculated as they are not required for the risk assessment, as confirmed by HSE Ecotoxicology.

For metabolite 1'-COOH-S-2840, the maximum occurrence in water was derived from the water phase of the water-sediment study. For 3'-OH-S-2840, the maximum % in water was derived from the aqueous indirect photolysis study instead of the water-sediment study, as it represented a realistic worst-case formation in surface water.

A PEC_{sw} for the S-2399 60 g/L EC formulation for a single application of 1.5 L product/ha on field cereals was also calculated. This was based on an application rate of 1.5 L product/ha and a formulation density is 0.9273 g/mL. Thus the mass of formulation applied is 1391 g/ha.

For first-tier calculations via drainflow, application is assumed to occur within the drainflow period (1 October – 30 April) and therefore no losses via dissipation of the active substance are considered in soil and the calculation is based on the full amount applied. First-tier drainflow assessments show that the PEC_{sw} for inpyrfluxam (0.692 µg/L) exceeds the RAC of 0.660 µg/L, indicating the need for a higher tier drainflow (HTDF) evaluation. Higher tier drainflow results are based on HSE modelling, using the UK CRD MACRO drainflow tool v2.2. The RAC is derived from an endpoint for fish.

The Denchworth scenario in the HTDF was not considered to be a relevant scenario for spring cereals within the context of this assessment, as soils of this type typically remain too waterlogged to be sufficiently workable to sow spring-sown crops. For full details, see the volume 3CP – B8 (Environmental Fate & Behaviour) document.

For the early application to winter cereals at BBCH 30 and the Denchworth wet scenario there are 3/30 exceedances of the RAC. All other soil scenarios have zero exceedances for both winter and spring cereals. The total percentage of safe years for early application to winter and spring cereals is 99.84 % for winter cereals and 100 % for spring cereals. This application pattern therefore met the criteria for being considered acceptable according to HSE guidance and no further assessment was required.

For the late application to winter cereals at BBCH 71, in the Denchworth wet scenario there are exceedances in 6/30 years (20 %). There are also 4/30 exceedance years (13.3

%) in the Denchworth medium scenario. Since more than 3/30 exceedances were observed, and the RAC was based on effects against fish, this information was referred to HSE Ecotoxicology for an evaluation of the exceedance length and magnitude. For further details, see Volume 3CP B-9 (Ecotoxicology). For late application to spring cereals, there was only one exceedance in the Hanslope wet scenario (1/30 exceedance years, 3.3%) and this GAP was also considered acceptable without further assessment required.

PECair

As the vapour pressure of inpyrfluxam is below the FOCUSair trigger value of 1×10^{-5} Pa, short range transport is not a likely route of exposure. For long range transport, the overall hydroxyl rate constant was determined to be 45.8565×10^{-12} cm³/molecule/s using AOPWIN v 1.92. The weighted global average tropospheric hydroxyl radical concentration is 1.5×10^6 mol/cm³ for a 12-hour period. This gives a half-life of 0.233 days (12 hour day) for inpyrfluxam. This does not meet the 2 day atmospheric half-life trigger to consider the potential for long-range environmental transport. Given the rapid degradation rate in air and low level of volatilisation, it can be concluded that there is a low risk of long range transport of inpyrfluxam and no further consideration of fate and behaviour in air is required.

Other routes of exposure

Exposure via other routes, e.g deposition of dust, indirect exposure of surface water from Sewage Treatment Plant or from amenity use is not expected for the proposed use of inpyrfluxam.

2.9. Effects on Non-target Species

2.9.1. Summary of effects on birds and other terrestrial vertebrates

Birds

Toxicity data addressing acute and long-term toxicity to birds for the active substance inpyrfluxam has been provided. For further details of the underlying studies see Section B.9 (CA). A full list of available endpoints is provided in the list of endpoints and in the relevant risk assessments for the representative formulation. The following endpoints have been used to perform the risk assessment:

Discussion about how these endpoints were chosen from the submitted studies is found in Section 3CP B.9.1.1.

Inpyrfluxam

Acute toxicity

The acute toxicity estimate used to address the toxicity of the active substance in the risk assessment is **LD₀ = 38 mg a.s./kg bw.**

Long-term/reproductive toxicity

The chronic toxicity estimate used to address the long-term/reproductive toxicity of the active substance in the risk assessment is **NOEL = 19 mg a.s./kg bw/d.**

Mammals

Toxicity data have been provided and considered within the human health assessment (see Section B.6 (CA) for details of the underlying studies). Endpoints for use in the mammalian risk assessment have been established for acute and long-term toxicity. The following endpoints have been used to perform the risk assessment:

Inpyrfluxam

Acute toxicity

The acute toxicity estimate used to address the toxicity of the active substance in the risk assessment is **LD₅₀ = 180 mg a.s/kg b.w.**

Long-term/reproductive toxicity

The chronic toxicity estimate used to address the long-term toxicity of the active substance in the risk assessment is **NOAEL = 25 mg a.s./kg b.w./day, based on foetus weight and body weights in dams.**

Endocrine disruption assessment for birds and mammals

For birds, when considering reproductive toxicity the NOAEL value was 19 mg a.s./kg bw/d for the zebra finch. Effects on mean egg production were observed at 1000 ppm in the bobwhite quail reproductive toxicity study and insufficient information was available to confirm that these were not treatment related. Currently there are no further tests available for assessing endocrine activity in birds and therefore HSE do not consider further testing to be required at this stage. In accordance with EFSA/ECHA 2018 guidance, the gross pathology findings should be reported. This was the case for the avian reproductive studies provided and no treatment related effects were observed.

For wild mammals, the toxicology data and conclusions for endocrine disruption were considered (see Section 2.6.8). It was possible to conclude for oestrogen, androgen,

steroidogenesis, and thyroid (EATS) modalities that the endocrine disruption criteria are not met for wild mammals.

Overall conclusions

Overall, HSE concludes that based on current EFSA/ECHA 2018 guidance, it is not possible to reach a conclusion for birds or reptiles when considering endocrine disruption. Regarding wild mammals, inpyrfluxam is not an endocrine disruptor when considering EATS modalities based on EFSA/ECHA 2018 guidance and agreed regulatory criteria. Endocrine disruption in terrestrial vertebrates has been sufficiently investigated according to the EFSA/ECHA 2018 guidance.

For full discussion of the ecotoxicology endocrine disruption assessment for birds and mammals, see Volume 3CA, section B.9.1.5.

2.9.2. Summary of effects on aquatic organisms

Toxicity data to address inpyrfluxam and relevant metabolites have been provided. The toxicity data used in the risk assessment are summarised here (active substance, Table 2.9.2 1; metabolites, Table 2.9.2 2; formulation, Table 2.9.2 3). For full details of all the available toxicity data see the list of endpoints and Section B.9 (CA and CP).

Table 2.9.2 - 1 Endpoints relevant for inpyrfluxam

Test substance	Test organism	Test system	Endpoint		Reference
Acute toxicity to fish					
Inpyrfluxam S-2399	<i>Oncorhynchus mykiss</i>	96-hour, static	LC ₅₀	0.031 mg a.s./L (t.w.a)	KCA 8.2.1/01 [REDACTED] 2014a
Inpyrfluxam S-2399	<i>Lepomis macrochirus</i>	96-hour, static	LC ₅₀	0.054 mg a.s./L (t.w.a)	KCA 8.2.1/02 [REDACTED] 2014b
Inpyrfluxam S-2399	<i>Pimephales promelas</i>	96-hour, static	LC ₅₀	0.050 mg a.s./L (t.w.a)	KCA 8.2.1/03 [REDACTED] 2014c
Inpyrfluxam S-2399	<i>Cyprinus carpio</i>	96-hour, static	LC ₅₀	0.067 mg a.s./L (t.w.a)	KCA 8.2.1/04 [REDACTED]

Test substance	Test organism	Test system	Endpoint		Reference
					2014d
Inpyrfluxam S-2399	<i>Cyprinodon variegatus</i>	96-hour, static	LC ₅₀	0.15 mg a.s./L (m.m)	KCA 8.2.1/05 [REDACTED] 2014e
Inpyrfluxam S-2399	<i>Poecilia reticulata</i>	96-hour, static	LC ₅₀	0.35 mg a.s./L (t.w.a)	KCA 8.2.1/06 [REDACTED] 2016c
Inpyrfluxam S-2399	<i>Oryzias latipes</i>	96-hour, static	LC ₅₀	0.79 mg a.s./L (t.w.a)	KCA 8.2.1/07 [REDACTED] 2016a
Inpyrfluxam S-2399	<i>Danio rerio</i>	96-hour, static	LC ₅₀	0.30 mg a.s./L (t.w.a)	KCA 8.2.1/08 [REDACTED] 2016b
Inpyrfluxam S-2399	Species sensitivity distribution (SSD)	96-hour, static	HC ₅	0.018 mg a.s./L (based on LC ₅₀ data)	KCA 8.2.1/09 [REDACTED] 2017
Chronic toxicity to fish					
Inpyrfluxam S-2399	<i>Pimephales promelas</i>	32-day, flow-through	LC ₁₀	0.0066 mg a.s./L (m.m)	KCA 8.2.2.1/01 [REDACTED] 2014
Bioconcentration in fish					
Inpyrfluxam S-2399	<i>Lepomis macrochirus</i>	31-day, flow-through	Lipid normalised, growth corrected, kinetic	215.4 L/kg (Total ¹⁴C residue basis)	KCA 8.2.2.3/01 [REDACTED] 2015

Test substance	Test organism	Test system	Endpoint		Reference
			bioconcentration factor (BCF _{kgL,TRR})		
Acute toxicity to invertebrates					
Inpyrfluxam S-2399	<i>Daphnia magna</i>	48-hour, static	EC ₅₀	1.1 mg a.s./L (t.w.a)	KCA 8.2.4.1/01 [REDACTED] 2014f
Inpyrfluxam S-2399	<i>Americamysis bahia</i>	48-hour, static	LC ₅₀	1.1 mg a.s./L (m.m)	KCA 8.2.4.2/01 [REDACTED] 2014g
Long-term toxicity to invertebrates					
Inpyrfluxam S-2399	<i>Daphnia magna</i>	21-day, static-renewal	NOEC	0.13 mg a.s./L (t.w.a)	KCA 8.2.5.1/01 [REDACTED] 2014h
			EC ₁₀ (reproduction)	0.21 mg a.s./L (t.w.a)	
Toxicity to sediment-dwelling organisms					
Inpyrfluxam S-2399	<i>Leptocheirus plumulosus</i>	28-day, static renewal	NOEC ^a	10.26 mg a.s./kg sediment (t.w.a)	KCA 8.2.5.4/03 [REDACTED] 2017
Toxicity to algae					
Inpyrfluxam S-2399	<i>Navicula pelliculosa</i>	96-hour, static	ErC ₅₀ (72 h)	10.1 mg a.s./L (m.m)	KCA 8.2.6.2/01 [REDACTED] 2015b
Inpyrfluxam S-2399	<i>Skeletonema costatum</i>	96-hour, static	ErC ₅₀ (96 h)	1.28 mg a.s./L (m.m)	KCA 8.2.6.2/03 [REDACTED] 2015d
Geomean of two diatom endpoints (<i>Skeletonema costatum</i> and <i>Navicula pelliculosa</i>)				3.60 mg a.s./L	-

Test substance	Test organism	Test system	Endpoint		Reference
Toxicity to aquatic macrophytes					
Inpyrfluxam S-2399	<i>Lemna gibba</i>	7-day, semi-static	ErC ₅₀	> 24 mg a.s./L (m.m)	KCA 8.2.7/01 [REDACTED] 2016

nom. = nominal; m.m. = arithmetic mean measured; g.m. = geometric mean measured; t.w.a = time-weighted average; i.m = initial measured.

^a Due to the lack of model fit robust EC₁₀ and EC₂₀ values could not be generated.

Endpoints in **bold** were used in risk assessment

Table 2.9.2 – 2: Summary of toxicity data related to the metabolites of inpyrfluxam

Test substance	Test organism	Test system	Endpoint (mg met./L)	Reference
Acute toxicity to fish				
3'-OH-S-2840	<i>Oncorhynchus mykiss</i>	96-hours, static	LC ₅₀ > 6.2 (m.m.)	CA 8.2.1/10 [REDACTED] 2016a
1'-COOH-S-2840	<i>Oncorhynchus mykiss</i>	96-hours, static	LC ₅₀ > 50 (m.m.)	CA 8.2.1/11 [REDACTED] 2016b

m.m. = mean measured

Table 2.9.2 – 3: Summary of available toxicity endpoints for the formulation S-2399 60 g/L EC

Test substance	Test organism	Test system	Endpoint	Result	Reference
S-2399 60 g/L EC^a	<i>Oncorhynchus mykiss</i>	96-hour, static	LC ₅₀	0.336 mg S-2399 6EC/L (nom) (0.022 mg a.s./L) (m.m)	CP 10.2.1/01 [REDACTED] 2020a
S-2399 60	<i>Daphnia magna</i>	48-hour,	EC ₅₀	3.97 mg S-	CP 10.2.1/02

Test substance	Test organism	Test system	Endpoint	Result	Reference
g/L EC ^a		static		2399 6EC/L (nom) (0.26 mg a.s./L) (m.m)	██████████ 2020b
S-2399 60 g/L EC ^a	<i>Pseudokirchneriella subcapitata</i>	72-hour, static	E _r C ₅₀	6.83 mg S-2399 6EC/L (nom) (0.447 mg a.s./L) (m.m)	CP 10.2.1/03 ██████████ 2020c

m.m = mean measured concentration; nom = nominal concentration

a Active substance content of the formulation; density 0.9273 g/mL, 60.68 g a.s./L (corresponding to 6.544% w/w)

For the active substance acute fish toxicity data, a SSD was fitted and HC₅ estimated for use in risk assessment. A geomean of the two diatom endpoints was calculated for use in risk assessment.

Bioaccumulation

The submitted bioaccumulation study ██████████ / ██████████ (2015/2020) was found to be valid and suitable for use in risk assessment. A summary of the BCF estimates is presented in the table below.

Table 2.9.2 – 4: Agreed HSE estimates for BCF_{SSL, TRR}, BCF_{kgL, TRR}, BCF_{SSL, S-2399}, and t_{1/2g}

Treatment group (nominal concentration, µg/L)	BCF _{SSL, TRR} (L/kg fish)	BCF _{kgL, TRR} (L/kg fish)	BCF _{SSL, S-2399} (L/kg fish)	t _{1/2g} (days)
0.2	211.8	215.4	38.4	0.276
0.6	185.6	189.3	33.1	0.401

BCF estimates are in close agreement across estimation procedure (steady-state vs kinetic) and treatment level. The highest estimate in terms of TRR and inpyrfluxam (S-2399) are 215.4 L/kg and 38.4 L/kg respectively.

Endocrine disruption hazard assessment for aquatic organisms

For the inpyrfluxam endocrine disruption assessment, two studies testing aquatic organisms and measuring endocrine parameters were conducted: Fish Short Term Reproduction Assay (FSTRA) testing Zebra fish ([REDACTED] 2021) and an Amphibian Metamorphosis Assay (AMA) testing African clawed frog ([REDACTED] 2021). Two early life stage studies testing Fathead Minnow ([REDACTED] 2014.) and Sheepshead Minnow ([REDACTED] 2014) were also considered as they included parameters that are sensitive to but not diagnostic of Estrogen, Androgen, Thyroid and Steroidogenesis modalities (EATS).

In the ELS study testing the fathead minnow (*P. promelas*), a $LC_{10} = 6.6 \mu\text{g/L}$ (systemic toxicity) was established. Statistically significant effects on live normal larvae at hatch, body length and weight were reported for $13 \mu\text{g/L}$.

In the ELS study testing the sheepshead minnow (*C. variegatus*), systemic toxicity (reduced larval survival) was demonstrated from $15 \mu\text{g/L}$ onwards. Statistically significant reductions in hatching success and percentage of normal live larvae at hatch were also recorded from $63 \mu\text{g/L}$ onwards.

In the FSTRA study testing Zebra fish, histopathology was not performed due to it not being a data requirement in the guidelines. As a result, the study was based solely on VTG levels and effects sensitive to, but not diagnostic of EATS. A statistically significant increase in VTG was noted in males when outliers were removed, and a statistically significant reduction in VTG in females was noted when outliers were removed. However, no statistically significant effects were noted when outliers were included for both males and females. The measured concentrations of vitellogenin were in-line with the OECD 229 guidelines where it says: 'As a guide, the VTG levels in control groups of males and females should be distinct and separated by about three orders of magnitude in fathead minnow and zebrafish'. Ultimately, the measured effects did not indicate adverse effects on EAS modalities.

For the submitted AMA study, exposure to inpyrfluxam resulted in reductions for T-mediated parameters developmental stage and normalised hind limb length. Delayed development, however, is not by itself an indicator of anti-thyroidal activity and needs to be confirmed by histopathological analysis of the thyroid. There was no increase in the prevalence or severity of either follicular hypertrophy or hyperplasia between the control and the top concentration tested ($43 \mu\text{g/L}$). Therefore, when the observed reductions for T-mediated parameters developmental stage and normalised HLL are interpreted in conjunction with other results, particularly the lack of histopathological effects, they do not support a conclusion of T-mediated endocrine disruption. In conclusion, using the EFSA/ECHA 2018 guidance, inpyrfluxam does not meet the T modality ED criteria for non-target organisms.

2.9.3. Summary of effects on arthropods

Bees

The toxicity endpoint for bees are summarised in the table below.

Table 2.9.3 – 1: Inpyrfluxam toxicity endpoints for bee risk assessment

Test Item	Study type	Species	Endpoint	Results	References	
Acute adult						
Inpyrfluxam	48 h acute oral	Apis mellifera	LD ₅₀	>111.3 µg a.s./bee	KCA 8.3.1.1.1/01	
Inpyrfluxam	48 h acute contact			>100 µg a.s./bee	2015	
Inpyrfluxam	48 h acute oral	Bombus terrestris	LD ₅₀	>95.1 µg a.s./bee	KCA 8.3.1.1.1/02	
Inpyrfluxam	48 h acute contact			>100 µg a.s./bee	2016	
S-2399 60 g/L EC ^a	48 h acute oral	Apis mellifera	LD ₅₀	274.95 µg product/bee (17.99 µg a.s./bee)	KCP 10.3.1.1.1/01	
	48 h acute contact			252.91 µg product/bee (16.55 µg a.s./bee)	2019	
S-2399 60 g/L EC ^a	48 h acute oral	Bombus terrestris	LD ₅₀	> 532.69 µg product/bumblebee (>34.74 µg a.s./bumblebee)	KCP 10.3.1.1.1/02	
	48/72 h acute contact	Bombus terrestris		> 3066.67 µg product/bumblebee (>200 µg a.s./bumblebee)		2020
Chronic adult						
S-2399 60 g/L EC ^a	10 d chronic	Apis mellifera	LDD ₅₀	133.83 µg product/bee/d (8.76 µg a.s./bee/day)	KCP 10.3.1.2/01	
			NOEC	3157.27 mg product/kg (206.61 mg a.s./kg)		2021a
			NOEDD	46.56 µg product/bee/day		

Test Item	Study type	Species	Endpoint	Results	References
				(3.05 a.s./bee/day)	
Larvae					
S-2399 60 g/L EC^a	22 d chronic	<i>Apis mellifera</i>	ED ₅₀	275.23 µg product/larva (18.01 µg a.s./larva)	KCP 10.3.1.3/01 [REDACTED] 2021b
			NOED	162.71 µg product/larva (10.65 µg a.s./larva)	

Non-target arthropods other than bees

No studies on non-target arthropods other than bees have been conducted with the active substance. Data are available with the formulation S-2399 60 g/L EC on *Aphidius rhopalosiphi* and *Typhlodromus pyri*. The studies were conducted as 2D glass plate studies for first tier assessment. The endpoints are as follows:

LD₅₀ for *A. rhopalosiphi* = 49.1 g a.s/ha

LD₅₀ for *T. pyri* = 60.68 g a.s/ha

2.9.4. Summary of effects on non-target soil meso- and macrofauna

Toxicity data for inpyrfluxam, its metabolites and formulation have been provided. The toxicity endpoints for earthworms are presented in Table 2.9.4 1. The toxicity endpoints for other soil macroorganisms are presented in Table 2.9.4 2.

Table 2.9.4 – 1: Endpoints used in the earthworm risk assessment for inpyrfluxam, its metabolites and S-2399 60 g/L EC

Test item	Exposure system	Species	Endpoint	Results	References
S-2399 TG	Soil 56 d chronic 5% peat content	<i>Eisenia fetida</i>	EC ₁₀	21.5 mg a.s./kg soil dw	KCA 8.4.1/01 [REDACTED] 2016a
			NOEC	6.25 mg a.s./kg soil dw	
			NOEC _{corr}	3.125 mg a.s./kg soil dw	
3'-OH-S-2840	Soil 56 d chronic	<i>Eisenia fetida</i>	EC ₁₀	>100 mg/kg soil dw	KCA 8.4.1/02
			NOEC	100 mg/kg soil dw	

	5% peat content		NOEC _{corr}	50 mg/kg soil dw	2016a
1'-COOH-S-2840	Soil 56 d chronic 5% peat content	<i>Eisenia fetida</i>	EC ₁₀	52.4 mg/kg soil dw	KCA 8.4.1/03
			NOEC	50 mg/kg soil dw	2016b
S-2399 6EC^a	Soil 56 d chronic 10% peat content	<i>Eisenia andrei</i>	NOEC	23.81 mg product/kg soil dw (1.56 mg a.s./kg soil dw)	KCP 10.4.1.1/01
			NOEC _{corr}	11.91 mg product/kg soil dw (0.78 mg a.s./kg soil dw)	2019a

^a Active substance content of the formulation; density 0.9273 g/mL, 60.68 g a.s./L (corresponding to 6.544% w/w)

Endpoints highlighted in **bold** used in the risk assessment (lowest of the NOEC and EC₁₀)

Due to log P_{ow} > 2 (log P_{ow} = 3.65 for S-2399 at pH 7.1 – 7.3; log P_{ow} = 2.53 for 3'-OH-S-2840 at pH 6.5), endpoints from earthworm studies conducted in artificial soil were corrected for inpyrfluxam and 3'-OH-S-2840 to account for the difference in organic matter in agricultural soils.

Table 2.9.4 – 2: Summary of toxicity endpoints for inpyrfluxam and its metabolites for non-target soil meso- and macrofauna other than earthworms

Test item	Exposure system	Species	Endpoint	Results	References
S-2399 TG	Soil 14 d, chronic 5% peat content	<i>Hypoaspis aculeifer</i>	EC ₁₀	>100 mg a.s./kg soil dw	CA 8.4.2/04 2016c
			NOEC	100 mg a.s./kg soil dw	
			NOEC _{corr}	50 mg a.s./kg soil dw	
S-2399 TG	Soil 28 d, chronic 5% peat content	<i>Folsomia candida</i>	EC ₁₀	>100 mg a.s./kg soil dw	CA 8.4.2/01 2016b
			NOEC	100 mg a.s./kg soil dw	
			NOEC _{corr}	50 mg a.s./kg soil	

Test item	Exposure system	Species	Endpoint	Results	References
				dw	
3'-OH-S-2840	Soil 14 d, chronic 5% peat content	<i>Hypoaspis aculeifer</i>	EC ₁₀	>100 mg/kg soil dw	CA 8.4.2/05 [REDACTED] 2016e
			NOEC	100 mg/kg soil dw	
			NOEC _{corr}	50 mg a.s./kg soil dw	
3'-OH-S-2840	Soil 28 d, chronic 5% peat content	<i>Folsomia candida</i>	EC ₁₀	>100 mg/kg soil dw	CA 8.4.2/02 [REDACTED] 2016c
			NOEC	100 mg/kg soil dw	
			NOEC _{corr}	50 mg a.s./kg soil dw	
1'-COOH-S-2840	Soil 14 d, chronic 5% peat content	<i>Hypoaspis aculeifer</i>	EC ₁₀	>100 mg/kg soil dw	CA 8.4.2/06 [REDACTED] 2016f
			NOEC	100 mg/kg soil dw	
1'-COOH-S-2840	Soil 28 d, chronic 5% peat content	<i>Folsomia candida</i>	EC ₁₀	>100 mg/kg soil dw	CA 8.4.2/03 [REDACTED] 2016d
			NOEC	100 mg/kg soil dw	
S-2399 6EC^a	Soil 14 d, chronic 5% peat content	<i>Hypoaspis aculeifer</i>	EC ₁₀	233 mg product/kg soil dw	CP 10.4.2.1/01 [REDACTED] 2019b
			NOEC	154 mg product/kg soil dw (10.08 mg a.s./kg soil dw)	
			NOEC _{corr}	77 mg product/kg soil dw (5.04 mg a.s./kg soil dw)	
S-2399 6EC^a	Soil 28 d, chronic 5% peat content	<i>Folsomia candida</i>	NOEC	50 mg product/kg soil dw (3.27 mg a.s./kg soil dw)	CP 10.4.2.1/02 [REDACTED] 2019c
			NOEC _{corr}	25 mg product/kg soil dw (1.635 mg a.s./kg)	

Test item	Exposure system	Species	Endpoint	Results	References
				soil dw)	

^a Active substance content of the formulation; density 0.9273 g/mL, 60.68 g a.s./L (corresponding to 6.544% w/w)

Endpoints highlighted in **bold** used in the risk assessment (smallest of NOEC and EC₁₀, corrected)

Due to log Pow > 2 (log Pow = 3.65 for S-2399 at pH 7.1 – 7.3; log Pow = 2.53 for 3'-OH-S-2840 at pH 6.5), endpoints from earthworm studies conducted in artificial soil were corrected for S-2399 and 3'-OH-S-2840 to account for the difference in organic matter in agricultural soils.

2.9.5. Summary of effects on soil nitrogen transformation

A summary of the available data and endpoints used in the risk assessment is provided in table below. For more details on the fulfilment of data requirements, please refer to Section B.9 (CP).

Table 2.9.5 – 1: Summary of endpoints for inpyrfluxam (S-2399) and its metabolites

Test Item	Exposure system	Results	References
S-2399 TG	28 d natural soil	Effects < 25% after 28 days at 0.27 and 1.33 mg a.s./kg soil dw	CA 8.5/01 [REDACTED] 2016a
3'-OH-S-2840	28 d natural soil	Effects < 25% after 28 days at 0.06 and 0.3 mg/kg soil dw	CA 8.5/02 [REDACTED] 2016b
1'-COOH-S-2840	28 d natural soil	Effects < 25% after 28 days at 0.1 and 0.5 mg/kg soil dw	CA 8.5/03 [REDACTED] 2016c

2.9.6. Summary of effects on terrestrial non-target higher plants

A summary of the effects on seedling emergence and vegetative vigour is provided in the table below.

Table 2.9.6 - 1: Summary of the effects on terrestrial non-target plants following exposure to 'S-2399 60 g/l EC'

Test type	Test substance	Test species	Endpoint	Results (g a.s./ha)	References
21 d Seedling emergence	S-2399 60 g/l EC ^a	<i>Lolium perenne</i> ^m <i>Allium cepa</i> ^m <i>Brassica napus</i> ^d <i>Glycine max</i> ^d <i>Lactuca sativa</i> ^d <i>Beta vulgaris</i> ^d	ER ₅₀	≥ 91	CP 10.6.2/01 [REDACTED] 2020a
21 d Vegetative vigour	S-2399 60 g/l EC ^a	<i>Lolium perenne</i> ^m <i>Allium cepa</i> ^m <i>Brassica napus</i> ^d <i>Glycine max</i> ^d <i>Lactuca sativa</i> ^d <i>Beta vulgaris</i> ^d	ER ₅₀	≥ 91	CP 10.6.2/02 [REDACTED] 2020b

^a Active substance content of the formulation; density 0.9273 g/mL, 60.68 g a.s./L (corresponding to 6.544% w/w) m: monocotyledoneae; d: dicotyledoneae

Endpoints highlighted in **bold** used in the risk assessment

2.9.7. Summary of effects on other terrestrial organisms (flora and fauna)

No further data was submitted. HSE considers there are no data gaps for the ecotoxicology assessment of inpyrfluxam.

2.9.8. Summary of effects on biological methods for sewage treatment

One study was submitted assessing the effects of inpyrfluxam on biological sewage treatment processes. The following endpoint is available.

Table 2.9.8 -1: Endpoint for activated sludge exposed to inpyrfluxam

Test item	Test system	Endpoint (mg a.s./L)	Reference
Inpyrfluxam	Activated sludge respiration inhibition	EC ₅₀ (3h) > 100	[REDACTED] (2018)

2.9.9. Summary of product exposure and risk assessment

2.9.9.1. Risk assessment for birds and mammals

Birds

The results of the risk assessments of the active substance for its representative formulation are summarised here. Risk assessments were conducted according to the EFSA Bird and Mammal Guidance (2009) document.

Risk assessment for ‘Inpyrfluxam’

The risk to birds from the active substance was assessed based on the proposed use in-field on cereals. The maximum GAP is 1 x 0.09 kg a.s./ha BBCH 30 – 71.

The acute risk to birds from inpyrfluxam was shown to be unacceptable at the screening step with a TER of 2.66. The acute trigger value was 10. The risk was also unacceptable at Tier 1 when considering the generic focal species small insectivorous bird “passerine” at cereals BBCH 71-89 with a TER of 7.33 compared to a trigger value of 10. The acute risk was resolved by the use of a geometric mean refinement and a trigger value of 1. No further consideration was required.

The long-term/reproductive risk to birds from inpyrfluxam was shown to be acceptable at the screening step. For cereals at the application rate of 0.09 kg a.s./ha the TER = 6.15. The long-term/reproductive trigger value was 5. No further consideration was required.

Secondary poisoning

As the log Pow value for inpyrfluxam is > 3 (3.65), consideration of the risk to earthworm-eating and fish-eating birds was required. The TERs were 62.33 and 667.59, respectively, compared to trigger values of 5. No further consideration was required.

Drinking water

An acceptable acute and long-term/reproductive risks for exposure of birds to inpyrfluxam via drinking water was established for the puddle scenario.

Metabolite risk assessment

Inpyrfluxam metabolites formed in plant metabolism studies (primary crops: apple, soyabean, rice, and potato) at $\geq 10\%$ total reactive residues (TRR) or $< 10\%$ TRR but ≥ 0.05 mg eq./kg were: 3'-OH-S-2840, 1'-CH₂OH-S-2840, N-des-Me-S-2840, N-des-Me-DFPA, Glc-NDM-S-2399A, Gly-1'-CH₂OH-S-2840, DFPA-CONH₂, 1'-COOH-S-2840 and DFPA, N-des-Me-1'-CH₂OH-S-2840.

For the metabolites 1'-COOH-S-2840, 1'-CH₂OH-S-2840 and DFPA-CONH₂, no further consideration was required based on these metabolites being formed at significant

amounts (> 10% TRR) in the hen metabolism studies. Gly-1'-CH₂OH-S2840 did not require further consideration as the risk is covered by the metabolite 1'-CH₂OH-S-2840 based on information provided by HSE toxicology that can also be applied to birds.

The screening step and tier 1 (where relevant) acute and long-term/reproductive risk assessments for the relevant metabolites are presented below. 'Inpyrfluxam' is intended for use in-field on cereals at 1 x 0.09 kg a.s/ha BBCH 30 -71.

As an initial worst-case assessment, the maximum application rate of the parent was used in the below risk assessments and as no toxicity data with birds is available for any of the relevant metabolites, it was assumed that they are 10 times more toxic than the active substance. For the reproductive assessment, An fTWA of 1 was used as the pattern of decline of the metabolite is not as straightforward as the active substance since residues initially increase before decreasing. Therefore, a worst-case assumption of a 100% conversion from parent at start and maintenance of this over the whole averaging period was used at first tier.

The acute risk to birds from 3'-OH-S-2840, N-des-Me-S-2840, N-des-Me-DFPA, Glc-NDM-S-2399A, DFPA and N-des-Me-1'-CH₂OH-S-2840 was not acceptable at Tier 1, with DDD = 1.08 mg/kg bw/d and TER = 3.52 compared to the acute trigger value of 10 for small omnivorous bird "lark" at BBCH 30-39, and DDD = 0.65 and TER = 5.86 at BBCH ≥ 40 for small omnivorous bird "lark". Additionally, small insectivorous bird "passerine" at BBCH 71-89 had a DDD of 5.18 and a TER of 0.73, which is also unacceptable with a trigger value of 10. Late season – seed heads for small granivorous/insectivorous bird "bunting" had a DDD of 0.36 and a TER of 10.56; which demonstrated an acceptable risk. Further consideration was required, where the DDD for the failing first tier scenarios was amended based on the metabolite with the highest percentage TRR (N-des-Me-DFPA at 28% TRR) as well as assuming 10x greater toxicity than the parent. Acceptable acute risk was demonstrated for BBCH 30-39 and BBCH ≥ 40 with this amendment with TER values >10 (12.57 and 20.94, respectively). Unacceptable risk was demonstrated for cereals late post-emergence (May-June) BBCH 71-89 with a TER value of 2.62 as was considered for the parent. However, this was resolved based on the geometric mean refinement referenced above when comparing to a trigger value of 1. No further consideration was required.

The long-term/reproductive risk assessment was unacceptable at the screening stage. For small omnivorous birds, the TER was 0.33 (compared to a trigger value of 5), based on the same application rate as the parent and assuming 10 times greater toxicity in the absence of toxicity data for the metabolites. An unacceptable risk was also demonstrated at Tier 1, with BBCH 30-39 consideration for small omnivorous birds "lark" obtaining a TER value of 3.90, Cereals late post-emergence (May-June) BBCH 71-89 had a TER of 0.94 and late season – seed heads was also unacceptable with a TER of 4.49. However, BBCH ≥ 40 for small omnivorous bird "lark" demonstrated acceptable risk with a TER value of 6.39. compared to a trigger value of 5. Further consideration was required, with the DDD for all

generic focal species being adjusted for the metabolite with the highest percentage TRR in the residue studies (28% N-des-Me-DFPA). An acceptable risk was demonstrated for BBCH 30-39 (DDD = 0.13, TER = 13.96) and late season – seed heads (DDD = 0.12, TER = 15.8). However, unacceptable risk was still demonstrated for cereals late post-emergence (May-June) BBCH 71-89 (DDD = 0.56, TER = 3.37), leaving the reproductive risk to birds from the metabolite N-des-Me-DFPA unresolved. Following this, a risk assessment was carried out for the scenario of cereals late post-emergence (May-June) BBCH 71-89 with the five remaining metabolites that were not present in significant amounts in the hen metabolism studies using the same approach of assuming 10x greater toxicity and refining the DDD by the maximum %TRR. Acceptable risk was demonstrated for N-des-Me-S-2840, Glc-NDM-S-2399A and N-des-Me-1'-CH₂OH-S-2840. However, unacceptable reproductive risk was present for the metabolites DFPA (DDD = 0.47, TER = 4.0) and 3'-OH'-S-2840 (DDD = 40.45, TER 4.26), as well as N-des-Me-DFPA (DDD = 0.56, TER = 3.39).

Ultimately, the reproductive risk to birds from metabolites found in food items in cereals late post-emergence (May-June) BBCH 71-89 has been resolved on a weight of evidence approach that uses available mammalian toxicology data for the metabolites that demonstrated each was of similar or much less toxicity compared to the parent, confirming that assuming 10 x toxicity compared to the parent was a conservative assumption. Additionally, based on similar levels of toxicity between the active and the metabolites, as demonstrated from extrapolation of mammalian toxicology data, the TER values for N-des-Me-DFPA, 3'-OH'-S-2840 and DFPA would be 33.9, 42.6 and 40.0, respectively, based on 1:1 toxicity. These TER values are greater than the standard reproductive trigger value of 5 and demonstrate an acceptable risk. Based on this weight of evidence approach, no further consideration was required and acceptable reproductive risk to birds from metabolites on inpyrfluxam has been concluded.

Secondary poisoning

No log Pow values are available for the metabolites N-des-Me-S-2840, N-des-Me-DFPA, Glc-NDM-S-2399A, DFPA, or N-des-Me-1'-CH₂OH-S-2840 and so it is not known whether these metabolites would exceed the trigger value for consideration. None of these metabolites were identified as environmentally significant in any environmental compartment by HSE Environmental Fate and Behaviour, however, and therefore no further consideration is required.

Overall conclusion for the risk to birds from 'Inpyrfluxam'

The risk to birds from 'Inpyrfluxam' is considered to be acceptable for the proposed uses.

Mammals

The results of the risk assessments of the active substance for its representative formulation are summarised here. Risk assessments were conducted according to the EFSA Bird and Mammal Guidance Document (2009).

Risk assessment for 'Inpyrfluxam'

The risk to mammals from the active substance was assessed based on the proposed use in-field on cereals. For cereals, the maximum GAP is 1 x 0.09 kg a.s./ha BBCH 30 – 69.

The acute risk to mammals from inpyrfluxam was shown to be acceptable at the screening step. For potatoes at 1 x 0.09 kg a.s./ha the DDD = 10.65 mg a.s./ha and the TER = 16.9. The acute trigger was 10. No further consideration was required.

The chronic risk to mammals from inpyrfluxam was shown to be acceptable at the screening step. For potatoes at 1 x 0.09 kg a.s./ha the DDD = 2.3 mg a.s./ha and the TER = 10.9. The long-term trigger was 5. No further consideration was required.

Secondary poisoning

As the log Pow for inpyrfluxam is > 3 (3.65) consideration of the risk to earthworm-eating and fish-eating mammals was required. The TERs were 67.28 and 983.57, respectively, compared to trigger values of 5. No further consideration was required.

Drinking water

An acceptable acute and chronic risks for exposure of mammals to inpyrfluxam via drinking water were established for the puddle scenario.

Metabolite risk assessment

Inpyrfluxam metabolites formed in plant metabolism studies (primary crops: apple, soyabean, rice, and potato)) at $\geq 10\%$ total reactive residues (TRR) or $< 10\%$ TRR but ≥ 0.05 mg eq./kg were 3'-OH-S-2840, 1'-CH₂OH-S-2840, N-des-Me-S-2840, N-des-Me-DFPA, Glc-NDM-S-2399A, Gly-1'-CH₂OH-S-2840, DFPA-CONH₂, 1'-COOH-S-2840 and DFPA, N-des-Me-1'-CH₂OH-S-2840.

For the metabolites 1'-COOH-S-2840 and N-des-Me-1'-CH₂OH-S-2840, no further consideration was required based on the rat metabolism studies.

Rat toxicity data was available for N-des-Me-DFPA, DFPA and DFPA-CONH₂. from which HSE Toxicology confirmed that the risk to mammals from these metabolites is covered by the risk assessment conducted for the parent.

The applicant stated that the toxicity of 1'-CH₂OH-S-2840 is covered by the toxicity of the parent as ADME data show that it represents > 10% of urinary and biliary excretion; therefore, this can be excluded.

Studies with 3'-OH-S-2840 show them to have comparable or lower toxicity to the parent. As a result, this can also be excluded.

For Gly-1'-CH₂OH-S-2840, the following is stated by HSE toxicology: *“As the sugar conjugate of 1'-CH₂OH-S-2840, a predicted major rat metabolite, covered by parent – the sugar will be cleaved in the GI tract releasing the predicted major rat metabolite”*. Therefore, HSE Ecotoxicology agreed that the risk from this metabolite is covered by 1'-CH₂OH-S-2840, which is a major rat metabolite; therefore does not need consideration.

HSE toxicology consideration for N-des-Me-S-2840 provided the following: “No additional relevant alert for general toxicity was identified in the comparative QSAR analysis compared to inpyrfluxam”. Based on this, HSE Ecotoxicology can exclude this metabolite and no further consideration is required as the risk is covered by the parent.

In relation to Glc-NDM-S-2399A, HSE toxicology state the following *“As the conjugated form of the metabolite N-des-Me-S-2840, the toxicity profile of this metabolite is expected to be comparable / less severe compared to its aglycon form N-des-Me-S-2840; no concern for genotoxicity was identified in the comparative QSAR analysis of N-des-Me-S-2840 compared to inpyrfluxam”*. Again, HSE agree with the above consideration and can exclude the above metabolite as the risk is covered by the parent.

As a result, all metabolites were able to be excluded and no further consideration was required for exposure via diet nor secondary poisoning.

Overall conclusion for the risk to mammals from 'Inpyrfluxam'

The risk to mammals from 'Inpyrfluxam' is considered to be acceptable for the proposed uses.

2.9.9.2. Risk assessment for aquatic organisms

The risk assessments for inpyrfluxam, its metabolites 3'-OH-S-2840 and 1'-COOH-S-2840, and its formulation S-2399 6E0 g/L C are summarised below. All risk assessments relate to a 90 g a.s./ha application to cereals (BBCH 30 – 71) For additional information, please refer to Section B.9 (CP).

Inpyrfluxam

The first-tier risk assessment is presented below.

Table 2.9.9.2 – 1: First-tier risk assessment for exposure to inpyrfluxam after use on cereals at 90 g a.s./L

Group		Fish acute	Fish prolonged	Inverteb. acute	Inverteb. prolonged	Algae	Aquatic macrophytes	Group	Sed. Dwell. Prolonged
Test species		<i>Oncorhynchus mykiss</i>	<i>P. promelas</i>	<i>Daphnia magna</i>	<i>Daphnia magna</i>	Geomea n of 2 diatoms	<i>Lemna gibba</i>	Test species	Geomea n of two species
Endpoint (µg/L)		LC ₅₀	Geomea n LC ₅₀	EC ₅₀	EC ₁₀	Geomea n ErC ₅₀	ErC ₅₀	Endpoint	NOEC
		31	6.6	1100	210	3600	24000	(µg/kg)	10260
AF		100	10	100	10	10	10	AF	10
RAC (µg/L)		0.31	0.66	11	21	360	2400	RAC (µg/kg)	1026
Entry route	PEC _s w (µg/L)	PEC/RAC						PEC _{sed} (µg/kg)	PEC/RAC
Spray drift (1 m)	0.831	2.68	1.26	0.076	0.040	0.0023	0.00035	14.516	0.014
Drainflow	0.692	2.23	1.05	0.063	0.033	0.0019	0.00029	12.093	0.012

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in bold.

An acceptable risk was demonstrated for all scenarios at the first tier except for acute and prolonged fish exposure via spray drift and drainflow.

An acceptable risk to fish from exposure via spray drift was demonstrated using a 5 m buffer zone (Table 2.9.9.2-2). No further consideration is required.

Table 2.9.9.2 – 2: Refined spray drift exposure assessment for inpyrfluxam usage in cereals through the use of a 5 m buffer zone

Intended use		Cereals	
Active substance		S-2399	
Application rate [g a.s./ha]		1 × 90	
Nozzle	No-spray	Default distance	Rautmann drift

reduction	buffer [m]	1 m	5 m
	Exposure Scenario	PEC _{sw} [µg/L]	
None	Drift	0.831	0.171
Tier 1-RAC [µg/L]		Acute fish	
0.31		PEC/RAC ratio	
None	Drift	2.68	0.55
Tier 1-RAC [µg/L]		Chronic fish	
0.66		PEC/RAC ratio	
None	Drift	1.26	0.26

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**.

The acute risk to fish from exposure via drainflow was resolved using a Species Sensitivity Distribution (SSD) derived endpoint refinement. The Tier 2B risk assessment is presented below.

Table 2.9.9.2 – 3: Refined acute fish drainflow exposure assessment for inpyrfluxam usage in cereals through the use of a RAC derived from a SSD

Group		Fish acute
Test species		Based on 8 species
Endpoint		HC ₅
(µg/L)		17.9
AF		9
RAC (µg/L)		1.99
Entry route	PEC _{sw} (µg/L)	PEC/RAC
Drainage	0.692	0.348

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**.

Using the refined RAC, an acceptable acute risk to fish via drainage can be concluded.

The prolonged risk to fish via drainflow was resolved through higher tier drainflow (HTDF) modelling. For further information please refer to the Section B.8 and B.9 (CP). The higher tier drainflow modelling reported > 10 % exceedance years. A detailed case-by-case

assessment was performed, which concluded, based on an assessment that accounts for exceedance duration, an acceptable risk to fish from chronic exposure via drainflow.

In conclusion, an acceptable risk to all aquatic organisms, except fish, was concluded at the first tier for inpyrfluxam. An acceptable acute and prolonged risk to fish for exposure via spray drift was demonstrated with the implementation of a 5 m buffer zone. An acceptable acute risk to fish for exposure via drainflow was demonstrated at Tier 2B using a SSD refined RAC. An acceptable prolonged risk to fish for exposure via drainflow was demonstrated through a detailed case-by-case assessment of the HTDF modelling results.

Metabolites of inpyrfluxam

Only an acute fish study was submitted for 3'-OH-S-2840 and 1'-COOH-S-2840. Based on the assessment scheme presented in Section 10.2.4 of EFSA Journal 2013;11(7):3290, a 1:1 toxicity extrapolation was performed between the metabolites and inpyrfluxam in the first instance. The risk assessment for each metabolite is presented below.

Table 2.9.9.2 – 4: Aquatic organisms: acceptability of risk (PEC/RAC < 1) for the 3'-OH-S-2840 metabolite, based on UK national modelling for the use of inpyrfluxam in cereals

Group		Fish acute	Fish chronic	Invertebrate acute	Invertebrate chronic	Algae
Test species		<i>O. mykiss</i>	<i>extrapolated</i>	<i>extrapolated</i>	<i>extrapolated</i>	<i>extrapolated</i>
Endpoint		LC ₅₀	EC ₁₀	EC ₅₀	EC ₁₀	ErC ₅₀
(µg/L)		>6200	6.6	1100	210	3600
AF		100	10	100	10	10
RAC (µg/L)		62	0.66	11	21	360
Entry route	PEC _{sw} (µg/L)	PEC / RAC				
Drift (1 m)	0.075	0.0012	0.1136	0.0068	0.0036	0.0002
Drainage	0.210	0.003	0.318	0.019	0.01	0.001

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**.

Table 2.9.9.2 – 5: Aquatic organisms: acceptability of risk (PEC/RAC < 1) for the 1'-COOH-S-2840 metabolites, based on UK national modelling for the use of inpyrfluxam in cereals

Group		Fish acute	Fish chronic	Invertebrate acute	Invertebrate chronic	Algae
Test species		<i>O. mykiss</i>	<i>extrapolated</i>	<i>extrapolated</i>	<i>extrapolated</i>	<i>extrapolated</i>
Endpoint		LC ₅₀	EC ₁₀	EC ₅₀	EC ₁₀	ErC ₅₀
(µg/L)		>50000	6.6	1100	210	3600
AF		100	10	100	10	10
RAC (µg/L)		500	0.66	11	21	360
Entry route	PEC _{sw} (µg/L)	PEC / RAC				
Drift (1 m)	0.091	0.0002	0.1379	0.0083	0.0043	0.0003
Drainage	0.863	0.002	1.31	0.078	0.041	0.002
Ground water	0.180	0.0004	0.273	0.016	0.009	0.0005

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**.

For the proposed 90 g a.s./ha use on cereals, an acceptable spray drift risk to aquatic organisms can be concluded for all relevant inpyrfluxam metabolites.

For ground water, no assessment is required for 3'-OH-S-2840 as the highest PEC_{gw} = 0.01 µg/L, which is below the 0.1 µg/L trigger. For 1'-COOH-S-2840, the PEC_{gw} = 1.802 µg/L (spring cereals, late scenario, Hamburg, PEARL, see Section B8 (3CP) for more details) was divided by 10, to represent the dilution factor that occurs when ground water becomes surface water. This is in accordance with SANCO/3268/2001 (2002). An acceptable risk can be concluded for all organism groups.

However, for drainage exposure, the chronic fish scenario indicates an unacceptable risk for metabolite 1'-COOH-S-2840 when using a RAC of 0.66 µg/L. A 1:1 toxicity extrapolation between chronic fish endpoints is likely overly conservative based on the relative toxicities of 1'-COOH-S-2840 and inpyrfluxam acute fish endpoints. After molecular weight adjustment, the acute fish endpoint for 1'-COOH-S-2840 is 1,480 times higher than that of the a.s.. As the chronic fish endpoint for inpyrfluxam is also based on a mortality endpoint, larval survival, it is the view of HSE Ecotoxicology that a revised chronic fish RAC for 1'-COOH-S-2840 can be reported that more accurately reflects the relative toxicities of the two chemicals. The toxicity relationship between the fish acute endpoints for 1'-COOH-S-2840 and inpyrfluxam was used to estimate a chronic fish

endpoint for 1'-COOH-S-2840, which was then adjusted by an AF = 100 to address the uncertainty in the extrapolation. This yielded a RAC = 106.5 µg met./L for 1'-COOH-S-2840. Using this refined RAC resulted in a PEC/RAC = 0.0081, indicating an acceptable chronic risk to fish for exposure to 1'-COOH-S-2840 via drainflow.

Formulation 'S-2399 60 g/L EC'

'S-2399 60 g/L EC' presented a > 3 fold increase in toxicity for aquatic invertebrates and algae. Additional spray drift risk assessments were performed for these organism groups. For completeness, a formulation risk assessment for fish was also performed.

Table 2.9.9.2 – 6: First-tier risk assessment for exposure to S-2399 60 g/L EC after use on cereals at 90 g a.s./L

Group		Fish	Inverteb. acute	Algae
Test species		<i>O. mykiss</i>	<i>D. magna</i>	<i>P. subcapitata</i>
Endpoint		LC ₅₀	EC ₅₀	EC ₅₀
(µg a.s./L)		22	260	447
AF		100	100	10
RAC (µg a.s./L)		0.22	2.6	44.7
Entry route	PEC _{sw} a.s./L) (µg	PEC/RAC		
Spray drift (1 m)	0.831	3.78	0.320	0.0186
Spray drift (5 m)	0.171	0.78	-	-

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**.

For algae, *Pseudokirchneriella subcapitata* (green algae) was not the most sensitive algal taxonomic group tested for the active substance. Diatoms were the most sensitive with an EC₅₀ geomean = 3.6 mg a.s./L. For *Pseudokirchneriella subcapitata*, the only algal species with active substance and product data available, the formulation is 51.45 more toxic than the active substance. For the formulation risk assessment, HSE applied this factor to the active substance diatom geomean to account for the different sensitivities between different algal taxonomic groups (estimated formulation diatom EC₅₀geomean = 70.0 µg a.s./L).

Table 2.9.9.2 – 7: Formulation risk assessment for algae correcting for most sensitive algal taxonomic group

Group		Algae
Test species		Adjusted diatom geomean
Endpoint		Geomean
(µg a.s/L)		70
AF		10
RAC (µg a.s/L)		7
Entry route	PEC _{sw} (µg/L)	PEC/RAC
Spray drift (1 m)	0.831	0.119

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in **bold**.

After using an approximate estimate of the formulation endpoint for the most sensitive algal taxonomic group as an input for the formulation risk assessment, an acceptable risk to algae was still concluded. Although the method for approximating the formulation endpoint is simplistic, the large margin of safety addresses any potential uncertainties associated with this approach.

Conclusion

Inpyrfluxam:

An acceptable risk to all aquatic organisms, except fish, was concluded at the first tier for inpyrfluxam. An acceptable acute and prolonged risk to fish for exposure via spray drift was demonstrated with the implementation of a 5 m buffer zone. An acceptable acute risk to fish for exposure via drainflow was demonstrated at Tier 2B using a SSD refined RAC. An acceptable prolonged risk to fish for exposure via drainflow was demonstrated through a detailed case-by-case assessment of the HTDF modelling results.

Metabolites:

An acceptable risk to all aquatic organisms was demonstrated at the first tier for 3'-OH-S-2840. For 1'-COOH-S-2840, an acceptable risk was demonstrated for all aquatic organisms at the first tier once the chronic fish RAC was revised to reflect the reduced toxicity of 1'-COOH-S-2840 to fish.

Formulation 'S-2399 60 g/L EC':

An acceptable risk to all aquatic organism groups was demonstrated at the first tier for exposure to the formulation via spray drift with a 5 m buffer zone.

2.9.9.3. Risk assessment for bees

The acute risk to adult honeybees was assessed in accordance with the SANCO/10329/2002 rev.2 guidance document. The critical acute contact and oral LD₅₀ values were compared with the maximum individual application rate for the representative uses to derive a Hazard Quotient (HQ) for each exposure route. The first-tier risk assessment is presented below.

Table 2.9.9.3 – 1: First-tier assessment of the risk for bees due to the use of S-2399 60 g/L EC in cereals

Substance	Endpoint	Application rate (g a.s./ha)	LD ₅₀ (µg a.s./bee)	Calculated Q _H	Acceptable Risk? (Q _H ≤ 50)
Inpyrfluxam	Acute oral	90	>111.3	< 0.809	yes
	Acute contact	90	>100	< 0.900	yes
S-2399 60 g/L EC	Acute oral	90	17.99	5.00	yes
	Acute contact	90	16.55	5.44	yes

All calculations of Q_Hs for the acute oral and contact honeybee studies fell below the trigger value of 50, indicating an acceptable acute risk to honeybees for the active substance and formulation for the proposed use of up to 90 g a.s./ha.

Although chronic studies for adult and larvae honeybees are also available for the product S-2399 60 g/L EC, as they do not form part of the risk assessment scheme under the current SANCO/10329/2002 rev.2 guidance document they were not used in the risk assessment.

There is an acceptable acute risk of inpyrfluxam to adult honeybees, as assessed using the hazard quotient approach. HSE considers an acceptable risk to honeybees can be concluded for the proposed use.

2.9.9.4. Risk assessment for non-target arthropods other than bees

The risk assessment for non-target arthropods other than bees (NTA) is based on ESCORT II guidance. The risk assessment is as follows:

Table 2.9.9.4-1 First tier assessment of the in-field risk for non-target arthropods due to the use of S-2399 60 g/L EC in cereals

Product		S-2399 60 g/L EC	
Application rate (g a.s./ha)		1 × 90	
MAF		1.0	
Test species Tier 1	LR₅₀ (lab.) (g a.s./ha)	PER_{in-field} (g/ha)	HQ_{in-field} criterion: HQ ≤ 2
<i>Typhlodromus pyri</i>	60.68	90	1.48
<i>Aphidius rhopalosiphi</i>	49.1		1.83

MAF: Multiple application factor; PER: Predicted environmental rate; HQ: Hazard quotient.

Table 2.9.9.4 - 2 First-tier assessment of the off-field risk for non-target arthropods due to the use of S-2399 60 g/L EC in cereals

Product	S-2399 60 g/L EC					
Application rate (g a.s./ha)	90					
MAF	1.0					
VDF	10 (Tier 1)					
Test species Tier 1	LR₅₀ (lab.) (g a.s./ha)	Drift rate (%)	PER_{off-field} (g/ha)	CF	Corrected PER_{off-field} (g/ha)	HQ_{off-field} criterion: HQ ≤ 2
<i>Typhlodromus pyri</i>	60.68	2.77	0.25	10	2.5	0.04
<i>Aphidius rhopalosiphi</i>	49.1					0.05

MAF: Multiple application factor; vdf: Vegetation distribution factor; PER: Predicted environmental rate; CF: Correction factor; HQ: Hazard quotient.

All endpoints exceed the in- and off-field PER values. Therefore acceptable risks are concluded for non-target arthropods other than bees (NTA) and the proposed outdoor uses of S-2399 60 g/L EC.

2.9.9.5. Risk assessment for non-target soil meso- and macrofauna

The risk assessment was performed according to the SANCO/10329/2002 rev.2 guidance document. The standard risk assessment is based on TER values. If the long-term TER is below 5 further consideration of the risk is required. The toxicity endpoints have been corrected by a factor of 2 where the Log P_{ow} of the relevant substance is below 2. The risk assessment for earthworms is presented below.

Table 2.9.9.5 – 1: First-tier assessment of the acute and chronic risk for earthworms due to the use of S-2399 60 g/L EC in cereals

Chronic effects on earthworms			
Test compound	NOEC_{corr} (mg/kg dw)	PEC_{soil, accumulation} (mg/kg dw)	TER_{lt} (criterion TER ≥ 5)
S-2399 60 g/L EC (mg a.s./kg dw)	0.78	0.069	11.3
Inpyrfluxam	3.125	0.069	45.3
3'-OH-S-2840	50	0.030	1667
1'-COOH-S-2840	50	0.087	575

An acceptable risk for the a.s., its metabolites and representative formulation can be concluded.

The risk assessment for other non-target soil meso- and macro-fauna is presented in the table below.

Table 2.9.9.5 – 2: First-tier assessment of the chronic risk for other non-target soil organisms (meso- and macro-fauna) due to the use S-2399 60 g/L EC in cereals

Chronic effects on other soil macro- and mesofauna			
Test compound	NOEC/NOEC_{corr} (mg/kg dw)	PEC_{soil, accumulation} (mg/kg dw)	TER_a (criterion TER ≥ 5)
<i>Folsomia candida</i>			
S-2399 60 g/L EC (mg a.s./kg dw)	1.64	0.069	23.8
Inpyrfluxam	50	0.069	725
3'-OH-S-2840	50	0.030	1667
1'-COOH-S-2840	100	0.087	1149
<i>Hypoaspis aculeifer</i>			
S-2399 60 g/L EC (mg a.s./kg dw)	5.04	0.069	73
Inpyrfluxam	50	0.069	725
3'-OH-S-2840	50	0.030	1667
1'-COOH-S-2840	100	0.087	1149

An acceptable risk for the a.s., its metabolites and representative formulation can be concluded.

2.9.9.6. Risk assessment for soil microorganisms

The risk assessment was performed according to the SANCO/10329/2002 rev.2 guidance document. The magnitude of effect was compared to the untreated control. PEC_{soil} values were compared to concentrations at which < 25 % effects on nitrogen transformation were observed.

Table 2.9.9.6 - 1 Assessment of the risk for effects on soil micro-organisms due to the use of S-2399 60 g/L EC in cereals

Test compound	Max. conc. with effects $\leq 25\%$ (mg/kg dw)	PEC _{soil} , accumulation (mg/kg dw)	Risk acceptable?
S-2399 TG	1.33	0.069	Yes
3'-OH-S-2840	0.3	0.030	Yes
1'-COOH-S-2840	0.5	0.087	Yes

The results show that S-2399 had no effects of $\geq 25\%$ compared to the control on soil microbial activity up to a maximum tested concentration of 1.33 mg a.s./kg soil, after 28 days, which is considerably higher than the PEC_{soil} accumulation. No effects of $\geq 25\%$ compared to the control were noted with any of the metabolites at concentrations exceeding the PEC values. An acceptable risk to non-target soil micro-organisms can be concluded.

2.9.9.7. Risk assessment for terrestrial non-target higher plants

The following endpoints are available from the tests submitted by the applicant:

Table 2.9.9.7-1: Ecological toxicity endpoints from submitted studies

Test type	Test substance	Test species	Endpoint	Results (g a.s./ha)	References
21 d Seedling emergence	S-2399 6EC ^a	<i>Lolium perenne</i> ^m <i>Allium cepa</i> ^m <i>Brassica napus</i> ^d <i>Glycine max</i> ^d <i>Lactuca sativa</i> ^d <i>Beta vulgaris</i> ^d	ER ₅₀	≥ 91	CP 10.6.2/01 and 2020a
21 d Vegetative vigour	S-2399 6EC ^a	<i>Lolium perenne</i> ^m <i>Allium cepa</i> ^m <i>Brassica napus</i> ^d <i>Glycine max</i> ^d <i>Lactuca sativa</i> ^d <i>Beta vulgaris</i> ^d	ER ₅₀	≥ 91	CP 10.6.2/02 and 2020b

^a Active substance content of the formulation; density 0.9273 g/mL, 60.68 g a.s./L (corresponding to 6.544% w/w) m: monocotyledoneae; d: dicotyledoneae

According to the Terrestrial Guidance Document, the risk to non-target terrestrial plants should be considered acceptable if less than a 50% effect on at least six species is seen at the highest nominal application rate (single application).

For inpyrfluxam, studies on seedling emergence and vegetative vigour of terrestrial higher plants with a maximum test rate of 91 g a.s./ha were conducted using the formulation S-2399 60 g/L EC. The results showed all ER₅₀ values to be > 91 g a.s./ha for all plant species tested with <50% effects.

As the ER₅₀ values for the active substance exceed the maximum proposed application rates of 90 g a.s./ha in cereals, an acceptable risk to non-target terrestrial plants for the intended uses of S-2399 60 g/L EC can be concluded.

2.9.9.8. Risk assessment for other terrestrial organisms (flora and fauna)

No further data was submitted. HSE considered there are no data gaps for the ecotoxicology assessment of inpyrfluxam.

2.9.9.9. Risk assessment for biological methods for sewage treatment

No effects exceeding 50% were observed during the range-finding assessment conducted by the applicant. The results from the range-finding assessment negated the need for a definitive exposure assessment on sewage. The results indicate that microbial activity in these systems is at low risk from exposure to inpyrfluxam. The worst-case PEC_{sw} is 0.831 µg/L, which is orders of magnitude lower than the EC₅₀ value of 100 mg/L. This provides a wide margin of safety, which helps alleviate concerns over the number of replicates used and the test not being conducted at the highest possible concentration (1000 mg/L). As such, the risks to the processes underlying biological treatment of sewage are considered acceptable at the proposed application rate.

2.10. Classification and Labelling

Proposed classification according to assimilated Regulation No 1272/2008 on the classification, labelling and packaging of substances and mixture.

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification¹⁾	Reason for no classification²⁾
2.1.	Explosives				
2.2.	Flammable gases				

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification¹⁾	Reason for no classification²⁾
2.3.	Flammable aerosols				
2.4.	Oxidising gases				
2.5.	Gases under pressure				
2.6.	Flammable liquids				
2.7.	Flammable solids				
2.8.	Self-reactive substances and mixtures				
2.9.	Pyrophoric liquid				
2.10.	Pyrophoric solids				
2.11.	Self-heating substances and mixtures				
2.12.	Substances and mixtures which in contact with water emit flammable gases				
2.13.	Oxidising liquid				
2.14.	Oxidising solids				

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification¹⁾	Reason for no classification²⁾
2.15.	Oxidising peroxides				
2.16.	Substance and mixtures corrosive to metals				
3.1.	Acute toxicity – oral	Cat 3 (H301)	-	-	LD50 is 180 mg/kg
	Acute toxicity – dermal	Not classified	-	-	-
	Acute toxicity – inhalation	Not classified	-	-	-
3.2.	Skin corrosion / irritation	Not classified	-	-	-
3.3.	Serious eye damage / eye irritation	Not classified	-	-	-
3.4.	Respiratory sensitisation	Not classified	-	-	-
	Skin sensitisation	Not classified	-	-	-
3.5.	Germ cell mutagenicity	Not classified	-	-	-
3.6.	Carcinogenicity	Not classified	-	-	-

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification¹⁾	Reason for no classification²⁾
3.7.	Reproductive toxicity	Not classified	-	-	-
3.8.	Specific target organ toxicity – single exposure	Not classified	-	-	-
3.9.	Specific target organ toxicity – repeated exposure	Not classified	-	-	-
3.10.	Aspiration hazard	Not classified	-	-	-
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1; H400: Very toxic to aquatic life. Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects.	Acute M-Factor of 10 Chronic M-Factor of 10		
5.1.	Hazardous to the ozone layer				

¹⁾Including specific concentration limits (SCLs) and M-factors

²⁾Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Signal word:

Danger

Hazard Statements:

H301: Toxic if swallowed

H410: Very toxic to aquatic life with long lasting effects

Precautionary statements:

P264: Wash thoroughly after handling

P270: Do not eat, drink or smoke when using this product.

P391 '*Collect spillage*'

P501 '*Dispose of contents/container to a licensed hazardous-waste disposal contractor or collection site except for empty clean containers which can be disposed of as non-hazardous waste.*'

Proposed notes assigned to an entry:

Notes in accordance with assimilated CLP Regulation, Annex VI, Section 1.1.3.

None.

2.11. Relevance of Metabolites in Groundwater

This relevance assessment has been performed in accordance with the guidance document [Sanco/221/2000 – rev.11](#) (October 2021), as it applies in GB .

Use of mean or most conservative sorption endpoints for metabolite 1'-COOH-S-2840 was considered in the groundwater assessment. Use of either set of endpoints resulted in the same regulatory outcome, with 80th percentile PEC_{gw} values exceeding both the 0.1 µg/L trigger value and 0.75 µg/L in some scenarios. Therefore the relevance assessment is based on mean parameters.

2.11.1. STEP 1: Exclusion of degradation products of no concern

Metabolites 3'-OH-S-2840 and 1'-COOH-S-2840 could not be excluded as degradation products of no concern. They have therefore both been assessed at STEP 2.

2.11.2. STEP 2: Quantification of potential groundwater contamination

The 80th percentile PEC_{gw} values for the proposed uses have been calculated with the FOCUS PEARL v5.5.5, PELMO v6.6.4 and MACRO v5.5.4 models and this is reported in section B.8.3 of Volume 3CP, Section 8 of the DAR. Parent and metabolite 3'-OH-S-2840

80th percentile PECgw values were below the 0.1 µg/L trigger value in all scenarios and no further consideration is required for these compounds.

The 80th percentile PECgw values for metabolite **1'-COOH-S-2840** (with mean sorption values) were >0.1 µg/L in all 36 of the scenarios modelled (16 in PELMO & 16 in PEARL, plus 4 in MACRO), reaching a **maximum of 1.802 µg/L**. The 80th percentile PECgw values were >0.1 µg/L but <0.75 µg/L in 6 scenarios, >0.75 µg/L but <10 µg/L in 30 scenarios and >10 µg/L in no scenarios.

Further consideration by toxicology, efficacy and residue specialists for metabolite **1'-COOH-S-2840** is required and this is provided below.

2.11.3. STEP 3: Hazard assessment – identification of relevant metabolites

2.11.3.1. STEP 3, Stage 1: screening for biological activity

The parent compound inpyrfluxam and its metabolites 1'-COOH-S-2840 were screened for fungicidal activity against *Septoria tritici* and *Puccinia recondita*. At all concentrations tested, inpyrfluxam provided 100% disease control of both species of pathogen. In comparisons, all tested concentrations of 1'-COOH-S-2840 had no effect on either species. Therefore, 1'-COOH-S-2840 is not relevant at stage 1 and can proceed to stage 2 of Step 3.

2.11.3.2. STEP 3, Stage 2: screening for genotoxicity

1'-COOH-S-2840 was tested for genotoxicity (covering gene mutations, clastogenicity and aneugenicity) in an Ames, in vitro mammalian cell gene mutation, in vitro chromosomal aberration and in vitro micronucleus tests. These studies have been evaluated by HSE and a summary of the findings are presented in Section B.6.8.1 of the DAR. All the studies were conducted to GLP and OECD guidelines and were negative. Thus, 1'-COOH-S-2840 is not genotoxic and can proceed to stage 3 of Step 3.

2.11.3.3. STEP 3, Stage 3: screening for toxicity

Inpyrfluxam is classified under the GB CLP Regulation as acutely toxic Cat.3 (H301) but is not classified for STOT-RE, reproductive toxicity or carcinogenicity. As the acute toxicity classification of the parent would make 1'-COOH-S-2840 relevant, the metabolite was tested in an acute oral study (Section B.6.8.1 of the DAR). 1'-COOH-S-2840 was not acutely toxic by the oral route (LD₅₀ > 2000 mg/kg bw). Therefore, 1'-COOH-S-2840 is not relevant at Step 3 and can proceed to Step 4.

2.11.4. STEP 4: Exposure assessment – threshold of concern approach

1'-COOH-S-2840 is present in groundwater at a maximum level of 1.802 µg/L. As this exceeds the 0.75 µg/L threshold of toxicological concern, a refined risk assessment is required to further consider potential relevance (see Step 5 below).

2.11.5. STEP 5: Refined risk assessment

As 1'-COOH-S-2840 is not in the plant or animal residue definition for risk assessment, it was not estimated in food during the consumer risk assessment.

PECgw calculations after leaching from soil for 1'-COOH-S-2840 indicate that potential exposure to 1'-COOH-S-2840 is $> 0.75 \mu\text{g/L}$ but $< 10 \mu\text{g/L}$, with maximum PECgw of $1.802 \mu\text{g/L}$.

1'-COOH-S-2840 is a major rat metabolite and the toxicity profile of this metabolite can be considered to be equivalent to that of the parent substance. Therefore, the ADI of **inpyrfluxam (0.6 mg/kg bw/day)** could be used for risk assessment purposes.

In relation to the drinking water contribution, the highest intake is expected for an infant (< 4 months). EFSA Guidance on pesticides in foods for infants and young children estimates the water consumption of bottle-fed infants as 1.135 L/d (EFSA Journal 2018; 16(6) 5286, 75 pp.). Estimated intakes of 1'-COOH-S-2840 from drinking water for the critical consumer group (infants) are $0.00041 \text{ mg/kg bw/day}$. This represents 0.7% of the ADI for the metabolite ($0.06 \text{ mg/kg bw/day}$).

Conclusion

As the estimated intake of 1'-COOH-S-2840 from drinking water is $\leq 100 \%$ of the ADI for inpyrfluxam (considered appropriate for 1'-COOH-S-2840) and dietary intakes from other sources are not expected, no further consideration is required

In conclusion, 1'-COOH-S-2840 contributes 0.7% of the ADI of the metabolite. As the estimated intakes of 1'-COOH-S-2840 following the proposed use of inpyrfluxam are below the ADI of $0.06 \text{ mg/kg bw/day}$, no harmful effect on human health is expected.

2.11.6. Overall conclusion

Metabolite 1'-COOH-S-2840 is not a relevant groundwater metabolite of inpyrfluxam.

2.12. Consideration of Isomeric Composition in the Risk Assessment

2.12.1. Identity and physical chemical properties

Although inpyrfluxam exhibits optical isomerism, only the R-enantiomer is considered as the active substance as reflected in its IUPAC PIN.

2.12.2. Methods of analysis

Where applicable, appropriate methods of analysis that are able to distinguish between enantiomers have been used in support of risk assessment studies.

Based on the proposed residue definitions, monitoring methods able to distinguish between relevant enantiomers are not required.

2.12.3. Mammalian toxicology

Although inpyrfluxam exhibits optical isomerism, only the R-enantiomer is considered as the active substance. The S-enantiomer is present at significantly lower levels and is regarded as an impurity. Overall, there is no impact of the isomeric composition of inpyrfluxam on the human health risk assessment. In addition, all toxicological studies were conducted using material of confirmed enantiomeric purity, containing predominantly the R-enantiomer. Therefore, the substance tested in all toxicological studies is a true reflection of the exposure to inpyrfluxam, as marketed.

Metabolite 1'-COOH-S-2840 in plants and livestock consists of two isomeric pairs, 1'-COOH-S-2840A (pair of isomers) and 1'-COOH-S-2840B (pair of isomers). This is different to how the metabolite was reported in the rat metabolism study (as 1'-COOH-S-2840). However, information from the livestock metabolism study shows that this metabolite is also likely to be present as A and B forms in the rat. Since there is no evidence of a marked isomeric shift in the residue studies, there is no need to apply an adjustment factor to conduct the consumer risk assessment.

Operator, Worker, Bystander and Resident exposure

It is considered that inpyrfluxam does not have any isomeric concerns, therefore, there is no significant impact on the risk assessment for operator, worker, bystander, and resident exposure.

2.12.4. Residues and Consumer risk assessment

Isomers- Parent- inpyrfluxam

In some of the primary crop plant metabolism studies, where detectable residues were analysed for residues and where residues of parent inpyrfluxam were extracted, these were analysed using chiral methodology to determine whether the residues were found as R-isomer (inpyrfluxam) or whether any S-isomer was found. These reports showed that only R-isomer was present (apple rinse, apple peels, apple pulp, rice forage and straw (in the granular study), rice foliage, straw, hulls and grain (in the rice foliar study) and in soya bean matrices (forage, hay, edamame pods, and mature pods)). In the radiolabelled hydrolysis study (see section on the nature of the residues over processing. Vol 3 B.7.5.1) the solutions at time 0 and termination of the study were analysed and shown not to contain any S-isomer. This potential for conversion from R-isomer (inpyrfluxam) to S-isomer was not assessed in the rotational crop metabolism samples (section B.7.6.1). The evidence taken together indicates that R-isomer of inpyrfluxam is stable and does not convert to S-isomer, either in terms of high temperature hydrolysis conditions or during metabolism.

In animal metabolism samples (hen fat - hexane extracts and goat liver- hexane extracts) chiral methodology was used to confirm the stability of the R-isomer. Again there was no marked conversion from the R-isomer. The hen fat extracts were mainly R-isomer (3-4% S-isomer). The goat liver extracts were 100% R-isomer.

Therefore for consumer risk assessment purposes, no conversion factor needs to be applied to either products of plant or animal origin to account for the potential of isomer conversion in plants or animals.

Isomers - Metabolites

In the residues metabolism studies (and nature of the residues in high temperature hydrolysis studies) some metabolites were specifically analysed as the 'A' and 'B' isomers of the various metabolites. Commonly whilst these were specifically determined as 'A' and 'B' they were often summed for the purpose of summary of residues results.

The applicant has explained (in their N5 document) that "For metabolites substituted on the 1-methyl groups of the indane (1'-CH₂OH-S-2840, 1'-COOH-S-2840), a second chiral centre was introduced, and this is expected to be racemic. Two diastereomer pairs could be separated on standard RP-HPLC columns, resulting in "A" and "B" compounds. These were summed together to ensure the total racemic mixture was quantified for risk assessment purposes."

Considering the prevalence of 'A' and 'B' forms for both 1'-COOH-S2480 and 1'-CH₂OH-S2480 there are variable results in the metabolism data, but both feature (in plants and animals). There is not evidence that there is just a shift in only one direction in terms of formation in the metabolism studies.

Additionally in the magnitude of residues trials on wheat and barley, the 'A' and the 'B' isomer pairs for 1'-COOH-S-2840 and 1'-COOH-S-2840 were reported separately (see section 2.7.4), and the amounts in wheat and barley grain and straw are similar across the 'A' and the 'B' forms.

2.12.5. Environmental fate

Inpyrfluxam contains a chiral centre and exists as both R- and S-isomers. The enantiomeric ratio of parent and 1'COOH-S-2840 (and, where appropriate, chiral minor metabolites) were monitored throughout the studies via chiral HPLC analysis. The active substance is present predominantly as the R-isomer and the ratio of the two isomers did not change during the studies. Inpyrfluxam degrades via two main mechanisms, forming 3'-OH-S 2399 via one route of degradation and forming 1'COOH-S-2840 (and associated minor metabolites) via the other route. Conclusions regarding chirality for 3'-OH-S-2840, are the same as for the parent. Metabolites formed by the second route however also contain an additional chiral carbon that results in the formation of two sets of isomer pairs and further complicates stereoisomer considerations.

Metabolite 1'-COOH-S-2840 consists of two enantiomeric pairs, 1'-COOH-S-2840A and 1'-COOH-S-2840B. 1'-COOH-S-2840A and 1'-COOH-S-2840B are then diastereomers of each other. GB Guidance, 'Guidance on the environmental fate and behaviour of plant protection products that include stereoisomers' provides recommendations for consideration of adsorption studies for diastereomers to be used alongside the EFSA Guidance document, 'Guidance of EFSA on risk assessments for active substance of plant protection products that have stereoisomers as components and impurities and for transformation products of active substances that may have stereoisomers' (2019). The need for including both diastereomers separately or using mean values of the adsorption parameters of 1'-COOH-S-2840A and B in the exposure assessment has been considered in line with this guidance. It was determined that the approach taken did not have an impact on subsequent areas of the risk assessment and both lead to the same regulatory outcome. To ensure simplicity and consistency for future products, HSE recommends that modelling can be based on average substance parameters and it is not necessary to consider the diastereomers separately.

2.12.6. Ecotoxicology

The active substance inpyrfluxam is a resolved isomer and not a mixture of isomers. Chiral analysis of selected samples was undertaken in plant, animal and environmental metabolism studies and in no case was any isomerisation observed. Therefore, no further consideration of the risk to non-target organisms from enantiomers of inpyrfluxam is required.

For metabolites substituted on the 1-methyl groups of the indane (1'-CH₂OH-S-2840, 1'-COOH-S-2840), a second chiral centre was introduced, and this is expected to be racemic. Two diastereomer pairs could be separated on standard RP-HPLC columns, resulting in "A" and "B" compounds. These were summed together to ensure the total racemic mixture was quantified for risk assessment purposes.

Risk to birds

No data on the risk to birds from enantiomers of the above metabolites has been provided. However, in the bird metabolism risk assessment, the A and B isomers for each metabolite were summed and meet the criteria for being considered as a major metabolite in the hen metabolism study; therefore, the risk to birds from the isomers of 1'-CH₂OH-S-2840, 1'-COOH-S-2840 is ultimately addressed by the risk from the parent (inpyrfluxam).

Risk to mammals

HSE toxicology have confirmed that no consideration of the risk to mammals from enantiomers of metabolites is required; therefore, no further consideration has been made by HSE ecotoxicology.

Risk to aquatic organisms

HSE environmental fate and behaviour have confirmed that for inpyrfluxam, the enantiomeric ratio did not change and a single assessment for the sum of the enantiomers was considered appropriate.

Of the two metabolites, only 1'-COOH-S-2840 is a major metabolite in the environment. This metabolite was investigated by HSE environmental fate and behaviour and it was concluded that the enantiomers did not need to be considered separately.

1'-CH₂OH-S-2840 does not meet the environmental triggers of >10 % or >5 % at two consecutive timepoints; therefore, from a HSE environmental fate and behaviour concluded that it isn't necessary to consider the enantiomers.

As a result, no further consideration of the risk to aquatic organisms from enantiomers is required.

Risk to bees

HSE residues have confirmed that no significant shift in isomers of the parent (inpyrfluxam) was observed. No assessment was conducted for the isomers of 1'-CH₂OH-S-2840 and 1'-COOH-S-2840. As a result, no further consideration of the risk to bees from the parent or relevant metabolites is required by HSE ecotoxicology.

Risk to non-target arthropods (NTAs)

HSE residues have confirmed that no significant shift in isomers of the parent (inpyrfluxam) was observed. No assessment was conducted for the isomers of 1'-CH₂OH-S-2840 and 1'-COOH-S-2840. As a result, no further consideration of the risk to non-target arthropods from the parent or relevant metabolites is required by HSE ecotoxicology.

Risk to soil micro and micro-organisms

As per the risk to aquatic organisms, no further consideration of the risk to soil organisms is required based on the conclusions of HSE environmental fate and behaviour.

Risk to NTPs

HSE efficacy and residues have both confirmed that no consideration of enantiomers is required; therefore, no further consideration of the risk from enantiomers of the parent and metabolites to non-target plants is required.

2.13. Residue Definitions

2.13.1. Definition of the residues for exposure/risk assessment

Food of plant origin: Sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam

Food of animal origin: a residue definition for dietary risk does not need to be proposed at this time

Honey: a residue definition for dietary risk does not need to be proposed at this time

Soil: Inpyrfluxam, 1'-COOH-S-2840 (sum of isomers), 3'-OH-S-2840

Groundwater: Inpyrfluxam, 1'-COOH-S-2840 (sum of isomers), 3'-OH-S-2840

Surface water: Inpyrfluxam, 1'-COOH-S-2840 (sum of isomers), 3'-OH-S-2840

Sediment: Inpyrfluxam, 3'-OH-S-2840

Air: Inpyrfluxam

2.13.2. Definition of residues for monitoring

Food of plant origin: Inpyrfluxam

Food of animal origin: Inpyrfluxam

Honey: Inpyrfluxam

Soil: Inpyrfluxam, 1'-COOH-S-2840 (sum of isomers)

Groundwater: Inpyrfluxam

Surface water: Inpyrfluxam

Sediment: No ecotoxicologically relevant compounds

Air: Inpyrfluxam

Body tissue/fluid: 1'-COOH-S-2840 (sum of isomers)

HSE Ecotoxicology contribution to definition of residues for monitoring

For soil, surface water and sediment, residues for monitoring were determined by the requirement for an active substance assessment and if metabolites pose a higher risk to non-target organisms than the active substance. For groundwater, the PEC_{gw} combined with a 10-fold dilution was compared to the PEC_{sw} via drainflow to determine if the drainflow assessment was protective for groundwater. Justification for each compartment is outlined below.

For the soil compartment, an active substance assessment is required, resulting in the inclusion of inpyrfluxam. 1'-COOH-S-2840 is included based on the soil micro-organism risk assessment. $PEC_{soil, accumulation}$ were compared to the highest concentration tested resulting in less than 25 % effects in the soil nitrogen transformation study. The calculated margins of safety (MoS) demonstrated that 1'-COOH-S-2840 and 3'-OH-S-2840 pose a higher risk than the active substance (MoS inpyrfluxam = 19, MoS 1'-COOH-S-2840 = 5.75, MoS 3'-OH-S-2840 = 10). HSE Environmental fate confirmed that 3'-OH-S-2840 forms at a lower level and degrades faster than 1'-COOH-S-2840 so its PEC will never be higher than 1'-COOH-S-2840. Therefore, the risk assessment for 1'-COOH-S-2840 will always be protective of 3'-OH-S-2840 and only 1'-COOH-S-2840 needs to be defined as ecotoxicologically relevant in soil.

For the groundwater compartment, a 10-fold dilution was applied to the 1'-COOH-S-2840 PEC_{gw} , resulting in 0.18 µg/L. This was compared to the PEC_{sw} for drainflow of 0.863 µg/L. This suggests that groundwater is a less critical route of exposure compared to drainflow. HSE Environmental fate and behaviour confirmed that this would likely be the case for other GAPs. Consequently, 1'-COOH-S-2840 has not been included in the definition of residues for monitoring for the groundwater compartment as it was not included for surface water.

For the surface water compartment, an active substance assessment is required, resulting in the inclusion of inpyrfluxam. For the lower tier drainflow assessment, the PEC/RAC for 1'-COOH-S-2840 (1.31) was higher than inpyrfluxam (1.05). This was based on a 1:1 extrapolation for the chronic endpoints between inpyrfluxam and 1'-COOH-S-2840, which HSE Ecotoxicology considered overly conservative in this instance. This was based on the 1480-fold reduction in acute mortality toxicity for 1'-COOH-S-2840 relative to inpyrfluxam. Furthermore, for 1'-COOH-S-2840, if the active substance's sub-lethal chronic endpoint was representative of the metabolite, the ratio between the acute endpoint (>50,000 µg/L) and chronic endpoint (7.5 µg/L) would exceed 6,667. Considering the historical data reviewed in EFSA Journal (2005) 301, 1-45, such an acute-to-chronic toxicity ratio is highly unlikely. Supporting this is the absence of any toxic symptoms recorded during the acute fish toxicity study for 1'-COOH-S-2840. Therefore, it is the view of HSE Ecotoxicology that 1'-COOH-S-2840 should not be included as an ecotoxicologically relevant compound for surface water.

For the sediment compartment, according to Regulation (EU) No 283/2013, “*when accumulation of an active substance in aquatic sediment is indicated or predicted by environmental fate studies, the impact on a sediment-dwelling organism shall be assessed. The chronic risk to Chironomus riparius or Lumbriculus spp. shall be determined*”. EFSA Journal 2013;11(7):3290 footnote 30 expands on this by identifying the relevant fate study and level of active substance sediment accumulation. It outlines that a sediment dwelling organism study is required when a “*water/sediment study showed > 10 % of applied radioactivity at or after day 14 present in the sediment and chronic daphnia test (or other comparable study with insects) NOEC < 0.1 mg/L*”. Regardless of the results from the water/sediment study, there was no chronic aquatic invertebrate NOEC < 0.1 mg/L. Therefore, no sediment-dwelling organism study is required according to EFSA Journal 2013;11(7):3290. From this, no risk assessment for the sediment compartment is required, resulting in no ecotoxicologically relevant compounds.

Level 3

INPYRFLUXAM

3. Proposed Decision with Respect to the Application

3.1. Background to the proposed decision

3.1.1. Proposal and acceptability against the decision making criteria – Article 4 and annex II of assimilated Regulation No 1107/2009

3.1.1.1. Article 4				
		Yes	No	
i)	It is considered that Article 4 of assimilated Regulation No 1107/2009 is complied with. Specifically the competent authority considers that authorisation in at least one plant protection product containing the active substance for at least one of the representative uses.	X		It is considered that Article 4 of assimilated Regulation No 1107/2009 is complied with for inpyrfluxam for use as a fungicide on barley and wheat (refer to Level 1, Table 1.5.1 for details of the representative uses considered).
3.1.1.2. Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		It is considered that a sufficiently complete dossier has been submitted which enables a regulatory decision on approval of inpyrfluxam to be made and to establish that risks are acceptable and no critical areas of concern are identified.

				There are data gaps identified (see (ii) below).
ii)	<p>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:</p> <p>(a) the data requirements have been amended or refined after the submission of the dossier; or</p> <p>(b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.</p>	X	X	<p>The data gaps identified at Level 3.1.4 are considered to be confirmatory in nature and are not required to support the approval of inpyrfluxam. However, the following data should be provided to support product authorisation for cereal crops:</p> <ul style="list-style-type: none"> — scale up from pilot plant to full scale manufacture new 5 batch analysis supporting the commercial scale technical specification must be submitted. In addition, the toxicological significance of any changes in the impurity profile must be addressed. - an assessment of the effect of water treatment processes on the nature of residues present in surface water, when surface water is abstracted for drinking (once GB guidance is adopted).
3.1.1.3. Restriction on approval				
		Yes	No	
	It is considered that in line with Article 6 of assimilated Regulation No 1107/2009 approval should be subject to conditions and restrictions.	X		<p>(a) the minimum degree of purity of the active substance;</p> <ul style="list-style-type: none"> - minimum purity 940 g/L. <p>(b) the nature and maximum content of certain impurities;</p> <ul style="list-style-type: none"> - not applicable.

			<p>(c) restrictions arising from the evaluation of the information referred to in Article 8 of 1107/2009 taking account of the agricultural, plant health and environmental, including climatic, conditions in question;</p> <p>- not applicable.</p> <p>(d) type of preparation;</p> <p>- not applicable</p> <p>(e) manner and conditions of application;</p> <p>- Due to the risk to aquatic organisms from exposure via spray drift a 5 m buffer zone for all representative uses is proposed.</p> <p>(f) submission of further confirmatory information to the competent authority, where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge;</p> <p>- not applicable.</p> <p>(g) designation of categories of users, such as professional and non-professional;</p> <p>- not applicable.</p> <p>(h) designation of areas where the use of plant protection products, including soil treatment products, containing the</p>
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				<p>active substance may not be authorised or where the use may be authorised under specific conditions;</p> <p>- not applicable.</p> <p>(i) the need to impose risk mitigation measures and monitoring after use;</p> <p>- Due to the risk to aquatic organisms from exposure via spray drift a 5 m buffer zone for all representative uses is proposed.</p> <p>(j) any other particular conditions that result from the evaluation of information made available in the context of assimilated Regulation No 1107/2009.</p> <p>- not applicable.</p>
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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).	X		The dossier contains the information needed to establish, the Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL), Acute Reference Dose (ARfD) and Acute Acceptable Operator Exposure Level (AAOEL).

	<p>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:</p> <p>(a) permits any residue of concern to be defined;</p> <p>(b) reliably predicts the residues in food and feed, including succeeding crops</p> <p>(c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing;</p> <p>(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;</p> <p>(e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.</p>	X		<p>Data on residues are sufficient for the approval of the active substance.</p> <p>Acceptable data have been submitted to propose residue definitions in plants and animal products.</p> <p>Acceptable data have been provided on residues in primary crops and rotational crops, the effects of processing and residues in animal products.</p> <p>Suitable data are available on methods of analysis for the determination of residues of inpyrfluxam both for risk assessment and enforcement purposes.</p> <p>A consumer risk assessment has been concluded on the basis of the residues data supplied.</p>
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	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.	X		For all representative uses.
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.	X		The applicant has satisfactorily addressed all of the efficacy requirements for a new active substance. Effectiveness against a range of major diseases has been demonstrated for the proposed uses. Crop safety of inpyrfluxam to the proposed crops has been supported. Additionally, the resistance risk has been appropriately addressed. Further information will be examined at the product authorisation stage to ensure that the product itself fully complies with the data requirements for efficacy.
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.	X		This applies to all representative uses.

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/diastereoisomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	X		<p>Acceptable data have been submitted to support the manufacturing sites of inpyrfluxam and the proposed specification based on pilot scale manufacturing is considered supported by the available data. Following scale-up from pilot plant to full scale manufacture, data to confirm the commercial scale technical specification must be submitted. In addition, the toxicological significance of any changes in the impurity profile must be addressed.</p> <p>None of the impurities identified in technical inpyrfluxam are considered of toxicological or ecotoxicological relevance.</p>
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	-	-	There is currently no FAO Specification for inpyrfluxam.
	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 currently no FAO Specification for inpyrfluxam.

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.	X		Acceptable methods have been submitted for the determination of inpyrfluxam and all significant and relevant impurities in the technical material as manufactured. (Refer also to Level 2, Section 2.1).
	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	X		<p>Acceptable methods have been submitted for the determination of inpyrfluxam and selected metabolites in various matrices used in support of all areas of the risk assessment.</p> <p>Acceptable methods have been submitted for the determination of inpyrfluxam and selected metabolites in various matrices for use in post-approval monitoring and control to support the representative use. However further information is to be submitted to confirm the acceptability of the analytical method proposed for monitoring of 1'-COOH-S-2840 in body tissue.</p>

				<p>Further information is expected regarding the stability of extracts and standard stability for analytical method used for monitoring in body tissue.</p> <p>The stability of standards and extracts for the body tissue method has been sufficiently addressed.</p>
	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 assimilated Regulation No 1107/2009.	X		Refer to Level 2, Section 2.2 for further details.
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.	X		<p>ADI = 0.06 mg/kg bw/day based on increased incidence and frequency of vomiting, changes in clinical chemistry indicative of liver damage changes (ALP by >60%, GGTP by >50%), increased liver weights (>10%) (>15%), and histopathological findings of the liver (diffuse hepatocyte hypertrophy) and adrenal gland (zona fasciculata cell vacuolation) at the LOAEL of 30 mg/kg bw/day in the one-year toxicity study in dogs (NOAEL of 6 mg/kg bw/day).</p> <p>AOEL = 0.04 mg/kg bw/day based on increased incidence and frequency of vomiting, changes in clinical</p>

				<p>chemistry indicative of liver damage changes (ALP by >60%, GGTP by >50%), increased liver weights (>10% (>15%), and histopathological findings of the liver (diffuse hepatocyte hypertrophy) and adrenal gland (zona fasciculata cell vacuolation) at the LOAEL of 30 mg/kg bw/day in the one-year toxicity study in dogs (NOAEL of 6 mg/kg bw/day; post-hepatic systemic bioavailability value of 60%).</p> <p>ARfD = 0.3 mg/kg bw/ based on systemic effects (reduced motor activity and body temperature) at the LOAEL of 200 mg/kg bw in the rat (oral gavage) acute neurotoxicity study (NOAEL of 30 mg/kg bw).</p> <p>AAOEL of 0.2 mg/kg bw based on systemic effects (reduced motor activity and body temperature) at the LOAEL of 200 mg/kg bw in the rat (oral gavage) acute neurotoxicity study (NOAEL of 30 mg/kg bw; post-hepatic systemic bioavailability value of 60%).</p>
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, the substance SHOULD BE classified or proposed for		X	Overall, it is concluded that inpyrfluxam is not genotoxic and the data requirements of assimilated Regulation 283/2013 have been met. Therefore, classification of inpyrfluxam for mutagenicity In accordance with Regulation (EC) N° 1272/2008 as it applies in GB, is not warranted.

	classification , in accordance with the provisions of assimilated Regulation No 1272/2008, as mutagen category 1A or 1B.			
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 in relation to the relevant constituent territory 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 assimilated Regulation No 1272/2008, as carcinogen category 1A or 1B.		X	Long term oral administration of inpyrfluxam was not carcinogenic in the rat or mouse. Therefore, classification of inpyrfluxam for carcinogenicity in accordance with Regulation (EC) N° 1272/2008 as it applies in GB, is not required.
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,	-	-	Not applicable.

	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 assimilated Regulation No 396/2005.			
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 the Authority, the substance SHOULD BE classified or proposed for classification , in accordance with the provisions of assimilated Regulation No 1272/2008, as toxic for reproduction category 1A or 1B.		X	Inpyrfluxam does not affect fertility in rats and is not a specific developmental toxicant in rats or rabbits. In accordance with Regulation (EC) N° 1272/2008 as it applies in GB, classification of inpyrfluxam for reproductive and developmental toxicity is not required.
ii)	Linked to above classification proposal.	-	-	Not applicable.

	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 assimilated Regulation No 396/2005.			
Impact on Human Health – proposed endocrine disrupting properties and classification				
		Yes	No	
i)	It is considered that the substance SHOULD BE classified or proposed for classification in accordance with the provisions of assimilated Regulation No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties		X	Inpyrfluxam should not be classified as carcinogenic category 2 and toxic for reproduction category 2 in accordance with Regulation (EC) N° 1272/2008 as it applies in GB.
ii)	It is considered that the substance SHOULD BE classified or proposed for classification in accordance with the provisions of assimilated Regulation No		X	Inpyrfluxam should not be classified as toxic for reproduction category 2 in accordance with Regulation

	1272/2008, as toxic for reproduction category 2 and in addition the competent authority considers the substance has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties			<p>(EC) N° 1272/2008 as it applies in GB, and does not have specific effects on endocrine organs.</p> <p>In addition, inpyrfluxam does not meet the ED (endocrine disruption) criteria of Regulation (EC) No 2018/605 of 19 April 2018, amending Annex II to Regulation (EC) No 1107/2009. HSE concludes that for the EATS-modalities inpyrfluxam is not an ED and its ED potential has been sufficiently investigated.</p>
iii)	<p>Linked to either i) or ii) immediately above.</p> <p>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 assimilated Regulation No 396/2005.</p>	-	-	Not applicable.

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 assimilated Regulation No 1107/2009 Annex II Section 3.7.1.		X	<p>Inpyrfluxam meets the POP criterion for persistence in soil (DT₅₀ >6 months based on a weight of evidence approach) and in sediment (DT₅₀ in sediment >6 months).</p> <p>Inpyrfluxam does not meet the POP criterion for long range atmospheric transport as it has an atmospheric half-life <2 days.</p> <p>Inpyrfluxam does not meet the POP criterion for bioaccumulation as it has a BCF < 5000 L/kg</p>
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 assimilated Regulation No 1107/2009 Annex II Section 3.7.2.		X	<p>P: Inpyrfluxam meets the persistence criterion in soil (DT₅₀ >120 days based on a weight of evidence approach) and sediment (DT₅₀ in freshwater sediment >120 days).</p> <p>B: Inpyrfluxam has a BCF ≤ 2000 L/kg. Therefore, it does not meet the criterion for bioaccumulation.</p> <p>T: The <i>P. promelas</i> EC₁₀ = 0.0066 mg/L. Therefore, inpyrfluxam meets the Toxicity criterion of NOEC/EC/10</p>

				(long-term) < 0.01 mg/L for marine or freshwater organisms.
Very persistent and very bioaccumulative substance (vPvB)				
		Yes	No	
	It is considered that the active substance FULFILS the criteria of a very persistent and very bioaccumulative substance (vPvB) as laid out in assimilated Regulation No 1107/2009 Annex II Section 3.7.3.		X	<p>vP: Inpyrfluxam meets the very persistent criterion in soil (DT_{50} > 180 days based on a weight of evidence approach) and sediment (DT_{50} in freshwater sediment > 120 180 days).</p> <p>vB: Inpyrfluxam has a BCF < 5000 L/kg. Therefore, it does not meet the criterion for bioaccumulation.</p>
Ecotoxicology				
		Yes	No	
	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 competent authority is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the	X		<p>Birds and mammals: A screening assessment demonstrated an acceptable risk to birds and mammals from all proposed uses.</p> <p>Aquatic organisms: An acceptable risk to aquatic organisms was demonstrated using a 5 m buffer zone for spray drift exposure. For drainflow exposure, an acceptable risk was demonstrated using a SSD refined acute fish endpoint and HTDF modelling for the risk to fish through chronic exposure.</p>

	active substance, safener or synergist is expected to affect adversely by the intended use.			<p>Bees: An acceptable risk to bees was demonstrated at the first tier.</p> <p>Non-target arthropods other than bees: A tier 1 risk assessment demonstrated an acceptable risk to non-target arthropods other than bees from all proposed uses.</p> <p>Soil organisms: An acceptable risk to soil macro invertebrates and soil micro-organisms was demonstrated at the first tier.</p> <p>Non-target plants : A screening assessment demonstrated an acceptable risk to non-target plants from all proposed uses.</p>
	It is considered that, on the basis of the assessment of nationally or internationally agreed test guidelines, the substance HAS endocrine disrupting properties that may cause adverse effects on non-target organisms.		X	<p><u>Birds and mammals: potential endocrine disrupting properties</u></p> <p>Based on current EFSA/ECHA 2018 guidance, it is not possible to reach a conclusion for birds or reptiles when considering endocrine disruption. Regarding wild mammals, inpyrfluxam is not an endocrine disruptor when considering EATS modalities based on EFSA/ECHA 2018 guidance and agreed regulatory criteria.</p> <p><u>Aquatic organisms: potential endocrine disrupting properties</u></p>

				Based on current guidance and following consideration of EATS modalities, inpyrfluxam does not meet the criteria of being an endocrine disruptor (ED) for aquatic organisms.
	<p>Linked to the consideration of the endocrine properties immediately above.</p> <p>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.</p>	-	-	Not applicable.
	<p>It is considered that it is established following an appropriate risk assessment on the basis of nationally 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:</p> <p>— will result in a negligible exposure of honeybees, or</p> <p>— has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.</p>	X		Based on available data, an acceptable risk to bees was demonstrated for the proposed uses.

Residue definitions			
		Yes	No
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	X	
			<p>As detailed in section 2.7.3:</p> <p>RD-Enf for plants: Inpyrfluxam</p> <p>RD-RA for plants: Sum of inpyrfluxam and its metabolites 1'-CH₂OH-S-2840 (A and B isomers, free and conjugate) and 3'-OH-S-2840, expressed as inpyrfluxam</p> <p>As detailed in section 2.7.6:</p> <p>RD-RA for livestock: this residue definition is not being proposed at this time (for the intended uses currently assessed)</p> <p>RD-Enf for livestock: Inpyrfluxam</p> <p>RD-RA for honey: this residue definition is not being proposed at this time (for the intended uses currently assessed)</p> <p>RD-Enf for honey: Inpyrfluxam</p>
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	X	
			Refer to Volume 1, Level 2, section 2.7.10 for a summary of the groundwater exposure assessment.

the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, 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 assimilated Regulation No 1107/2009.			It is considered that inpyrfluxam and metabolite 3'-OH-S-2840 present a low risk of contamination of groundwater at >0.1 µg/L for the uses proposed. While metabolite 1'-COOH-S-2840 (A and B combined) is predicted to be >0.1 µg/L for the proposed uses, a toxicological relevance assessment has demonstrated that the risk is acceptable.
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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	X		<p>[If yes identify the criteria considered met by the substance ie.</p> <ul style="list-style-type: none"> - its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories – No. - it meets two of the criteria to be considered as a PBT substance - Inpyrfluxam fulfils 2 out of 3 of the criteria of a persistent, bioaccumulative and

				<p>toxic substance (PBT) as laid out in Regulation 1107/2009 (for persistence and toxicity – see 3.1.1.4 above).</p> <ul style="list-style-type: none"> - there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones) – No. - it contains a significant proportion of non-active isomers – No. - it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008 as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4, - No. - if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse
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				effects in humans if the substance has not been excluded in the criteria laid down in point 3.6.5 - No.]
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3.1.3. Proposal – Low risk active substance

Low-risk active substance				
		Yes	No	
	<p>It is considered that the active substance shall be considered of low risk.</p> <p>(a) In particular it is considered that the substance should NOT be classified or proposed for classification in accordance with assimilated Regulation No 1272/2008 as at least one of the following:</p> <ul style="list-style-type: none"> — carcinogenic category 1A, 1B or 2,, — mutagenic category 1A, 1B or 2, — toxic to reproduction category 1A, 1B or 2, — sensitising chemicals category 1, — serious damage to eye category 1, 		X	<p>Inpyrfluxam cannot be considered a low risk substance because it is persistent in soil and because it is proposed to be classified for aquatic life as detailed below in accordance with Regulation (EC) No 1272/2008.</p> <ul style="list-style-type: none"> - carcinogenic – no classification proposed - mutagenic – no classification proposed - toxic to reproduction – no classification proposed - sensitizing chemicals – no classification proposed - very toxic or toxic – yes <p>Aquatic Chronic Category 1: - 'H410 very toxic to aquatic life with long lasting effects'</p> <p>Acute Tox 3 (H301) – Toxic if swallowed</p> <ul style="list-style-type: none"> - explosive – no classification proposed - corrosive – no classification proposed <p>In addition, it is considered that the substance is NOT:</p>

<p>— respiratory sensitiser category 1,</p> <p>— acute toxicity category 1, 2 or 3,</p> <p>— specific Target Organ Toxicant, category 1 or 2,</p> <p>— toxic to aquatic life of acute and chronic category 1 on the basis of appropriate standard tests,</p> <p>— explosive,</p> <p>— skin corrosive, category 1A, 1B or 1C;</p> <p>(b) it has been identified as priority substance and is listed in Annex 10 to Directive 2000/60/EC substance Directive 2000/60/EC;</p> <p>(c) it is deemed to be an endocrine disruptor;</p> <p>(d) it has neurotoxic or immunotoxic effects.</p> <p>In addition it is considered that the substance is NOT:</p>		<p>In addition, inpyrfluxam is neurotoxic in dogs at highly toxic doses.</p> <p>However, it is considered that the substance is NOT:</p> <ul style="list-style-type: none"> - persistent (half-life in soil more than 60 days) - Inpyrfluxam is persistent in soil. - has a bioconcentration factor higher than 100 – No - is deemed to be an endocrine disruptor – No - has neurotoxic or immunotoxic effects - No
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	<p>— persistent (half-life in soil is more than 60 days) or its bio-concentration factor is higher than 100.</p> <p>However, a naturally occurring active substance which does not correspond to any of points (a) to (d) above may be considered as being of low-risk, even if it is persistent (half-life in soil is more than 60 days) or its bio-concentration factor is higher than 100.</p>			
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3.1.4. List of studies to be generated, still on-going or available but not assessed

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 assessed
3.1.4.1. Identity of the active substance or formulation				
Following scale-up from pilot plant to full scale manufacture new 5-batch analysis	Required for all representative uses.	X		

supporting the commercial scale technical specification must be submitted. In addition, the toxicological significance of any changes in the impurity profile must be addressed.				
3.1.4.2. Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
None required				
Study for determining the explosive properties of the active substance as manufactured is required.			X – Expected Nov 2025 Data has been provided.	
Tank mixing study is required to address B.2.9 – Physical and chemical compatibility of tank mixtures.			X – Expected Nov 2025 Data has been provided.	

3.1.4.3. Data on uses and efficacy				
None required				
3.1.4.4. Data on handling, storage, transport, packaging and labelling				
None required				
3.1.4.5. Methods of analysis				
None required				
Stability of analytical methods for determination of 1'-COOH-S-2840 in animal tissue		X	Data has been provided.	
3.1.4.6. Toxicology and metabolism				
None required				
3.1.4.7. Residue data				
None required				
3.1.4.8. Environmental fate and behaviour				
An assessment of the effect of water treatment processes on the nature of residues of an active	Required for all representative uses.	X		

substance or metabolite present in surface water and/or groundwater, when surface water is abstracted for the production of drinking water (once GB guidance is adopted).				
3.1.4.9. Ecotoxicology				
None required				

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 assimilated Regulation 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)
1	None	-

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 assimilated Regulation 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 assimilated Regulation No 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)
1	None	-

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		Spring Wheat, Winter Wheat, Durum Wheat BBCH 30-71 (90 g as/ha)	Spring Barley, Winter Barley BBCH 30-71 (90 g as/ha)
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		

	Assessment not finalised		
Risk to wild non target terrestrial vertebrates	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised		
Risk to aquatic organisms	Risk identified		
	Assessment not finalised		
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached	X ¹	X ¹
	Parametric value of 10µg/L ^(a) breached		
	Assessment not finalised		
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 10-final, European Commission, 2003

¹PECgw values for metabolite 1'-COOH-S-2840 (A + B combined) exceed 0.1 µg/L in a number of scenarios for all uses of S-2399 60 g/L EC. Overall maximum PECgw for 1'-COOH-S-2840 was 1.802 µg/L (PEARL 5.5.5, Hamburg, spring cereals (late applications)), see section 2.11 for the assessment of relevance of this metabolite in groundwater.

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
Human Health – Developmental toxicity	In a developmental toxicity study ([REDACTED] (2017a); see DAR Vol 3 CA B6, section B.6.6.2) in which groups of 22-24 pregnant female Wistar Hannover rats received inpyrfluxam via oral gavage at doses of 0, 10, 25 or 80 mg/kg bw/day from gestation day 6 to 19, an unusual occurrence of cyclopia was noted in one foetus at the high dose. Although cyclopia is observed spontaneously, the incidence of cyclopia is quite low and this malformation had not appeared in the HCD (historical control data) of the testing facility. Therefore, relation to treatment could not be excluded and an additional developmental toxicity study in rats was conducted to determine whether the malformation was likely to be treatment related. In this study ([REDACTED] (2017b); see DAR Vol 3 CA B6, section B.6.6.2), groups of 39 or 40 pregnant female Wistar Hannover rats received inpyrfluxam via oral gavage at doses of 0 or 90 mg/kg bw/day from gestation day 6 to 19. Cyclopia was not observed in any foetuses. In this second study, the number of examined foetuses per group had increased to 533 compared to 309 in the previous study. The tested dose was increased from 80 to 90 mg/kg bw/day to confirm that a maximal tolerated dose had been achieved. It is also noted that cyclopia was not observed neither in F1 or F2 pups in the rat multigeneration study ([REDACTED] (2017); see DAR Vol 3 CA B6, section B.6.6.1) up to a dose of 86-113 mg/kg bw/day.

	<p>Therefore, HSE concludes that the incidence of cyclopia is not related to inpyrfluxam treatment.</p> <p>Does the ECP agree that the evidence supports the conclusion that the incidence of cyclopia in rats is not related to inpyrfluxam treatment?</p>
Human Health – Neurotoxicity	<p>In the 90-day repeat dose study in dogs (([REDACTED]) (2016); see DAR Vol 3 CA B6, section B.6.3.2), in which groups of 4 male and 4 female animals received inpyrfluxam in gelatin capsules at 0, 40, 160 or 700/500 mg/kg bw/day for 13 weeks, optic nerve fibre degeneration was noted at the top dose (700/500 mg/kg bw/day) in males (3/4 vs 0/4 in controls) and from the mid dose (160 mg/kg bw/day) in females (1/4 and 4/4 at 160 and 700/500 mg/kg bw/day respectively vs 0/4 in controls). However, significant systemic toxicity was noted at and above 160 mg/kg bw/day including vomiting, signs of anaemia, changes in clinical-chemistry parameters indicative of liver damage, increased liver weight and histopathological findings in the liver, gall bladder, kidney, thyroid and adrenal. The top dose of 700/500 mg/kg bw/day was highly toxic with additional signs of toxicity, such as mortality, clinical signs of toxicity, effects on body weight and food consumption, changes in urinalysis parameters and additional effects on other organs.</p> <p>In the one-year repeat dose study in dogs (([REDACTED]) (2017); see DAR Vol 3 CA B6, section B.6.3.3), in which groups of 4 male and 4 female animals received inpyrfluxam in gelatin capsule at 0, 2, 6, 30 or 160 mg/kg bw/day for 52 weeks, increased degeneration of the optic nerve was noted at 160 mg/kg bw/day in females (2/4 vs 1/4 in controls). However, significant systemic toxicity was noted at and above 30 mg/kg bw/day (vomiting, clinical chemistry parameters indicative of liver damage, increased liver weights, and histopathological findings of the liver) with the MTD (maximum tolerated dose) being reached at 30 mg/kg bw/day already.</p> <p>HSE concludes that the increased incidence in optic nerve degeneration in dogs occurred above the MTD and therefore it is unlikely to represent specific neurotoxicity.</p>

	Does the ECP agree that the evidence supports the conclusion that the observed optic fibre degeneration in dogs does not represent specific neurotoxicity?
Ecotoxicology – Reproductive bird risk assessment (metabolites)	<p>An unacceptable reproductive risk at Tier I was demonstrated for small insectivorous bird “passerine” at BBCH 71-89 from the metabolites N-des-Me-DFPA, 3’OH-S-2840 and DFPA. The assessment assumed 10 times greater toxicity than the parent (in the absence of metabolite toxicity data), the parent application rate, a time weighted average (TWA) of 1, and the daily dietary dose (DDD) was refined based on the highest percentage total radioactive residues (TRR) in the plant metabolism studies.</p> <p>A weight of evidence approach has been conducted based on extrapolation from the available mammalian data for these metabolites. Whilst there is uncertainty between extrapolating between mammals and birds, the active substance reproductive endpoints are similar and there is a moderate margin of safety in the mammalian reproductive risk assessment. N-des-Me-DFPA and DFPA both have mammalian toxicity endpoints lower than that of the active substance, and 3’OH-S-2840 is of a similar toxicity to the parent.</p> <p>Taken together, all metabolites exhibit equivalent or lower toxicity than the parent for mammals and HSE propose extending this to birds. Based on 1:1 toxicity, this would be sufficient to address the risk to small insectivorous bird “passerine” at BBCH 71-89, with TER values greater than the standard reproductive trigger value of 5.</p> <p>It is also noted that the metabolites were identified from the residues formed in plants and the risk assessment assumes birds will be exposed via consumption of these residues. However, the focal species of concern has a diet of 100% insects according to EFSA (2009) and it is uncertain whether these residues formed in plants could be carried across to insects.</p> <p>Overall, HSE considers it unlikely that N-des-Me-DFPA, 3’OH-S-2840 and DFPA are more toxic to birds than the parent based on the above weight of evidence approach.</p>

	<p>The ECP is invited to advise on the reproductive bird risk assessment from metabolites, primarily N-des-Me-DFPA, 3'OH-S-2840, and DFPA, and whether the weight of evidence approach is sufficient to conclude an acceptable reproductive risk to small insectivorous bird "passerine" from application to cereals at BBCH 71-89.</p>
<p>Ecotoxicology – Aquatic higher tier drainflow assessment</p>	<p>An unacceptable chronic risk to fish was identified in the lower tier drainflow risk assessment based on a RAC = 0.66 µg/L for <i>P. promelas</i>. Higher tier drainflow (HTDF) modelling initially demonstrated an unacceptable chronic risk to fish (4 and 6 exceedances for Denchworth Medium and Wet, respectively), triggering the need for a case-by-case assessment taking into account the frequency, magnitude, and duration of these exceedances.</p> <p>The exceedance profiles were compared to the ELS study larval survival results for <i>P. promelas</i> and an acceptable risk was identified for 7/10 of the independent exceedance periods with a higher degree of certainty. This resulted in ≤ 3 exceedance periods for each soil-climate scenario, in-line with the criteria set out in the MACRO higher tier drainflow modelling guidance.</p> <p>The exceedance periods occurred exclusively during November – January, when fish larvae are not present in the environment. Furthermore, all 7 exceedance periods had durations of ≤ 2 days, meaning that the risks to more developed fish life stages (juveniles and adults) would be covered by the acute fish risk assessment, which utilises 4-day exposure hazard studies. When the acute RAC of 1.99 µg/L is compared to the PEC_{sw,max} for the 7 short exceedance periods, the PEC/RAC values are all < 1.</p> <p>The chronic RAC is set by effects on larval survival and therefore the Specific Protection Goal (SPG) for the Ecological Threshold Option (ETO), requiring negligible effects on individual survival for fish with a high degree of certainty, is relevant to the HTDF results (EFSA aquatic guidance (2013)). The 3/30 exceedance year criterion aims to provide an equivalent level of protection as the 90th percentile PEC in other exposure assessments. For these assessments we</p>

	<p>accept a reasonable worst case exposure estimate is more appropriate than an absolute worst case.</p> <p>HSE believes we have satisfactorily addressed the SPG for fish within the context of existing regulatory approaches. Does the ECP have any concerns surrounding our approach to this case-by-case assessment?</p>
Residues	<p>Whilst the residue definitions were considered in the context of the current intended uses on wheat and barley informed by the broad range of analytes in the primary crop trials on these crops, the candidates for inclusion in the residue definitions were also considered more broadly beyond the intended GAP. The proposed plant residue definitions could be suitable as a universal residue definition for all crops, based on the availability and findings in the metabolism studies across different crop groups and use scenarios (foliar, granular, and seed treatment uses).</p> <p>Expert consultation is invited to advise on whether the approach taken by HSE for the residue definitions to set a universal residue definition to cover all crops, but advising that further data may be required (on the potential for some metabolites to form in foods when generating further field trials for some future intended uses) is an appropriate approach.</p>

3.2. Proposed Decision

It is proposed that:

Inpyrfluxam can be approved under assimilated Regulation No 1107/2009 as a candidate for substitution.

It is considered that it should be specified that conditions of use shall include risk mitigation measures, where appropriate.

To mitigate the risk to aquatic organisms from exposure via spray drift, a 5 m buffer zone is required. The following risk mitigation label phrasing is required:

To protect aquatic organisms respect an unsprayed buffer zone to surface water bodies in line with LERAP requirements.

DO NOT ALLOW DIRECT SPRAY from horizontal boom sprayers to fall within 5 m of the top of the bank of a static or flowing water body, unless a Local Environment Risk Assessment for Pesticides (LERAP) permits a narrower buffer zone, or within 1 m of the top of a ditch which is dry at the time of application. Aim spray away from water.

This product qualifies for inclusion within the Local Environment Risk Assessment for Pesticides (LERAP) scheme. Before each spraying operation from a horizontal boom sprayer, either a LERAP must be carried out in accordance with CRD's published guidance or the statutory buffer zone must be maintained. The results of the LERAP must be recorded and kept available for three years.

Further Information to confirm the approval of the substance

It is proposed that the competent authority concerned shall request the submission of confirmatory information:

- (a) where new data requirements are established during the evaluation process, or
- (b) as a result of new scientific and technical knowledge, or
- (c) to increase confidence in the decision.

1. Following scale-up from pilot plant to full scale manufacture new 5-batch analysis supporting the commercial scale technical specification must be submitted. In addition, the toxicological significance of any changes in the impurity profile must be addressed.

2. An assessment of the effect of water treatment processes on the nature of residues of the active substance or metabolites present in surface water, when surface water and/or

groundwater is abstracted for the production of drinking water (once GB guidance is adopted).

The applicant shall submit the relevant information set out in points (1) and (2) to the GB Competent Authorities and HSE as the reviewing Competent Authority by [1 year from approval of the active substance].

The applicant shall submit the relevant information set out in point (2) to the GB Competent Authorities and HSE as the reviewing Competent Authority, two years after adoption of a GB guidance document on evaluation of the effect of water treatment processes on the nature of residues present in surface and groundwater.

3.3. Rationale for the conditions and restrictions to be associated with the approval or authorisation(s), as appropriate

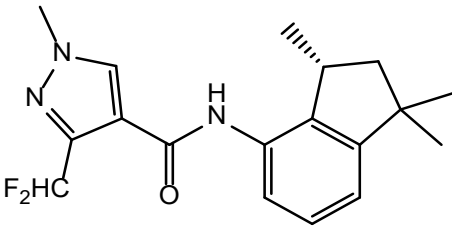
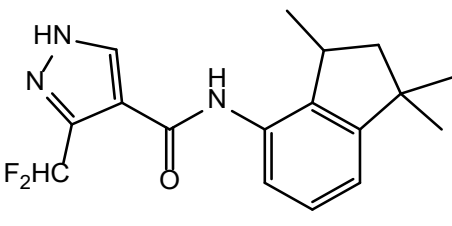
3.3.1. Particular considerations proposed to be taken into account to manage the risks identified

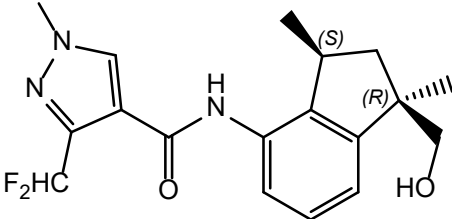
Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
<p>To mitigate the risk to aquatic organisms from exposure via spray drift, a 5 m buffer zone is required. The following risk mitigation label phrasing is required:</p> <p><i>To protect aquatic organisms respect an unsprayed buffer zone to surface water bodies in line with LERAP requirements.</i></p> <p><i>DO NOT ALLOW DIRECT SPRAY from horizontal boom sprayers to fall within 5 m of the top of the bank of a static or flowing water body, unless a Local Environment Risk Assessment for Pesticides (LERAP) permits a narrower buffer zone, or within 1 m of the top of a ditch which is dry at the time of application. Aim spray away from water.</i></p> <p><i>This product qualifies for inclusion within the Local Environment Risk Assessment for</i></p>	<p>All representative uses.</p>

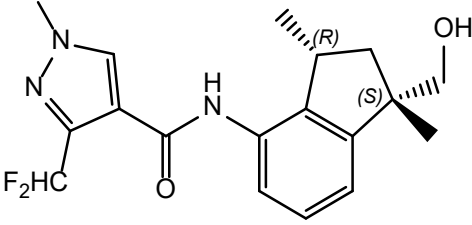
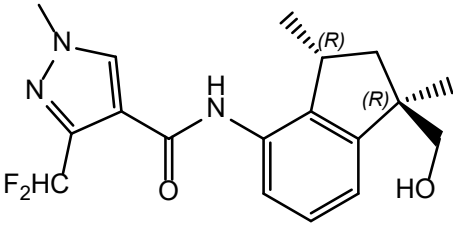
<p><i>Pesticides (LERAP) scheme. Before each spraying operation from a horizontal boom sprayer, either a LERAP must be carried out in accordance with CRD's published guidance or the statutory buffer zone must be maintained. The results of the LERAP must be recorded and kept available for three years.</i></p>	
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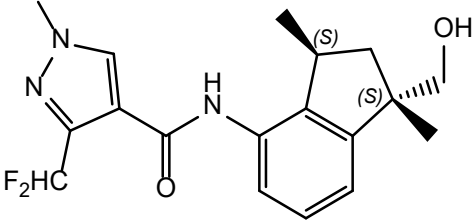
3.4. Appendices

3.4.1. Metabolites and their codes

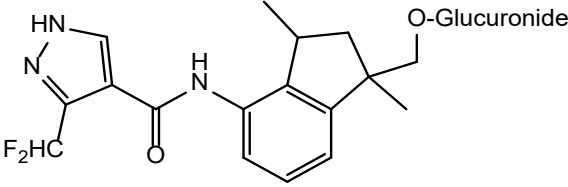
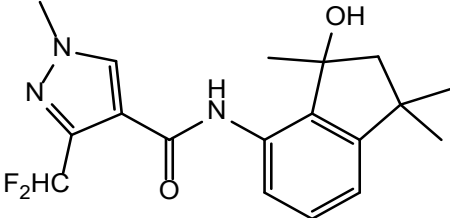
Chemical Name	Alt Name	Code	Structure	Found in?
(R)-3-(difluoromethyl)-1-methyl-N-(1,1,3-trimethyl-2,3-dihydro-1H-inden-4-yl)-1H-pyrazole-4-carboxamide	Inpyrfluxam	S-2399		Not applicable (parent compound)
3-(difluoromethyl)-N-(1,1,3-trimethyl-2,3-dihydro-1H-inden-4-yl)-1H-pyrazole-4-carboxamide	N-des-Me-S-2840	-		Soil (aerobic) Water sediment Rat Rat, dog and human microsomes NOR: Soybean forage, hay, pods and seed Rice plant, straw, hulls and grain

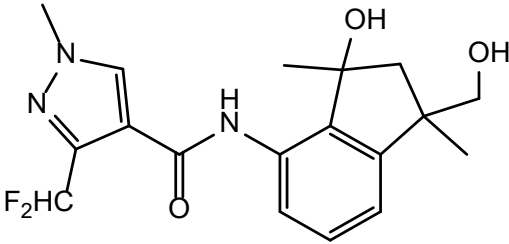
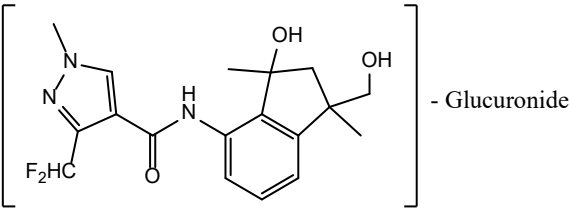
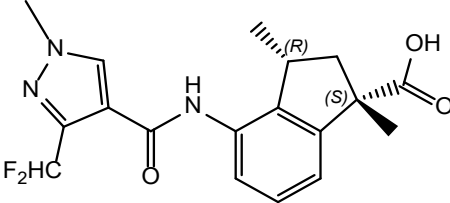
Chemical Name	Alt Name	Code	Structure	Found in?
				<p>Rotated lettuce, radish and sorghum</p> <p>NOR: Hen liver, egg and fat</p>
3-(difluoromethyl)- <i>N</i> -((1 <i>R</i> ,3 <i>S</i>)-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -inden-4-yl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	1'-CH ₂ OH-S-2840A	-		<p>Rat</p> <p>Rat, dog and human microsomes</p> <p>NOR: Soybean hay</p> <p>Rice plant, straw, hulls and grain</p> <p>Potato tuber</p> <p>Rotated lettuce, radish and sorghum</p>

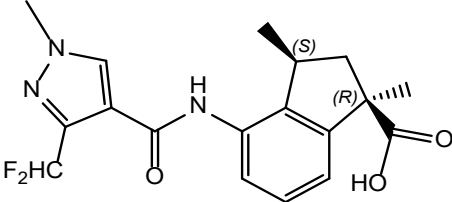
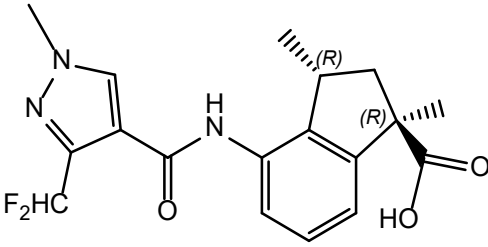
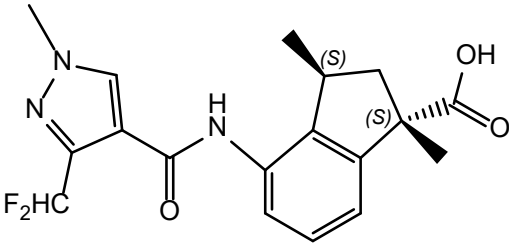
Chemical Name	Alt Name	Code	Structure	Found in?
3-(difluoromethyl)- <i>N</i> -((1 <i>S</i> ,3 <i>R</i>)-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -inden-4-yl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	1'-CH ₂ OH-S-2840A	-		<p>MOR: Wheat plant, straw and grain</p> <p>Barley plant, straw and grain</p> <p>Potato tuber</p> <p>Rotated wheat straw</p> <p>NOR: Hen egg, muscle and fat</p> <p>Goat liver, kidney, muscle, fat and milk</p>
3-(difluoromethyl)- <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -inden-4-yl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	1'-CH ₂ OH-S-2840B	-		<p>Rat</p> <p>Rat, dog and human microsomes</p> <p>NOR: Apple fruit</p>

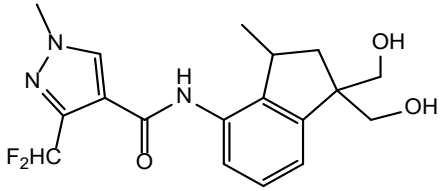
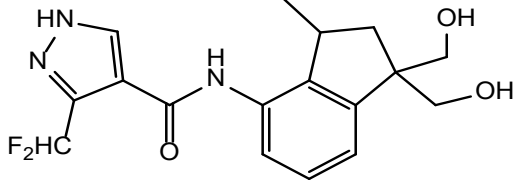
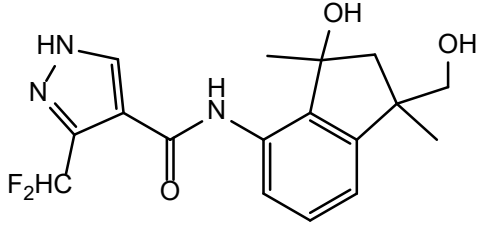
Chemical Name	Alt Name	Code	Structure	Found in?
3-(difluoromethyl)- <i>N</i> -((1 <i>S</i> ,3 <i>S</i>)-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -inden-4-yl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	1'-CH ₂ OH-S-2840B	-		<p>Soybean forage, hay, pods and seed</p> <p>Rice plant, straw, hulls and grain</p> <p>Potato tuber</p> <p>Rotated lettuce, radish and sorghum</p> <p>MOR: Wheat plant, straw and grain</p> <p>Barley plant, straw and grain</p> <p>Potato tuber</p> <p>Rotated wheat straw</p> <p>NOR: Hen egg, muscle and fat</p> <p>Goat liver, kidney, muscle, fat and milk</p> <p>MOR: Hen egg and liver</p> <p>Cow liver and kidney</p>

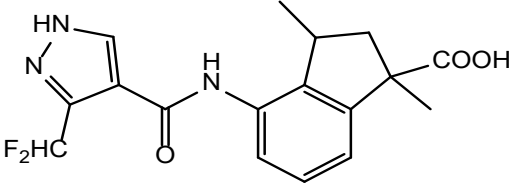
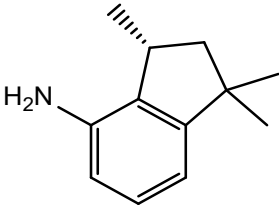
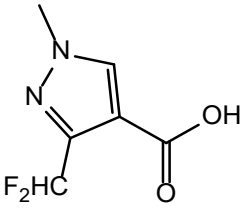
Chemical Name	Alt Name	Code	Structure	Found in?
(R)-3-(difluoromethyl)-N-(7-hydroxy-1,1,3-trimethyl-2,3-dihydro-1H-inden-4-yl)-1-methyl-1H-pyrazole-4-carboxamide	7'OH-S-239	-		Rat Rat, dog and human microsomes
3-(difluoromethyl)-N-((1R,3S)-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1H-inden-4-yl)-1H-pyrazole-4-carboxamide	N-des-Me-1'-CH ₂ OH-S-2840A	-		Rat Rat and human microsomes NOR: Rotated radish and sorghum
3-(difluoromethyl)-N-((1S,3R)-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1H-inden-4-yl)-1H-pyrazole-4-carboxamide	N-des-Me-1'-CH ₂ OH-S-2840A	-		MOR: Rotated wheat straw
3-(difluoromethyl)-N-((1R,3R)-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1H-inden-4-yl)-1H-pyrazole-4-carboxamide	N-des-Me-1'-CH ₂ OH-S-2840B			Rat Rat and human microsomes NOR: Rotated lettuce, radish and sorghum
3-(difluoromethyl)-N-((1S,3S)-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1H-inden-4-yl)-1H-pyrazole-4-carboxamide	N-des-Me-1'-CH ₂ OH-S-2840B			MOR: Rotated wheat straw

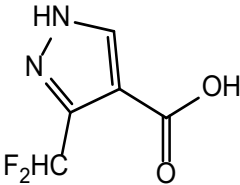
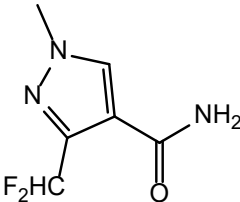
Chemical Name	Alt Name	Cod e	Structure	Found in?
Glucuronide of <i>N</i> -[(1 <i>RS</i> ,3 <i>RS</i> ;1 <i>RS</i> ,3 <i>S</i> <i>R</i>)-2,3-dihydro-1,3-dimethyl-1-(hydroxymethyl)-1 <i>H</i> -inden-4-yl)]-3-(difluoromethyl)-1 <i>H</i> -pyrazole-4-carboxamide	glucuronide of <i>N</i> -des-Me-1'-CH ₂ OH-S-2840	-		Rat
3-(difluoromethyl)- <i>N</i> -(3-hydroxy-1,1,3-trimethyl-2,3-dihydro-1 <i>H</i> -inden-4-yl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	3'-OH-S-2840	-		Soil (aerobic) Water/sediment Aqueous photolysis Rat Rat, dog and human microsomes NOR: Apple fruit Soybean forage, hay, pods and seed Rice plant, straw, hulls and grain Potato tuber Rotated lettuce, radish and sorghum MOR: Wheat plant and straw

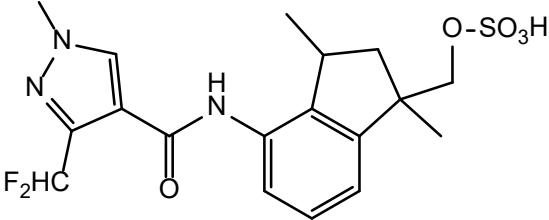
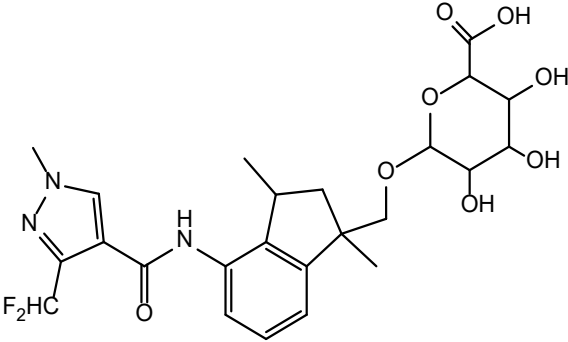
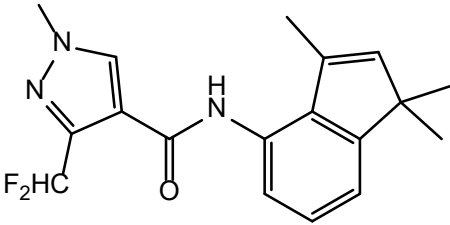
Chemical Name	Alt Name	Cod e	Structure	Found in?
				<p>Barley plant, straw and grain</p> <p>Potato tuber</p> <p>Rotated wheat straw</p> <p>NOR: Hen egg and fat</p> <p>Goat kidney and fat</p>
<i>N</i> -[(1 <i>RS</i> ,3 <i>RS</i> ;1 <i>RS</i> ,3 <i>S</i> <i>R</i>)-2,3-dihydro-1,3-dimethyl-3-hydroxy-1-(hydroxymethyl)-1 <i>H</i> -inden-4-yl)]-1-methyl-3-(difluoromethyl)-1 <i>H</i> -pyrazole-4-carboxamide	1'-CH ₂ OH-3'-OH-S-2840	-		<p>Rat</p> <p>Rat microsomes</p>
Glucuronide of <i>N</i> -[(1 <i>RS</i> ,3 <i>RS</i> ;1 <i>RS</i> ,3 <i>S</i> <i>R</i>)-2,3-dihydro-1,3-dimethyl-3-hydroxy-1-(hydroxymethyl)-1 <i>H</i> -inden-4-yl)]-1-methyl-3-(difluoromethyl)-1 <i>H</i> -pyrazole-4-carboxamide	glucuronide of 1'-CH ₂ OH-3'-OH-S-2840	-		Rat
(1 <i>S</i> ,3 <i>R</i>)-4-(3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamido)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -indene-1-carboxylic acid	1'-COOH-S-2840A	-		<p>Soil (aerobic)</p> <p>Water/sediment</p> <p>Rat</p>

Chemical Name	Alt Name	Code	Structure	Found in?
(1 <i>R</i> ,3 <i>S</i>)-4-(3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamido)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -indene-1-carboxylic acid	1'-COOH-S-2840A	-		<p>NOR: Potato tuber</p> <p>Rotated lettuce, radish and sorghum</p> <p>MOR: Wheat plant and straw</p> <p>Barley plant, straw and grain</p> <p>Potato tuber</p> <p>Rotated wheat straw</p> <p>NOR: Hen liver, egg, muscle, fat</p> <p>Goat liver, kidney, muscle, fat and milk</p>
(1 <i>R</i> ,3 <i>R</i>)-4-(3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamido)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -indene-1-carboxylic acid	1'-COOH-S-2840B			<p>Soil (aerobic)</p> <p>Water/sediment</p> <p>Rat</p> <p>NOR: Potato tuber</p>
(1 <i>S</i> ,3 <i>S</i>)-4-(3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamido)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -indene-1-carboxylic acid	1'-COOH-S-2840B	-		<p>Rotated lettuce, radish and sorghum</p> <p>MOR: Wheat plant and straw</p>

Chemical Name	Alt Name	Code	Structure	Found in?
				<p>Barley plant, straw and grain</p> <p>Rotated wheat straw</p> <p>NOR: Hen liver, egg, muscle, fat</p> <p>Goat liver, kidney, muscle, fat and milk</p> <p>MOR: Hen liver</p>
<i>N</i> -(1,1-bis(hydroxymethyl)-3-methyl-2,3-dihydro-1 <i>H</i> -inden-4-yl)-3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	1',1'-bis(CH ₂ OH)-S-2840	-		<p>Rat</p> <p>NOR: Goat kidney</p>
<i>N</i> -(1,1-bis(hydroxymethyl)-3-methyl-2,3-dihydro-1 <i>H</i> -inden-4-yl)-3-(difluoromethyl)-1 <i>H</i> -pyrazole-4-carboxamide	N-des-Me-1',1'-bis(CH ₂ OH)-S-2840	-		Rat
3-(difluoromethyl)- <i>N</i> -(3-hydroxy-1-(hydroxymethyl)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -inden-4-yl)-1 <i>H</i> -pyrazole-4-carboxamide	N-des-Me-1'-CH ₂ OH-3'-OH-S-2840	-		Rat

Chemical Name	Alt Name	Code	Structure	Found in?
4-(3-(difluoromethyl)-1 <i>H</i> -pyrazole-4-carboxamido)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -indene-1-carboxylic acid	N-des-Me-1'-COOH-S-2840	-		Rat
(<i>R</i>)-1,1,3-trimethyl-2,3-dihydro-1 <i>H</i> -inden-4-amine	ATMI	-		Water sediment
3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxylic acid	DFPA	-		Soil (aerobic) Water/sediment Aqueous photolysis NOR: Rice plant, straw, hulls and grain Potato tuber Rotated lettuce, radish and sorghum MOR: Wheat plant and straw Barley plant, straw and grain Potato tuber

Chemical Name	Alt Name	Cod e	Structure	Found in?
3-(difluoromethyl)-1 <i>H</i> -pyrazole-4-carboxylic acid	N-des-Me-DFPA	-		<p>Soil (aerobic)</p> <p>NOR: Soybean pods and seed (sugar conjugate) Potato tuber Rotated lettuce, radish and sorghum</p> <p>MOR: Wheat plant and straw Barley plant, straw and grain</p>
3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamide	DFPA-CONH ₂			<p>Aqueous photolysis</p> <p>NOR: Rice plant, straw, hulls and grain</p> <p>Rotated lettuce, radish and sorghum</p> <p>MOR: Wheat plant and straw</p> <p>Barley plant and straw</p> <p>NOR: Hen egg and muscle</p> <p>Goat liver, muscle and milk</p>

Chemical Name	Alt Name	Code	Structure	Found in?
(4-(3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamido)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -inden-1-yl)methyl hydrogen sulfate	1'-CH ₂ OH-S-2840-sulfate	-		NOR: Hen liver, egg, muscle and fat
6-((4-(3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazole-4-carboxamido)-1,3-dimethyl-2,3-dihydro-1 <i>H</i> -inden-1-yl)methoxy)-3,4,5-trihydroxytetrahydro-2 <i>H</i> -pyran-2-carboxylic acid	Glu-1'-CH ₂ OH-S-2840	-		Rat NOR: Goat liver, kidney and muscle
3-(difluoromethyl)-1-methyl- <i>N</i> -(1,1,3-trimethyl-1 <i>H</i> -inden-4-yl)-1 <i>H</i> -pyrazole-4-carboxamide	3'-OH-S-2840-dehydrate	-		Soil (aerobic) Buffer solution (simulated processing; pasteurization, baking/brewing/boiling, sterilization)

NOR: nature of residue (metabolism) study

MOR: magnitude of residue (field trial/feeding) study

3.4.2. Guidance documents uses in this assessment

Non-dietary human exposure

- EFSA (2014). 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.

- EFSA (2022). Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products, EFSA Journal 2022;20(1):7032.

Ecotoxicology

Birds & Mammals:

- EFSA (2009). Guidance document on risk assessment for birds and mammals. EFSA Journal 2009;7(12):1438

Aquatic Organisms:

- EFSA (2013). Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290
- SANCO/3268/2001 rev.4 final (2002). Guidance Document on Aquatic Ecotoxicology in the context of the Directive 91/414/EEC

Guidance for the identification of endocrine disruptors:

- European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC), (2018). Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal, 16(6), e05311.

Bees/Soil organisms/Non-target plants:

- SANCO/10329/2002 (rev 2 final). Guidance document on terrestrial ecotoxicology under council directive 91/414/EEC.

Non-target arthropods:

- ESCORT 2 (Candolfi et al., 2001). Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods.

Residues

- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in crops. No. 501, OECD, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in rotational crops. No 502, Paris 2007.

- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in livestock, No. 503, OECD, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Residues in rotational crops (limited field studies). No 504, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Residues in livestock. No 505, Paris 2007.
- OECD, 2007. OECD Guidelines for the testing of chemicals – Stability of pesticide residues in stored commodities. No 506, OECD, Paris 2007.
- OECD, 2007. OECD Guidelines for the testing of chemicals – Nature of the pesticide residues in processed commodities, high temperature hydrolysis. No 507, Paris 2007.
- OECD, 2008. OECD Guidelines for the testing of chemicals – Magnitude of pesticide residues in processed commodities. No 508, Paris 2008.
- OECD, 2009. OECD Guidelines for the testing of chemicals – Crop field trial. No 509, 2009 and 2021 update.
- OECD, 2009, Guidance document on the definition of residue, (ENV/JM/MONO(2009)30), Series on testing and assessment No. 63 and Series on pesticides No. 31
- OECD, 2008, Guidance document on magnitude of pesticide residues in processed commodities, (ENV/JM/MONO(2008)23), Series on testing and assessment No. 96
- OECD, 2016, Guidance document on crop field trials, (ENV/JM/MONO(2011)50/REV1), Series on testing and assessment No. 164 and Series on pesticides No. 66
- OECD, 2018, Guidance document on residues in rotational crops, (ENV/JM/MONO(2018)9), Series on testing and assessment No. 279 and Series on pesticides No. 97
- Estimation of animal intakes and HR, STMR and MRL calculations for products of animal origin, EFSA, September 2015
- EFSA guidance on the 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)

- EFSA, 2018, Recommendations on the use of the proportionality approach in the framework of risk assessment for pesticide residues
- EFSA , 2019, Guidance of EFSA on risk assessments for active substances of plant protection products that have stereoisomers as components or impurities and for transformation products of active substances that may have stereoisomers

3.5. Reference List

To be completed at a later stage.

None.

Further information

For information about health and safety, or to report inconsistencies or inaccuracies in this guidance, visit www.hse.gov.uk.

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