MCL Report for:

3-(difluoromethyl)-1-methyl-*N*-[(3*R*)-1,1,3-trimethyl-2,3-dihydro-1*H*-inden-4-yl]pyrazole-4-carboxamide; inpyrfluxam (ISO)

Proposal for mandatory classification and labelling (MCL) based on Annex VI, Part 2 of the retained CLP Regulation (EU) No. 1272/2008 as amended for Great Britain

EC Number: -

CAS Number: 1352994-67-2

May 2026

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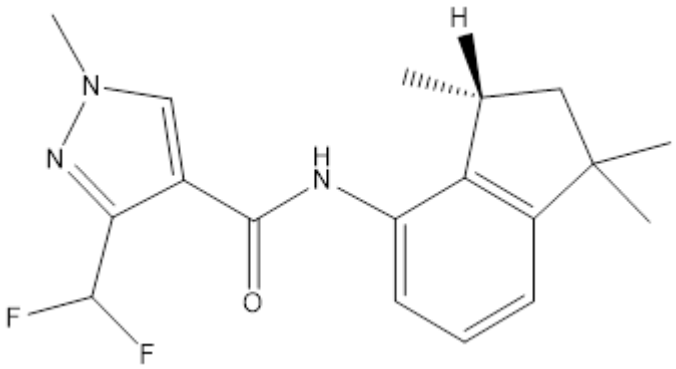
Identity of the substance

Name and other identifiers of the substance

Table 1. Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	3-(difluoromethyl)-1-methyl-*N*-[(3*R*)-1,1,3-trimethyl-2,3-dihydro-1*H*-inden-4-yl]-1*H*-pyrazole-4-carboxamide
Other names (usual name, trade name, abbreviation)	S-2399
ISO common name (if available and appropriate)	Inpyrfluxam
EC number (if available and appropriate)	-
EC name (if available and appropriate)	-
CAS number (if available)	1352994-67-2
Other identity code (if available)	CIPAC: 1005
Molecular formula	$C_{18}H_{21}F_2N_3O$
Structural formula	
SMILES notation (if available)	Not available
Molecular weight or molecular weight range	333.38 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	N/A
Description of the manufacturing process and identity of the source (for UVCB substances only)	N/A

Degree of purity (%) (if relevant for the entry in Annex VI)	N/A

1.1 Composition of the substance

Table 1: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current MCL on GB MCL list (if applicable)
N/A (Confidential)		

Table 2: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current MCL on GB MCL list (if applicable)	The impurity contributes to the classification and labelling?
N/A (Confidential)			

Table 3: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current MCL on GB MCL list (if applicable)	The additive contributes to the classification and labelling?
N/A (Confidential)				

2. Proposed mandatory classification and labelling

Table 5: Proposed mandatory classification and labelling according to the GB CLP criteria

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current GB MCL list entry	No Current GB MCL list entry										
Proposed Classification	TBD	3-(difluoromethyl)-1-methyl-*N*-[(3*R*)-1,1,3-trimethyl-2,3-dihydro-1*H*-inden-4-yl]pyrazole-4-carboxamide; inpyrfluxam (ISO)		1352994-67-2	Acute Tox. 3 Aquatic Acute 1 Aquatic Chronic 1	H301 H400 H410	Dgr GHS06 GHS09	H301 H400 H410		ATE = 180 mg/kg bw M-factor = 10 M-factor = 10	
Resulting entry on GB MCL list	TBD	3-(difluoromethyl)-1-methyl-*N*-[(3*R*)-1,1,3-trimethyl-2,3-dihydro-1*H*-inden-4-yl]pyrazole-4-carboxamide; inpyrfluxam (ISO)		1352994-67-2	Acute Tox. 3 Aquatic Acute 1 Aquatic Chronic 1	H301 H400 H410	Dgr GHS06 GHS09	H301 H400 H410		ATE = 180 mg/kg bw M-factor = 10 M-factor = 10	

TBD: to be determined

Table 6: Reason for not proposing mandatory classification and status under public consultation

Hazard class	Classification / reason for no classification	Within the scope of public consultation
Explosives	No classification, data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Hazard class not applicable	No
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Hazard class not applicable	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	No classification, data conclusive but not sufficient for classification	Yes
Self-reactive substances	No classification, data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	No classification, data conclusive but not sufficient for classification	Yes
Self-heating substances	No classification, data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	No classification, data conclusive but not sufficient for classification	Yes
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	No classification, data conclusive but not sufficient for classification	Yes
Organic peroxides	No classification, data conclusive but not sufficient for classification	Yes
Corrosive to metals	Not assessed	No
Acute toxicity via oral route	Acute Tox. 3; H301 (ATE = 180 mg/kg bw)	Yes
Acute toxicity via dermal route	No classification, data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	No classification, data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	No classification, data conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	No classification, data conclusive but not sufficient for classification	Yes
Respiratory sensitisation	No classification, data lacking	Yes
Skin sensitisation	No classification, data conclusive but not sufficient for classification	Yes
Germ cell mutagenicity	No classification, data conclusive but not sufficient for classification	Yes
Carcinogenicity	No classification, data conclusive but not sufficient for classification	Yes
Reproductive toxicity	No classification, data conclusive but not sufficient for classification	Yes

Hazard class	Classification / reason for no classification	Within the scope of public consultation
Specific target organ toxicity-single exposure	No classification, data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-repeated exposure	No classification, data conclusive but not sufficient for classification	Yes
Aspiration hazard	No classification, data lacking	Yes
Hazardous to the aquatic environment	Aquatic Acute 1; H400 (M=10)	Yes
Hazardous to the ozone layer	Aquatic Chronic 1; H410 (M=10)	Yes

3. History of the classification and labelling

Inpyrfluxam is a new pesticidal active substance in Great Britain (GB) under Regulation (EC) 1107/2009 as it has effect in Great Britain (hereinafter referred to as Regulation 1107/2009).

Inpyrfluxam does not have an existing entry on the GB mandatory classification and labelling (MCL) list or on Annex VI of EU CLP. However, in the EU, a harmonised classification and labelling (CLH) dossier has been submitted to ECHA by the Netherlands. The legal deadline for the EU Risk Assessment Committee to adopt an opinion on the classification is 21st August 2027.

In the EU, notifiers have submitted self-classifications for this substance to ECHA's Classification and Labelling Inventory[1]. A breakdown of these notifications is provided below:

39 notifiers have classified the substance as Aquatic Acute 1 (H400) with an M-factor of 10 and Aquatic Chronic 1 (H410) with an M-factor of 10.

1 notifier has additionally classified the substance as Acute Tox. 3 (H301) and indicated vPvM properties (EUH451) alongside the environmental hazards.

1 notifier has classified the substance as Acute Tox. 4 (H302), Skin Irrit. 2 (H315), Eye Irrit. 2 (H319) and STOT SE 3 (H335).

[1] Available at https://echa.europa.eu/home

4. Justification that action is needed

Inpyrfluxam is a new pesticidal active substance in the meaning of Regulation EC 1107/2009 and, as such, shall normally be subject to the mandatory classification and labelling process in GB in accordance with Article 36 (2) and Article 37A of the retained CLP Regulation (EC) NO. 1272/2008 as amended for Great Britain (hereafter referred to as GB CLP). This report has been prepared by technical experts at HSE, acting in its capacity as the GB CLP Agency (hereinafter referred to as “the Agency”), with support from the Environment Agency.

5. Identified uses

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.

6. Data sources

This MCL report relies exclusively on the data submitted in the context of the application for approval as an active substance under Regulation (EC) 1107/2009 as it applies in Great Britain.

Draft assessment report – DAR – Volume 3, Annex B.1; Identity of the Active Substance - 2026

Draft assessment report – DAR – Volume 3, Annex B.2; Physical & Chemical Properties – 2026

Draft assessment report – DAR – Volume 3, Annex B.4; Further Information - 2026

Draft assessment report – DAR – Volume 3, Annex B.5; Methods of Analysis - 2026

Draft assessment report – DAR – Volume 3, Annex B.6; Toxicology & Metabolism Data – 2026

Draft assessment report – DAR – Volume 3, Annex B.7; Residue Data – 2026

Draft assessment report – DAR – Volume 3, Annex B.8; Environmental Fate – 2026

Draft assessment report – DAR – Volume 3, Annex B.9; Ecotoxicology Data – 2026

Draft assessment report – DAR – Volume 4; Confidential information – 2026

At the time of preparation of this report, there was no REACH registration dossier for inpyrfluxam (April 2026)

7. Physicochemical properties

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g., measured or estimated)
Physical state at 20°C and 101,3 kPa	**Pure (PAI):** Beige solid, granular form (25 °C). **Technical (TGAI):** White solid, powder form (20 °C).	Butler (2015) Study report number: 41304120 (TPP-0006) Woolley (2015) Study report number: 41304529 (TPP-0007)	Visual inspection (EPA/OCSPP 830.6302/6303).
Melting/freezing point	Inpyrfluxam (PAI): 104 °C.	Walker, J. A. (2016) Study report number: 41501169 (TPP-0010)	OECD TG 102 (Capillary tube method); EC Method A.1; EPA/OCSPP 830.7200.
Boiling point	The boiling point of inpyrfluxam was not determinable; the test item decomposed on heating from approximately 237 °C.	Walker, J. A. (2016) Study report number: 41501169 (TPP-0010)	OECD TG 103, (Siwoloboff method), EPA/OCSPP 830.7220
Relative density	1.24 at 20 °C (PAI); 1.23 at 20 °C (TGAI).	Walker, J. A. (2016) Study report number: 41501169 Walker, J. A. (2016) Study report number: 41501170 (TPP-0012)	OECD TG 109; (Gas comparison pycnometer method)
Vapour pressure	Vapour pressure (calculated by extrapolation from vapour pressure curve): 3.81 × 10^{-8} Pa at 20 °C; 1.20 × 10^{-7} Pa at 25 °C.	Butler, R. E. (2014) Study report number: 41304332 (TPP-0003)	OECD TG 104 (Vapour pressure balance); EC Method A.4; EPA/OCSPP 830.7950. Purity: 99.9% (PAI).

Property	Value	Reference	Comment (e.g., measured or estimated)
Surface tension	60.4 mN/m at 21.3 ± 0.5 °C (90 % saturated solution).	Walker, J. A. (2016) Study report number: 41501169 (TPP-0010)	OECD TG 115; Ring method. Not surface active.
Water solubility	1.64 × 10^{-2} g/L at 20 °C (pH 5.5–5.8).	O'Connor, B. J. (2013) 41303367 (TPP-0001)	OECD TG 105 (flask method); EC Method A.6; EPA/OCSPP 830.7840. Moderately soluble.
Partition coefficient n-octanol/water	Log Pow = 3.65 at 25 °C (pH 7.1–7.3).	O'Connor, B. J. (2013) Study report number: 41303719 (TPP-0002)	OECD TG 107 (flask method); EC Method A.8; EPA/OCSPP 830.7550.
Flash point	No data available.	-	Not considered as inpyrfluxam does not have a melting point below 40 °C.
Flammability	Inpyrfluxam failed to ignite during application of the test flame and is not highly flammable.	Tremain, S. P. (2017) Study report number: XR24YD (TPP-0024)	EC Test A.10. Not classified as a flammable solid.
Explosive properties	Explosive properties cannot be concluded; existing data are not acceptable.	Tremain (2017) Study report number: XR24YD (TPP-0024); Walker (2016) Study report number: 41501170 (TPP-0012)	UN RTDG App. 6 (theoretical) and EC Test A.14. Presence of contiguous N atoms (pyrazole ring) prevents negative conclusion. Additional data expected November 2025.
Self-ignition temperature	No relative self-ignition temperature observed up to 114 °C.	Tremain, S. P. (2017) Study report number: XR24YD (TPP-0024)	EC Test A.16. Not classified as a self-heating substance.
Oxidising properties	Not oxidizing.	Tremain (2017) XR24YD (TPP-0024)	UN RTDG App. 6 (theoretical). Not classified as oxidising solid.
Granulometry	No data available.	-	-

Property	Value	Reference	Comment (e.g., measured or estimated)
Stability in organic solvents and identity of relevant degradation products	Inpyrfluxam was readily soluble in acetone, dichloromethane, ethyl acetate, methanol, toluene and n-octanol, and moderately soluble in n-hexane at 20 °C.	Walker, J. A. (2016) 41501170 (TPP-0012)	OECD TG 105
Dissociation constant	No dissociation observed in the pH range 1–12.	Butler, R. E. (2014) 41304121 (TPP-0005)	Based on UV-Visible spectra; dissociation not triggered.
Viscosity	No data available.	-	-

8. Evaluation of physical hazards

8.1 Explosives

Table 8: Summary of studies on explosive properties

Method	Results	Remarks	Reference
UN RTDG Appendix 6 (theoretical estimation)	Applicant predicted negative explosive properties based on oxygen balance (< −200).	Not acceptable. Presence of contiguous nitrogen atoms (pyrazole ring) prevents a negative conclusion based on theory alone.	Tremain, S. P. (2017); XR24YD
EC Test A.14 (DSC / BAM fall hammer)	CTS determined as 230 °C. No explosion or ignition observed in BAM fall hammer tests.	Not acceptable. Onset and exothermic decomposition temperatures not determined.	Walker, J. A. (2016); 41501170
Differential scanning calorimetry	The onset of exothermic decomposition was 137.9 and 373.3 °C. The total decomposition energy was 309.9 J. g^{-1}	Acceptable Not classified as an explosive substance because the onset of exothermic decomposition was <500 °C and the total decomposition energy was <500 J. g-1.	Younis, S. (2025) Report No: TPP-0061

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

Inpyrfluxam (technical grade) has been assessed for explosive properties using theoretical considerations (UN RTDG Appendix 6), experimental testing (EC Test A.14) and differential scanning calorimetry. The theoretical assessment was not accepted due to the

presence of contiguous nitrogen atoms within the pyrazole ring, which is a structural alert for explosive properties. Experimental testing did not observe explosion or ignition; however, the data were considered insufficient as key parameters, including exothermic decomposition temperature and onset of decomposition, were not determined. Therefore, differential scanning calorimetry was performed which showed that the onset of exothermic decomposition was 137.9 and 373.3 °C. The total decomposition energy was 309.9 J. g^{-1}

8.1.2 Comparison with the GB CLP criteria

Not classified as an explosive substance as the onset of exothermic decomposition was <500 °C and the total decomposition energy was <500 J. g^{-1}.

8.1.3 Conclusion on classification and labelling for explosive properties

Not classified – data conclusive but not sufficient for classification.

8.2 Flammable solids

Table 9: Summary of studies on solids

Method	Results	Remarks	Reference
EC Test A.10	Inpyrfluxam failed to ignite during two minutes of flame application and was not highly flammable.	Not classified as a flammable solid.	Tremain, S. P. (2017); XR24YD

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

Inpyrfluxam (technical grade) was tested for flammability using EC Method A.10. The substance did not ignite during application of the test flame and did not sustain combustion.

8.2.2 Comparison with the GB CLP criteria

Inpyrfluxam does not meet the criteria for classification as a flammable solid under GB CLP.

8.2.3 Conclusion on classification and labelling for flammable solids

Not classified – data conclusive but not sufficient for classification.

8.3 Self-reactive substances

Table 10: Summary of studies on self-reactivity

Method	Results	Remarks	Reference
EC Test A.14 / thermal stability (DSC)	No shock sensitivity observed. Decomposition occurred from ~250 °C.	No evidence of self-reactive behaviour.	Walker, J. A. (2016); 41501169

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

Inpyrfluxam was assessed using data from explosive and thermal stability studies. No shock sensitivity was observed and decomposition occurred only at elevated temperatures. No chemical groups associated with self-reactive substances (such as peroxides or azo groups) are present.

8.3.2 Comparison with the GB CLP criteria

Inpyrfluxam is not thermally unstable under normal conditions of use and does not undergo self-accelerating decomposition.

8.3.3 Conclusion on classification and labelling for self-reactive substances

Not classified – data conclusive but not sufficient for classification.

8.4 Pyrophoric solids

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

Experience in handling and use of inpyrfluxam indicates that it does not ignite spontaneously on contact with air. No ignition was observed during flammability testing.

8.4.2 Comparison with the GB CLP criteria

Inpyrfluxam does not ignite within five minutes of exposure to air and therefore does not meet the criteria for a pyrophoric solid.

8.4.3 Conclusion on classification and labelling for pyrophoric liquids/solids

Not classified – data conclusive but not sufficient for classification.

8.5 Self-heating substances

Table 11: Summary of studies on self-heating substances

Method	Results	Remarks	Reference
EC Test A.16	No relative self-ignition temperature observed up to 114 °C.	Not classified as a self-heating substance.	Tremain, S. P. (2017); XR24YD

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

Inpyrfluxam was tested using EC Method A.16. No self-heating behaviour or ignition was observed up to 114 °C.

8.5.2 Comparison with the GB CLP criteria

Inpyrfluxam does not meet the criteria for classification as a self-heating substance.

8.5.3 Conclusion on classification and labelling for self-heating substances

Not classified – data conclusive but not sufficient for classification.

8.6 Substances which in contact with water emit flammable gases

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

Inpyrfluxam does not contain metals or metalloids and no gas evolution was observed during water contact or chemical incompatibility testing.

8.6.2 Comparison with the GB CLP criteria

The classification procedure for this hazard class does not apply.

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

Not classified – data conclusive but not sufficient for classification.

8.7 Oxidising solids

Table 12: Summary of studies on oxidising solids

Method	Results	Remarks	Reference
UN RTDG Appendix 6 (theoretical)	Oxidising properties predicted negative.	Not classified as an oxidising solid.	Tremain, S. P. (2017); XR24YD

8.7.1 Short summary and overall relevance of the provided information on oxidising liquids/solids

Inpyrfluxam was assessed for oxidising properties using theoretical considerations. Although oxygen and fluorine atoms are present, these are bonded only to carbon atoms and do not confer oxidising behaviour.

8.7.2 Comparison with the GB CLP criteria

Inpyrfluxam does not cause or enhance combustion and does not meet the criteria for an oxidising solid.

8.7.3 Conclusion on classification and labelling for liquids/solids

Not classified – data conclusive but not sufficient for classification.

8.8 Organic peroxides

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

Inpyrfluxam does not contain the bivalent –O–O– structure required for classification as an organic peroxide.

8.8.2 Comparison with the GB CLP criteria

Inpyrfluxam does not meet the criteria for classification as an organic peroxide.

8.8.3 Conclusion on classification and labelling for organic peroxides

Not classified – data conclusive but not sufficient for classification.

8.9 Corrosive to metals

Not assessed.

9. Toxicokinetics (absorption, metabolism, distribution and elimination)

The absorption, distribution, metabolism, and excretion (ADME) profile and plasma kinetics of inpyrfluxam have been evaluated in rats by the oral route in two studies: one conducted with a single administration and the other with repeated administration for 14 days. In addition, two *in vitro* metabolism studies were performed to compare the metabolic fate of inpyrfluxam across species.

For the *in vivo* investigations, radiolabelled test material was used in some experiments, employing either [pyrazolyl-4-14C]-inpyrfluxam or [phenyl-14C]-inpyrfluxam. The positions of the radiolabels on the pyrazolyl and phenyl moieties are illustrated in Figures 1 and 2 below.

Figure 1: Location of radiolabel in [pyrazolyl-4-^{14}C] labelled inpyrfluxam molecules.

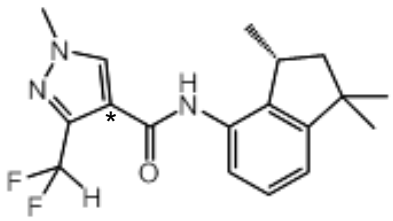


Figure 2: Location of radiolabel in [phenyl-^{14}C] labelled inpyrfluxam

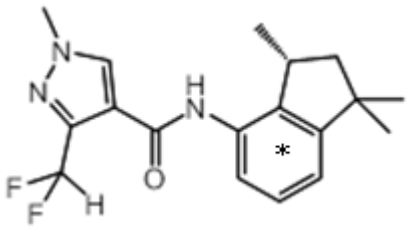


Table 13: Summary of toxicokinetic studies

Method	Results	Remarks	Reference
ADME study OECD TG 417 (2010) GLP Test substance: - [pyrazolyl-14C] inpyrfluxam, Lot CFQ41802, purity ≥98.4% - [phenyl-14C] inpyrfluxam, Lot CFQ41473, purity ≥99.3% - Unlabelled inpyrfluxam (S-2399 A.S.), Lot YT3424G, purity 99.9%, optical isomer ratio 100% Doses: 1 mg/kg bw and 150 mg/kg bw by oral gavage (single dose) Wistar Hannover rats (males and females, groups of 4–12 depending on experiment, with bile-duct cannulated rats used in one arm)	**Absorption:** In bile-cannulated rats, oral absorption estimated at 96% administered dose (AD) at 1 mg/kg bw (urine + bile + carcass). Absorption rapid (Tmax 1 h at 1 mg/kg; 8–24 h at 150 mg/kg). No evidence of saturation at high dose. **Distribution:** Radioactivity widely distributed. Highest levels in liver, kidney, adrenal, heart. At 1 mg/kg, tissue Tmax 0.25–1 h; half-lives 2–8 h. At 150 mg/kg, Tmax 1–8 h; half-lives 7–48 h. No bioaccumulation. Carcass residues ≤0.2% AD at 168 h. **Metabolism:** Extensively metabolised. 43–44 metabolites detected, 12 identified/quantified (incl. 2 glucuronides). Main pathways: N-demethylation, oxidation of 1′,1′-dimethyl group of indane ring → hydroxymethyl and carboxylic acid derivatives; glucuronidation. Minor hydroxylation (3′, 7′). Major urinary metabolites: 1′-COOH-S-2840, N-desMe-1′-COOH-S-2840 (>10% AD). Parent detected only in low amounts in faeces. **Excretion:** Elimination rapid and complete (>90% AD in 2–3 d; >67% in 24 h). Excretion via urine (49–61% AD) and faeces (39–48% AD), with significant biliary contribution (47–69% AD). No excretion via expired air. Enterohepatic recirculation evident.	Acceptable	KCA 5.1.1/01, Anonymous (2016a)

Method	Results	Remarks	Reference
Repeated exposure ADME study OECD TG 417 (2010) GLP: Yes Wistar Hannover rats. Oral gavage of [pyrazolyl-4-^{14}C] inpyrfluxam at 1 mg/kg bw/day for 14 consecutive days. Radiolabelled inpyrfluxam (purity ≥98.4%, Lot CFQ41802); unlabelled inpyrfluxam (purity 99.9%, Lot YT3424G). Males (n=6–7) and females (n=5–6); 4/sex/group analysed.	**Absorption:** Tmax reached at 1 h in males (Cmax 0.198 µg eq./g) and 2 h in females (Cmax 0.214 µg eq./g). Elimination half-lives were 12 h (males) and 9 h (females). AUC values were 2.04 and 2.10 µg eq·h/g in males and females, respectively. Blood/plasma ratios 0.8–1.7; no clear sex differences. **Distribution:** Low tissue levels 7 days post-dosing; highest in liver (0.035 ppm in males, 0.020 ppm in females). Total residues 0.2% AD (males) and 0.1% AD (females); carcass 0.1% AD in both sexes. No evidence of bioaccumulation. **Metabolism:** Inpyrfluxam extensively metabolised. 12 metabolites (incl. 2 conjugates) identified. Major urinary metabolites: 1′-COOH-S-2840 (14–15% AD), N-desMe-1′-COOH-S-2840 (≤3.1% AD). Major faecal metabolites: N-desMe-1′-CH_2OH-S-2840 (≤10% AD), 1′-CH_2OH-3′-OH-S-2840, glucuronide of 1′-CH_2OH-S-2399 (≤9.3% AD). Parent compound only in trace amounts in faeces. **Excretion:** Rapid and complete. >90% of AD excreted within 24 h post-dosing. Cumulative excretion: 94.7% AD in males (urine 33%, faeces 61.5%), 96.4% AD in females (urine 51.6%, faeces 44.8%). Slightly higher urinary elimination in females; no other sex differences.	Acceptable	KCA 5.1.1/02, Anonymous (2016b)

Method	Results	Remarks	Reference
***In vitro* metabolism study using rat (male and female) and human liver microsomes.** Guideline: Not conducted under OECD TG, but compared to EFSA PPR Panel Opinion (2021). GLP: Yes. Species/Strains: Rat (male and female) and human liver microsomes. Dose level: 10 µM Test Material radiolabelled: [pyrazolyl-4-14C] S-2399 ([pyrazolyl-4-14C] inpyrfluxam); Purity: ≥98.4%. Test Material unlabelled: S-2399 A.S (inpyrfluxam); Purity: 99.9%. incubation for 15 min in presence of NADPH.	**Extent of metabolism:** Inpyrfluxam was extensively metabolised, with 10 metabolites detected and 6 identified/quantified. **Major metabolites:** • 1'-CH2OH-S-2840: 36% of administered radioactivity (AR) in humans, 41% AR in male rats, 10% AR in female rats. • N-des-Me-S-2840: 29% AR in humans, 7% AR in male rats, 20% AR in female rats. **Minor metabolites:** N-des-Me-1'-CH2OH-S-2840 (5% AR humans, 5% AR male rats), 3'-OH-S-2840 (2% AR Humans, 10% AR male rats), 7'-OH-S-2399 (3% AR male rats, 1% AR humans), 1'-CH2OH-3'-OH-S-2840 (7% AR male rats only). **Unidentified metabolites:** Four detected only in male rats (6% AR). **Metabolic pathways:** N-demethylation and oxidation of the 1',1'-dimethyl group of the indane ring were the main reactions. Hydroxylation at the 3' and 7' positions of the indane ring occurred as minor reactions. Pathways were consistent between rat and human microsomes. No unique human metabolites were observed. Residual parent compound (S-2399) accounted for 27% AR in human, 21% AR in male rat, and 69% AR in female rat microsomes, indicating substantially lower metabolic turnover in females.	Acceptable	KCA 5.1.1/03, Anonymous (2017)

Method	Results	Remarks	Reference
In vitro metabolism study using dog (male and female) liver microsomes. GLP: Yes [pyrazolyl-4-14C] inpyrfluxam (≥98.4% purity), unlabelled inpyrfluxam (99.9% purity). 10 µM inpyrfluxam incubated with microsomes in presence of 3 mM NADPH (3 replicates). Positive control: [4-14C] testosterone (100 µM).	Inpyrfluxam was stable in buffer without microsomes (100% radioactivity after 15 min). After incubation, 59% AR (male) and 68% AR (female) remained as parent compound. **Major metabolites:** N-des-Me-S-2840 (19% AR males; 17% females) and 1'-CH2OH-S-2840 (16% AR males; 11% females). **Minor metabolites:** 3'-OH-S-2840 (3% AR males; not detected in females) and 7'-OH-S-2399 (4% AR males; 5% females). **Catalytic activity (Major Metabolities):** N-des-Me-S-2840 formed at 124 pmol/min/mg (males) and 113 pmol/min/mg (females); 1'-CH2OH-S-2840 at 105 pmol/min/mg (males) and 70 pmol/min/mg (females).	Acceptable	KCA 5.1.1/04, Anonymous (2018)

9.1 Short summary and overall relevance of the provided toxicokinetic information

The ADME profile of inpyrfluxam has been investigated in two *in vivo* studies in rats, with single and repeated oral administration of radiolabeled test material, including a bile-duct cannulation experiment. In addition, comparative *in vitro* metabolism studies were conducted using liver microsomes from rats, dogs and humans.

Absorption

In rats, absorption of inpyrfluxam from the gastrointestinal tract was rapid and essentially complete. Following a single oral dose at 1 mg/kg bw, plasma peak concentrations (Tmax) were achieved at 1 hour with a Cmax of 1.77 µg eq/g in males and 1.63 µg eq/g in females. At the higher dose of 150 mg/kg bw, Tmax was delayed to 8 hours, with Cmax values of 270 µg eq/g in males and 382 µg eq/g in females. The Cmax and AUC values increased linearly with dose, with no evidence of saturation. In bile-duct cannulated rats, oral absorption was determined to be 96% of the administered dose (AD) at 1 mg/kg bw, supporting the assignment of a default oral absorption value of 100%. Post-hepatic systemic availability was estimated at 60%, based on the fraction of dose excreted into bile within the first 6 hours. Repeated daily

dosing at 1 mg/kg bw confirmed rapid uptake, with Tmax values at 1 h in males and 2 h in females. No data are available for inhalation absorption, therefore a default value of 100% is applied. Dermal absorption, determined *in vitro* using the representative product S-2399 60 g/L EC, was 8.8% for the concentrate and 20% for the dilution.

Distribution

Inpyrfluxam and its metabolites were widely distributed to tissues, with higher concentrations in blood, plasma, liver, kidney, adrenal and heart. In the single dose study at 1 mg/kg bw, tissue Tmax values were observed between 0.25–1 hour, while at 150 mg/kg bw these were reached between 1–8 hours. Tissue elimination half-lives ranged from 2–8 h at the low dose and 7–48 h at the high dose. At 168 h post-dose, total radioactive residues in the carcass were low (0.1–0.2% AD), indicating limited retention. Plasma levels declined to near-background within 72 hours, with half-lives of 12–17 hours in both sexes. After repeated dosing for 14 days at 1 mg/kg bw, tissue residues remained very low (0.2% AD in males, 0.1% AD in females, 7 days after final administration), confirming no evidence of bioaccumulation.

Metabolism

Inpyrfluxam was extensively metabolised in both single- and repeat-dose rat studies. Twelve metabolites, including two conjugates, were identified and quantified. Major pathways included N-demethylation and oxidation of the 1′,1′-dimethyl group of the indane ring, yielding carboxylic acid derivatives, followed by glucuronidation. Minor metabolic routes involved hydroxylation at the 3′ and 7′ positions of the indane ring. In rats, the principal metabolites were 1′-COOH-S-2840 and N-desMe-1′-COOH-S-2840 in urine, and the glucuronide of 1′-CH2OH-S-2840 in bile. *In vitro* metabolism studies in human and dog liver microsomes demonstrated similar profiles, with no unique human metabolites identified.

Excretion

Elimination was rapid and largely complete across all studies. In the single-dose study, >67% AD was excreted within 24 hours and >90% within 2–3 days. Excretion occurred via urine (49–61% AD) and bile (47–69% AD), with faecal excretion accounting for 39–48% AD at 168 hours, much of which originated from biliary excretion. Enterohepatic recirculation was evident. In the repeated-dose study, elimination followed a similar pattern, with >90% AD excreted within 24 h after cessation of dosing, predominantly via urine (33–52% AD) and faeces (45–62% AD).

Toxicokinetic information from toxicodynamic studies

Additional toxicokinetic information supporting systemic absorption and exposure is available from repeated-dose toxicity studies in rats, dogs and mice, in which plasma concentrations of inpyrfluxam were measured.

In a 28-day dietary study in rats (500, 1000, 3000 and 5000 ppm; corresponding to 44.4, 85.9, 246.4 and 406.5 mg/kg bw/day in males and 47.4, 91.4, 263.0 and 377.8 mg/kg bw/day in females), plasma concentrations were determined at the end of treatment. Plasma levels were comparable at the two lower dose levels in both sexes, while a dose-related increase was observed in males from 85.9 mg/kg bw/day onwards. No clear dose-dependency was evident in females.

In a one-year oral toxicity study in dogs (0, 2, 6, 30 and 160 mg/kg bw/day), plasma concentrations were measured at multiple time points (pre-dose and up to 24 hours post-dose) on day 1 and at weeks 13, 26 and 52. Inpyrfluxam was detected in plasma at all dose levels except at 2 mg/kg bw/day, where concentrations were below the limit of quantification. Systemic exposure increased in a dose-dependent manner, with no apparent differences between males and females and no evidence of accumulation following repeated administration.

In a long-term study in rats (up to approximately 86.4 mg/kg bw/day in males and 95.9 mg/kg bw/day in females), plasma concentrations were measured at weeks 14, 26 and 51. Inpyrfluxam was detectable in females at all dose levels, whereas in males it was quantifiable only at the high dose. Plasma concentrations increased with dose in females, and at the highest dose levels, systemic exposure was higher in females than in males. No accumulation was observed following repeated dosing.

Similarly, in a long-term study in mice (up to approximately 826 mg/kg bw/day in males and 790 mg/kg bw/day in females), plasma concentrations measured at the end of treatment were detectable at mid and high dose levels but below the limit of quantification at the low dose. A dose-dependent increase in plasma levels was observed in both sexes, with higher concentrations in males at the highest dose. No evidence of accumulation was identified.

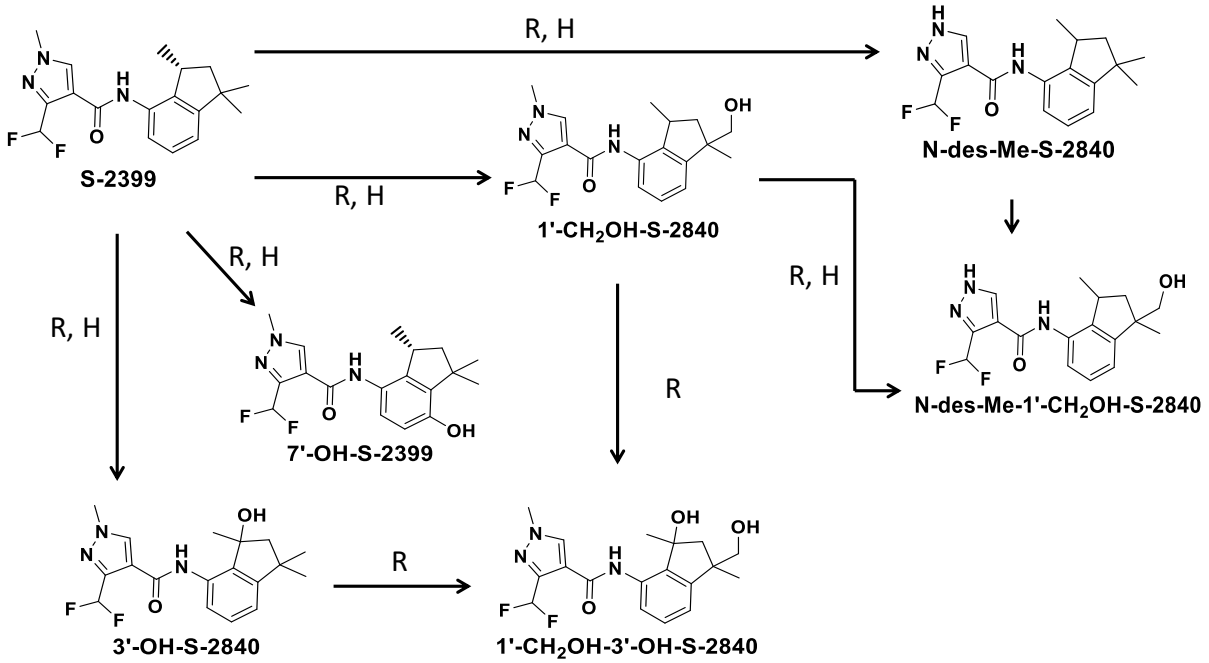
Overall, these data provide additional confirmation of systemic absorption, dose-dependent exposure, and the absence of bioaccumulation following repeated oral administration. No further toxicokinetic-specific information was identified from the available toxicodynamic studies.

Overall conclusion

Inpyrfluxam is rapidly and extensively absorbed following oral administration, with an estimated oral absorption of approximately 96% in rats based on bile-duct cannulation data; for risk assessment purposes a conservative oral absorption value of 100% is applied. Systemic availability post-hepatic first-pass metabolism was estimated at 60%. Dermal absorption values were 8.8% for the concentrate and 20% for the dilution, while inhalation absorption is conservatively set at 100%. The compound and its metabolites are widely distributed in tissues, with highest concentrations generally observed in the liver, kidney, adrenal glands and heart, but residues decline rapidly and no evidence of

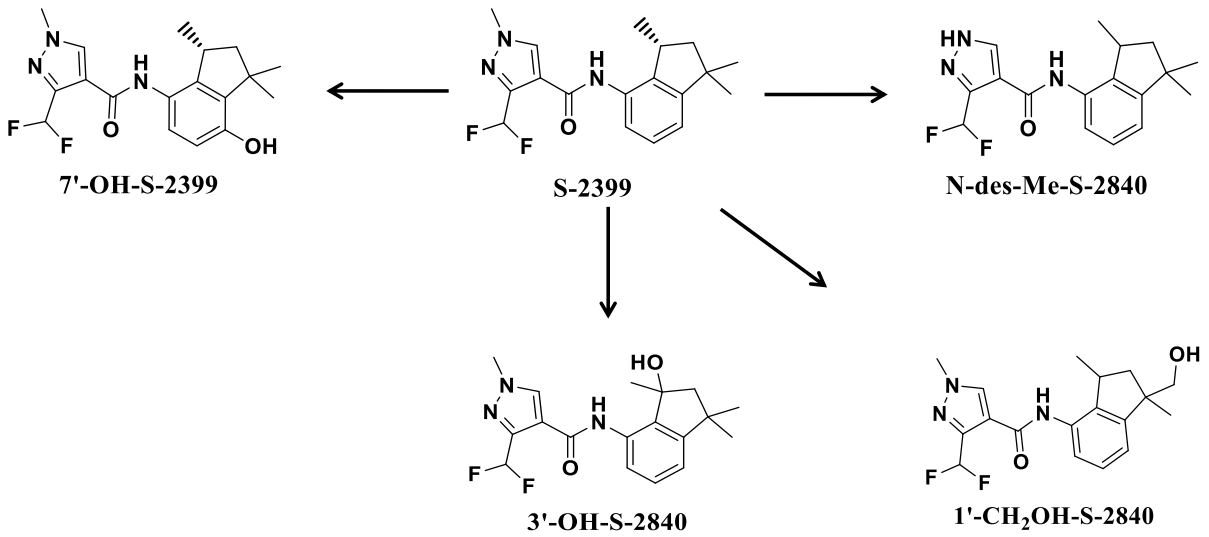
bioaccumulation was observed. Inpyrfluxam undergoes extensive metabolism involving N-demethylation, oxidation of the indane ring, and conjugation, with 43–44 metabolites detected, of which 12 were identified and/or quantified. Elimination is rapid and complete, primarily via urine and bile, with evidence of enterohepatic cycling. No unique human metabolites have been identified.

Figure 3: Proposed metabolic pathway of inpyrfluxam in human and rat liver microsomes.



R : Rat liver microsomes
H : Human liver microsomes

Figure 4: Proposed metabolic pathway of inpyrfluxam in dog liver microsomes



10. Evaluation of health hazards

10.1 Acute toxicity – oral route

Table 14: Summary of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Effects	Reference
Acute oral toxicity study, gavage OECD TG 423 (2001) GLP Deviations: Minor deviation due to 12h light suspension for a minute because of accidental blackout. No impact on the integrity of the study and data obtained.	Rat, RccHan Wistar Female N = 3/dose	Inpyrfluxam (S-2399 Technical Grade) Lot/Batch: 13CG0617G Purity: 95.0%	50 mg/kg bw (single dose) 300 mg/kg bw (single dose)	50 < LD_{50} < 300 mg/kg bw	**Mortality**: 2/3 at 300 mg/kg bw. No mortality at 50 mg/kg bw. **Clinical Signs**: Decreased spontaneous activity, ataxic gait, loss of righting reflex, prone or lateral position. Recovery in surviving animal by Day 1.	KCA 5.2.1/01, Anonymous (2015a)
Acute oral toxicity study, up-and-down procedure, gavage OECD TG 425 (2008) GLP	Rat, RccHan Wistar Female N= 2 at 57mg/kg bw, 3 at 180 mg/kg bw and 1 at 570 mg/kg bw.	Inpyrfluxam (S-2399 Technical Grade) Lot/Batch: 13CG0617G Purity: 95.0%	57, 180 and 570 mg/kg bw (all single dose)	LD_{50}: 180 mg/kg bw (95% CI: 30.08 to 735 mg/kg bw)	**Mortality**: 2/3 at 180 mg/kg bw, 1/1 at 570 mg/kg bw. No mortality at 57 mg/kg bw.	KCA 5.2.1/02, Anonymous (2017a)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Effects	Reference
Deviations: Dose levels of 57, 180, and 570 mg/kg bw used instead of 55, 175, and 550 mg/kg bw. No impact on the integrity of the study and data obtained.					**Clinical Signs**: Reduction in spontaneous activity, ataxic gait observed in animals that received 180mg/kg bw/day and 570 mg/kg bw day. No clinical signs at 57 mg/kg bw.	

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

The acute oral toxicity of inpyrfluxam was evaluated through two GLP-compliant studies conducted in rats. The first study employed the toxic class method according to OECD TG 423, while the second utilised the up-and-down procedure according to OECD TG 425 (2008).

In the first study (Anonymous (2015a)), three groups of female RccHan:WIST rats were sequentially administered inpyrfluxam at doses of 300 mg/kg bw and 50 mg/kg bw. This study estimated a LD_{50} of $50 < LD_{50} < 300$ mg/kg bw. The results are summarised in Table 15:

Table 15: Acute oral toxicity of inpyrfluxam in rats

Dose (mg/kg bw)	Toxicological results* Deaths/ Clinical signs / Animals used	Duration of signs	Time of death	LD_{50} (mg/kg bw)
300	2/3/3	0.5-4 h	4 h – 1 d	$50 < LD_{50} < 300$ mg/kg bw
50	0/1/6	2 h	NA	

* number of animals which died/number of animals with clinical signs/number of animals used; NA: not applicable

In the second available study (Anonymous (2017a)), 2 female rats were administered single doses of 57 mg/kg bw, 3 female rats were administered single doses of 180 mg/kg bw and 1 individual female rat was administered a single dose of 570 mg/kg bw of inpyrfluxam, respectively. This study reported a LD_{50} of 180 mg/kg bw. The results of this study are detailed in Table 16:

Table 16: Acute oral toxicity of inpyrfluxam in rats – up and down procedure

Dose (mg/kg bw)	Results*	Duration of signs	Time of death	LD_{50} (mg/kg bw)
57	0/0/2	NA	NA	180 (95% confidence interval 30.08 to 735 mg/kg)
180	2/3/3	0.5-4 h	4 h	
570	1/1/1	1 h	2 h	

* number of animals which died/number of animals with clinical signs/number of animals used; NA: not applicable

Clinical signs were observed only in animals administered 180 mg/kg bw and 570 mg/kg bw, with 3/3 and 1/1 animals affected, respectively. Clinical signs included reduced spontaneous activity and ataxic gait. The surviving animal at 180 mg/kg bw recovered by Day 1, while the animal at 570 mg/kg bw died within 2 hours. No clinical signs were noted in animals receiving 57 mg/kg bw. There were no changes in the body weight of the surviving animals, although body weight was decreased in some of the animals that died.

10.1.2 Comparison with the GB CLP criteria

According to GB CLP, substances with acute oral LD_{50} values greater than 50 mg/kg bw but less than or equal to 300 mg/kg bw should be classified in Category 3 (H301: Toxic if swallowed). The acute oral LD_{50} value for inpyrfluxam, determined in the second study (OECD TG 425, up-and-down procedure), was estimated at 180 mg/kg bw. This value places it within the range for Category 3 classification. The 95% confidence interval (30.08 mg/kg bw to 735 mg/kg bw) is noted, but the classification is based on the best estimate (180 mg/kg bw).

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results from the GLP-compliant studies conducted according to OECD guidelines, **inpyrfluxam meets the criteria for classification as Category 3 (H301) for acute oral toxicity, with an ATE value of 180 mg/kg bw/day.**

10.2 Acute toxicity – dermal route

Table 17: Summary of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Effects	Reference
Acute dermal toxicity study OECD TG 402 (1987) GLP	Rat, RccHan Male and female (5/sex)	Inpyrfluxam (S-2399 Technical Grade) Lot/Batch: 13CG0617G Purity: 95.0%	2000 mg/kg bw (single dose, 24 hours)	> 2000 mg/kg bw	No mortality or changes in body weight observed. No other clinical signs or macroscopic pathological findings.	KCA 5.2.2/01, Anonymous (2015b)

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

The acute dermal toxicity of inpyrfluxam was investigated through a GLP-compliant study conducted according to OECD TG 402 (1987). The study involved 5 male and 5 female RccHan:WIST rats exposed to a single dose of 2000 mg/kg bw of inpyrfluxam on their clipped dorsal skin for 24 hours. The study design deviated from OECD TG 402 (2017), which recommends that acute dermal toxicity testing be conducted in a single sex (typically females) and that animals are dosed sequentially, with classification outcomes generally achievable using two animals at a dose level, following an initial range-finding step. In contrast, this study used ten animals (five per sex) dosed in parallel. However, the Agency consider that these deviations do not impact the validity or reliability of the study results.

No mortality or significant changes in body weight were observed in either male or female rats throughout the study. A scab observed on the dorsal neck of one male rat between days 12 and 14 was considered unrelated to the treatment as it appeared at a non-application site. No other clinical signs of toxicity or macroscopic pathological findings were reported. The study concluded that the acute dermal LD_{50} of inpyrfluxam is greater than 2000 mg/kg bw.

10.2.2 Comparison with the GB CLP criteria

According to GB CLP, substances with acute dermal LD_{50} values greater than 2000 mg/kg bw are not classified for acute dermal toxicity. The findings from this study, which indicate an acute dermal LD_{50} of >2000 mg/kg bw for inpyrfluxam, do not meet the criteria for classification as acutely toxic via the dermal route.

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Not classified – data conclusive but not sufficient for classification.

10.3 Acute toxicity – inhalation route

Table 18: Summary of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Effects	Reference
Acute inhalation toxicity study, nose only OECD TG 403 (2009) GLP	Rat, RccHan Male and Female N = 5/sex	Inpyrfluxam (S-2399 Technical Grade) Lot/Batch: 13CG0617G Purity: 95.0% MMAD : 3.59 µm	Target concentration:2 mg/L Actual concentration: 2610 mg/m³ Exposure duration: 4 hours	> 2.0 mg/L	One female rat died during exposure. Ataxic gait, lateral position (on day 0), and decreased spontaneous activity (on day 1) were observed in the same female, with recovery by day 2. Wet fur observed in all animals was attributed to restraint in holding tubes.	KCA 5.2.3/01, Anonymous (2015c)

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

The acute inhalation toxicity of inpyrfluxam was assessed in a GLP-compliant study conducted according to OECD TG 403 (2009). The study involved 5 male and 5 female RccHan:WIST rats, which were exposed (nose only) to a mist aerosol of inpyrfluxam at a target concentration of 2 mg/L for 4 hours. The actual concentration achieved was 2610 mg/m³. The mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) of the aerosol particles were 3.59 µm and 2.35 µm, respectively, in accordance with the guideline. More animals were used than required by the guideline. This deviation does not impact the acceptability or reliability of the study results.

One female rat died during the exposure period, with clinical signs including ataxic gait, lateral position, and decreased spontaneous activity, all of which resolved by day 2. The death of the female rat and the subsequent observation of white substance retention in the nasopharynx and trachea are considered by the Agency to be related to the inhaled test substance. Despite these observations, the LC_{50} for inpyrfluxam was determined to be >2.0 mg/L, the maximum achievable concentration in this study.

The study results are summarised in Table 19:

Table 19: Acute inhalation toxicity of inpyrfluxam in rats

Concentration (mg/L)	Toxicological results*	Duration of signs	LC_{50} (mg/L) 14 days
male rats			
2.0	0/0/5	NA	>2.0
female rats			
2.0	1/1/5	1 h – day 1	>2.0

* number of animals which died/number of animals with clinical signs/number of animals used; NA: not applicable

10.3.2 Comparison with the GB CLP criteria

According to GB CLP, substances are classified for acute inhalation toxicity based on their LC_{50} values. The classification thresholds for acute inhalation toxicity include Category 4 for substances with an LC_{50} between 1.0 and 5.0 mg/L for dusts/mists. In this study, the LC_{50} for inpyrfluxam was determined to be greater than 2.0 mg/L (the maximum achievable concentration), therefore this study does not support classification according to the GB CLP criteria.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Not classified – data conclusive but not sufficient for classification.

10.4 Specific target organ toxicity – single exposure (STOT SE)

Information on the potential for inpyrfluxam to cause specific target organ toxicity following single exposure is available from the acute toxicity studies presented in Sections 10.1 – 10.3. In addition, the neurotoxic potential of inpyrfluxam has been investigated in Wistar rats following oral administration, either by gavage or via the diet. The dataset includes two acute neurotoxicity studies (a dose-range finding study and a definitive study) as well as a sub-chronic neurotoxicity study (described in detail in the STOT RE section). All studies were conducted in compliance with GLP and in accordance with OECD test guidelines.

Table 20: Summary of animal studies on STOT SE (in addition to the acute toxicity studies)

Method, guideline, deviations if any, species, strain, sex, no/group, reference	Test substance, route of exposure, dose levels, duration of exposure	Results
Acute Neurotoxicity Study (Range-finding) OECD TG 424 (1997) GLP: Yes Species/strain: Wistar rats. Sex: male and female. Group size: 3/sex/dose. Deviation: only 3 animals/sex/dose (guideline recommends 10/sex/dose). Anonymous (2015c)	Test material: S-2399 Technical Grade (inpyrfluxam) Route: Oral gavage. Dose levels: 0, 10, 30, 100, 200, 400 mg/kg bw (single administration). Duration: 7-day observation following single dosing.	**Mortality**: 1 female each at 200 and 400 mg/kg bw. **Clinical signs:** (mainly 200–400 mg/kg bw, esp. females): prone position, tremors, ataxia, abnormal gait, staggering, hypothermia, anaesthesia, laboured respiration, reduced motor activity, decreased muscle tone, alertness and exploration. Effects peaked 1–5 h post-dose. No treatment-related changes in body weight or necropsy findings. Dose of 200 mg/kg bw selected as top dose for the main acute neurotoxicity study.
Acute Neurotoxicity Study of Inpyrfluxam in Rats – main study OECD TG 424 (1997); GLP. Species/strain: Wistar rats. Sex: male and	Test material: S-2399 Technical Grade (inpyrfluxam) Route: Oral gavage. Dose levels: 0, 30, 100, 200 mg/kg bw (single administration). Duration: 14-day observation with full	**Mortality/clinical signs:** No mortality. At 200 mg/kg bw, decreased muscle tone in 2 females on Day 1 (resolved by Day 2). **Functional observation battery:** At 100 and 200 mg/kg bw in females, significant decreases in body temperature and motor activity (0–60 min after dosing, week 2). These were attributed to systemic rather than neurotoxic effects, as no neuropathology observed. **Body weight, necropsy, histopathology:** No treatment-related effects in either sex. **Conclusions:** Adverse systemic effects (↓ body temperature, ↓ motor activity) from 100 mg/kg bw in females.

female. Group size: 10/sex/dose. Deviations: None. Anonymous (2016b)	OECD 424 neurotoxicity battery.	

10.4.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

Information on the potential for inpyrfluxam to cause specific target organ toxicity is available from the acute toxicity studies (oral, dermal, inhalation) and from dedicated neurotoxicity investigations (acute and sub-chronic) conducted in rats.

Two GLP-compliant acute oral toxicity studies were performed in female RccHan:WIST rats according to OECD TG 423 and 425. clinical signs included reduced spontaneous activity, ataxia, prone position and loss of righting reflex at ≥180 mg/kg bw. Mortality was observed at 180 and 570 mg/kg bw, while recovery occurred in survivors within one day.

A GLP-complaint acute dermal toxicity study in rats (OECD TG 402) reported no treatment-related mortality, systemic effects, or pathological findings.

In a GLP-complaint acute inhalation toxicity study (OECD TG 403, mist aerosol), one female died during exposure, with signs of ataxia, lateral position and decreased activity, but these resolved by Day 2 in survivors. The findings were not indicative of specific target organ toxicity.

The neurotoxic potential of inpyrfluxam has been investigated in a series of GLP-compliant studies. In the acute dose-range finding study (OECD TG 424), mortality and adverse clinical signs (tremors, abnormal gait, reduced muscle tone, laboured respiration, hypoactivity) were noted at ≥200 mg/kg bw. In the definitive acute neurotoxicity study (OECD TG 424), systemic effects (decreased body temperature, motor activity, reduced muscle tone) were observed in females from 100 mg/kg bw. However, no consistent neurotoxic pattern was seen, and no neuropathological changes were detected. A NOAEL of 30 mg/kg bw was identified for systemic toxicity, and a NOAEL of 200 mg/kg bw (highest dose tested) for neurotoxicity.

Overall, inpyrfluxam exhibits acute oral toxicity (Category 3, H301), but there is no evidence of specific target organ toxicity after a single exposure. Observed neurobehavioural effects are considered secondary to systemic toxicity.

10.4.2 Comparison with the GB CLP criteria

According to GB CLP, specific target organ toxicity (single exposure) refers to specific, non-lethal target organ effects arising from a single exposure to a substance. Classification in Categories 1 and 2 is applied to substances causing significant or severe organ toxicity, while Category 3 applies to substances causing transient respiratory tract irritation or narcotic effects.

For inpyrfluxam, the acute oral toxicity studies established an LD_{50} value within the range for Category 3 (H301: Toxic if swallowed). This classification is addressed under the acute toxicity endpoint rather than STOT SE. Acute dermal and inhalation studies showed no evidence of specific target organ toxicity, with LD_{50} and LC_{50} values exceeding the classification thresholds.

The acute neurotoxicity studies identified transient systemic effects (reduced motor activity, body temperature, food consumption, and body weight), but no consistent evidence of specific neurotoxicity. Importantly, no neuropathological findings were observed at any dose level. The effects observed are therefore considered to reflect generalised systemic toxicity rather than specific target organ toxicity.

No evidence of respiratory tract irritation or narcotic effects was observed in the inhalation study. No human data are available.

On this basis, the available data for inpyrfluxam does not support classification in STOT SE Categories 1, 2 or 3 under the GB CLP Regulation.

10.4.3 Conclusion on classification and labelling for STOT SE

Not classified - data conclusive but not sufficient for classification.

10.5 Skin corrosion/irritation

Table 21: Summary of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
Primary skin irritation test OECD TG	Rabbit, New Zealand White Male N = 3	Inpyrfluxam (S-2399 Technical Grade) Lot/Batch: 13CG0617G	0.5 g moistened with corn oil, 4 hours exposure	**Observations:** No signs of skin irritation, clinical signs, or toxicity observed throughout the observation period.	Anonymous (2015a)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
404 (2002) GLP No deviations		Purity: 95.0%		**Mean scores/animal**: Primary Skin Irritation Index = 0 **Reversibility**: Not applicable, as no irritation was observed.	
In vitro EpiDerm™ Skin Irritation Test (EPI-200) OECD TG 439 (2021) GLP No Deviations	Reconstructed human epidermis (EpiDerm™), triplicate tissues	Inpyrfluxam (S-2399 Technical Grade) Lot/Batch: 13CG0617G Purity 95.0%	25 mg/tissue, 60 min exposure (35 min at 37 °C, remainder at room temperature), followed by 42 h post-exposure	No direct tissue binding or MTT reduction observed in preliminary checks. Negative (PBS) and positive (5% SDS) controls performed as expected. Mean viability: 104.2% of negative control after 60 min exposure. Not irritating to skin under test conditions.	KCA 5.2.4/02 Anonymous (2025a)

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

The skin irritation potential of inpyrfluxam was evaluated in both *in vivo* and *in vitro* GLP-compliant studies conducted according to OECD test guidelines.

In an *in vivo* study performed in accordance with OECD TG 404 (2002), three male New Zealand White rabbits received a 4-hour dermal application of 0.5 g of inpyrfluxam moistened with corn oil to intact clipped dorsal skin. No erythema, oedema, clinical signs, or systemic effects were observed throughout the study period, and the primary irritation index was 0. The substance was therefore concluded to be non-irritating to rabbit skin under the conditions of this test.

An *in vitro* study conducted in line with OECD TG 439 (2021) using reconstructed human epidermis (EpiDerm™ SIT, EPI-200) also showed no irritation potential. Triplicate tissues were exposed to 25 mg of inpyrfluxam for 60 minutes (35 minutes at 37 °C and the remaining time at room temperature), followed by approximately 42 hours of post-exposure incubation. There was no evidence of tissue binding or interference with the MTT assay, all validity criteria were satisfied, and the controls performed as expected. Mean

tissue viability following treatment was 104.2% relative to the negative control, confirming that inpyrfluxam does not reduce cell viability in this assay.

Overall, the findings from both OECD TG 404 and OECD TG 439 studies demonstrate consistent evidence that inpyrfluxam does not cause skin irritation under the experimental conditions tested.

10.5.2 Comparison with the GB CLP criteria

Under the GB CLP, classification for skin irritation applies where *in vitro* reconstructed epidermis assays (OECD TG 439) show tissue viability below 50 percent or where *in vivo* studies demonstrate significant or persistent irritation.

In the OECD TG 439 study, inpyrfluxam yielded a mean tissue viability of 104.2 percent, satisfying all validity criteria and remaining well above the 50 percent threshold. Likewise, in the OECD TG 404 in vivo study, the primary irritation index was 0 and no erythema or oedema was observed.

These results indicate that inpyrfluxam does not meet the criteria for classification as a skin irritant under GB CLP.

10.5.3 Conclusion on classification and labelling for skin corrosion/irritation

Not classified - data conclusive but not sufficient for classification.

10.6 Serious eye damage/eye irritation

Table 22: Summary of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Primary eye irritation test OECD TG 405 (2002) GLP Deviations: No scientific justification	Rabbit, New Zealand White Male N = 6 (3 unwashed, 3 washed)	Inpyrfluxam (S-2399 Technical Grade) Lot/Batch: 13CG0617G Purity: 95.0%	0.1 mL (67 mg w/w) applied to the lower everted lid of the right eye 72 hours observation	**Observations and time point of onset**: Unwashed Group: Conjunctiva redness (grade 1) in all three rabbits at 24 hours Chemosis (grade 1) and discharge (grade 2) in one rabbit at 24 hours Recovery in all rabbits by 48 hours	Anonymous (2015b)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
for satellite group; incorrect number of animals used; unwashed group not observed at 1 hour to ensure solid substance removal.				Washed Group: No signs of irritation observed during the observation period. **Mean scores/animal**: Not explicitly provided **Reversibility**: Full recovery observed in unwashed group by 48 hours	
In vitro EpiOcular™ Eye Irritation Test (OCL-200), OECD TG 492 (2024); GLP No deviations	Reconstructed human corneal epithelium (EpiOcular™, triplicate tissues)	Inpyrfluxam (S-2399, Technical Grade) Lot 13CG0617G, Purity 95.0%	50 mg/tissue, 6 h exposure followed by 18 h post-incubation	No direct tissue binding or MTT reduction in preliminary checks. Negative (distilled water) and positive (methyl acetate) controls gave expected responses. **Mean viability:** 96.4% of negative control after 6 h exposure. Not an eye irritant under test conditions.	KCA 5.2.5/02, Anonymous (2025b)

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

The eye irritation potential of inpyrfluxam was evaluated in both *in vivo* and *in vitro* GLP-compliant studies conducted according to OECD test guidelines.

In an *in vivo* study performed in accordance with OECD TG 405 (2002), six male New Zealand White rabbits received 0.1 mL of inpyrfluxam instilled into the lower conjunctival sac of one eye. Three animals formed an unwashed group, and three underwent saline irrigation 30 seconds post-instillation. In the unwashed group, transient conjunctival redness (grade 1) was observed in all animals at 24 hours, with grade 1 chemosis and grade 2 discharge noted in one rabbit. All effects resolved fully within 48 hours, and no

corneal opacity, iris involvement, systemic toxicity, or mortality occurred. No irritation was seen in the washed group.

The detailed irritation scores for the unwashed group are presented in Table 23:

Table 23: Irritation scores from rabbits treated with inpyrfluxam- unwashed group

Unwashed group		**Rabbit No.**	**1 h**	**24 h**	**48 h**	**72 h**
Conjunctiva	Chemosis	1	0	0	0	0
		2	0	0	0	0
		3	0	1	0	0
	Redness	1	0	1	0	0
		2	0	1	0	0
		3	0	1	0	0
Iris	Congestion	1	0	0	0	0
		2	0	0	0	0
		3	0	0	0	0
Cornea	Degree of Opacity	1	0	0	0	0
		2	0	0	0	0
		3	0	0	0	0

These findings suggest that inpyrfluxam does not cause significant eye irritation under the conditions tested.

Eye irritation was also evaluated using the reconstructed human EpiOcular™ model in a GLP-compliant OECD TG 492 (2024) study. Triplicate tissues were exposed to 50 mg of inpyrfluxam for 6 hours, followed by approximately 18 hours of post-exposure incubation. There was no evidence of test material interference with the MTT assay, all acceptance criteria were met, and the controls responded appropriately. Mean tissue viability was 96.4% relative to the negative control, demonstrating an absence of *in vitro* irritation potential.

Overall, both OECD TG 405 and OECD TG 492 studies demonstrate that inpyrfluxam does not cause significant eye irritation or serious eye damage under the conditions tested.

10.6.2 Comparison with the GB CLP criteria

Under the GB CLP Regulation (EC) No 1272/2008, substances are classified for eye irritation where validated *in vitro* reconstructed eye models (OECD TG 492) show tissue viability below 60%, or where *in vivo* studies demonstrate persistent irritation or irreversible ocular damage.

In the OECD TG 492 study, inpyrfluxam produced a mean tissue viability of 96.4 percent, fulfilling all assay validity criteria and remaining well above the 60% classification threshold.

Consistent with these findings, the OECD TG 405 *in vivo* study reported only mild (grade 1) conjunctival effects that resolved within 48 hours, with no corneal opacity or irreversible responses.

Evidence from the *in vitro* and *in vivo* studies demonstrates that inpyrfluxam does not meet the criteria for classification as an eye irritant or as causing serious eye damage under GB CLP.

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

Conclusion: not classified – data conclusive but not sufficient for classification.

10.7 Respiratory sensitisation

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

There are no data or appropriate studies conducted in animals to inform on the potential of inpyrfluxam to cause respiratory sensitisation.

10.7.2 Conclusion on classification and labelling for respiratory sensitisation

No classification – data lacking

10.8 Skin sensitisation

Table 24: Summary of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
Maximisation test OECD TG 406 (1992), No deviations	Guinea pig (Hartley, albino), females, 20 test	Inpyrfluxam (S-2399 Technical Grade), Batch: 13CG0617G, Purity: 95%	Intradermal induction: 0.2%, Topical induction: 50%, Challenge:	No sensitising effects observed; Sensitisation rate: 0%	KCA 5.2.6/01, Anonymous (2015c)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
			25%		

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

The skin sensitisation potential of inpyrfluxam was evaluated in a Guinea Pig Maximisation Test (GPMT) with female albino Hartley guinea pigs. During a preliminary dose-finding stage, a 50% concentration of inpyrfluxam caused slight erythema, while 25% induced no reaction. The intradermal injection of 1% or 0.5% led to adverse effects including mortality and clinical signs such as ataxic gait and tremor, whereas 0.2% produced no abnormal effects. Based on these findings, a concentration of 0.2% was used for intradermal induction, 50% for topical induction, and 25% for the challenge phase in the main study. No sensitisation responses were observed in treated animals, resulting in a sensitisation rate of 0%. The study included appropriate controls, which yielded expected outcomes, and no mortality or clinical signs of toxicity were recorded in any of the test or control animals. The findings suggest that inpyrfluxam does not exhibit sensitising effects on the skin of guinea pigs.

10.8.2 Comparison with the GB CLP criteria

According to the GB CLP criteria (Regulation 1272/2008), a substance is classified as a skin sensitiser if it elicits an allergic response in test animals. In this study, the sensitisation rate observed in guinea pigs treated with inpyrfluxam was 0%. No skin reactions were detected during either the induction or the challenge phases. Positive and negative controls behaved as expected. both negative and positive controls, supports this conclusion. Based on these results, inpyrfluxam is not classified as a skin sensitiser under the GB CLP Regulation.

10.8.3 Conclusion on classification and labelling for skin sensitisation

Not classified – data conclusive but not sufficient for classification.

10.9 Specific target organ toxicity – repeated exposure (STOT RE)

The repeated dose toxicity of inpyrfluxam has been evaluated primarily via the oral route. The available studies include a preliminary 28-day range-finding study in rats; sub-chronic (90-day) toxicity studies in rats, mice, and dogs; and a chronic (1-year) oral toxicity study in dogs. In addition, a 28-day dermal toxicity study has been conducted in rats to assess systemic effects following dermal exposure. There is also a 90-day oral repeated dose neurotoxicity study in rats.

Table 25: Summary of animal studies on STOT RE

Note: ↑↓ denote an increase or decrease in a parameter with respect to the control value
Statistical significance: * $p \leq 0.05$, ** $p \leq 0.01$
abs. = absolute rel. = relative
M = Males / F = Females
NS = Change was not statistically significant

Method, guideline, deviations if any, species, strain, sex, no/group, reference **(Adjusted) guidance values for classification**	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**
Rat Studies (oral)		
28-day (range finding study) Wistar Hannover rats 6/sex/group; additional 4/sex for TK Similar to OECD TG 407 Non-GLP KCA 5.3.1/01, Anonymous (2014) Adjusted guidance values for classification: Cat 1: ≤ 30 mg/kg bw/d Cat 2: ≤ 300 mg/kg bw/d	Inpyrfluxam (S-2399 Technical Grade) Purity: 99.2% Dietary route 0, 500, 1000, 3000, 5000 ppm Equivalent to: Males (M): 0, 44.4, 85.9, 246.4, 406.5 mg/kg bw/day Females (F): 0, 47.4, 91.4, 263.0, 377.8 mg/kg bw/day	No treatment-related mortalities **<u>5000 ppm (406.5 / 377.8 mg/kg bw/day M / F)</u>** ↓ body weight (Day 29): 20.3%** (M), 12.9%** (F) ↓ body weight gain: 41.5% (M), 38.1%** (F) ↑ total cholesterol: 103.6%* (M), 115.7%* (F) ↑ phospholipids: 66.7%** (M), 77.4%* (F) ↑ triglycerides: NS (M), 323.5%** (F) ↑ γ-GTP: 1400%** (M), 500%* (F) ↑ liver weights (absolute): 7.7% (M), 19.3%** (F) ↑ liver weights (relative): 35.9%** (M), 38.9%** (F) ↓ kidney weight (absolute): 20.1%** (M), 14.1%** (F) ↓ thymus weight (absolute): 42.1%** (M) ↓ ovary weight (absolute): 20.5%* (F) ↓ uterus weight (absolute): 32.5% (F) **Histopathological findings at 5000 ppm** Liver: diffuse hepatocellular hypertrophy (6/6 M**, 6/6 F**) Thyroid: follicular cell hypertrophy (6/6 M**, 5/6 F*) Adrenals: Vacuolation, zona fasciculata (5/6 M**, 4/6 F*) Vacuolation, zona glomerulosa (6/6 M**) Bone marrow: fatty infiltration (5/6 M**, 6/6 F*) Kidneys: hyaline droplets in proximal tubular cells (4/6 M*) Thymus: atrophy (3/5 M, slight); increased tingible macrophages (1/5 M, 2/6 F, slight) Ovary: Interstitial gland vacuolation – total (6/6 F**) Interstitial gland increase (5/6 F**)

		Uterus: atrophy (2/6 F) **3000 ppm (246.4 / 263.0 mg/kg bw/day M / F)** ↓ body weight (Day 29): 10.3%** (M), 7.3%** (F) ↓ body weight gain: 23.1% (M), 25.4%** (F) ↑ total cholesterol: 50%* (M), 100%* (F) ↑ phospholipids: 30.6%* (M), 70.8%* (F) ↑ triglycerides: NS (M), 217.6%** (F) ↑ γ-GTP: 650%** (M), 300%* (F) ↑ liver weights (absolute): 4.0% (M), 14.7%** (F) ↑ liver weights (relative): 16.3%** (M), 25.1%** (F) ↓ ovary weight (absolute): 19.2%* (F) ↓ uterus weight (absolute): 6.9% (F) ↓ absolute kidney weight: 11.9%** (F) **Histopathology:** similar findings as at 5000 ppm (but with lower incidence/severity). At 3000 ppm, treatment-related histopathological findings included diffuse hepatocellular hypertrophy (3/6 males, 6/6 females), thyroid follicular cell hypertrophy (4/6 males, 3/6 females), adrenal cortical vacuolation affecting the zona fasciculata (2/6 males, 1/6 females) and zona glomerulosa (5/6 males), ovarian interstitial gland vacuolation (observed in 2/6 females), uterine atrophy (2/6 females), and fatty infiltration in the bone marrow (1/6 males, 5/6 females). **1000 ppm (85.9 / 91.4 mg/kg bw/day M / F)** No statistically significant changes in body weight; adrenal vacuolation (zona glomerulosa) (M); minor changes in clinical chemistry (not dose-related). **500 ppm (44.4 / 47.4 mg/kg bw/day M / F)** No treatment-related findings.
90-day repeated dose oral toxicity study Rat, Wistar Hannover, 10/sex/group OECD TG 408 (1998) GLP	Inpyrfluxam (S-2399 Technical Grade) Purity: 95% Dietary route 0, 150, 500, 2000, 4000 ppm	**4000 ppm (255 / 292 mg/kg bw/day M/F)** ↓ body weight: 17% (M**), 19% (F**) ↓ body weight gain: 26% (M**), 39% (F**) ↓ food consumption: up to 17% (F**) ↑ GGTP: 414% (M**), 438% (F**) ↑ ALP: 28% (F*) ↓ glucose: 14% (F*) ↑ phosphorous: 14% (M*) ↑ liver weight (relative): 24% (M**), 36% (F**) ↓ kidney weight (absolute): 13% (F*)

Deviations from current guideline: (no T3/T4/TSH, LDL/HDL measurements, some reproductive endpoints missing) KCA 5.3.2/01, Anonymous (2016) Guidance values for classification: Cat 1: ≤ 10 mg/kg bw/d Cat 2: ≤ 100 mg/kg bw/d	Equivalent to: Males (M): 0, 9.72, 31.7, 123, 255 mg/kg bw/day Females (F): 0, 11.5, 37.5, 144, 292 mg/kg bw/day	↑ kidney weight (relative): 14% (M**) ↓ adrenal weight (absolute): 14% (F*) ↑ ovary weight (relative): 27% (F*) Histopathology: Hepatocyte hypertrophy (10/10 M**, 9/10 F**) Thyroid follicular hypertrophy (2/10 M, 7/10 F**) Adrenal vacuolation (5/10 M, 5/10 F*) Ovarian vacuolation (8/10 F**) **<u>2000 ppm (123 / 144 mg/kg bw/day M/F)</u>** ↓ body weight: 5% (M, NS), 10% (F**) ↓ body weight gain: 8% (M, NS), 21% (F**) ↓ food consumption: up to 17% (F**) ↑ GGTP: 114% (M**), 238% (F**) ↑ ALP: 34% (F*) ↑ liver weight (relative): 11% (M**), 19% (F**) ↑ ovary weight (relative): 16% (F, NS) Histopathology: Hepatocyte hypertrophy (4/10 M, 7/10 F**) Thyroid follicular hypertrophy (2/10 M, 4/10 F) Adrenal vacuolation (1/10 M, 3/10 F) Ovarian vacuolation (7/10 F*) **<u>500 ppm (31.7 / 37.5 mg/kg bw/day M/F)</u>** No adverse effects ↑ WBC, lymphocytes, neutrophils (M)—not dose-related No histopathological findings **<u>150 ppm (9.72 / 11.5 mg/kg bw/day M/F)</u>** No treatment-related effects
90-day repeated dose neurotoxicity study Rat, Wistar Hannover 10/sex/group OECD TG 424 GLP No Deviations	Inpyrfluxam, (S-2399 Technical Grade) Purity: 95% Oral **Dose levels**: Males: 0, 500, 2000, 4000 ppm → 0, 30, 118.9, 240 mg/kg bw/day	**No neurotoxicity observed at any tested dose.** Adverse systemic effects (body weight and food consumption) from 1000 ppm **Mortality/clinical signs**: None **Body weight**: ↓ Significant at 4000 ppm (males), 2000 ppm (females weeks 6–13), and 1000 ppm (females weeks 8 & 13). Considered adverse (≥10%)

KCA 5.7.1/03, Anonymous (2016) Guidance values for classification: Cat 1: ≤ 10 mg/kg bw/d Cat 2: ≤ 100 mg/kg bw/d	Females: 0, 500, 1000, 2000 ppm → 0, 35.2, 68, 133 mg/kg bw/day	**Food consumption**: ↓ Significant in males at 4000 ppm; in females from 1000 ppm (approx. 10% lower, treatment-related and adverse) **Functional tests**: ↓ Forelimb grip strength at 4000 ppm (males) and ↑ motor activity at 1000+ ppm (females) – both considered incidental, not adverse **Pathology**: No treatment-related findings at necropsy or histopathology **NOAEL (systemic)**: 500 ppm (35.2 mg/kg bw/day, females) **NOAEL (neurotoxicity)**: 2000 ppm (133 mg/kg bw/day, highest dose tested in females)
Rat Studies (dermal)		
28-day repeated dose dermal toxicity study Rat, Crl:CD, 10/sex/group OECD TG 410 (1981) GLP No deviations Anonymous (2015) Guidance values for classification: Cat 1: ≤ 20 mg/kg bw/d Cat 2: ≤ 200 mg/kg bw/d	Inpyrfluxam (S-2399 Technical Grade) Purity: 95% Dermal (occlusive, 6h/day) 0, 100, 300, 1000 mg/kg bw/day	**No adverse effects reported** **<u>1000 mg/kg bw/day</u>** ↑ relative heart weight (M), not adverse (within HCD) **<u>300 mg/kg bw/day</u>** ↑ absolute and relative ovary weight (F), not adverse (no dose-response) Spermatic granuloma in epididymis (M), not adverse (no dose-response) **<u>100 mg/kg bw/day</u>** ↑ relative brain weight (F) Massive necrosis in liver (M) White patch in liver (M)
Mice Studies (oral)		
90-day repeated dose oral toxicity study Mice, ICR [Crlj:CD1(ICR)], males & females 10/sex/group	Inpyrfluxam (S-2399 Technical Grade) Purity: 95% Dietary route	No treatment-related mortality. No effect on body weight, weight gain or food consumption (M, F) **<u>7000 ppm (973 / 1097 mg/kg bw/day M / F)</u>** ↑ globulin: 12% (M**), 14% (F**) ↓ albumin: NS (M), ↓9% (F**)

OECD TG 408 (1998) GLP Deviations from current guideline (no T3/T4/TSH, LDL/HDL, some reproductive and endocrine endpoints, no ophthalmology, no FOB, no clotting time, Na/K not measured) KCA 5.3.2/02, Anonymous (2016a) Guidance values for classification: Cat 1: ≤ 10 mg/kg bw/d Cat 2: ≤ 100 mg/kg bw/d	0, 200, 800, 3500, 7000 ppm Equivalent to: Males (M): 0, 27.2, 111, 491, 973 mg/kg bw/day Females (F): 0, 31.7, 130, 559, 1097 mg/kg bw/day	↓ A/G ratio: 13% (M**), 20% (F**) ↑ total cholesterol: NS (M), 24% (F*) ↓ total bilirubin: 34% (M**), 23% (F**) ↑ glucose: 14% (M*) ↑ calcium: 4% (M*), NS (F) ↑ liver weight (absolute): 25% (M**), 24% (F**) ↑ liver weight (relative): 33% (M**), 29% (F**) Gross pathology: dark-coloured liver (4/10 M, 9/10 F), enlarged liver (3/10 M, 2/10 F) <u>Histopathology:</u> centrilobular hepatocyte fatty change (4/10 M), centrilobular hypertrophy (10/10 M**), diffuse hepatocyte hypertrophy (10/10 F**), thyroid follicular cell hypertrophy (5/10 M*, 1/10 F) **<u>3500 ppm (491 / 559 mg/kg bw/day M / F)</u>** ↑ globulin: 10% (M*) ↓ albumin: NS (M), 8% (F**) ↓ A/G ratio: 9% (M), 15% (F**) ↓ total bilirubin: 34% (M**), NS (F) ↑ glucose: 18% (M**) ↑ liver weight (absolute): 16% (M**), 7% (F, NS) ↑ liver weight (relative): 18% (M**), 11% (F*) Histopathology: centrilobular hepatocyte fatty change (3/10 M), centrilobular hypertrophy (8/10 M**), diffuse hepatocyte hypertrophy (4/10 F*) **<u>800 ppm (111 / 130 mg/kg bw/day M / F)</u>** No adverse effects No histopathological findings **<u>200 ppm (27.2 / 31.7 mg/kg bw/day M / F)</u>** No treatment-related effects
<u>Dog Studies</u>		
90-day repeated dose oral toxicity study Dog, Beagle, 4/sex/group OECD TG 409 (1998) GLP No deviations	Inpyrfluxam (S-2399 Technical Grade) Purity: 95% Oral capsule route 0, 40, 160, 700/500 mg/kg bw/day (High dose changed from 700mg/kg bw/day to	**<u>700/500 mg/kg bw/day</u>** ↑ mortality (1M, 2F); ↑ vomiting (M/F) ↓ body weight >10% (M/F*), ↓ food consumption (M/F**) ↑ ALP: up to 251% (M**, Week 13), 351% (F*) ↑ ALT: >50% (M/F) ↑ GGTP: >100% (M/F) ↓ TP: 20% (M**), 12% (F**) ↓ Alb: 24% (M**), 21% (F**) ↓ Glob: 19% (M*)

Anonymous (2016) Guidance values for classification: Cat 1: ≤ 10 mg/kg bw/d Cat 2: ≤ 100 mg/kg bw/d (nb: these guidance values apply to rats; there are no separate guidance values for dogs. The values should be used to interpret dog studies with caution).	500mg/kg bw/day on week 4)	↓ A/G ratio: 13% (M), 20% (F*) ↓ glucose: 13% (M**) ↓ cholesterol: 54% (M*), 48–52% (F*)(Week 13) ↓ Ca: 10% (M**), (Week 13) ↑ liver weight (rel.): 69% (M**), 57% (F**) Histopathology: hepatocyte hypertrophy (3/4 M*, 2/4 F*), eosinophilic inclusions (3/4 M, 1/4 F), single cell necrosis (3/4 F), pigment deposition (1/4 M, 2/4 F), bile duct inflammation (1/4 F), tubular vacuolation (2/4 M, 1/4 F), adrenal vacuolation (2/4 M, 2/4 F), splenic congestion (2/4 M, 2/4 F), optic nerve fibre degeneration (3/4 M, 4/4 F*) **160 mg/kg bw/day** ↑ vomiting (M/F) ↓ reticulocytes: 46% (F*) ↑ ALP: >200% (M/F) (Week 13) ↑ ALT: >50% (M/F) ↑ GGTP: 187% (M**), 90% (F**) ↓ cholesterol: 54% (M*), 48% (F*) ↓ TP: 20% (M**), 12% (F**) ↓ Alb: 21% (M**), 21% (F**) ↓ Glob: 19% (M*) ↓ A/G ratio: 7% (M), 20% (F*) ↓ glucose: 7–13% (M**, Week 13), 8% (F**) ↓ Ca: 8–10% (M**,), 6–12% (F*, **)** ↑ liver weight (rel.): 49% (M), 38% (F**) Histopathology: hepatocyte hypertrophy (4/4 M/F*), eosinophilic inclusions (1/4 F), single cell necrosis (1/4 M), pigment deposition (1/4 M), renal hypertrophy (3/4 M), adrenal vacuolation (2/4 M), thyroid follicular hypertrophy (1/4 F), gall bladder calculus (1/4 M), optic nerve fibre degeneration (1/4 F) **40 mg/kg bw/day** No adverse effects
Chronic toxicity (1-year) study Dog, Beagle, 4/sex/group OECD TG 452 (2009) GLP	Inpyrfluxam (S-2399 Technical Grade) Purity: 95% Oral (gelatin capsules)	**160 mg/kg bw/day** ↑ vomiting (M/F) ↑ ALP: +136–330% (M/F**) ↑ ALT: 50–85% (M*/F**) ↑ GGTP: 62–91% (M/F**) ↓ albumin: 25–30% (M**) ↓ A/G ratio: 44% (M/F*) ↓ total cholesterol: 10–12% (M/F, NS)

No deviations Anonymous (2017) Guidance values for classification: Cat 1: ≤ 2.5 mg/kg bw/d Cat 2: ≤ 25 mg/kg bw/d (nb: these guidance values apply to rats; there are no separate guidance values for dogs. The values should be used to interpret dog studies with caution).	0, 2, 6, 30, 160 mg/kg bw/day for 52 weeks	↓ Ca: 6% (M*) ↓ K: 12% (F**) ↑ liver weight absolute: +50% (M**), +31% (F*) ↑ liver weight relative: +54% (M**), +40% (F*) ↑ adrenal weight relative: +31% (F**) Gross pathology: dark-coloured liver (M), enlarged liver (M/F) Histopathology: diffuse hepatocyte hypertrophy (3/4 M, 3/4 F), cytoplasmic eosinophilic inclusion bodies in liver (1/4 M, 1/4 F), adrenal zona fasciculata cell vacuolation (1/4 M, 2/4 F), optic nerve fibre degeneration (1/4 M, 2/4 F) **30 mg/kg bw/day** ↑ vomiting (1F) ↑ ALP: +60–162% (M**) ↑ GGTP: +58–64% (M*/F*) ↓ albumin: 7–17% (M) ↓ A/G ratio: 12–25% (M) ↑ liver weight absolute: +32% (M*), +15% (F, NS) ↑ liver weight relative: +24% (M*), +19% (F, NS) Histopathology: diffuse hepatocyte hypertrophy (1/4 M), kidney cytoplasmic eosinophilic inclusion body (1/4 M, incidental), adrenal zona fasciculata vacuolation (2/4 M, 1/4 F), optic nerve fibre degeneration (1/4 M, 1/4 F) **3/6 mg/kg bw/day** No adverse effects

10.9.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

Rat Studies

28-day range finding study in rats (Anonymous, 2014)

A 28-day non-GLP toxicity study in Wistar Hannover rats was conducted to support dose selection for longer-term studies on inpyrfluxam. Groups of 6 rats/sex/dose received dietary concentrations of 0, 500, 1000, 3000 or 5000 ppm, corresponding to mean intakes of 0, 44/47, 86/91, 246/263 and 378/407 mg/kg bw/day in males/females, respectively. No

treatment-related mortality or abnormal clinical signs were seen at any dose. However, from 3000 ppm (246/263 mg/kg bw/day), statistically significant and dose-dependent reductions in body weight were observed in both sexes, with associated decreases in body weight gain. The effect was more slightly more pronounced in males; at the top dose (378/407 mg/kg bw/day), total weight gain was reduced by around 41% in males and 38% in females. Food consumption was unaffected, indicating a toxicological rather than dietary origin for the reduced growth.

Liver

Macroscopic examination revealed enlarged and darkened livers at the top dose. Relative liver weights were statistically significantly increased in both sexes from 3000 ppm; in females, relative liver weights were +25.1%** and + 38.9%** compared to controls at 263 and 378 mg/kg bw/d respectively, and in males, relative liver weights were +16.3%** and +35.9%** at 246 and 407 mg/kg bw/d. Histopathology revealed hepatocellular hypertrophy (from 246/263 mg/kg bw/day in males/females) and smooth endoplasmic reticulum proliferation (at 378/407 mg/kg bw/day in males/females). Marked changes in certain clinical chemistry parameters were noted from 246/263 mg/kg bw/d, including increases in total cholesterol, phospholipids and y-glutamyl transferase in both sexes. In females, a substantial increase in triglycerides was reported from 263 mg/kg bw/d, with levels exceeding 200% of the control value at the top dose. These clinical chemistry findings are indicative of altered hepatic function and lipid metabolism. Although some of the findings in the liver are consistent with an adaptive response, overall, the Agency considers that the effects in the liver from 246/263 mg/kg bw/d are adverse, noting the magnitude of the increases in liver weight and the changes in certain clinical chemistry parameters. However, at doses relevant for classification (i.e., ≤ 300 mg/kg bw/d), the Agency does not consider the effects in the liver to be significant or severe enough to warrant classification.

Kidney

Absolute kidney weights were decreased in both sexes at the top dose (-20.1%** in males, - 14.1%** in females), and in females at 263 mg/kg bw/d (-11.9%**), however this was likely due to the reduced body weights in these animals. There were no effects on relative kidney weight. Male rat-specific renal hyaline droplet accumulation associated with α2μ-globulin was observed from 246 mg/kg bw/d; this finding is not relevant to humans. Overall, the kidney findings do not represent significant or severe toxic effects, therefore do not support classification.

Other findings

In females, absolute ovary and uterus weights were reduced from 263 mg/kg bw/day, and ovarian vacuolation with uterine atrophy (slight) was observed at the same doses. Thyroid follicular cell hypertrophy was observed in both sexes from 246/263 mg/kg bw/d, however

this is likely to be secondary to the increased metabolism in the liver. Haematology investigations revealed statistically significant changes in erythrocyte parameters in males, however the changes were small in magnitude and lacked a dose–response, and were therefore considered incidental. Adrenal cortical vacuolation appeared in males from 86 mg/kg bw/day, and in both sexes from 246/263 mg/kg bw/day. Bone marrow fatty infiltration (slight to mild) was seen in females at 263 and in both sexes at the top dose (378/407 mg/kg bw/day). Atrophy of the thymus (slight) was reported in males at the top dose. None of these findings represent significant or severe toxicity that would warrant classification for STOT RE.

In summary, when inpyrfluxam was administered to rats at oral doses of up to 378/407 mg/kg bw/d for 28 days, adverse effects on body weight and body weight gain were reported. The main target organ was the liver, however at doses relevant for classification, the findings did not represent significant or severe toxicity.

90-day study in rats (Anonymous, 2016)

A GLP-compliant 90-day dietary toxicity study was conducted in Wistar Hannover rats in accordance with OECD TG 408 (1998). Groups of 10 rats/sex/dose received dietary concentrations of 0, 150, 500, 2000 or 4000 ppm for 92 days, corresponding to mean intakes of approximately 0, 9.7, 31.7, 123 and 255 mg/kg bw/day in males and 0, 11.5, 37.5, 144 and 292 mg/kg bw/day in females. The study pre-dated later updates to OECD TG 408; however, the omitted endocrine and reproductive endpoints were addressed in separate mechanistic and reproductive toxicity studies and do not affect the validity of the study.

There were no treatment-related deaths, clinical signs, or effects on grip strength or motor activity. In contrast, clear treatment-related effects on growth were observed. From 123/144 mg/kg bw/d, dose-related reductions in body weight, body weight gain and food consumption occurred in both sexes, with effects more pronounced in females. At 255/292 mg/kg bw/d, terminal body weight was reduced by approximately 17% in males and 18–19% in females, with corresponding reductions in cumulative body weight gain (up to 26% in males and 39% in females).

Liver

At necropsy, dark-coloured livers were observed at the top dose. Treatment-related, dose-dependent increases in relative liver weight were reported from 2000 ppm in both sexes: liver weights were +11%**, +24%** in males at 123 and 255 mg/kg bw/d respectively, and +19%**, +36%** in females at 144 and 292 mg/kg bw/d. Histopathology revealed diffuse hepatocellular hypertrophy in both sexes from 2000 ppm, increasing in incidence and severity at 4000 ppm. Haematological evaluation showed a treatment-related prolongation of prothrombin time at 4000 ppm in both sexes (statistically significant in females), consistent with an effect on the liver. Clinical chemistry findings consistent with changes in

liver function included marked, dose-related increases in γ-glutamyl transpeptidase observed in both sexes from 2000 ppm, accompanied in females by increases in alkaline phosphatase. Additional changes at the top dose included decreased glucose in females and increased inorganic phosphorus in males. Decreases in total bilirubin were considered non-adverse. At doses relevant for classification, no significant or severe effects were reported in the liver.

Kidney

At the top dose (255 mg/kg bw/d), increased relative kidney weight in males (+14%**) was associated with hyaline droplet accumulation in renal proximal tubules. This was related to α2μ-globulin and is therefore not relevant to humans. In females, reduced absolute kidney weight was recorded at the top dose (292 mg/kg bw/d), but was considered secondary to reduced body weights in these animals.

Other findings

Adrenal cortical vacuolation was seen in both sexes from 2000 ppm, and reduced relative adrenal weights were recorded in females at the top dose (-14%*). Increased ovary weights accompanied by interstitial gland vacuolation were recorded from 144 mg/kg bw/d. The effects in the adrenal gland and ovary were considered treatment-related and adverse. Thyroid follicular cell hypertrophy was reported in both sexes from 2000 ppm, although this is likely to be secondary to the effects on the liver. Minor reductions in MCV and MCH in females at the top dose were not considered adverse due to their low magnitude and lack of corroborating changes. Isolated increases in leukocyte parameters at 500 ppm lacked a dose–response and were considered incidental

Other organ weight changes were reported but were considered secondary to reduced body weight.

In conclusion, dietary administration of inpyrfluxam to rats for 90 days resulted in treatment-related effects from 2000 ppm (123 mg/kg bw/day in males; 144 mg/kg bw/day in females), characterised by reduced body weight and food consumption, effects on the liver (enzyme changes, increased liver weight and hepatocellular hypertrophy), altered coagulation, and histopathological changes in the adrenal, thyroid and ovary. At doses relevant for classification, no significant or severe toxicity was reported.

90-day oral neurotoxicity study in rats (Anonymous, 2016)

A 90-day oral neurotoxicity study (OECD TG 424, CLP) was conducted in Wistar Hannover rats to assess the potential neurotoxic effects of inpyrfluxam following repeated dietary exposure. Groups of 10 rats/sex/dose received inpyrfluxam via the diet for 91 consecutive days at concentrations of 0, 500, 2000 or 4000 ppm in males (mean intakes: 0, 30, 118.9 and 240 mg/kg bw/day) and 0, 500, 1000 or 2000 ppm in females (mean

intakes: 0, 35.2, 68 and 133 mg/kg bw/day). Dose selection was based on a preceding 90-day oral toxicity study in rats. The study was conducted in accordance with OECD TG 424 (1997) with no deviations and is considered reliable and acceptable.

There were no treatment-related deaths or clinical signs of toxicity in either sex. However, treatment-related reductions in body weight and food consumption were observed. In males, statistically significant decreases in body weight (>10%) occurred at 240 mg/kg bw/d throughout the study, accompanied by consistent reductions in food intake. In females, body weight reductions (>10%) were observed at the top dose (133 mg/kg bw/d) from mid-study onwards and at 68 mg/kg bw/d at isolated time points, with corresponding decreases in food consumption, particularly at the top dose.

Neurobehavioural assessments did not reveal evidence of neurotoxicity. A statistically significant decrease in forelimb grip strength was noted in high-dose males at the end of the study, and increased motor activity was observed in females from 1000 ppm at a single observation interval; however, these findings were isolated, lacked consistency, and were not supported by other functional, clinical or pathological indicators. They were therefore considered incidental and not adverse.

No treatment-related findings were observed at necropsy or on histopathological examination of nervous system tissues or other organs.

In conclusion, dietary administration of inpyrfluxam to rats for 90 days resulted in treatment-related and adverse effects on body weight and food consumption from 68 mg/kg bw/day in females and at 240 mg/kg bw/day in males, without evidence of neurotoxicity at any dose level. At doses relevant for classification, no evidence of significant or severe toxicity was observed.

28-day dermal toxicity study in rats (Anonymous, 2015)

A 28-day repeated-dose dermal toxicity study was conducted in rats in accordance with OECD TG 410 (1981) and under GLP conditions. Inpyrfluxam was administered to groups of Sprague Dawley Crl:CD rats (10/sex/dose) by 6-hour occlusive dermal application at dose levels of 0, 100, 300 or 1000 mg/kg bw/day for 28 consecutive days. Dose selection was based on a preceding acute dermal toxicity study in which no treatment-related effects were observed up to 2000 mg/kg bw, and the limit dose of 1000 mg/kg bw/day was therefore selected in line with the guideline.

No treatment-related effects were observed on mortality, clinical signs, body weight, food consumption, ophthalmology or urinalysis in either sex. Haematological evaluation showed a statistically significant increase in mean corpuscular haemoglobin (MCH) in females from 300 mg/kg bw/day; however, this change was within laboratory historical control ranges and was not considered treatment-related. Similarly, a decrease in sodium levels observed in females from 300 mg/kg bw/day was within historical control values.

Gross pathological examination identified isolated findings, including a yellowish patch in the epididymis in one male at 300 mg/kg bw/day and a white patch in the liver in one male at 100 mg/kg bw/day; these findings lacked a dose-response relationship and were not considered adverse. Organ weight analysis showed an increase in relative heart weight in males at 1000 mg/kg bw/day and increases in absolute and relative ovary weights, as well as relative brain weight, in females at lower doses; all changes were within historical control ranges or lacked dose-response and were not considered treatment-related or adverse. Histopathological findings, including a spermatic granuloma in the epididymis at 300 mg/kg bw/day and massive hepatocyte necrosis in the liver at 100 mg/kg bw/day, occurred in single animals only, correlated with gross findings, and were considered incidental.

In conclusion, repeated dermal exposure to inpyrfluxam for 28 days did not result in any treatment-related effects in rats. The results of this study do not support classification for STOT RE.

Mice Studies

90-day oral toxicity study in mice (Anonymous, 2016a)

A GLP-compliant 90-day dietary toxicity study was conducted in ICR [Crlj:CD1(ICR)] mice to evaluate the systemic toxicity of inpyrfluxam. Groups of 10 mice/sex/dose received dietary concentrations of 0, 200, 800, 3500 or 7000 ppm for approximately 13 weeks, corresponding to mean intakes of 0, 27.2, 111, 491 and 973 mg/kg bw/day in males and 0, 31.7, 130, 559 and 1097 mg/kg bw/day in females. The study was performed in accordance with OECD TG 408 (1998); deviations related to later guideline updates (e.g. endocrine- and reproductive-sensitive endpoints) were addressed in separate mechanistic, reproductive and long-term studies and do not affect the validity of the study.

There were no treatment-related deaths or clinical signs, and no effects on body weight, body weight gain, food consumption or haematological parameters in either sex at any dose level.

The target organ was the liver. At necropsy, dark-coloured and/or enlarged livers were observed at the top dose (973/1097 mg/kg bw/d) in both sexes. Consistent with these findings, dose-dependent increases in absolute and relative liver weights were observed from 491/559 mg/kg bw/d. At the top dose, relative liver weights were +33%* in males and +29%** in females. These liver weight changes correlated with histopathological findings from 491/559 mg/kg bw/d. Hepatocellular hypertrophy was observed in both sexes and centrilobular hepatocyte fatty change was reported in males. Changes in clinical chemistry parameters from 491/559 mg/kg bw/d were consistent with altered liver function. These consisted primarily of dose-dependent increases in globulin and corresponding reductions

in albumin/globulin ratio in both sexes, with decreases in albumin in females. Total cholesterol was also increased, reaching statistical significance in females at the top dose. Decreases in total bilirubin and isolated changes in glucose or calcium were not considered toxicologically relevant.

In the thyroid, follicular cell hypertrophy was observed at the top dose in both sexes, although the finding was statistically significant in males only. This finding was likely secondary to increased metabolism in the liver.

In conclusion, dietary administration of inpyrfluxam to mice for 90 days resulted in treatment-related effects in the liver from 491 mg/kg bw/d in males/559 mg/kg bw/d in females, with additional thyroid histopathology at the top dose. At doses relevant for classification (i.e., ≤ 100 mg/kg bw/d), there was no evidence of significant or severe toxicity.

Dog Studies

90-day oral toxicity study in dogs (Anonymous, 2017)

A 13-week toxicity study was conducted using inpyrfluxam in Beagle dogs (4 animals/sex/group), administered orally in gelatin capsules at dose levels of 0, 40, 160 or 700/500 mg/kg bw/day. The high dose was reduced from 700 to 500 mg/kg bw/day at week 4 due to marked toxicity, including decreased body weight and food consumption and vomiting of feed, with a temporary interruption of dosing at week 3. Overall, the top-dose group received 500 mg/kg bw/day for 13 weeks, corresponding to week 16 from treatment initiation. The study was conducted in compliance with GLP and OECD TG 409 (1998), with no deviations.

At the top dose, treatment-related mortality occurred, with one male and two females killed in extremis following deterioration in general condition. Clinical signs observed at this dose included reduced spontaneous motor activity, neurological signs such as staggering gait, changes in urine colour, and yellow discolouration of the eyes and/or oral mucosa. Histopathological examination of the animals killed in extremis revealed widespread lesions consistent with severe toxicity. No deaths occurred at any of the other doses, although vomiting was observed in both sexes from 160 mg/kg bw/day.

At the top dose, a sustained and marked reduction in body weight was observed in both sexes, exceeding 10% from early in the treatment period and persisting throughout the study, with statistical significance reached in males. These changes were accompanied by pronounced and persistent reductions in food consumption in both sexes, particularly during the early phase of treatment, and were considered treatment-related and adverse.

At 160 mg/kg bw/day, transient reductions in food consumption were observed in males during the early weeks of treatment; however, these effects were largely attributable to a

single animal, were not sustained, and were not considered adverse. No treatment-related effects on body weight were observed at this dose level.

Liver / gallbladder

Gross pathological examination revealed treatment-related and adverse findings in the liver from 160 mg/kg bw/day in both sexes. These comprised macroscopic changes in the liver, including dark discoloration and enlargement. Dose-dependent increases in absolute and relative liver weights were observed from 160 mg/kg bw/day in both sexes. Relative liver weights were +49%**, +69%** in males and + 38%**, +57%** in females at the mid- and top dose respectively. Histopathological examinations revealed hepatocellular hypertrophy, eosinophilic inclusions, single cell necrosis and pigment deposition from 160 mg/kg bw/d. Associated alterations in the gall bladder included calculi and biliary sludge. At the top dose, bile duct inflammation was also reported in 1/4 females. Treatment-related and adverse clinical chemistry changes were observed from 160 mg/kg bw/day in both males and females and were indicative of liver toxicity. These comprised marked increases in liver-associated enzymes, including alkaline phosphatase, γ-glutamyl transpeptidase and alanine aminotransferase, together with decreases in total cholesterol. In addition, dose-dependent decreases in albumin, globulin, albumin/globulin ratio and total protein were observed consistently at later timepoints from the mid dose and were considered treatment-related and adverse.

Increases in liver weight observed in males at 40 mg/kg bw/d were considered adaptive rather than adverse, as they were not accompanied by concordant changes in clinical chemistry parameters or histopathological findings beyond hepatocellular hypertrophy.

Kidney

In the kidneys, hypertrophy and cytoplasmic eosinophilic inclusion body in the proximal tubular cells were reported in males from 160 mg/kg bw/d. At the top dose, vacuolation in the proximal tubular cell was also reported in one male. Urinalysis findings were limited to decreased urine pH in males at the top dose.

Blood

Haematological changes consistent with anaemia were observed from 160 mg/kg bw/day in both sexes, characterised primarily by reductions in reticulocyte counts. Other haematological changes lacked a clear dose-response relationship or were inconsistent and not considered treatment-related.

Other findings

Histopathology revealed optic nerve fibre degeneration in females from 160 mg/kg bw/d and in both sexes at the top dose, however no findings were recorded during the

ophthalmological examinations. Changes were observed in certain clinical chemistry parameters, including triglycerides, aspartate aminotransferase, electrolytes, creatinine, glucose and total bilirubin, however the changes were inconsistent over time or lacked a dose-response relationship, and were therefore not considered treatment-related. Decreases in absolute heart weight were observed at the top dose in both sexes; however, in the absence of associated histopathological findings, these changes were considered secondary to reduced body weight rather than treatment-related toxicity. Statistically significant reductions in absolute and relative prostate weights were observed in males at the mid and top doses, but these effects were not associated with histopathological alterations and were therefore not considered adverse. Adrenal vacuolation was observed in males from 160 mg/kg bw/d and in both sexes at the top dose. Splenic congestion was also reported in both sexes at the top dose.

In conclusion, oral administration of inpyrfluxam to dogs for 13 weeks resulted in treatment-related adverse effects from 160 mg/kg bw/day, including vomiting, haematological changes indicative of anaemia, liver toxicity and adverse histopathological findings in multiple organs. The top dose (700/500 mg/kg bw/day) was highly toxic and resulted in mortality. In GB CLP, there are no guidance values for classification for dog studies. Therefore, the rat guidance values can be applied but with caution. At the low dose in this study (40 mg/kg bw/d, i.e., below the ≤ 100 mg/kg bw/d cut-off), there were no indications of significant or severe toxicity that would warrant classification. At the next highest dose (160 mg/kg bw/d), liver toxicity and altered liver function were observed, and a number of adverse findings were reported in other organs. However, as this dose is >1.5 times the guidance value for classification in the rat, it is questionable whether the findings are relevant for classification.

One-year oral toxicity study in dogs (Anonymous, 2016)

A one-year toxicity study was conducted in Beagle dogs in accordance with OECD TG 452 (2009). Inpyrfluxam was administered in gelatine capsules to 4 dogs/sex/group at dose levels of 0, 2, 6, 30 or 160 mg/kg bw/d for 52 weeks. Dose levels were selected based on the preceding 90-day dog study. In addition to standard guideline investigations, plasma concentrations of inpyrfluxam were determined on Day 1 and at weeks 13, 26 and 52 to characterise systemic exposure.

Inpyrfluxam was systemically available in both sexes, with plasma concentrations increasing in a dose-dependent manner at doses ≥6 mg/kg bw/day. Exposure was comparable between males and females, and no evidence of accumulation following repeated administration was observed over the treatment period. At 2 mg/kg bw/d, plasma concentrations were generally below the limit of quantification.

No mortality occurred in any treatment group. An increased incidence of vomiting of feed was observed at 160 mg/kg bw/d in both sexes and in a single female at 30 mg/kg bw/d.

No treatment-related effects were observed on body weight, food consumption, ophthalmology, haematology or urinalysis at any dose level.

Liver

Dose-related increases in absolute and relative liver weights were observed in both sexes from 30 mg/kg bw/d. Relative liver weights were +24%*, +54%** in males and +19%, +40%* in females at 30 and 160 mg/kg bw/d. At necropsy, an increased incidence of dark-coloured livers was observed in males and liver enlargement was observed in both sexes at 160 mg/kg bw/day. Histopathological examination revealed diffuse hepatocyte hypertrophy in males at 30 mg/kg bw/day and in both sexes at 160 mg/kg bw/day, along with cytoplasmic eosinophilic inclusion bodies in the liver at the top dose. Clinical chemistry changes indicative of liver toxicity were observed: at 160 mg/kg bw/day, both sexes showed marked increases in alkaline phosphatase, alanine aminotransferase and γ-glutamyl transpeptidase, accompanied by decreases in albumin, albumin/globulin ratio, total cholesterol and calcium in males, and decreases in potassium, triglycerides and total cholesterol in females. At 30 mg/kg bw/day, males showed consistent increasing trends in alkaline phosphatase and γ-glutamyl transpeptidase. All these changes were considered treatment-related.

Adrenal gland

Females had increased relative adrenal weights (+31%**) at 160 mg/kg bw/day, which was considered treatment-related. Adrenal zona fasciculata cell vacuolation was observed in both sexes from 30 mg/kg bw/day.

Optic nerve

Optic nerve fibre degeneration was reported in both sexes from 30 mg/kg bw/d. However, no findings were reported during the ophthalmological examinations, and no histopathological abnormalities were observed in related tissues. Furthermore, no clinical signs indicative of vision disorders were recorded. As, the toxicological significance of this finding isn’t clear.

Other findings

A single renal finding at 30 mg/kg bw/day (proximal tubular inclusion bodies in one male) was considered incidental due to the absence of a dose–response relationship.

In summary, following oral administration of inpyrfluxam to dogs for 52 weeks, the target organs were the liver, adrenal glands (at doses ≥ 30 mg/kg bw/d) and optic nerve at 160 mg/kg bw/d.

10.9.2 Comparison with the GB Classification Criteria

No human data are available. The assessment of STOT RE is therefore based on a weight of evidence assessment considering the animal studies described above. When considering animal data, classification for STOT RE is assigned on the basis of findings that indicate ‘significant’ or ‘severe’ toxicity, occurring at low or moderate doses, and considered to be relevant for humans. In this context ‘significant’ means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. ‘Severe’ effects are generally more profound or serious than ‘significant’ effects and are of a considerably adverse nature which significantly impact on health.

The guidance values (GV, see Table 24) are used to determined whether the findings warrant classification in Category 1 (i.e., significant or severe toxicity is observed at generally low doses) or Category 2 (significant or severe toxicity is observed at generally moderate doses). Findings at high doses generally do not support classification.

The liver was a target organ in both sexes of all three species tested. In mice, effects in the liver were observed from 491/559 mg/kg bw/d in a 90-day oral study, which is well above the GV for classification. In rats, increased liver weight accompanied by hepatocellular hypertrophy and enzyme induction was seen from 246/263 mg/kg bw/d in a 28-day oral study, which is below the adjusted guidance value (GV) for classification in category 2. The same effects were seen in the 90-day oral study in rats, but at doses above the GV. These findings are consistent with an adaptive metabolic response rather than a toxic effect in the liver, and therefore they do not support classification. In dogs, increased liver weight and hepatocyte hypertrophy were noted from 160 mg/kg bw/d in both the 90-day and 1-year study. Again, these findings are consistent with an adaptive metabolic response rather than a toxic effect in the liver and therefore do not support classification. Single cell necrosis was reported in 1 dog at 160 mg/kg bw/d in the 90-day study, which is an adverse finding indicative of liver toxicity. However, necrosis was not reported at the same dose in the 1-year study, and so the reliability of this finding is questionable. Furthermore, 160 mg/kg bw/d is considerably above the GV for category 2 in rats (100 mg/kg bw/d for a 90-day study), therefore the necrosis seen in a single animal does not warrant classification. Overall, the data do not support classification for effects in the liver.

Thyroid follicular cell hypertrophy was reported in all three species, but was only seen at doses relevant for classification in rats (i.e., from 246/263 mg/kg bw/d in the 28-day study). The findings in the thyroid are likely to be secondary to the increased metabolism in the liver, and not a specific toxic effect on the thyroid. Therefore, classification of effects in the thyroid is not warranted.

The kidney was a target organ in male rats. Increased kidney weight accompanied by hyaline droplet accumulation in the renal proximal tubules, associated with α2μ-globulin, was observed from 246 mg/kg bw/d in the 28-day study. This dose is below the adjusted

GV for Category 2, however nephropathy in male rats associated with α2μ-globulin is not considered to be relevant to humans (ECHA, 2024), therefore these findings do not support classification. In dogs, kidney findings were reported at 160 mg/kg bw/d in the 90-day study (hypertrophy and cytoplasmic eosinophilic inclusion body in the proximal tubular cells). These findings do not represent significant or severe toxicity; furthermore, the findings were only seen in males and were not consistent across studies – i.e., they were not reported at the same dose in the 1-year study. Overall, effects reported in the kidneys of rats and dogs do not warrant classification.

Other findings seen in rats at doses relevant for classification included reduced ovary weight, ovarian vacuolation, decreased uterus weight, slight uterine atrophy, bone marrow fatty infiltration (slight to mild) and adrenal cortical vacuolation. Although these findings are considered adverse, they are not considered to represent significant or severe toxicity and therefore do not support classification.

In dogs, optic nerve fibre degeneration was reported (from 160 mg/kg bw/d in both the 90-day study and the 1-year study). However, no findings were recorded during ophthalmological examinations, and no clinical signs indicative of vision disorders were reported. No histopathological findings were reported in related tissues. Effects in the optic nerve were not reported in rats or mice. As such, the toxicological significance of this finding is unclear, and it is not considered sufficient to justify classification.

Overall, STOT RE has been well investigated in rats, mice and dogs. The main target organ across all three species was the liver. At doses relevant for classification, there was no clear evidence of severe or significant toxicity, and therefore classification is not warranted.

10.9.3 Conclusion on classification and labelling for STOT RE

Not classified – conclusive but not sufficient for classification.

10.10 Germ cell mutagenicity

Table 26: Summary of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Bacterial reverse mutation test (OECD TG 471) Deviations: Use of AF-2 as a positive control for *WP2uvrA* without S9; justified and acceptable. GLP compliance: Yes	Inpyrfluxam (S-2399 Technical Grade) Batch ID:13CG0617G Purity: 95.0%	*S. typhimurium* strains TA100, TA1535, TA98, TA1537, and *E. coli* strain WP2uvrA. Pre-incubation method with and without S9 (Aroclor 1254-induced rat liver S9). Test concentrations: 313–5000 µg/plate for WP2uvrA and TA98; 19.5–625 µg/plate for TA100, TA1535, and TA1537. Vehicle control: DMSO. Positive controls included AF-2 (without S9 for WP2uvrA and TA98) and 2-aminoanthracene (with S9 for all strains).	**Negative.** No dose-dependent or statistically significant increase in revertant colonies was observed with or without S9. Precipitation was observed at ≥1500 µg/plate. Cytotoxicity was observed in some strains at 500 µg/plate and higher.	KCA 5.4.1/01, Anonymous (2014a/2017)
Chromosomal aberration test (OECD TG 473) Deviations: Scoring of 200 cells instead of 300 and lack of pH/osmolarity	Inpyrfluxam (S-2399 Technical Grade) Batch ID:13CG0617G Purity:	Tested on Chinese hamster lung cells (CHL/IU). Concentrations: 32.5–130 µg/mL (-S9 short-term), 42.5–170 µg/mL (+S9 short-term), and 0.188–1.5	**Negative.** No biologically relevant or statistically significant increase in structural aberrations. A slight increase at 1.5 µg/mL (-S9, 24 h) occurred under highly cytotoxic conditions and was	KCA 5.4.1/02, Anonymous (2014b)

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
measurements ; deviations did not impact validity. GLP compliance: Yes	95.0%	µg/mL (-S9 long-term). Controls: MMC for -S9 and CP for +S9.	deemed not-relevant. Positive and vehicle controls behaved as expected. Cytotoxicity based on relative increase in cell count (RICC). Precipitation observed at ≥425 µg/mL.	
Mammalian gene mutation test (OECD TG 476) Deviations: None GLP compliance: Yes	Inpyrfluxam (S-2399 Technical Grade) Batch ID:13CG0617G Purity: 95.0%	Chinese hamster lung fibroblast cells (V79). Test concentrations: 6.5–39 µg/mL (4 h -S9), 6.5–78 µg/mL (4 h +S9), and 13–78 µg/mL (24 h -S9). Cytotoxicity based on relative survival (RS), with precipitation observed at ≥104 µg/mL. Vehicle control: DMSO. Positive controls: EMS for -S9 and DMBA for +S9.	**Negative.** No biologically relevant/ reproducible increase in mutant colonies. Slight increases at high concentrations were attributed to excessive cytotoxicity (RS ≤7.7%) and were within historical control ranges. Positive and vehicle controls performed as expected.	KCA 5.4.1/03, Anonymous (2014)

Table 27: Summary of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Mouse micronucleus test (OECD TG 474, 1997) Deviations: 1. A single administration was performed without scientific justification. 2. No peripheral blood samples were analysed to confirm target organ exposure. GLP compliance: Yes	Inpyrfluxam (S-2399 Technical Grade) Batch ID:13CG0617G Purity: 95.0%	Tested on CD-1 mice. Single dose via oral gavage with bone marrow sampling at 24 h (all dose groups) and 48 h (800 mg/kg bw and control only). Dose levels: 200, 400, and 800 mg/kg bw. Vehicle control: corn oil (10 mL/kg). Positive control: cyclophosphamide (60 mg/kg bw). Bone marrow cytotoxicity assessed via PCE/erythrocyte ratio.	**Negative**. No significant increase in micronucleated PCEs was observed at any dose level in either sex. Clinical signs of toxicity and mortality occurred at 800 mg/kg bw. Positive and vehicle controls gave expected results, which were within historical control data. Deviations did not impact study integrity; systemic and target organ exposure were confirmed by bone marrow cytotoxicity, clinical signs of toxicity, and mortality at the highest dose.	KCA 5.4.2/01, Anonymous (2015)

10.10.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

Inpyrfluxam has been assessed for genotoxic potential through a combination of *in vitro* and *in vivo* studies, all conducted in compliance with GLP and OECD test guidelines. The *in vitro* battery included bacterial reverse mutation (OECD TG 471), chromosomal aberration (OECD TG 473) and mammalian cell gene mutation assays (OECD TG 476). These studies, performed across appropriate concentration ranges, showed no evidence of mutagenicity, clastogenicity, or aneugenicity.

An *in vivo* micronucleus test (OECD TG 474) evaluated inpyrfluxam's clastogenicity and aneugenicity in the somatic cells of CD-1 mice. No increase in micronucleated immature erythrocytes was observed at doses up to 800 mg/kg body weight. The study confirmed systemic and bone marrow exposure, evidenced by cytotoxic effects at higher doses, supporting the reliability of the negative result.

Tests for photomutagenicity were deemed unnecessary because inpyrfluxam showed no evidence of phototoxicity induction.

10.10.2 Comparison with the GB CLP criteria

Inpyrfluxam has been tested in three *in vitro* assays and one *in vivo* study in somatic cells. None of these studies showed any evidence of genotoxicity. Therefore, inpyrfluxam does not meet the requirements for classification for germ cell mutagenicity under GB CLP.

10.10.3 Conclusion on classification and labelling for germ cell mutagenicity

Not classified – conclusive but not sufficient for classification.

10.11 Carcinogenicity

The long-term toxicity and carcinogenic potential of inpyrfluxam were investigated in two separate studies: a combined chronic toxicity and carcinogenicity study in rats and a standalone carcinogenicity study in mice. Both studies were performed under GLP conditions and adhered to the respective OECD test guidelines, with no reported deviations.

Table 28: Summary of animal studies on carcinogenicity

Note: ↑↓ denote an increase or decrease in a parameter with respect to the control value
Statistical significance: * p ≤ 0.05, ** p ≤ 0.01
abs. = absolute
rel. = relative

Method, guideline, deviations if any, species, strain, sex, no/group **Reference**	**Test substance, dose levels duration of exposure**	**Results**
Long-term toxicity and carcinogenicity in rats (OECD TG 453, 2009) No deviations GLP compliant: Yes KCA 5.5/01 and KCA 5.5/02, Anonymous	Inpyrfluxam (S-2399 Technical Grade), 95% purity; Dietary exposure at 0, 150, 500, 2000 ppm (males only), 1500/1000 ppm (females only). Chronic toxicity (52 weeks, 21/group), Carcinogenicity (104 weeks, 51/group)	**Chronic toxicity phase (52 weeks):** At 2000 ppm (males) and 1500/1000 ppm (females), ↓ body weight (6% males; 24% females) and ↓ body-weight gain (8% males; 37% females), with reduced food consumption (particularly in females). Haematology: ↓ neutrophils (41%) and ↓ monocytes (40%) in females. Clinical chemistry (males): ↑ γ-glutamyl transpeptidase and ↑ albumin/globulin ratio (~16%) with ↓ globulin (~13%), indicative of liver effects. Organ weights: ↑ relative liver weight (11%) in males. No treatment-related adverse effects at 150 or 500 ppm. **Carcinogenicity phase (104 weeks):** At 2000 ppm (males) and 1500/1000 ppm (females), ↓ body weight (13% males; 19% females) and ↓ body-weight gain (18% males; 27% females), with reduced food consumption. Haematology: ↓ neutrophils (20% males;

Method, guideline, deviations if any, species, strain, sex, no/group **Reference**	**Test substance, dose levels duration of exposure**	**Results**
(2017)	Mean substance intakes (mg/kg bw/day): Chronic Toxicity (52 weeks): Males: 0, 6.77, 22.8, 95.9 mg/kg bw/day; Females: 0, 8.84, 30.1, 86.4 mg/kg bw/day Carcinogenicity (104 weeks): Males: 0, 5.85, 19.4, 78.4 mg/kg bw/day; Females: 0, 7.47, 25.5, 65.8 mg/kg bw/day	35% females) and ↓ monocytes (19% males; 28% females); ↓ white blood cell count (23%) in females. No treatment-related non-neoplastic lesions. No treatment-related effects at 150 or 500 ppm. **Neoplastic findings:** no treatment-related tumours.
Carcinogenicity Study in Mice (OECD TG 451, 2009) No deviations GLP-compliant: Yes KCA 5.5/03, Anonymous (2017)	Inpyrfluxam (S-2399 Technical Grade), 95% purity Species/Strain: Mice, ICR CD1 [Crlj:CD1(ICR)], M&F Dietary Exposure: 0, 700, 2000, 7000/5000 ppm <u>Mean substance intakes</u> *Males (satellite group):* 0, 77.1, 240 and 826 mg/kg bw/day *(carcinogenicity group):* 0, 77, 224, and 775 mg/kg bw/day	**Satellite group (52 weeks)** At **7000/5000 ppm** (826 mg/kg bw/day males; 790 mg/kg bw/day females): ↓ Body weight (6% males; 20% females) ↓ Body-weight gain (23% males; 35% females) Liver: hepatocellular hypertrophy (centrilobular in males; diffuse in females) Kidney: diffuse luminal dilatation of proximal renal tubules in males **At 2000 ppm (240 mg/kg bw/day males; 222 mg/kg bw/day females):** Centrilobular hepatocellular hypertrophy and renal tubular dilatation observed in males. No treatment-related adverse effects at **700 ppm**. **Carcinogenicity group (78 weeks)** **At 7000/5000 ppm (775 mg/kg bw/day males; 701 mg/kg bw/day females):** ↓ Body weight (13% males; 11% females) ↓ Body-weight gain (37% males; 24% females) Liver: hepatocellular hypertrophy (centrilobular in males; diffuse in females) Kidney: diffuse luminal dilatation of proximal renal tubules in males

Method, guideline, deviations if any, species, strain, sex, no/group Reference	Test substance, dose levels duration of exposure	Results
	Females: (chronic toxicity phase): 0, 72.9, 222, and 790 mg/kg bw/day *(carcinogenicity phase):* 0, 69.3, 210, and 701 mg/kg bw/day	Systemic amyloidosis affecting multiple organs in males **At 2000 ppm (224 mg/kg bw/day males; 210 mg/kg bw/day females):** Centrilobular hepatocellular hypertrophy in males Amyloid nephropathy in both sexes Amyloidosis in cervical lymph nodes and glandular stomach in females No treatment-related adverse effects at **700 ppm**. **Neoplastic findings:** no treatment-related tumours.

10.11.1 Short summary and overall relevance of the provided information on carcinogenicity

Rat chronic toxicity and carcinogenicity study

A combined chronic toxicity and carcinogenicity study was conducted in Wistar Hannover rats via dietary administration. The study followed OECD TG 453 (2009) under GLP conditions. Males received 0, 150, 500, or 2000 ppm (equivalent to 0, 6.77, 22.8, and 95.9 mg/kg bw/day in the 52-week phase; 0, 5.85, 19.4, and 78.4 mg/kg bw/day in the 104-week phase). Females received 0, 150, 500, or 1500 ppm (reduced to 1000 ppm from week 46 due to body weight loss; equivalent to 0, 8.84, 30.1, and 86.4 mg/kg bw/day in the 52-week phase; 0, 7.47, 25.5, and 65.8 mg/kg bw/day in the 104-week phase). The chronic toxicity phase lasted 52 weeks (21 rats/sex/group) and the carcinogenicity phase 104 weeks (51 rats/sex/group).

Plasma monitoring confirmed systemic exposure at all doses in females and only at the highest dose in males, with no evidence of accumulation.

Body weight and food consumption

At the highest dietary concentrations (2000 ppm in males; 1500/1000 ppm in females), reduced body weight and body-weight gain were observed in both phases. In the 52-week chronic toxicity phase (95.9 mg/kg bw/day in males; 86.4 mg/kg bw/day in females), final body weight was ↓6% in males and ↓24% in females, with body-weight gain ↓8% in males

and ↓37% in females. The reduction was statistically significant in females, while males showed only transient significance during the study.

In the 104-week carcinogenicity phase (78.4 mg/kg bw/day in males; 65.8 mg/kg bw/day in females), final body weight was ↓13% in males and ↓19% in females, with body-weight gain ↓18% in males and ↓27% in females, respectively. Reductions were statistically significant at most time points.

Food consumption was also reduced at the highest dose in both sexes in both phases.

Haematology

In the chronic phase, high-dose females showed decreased neutrophils (−41%) and monocytes (−40%). In the carcinogenicity phase, decreases in neutrophils (−20% males, −35% females), monocytes (−19% males, −28% females), and total white blood cells (−23% females) were observed at the highest dose. Changes at 19.4/25.5 mg/kg bw/day (e.g. increased haematocrit, Hb, neutrophils) were not dose-related and considered incidental.

Clinical chemistry

At 78.4 mg/kg bw/day in males, increases in γ-glutamyl transpeptidase (GGTP) and albumin/globulin ratio were noted, together with decreased globulin levels. In females, increased ALP was observed at 65.8 mg/kg bw/day. Bilirubin changes (↑ in males, ↓ in females) were not dose-related and not considered adverse.

Organ weights

Chronic phase (52 weeks): At 78.4 mg/kg bw/day in males, relative liver weight was increased (+11%), with smaller increases in heart (+10%) and testes (+9%). In females at 65.8 mg/kg bw/day, increases were seen in relative liver (+5%), kidney (+18%), adrenal (+18%), brain (+29%), thyroid (+11%), spleen (+6%) and uterus (+48%), along with decreased thyroid (−9%) and increased ovary weights (+25%) from 25.5 mg/kg bw/day.

Carcinogenicity phase (104 weeks): At 78.4 mg/kg bw/day in males, absolute thyroid (−71%), kidney (−21%), and adrenal (−23%) weights were decreased. In females at 65.8 mg/kg bw/day, relative brain weight was increased (+21%) and absolute kidney weight decreased (−15%). Many changes were considered secondary to reduced terminal body weights.

Histopathology

In the chronic phase, haemosiderin deposition in the spleen was increased in high-dose females but judged non-adverse. Minor non-neoplastic findings (e.g. alveolar macrophage accumulation, nephropathy, adrenal peliosis) were observed sporadically but without clear

treatment relationship. In the carcinogenicity phase, no treatment-related non-neoplastic changes were identified. No increases in tumour incidence were observed at any dose.

Conclusions

In this study, inpyrfluxam was **not carcinogenic** in rats when tested up to the maximum tolerated dose.

Mice carcinogenicity study

A carcinogenicity study of inpyrfluxam was conducted in ICR CD1 [Crlj:CD1(ICR)] mice via dietary administration. The study followed OECD TG 451 (2009) and was GLP-compliant. The test substance was administered at dietary concentrations of 0, 700, 2000, and 7000 ppm, with the top dose reduced to 5000 ppm at week 53 in males and week 52 in females due to excessive body weight loss. Based on food consumption and body weight data, these concentrations corresponded to mean intakes of approximately 77/69 mg/kg bw/day (M/F) at 700 ppm, 224/210 mg/kg bw/day (M/F) at 2000 ppm, and 775/701 mg/kg bw/day (M/F) at 7000/5000 ppm over the 78-week carcinogenicity phase. In the 52-week satellite groups, mean intakes were 77.1/72.9 mg/kg bw/day (M/F), 240/222 mg/kg bw/day (M/F), and 826/790 mg/kg bw/day (M/F) at the respective dose levels. The small differences between males and females reflect differences in food consumption relative to body weight.

The study consisted of two groups: a satellite group (52 weeks, 12 animals/sex/dose) and a carcinogenicity group (78 weeks, 52 animals/sex/dose). The satellite group was included to assess early toxic effects, whereas the carcinogenicity group was maintained for the full 78 weeks to evaluate long-term carcinogenic potential. Plasma analysis at week 52 confirmed the presence of inpyrfluxam at mid and high doses but not at the low dose.

No treatment-related mortality was reported in any of the dose groups. However, at 7000/5000 ppm, some males displayed signs of emaciation, pale skin, and pale-coloured eyes, which were considered treatment-related and adverse. Body weight and body weight gain reductions were observed in both the satellite and carcinogenicity groups, with a more pronounced effect at high doses. In the satellite group, males showed a 6% reduction in final body weight and a 23% reduction in body weight gain, while females exhibited 20% and 35% reductions, respectively. In the carcinogenicity group, the reductions were more pronounced in males, with final body weights lowered by 13% and body weight gain reduced by 37%. Females at high doses also showed reductions, albeit to a lesser extent, with 11% lower final body weight and 24% lower body weight gain.

Food consumption was also affected, particularly at high doses. In the satellite group, significant reductions were observed in males (weeks 1, 44, 48) and females (weeks 7 and 10). In the carcinogenicity group, similar reductions occurred in males (weeks 1, 7, 28, 40,

44, 48) and females (weeks 1-12, 36). However, these effects were transient and not sustained throughout the study.

Pathological examinations revealed notable gross and histopathological findings in the liver and kidneys. In the satellite group, males at high dose exhibited dark-coloured livers, and histological analysis showed centrilobular hepatocellular hypertrophy in mid- and high-dose males. Additionally, diffuse luminal dilation of renal proximal tubules was observed at the high dose in males. In the carcinogenicity group, similar hepatic and renal effects were noted, with an increase in diffuse hepatocellular hypertrophy in high-dose females. Amyloid nephropathy was present from 2000 ppm in both sexes and was statistically significant at 7000/5000 ppm in males.

A significant increase in systemic amyloidosis was observed, affecting multiple organs in high-dose males, including the heart, liver, kidney, thyroid, adrenal, mesenteric lymph nodes, duodenum, forestomach, and extra orbital lacrimal gland. In females, systemic amyloidosis was observed from 2000 ppm in the cervical lymph nodes and glandular stomach, with an increase at high doses. These findings were considered treatment-related and adverse.

No neoplastic findings were observed.

The study demonstrated that in mice, long-term dietary exposure to high doses of inpyrfluxam results in adverse toxicological effects, particularly in the liver and kidneys, with systemic amyloidosis observed from 2000 ppm. There were no carcinogenic effects observed in either sex at any dose.

10.11.2 Comparison with the GB CLP criteria

There is no evidence to suggest that inpyrfluxam induces carcinogenicity in humans; therefore, classification under Category 1A is not warranted.

Category 1B is designated for substances that are presumed to be carcinogenic to humans, primarily based on evidence from animal studies. However, the available studies on inpyrfluxam did not report any significant tumour findings that would justify classification under this category.

A substance is classified under Category 2 if there is evidence of carcinogenic effects in animal studies, though not strong enough to warrant placement in Category 1A or 1B. For inpyrfluxam to be considered for Category 2, there must be clear evidence of a treatment-related increase in tumour incidence in the available studies.

In both the rat and mouse studies, there were no neoplastic findings that could be attributed to inpyrfluxam exposure, even at the highest doses tested where systemic

toxicity was observed. Therefore, inpyrfluxam does not meet the criteria for Category 2 classification.

10.11.3 Conclusion on classification and labelling for carcinogenicity

Not classified – conclusive but not sufficient for classification.

10.12 Reproductive toxicity

10.12.1 Adverse effects on sexual function and fertility

Table 29: Summary of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group, reference	Test substance, dose levels duration of exposure	Results
Dose range-finding reproduction toxicity Study Rats, Wistar strain, 8/sex/group Non-guideline; non-GLP. KCA 5.6.1/01, Anonymous (2015a)	Inpyrfluxam (S-2399 Technical Grade) Purity: 95% Oral (dietary) administration Dietary doses: 0, 300, 1000, 2000, 4000 ppm. Equivalent to: M: 15.1, 50.4, 105, 203 mg/kg bw/day; F: 20.4, 68, 132, 254 mg/kg bw/day. Administered for 15 weeks (pre-mating to	**Parental toxicity:** **4000 ppm:** ↓ body weight (↓ up to 20%) and ↓ weight gain in both sexes; ↓ food consumption in males (weeks 1, 2, 7–10) and females (entire period); ↑ rel. liver weight in males (↑24%) and females (↑23%); ↓ absolute ovary weight (↓29%); ↑ rel. testes (↑19%) and epididymis (↑11%) in males; dark liver in 3 males. **2000 ppm:** ↓ weight gain in females (gestation/lactation); ↓ food consumption; ↑ rel. liver weight in males (↑16%); ↓ absolute ovary weight in females (↓18%). **1000 and 300 ppm:** No treatment-related findings. **Offspring:** **4000 ppm:** ↓ body weight from LD4 in M and F pups (↓ up to 56%); ↑ rel. brain weight (↑75% M, ↑95% F); ↓ abs. brain weight (↓12% M, ↓16% F); ↓ rel. spleen weight (↓30% M, ↓29% F); ↓ thymus weight (↓61% M, ↓72% F); ↓ uterus weight in F (↓56%). Eye enlargement (M and F) and opacity (M); histopathology: synechia, cataract, retinal atrophy, haemorrhage; delayed vaginal opening in F pups (+12 days). **2000 ppm:** ↓ pup body weight (↓ up to 27%); ↑ rel. brain weight (↑28% M, ↑29% F); ↓ spleen weight (↓34% both sexes); ↓ thymus weight (↓31% M); ↓ uterus weight (↓34%); eye enlargement in 1 female; delayed vaginal opening (+4 days).

Method, guideline, deviations if any, species, strain, sex, no/group, reference	Test substance, dose levels duration of exposure	Results
	necropsy of F1).	**1000 ppm:** ↓ thymus weight (↓16% F); ↓ uterus weight (↓21%). **300 ppm:** No treatment-related findings.
Two-generation reproductive toxicity study OECD TG 416 (2001) GLP compliant Rat, Wistar Hannover strain, 24/sex/group No deviations KCA 5.6.1/02, Anonymous (2017)	Inpyrfluxam (S-2399 Technical Grade) Purity 95% Dietary administration Dietary doses: 0, 150, 500, 1250 ppm (females) / 2000 ppm (males) Mean substance intakes: Males: 8.34, 27.8, 113 mg/kg bw/day Females: 10.9, 35.5, 86 mg/kg bw/day Duration: two successive generations (approx. 18 weeks per generation).	**Parental toxicity:** **F0 Generation** 1250/2000 ppm (113 mg/kg bw/day males, 86 mg/kg bw/day females): ↓ mean body weight (↓3.6% males, ↓5.7% females); ↓ body weight gain (↓5.6% males, ↓11% females); ↓ food consumption. Organ weights: ↑ relative liver weight (↑11.7% males, ↑16.8% females). ↑ absolute thyroid weight in females (↑26.1%), relative (↑33.3%). Histopathology: Thyroid follicular hypertrophy in females (16/24). 500 ppm (27.8 mg/kg bw/day males, 35.5 mg/kg bw/day females): Minor liver weight increases (females absolute ↑9.3%, relative ↑11.1%) considered non-adverse. **F1 Generation** 1250/2000 ppm (113 mg/kg bw/day males, 86 mg/kg bw/day females): ↓ mean body weight (↓8.6% males, ↓6.1% females); ↓ body weight gain (↓9.6% males, ↓5.7% females); ↓ food consumption. Organ weights: ↑ relative liver weight (↑7.8% males, ↑25.1% females). ↑ absolute thyroid weight in females (↑26.7%), relative (↑35.2%). Histopathology: Thyroid follicular hypertrophy in females (10/22). **Reproductive toxicity:** No adverse effects on fertility or reproductive performance in F0 and F1. **Offspring toxicity (F1 and F2):** 1250/2000 ppm: ↓ pup body weights during lactation (up to ↓8.2% males, ↓7.7% females); minor non-adverse organ weight changes; no gross

Method, guideline, deviations if any, species, strain, sex, no/group, reference	Test substance, dose levels duration of exposure	Results
		pathological observations.

10.12.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

Range-finding reproductive/developmental study (Anonymous, 2015a)

In this study, groups of 8 Wistar rats/sex/dose received inpyrfluxam via dietary administration at concentrations of 0, 300, 1000, 2000 or 4000 ppm (equivalent to 15.1, 50.4, 105 or 203 mg/kg bw/day in males and 20.4, 68, 132 or 254 mg/kg bw/day in females) for approximately 15 weeks, covering pre-mating, gestation, lactation, and weaning phases. Offspring (F1) continued on test diets until necropsy or assessments of sexual development.

Parental toxicity (F0)

There were no deaths or specific clinical signs observed. However, statistically significant decreases in body weight and body-weight gain were observed in males at 203 mg/kg bw/day. In females, statistically significant decreases in body weight and body-weight gain were observed from 132 mg/kg bw/day, including reductions of approximately 10–12% during lactation. Food consumption was also statistically significantly reduced in males at 203 mg/kg bw/day and in females from 132 mg/kg bw/day, with decreases observed at week 1 and during lactation days 7–14 at 132 mg/kg bw/day and throughout the treatment period at 254 mg/kg bw/day.

Organ-weight analysis revealed statistically significant increases in relative liver weight in males from 50.4 mg/kg bw/day, reaching 16% at 105 mg/kg bw/day and 24% at 203 mg/kg bw/day, with a statistically significant increase in absolute liver weight of 15% at 105 mg/kg bw/day. In females, relative liver weight was statistically significantly increased at 254 mg/kg bw/day (23%). A decrease in absolute ovary weight was observed at 132 mg/kg bw/day (18%) and at 254 mg/kg bw/day (29%). Increases in relative weights of the testes (19%) and epididymis (11%) were also noted in males at 203 mg/kg bw/day; however, these were considered by the applicant to be secondary to body weight reductions. Three males at 203 mg/kg bw/day presented with darkened livers. Although no histopathological analyses were conducted in this study, the Agency considers that the observed weight changes are consistent with systemic toxicity.

Reproductive toxicity

No adverse effects on mating, fertility, or litter outcomes were identified. However, a delay in the timing of vaginal opening was recorded in F1 weanlings at 132 mg/kg bw/day (4 days) and at 254 mg/kg bw/day (12 days). This delay is considered by the Agency to be secondary to reduced body weights during lactation and the post-weaning growth period, and not a direct reproductive effect.

Offspring toxicity (F1)

In F1 pups, statistically significantly reductions in body weight occurred from lactation day 4 at ≥132 mg/kg bw/day in both sexes. At 132 mg/kg bw/day, pup body weights were reduced by approximately 23–28% compared with controls across days 4–21. At 254 mg/kg bw/day, more pronounced reductions were observed, reaching 20–52% lower body weights across the same period in males and females. Eye enlargement, and in one case opacity, occurred at 132 and 254 mg/kg bw/day; histopathology confirmed ocular lesions such as cataract, synechia, haemorrhage, and retinal atrophy. Organ weight changes included significantly increased relative brain weights from 132 mg/kg bw/day (ranging from 28 to 95%) and reduced absolute brain weights at 254 mg/kg bw/day (12 to 16%). Decreases in spleen weight were observed at 254 mg/kg bw/day, with reductions of up to 30% in relative weight. Thymus weight was reduced from 203 mg/kg bw/day in males (by 31%) and from 68 mg/kg bw/day in females (by 16%), while uterus weight was decreased from 68 mg/kg bw/day, with the highest reduction of 56% seen at 254 mg/kg bw/day.

Conclusion

In this non-GLP, range-finding study, dietary administration of inpyrfluxam resulted in adverse effects in the parental animals, including reductions in body weight, food consumption, and changes in liver (males) and ovary (females) weights from 105/132 mg/kg bw/day (males/females). In the offspring, effects on body weight, brain, thymus, spleen, uterus, and eye morphology were noted from 68–132 mg/kg bw/day. These findings support the selection of a top dose below 132 mg/kg bw/day for the subsequent reproductive toxicity study in rats.

Two-generation reproductive toxicity study

A two-generation reproductive toxicity study was conducted in Wistar Hannover rats using dietary administration of inpyrfluxam at concentrations of 0, 150, 500 and 2000 ppm in males and 0, 150, 500 and 1250 ppm in females, as the highest dose differed between sexes. These concentrations corresponded to mean intakes of 8.34, 27.8 and 113 mg/kg bw/day in males and 10.9, 35.5 and 86 mg/kg bw/day in females. The study was performed in compliance with GLP and OECD TG 416 and included evaluations of general toxicity, reproductive performance and offspring development across two successive generations.

Parental toxicity (F0 generation)

In F0 parental animals, statistically significant reductions in body weight were observed in females at the highest dose (86 mg/kg bw/day) from week 2 onward and persisted throughout the study. In contrast, male body weights at the highest dose (113 mg/kg bw/day) were slightly lower than controls but were not statistically significant. For body-weight gain, statistically significant reductions were observed in high-dose females during the pre-mating period and overall treatment interval, whereas high-dose males showed only transient statistically significant decreases during the first two weeks of treatment. Overall differences in body weight relative to controls remained ≤10%

At the high dose, there were significant decreases in food consumption in F0 males during weeks 1 and 5 (113 mg/kg bw/day), and in F0 females during weeks 1, 2, 4, 5, 6 and 8, as well as on lactation days 7–14 (86 mg/kg bw/day).

In F0 females, increases in relative liver weights (+16.8%) were observed at 86 mg/kg bw/day. At this dose, there were also statistically significant increases in both absolute (+26.1%) and relative (+33.3%) thyroid weights, accompanied by histopathological findings of follicular cell hypertrophy (16/24 females compared with 3/24 controls).

In F0 males, increases in relative liver weights (+11.7%) were seen at 113 mg/kg bw/day, but thyroid weight changes were not observed. Histopathological evaluation confirmed diffuse hepatocyte hypertrophy in 7/24 high-dose males, whereas no such lesions were seen in controls or lower-dose groups. The applicant considered this effect non-adverse, as it did not result in a liver weight increase exceeding 15%.

Statistically significant increases in relative kidney weights were observed in F0 females from the mid-dose group onwards (35.5 mg/kg bw/day and above; 5% increase). However, the changes were small, showed no clear dose-response, and were not associated with any histopathology findings; they were therefore considered by the Agency as incidental and not adverse.

Increases in relative brain weight were also observed in F0 females at 86 mg/kg bw/day, but in the absence of histopathological correlates, these were considered by the Agency as secondary to the decreased terminal body weight and not adverse.

In F0 males, hyaline droplet deposition in proximal tubular cells was noted in 2/24 animals at 113 mg/kg bw/day. Based on supporting evidence from the 90-day toxicity study, these changes were attributed to α2μ-globulin deposition, a male rat–specific phenomenon without human relevance.

Overall, adverse and treatment-related effects were observed in the thyroid and liver of F0 females at the high dose of 86 mg/kg bw/day.

Parental toxicity (F1 generation)

In the F1 generation, high-dose males and females showed sustained reductions in body weight and body weight gain, although the mean body weights after 18 weeks of treatment were < 10% different to controls. Food consumption was also significantly reduced in high-dose males during Weeks 1–7 and in females during Weeks 6–8 and lactation days 7–14.

In females, statistically significant increases in liver weights were observed from the mid dose, with relative weights increased by 11.1% at the mid dose and by 25.1% at the high dose. At the high dose, thyroid weights were also increased (absolute +26.7%, relative +35.2%), accompanied by follicular cell hypertrophy in 10/22 animals. Relative brain weight was increased by 7%, but with no histopathological correlate this was not considered adverse. No liver or kidney lesions were observed in females.

In males, relative liver weight was increased by 7.8% at the high dose, with diffuse hepatocyte hypertrophy recorded in 11/22 animals. Histopathological findings also included increased hyaline droplet deposition in the proximal tubular cells of the kidney (7/22 animals), consistent with α2μ-globulin accumulation and not relevant to humans. Other organ weight changes at the high dose included increased relative kidney weight (+10.8%) and reproductive organ weights (testes +14.6%, epididymis +16%, seminal vesicles +14.6%), but these were not associated with adverse histopathology.

Overall, parental toxicity in the F1 generation was characterised by reduced body weight, body weight gain, and food consumption in both sexes at the high dose, and by increased liver and thyroid weights with histopathological thyroid follicular hypertrophy in females. In males, liver hypertrophy and renal hyaline droplet deposition were observed at the high dose but were not considered to be relevant for human health.

Reproductive toxicity

No adverse effects on fertility or reproductive performance were observed in either F0 or F1 generations. Oestrus cyclicity, mating and fertility indices, gestation length, and litter sizes were within normal ranges and comparable across all groups. The number of implantation sites and pups delivered did not show any significant treatment-related reductions. A delay in the completion of preputial separation in high-dose F1 males (by 1.6 days) was noted but this effect is attributed to lower body weight and therefore is not considered a direct reproductive effect by the registrant.

Offspring toxicity (F1 generation)

In F1 offspring, statistically significantly reduced body weights were observed in both sexes at the top dose during lactation, with reductions of up to 6.9% in females and 6.2% in males by day 21. One F1 pup presented with a thread-like tail at the high dose, though this was isolated to a single litter and not considered treatment-related due to similar findings in historical controls. Organ weight measurements showed small increases in

relative brain weight and decreases in spleen weight in both sexes at the top dose, though these were not associated with histopathological changes.

Offspring toxicity (F2 generation)

In F2 offspring, statistically significant decreases in terminal body weights were again observed in both sexes at the high dose, with up to 8.3% and 7.7% reductions in males and females, respectively. Similar to F1, there were statistically significant but small increases in relative brain weight and decreases in spleen and thymus weights in high-dose F2 weanlings. Uterus weights were also reduced in females at the top dose, with an 18% decrease in absolute weight. However, these effects presented with a lack of corresponding histopathological findings and were relatively small in magnitude.

Conclusion

In this GLP-compliant, OECD test guideline two-generation study, dietary administration of inpyrfluxam had no adverse effects on reproductive function in either generation. Adverse parental toxicity, including reductions in body weight, food consumption, and increases in liver and thyroid weights, were observed at the top dose in both F0 and F1 generations. Offspring toxicity, including reduced body weights during lactation, was also observed at the highest dose. A NOAEL of 500 ppm (27.8 mg/kg bw/day) was therefore identified for both parental and offspring toxicity.

10.12.3 Comparison with the GB CLP criteria

Inpyrfluxam has been evaluated in two dietary reproductive toxicity studies in rats: a preliminary one-generation range-finding study and a definitive two-generation study conducted in accordance with OECD TG 416 and GLP. These studies were performed in Wistar Hannover rats, with dose selection in the main study based on findings from the range-finding investigation.

There are no human data available to indicate reproductive toxicity, and therefore classification under Category 1A is not appropriate.

Under GB CLP criteria, classification in Category 2 may be considered when there is evidence from animal studies for specific adverse effects on sexual function or fertility, provided these are not solely secondary to general systemic toxicity. In the case of inpyrfluxam, no treatment-related effects on fertility, mating, conception, or gestation were observed in either generation, despite the presence of clear systemic toxicity at the highest dose levels tested. Furthermore, delays in sexual maturation were observed in F1 males, but these were considered secondary to reduced body weight and not indicative of direct reproductive toxicity.

Based on the available evidence, inpyrfluxam does not meet the criteria for classification under Category 2. Therefore, no classification for effects on sexual function and fertility is warranted under the GB CLP Regulation.

10.12.4 Adverse effects on development

The developmental toxicity of inpyrfluxam has been evaluated through oral administration (via gavage) in both rats and rabbits. The dataset comprises four studies conducted in rats, including two dose-range finding studies and two developmental toxicity studies. In rabbits, two studies were conducted: one dose-range finding study and one developmental toxicity study.

Table 30: Summary of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group, reference	**Test substance, dose levels duration of exposure**	**Results**
Preliminary dose-range finding study Wistar Hannover rats Non-GLP, non-guideline Females only, 7 animals/group. KCA 5.6.2/07, Anonymous (2012)	Inpyrfluxam (S-2399 Technical Grade) Oral gavage from GD 6–19 0, 12.5, 25, 50, 100 mg/kg bw/day	**Maternal toxicity:** At 100 mg/kg bw/day, 3/7 females died (GD 8–9), with clonic convulsions and lateral position preceding death. Irregular respiration noted in 6/7 animalsStatistically significant reductions in body weight and weight gain throughout the treatment period as below for dams: GD 6-9: -10 (±11.0)**(↓211%) GD 6-12: -4 (±16.4)*(↓115%) GD 6-15: 8 (±24.3)*(↓80%) GD 6-17: 16 (±31.8)*(↓72%) GD 6-20: 41 (±36.7)*(↓58.2%) Retention of foamy fluid in trachea (3 of 3), staining of the perinasal region (1 of 3) and small cecum (1 of 3) noted in dead animals From 25mg/kg bw/d transient prone positon and from 50mg/kg bw/d ataxic gait were observed 1h after administration, disapearing a few hours after dosing. **Developmental toxicity:** At 100 mg/kg bw/day, 28.6% decrease in mean number of live foetuses per litter and reduction in foetal weight. No malformations observed.
Dose-range finding study Wistar Hannover rats Non-GLP, non-	Inpyrfluxam (S-2399 Technical Grade) Oral gavage from GD 6–19. 0, 20, 40, 80 mg/kg	**Maternal toxicity:** **Body weight:** At 80 mg/kg bw/day, a statistically significant decrease in adjusted body weight was observed (268 ± 19 g compared to 294 ± 16 g in controls). **Body weight gain:** Marked, statistically significant reductions in body-weight gain were observed at 80 mg/kg bw/day across multiple intervals,

Method, guideline, deviations if any, species, strain, sex, no/group, reference	Test substance, dose levels duration of exposure	Results
guideline Females only. 7–8 animals/group KCA 5.6.2/01, Anonymous (2015b)	bw/day	including: GD 6–9: −1 ± 10 g (−108% vs control: 12 ± 5 g) GD 6–12: 10 ± 10 g (−60% vs control: 25 ± 6 g) GD 6–15: 23 ± 11 g (−44% vs control: 41 ± 5 g) GD 6–18: 55 ± 11 g (−29% vs control: 78 ± 10 g) GD 6–20: 79 ± 15 g (−27% vs control: 108 ± 14 g) **Food consumption:** Statistically significant reductions in food consumption were observed at 80 mg/kg bw/day: GD 6–9: 14.2 ± 4.7 g/day (**−35%** vs control: 21.7 ± 6.3 g/day) GD 9–12: 16.5 ± 3.5 g/day (**−29%** vs control: 23.3 ± 2.0 g/day) GD 15–18: 19.1 ± 3.1 g/day (**−20%** vs control: 23.8 ± 2.2 g/day) GD 18–20: 18.1 ± 3.7 g/day (**−27%** vs control: 24.9 ± 5.7 g/day) **Developmental toxicity:** Decrease in mean foetal weight at 80 mg/kg bw/day. No malformations observed. Dose of 80 mg/kg bw/day selected as top dose for definitive study.
Developmental toxicity study GLP-compliant, OECD TG 414 (2001) Wistar Hannover rats Females only, 22–24 animals/group Minor deviations: No T3/T4/TSH levels or AGD	Inpyrfluxam (S-2399 Technical Grade) Oral gavage from GD 6–19 0, 10, 25, 80 mg/kg bw/day	**Maternal toxicity:** At 80 mg/kg bw/day, statistically significant reductions in mean body weights (noted on GD 12, 18, and 20) and body weight gains (GD 6–9). Also, significant reduction in food consumption from GD 6–9 to termination. **Developmental toxicity:** Significant reduction in mean foetal weight at 80 mg/kg bw/day. One case of cyclopia observed at the high dose. Though other malformations were recorded, their incidence was similar to controls. The single case of cyclopia prompted an additional study.

Method, guideline, deviations if any, species, strain, sex, no/group, reference	Test substance, dose levels duration of exposure	Results
measured KCA 5.6.2/02, Anonymous (2017a)		
Developmental toxicity study Wistar Hannover rats. GLP-compliant, OECD TG 414 (2001) Females only 39–40 animals/group Minor deviations: No T3/T4/TSH levels or AGD measured. Single dose group only KCA 5.6.2/03, Anonymous 2017b)	Inpyrfluxam (S-2399 Technical Grade) Oral gavage from GD 6–19 0 or 90 mg/kg bw/day	**Maternal toxicity:** At 90 mg/kg bw/day, significant decreases in body weight and weight gain from GD 9, and in food consumption from GD 6–9 to termination. Isolated clinical signs (staggering gait, axillary mass) and kidney dilatation (3 animals) were considered incidental. Significant decrease in mean gravid uterine weight was observed. **Developmental toxicity:** Significant reduction in mean foetal weight. No cyclopia observed in any of the 533 foetuses examined. One case of microphthalmia observed but considered unrelated to treatment (noted previously in control group). Confirms cyclopia from previous study not treatment-related.
Dose-range finding study Japanese White rabbits Non-GLP, non-guideline Females only,	Inpyrfluxam (S-2399 Technical Grade) Oral gavage from GD 6–27 0, 15, 50, 150 mg/kg bw/day	**Maternal toxicity:** No treatment-related effects on mortality, clinical signs, body weight, weight gain, or food consumption. **Developmental toxicity:** No effects on foetal parameters. Conclusion: None of the tested doses reached the maximum tolerated dose. A higher top dose was recommended for subsequent studies.

Method, guideline, deviations if any, species, strain, sex, no/group, reference	Test substance, dose levels duration of exposure	Results
8 animals/group No deviations KCA 5.6.2/04, Anonymous (2015c)		
Dose-range finding study Japanese White rabbits Non-GLP, non-guideline Females only, 8 animals/group No deviations KCA 5.6.2/05, Anonymous (2015d)	Inpyrfluxam (S-2399 Technical Grade) Oral gavage from GD 6–27 0, 300, 500, 1000 mg/kg bw/day,	**Maternal toxicity:** From 300 mg/kg bw/day: clinical signs (lateral/prone position, convulsions, bradypnoea), abortions (in 3/8 dams), ↓ body weight and weight gain, ↓ food consumption. From 500 mg/kg: mortality (1/8 at 500 mg/kg bw/d and 4/8 at 1000 mg/kg bw/d) and early sacrifice of all remaining animals at 500 and 1000 mg/kg bw/d due to severe toxicity. Gross pathology in stomach and intestine from 300 mg/kg in affected animals. **Developmental toxicity:** No foetal effects observed at 300 mg/kg bw/day; higher dose groups could not be evaluated due to early sacrifice.
Definitive developmental toxicity study Japanese White rabbits GLP-compliant, OECD TG 414 (2001) Females only, 23–25 animals/group No deviations	Inpyrfluxam (S-2399 Technical Grade) Oral gavage from GD 6–27 0, 20, 60, 200 mg/kg bw/day	**Maternal toxicity:** At 200 mg/kg bw/day: red discharge and abortions (2/25), ↓ body weight gain (GD 6–21), ↓ food consumption (GD 6–18). These effects are considered treatment-related and adverse. **Developmental toxicity:** No treatment-related changes in foetal weight, resorptions, deaths, malformations, or variations in any group.

Method, guideline, deviations if any, species, strain, sex, no/group, reference	Test substance, dose levels duration of exposure	Results
KCA 5.6.2/06, Anonymous (2017c)		

*: p ≤ 0.05; **: p ≤ 0.01

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

Rat Studies

Preliminary dose-range finding study

In a preliminary developmental range-finding study (Anonymous 2012), inpyrfluxam was administered to groups of 7 pregnant Wistar Hannover rats by oral gavage at dose levels of 0, 12.5, 25, 50 or 100 mg/kg bw/day from gestation day (GD) 6 to 19. All animals were sacrificed on GD 20 for the assessment of maternal and developmental toxicity. The study was not conducted in compliance with GLP or OECD test guidelines.

Parental toxicity
Clear maternal toxicity was observed at the highest dose tested. Three out of seven females in the 100 mg/kg bw/d group died on GD 8 or 9, following clinical signs including clonic convulsions and lateral positioning. Irregular respiration was observed in six of seven animals at this dose, occurring approximately 3–4 hours post-dosing and resolving by the next day in surviving animals. Other clinical signs included staining in the periocular, perinasal, perioral and genital regions, as well as on the ventral neck and body surface. Transient prone posture was seen in 1/7, 6/7 and 7/7 animals at 25, 50 and 100 mg/kg/day, respectively, while ataxic gait occurred in 3/7 and 6/7 animals at 50 and 100 mg/kg/day. These signs appeared within an hour of dosing and resolved within a few hours.

Marked reductions in body weight gain were evident at 100 mg/kg bw/day across all time intervals. From GD 6–9, mean body weight gain was –10 g (±11.0) compared to 9 g (±4.6) in controls (↓211%, $p<0.01$). Between GD 6–12, weight gain was –4 g (±16.4) versus 26 g (±4.0) in controls (↓115%, $p<0.05$), and from GD 6–20, overall weight gain was reduced by 58.2% (41 g vs. 98 g in controls). Gross pathological findings in the deceased animals included retention of foamy fluid in the trachea (3/3), perinasal staining (1/3), and a small caecum (1/3), all considered treatment-related.

Foetal toxicity
Developmental toxicity was also apparent at the high dose. A 28.6% reduction in the mean number of live foetuses per litter was recorded, along with a significant decrease in mean foetal weight. No external or internal malformations were reported at any dose level.

Conclusion
In summary, maternal exposure to inpyrfluxam at doses up to 100 mg/kg bw/day resulted in significant maternal and developmental toxicity at the highest dose tested. Maternal effects included mortality, clinical signs (particularly convulsions and respiratory distress), and substantial reductions in body weight gain. Developmental toxicity was characterised by reduced litter size and foetal weight. As the top dose exceeded the maximum tolerated dose and the study was not intended to determine a point of departure, lower dose levels were selected for the subsequent developmental toxicity study in rats.

Second dose-range finding study

A second range-finding developmental toxicity study was conducted in pregnant Wistar Hannover rats to refine dose selection for a subsequent definitive investigation (Anonymous, 2015b). The study was not performed in compliance with GLP standards or OECD test guidelines. The test material, inpyrfluxam (S-2399 Technical Grade; 95% purity, Lot 13CG0617G), was administered by oral gavage to groups of 7–8 pregnant females at doses of 0, 20, 40, or 80 mg/kg bw/day from gestation day (GD) 6 to 19. Animals were sacrificed on GD 20 for evaluation of maternal and developmental toxicity. Dose selection was based on findings from the previous study by Anonymous (2012).

Parental toxicity

Clear maternal toxicity was observed at the highest dose tested (80 mg/kg bw/day). Statistically significant reductions in mean body weight gain were recorded throughout the dosing period. From GD 6–9, mean weight gain in the high-dose group was −1 g (±10), compared with +12 g (±5) in controls ($p \leq 0.01$). Between GD 6–12, weight gain was reduced to 10 g (±10) versus 25 g (±6) in the control group. Overall weight gain from GD 6–20 was 79 g (±15) at the high dose, compared to 108 g (±14) in controls. Adjusted terminal body weight at GD 20 was also statistically significantly lower at the top dose, -9% compared to controls.

Food consumption was similarly affected, with statistically significant reductions recorded at several intervals in the 80 mg/kg group. From GD 6–9, mean intake was 14.2 g/day (±4.7), compared to 21.7 g/day (±6.3) in the control group ($p \leq 0.05$). Further reductions were observed from GD 9–12 (16.5 g/day ±3.5 vs. 23.3 g/day ±2.0; $p \leq 0.01$), GD 15–18 (19.1 g/day ±3.1 vs. 23.8 g/day ±2.2; $p \leq 0.01$), and GD 18–20 (18.1 g/day ±3.7 vs. 24.9 g/day ±5.7; $p \leq 0.05$).

Foetal toxicity

At 80 mg/kg bw/day, a statistically significant reduction in mean foetal weight was observed. No other treatment-related effects were reported in any group. There were no malformations or developmental variations recorded.

Conclusion

In summary, this second range-finding study identified 80 mg/kg bw/day as the dose at which maternal and developmental toxicity became evident. Inpyrfluxam elicited adverse effects on maternal body weight, weight gain, and food consumption, as well as reductions in foetal weight at this dose level. While the study was not GLP-compliant and not designed to determine a definitive NOAEL, the findings were sufficient to support the selection of 80 mg/kg bw/day as the top dose for the subsequent definitive developmental toxicity study in rats.

OECD TG 414 developmental toxicity study (KCA 5.6.2/02)

A developmental toxicity study was conducted in pregnant Wistar Hannover rats to evaluate the potential maternal and developmental effects of inpyrfluxam following oral administration (Anonymous, 2017a). The study was performed in compliance with GLP and in accordance with OECD TG 414 (2001). Although plasma levels of thyroid hormones (T3, T4, and TSH) in dams at termination and measurements of anogenital distance (AGD) in foetuses were not assessed, these omissions were not considered to impact the study's validity. Dose levels of 0, 10, 25, and 80 mg/kg bw/day were selected based on results from a prior range-finding study (Anonymous, 2015b). Inpyrfluxam was administered once daily by oral gavage from gestation day (GD) 6 to 19 to groups of 22–24 pregnant females.

Parental toxicity

At the highest dose level (80 mg/kg bw/day), clear signs of maternal toxicity were observed.

Statistically significant reductions in mean body weight were recorded at 80 mg/kg bw/day, with values of 260 g, 300 g, and 322 g on GD 12, 18, and 20, respectively, compared with 272 g, 321 g, and 348 g in controls. Corresponding body weight gains were also statistically significantly lower, beginning as early as GD 6–9 (0 g vs. 10 g) and remaining suppressed until GD 20 (72 g vs. 98 g).

These effects persisted throughout the dosing period and were considered treatment-related and adverse. In parallel, food consumption was also statistically significantly reduced in the high-dose group from GD 6–9 and remained suppressed until termination. Despite these effects, there were no treatment-related changes in mean gravid uterine weight, the number of corpora lutea, or implantations, suggesting no impairment of implantation or early pregnancy maintenance.

Foetal toxicity

At 80 mg/kg bw/day, mean foetal weights of both sexes were statistically significantly reduced (males: 3335 mg vs. 3736 mg in controls; females: 3168 mg vs. 3546 mg). A slight reduction in mean foetal weight was also noted at 10 mg/kg bw/day (males: 3592 mg, females: 3409 mg), but as no effect was seen at 25 mg/kg bw/day, this was considered incidental. There were no statistically significant differences in sex ratio between control and treated groups.

Malformations were observed sporadically across all groups, with incidences comparable to controls and no consistent dose-relationship. External malformations included a single case of cyclopia with proboscis in one foetus at 80 mg/kg bw/day. As this malformation is extremely rare and absent from the testing facility's historical control database, a treatment-related origin could not be excluded. Accordingly, a specific follow-up study was conducted (Anonymous, 2017b), which demonstrated no cases of cyclopia at 90 mg/kg bw/day in a larger cohort, thereby confirming that the original finding was incidental and not treatment related. Other malformations included localised oedema (25 mg/kg bw/day), meningocele (control), overriding aorta (25 mg/kg bw/day), and microphthalmia (control), all of which were considered incidental. Skeletal malformations such as fused sternebra and rib cartilage anomalies occurred at low incidence across all groups, including controls, and were within historical control ranges.

Foetal variations were common in all groups (e.g. supernumerary ribs, rib cartilage changes, vertebral anomalies), with no dose-related pattern and no statistically significant differences in mean litter incidences between control and treated groups, except for wavy rib, which was statistically significantly lower in treated groups than in controls. No treatment-related pattern of variations was identified.

Conclusion

In summary, administration of inpyrfluxam to pregnant rats at doses up to 80 mg/kg bw/day resulted in maternal toxicity characterised by reduced body weight, decreased weight gain, and suppressed food consumption, alongside developmental toxicity manifested as reduced foetal weight and a potential increase in rare malformations. A maternal NOAEL of 25 mg/kg bw/day was established based on the effects observed at 80 mg/kg bw/day. The same dose was also identified as the developmental NOAEL, considering the reduction in foetal weight and the occurrence of cyclopia at the high dose.

OECD TG 414 developmental toxicity study (KCA 5.6.2/03)

An additional developmental toxicity study was conducted in pregnant Wistar Hannover rats to clarify whether the single case of cyclopia observed in a previous study was treatment-related (Anonymous, 2017b). The study was performed in compliance with GLP and in accordance with OECD TG 414 (2001). To improve the likelihood of detecting rare developmental anomalies, the study employed a higher dose (90 mg/kg bw/day vs. 80 mg/kg previously) and a larger group size (39–40 animals/group).

Parental toxicity

Inpyrfluxam (S-2399 Technical Grade; 95% purity; Lot 13CG0617G) was administered by oral gavage at 0 or 90 mg/kg bw/day from gestation day (GD) 6 to 19. Maternal toxicity was evident at the high dose. Significant reductions in both body weight and body weight gain were observed beginning on GD 9 and continuing through to GD 20. Gravid uterine weight was also significantly lower in treated animals. Food consumption was significantly decreased from GD 6–9 and remained suppressed until the end of the dosing period.

Mild clinical signs were observed in a number of animals; one dam exhibited staggering gait on GD 12, and another developed a localised mass in the axillary region from GD 18 to 20. Dilated kidneys were noted in three animals at necropsy. However, these findings occurred at a low frequency and were not considered to be treatment-related. The DAR reviewed this interpretation and agreed that the observation was unrelated to treatment. There were no significant differences in the number of corpora lutea or implantations between treated and control groups.

Foetal toxicity

A statistically significant reduction in mean foetal weight was observed in the treated group and considered to be an adverse, treatment-related effect associated with maternal toxicity. No other developmental parameters, including the number of live foetuses, the incidence of resorptions or foetal deaths, or the sex ratio, were affected by treatment. One foetus exhibited microphthalmia, but this was not considered treatment-related, as a similar observation had previously occurred in a control animal (Anonymous, 2017a). The DAR reviewed this interpretation and agreed that the observation was unrelated to treatment. Crucially, no cases of cyclopia were observed among the 533 foetuses examined, compared with 309 foetuses evaluated in the earlier OECD TG 414 study (KCA 5.6.2/02). Additionally, cyclopia had not been detected in any F1 or F2 pups in a multigeneration reproductive toxicity OECD TG 416 study in rats at doses up to 113 mg/kg bw/day (detailed in the sexual function and fertility section).

Conclusion

Oral administration of inpyrfluxam at 90 mg/kg bw/day to pregnant Wistar Hannover rats resulted in maternal toxicity, as evidenced by reduced maternal body weight, body weight gain, food consumption, and gravid uterine weight. Foetal weight was also adversely affected. However, the absence of cyclopia in this extended investigation, combined with negative findings from multigeneration studies, supports the conclusion that the previously observed case of cyclopia was not causally related to inpyrfluxam treatment.

Rabbit studies

Preliminary dose range finding study

A preliminary developmental toxicity range-finding study was conducted in pregnant Japanese White rabbits to evaluate potential maternal and developmental effects of inpyrfluxam and to inform dose selection for subsequent investigations (Anonymous, 2015c). The study was not performed in compliance with GLP or OECD test guidelines but was accepted as supporting data. The test substance, S-2399 Technical Grade inpyrfluxam (95% purity; Lot 13CG0617G), was administered by oral gavage at doses of 0, 15, 50, or 150 mg/kg bw/day to groups of eight pregnant females from gestation day (GD) 6 to 27. Animals were monitored for signs of toxicity, mortality, body weight, weight gain, and food consumption, and were sacrificed on GD 28 for evaluation of gross pathology and uterine contents.

Parental toxicity

Inpyrfluxam was well tolerated at all dose levels. No clinical signs of maternal toxicity were observed, and there were no treatment-related effects on maternal body weight, body weight gain, or food consumption. Gross pathological examination revealed no abnormalities in any of the treated animals.

Foetal toxicity

Developmental parameters, including the number of implantations, live foetuses, mean foetal weights, and morphological evaluations, showed no treatment-related effects at any dose. No malformations or variations were identified across the groups.

Conclusion

In summary, administration of inpyrfluxam at doses up to 150 mg/kg bw/day during gestation did not result in any adverse maternal or developmental effects in rabbits. Since no signs of systemic or developmental toxicity were observed at the highest dose tested, it was concluded that the maximum tolerated dose (MTD) had not been reached. As a result, a higher dose level was considered appropriate for the top dose in a subsequent range-finding study.

Second dose range finding study

A second dose range-finding developmental toxicity study was performed in pregnant Japanese White rabbits to identify the maximum tolerated dose (MTD) of inpyrfluxam prior to conducting a definitive study (Anonymous, 2015d). The study was not conducted in compliance with GLP or OECD test guidelines but was considered acceptable for dose selection purposes. Inpyrfluxam was administered once daily by oral gavage at doses of 0, 300, 500, or 1000 mg/kg bw/day from gestation day (GD) 6 to 27. Groups comprised eight

pregnant females. Animals were monitored for clinical signs, body weight, food intake, and mortality. Surviving animals were sacrificed on GD 28 for evaluation of gross pathology and uterine contents.

Parental toxicity

Marked maternal toxicity was evident from 300 mg/kg bw/day onwards. At 500 mg/kg bw/day, one doe died, and the remaining seven were euthanised in extremis on GD 17 or 18 due to severe clinical deterioration. At 1000 mg/kg bw/day, two animals died spontaneously, while four were killed in extremis by GD 6 or 7. Clinical signs of toxicity included prone and lateral positioning, decreased spontaneous activity, convulsions, bradypnoea, and loose stools. These effects were consistently observed at 300 mg/kg bw/day and became more frequent and severe at higher doses. Abortion was recorded in three animals at 300 mg/kg bw/day; no abortions occurred in the other dose groups. Gross pathological examinations revealed stomach and large intestine lesions in animals that died or were sacrificed early, which were considered treatment-related. No gross abnormalities were found in animals that survived to terminal sacrifice.

Maternal body weight and weight gain were significantly reduced at both 300 and 500 mg/kg bw/day, in parallel with marked decreases in food consumption. These effects were considered adverse and directly associated with treatment. Despite this, gravid uterine weight, number of corpora lutea, implantation sites, and food consumption remained unaffected at 300 mg/kg bw/day in animals that completed the study.

Foetal toxicity

No treatment-related effects on developmental endpoints were observed at 300 mg/kg bw/day. Parameters including the number of live foetuses, resorptions, sex ratio, and mean foetal weights were comparable to controls. Additionally, no external, visceral, or skeletal malformations were recorded at this dose. Due to the early mortality and sacrifice of animals at 500 and 1000 mg/kg bw/day, developmental outcomes at these dose levels could not be evaluated.

Conclusion

In conclusion, administration of inpyrfluxam at doses of 300 mg/kg bw/day and above produced clear maternal toxicity in rabbits, including mortality, clinical signs, abortions, reduced body weight gain, decreased food consumption, and pathological changes. While no developmental toxicity was identified at 300 mg/kg bw/day, the level of maternal toxicity at this dose suggested that it exceeded the MTD. Therefore, for the subsequent developmental toxicity study, a top dose between 150 and 300 mg/kg bw/day was considered appropriate to balance maternal survival with sensitivity to detect developmental effects.

OECD TG 414 developmental toxicity study (KCA 5.6.2/06)

This developmental toxicity study was conducted in pregnant Japanese White rabbits to evaluate potential maternal and developmental effects following repeated oral exposure to inpyrfluxam (Anonymous, 2017c). The study was performed in compliance with GLP and in accordance with OECD TG 414 (2001), with no deviations. Based on prior dose range-finding studies (Anonymous, 2015d), dose levels of 0, 20, 60, and 200 mg/kg bw/day were selected. Groups of 23 to 25 pregnant rabbits were dosed once daily via oral gavage from gestation day (GD) 6 to 27. Animals were sacrificed on GD 28 for evaluation of maternal and foetal endpoints.

Parental toxicity

Maternal toxicity was evident at the high dose of 200 mg/kg bw/day. Two does aborted on GD 21 and GD 23, and red discharge was observed in their cage trays. Although overall maternal body weights did not differ significantly from controls, body weight gain was statistically significantly reduced in the high-dose group during multiple gestational intervals. Specifically, weight gain from GD 6–9 was −15 ± 38 g, from GD 6–12 was −27 ± 89 g, and from GD 6–21 was +65 ± 174 g, all statistically significantly reduced compared to controls. Marked body weight decreases were observed in the animals that aborted. Adjusted maternal body weight (excluding gravid uterine weight) was also reduced at the high dose (3235 ± 218 g) compared to controls (3340 ± 246 g).

Statistically significant reductions in food consumption were observed at 200 mg/kg bw/day during GD 6–9 (149 ± 32 g/day), GD 9–12 (109 ± 47 g/day), GD 12–15 (100 ± 52 g/day), and GD 15–18 (126 ± 59 g/day). These effects were especially pronounced in animals that aborted, some of which ceased feeding entirely.

Foetal toxicity

Despite the maternal effects at 200 mg/kg bw/day, there were no treatment-related impacts on reproductive parameters. The number of corpora lutea, implantation sites, live foetuses, and the incidence of resorptions or foetal deaths remained comparable across all groups. Mean gravid uterine weight was slightly lower in the high-dose group (446 ± 124 g) compared to controls (484 ± 131 g), but this was not considered adverse. Mean foetal weights for both sexes were similar among groups, and no deviations in sex ratio were observed. There were no significant differences in the proportion of does with malformed or variant foetuses between treatment and control groups. Furthermore, no treatment-related external, skeletal, or visceral malformations or variations were reported.

Conclusion

Daily oral administration of inpyrfluxam to pregnant rabbits at doses up to 200 mg/kg bw/day resulted in maternal toxicity at the highest dose, characterised by abortion,

reduced food intake, and decreased body weight gain. These findings were considered treatment-related and adverse. In contrast, no evidence of developmental toxicity was observed at any dose level.

10.12.6 Comparison with the GB CLP criteria

Inpyrfluxam has been tested in prenatal developmental toxicity studies in rats and rabbits conducted in accordance with GLP and OECD test guidelines. In rats, developmental toxicity in the form of reduced foetal weight was observed at 80 mg/kg bw/day, alongside marked maternal toxicity. A single case of cyclopia reported at the high dose was not replicated in a follow-up study at 90 mg/kg bw/day and is considered incidental. In rabbits, no developmental effects were seen at doses up to 200 mg/kg bw/day, although maternal toxicity (reduced food intake, weight gain, and abortion) was evident at this dose.

Classification in Category 1A for effects on development is warranted when there is evidence that a substance causes developmental toxicity in humans. No human data are available, therefore classification in Category 1A is not appropriate.

Classification in Category 1B requires clear evidence from animal studies of adverse developmental effects occurring independently of maternal toxicity. In the case of inpyrfluxam, no treatment-related malformations were reported in rats or rabbits. In rats, reduced foetal weight was reported but only at doses which caused significant maternal toxicity. No effects on foetal body weight were reported in rabbits. The Agency considers the effects on foetal weight in rats to be secondary to maternal toxicity, rather than a specific developmental effect. Overall, the available data do not support classification in Category 1B.

Classification in Category 2 applies where there is some evidence from animal studies suggesting a concern for human reproductive toxicity, generally in the absence of sufficient data for Category 1 classification. However, inpyrfluxam has been tested in GLP and guideline-compliant studies in both rats and rabbits. In both species, there was no evidence of specific developmental toxicity at doses that did not also elicit maternal toxicity. Therefore, the criteria for classification in Category 2 are also not met.

Overall, it can be concluded that inpyrfluxam is not a developmental toxicant. Classification for developmental toxicity is not warranted.

10.12.7 Adverse effects on or via lactation

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

In a one-generation dose-range finding study (KCA 5.6.1/01; Anonymous, 2015a), mean pup body weights were reduced in the 2000 and 4000 ppm groups at lactation days 4, 7,

14 and 21. At 4000 ppm, reductions of approximately 25–50% compared with controls were observed. These effects were considered secondary to maternal toxicity, characterised by marked reductions in maternal body weight and body-weight gain (>20% during lactation), decreased food consumption, and the occurrence of cannibalism.

At 2000 ppm, pup body weights were reduced by approximately 25% compared with controls. These effects were also attributed to maternal toxicity, as maternal body weight was reduced by approximately 10–12% during lactation and food consumption was decreased.

In the main two-generation study (KCA 5.6.1/02; Anonymous, 2017), pup body weights were reduced at the highest dose of 1250 ppm on lactation days 14 and 21. However, these reductions were not considered adverse, as the magnitude of change relative to controls was less than 10%.

10.12.9 Comparison with the GB CLP criteria

Substances are considered for classification for effects on or via lactation where there is evidence indicating a hazard to infants during the breastfeeding period. This may be supported by human data, findings from animal studies demonstrating adverse effects in offspring due to transfer of the substance via milk or effects on milk quality, or toxicokinetic information indicating that the substance may be present in milk at potentially harmful levels.

However, the available data for inpyrfluxam, including the one- and two-generation studies, do not demonstrate adverse effects in offspring attributable to exposure via milk, nor do they indicate any impact on milk quality.

Therefore, inpyrfluxam does not meet the criteria for classification for effects on or via lactation.

10.12.10 Conclusion on classification and labelling for reproductive toxicity

There was no evidence to suggest that inpyrfluxam has an adverse effect on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring (including effects on lactation or via lactation), therefore classification with this endpoint is not warranted.

Not classified – conclusive but not sufficient for classification.

10.13 Aspiration hazard

Hazard class not applicable.

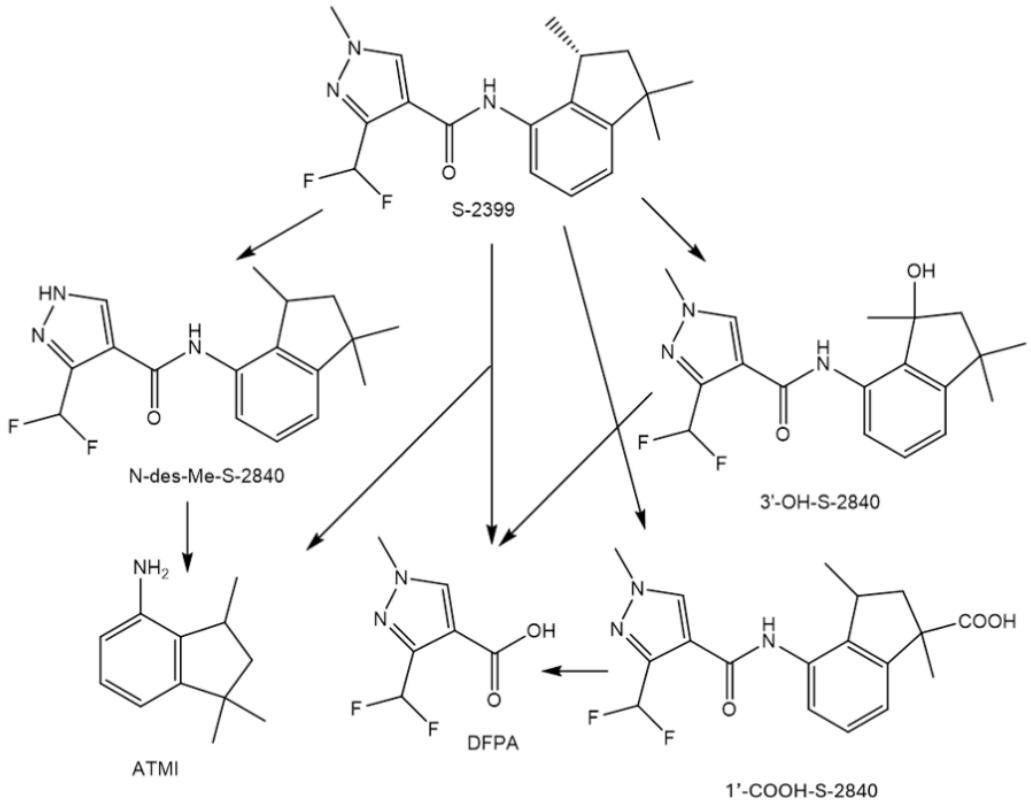
11. Evaluation of environmental hazards

11.1 Rapid degradability of organic substances

Table 31: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Ready biodegradation OECD TG 301 B, GLP (good laboratory practice)	Not readily biodegradable. 60% CO_2 evolution was not achieved within 10 day window by day 28.	Valid	Griffith, A.W., 2016 (section CA.B.8.2.2.1)
Aqueous hydrolysis OECD TG 111, GLP	Stable (< 10% degradation) at pH 4, 7, and 9 (50°C) over 5 day period.	Valid	Freedlander, S., 2016 (section CA.B.8.2.1.1)
Aerobic mineralisation OECD TG 309, GLP	No significant degradation, DT_{50} > 1000 days (pelagic test).	Valid	Yeomans, P., 2017 (section CA.B.8.2.2.2)
Water/sediment simulation OECD TG 308, GLP	Maximum whole system $DegT_{50}$: > 10,000 days. Mineralisation: maximum 0.5% AR (applied radioactivity) pyrazolyl label, 0.4% AR phenyl label.	Valid	Gohre, K., 2017 (section B.8.2.2.3.1) Aston, J. & Gohre, K., 2017 (section CA.B.8.2.2.3.2)
Direct photochemical degradation OECD TG 316, GLP	DT_{50} not calculated as degradation was negligible.	Valid	Ponte, M., 2015a (section B.8.2.1.2)
Indirect photochemical degradation OECD TG 316, GLP	Maximum DT_{50}: 74.4 days (equivalent to 179 summer days at 30-50°N).	Valid	Ponte, M., 2015b (section B.8.2.1.3)

Figure 11.1-1 Degradation scheme of inpyrfluxam (water/sediment, B.8.2.2.3.1)



11.1.1 Ready biodegradability

The rate of biological degradation of inpyrfluxam was investigated in a CO2 evolution study. The study was conducted in accordance with OECD Guideline 301 B and to GLP. A suspension of 15.2 mg/L inpyrfluxam in a mineral medium (equal to 36.7 mg/L Theoretical carbon dioxide (ThCO2) , or 10.0 mg/L carbon) was inoculated and stirred in closed-system flasks at a constant temperature (22 ± 2 °C) for 28 days under aerobic conditions in the dark. Sample flasks were supplied with CO2-free air under positive pressure and connected to CO2 traps. Degradation was monitored by sequential sampling of the traps to quantify evolved CO2 and therefore degradation. After 28 days the cumulative net evolved CO2 was -2.58%, that is, less CO2 evolved than the blank control samples. The reference compound sodium benzoate showed 70.54% degradation after 14 days, and the toxicity control showed 33.70% degradation after 14 days, demonstrating the validity of the study according to the OECD 301 B guidelines. Therefore, inpyrfluxam was not observed to be readily biodegradable.

11.1.2 BOD_5/COD

Not applicable

11.1.3 Hydrolysis

The hydrolytic degradation of inpyrfluxam was assessed (using one radiolabel position, on the pyrazolyl ring) in one study conducted in accordance with OECD Guideline 111 and to GLP. The assessment was conducted at pH 4, 7 and 9 at 50 °C, in the dark for 5 days. Inpyrfluxam was hydrolytically stable in all sterile buffer solutions, with <10% degradation. As such, inpyrfluxam was found to be stable to hydrolysis in sterile solutions under environmentally conservative pH and temperature conditions.

11.1.4 Other convincing scientific evidence

11.1.4.1 Field investigations and monitoring data

Not applicable

11.1.4.2 Inherent and enhanced ready biodegradability tests

Not applicable

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

A study of aerobic mineralisation in surface water was carried out in accordance with OECD Guideline 309 and to GLP. The assessment was undertaken using two radiolabel positions (pyrazolyl and phenyl ring positions), at two test concentrations (0.01 and 0.1 mg/L) under aerobic conditions in the laboratory in the dark at 20 ± 2 °C for a maximum of 61 days.

Inpyrfluxam degraded slowly in the phenyl label, high concentration samples, with a DT_{50} of 1540 days (single first order kinetics). Degradation was found to not be statistically significant for all other samples and so modelled DT_{50} values were not accepted, and conservative DT_{50} values of > 10,000 days were taken forward instead. No individual metabolites were detected > 5% AR in any samples and as such, peaks were not assigned. Maximum mineralisation to CO_2 was 0.4% AR, determined from the phenyl, high concentration samples at 30 DAT (days after treatment) in non-sterile conditions.

The route and rate of degradation of inpyrfluxam was investigated in five water sediment systems, across two studies. Two radiolabel positions (pyrazolyl and phenyl) were used in one study, and one radiolabel position (pyrazolyl) in the other. In both studies, the water sediment systems (of contrasting physicochemical characteristics) were treated and sampled under dark, aerobic conditions in the laboratory. The studies were conducted in accordance with OECD Guideline 308 and to GLP. Inpyrfluxam degradation varied across the water/sediment systems. The formation of CO_2 reached a maximum mean of 0.5% AR at 111 DAT (study end).

Overall the behaviour of inpyrfluxam was characterised by some degradation of the parent compound in the water column to major metabolites (3'-OH-S-2840 and 1'-COOH-S-2840) and significant dissipation of the parent compound from the water column to the sediment

compartment (longest water $DissT_{50}$: 34.28 days (Double First Order in Parallel kinetics – back-calculated from DT_{90} / 3.32)). No significant decline of the parent compound was then noted in the sediment compartments ($DissT_{50}$ 1000 days default used).

The maximum amount of inpyrfluxam remaining in each whole water/sediment system at study end (111 or 112 DAT) ranged from 69.8% to 90.2% AR. Therefore, 70% inpyrfluxam degradation was not observed in any whole water/sediment system within 28 days.

The degradation of inpyrfluxam followed a similar initial degradation pattern across the test systems and radiolabels. The primary metabolite 3'-OH-S-2840 was observed in all systems, with maximums between 1.9% AR and 6.8% AR, peaking between 30 DAT and 111 DAT, associated more with the sediment compartment. The primary metabolite 1'-COOH-S-2840 was formed in all systems, with maximums between 0.9% AR and 13.1% AR, peaking between 62 DAT and 112 DAT, associated more with the water compartment.

11.1.4.4 Photochemical degradation

Direct and indirect photochemical degradation were assessed in accordance with OECD Guideline 316 and to GLP.

Significant direct photolysis sterile buffer was not observed and is expected to be negligible.

DT_{50} values for indirect photochemical degradation in sterile natural water after for correction for the dark control were 179 days for the pyrazolyl label and 80 days for the phenyl label with average summer irradiation at 30-50 ºN. Phenyl-labelled metabolite 3'-OH-S-2840 reached a mean maximum of 8.6% AR with no other metabolites >5% AR.

Photolysis is of uncertain relevance as a route of degradation in typical European aquatic environments and, given the available data, there is insufficient information in this case to evaluate photodegradation in terms of mineralisation or transformation to non-classifiable substances. Therefore, aquatic photolysis is not considered further in relation to meeting the criteria for rapid degradation.

11.1.4.5 Conclusion on 'rapid degradability'

In terms of abiotic degradation, the substance is stable to hydrolysis and, whilst photolysis is of unclear relevance for hazard classification purposes, less than 70% degradation in 28 days was observed.

In a reliable ready biodegradation study there was no quantifiable degradation of inpyrfluxam after 28 days, based on evolved CO_2. It is therefore not considered readily biodegradable. Slow primary degradation was observed in one of the four aerobic mineralisation study samples, while a statistically significant degradation rate could not be determined from the other three samples. No individual metabolites were formed >5%, and

degradation products were not assigned. In the whole water/sediment systems, there was 69.8 to 90.2% AR remaining as inpyrfluxam at study end (111 or 112 DAT) and so clearly the 70% degradation criteria within 28 days was not met. As such, inpyrfluxam is not considered to be rapidly degradable.

No kinetic assessment was undertaken on the metabolites formed in the water/sediment simulation study, with default values of 1000 days used in the exposure assessment. Therefore, none of the metabolites are classed as being rapidly degradable either.

Overall, inpyrfluxam does not meet the CLP criteria to be classed as “rapidly degradable” in the environment. There is no evidence to suggest that the active substance is at least 70% degraded in the aquatic environment within 28 days and insufficient information to conclude that that the degradants are non-hazardous under the classification criteria.

11.2 Environmental transformation of metals or inorganic metals compounds

Not applicable.

11.3 Environmental fate and other relevant information

11.3.1 Volatilisation

The vapour pressure of inpyrfluxam is 3.81 x 10^{-8} Pa (20 °C) and so does not meet the FOCUS (FOrum for Co-ordination of pesticide fate models and their Use) air trigger of 1 x 10^{-5} Pa (20 °C) for the potential of short range transport from application to crops. Inpyrfluxam is unlikely to be subject to long-range transport as the atmospheric half-life due to degradation by hydroxyl radicals is estimated to be 0.233 days (12 hour day).

The Henry’s law constant of inpyrfluxam is 7.74x10^{-7} Pa m^3/mol, therefore volatilisation from surface water is expected to be negligible.

11.4 Bioaccumulation

A bioaccumulation study , conducted according to OECD 305 (2012), has been performed, summarised in the table below and discussed further in 11.4.2.

Table 32: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
Bioaccumulation in fish OECD 305 GLP	$BCF_{kgL, TRR}$ = 215.4 L/kg $BCF_{SSL, S-2399}$ = 38.4 L/kg	Study considered suitable for use in hazard classification.	Anon (2015/2020)

11.4.1 Estimated bioaccumulation

No bioaccumulation estimation procedure was required as bioaccumulation was experimentally determined.

11.4.2 Measured partition coefficient and bioaccumulation test data

The log P_{ow} = 3.65 for inpyrfluxam. Guidance on the Application of CLP Criteria (ECHA, 2024)[2] states, "experimentally derived BCF values of high quality are ultimately preferred for classification purposes". The available bioaccumulation in fish study was concluded to be acceptable for hazard classification purposes. A brief study summary is provided below, focusing on the results.

Amended Report [14C]S-2399 – Flow-Through Bioconcentration and Metabolism Study with Bluegill Sunfish (Lepomis macrochirus) Anon (2015/2020)

The bioaccumulation of inpyrfluxam (S-2399) was determined using juvenile Bluegill Sunfish (Lepomis macrochirus). The study followed OECD 305 (2012) alongside Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (2017) for the analysis. All validity criteria for OECD 305 (2012) were met except for a minor temperature deviation that was judged not to have impacted the results. Two water concentrations were tested: 0.2 µg/L and 0.6 µ/L. A concurrent solvent control was also run. Fish were exposed during a 28-day uptake phase, which was followed by a 3-day depuration phase. Samples were pooled at each timepoint to yield one replicate. Pooling occurred to counteract the rapid depuration of inpyrfluxam and improve HPLC method sensitivity.

A summary of the steady-state BCF (BCF_{SS}) and kinetic BCF (BCF_k) estimation process is presented in Table 11.4-1, Table 11.4-2, Table 11.4-3, Figure 11.4-1 and Figure 11.4-2 below. Lipid corrections were performed using 4.26 % (an average of all lipid wet weights

[2] Guidance on the Application of the CLP Criteria, Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Version 6.0, Jan 2024, Reference: ECHA-24-G-01-EN, DOI: 10.2823/74224

across the exposure period) for the 0.2 µg/L treatment group and 4.42 % for the 0.6 µg/L treatment group.

Table 11.4-1 Recalculated $C_{f,\ TRR}$*, $C_{w,\ TRR}$, BCF_{TRR} and $BCF_{L,TRR}$

Concentration (µg TRR/L)	$C_{f,TRR}$ at steady-state (arithmetic mean, µg TRR/kg)	$C_{w,TRR}$ at steady-state (twa mean, µg TRR/L)	BCF_{TRR} (L/kg fish)	$BCF_{L,TRR}$ (L/kg fish)
0.2	38.25	0.212	180.42	211.77
0.6	98.43	0.600	164.05	185.58

* TRR = total radioactive residues

For the low concentration, steady state was defined from Day 1 to 14. Technically the low concentration did not reach steady state, with no four successive concentrations within ± 20 % of each other. This, however, was likely due to variation in the data associated with the use of one pooled sample at each timepoint, rather than a true failure to reach steady state. For example, between Day 1 to 14 the TRR in fish tissue increased by 26.4 % from 34.9 to 44.1 µg/kg, then decreased to 34.5 µg/kg on Day 21. The comparable concentration for Day 1 and Day 21 supports the interpretation that the 26.4 % increase between Day 1 to 14 was due to experimental variation rather than a failure to reach steady state. The Agency took a pragmatic approach and defined steady state as between Day 1 and 14 for the low concentration, despite the exceedance of the 20 % threshold. The average concentration within this time frame is 38.25 µg TRR/kg.

Table 11.4-2 Recalculated $C_{f,\ S\text{-}2399}$, $C_{w,\ S\text{-}2399}$, $BCF_{S\text{-}2399}$ and $BCF_{L,\ S\text{-}2399}$

Concentration (µg S-2399/L)	$C_{f,S\text{-}2399}$ at steady-state (arithmetic mean, µg S-2399/kg)	$C_{w,S\text{-}2399}$ at steady-state (twa mean, µg S-2399/L)	$BCF_{S\text{-}2399}$ (L/kg fish)	$BCF_{L,S\text{-}2399}$ (L/kg fish)
0.2	6.93	0.212	32.73	38.42
0.6	17.58	0.600	29.25	33.09

For the high concentration, steady state was defined from Day 3 to 21. Steady state based on the four successive timepoint definition is not reached. However, Day 3 to 21 appears a suitable candidate for steady state. Between Day 3 and 21, the largest difference is between Day 7 (88.2 µg/kg) and Day 21 (111 µg/kg), a 25.9 % increase. This is followed by a reduction to 92 µg/kg on Day 28, again suggesting that experimental variation explains the pattern of results between Day 3 and 21. Consequently, Day 3 to 21 is selected as the steady state. The average concentration within this time frame is 98.43 µg TRR/kg.

```
##
## Formula: cfish.data ~ RunModel_Aqueous(time.data, cwater, tdepur, fitk1,
##     fitk2)
##
## Parameters:
##       Estimate Std. Error t value Pr(>|t|)
## fitk1 460.8011   144.8704   3.181   0.0191 *
## fitk2   2.5239     0.8121   3.108   0.0209 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 3.469 on 6 degrees of freedom
##
## Number of iterations to convergence: 4
## Achieved convergence tolerance: 7.039e-06
```

```
##          Estimate Std.Error      2.5%    97.5%         Unit
## k1       460.8    144.87    176.86    744.75   L/kgFish/day
## k2         2.5239   0.81213   0.93212   4.1157        1/day
## k2g        2.5105   0.81213   0.91874   4.1023        1/day
## BCFK     182.57     6.9482  168.96    196.19       L/kgFish
## BCFKg    183.55     7.0708  169.69    197.41       L/kgFish
## tHalfg     0.2761   0.08932   0.10104   0.4512         day
## BCFKgLip 203.94     7.8565  188.54    219.34       L/kgFish
```

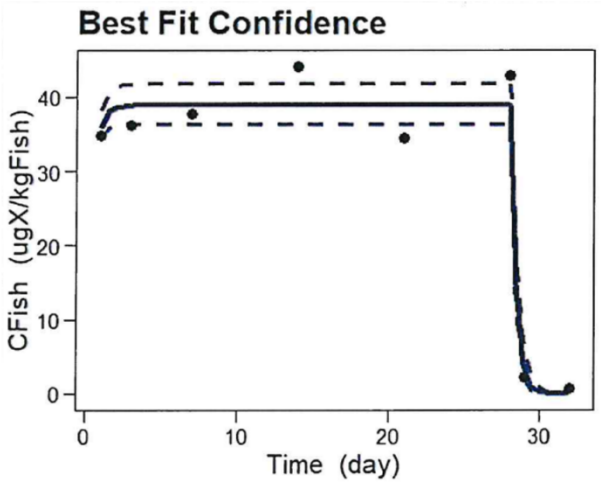


Figure 11.4-1 Parameter estimates and model prediction with 95 % confidence limits for the low concentration (0.2 µg/L) treatment group (untransformed model).

```
##
## Formula: cfish.data ~ RunModel_Aqueous(time.data, cwater, tdepur, fitk1,
##     fitk2)
##
## Parameters:
##       Estimate Std. Error t value Pr(>|t|)
## fitk1 289.1346    60.7531   4.759  0.00313 **
## fitk2   1.7411     0.3746   4.648  0.00351 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 8.741 on 6 degrees of freedom
##
## Number of iterations to convergence: 4
## Achieved convergence tolerance: 2.369e-07
```

```
##           Estimate Std.Error      2.5%    97.5%         Unit
## k1       289.13     60.753   170.06    408.21   L/kgFish/day
## k2         1.7411    0.37463   1.0068    2.4754        1/day
## k2g        1.7277    0.37463   0.99345   2.462         1/day
## BCFK     166.06      6.4884  153.35    178.78       L/kgFish
## BCFKg    167.35      6.6052  154.4     180.3        L/kgFish
## tHalfg     0.40119   0.08699   0.23069   0.5717         day
## BCFKgLip 176.9       6.9822  163.22    190.59       L/kgFish
```

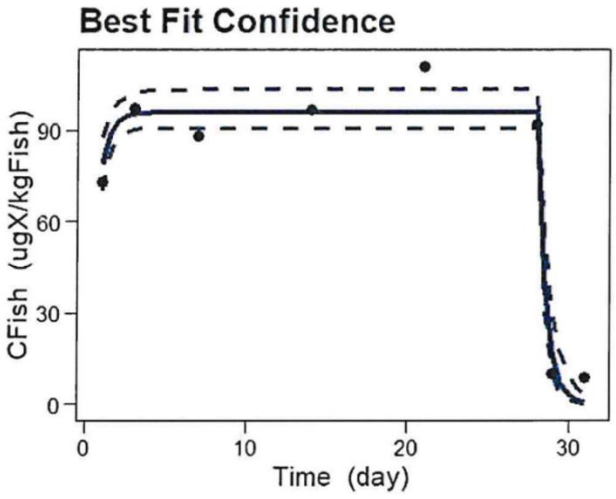


Figure 11.4-2 Parameter estimates and model prediction with 95 % confidence limits for the high concentration (0.6 µg/L) treatment group (untransformed model).

The BCF_{kgL} estimates from Figure 11.4-1 and Figure 11.4-2 were not corrected by the lipid correction factor agreed by the Agency (4.26 % for the 0.2 µg/L treatment group and 4.42 % for the 0.6 µg/L treatment group). The agreed lipid correction factors are used to yield the final BCF estimates in the table below.

Table 11.4-3 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

A $BCF_{k, S-2399}$ was not estimated due to the rapid depuration of inpyrfluxam below the LOD.

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.

The study is considered suitable for use in CLP hazard assessment.

The study provides a reliable, experimentally derived BCF, which is preferred for classification purposes. Annex 3 of the Guidance to Regulation (EC) No 1272/2008 (ECHA, 2017) states, "*the BCF from radio-labelled studies should, preferentially, be based on the parent compound*". Therefore, the key BCF endpoint for classification purposes is **38.4 L/kg**, which is below the trigger of 500.

To conclude, inpyrfluxam does not meet the hazard classification criterion for potential bioaccumulation.

11.5 Acute aquatic hazard

Studies available during the registration of inpyrfluxam as a pesticide active substance under Regulation 1107/2009 are summarised in **Error! Reference source not found.**. All the listed studies have been conducted according to GLP. The studies have been evaluated, considered reliable and deemed suitable for hazard classification purposes, unless otherwise stated. Only studies submitted testing the technical substance, inpyrfluxam, have been summarised below. Formulation studies submitted in the context of the active substance renewal under Regulation 1107/2009 have not been considered further. The most toxic endpoint for each organism group is highlighted in **bold**.

Note that the available acute toxicity data available for the metabolites of inpyrfluxam (3'-OH-S-2840 and 1'-COOH-S-2840), considered relevant under Regulation 1107/2009, are summarised in Annex I. This information is included for information only: none of the metabolites exhibit equivalent toxicity to inpyrfluxam and do not require aquatic hazard classification in isolation. Accordingly, they are not considered to impact the hazard classification of inpyrfluxam.

Table 33: Summary of relevant information on acute aquatic toxicity of technical inpyrfluxam

Method	Species	Test material	Results	Reference
Fish				
Acute toxicity to fish **OECD 203; GLP** **96-hour, static exposure**	***Oncorhynchus mykiss***	**Test material: Inpyrfluxam** **Lot/Batch: 13CG0617G** **Purity: 95.0%**	**LC_{50} = 0.031 mg a.s./L (t.w.a.)[a]**	**Anon (2014a)**
Acute toxicity to fish OECD 203; GLP 96-hour, static exposure	*Lepomis macrochirus*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	LC_{50} = 0.054 mg a.s./L (t.w.a.)	**Anon** (2014b)
Acute toxicity to fish OECD 203; GLP 96-hour, static exposure	*Pimephales promelas*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	LC_{50} = 0.050 mg a.s./L (t.w.a)	**Anon** (2014c)
Acute toxicity to fish OECD 203; GLP 96-hour, static exposure	*Cyprinus carpio*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	LC_{50} = 0.067 mg a.s./L (t.w.a)	**Anon** (2014d)

Acute toxicity to fish OECD 203; GLP 96-hour, static exposure	*Cyprinodon variegatus*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	LC_{50} = 0.15 mg a.s./L (m.m.)[b]	**Anon** (2014e)
Acute toxicity to fish OECD 203; GLP 96-hour, static exposure	*Poecilia reticulata*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	LC_{50} = 0.35 mg a.s./L (t.w.a)	Anon (2016c)
Acute toxicity to fish OECD 203; GLP 96-hour, static exposure	*Oryzias latipes*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	LC_{50} = 0.79 mg a.s./L (t.w.a)	Anon (2016a)
Acute toxicity to fish OECD 203; GLP 96-hour, static exposure	*Danio rerio*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	LC_{50} = 0.30 mg a.s./L (t.w.a)	Anon (2016b)
Aquatic invertebrates				

Acute Immobilization **OECD 202; GLP** **48-hour, static exposure**	***Daphnia magna***	**Test material: Inpyrfluxam** **Lot/Batch: 13CG0617G** **Purity: 95.0%**	**EC_{50} = 1.1 mg a.s./L (t.w.a)**	**KCA 8.2.4.1/01** **Shaw, A.C. (2014f)**
Acute mortality OCSPP Draft Guideline 850.1035; GLP 96-hour, static exposure	*Americamysis bahia*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	LC_{50} = 1.1 mg a.s./L (m.m.)	8.2.4.2/01 Shaw, A.C. (2014g)
Algae				
Algal growth inhibition OECD 201; GLP 96-hour, static exposure	*Pseudokirchneriella subcapitata*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	E_rC_{50} (72 h) > 23 mg a.s./L (m.m.)	KCA 8.2.6.1/01 Softcheck, K.A. (2015a)
Algal growth inhibition OECD 201; GLP 72-hour, static exposure	*Navicula pelliculosa*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	E_rC_{50} (72 h) = 10.1 mg a.s./L (m.m.)	KCA 8.2.6.2/01 Softcheck, K.A. (2015b)
Algal growth inhibition OECD 201; GLP 96-hour, static exposure	*Anabaena flos-aquae*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	Not determined[c]	KCA 8.2.6.2/02 Softcheck, K.A. (2015c)
Algal growth inhibition **OECD 201; GLP** **96-hour, static exposure**	***Skeletonema costatum***	**Test material: Inpyrfluxam** **Lot/Batch: 13CG0617G**	**E_rC_{50} (96 h) = 1.28 mg a.s./L (m.m.)**	**8.2.6.2/03** **Softcheck, K.A. (2015d)**

		Purity: 95.0%		
Aquatic plants				
Growth inhibition test **OECD 221; GLP** **7-day, semi-static exposure**	***Lemna gibba***	**Test material: Inpyrfluxam** **Lot/Batch: 13CG0617G** **Purity: 95.0%**	**E_rC_{50} > 24 mg a.s./L (m.m.) (frond density and dry weight)**	**KCA 8.2.7/01** **Kirkwood, A. (2016)**
Further testing on aquatic organisms				
Growth inhibition test **OCSPP Draft Guideline 850.1025; GLP** **96-hour, flow-through exposure**	***Crassostrea virginica***	**Test material: Inpyrfluxam** **Lot/Batch: 13CG0617G** **Purity: 95.0%**	**EC_{50} > 0.99 mg a.s./L (m.m.)**	**KCA 8.2.8/01** **Shaw, A. (2016)**

[a] t.w.a. = time-weighted average

[b] m.m. = mean measured

[c] Categorised as Not Reliable by the Agency due to failure to meet validity criteria relating to control growth rate.

11.5.1 Acute (short-term) toxicity to fish

Acute fish studies considered acceptable are summarised below.

S-2399 TG - Acute Toxicity Test with Rainbow Trout (Oncorhynchus mykiss) Under Static Conditions Anon (2014a)

The acute toxicity of inpyrfluxam to *O. mykiss* was estimated using the OECD 203 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 203, which were unlikely to have impacted the study outcome, were identified by the Agency. The majority of these deviations stemmed from evaluating the study against OECD 203 (2019) instead of OECD 203 (1992), the guideline version available when the study was carried out. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance stayed within ± 20 % of the nominal concentration throughout the study.

The 96-hour LC_{50}, estimated using mean measured concentrations, was 0.031 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

S-2399 TG - Acute Toxicity Test with Bluegill Sunfish (Lepomis macrochirus) Under Static Conditions Anon (2014b)

The acute toxicity of inpyrfluxam to *L. macrochirus* was estimated using the OECD 203 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 203, which were unlikely to have impacted the study outcome, were identified by the Agency. The majority of these deviations stemmed from evaluating the study against OECD 203 (2019) instead of OECD 203 (1992), the guideline version available when the study was carried out. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study (70 to 122 %). There was large mortality variation between the two 0.058 mg a.s./L replicates, the only concentration that elicited partial mortality, after 96 hours, leading to uncertainty in the reported LC_{50} endpoint. There was, however, no mortality at the 0.035 mg S-2399/L concentration. For the purposes of CLP, the 0.031 mg S-2399/L endpoint for *O. mykiss* above can be considered protective of the uncertainty in the *L. macrochirus* endpoint, particularly when the lack of mortality at 0.035 mg S-2399/L for *L. macrochirus* is accounted for.
The 96-hour LC_{50}, estimated using mean measured concentrations, was 0.054 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

S-2399 - Acute Toxicity Test with Fathead Minnow (Pimephales promelas) Under Static Conditions Following OECD Guideline #203, OPPTS Draft Guideline 850.1075, JMAFF 12 NohSan, No. 8147 Fish, Acute Toxicity Test (2-7-1-1) and The Official Journal of the European Communities, L383A, Method C.1, Acute Toxicity for Fish Anon (2014c)
The acute toxicity of inpyrfluxam to *P. promelas* was estimated using the OECD 203 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 203, which were unlikely to have impacted the study outcome, were identified by the Agency. The majority of these deviations stemmed from evaluating the study against OECD 203 (2019) instead of OECD 203 (1992), the guideline version available when the study was carried out. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study.
The 96-hour LC_{50}, estimated using mean measured concentrations, was 0.050 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

S-2399 TG - Acute Toxicity Test with Common Carp (Cyprinus carpio) Under Static Conditions Anon (2014d)
The acute toxicity of inpyrfluxam to *C. carpio* was estimated using the OECD 203 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 203, which were unlikely to have impacted the study outcome, were identified by the Agency. The majority of these deviations stemmed from evaluating the study against OECD 203 (2019) instead of OECD 203 (1992), the guideline version available when the study was carried out. Five geometrically

spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study.
The 96-hour LC_{50}, estimated using mean measured concentrations, was 0.067 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

Acute Toxicity to Sheepshead Minnow (Cyprinodon variegatus) Under Static Conditions Anon (2014e)
The acute toxicity of inpyrfluxam to *C. variegatus* was estimated using the OECD 203 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 203, which were unlikely to have impacted the study outcome, were identified by the Agency. The majority of these deviations stemmed from evaluating the study against OECD 203 (2019) instead of OECD 203 (1992), the guideline version available when the study was carried out. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance stayed within ± 20 % of the nominal concentration during the study.
The 96-hour LC_{50}, estimated using mean measured concentrations, was 0.15 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

Acute Toxicity Study of S-2399 TG with Guppy (Poecilia reticulata) Anon (2016c) The acute toxicity of inpyrfluxam to *P. reticulata* was estimated using the OECD 203 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 203, which were unlikely to have impacted the study outcome, were identified by the Agency. The majority of these deviations stemmed from evaluating the study against OECD 203 (2019) instead of OECD 203 (1992), the guideline version available when the study was carried out. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study.
The 96-hour LC_{50}, estimated using mean measured concentrations, was 0.35 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

Acute Toxicity Study of S-2399 TG with Japanese medaka (Oryzias latipes) Anon (2016a)
The acute toxicity of inpyrfluxam to *O. latipes* was estimated using the OECD 203 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 203, which were unlikely to have impacted the study outcome, were identified by the Agency. The majority of these deviations stemmed from evaluating the study against OECD 203 (2019) instead of OECD 203 (1992), the guideline version available when the study was carried out. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study.
The 96-hour LC_{50}, estimated using mean measured concentrations, was 0.79 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

Acute Toxicity Study of S-2399 TG with Zebrafish (Danio rerio) Anon (2016b)
The acute toxicity of inpyrfluxam to *D. rerio* was estimated using the OECD 203 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 203, which were unlikely to have impacted the study outcome, were identified by the Agency. The majority of these deviations stemmed from evaluating the study against OECD 203 (2019) instead of OECD 203 (1992), the guideline version available when the study was carried out. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study.
The 96-hour LC_{50}, estimated using mean measured concentrations, was 0.30 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

Overall conclusion
The eight available acute fish toxicity endpoints for inpyrfluxam are sufficient to determine an acute hazard classification for fish. Since the purpose of classification is to characterise hazard in the aquatic environment, the result showing the highest toxicity has been chosen. **The endpoint selected for use in hazard classification is the 96-hour LC_{50} of 0.031 mg a.s./L for *Oncorhynchus mykiss* (Anon (2014a)).** During the aquatic risk assessment, a Species Sensitivity Distribution (SSD) was fitted to the eight submitted acute fish studies. An **HC_5 = 17.9 µg/L (95 % CI = 3.35 to 42.7 µg/L)** was estimated from the resulting distribution.For inpyrfluxam, fish are the most acutely sensitive group of organisms tested and will be selected for acute hazard classification.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

Two acute aquatic invertebrate studies were considered acceptable and summarised below.

S-2399 TG - Acute Toxicity to Water Fleas (Daphnia magna) Under Static Conditions Shaw, A.C. (2014f)
The acute toxicity of inpyrfluxam to *D. magna* was estimated using the OECD 202 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 202, which were unlikely to have impacted the study outcome, were identified by the Agency. Six geometrically spaced concentrations were tested. Measured concentrations of the active substance stayed within ± 20 % of the nominal concentration during the study.
The 96-hour EC_{50}, estimated using mean measured concentrations, was 1.1 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

S-2399 TG: - Acute Toxicity to Mysids (Americamysis bahia) Shaw, A.C. (2014g)
The acute toxicity of inpyrfluxam to *A. bahia* was estimated using the OCSPP Draft Guideline 850.1035 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OCSPP Draft Guideline

850.1035, which were unlikely to have impacted the study outcome, were identified by the Agency. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance stayed within ± 20 % of the nominal concentration during the study.
The 96-hour LC_{50}, estimated using mean measured concentrations, was 1.1 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

Overall conclusion
The two available acute aquatic invertebrate toxicity endpoints for inpyrfluxam are sufficient to determine an acute hazard classification for aquatic invertebrates. Since the purpose of classification is to characterise hazard in the aquatic environment, the result showing the highest toxicity has been chosen. **The endpoint selected for use in hazard classification is the 96-hour EC_{50} of 1.1 mg a.s./L for *Daphnia magna* (Shaw, A.C. (2014f)).** For inpyrfluxam, aquatic invertebrates are not the most acutely sensitive group of organisms tested and will not be selected for acute hazard classification.

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

Five algal and aquatic plant studies were submitted to the Agency and four studies were considered acceptable for use in hazard classification. The *Anabaena flos-aquae* algal study (Softcheck, K.A. (2015c)) was considered unreliable as it failed to meet the validity criteria associated with control variation. The Agency notes that the reported E_rC_{50} > 27 mg a.s./L was higher than the *S. costatum* endpoint. Consequently, it will not be discussed further.

S-2399 TG – 96-Hour Toxicity Test with the Freshwater Green Alga, Pseudokirchneriella subcapitata Softcheck, K.A. (2015a)
The toxicity of inpyrfluxam to *P. subcapitata* was estimated using the OECD 201 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 201, which were unlikely to have impacted the study outcome, were identified by the Agency. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study.
The 72-hour E_rC_{50}, estimated using mean measured concentrations, was > 23 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

S-2399 TG: Toxicity Test with the Freshwater Diatom, Navicula pelliculosa Softcheck, K.A. (2015b)
The toxicity of inpyrfluxam to *N. pelliculosa* was estimated using the OECD 201 guideline. The study was conducted according to GLP throughout. The validity criterion for the mean CV of section-by-section specific growth rate in the control group after 72 hours was not met. It was, however, met for the solvent control. Consequently, the solvent control was selected as the reference group for all statistical analyses. the Agency considered this an

acceptable approach. Seven geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study.
The 72-hour E_rC_{50}, estimated using mean measured concentrations, was 10.1 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

S-2399 TG: Toxicity Test with the Marine Diatom, Skeletonema costatum Softcheck, K.A. (2015d)
The toxicity of inpyrfluxam to *S. costatum* was estimated using the OECD 201 guideline. The study was conducted according to GLP throughout. The solvent control failed the validity criterion relating to the CV of the section-by-section specific growth rates at 72 and 96 hours. However, as the growth rate in the normal control, which met validity criteria at both timepoints, was identical to the solvent control, and the failure to meet the validity criteria at 96 hours for the solvent control was only marginal, the Agency accepted the 96-hour E_rC_{50}. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study.
The 96-hour E_rC_{50}, estimated using mean measured concentrations, was 1.28 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

S-2399 TG: 7-Day Toxicity Test with Duckweed (Lemna gibba) Kirkwood, A. (2016)
The toxicity of inpyrfluxam to *L. gibba* was estimated using the OECD 221 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OECD 221, which were unlikely to have impacted the study outcome, were identified by the Agency. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study.
The 96-hour E_rC_{50}, estimated using mean measured concentrations, was > 24 mg S-2399 TG/L for both frond density and dry weight. The study was considered suitable for use in CLP hazard assessment.

Overall conclusion
The four algal and aquatic plant toxicity endpoints for inpyrfluxam deemed suitable for use in hazard classification are sufficient to determine an acute hazard classification for algae and aquatic plants. Since the purpose of classification is to characterise hazard in the aquatic environment, the result showing the highest toxicity has been chosen. **The endpoint selected for use in hazard classification is the 96-hour E_rC_{50} of 1.28 mg a.s./L for *Skeletonema costatum* (*Softcheck, K.A. (2015d)*).** For inpyrfluxam, algae and aquatic plants are not the most acutely sensitive group of organisms tested and will not be selected for acute hazard classification.

11.5.4 Acute (short-term) toxicity to other aquatic organisms

One additional acute study was submitted that selected the Eastern Oyster.

S-2399 TG: Acute Toxicity to Eastern Oyster (Crassostrea virginica) Under Flow-Through Conditions Shaw, A. (2016)
The toxicity of inpyrfluxam to *C. virginica* was estimated using the OCSPP Draft Guideline 850.1025 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Only minor deviations from OCSPP Draft Guideline 850.1025, which were unlikely to have impacted the study outcome, were identified by the Agency. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance stayed within ± 20 % of the nominal concentration during the study.
The 96-hour E_rC_{50} (shell deposition), estimated using mean measured concentrations, was > 0.99 mg S-2399 TG/L. The study was considered suitable for use in CLP hazard assessment.

Overall conclusion
Guidance to Regulation (EC) No 1272/2008 (ECHA, 2017) states, "*Data on other species shall also be considered if the test methodology is suitable*". As OCSPP guidelines are standardised and used frequently in the US, the test methodology can be considered suitable. **The endpoint selected for use in hazard classification is the 96-hour EC_{50} of >0.99 mg a.s./L for *Crassostrea virginica* (*Shaw, A. (2016)*).** For inpyrfluxam, the Eastern Oyster is not the most acutely sensitive species tested and will not be selected for acute hazard classification.

11.6 Long-term aquatic hazard

Studies available during the registration of inpyrfluxam as a pesticide active substance under Regulation 1107/2009 are summarised in

Table 11.6-1. All the listed studies have been conducted according to GLP. The studies have been evaluated, considered reliable and deemed suitable for hazard classification purposes, unless otherwise stated. Only studies submitted testing the technical substance, inpyrfluxam, have been summarised below. Formulation studies submitted in the context of the active substance renewal under Regulation 1107/2009 have not been considered further. The most toxic endpoint for each organism group is highlighted in **bold**. The classification scheme according to Regulation (EC) No 1272/2008 is limited in scope and does not, as yet, include aquatic sediments. Consequently, studies selecting a spiked sediment exposure regime have been omitted from

Table 11.6-1.

Table 11.6-1 Summary of chronic aquatic toxicity studies for technical inpyrfluxam

Method	Species	Test material	Results[1]	Reference
Fish				
Fish early-life stage toxicity **OECD 210; GLP** **32 days, flow-through exposure**	***Pimephales promelas***	**Test material: Inpyrfluxam** **Lot/Batch: 13CG0617G** **Purity: 95.0%**	**$LC_{10,\ larval\ survival}$ = 0.0066 mg a.s./L (95 % CI = 0.0040 to 0.0093) (m.m.)[a]**	**Anon (2014)**
Fish early-life stage toxicity OECD 210; GLP 34 days, flow-through exposure	*Cyprinodon variegatus*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	NOEC $_{larval\ survival}$ = 0.009 mg a.s./L (larval survival) (m.m.)	Anon (2017)
Aquatic invertebrates				

Reproduction Study **OECD 211; GLP** **21-day, semi-static**	***Daphnia magna***	**Test material: Inpyrfluxam** **Lot/Batch: 13CG0617G** **Purity: 95.0%**	**$EC_{10,\ reproduction}$ = 0.21 mg a.s./L (t.w.a.)[b]**	**KCA 8.2.5/01** **Shaw, A.C. (2014h)**
Reproduction Study US EPA OCSPP 850.1350; GLP 28-day, flow-through	*Americamysis bahia*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	Not determined[c]	KCA 8.2.5.2/02 Marini, J. (2016/2020)
Algae				
Algal growth inhibition OECD 201; GLP 96-hour, static exposure	*Pseudokirchneriella subcapitata*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	72-hour E_rC_{10} = 6.4 mg a.s./L (m.m.)	KCA 8.2.6.1/01 Softcheck, K.A. (2015a)
Algal growth inhibition OECD 201; GLP 96-hour, static exposure	*Navicula pelliculosa*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	72-hour E_rC_{10} = 3.44 mg a.s./L (m.m.)	KCA 8.2.6.2/01 Softcheck, K.A. (2015b)
Algal growth inhibition OECD 201; GLP 96-hour, static exposure	*Anabaena flos-aquae*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	Not determined[d]	KCA 8.2.6.2/02 Softcheck, K.A. (2015c)
Algal growth inhibition **OECD 201; GLP** **96-hour, static exposure**	***Skeletonema costatum***	**Test material: Inpyrfluxam** **Lot/Batch: 13CG0617G**	**96-hour E_rC_{10} = 0.34 mg a.s./L (m.m.)**	**KCA 8.2.6.2/03** **Softcheck, K.A. (2015d)**

		Purity: 95.0%		
Aquatic plants				
Growth inhibition test OECD 221; GLP 7-day, semi-static exposure	*Lemna gibba*	Test material: Inpyrfluxam Lot/Batch: 13CG0617G Purity: 95.0%	**E_rC_{10} > 24 mg a.s./L (m.m.)**	KCA 8.2.7/01 Kirkwood, A. (2016)

[a] m.m. = mean measured
[b] t.w.a. = time-weighted average
[c] Failed to determine an overall study NOEC. Was used as supporting information only.
[d] Categorised as Not Reliable by the Agency due to failure to meet validity criteria relating to control growth rate.

11.6.1 Chronic toxicity to fish

Two long-term fish toxicity studies considered acceptable are summarised below.

S-2399 TG - Early life-stage toxicity test with fathead minnow, Pimephales promelas Anon (2014)
The long-term toxicity of inpyrfluxam to *P. promelas* was estimated using the fish early life stage OECD 210 guideline. All validity criteria were met, with the study conducted according to GLP throughout. Five geometrically spaced concentrations were tested (0.0016, 0.0027, 0.0046, 0.0075, and 0.013 mg a.s./L (m.m.)). Measured concentrations of the active substance stayed within ± 20 % of the nominal concentration throughout the study. Embryo hatching success, live normal larvae at hatch, larval survival, larval length and larval wet weight were the main response variables reported. Only minor deviations from OECD 210, which were unlikely to have impacted the study outcome, were identified by the Agency. The majority of these deviations stemmed from evaluating the study against OECD 210 (2013) instead of OECD 210 (1992), the guideline version available when the study was carried out. A LC_{10} = 0.0066 mg/L, based on larval survival, was accepted by the Agency. NOEC = 0.013mg/L for % hatching success and NOEC = 0.0075 mg/L for % live normal larvae, length and weight were also reported. The study was considered suitable for use in CLP hazard assessment.

S-2399 TG - Early life-stage toxicity test with sheepshead minnow, Cyprinodon variegatus Anon (2017)
The long-term toxicity of inpyrfluxam to *C. variegatus* was estimated using the fish early life stage OECD 210 guideline. The study was conducted according to GLP throughout. The validity criterion regarding temperature staying within the range specified for the test species (*C.variegatus*, 25 ± 1.5 °C) was not met according to the continuous measurement in one replicate. The Agency considered this a small deviation with minimal impact on the

study outcome for several reasons: 1) temperature remained within ± 1.5 °C between test chambers and successive days during the test, and daily temperature measurements remained within 25 ± 1.5 °C (24 – 26 °C); 2) temperatures of 26 to 27 ºC are suitable for sheepshead minnow embryos and larvae, and are recommended by sheepshead minnow full life-cycle guideline literature (U.S. EPA 1996)[3]; 3) hatching success and larval survival exceeded the acceptability criteria for both controls; and 4) all other validity criteria were met. Accordingly, the study was considered acceptable for use in hazard classification. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study. As a result, endpoints were determined using mean measured concentrations (0.009, 0.015. 0.034, 0.063 and 0.13 mg a.s./L). Embryo hatching success, live normal larvae at hatch, larval survival, larval length and larval wet weight were the main response variables reported. Only minor deviations from OECD 210, which were unlikely to have impacted the study outcome, were identified by the Agency. The Agency amended the reported NOEC from 0.034 mg/L to 0.009 mg/L based on the clear concentration-response presented for larval survival, with statistically significant effects at 0.015 and 0.034 mg/L. This decision resulted in the 34-day NOEC, estimated using mean measured concentrations, being set at 0.009 mg S-2399/L. The study was considered suitable for use in CLP hazard assessment.

Overall conclusion
The two available long-term fish toxicity endpoints for inpyrfluxam are sufficient to determine a long-term hazard classification for fish. Since the purpose of classification is to characterise hazard in the aquatic environment, the result showing the highest toxicity has been chosen. **The endpoint selected for use in hazard classification is the 32-day LC_{10} of 0.0066 mg a.s./L for *Pimephales promelas* (*Anon (2014)*).** For inpyrfluxam, fish are the most chronically sensitive group of organisms tested and will be selected for chronic/long-term hazard classification.

11.6.2 Chronic toxicity to aquatic invertebrates

Two long-term aquatic invertebrate toxicity studies considered acceptable are summarised below.

S-2399 TG – Full Life-Cycle Toxicity Test with Water Fleas, Daphnia magna Under Static-Renewal Conditions Shaw, A.C. (2014h)
The long-term toxicity of inpyrfluxam to *D. magna* was estimated using OECD 211. All validity criteria were met, with the study conducted according to GLP throughout. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance stayed within ± 20 % of the nominal concentration during the study. Parental

[3] U.S. EPA, 1996b. Office of Chemical Safety and Pollution Prevention. Ecological Effects Test Guideline, OCSPP 850.1500. Fish Life Cycle Toxicity. “Public Draft”. EPA 712-C-96-122. April 1996. U.S. Environmental Protection Agency. Washington, D.C

survival, reproduction (offspring per female), body length and dry weight were the main response variables reported. Only minor deviations from OECD 211, which were unlikely to have impacted the study outcome, were identified by the Agency. The 21-day EC_{10}, estimated using mean measured concentrations, was 0.21 mg S-2399/L. The EC_{10} was preferred to the NOEC in accordance with Section 4.1.3.1.1 of Guidance to Regulation (EC) No 1272/2008 (ECHA, 2017). The study was considered suitable for use in CLP hazard assessment.

S-2399 TG - Life-Cycle Toxicity Test with Mysids (Americamysis bahia) Marini, J. (2016/2020)
The long-term toxicity of inpyrfluxam to *A. bahia* was estimated using US EPA OCSPP 850.1350. All validity criteria were met, with the study conducted according to GLP throughout. Five geometrically spaced concentrations were tested. Measured concentrations of the active substance deviated from ± 20 % of the nominal concentration during the study. Consequently, mean measured concentrations were used to calculate endpoints. Parental survival, reproduction (offspring per female), body length, dry weight and offspring survival were the main response variables reported. Only minor deviations from US EPA OCSPP 850.1350, which were unlikely to have impacted the study outcome, were identified by the Agency. There were, however, inconclusive results for offspring number per female, a key reproductive endpoint. There was a > 19 % reduction for all treatment groups except 0.36 mg/L when compared to the control (> 12 % reduction compared to the solvent control), no clear concentration-response and, consequently, no clear NOEC level. Owing to the limited interpretability of the results, the Agency determined that the study was suitable only as supporting information for CLP hazard assessment.

Overall conclusion
The one available, reliable long-term aquatic invertebrate toxicity endpoint for inpyrfluxam is sufficient to determine a long-term hazard classification for aquatic invertebrates. **The endpoint selected for use in hazard classification is the 96-hour EC_{10} of 0.21 mg a.s./L for *Daphnia magna* (*Shaw, A.C. (2014h)*)**.
For inpyrfluxam, aquatic invertebrates are not the most chronically sensitive group of organisms tested and will not be selected for long-term/chronic hazard classification.

11.6.3 Chronic toxicity to algae or other aquatic plants

The studies outlined in Section **Error! Reference source not found.** for acute hazard assessment were used again for chronic hazard assessment.

Overall conclusion
The four algal and aquatic plant toxicity endpoints for inpyrfluxam deemed suitable for use in hazard classification are sufficient to determine a long-term hazard classification for algae and aquatic plants. Since the purpose of classification is to characterise hazard in

the aquatic environment, the result showing the highest toxicity has been chosen. **The endpoint selected for use in hazard classification is the 96-hour E_rC_{10} of 0.34 mg a.s./L for *Skeletonema costatum* (*Softcheck, K.A. (2015d)*).** For inpyrfluxam, algae and aquatic plants are not the most acutely sensitive group of organisms tested and will not be selected for acute hazard classification.

11.6.4 Chronic toxicity to other aquatic organisms

No further chronic toxicity studies were available where exposure to inpyrfluxam was through the water phase.

11.7 Comparison with the GB CLP criteria

11.7.1 Acute aquatic hazard

Acute endpoints for fish, crustacea and algae are available, covering a range of trophic levels and taxa that are considered as surrogates for all aquatic organisms. The lowest available acute endpoint between and within the different trophic levels is LC_{50} = **0.031 mg/L** for *O. mykiss* or a HC_5 = 0.0179 mg/L, estimated from a SSD of the eight acute fish endpoints. Both endpoints are < 1 mg/L, resulting in **Category Acute 1** classification. Furthermore, 0.01 < LC_{50}/HC_5 ≤ 0.1 mg/L, resulting in an acute M factor of **10**.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Rapid degradability
Inpyrfluxam is considered to be ‘not rapidly degradable’ according to the CLP criteria, this decision has been explained in full in the environmental fate section (Section 11.1.4.5).

Bioaccumulation
A bioaccumulation in fish study is available (Anon 2015/2020), conducted according to OECD 305 (2012). The study provides a high quality experimentally derived BCF, which is preferred for classification purposes. Annex 3 of the Guidance to Regulation (EC) No 1272/2008 (ECHA, 2017) states, “*the BCF from radio-labelled studies should, preferentially, be based on the parent compound*”. Therefore, the BCF of interest for classification purposes is **38.4 L/kg**, which is below the trigger of 500.

To conclude, inpyrfluxam does not meet the criterion for potential bioaccumulation.

Chronic toxicity
Long-term endpoints for fish, crustacea and algae are available, covering a range of trophic levels and taxa that are considered as surrogates for all aquatic organisms. The long-term hazard category is determined using the available chronic toxicity data. The lowest available long-term endpoint between and within the different trophic levels is

0.0066 mg/L for *P. promelas*. This endpoint is < 0.1 mg/L, resulting in **Category Chronic 1** classification. Furthermore, 0.001 < LC_{10} ≤ 0.01 mg/L. As inpyrfluxam is a non-rapidly degradable substance, this results in a chronic M factor of **10**. The Agency notes that no long-term toxicity data is available for the most sensitive species according to the acute toxicity data (*O. mykiss*). If the acute toxicity endpoint of 0.031mg a.s./L for *O. mykiss* is used to determine the chronic classification, this also results in a **Category Chronic 1** classification with a **chronic M factor of 10**.

11.8 Conclusion on classification and labelling for environmental hazards

To conclude, inpyrfluxam does not meet the criteria for potential bioaccumulation (measured BCF < 500), is 'non-rapidly degradable', and its toxicity to fish results in the following acute and chronic hazard classification categories (with associated M-factors) for the aquatic environment.

Classification:
Aquatic Acute 1; H400: Very toxic to aquatic life. Acute M-Factor of 10 **Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects. Chronic M-Factor of 10**

12. Evaluation of additional hazards

Not assessed in this dossier.

13. Additional labelling

No additional labelling is proposed.

14. References

ECHA (2024) Guidance on the Application of the CLP Criteria Part 3: Health Hazards Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 5.0 Nov 2024. Available at: https://echa.europa.eu

For all other references, see the Draft Assessment Report (see Section 6. Data Sources for further information).

15. Annexes

Annex I: Available aquatic toxicity data on degradants of inpyrfluxam

The available acute toxicity data available for the degradants of inpyrfluxam (3'-OH-S-2840 and 1'-COOH-S-2840), considered relevant under Regulation 1107/2009, are summarised in the table below. This information is included for information only: none of the degradants exhibit equivalent acute toxicity to inpyrfluxam and, therefore, do not require hazard classification in isolation.

Species	**Test material**	**Results**	**Reference**
Fish			
Oncorhynchus mykiss	3'-OH-S-2840	LC_{50} > 6.2 mg /L (m.m.)	Anon (2016a)
Oncorhynchus mykiss	1'-COOH-S-2840	LC_{50} > 50 mg /L (m.m.)	Anon (2016b)

m.m. = mean measured

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