Draft Assessment Report

Evaluation of Active Substances

Plant Protection Products

Prepared according to **Regulation (EC) 1107/2009**
as it applies in Great Britain

Pydiflumetofen

Volume 1

Great Britain

September 2023

Version History

When	What
October 2022	Initial GB DAR
June 2023	Post Expert Committee on Pesticides (ECP) Independent Scientific Advice (ISA)
September 2023	Update following consideration of new ED data for Ecotoxicology

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Level 1

PYDIFLUMETOFEN

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

1.1. CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED

1.1.1. Purpose for which the draft assessment report was prepared

This draft assessment report has been prepared to evaluate the dossier for the new, pesticidal active substance SYN545974 (ADEPIDYNTM; ISO common name: pydiflumetofen)and its formulated product "MIRAVIS PLUS – A21857B". This dossier was submitted by Syngenta Crop Protection AG ("Syngenta") for the first approval of this substance in Great Britain (GB) under retained Regulation No 1107 with the evaluation performed by the Chemicals Regulation Division of the Health and Safety Executive. Syngenta also have an ongoing application for the approval of pydiflumetofen as a new active substance in the EU, with the evaluation being performed by the France as Rapporteur Member State (RMS) and Austria as Co- Rapporteur Member State (Co-RMS).

Pydiflumetofen is a new broad spectrum fungicide of the chemical group of N-methoxy-(phenyl-ethyl)-pyrazole-carboxamide, to deliver disease control across multiple crops. The original GB dossier was the same CA as the dossier submitted to Europe, but refers to a different representative product. The dossier contains data and information to support several representative uses of the active substance to demonstrate that, for the representative product "MIRAVIS PLUS – A21857B", the requirements of Regulation 1107, Article 4 can be met.

"MIRAVIS PLUS – A21857B", is an emulsifiable concentrate (EC) formulation containing 62.5 g active substance/L. The current GB product application is for approval of "MIRAVIS PLUS – A21857B" for use on a variety of crops. However, the representative uses of "MIRAVIS PLUS – A21857B" presented in the dossier, and evaluated in this report, are for the use of "MIRAVIS PLUS – A21857B" on winter and spring wheat, durum wheat, winter and spring barley, winter and spring oats, winter and spring rye, winter and spring triticale, and winter and spring oilseed rape. These uses are the proposed major applications of pydiflumetofen and have been evaluated as they are representative of exposure scenarios that allow an appropriate evaluation of the risk to humans and the environment from the use of pydiflumetofen.

This dossier is the application for the first approval of pydiflumetofen in accordance with Regulation 1107. Currently, pydiflumetofen does not have an entry under Annex VI of Regulation (EC) No 1272/2008. However, a mandatory classification and labelling report has been prepared under GB CLP by HSE, with HSE acting as the Agency. This will be submitted to the Secretary of State, with consent from the devolved administrations to follow the aligned evaluation process.

1.1.2. Regulatory history for use in Plant Protection Products

SYN545974 (pydiflumetofen) is a new active substance and products containing it have not previously been authorised in Great Britain.

1.1.3. Evaluations carried out under other regulatory contexts

Pydiflumetofen is a new fungicidal active substance developed by the applicant (Syngenta). Syngenta provided a dossier in support of their application for first approval of this pesticide in Great Britain in accordance with Regulation No. 1107. No registrations of authorisations of pydiflumetofen containing products currently exist in the UK or EU Member States, however there are authorisations for products in Argentina, Australia, Canada, New Zealand, and the United States.

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

1.2. APPLICANT INFORMATION

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

Syngenta Crop Protection AG
Schwarzwaldalle 215
P.O. Box
CH-4002 Basel; Switzerland

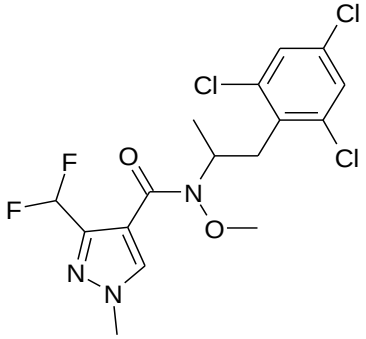
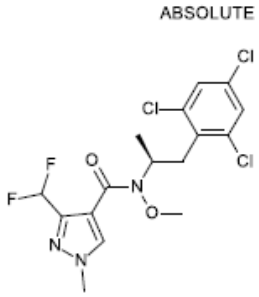
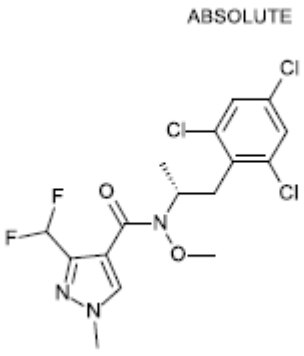
Contact person:
[redacted]

1.2.2. Producer or producers of the active substance

Syngenta Crop Protection AG
Address: Schwarzwaldalle 215
P.O. Box
CH-4002 Basel; Switzerland
Contact: [redacted]
Telephone number: [redacted]
E-mail: [redacted]

1.3. IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1. Common name proposed or ISO-accepted and synonyms	Pydiflumetofen
1.3.2. Chemical name (IUPAC and CA nomenclature)	
IUPAC	3-(difluoromethyl)-N-methoxy-1-methyl-N-[(2Ξ)-1-(2,4,6-trichlorophenyl)propan-2-yl]-1H-pyrazole-4-carboxamide
CA	3-(difluoromethyl)-N-methoxy-1-methyl-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1H-pyrazole-4-carboxamide
1.3.3. Producer's development code number	SYN545974
1.3.4. CAS, EEC and CIPAC numbers	
CAS	1228284-64-7
EEC	Not available
CIPAC	999
1.3.5. Molecular and structural formula, molecular mass	
Molecular formula	$C_{16}H_{16}Cl_3F_2N_3O_2$

Structural formula	 Pydiflumetofen consists of two enantiomers as a racemate (50:50) SYN546968: (S)-3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid methoxy-[1-methyl-2-(2,4,6-trichloro-phenyl)-ethyl]-amide  SYN546969: (R)-3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid methoxy-[1-methyl-2-(2,4,6-trichloro-phenyl)-ethyl]-amide 
Molecular mass	426.7 g mol^{-1}
1.3.6. Method of manufacture (synthesis pathway) of the active substance	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR.
1.3.7. Specification of purity of the active substance in g/kg	Minimum 980 g/kg

1.3.8. Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1. *Additives*	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR.
1.3.8.2. *Significant impurities*	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR.
1.3.8.3. *Relevant impurities*	There are no relevant impurities in pydiflumetofen technical material.
1.3.9. Analytical profile of batches	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR.

1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1. Applicant	Syngenta Crop Protection AG CH 4058 – Basel Switzerland Contact: [redacted] Syngenta Crop Protection AG Jealott's Hill Bracknell, Berkshire RG42 6EX United Kingdom [redacted]
1.4.2. Producer of the plant protection product	Syngenta Crop Protection AG CH 4058 – Basel Switzerland
1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product	Proposed Trade name: MIRAVIS PLUS Company code number: A21857B
1.4.4. Detailed quantitative and qualitative information on the composition of the plant protection product	
1.4.4.1. **Composition of the plant protection product**	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR
1.4.4.2. **Information on the active substances**	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR
1.4.4.3. **Information on safeners, synergists and co-formulants**	Confidential information. Please refer to the Volume 4 (Confidential Information) section of the DAR
1.4.5. Type and code of the plant protection product	Emulsifiable Concentrate (EC)
1.4.6. Function	Fungicide

1.4.7. Field of use envisaged	Winter and spring wheat, durum wheat, winter and spring barley, winter and spring oats, winter and spring rye, winter and spring triticale, and winter and spring oilseed rape.
1.4.8. Effects on harmful organisms	Pydiflumetofen is a foliar fungicide in the carboxamide chemical group that acts by inhibition of respiration at complex II (succinate-dehydrogenase). Pydiflumetofen is a lipophilic molecule with limited solubility and limited xylem translocation; it does not move in the phloem and has no vapour activity. Pydiflumetofen has low uptake into leaf tissues, and limited systemicity of absorbed compound resulting in a substance with predominantly protectant properties. However, although translaminar and xylem systemic properties of pydiflumetofen are limited, the molecule also reduces intercellular mycelial growth and thus may provide some curative activity. Pydiflumetofen is most active at stages of the fungal life cycle which are particularly energy demanding. It shows strong effects in early growth stages; it inhibits spore germination and germ tube growth and consequently hinders establishment of the fungus in the host plant.

1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT

1.5.1. Details of representative uses

1.5.1.1 Initial intended uses in Great Britain

Crop and/or situation (a)	Region	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (m)	Remarks (*)
					Type (d-f)	Concentration of a.s. g/L (i)	Method / kind (f-h)	Timing / Growth stage and season (j)	Max number a) per use b) per crop / season (k)	Minimum Interval between applications	L product/ha a) max. rate per appl. b) max. total rate per crop/season	g a.s./ha a) max. rate per appl. b) max. total rate per crop/season (l)	Water volume L/ha		
Barley (winter and spring)	GB	Miravis Plus	F	*Pyrenophora teres* *Rhynchosporium secalis* *Ramularia collo-cygni* *Puccinia hordei* *Erysiphe graminis*	EC	62.5	Foliar	BBCH 30-59	a) 1 b) 1	N.A.	a) 2.65 b) 2.65	a) 166 b) 166	100-300	Defined by latest time of application	
				Fusarium spp.				BBCH 55-65			a) 3.2 b) 3.2	a) 200 b) 200			
Wheat (winter and spring), Durum wheat, Spelt	GB	Miravis Plus	F	*Septoria tritici* *Septoria nodorum* *Puccinia recondita* *Pyrenophora tritici-repentis* *Erysiphe graminis*	EC	62.5	Foliar	BBCH 30-69	a) 1 b) 1	N.A.	a) 2.65 b) 2.65	a) 166 b) 166	100-300	Defined by latest time of application	
				Fusarium spp.				BBCH 61-69			a) 3.2 b) 3.2	a) 200 b) 200			
Oats (winter and spring)	GB	Miravis Plus	F	*Fusarium* spp.	EC	62.5	Foliar	BBCH 55-65	a) 1 b) 1	N.A.	a) 3.2 b) 3.2	a) 200 b) 200	100-300	Defined by latest time of application	
Triticale (winter and spring),	GB	Miravis Plus	F	*Fusarium* spp.	EC	62.5	Foliar	BBCH 61-69	a) 1 b) 1	N.A.	a) 3.2 b) 3.2	a) 200 b) 200	100-300	Defined by latest time of application	

Rye (winter and spring															
Oilseed rape (winter and spring)	GB	Miravis Plus	F	*Sclerotinia sclerotiorum*	EC	62.5	Foliar	BBCH 57-69	a) 1 b) 1	N.A.	a) 3.2 b) 3.2	a) 200 b) 200	100-300	Defined by latest time of application	1 application every 3 years

* For uses where the column "Remarks" is marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).

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

(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)

(c) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds

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

(e) GCPF Codes – GIFAP Technical Monograph N° 2, 1989

(f) All abbreviations used must be explained

(g) Method, e.g. high-volume spraying, low volume spraying, spreading, dusting, drench

(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant – type of equipment used must be indicated

(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluroxypyr). In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).

(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(k) Indicate the minimum and maximum number of application possible under practical conditions of use

(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha

(m) PHI - minimum pre-harvest interval

1.5.2. Further information on representative uses

Method of application

Miravis Plus is applied as a foliar spray using conventional crop spraying equipment in a water volume of 100 300 L/ha. See table 1.5.1. above for the application rates applied to each crop.

Number and timing of applications and duration of protection

Table 1.5.2-1 – Proposed uses of Miravis Plus

Crop(s)	Pathogen(s)	Timing	Application rate		Maximum number of applications
			L product/ha	g a.s. pydiflumetofen/ha	
Winter barley, Spring barley	*Pyrenophora teres* *Rhynchosporium secalis* *Ramularia collo-cygni* *Puccinia hordei* *Erysiphe graminis*	BBCH 30-59	2.65	166	1
	Fusarium spp.	BBCH 55-65	3.2	200	1
Winter wheat, Spring wheat, Durum wheat, Spelt	*Septoria tritici* *Septoria nodorum* *Puccinia recondita* *Pyrenophora tritici-repentis* *Erysiphe graminis*	BBCH 30-69	2.65	166	1
	Fusarium spp.	BBCH 61-69	3.2	200	1
Winter oats, Spring oats	*Fusarium spp.*	BBCH 55-65	3.2	200	1
Winter triticale, Spring triticale, Winter rye, Spring rye	*Fusarium spp.*	BBCH 61-69	3.2	200	1
Winter oilseed rape, Spring oilseed rape	*Sclerotinia sclerotiorum*	BBCH 57-69	3.2	200	1

Pydiflumetofen is best used as a protectant treatment or in the earliest stages of disease development.

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

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

Proposed instructions for use

Pydiflumetofen is proposed for use in agriculture as a foliar fungicide in winter and spring wheat, durum wheat, winter and spring barley, winter and spring oats, winter and spring rye, winter and spring triticale, and winter and spring oilseed rape. See section 1.5.1. and table 1.5.2-1 above for further details.

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

MRLs have been proposed based on the GB uses (Table 1.5.1) of winter and spring wheat, durum wheat, spelt, winter and spring barley, winter and spring oats, winter and spring rye, winter and spring triticale, and winter and spring oilseed rape – see Volume 1, Section 2.7.10.

Additional MRLs have been applied for which HSE have assessed currently as a small number of additional uses for MRL assessment (Table 1.5.3), including uses on Carrots, Parsley roots and Parsnip. These uses have been considered for residues assessment (and consumer risk) to support MRL setting in this assessment report alongside the representative uses. These crops are anyhow impacted by the possibility of there being uptake of residues into these crops as rotational crop residues following use of pydiflumetofen on the representative use crops. As such, the overall consumer risk assessment in this assessment report is impacted minimally by including these root crops as additionally assessed primary crop uses. Please see the residues evaluation in section 2.7. Syngenta have also applied for Import Tolerances and other crop uses that will need onward assessment for GB MRLs, on a wide variety of crops. These wider uses will be assessed with a more comprehensive evaluation of further uses after the active substance approval, which from a GB perspective, also needs to consider the ~~acceptability~~ assessment of the CODEX MRLs for pydiflumetofen. Please see section 2.7.11.

Table 1.5.3 – GAP of proposed MRLs

Crop and/or situation (i)	GB or Country for IT	Product name	F or G or I (ii)	Pests or Group of pests (iii)	Preparation type (iv)	Preparation conc. a.s. (v)	App Method kind (vi)	Range of growth stages & season (vii)	No of apps min-max (viii)	Interval between apps (min)	App rate per treatment (kg a.s/hL) min-max (ix)	Water per treatment (L/ha) min-max	App rate per treatment (kg a.s./ha) min-max (x)	PHI (days) (xi)	Remark
Carrots	GB	*A19649H (Miravis)*	*F*	*Powdery mildew (Erysiphe heraclei ERYSHE) Alternaria dauci (ALTDA)*	*SC*	*200 g/L*	*Foliar spray*	*BBCH14-49*	2	*14*	-	*300-1000*	*0.07*	*14*	
Parsley roots	GB	*A19649H (Miravis)*	*F*	*Powdery mildew (Erysiphe heraclei ERYSHE) Alternaria dauci (ALTDA)*	*SC*	*200 g/L*	*Foliar spray*	*BBCH21-49*	2	*14*	-	*200-600*	*0.07*	*14*	
Parsnip	GB	*A19649H (Miravis)*	*F*	*Powdery mildew (Erysiphe*	*SC*	*200 g/L*	*Foliar spray*	*BBCH14-49*	2	*14*	-	*300-1000*	*0.07*	*14*	

Crop and/or situation ([i])	GB or Country for IT	Product name	F or G or I ([ii])	Pests or Group of pests ([iii])	Preparation type ([iv])	Preparation conc. a.s. ([v])	App Method kind ([vi])	Range of growth stages & season ([vii])	No of apps min-max ([viii])	Interval between apps (min)	App rate per treatment (kg a.s/hL) min-max ([ix])	Water per treatment (L/ha) min-max	App rate per treatment (kg a.s./ha) min-max ([x])	PHI (days) ([xi])	Remark
				heraclei ERYSHE) Alternaria dauci (ALTDA)											

1.5.4. Overview on authorisations in EU Member States

Whilst Pydiflumetofen is not yet approved in the EU, an application is currently undergoing consideration for the approval of prydiflumetofen as a new active substance (NAS) within the EU (France are the RMS, Austria are the Co-RMS). Therefore there are currently no authorization for the use of plant protection products containing Pydiflumetofen within EU Member States. The representative uses being considered in the EU Pydiflumetofen application are detailed in table 1.5.4.1, below.

Table 1.5.4.1 – Representative uses under consideration in the EU Pydiflumetofen application

Crop and/or situation (a)	Member State	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (m)	Remarks (*)
					Type (d-f)	Concentration of a.s. g/L (i)	Method / kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	g a.s /hL min - max (l)	Water L/ha Min-max	g a.s./ha min-max (l)		
Pome fruit (apple, pear)	EU	A19649B	F	Powdery mildew *(Podosphaera leucotricha)* + scab *(Venturia inaequalis)* scab *(Venturia pyrina*	SC	200	Foliar spray	BBCH 56-79	3	7.		400-1500	50	65	0.14l/Ha LWA in 18000m² LWA/ha = 0.25 l/ha (17ml/hl)
Grapes (wine & table)	EU	A19649B	F	Grey mould (*Botrytis cinerea*)	SC	200	Foliar spray	BBCH 67-89	2	14		500-1400	200	21	
Grapes (wine & table)	EU	A19649B	F	Powdery mildew (*Uncinula necator*)	SC	200	Foliar spray	BBCH 13-77	2	10		150-1000	40	21	
Potato	EU	A19649B	F	Early blight (Alternaria solani)	SC	200	Foliar spray	BBCH 31-89	3	14		200-500	40	7	
Fruiting vegetables (tomato)	EU	A19649B	F	Early blight (Alternaria solani)	SC	200	Foliar spray	BBCH 51-89	2	7		300-1000	70	1	
Edible cucurbit, (cucumber, courgette)	EU	A19649B	F	Powdery mildew (Sphaerotheca fuliginea) and Erysiphe sp)	SC	200	Foliar spray	BBCH 20-89	2	7		300-1000	50	1	Equivalent to 25 mL/hL
Inedible cucurbit (melon, watermelon)	EU	A19649B	F	Powdery mildew (Sphaerotheca fuliginea) and Erysiphe sp)	SC	200	Foliar spray	BBCH 20-89	2	7		300-1000	50	1	Equivalent to 25 mL/hL
Flowering brassica (broccoli,cauliflower), leafy brassica (kale), head brassica (cabbage)	EU	A19649B	F	Alternaria sp and Mycosphaerella sp.	SC	200	Foliar spray	BBCH 21-49	2	14		200-600	70	14	
Head brassica (Brussels sprout), kohlrabi	NEU	A19649B	F	Alternaria sp and Mycosphaerella sp.	SC	200	Foliar spray	BBCH 21-49	2	14		200-600	70	14	Uses sought in Northern EU only

Level 2

PYDIFLUMETOFEN

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

2.1. IDENTITY

Acceptable data and information have been submitted to support the manufacturing process of pydiflumetofen and the proposed specification is considered supported by the available data, based on full scale manufacturing at one site and pilot scale manufacturing at a second site. None of the impurities identified in technical pydiflumetofen are considered to be of toxicological or ecotoxicological relevance.

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

2.2. PHYSICAL AND CHEMICAL PROPERTIES

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

Pydiflumetofen is a white opaque solid in the form of a fine, non-free flowing powder, with a melting point of 113°C (pure). Pydiflumetofen is not classified as flammable, explosive, or oxidising, and is not a self-heating substance. The pure active substance is slightly soluble in pure water (1.5 mg/L at pH 6.6), with no dissociation observed within the pH range 2-12. It has a n-octanol/water partition coefficient log P_{OW} of 3.8 at 25 °C, indicating the potential to bioaccumulate. UV/VIS, IR, NMR, and MS spectra are available for the active substance and are consistent with its structure.

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

The representative formulation 'Miravis Plus' (A21857B) is an emulsifiable concentrate (EC) containing 62.5 g/L pydiflumetofen.

The appearance of the product is that of light-yellow liquid with a 'solvent-like' odour. It is considered not to have explosive and oxidising properties and is not classified as flammable. It has an auto-ignition temperature of 400 °C, which indicates that the formulation is not self-heating. When diluted with 1 % deionised water the pH value is 5.8. The dynamic viscosity at 40 °C is 20.8 mPa/s, which would indicate a kinematic viscosity < 20.5 mm2/s, however when considered together with the composition of the product a classification for aspiration hazard is not required. The surface tension of the neat product is 31.4 mN/m and 36.8 mN/m at a dilution of 0.1 %, indicating that the product is surface active. It's technical characteristics are acceptable for a EC formulation.

Following both 7 days at 0 °C and 2 weeks at 54 °C, neither the active substance content nor the physical, chemical, and technical properties were changed, indicating acceptable stability at low and high temperatures. Data to support a shelf life of 2 years at ambient temperature when stored in HDPE containers were also submitted demonstrating acceptable stability of both the active substance content and the physical, chemical, and technical properties.

No data on physical or chemical compatibility of tank mixes were submitted. The draft label submitted for 'Miravis Plus' (A21857B) indicates that it must always be used in mixture with another product for resistance management reasons on cereal crops. Therefore, compatibility data will be required to support the authorisation of the product.

2.3. DATA ON APPLICATION AND EFFICACY

2.3.1. Summary of effectiveness

The applicant has provided sufficient data to establish the appropriateness of the GAP and the effectiveness of the proposed formulation. The biological assessment dossier and individual trials reports will be fully evaluated at the product authorisation stage. Overall, the data provided are sufficient to confirm that pydiflumetofen and the

associated representative formulation (Miravis Plus) are sufficiently effective, and the proposed GAP is realistic and fulfils the needs of a risk envelope. For further details see DAR Volume 3CP B3.

2.3.2. Summary of information on the development of resistance

Pydiflumetofen is a member of the SDHI fungicide group, known as complex II respiration inhibitors (FRAC Code 7). SDHIs do not show cross resistance with other chemical classes such as strobilurins, benzimidazoles, anilinopyrimidines or demethylation inhibitors. Therefore, no cross resistance to fungicides from different mode of action groups is expected. However, within the SDHI group, cross-resistance is expected and has been shown using field isolates and lab mutants. The similar overall chemical structures of SDHIs leads to similar intermolecular interaction at the target site. However, the effect of the various mutations in resistance isolates on the activity of the different SDHIs is specific regarding the respective pathogen - active substance combination.

Pydiflumetofen is a single site inhibitor and resistance, which is due to target site mutations in the SDH subunit genes, has been selected by SDHI usage. SDHI fungicides are currently classified as having a medium to high resistance risk by FRAC. *Septoria tritici*, *Pyrenophora teres* and *Pyrenophora tritici-repentis* are classified as having a medium resistance risk, whereas the other target pathogens of Miravis Plus have a low resistance risk.

To manage the resistance risk, use recommendations must be aligned to FRAC and FRAG-UK guidelines, including limiting the number of applications of pydiflumetofen and other SDHI containing products in a given crop and alternation and tank mixture with effective products from different mode of action groups. Other cultural control methods should be incorporated into the resistance management strategy, including but not limited to, hygienic practices, crop rotation, and the use of disease resistance crop varieties. The exact management strategy for products containing pydiflumetofen can be considered at the product authorisation stage. For further details see DAR Volume 3CP B3.

2.3.3. Summary of adverse effects on treated crops

The applicant has provided sufficient data to examine the effects of the active substance and representative formulation on the treated crops, when applied in accordance with the proposed GAP. Phytotoxic effects were rarely observed from the proposed uses and any symptoms reported were minor. No negative effects on yield, quality, germination or transformation processes were observed. For further details see DAR Volume 3CP B3.

Overall, the proposed GAP is realistic in terms of its crop safety in the proposed crops. A detailed evaluation of all potential adverse effects on the treated crops, including phytotoxicity, yield quantity and quality, effects on plant parts for propagation and transformation processes, must be conducted at the product authorisation stage.

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

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

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

Candidate for substitution: efficacy activity

Both isomers were shown to have efficacy activity (see section B.3.9. of DAR Volume 3CA B3).

2.4. FURTHER INFORMATION

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

The applicant has provided the following information :

Storage

Requirements for storage areas and containers:

No special storage conditions required.
Keep containers tightly closed in a dry, cool and well-ventilated place.
Keep out of the reach of children.
Keep away from food, drink and animal feeding stuffs.

Advice on safe handling:
No special protective measures against fire required.
Avoid contact with skin and eyes.
When using, do not eat, drink or smoke.

Land transport

ADR/ RID:		
UN-Number:		3077
Class:		9
Labels:		9
Packaging group	III	
Proper shipping name :		ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (PYDIFLUMETOFEN)
Tunnel restriction code:		E

Sea transport

IMDG:		
UN-Number:		3077
Class:		9
Labels:		9
Packaging group	III	
Proper shipping name :		ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (PYDIFLUMETOFEN)
Marine pollutant :		Marine pollutant

Air transport

IATA-DGR		
UN-Number:		3077
Class:		9
Labels:		9
Packaging group	III	
Proper shipping name :		ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (PYDIFLUMETOFEN)

Fire

Suitable extinguishing media:

Extinguishing media - small fires: Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Extinguishing media - large fires: Use alcohol-resistant foam or water spray.

Extinguishing media which shall not be used for safety reasons:

Do not use a solid water stream as it may scatter and spread fire.

Specific hazards during fire fighting:

As the product contains combustible organic components, fire will produce dense black smoke containing hazardous products of combustion. Exposure to decomposition products may be a hazard to health.

Special protective equipment for firefighters:

Wear full protective clothing and self-contained breathing apparatus.

Further information minimise the hazards arising:

Do not allow run-off from fire fighting to enter drains or water courses. Cool closed containers exposed to fire with water spray.
Hazardous decomposition products likely to be generated in the event of fire: Combustion or thermal decomposition will evolve toxic and irritant vapours.
Hazardous reactions: No hazardous reactions by normal handling and storage according to provisions.

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

2.4.2. Summary of procedures for destruction or decontamination

The applicant states the following in the dossier:

The active substance SYN545974, can be disposed of safely by incineration in a modern incinerator, licensed to treat special contaminated waste, which fulfils the following conditions: temperature > 800°C, minimum residence time within the incinerator: 2 seconds, equipped with a washing unit for flue gases. The ashes have to be disposed of at a suitable, approved waste disposal site. Wash water has to be disposed of via a suitable waste water treatment plant.
The halogen content is well below 60 % and therefore not critical. The reaction products are completely destroyed at temperatures above 800 °C.

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

2.4.3. Summary of emergency measures in case of an accident

The applicant states the following in the dossier:

Environmental precautions

Avoid dust formation. Do not flush into surface water or sanitary sewer system. If the product contaminates rivers and lakes or drains inform respective authorities.

Methods for cleaning up

Contain spillage, pick up with an electrically protected vacuum cleaner or by wet-brushing and transfer to a container for disposal according to local / national regulations.
Do not create a powder cloud by using a brush or compressed air. Clean contaminated surface thoroughly.
Do not contaminate ponds, waterways or ditches with chemical or used container.
Do not dispose of waste into sewer.
Where possible recycling is preferred to disposal or incineration.
If recycling is not practicable, dispose of in compliance with local regulations.

Additional advice

If the product contaminates rivers and lakes or drains inform respective authorities.
No other methods are proposed for the disposal of the active substance.
Where larger quantities are concerned, consult the supplier.

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

2.5. METHODS OF ANALYSIS

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

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

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

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

Extraction efficiency of the methods used to determine residues for data generation is sufficiently proven for high acid commodities, high oil commodities, high water commodities and dry commodities (high protein/high starch), and for products of animal origin.

2.5.2. Methods for post control and monitoring purposes

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

For the determination of residues in plants, extraction efficiency was not determined for commodities in the high oil crop group.

For the determination of residues in air the validated LOQ of 30 µg/m3 does not comply with the required LOQ which is calculated using the proposed $AOEL_{systemic.}$of 0.05 mg/kg bw/day. Therefore, further method validation data is required to support as lower LOQ of 15 µg/m^3.

The following data are required:

- Data to address extraction efficiency high oil crops for the QuEChERS monitoring method using acetonitrile/water (50/50, v/v).
- Validation data for the method for the monitoring of residues in air to support a lower LOQ of 15 µg/m^3.

A summary of the monitoring methods is presented below:

Matrix/Crop group	Analytes(s)	Method	LOQ	ILV?	Fully validated
High water High acid High oil High protein High starch Difficult to analyse (coffee bean)	Pydiflumetofen	LC-MS/MS [QuEChERS method EN 15662]	0.01 mg/kg	Yes	Yes, however data to address extraction efficiency for high oil crops are required. The proposed residues definition for monitoring is: pydiflumetofen
Egg Fat Liver Milk Meat (bovine) Blood	Pydiflumetofen	LC-MS/MS [QuEChERS method EN 15662]	0.01 mg/kg	Yes	Yes. The proposed residues definition for monitoring is: pydiflumetofen

Matrix/Crop group	Analytes(s)	Method	LOQ	ILV?	Fully validated
Egg Fat Kidney Liver Milk Muscle Blood	2,4,6-trichlorophenol (Free and conjugated)	LC-MS/MS	0.01 mg/kg	Yes	Yes, but not required for product of animal origin as the proposed residues definition for monitoring is: pydiflumetofen (method applicable to body fluids and tissues, see bloew)
Soil Sediment	Pydiflumetofen	LC-MS/MS	0.5 µg/kg	n/a	Yes LOQ < EC_{10} for most sensitive soil organism (5.45 mg a.s/kg dw soil; earthworm) The proposed residues definition for monitoring is: pydiflumetofen
Surface water Ground water	Pydiflumetofen	LC-MS/MS	0.05 µg/L	Yes	Yes LOQ < most sensitive NOEC The proposed residues definition for monitoring is: pydiflumetofen
Air	Pydiflumetofen	LC-MS/MS	30 µg/m^3	n/a	No LOQ > "c" (15 µg/m^3 based on $AOEL_{systemic}$) The proposed residues definition for monitoring is: pydiflumetofen
Whole blood	2,4,6-trichlorophenol (Free and conjugated)	Method for products of animal origin included validation for blood			Yes The proposed residues definition for monitoring is: 2,4,6- trichlorophenol (Free and conjugated)
Body tissues	2,4,6-trichlorophenol (Free and conjugated)	Refer to the method for liver			Yes The proposed residues definition for monitoring is: 2,4,6- trichlorophenol (Free and conjugated)

2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

This section summarises all the toxicological data which are relevant for the approval of pydiflumetofen in GB under Regulation EC No 1107/2009 in accordance with the requirements of Regulation EC No 283/2013.

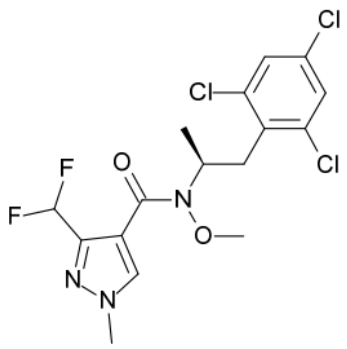
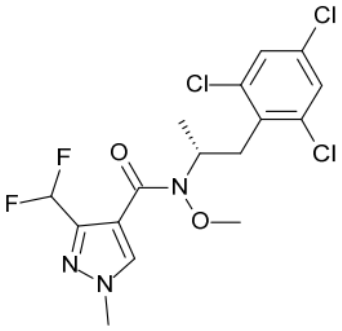
An EU peer-reviewed DAR[1], EFSA Conclusion[2] and RAC Opinion[3] on harmonized classification are available for pydiflumetofen. Therefore, HSE has performed an independent evaluation of the available data but made use of the assessments already available at EU level as appropriate. The summaries in this Vol. 1 have been produced independently by HSE. New information generated and submitted by the applicant following the completion of the EU process, has been fully evaluated by HSE. With regard to the classification of pydiflumetofen, HSE has already produced and published a Technical Report[4] supporting the Mandatory Classification & Labelling (MCL) of the substance in GB.

Pydiflumetofen (also called SYN545974 or ADEPIDYNTM) is a new broad spectrum fungicide of the chemical group of N-methoxy-(phenyl-ethyl)-pyrazole-carboxamide. The mode of action of the active substance is respiration inhibition at complex II (Succinate-DeHydrogenase) in mitochondria of phytopathogenic fungi, thus SYN545974 belongs to the SDHI fungicide group. There is no cross resistance between compounds belonging to this group and strobilurin (QoI) or triazole (DMI) chemistry.

Pydiflumetofen has a very broad spectrum of disease control across multiple crops. It delivers very good efficacy against leaf spots (such as Venturia sp. and Alternaria sp.), powdery mildews and Botrytis.

The technical specification is supported by the toxicological assessment based on additional genotoxicity testing performed with a spiked batch of pydiflumetofen (with levels of impurities above their specification). All analytical methods used in the toxicological studies for the identification and quantification of pydiflumetofen and its metabolites are considered validated by HSE.

Pydiflumetofen contains two enantiomers, both of which are biologically active. The two enantiomers are separately numbered SYN546968 and SYN546969. The technical specification of pydiflumetofen covers an enantiomer ratio of 1 (in all cases expressed as SYN546968/SYN546969, i.e. an enantiomer fraction ratio for SYN546968:SYN546969 of 50:50).

ABSOLUTE 	ABSOLUTE 
SYN546968 (S)-3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid methoxy-[1-methyl-2-(2,4,6-trichloro-phenyl)-ethyl]-amide	SYN546969 (R)-3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid methoxy-[1-methyl-2-(2,4,6-trichloro-phenyl)-ethyl]-amide

[1] Peer review of the pesticide risk assessment of the active substance pydiflumetofen (wiley.com)
[2] Peer review of the pesticide risk assessment of the active substance pydiflumetofen (wiley.com)
[3] [04.01-ML-014.03] (europa.eu)
[4] Updating the GB mandatory classification and labelling list (GB MCL List) (hse.gov.uk)

2.6.1. Summary of absorption, distribution and excretion in mammals

The ADME properties of pydiflumetofen were investigated by the oral route in several rat studies. The excretion and metabolism of pydiflumetofen were also investigated in mice by the oral route. The blood pharmacokinetic profile of pydiflumetofen following repeat oral dosing of non-radiolabelled test material was determined in rats, mice, rabbits and dogs (for the dog, the data are presented in the short-term toxicity section). These blood kinetic data were used to support dose level selection for some toxicity studies based on linear versus non-linear kinetics of the parent substance. In addition, intravenous (iv) administration of the radiolabelled test substance and measurement of radioactivity in blood and/or excreta were used to establish the oral bioavailability of pydiflumetofen in rats.

In the rat, preliminary ADME studies using [pyrazole-5-^{14}C]- and [phenyl-U-^{14}C]- radiolabelled pydiflumetofen indicated that pydiflumetofen was metabolically cleaved between the pyrazole and phenyl moieties. Therefore, subsequent ADME studies used both radiolabels. Bile duct cannulated rats were used in the main ADME study, as the preliminary study showed that greater than 20% of the administered dose was excreted in faeces. Additionally, metabolism was investigated in human and rat microsomes in vitro.

The table below provides an overview of the available studies.

Title	Reference
A Preliminary Study of Pharmacokinetics, Absorption, Metabolism and Excretion in Rats Following Single Oral and Intravenous Administration of ^{14}C-SYN545974	[redacted] (2015). SYN545974_10188
The Absorption and Excretion of [Phenyl-U-^{14}C] and [Pyrazole-5-^{14}C] SYN545974 Following Single Oral Administration in the Rat	[redacted] (2015).
Tissue Depletion of [Phenyl-U-^{14}C] and [Pyrazole-5-^{14}C] SYN545974 Following Single Oral Administration in the Rat	[redacted] (2015a).
The Pharmacokinetics of [Phenyl-U-^{14}C] and [Pyrazole-5-^{14}C]-SYN545974 Following Single Oral and Intravenous Administration in the Rat	[redacted] (2015).
Biotransformation of [^{14}C]-SYN545974 in Rat	[redacted] (2015).
Pharmacokinetics of SYN545974 in the Rat Following Multiple Oral and Single Intravenous Administration	[redacted] (2014).
Pharmacokinetics of SYN545974 in the Mouse Following Multiple Oral and Single Intravenous Administration	[redacted] (2014a).
The Excretion and Biotransformation of [Phenyl-U-^{14}C] and [Pyrazole-5-^{14}C]-SYN545974 Following Single Oral Administration in the Mouse	[redacted] (2015).
SYN545974 - Oral (Gavage) Toxicokinetic Study in the Pregnant Rabbit.	[redacted] (2015).
Adepidyn – In Vitro Comparative Metabolism of [Phenyl-U-14C]Adepidyn and [Pyrazole-5-14C] Adepidyn in Human and Rat Liver Microsomes.	[redacted] (2017)

Absorption

After a single gavage dose of 5 mg/kg bw pydiflumetofen, **oral absorption** was **85-90%** (sum of material excreted in urine, bile, cage wash and remaining carcass, excluding GI tract) in rats. Absorption decreased to 50-55% as dose increased to 100 mg/kg bw and further decreased to 19-24% at 300 mg/kg bw, as also shown by the increased amount of unchanged parent in faeces. Bile was the major route of excretion, indicating a significant first-pass effect. Indeed, post-hepatic systemic **bioavailability (F)** following oral dosing was approximately **50%**. Bioavailability may be a more appropriate parameter than oral absorption in adjusting the AOEL and AAOEL.

Tissue distribution

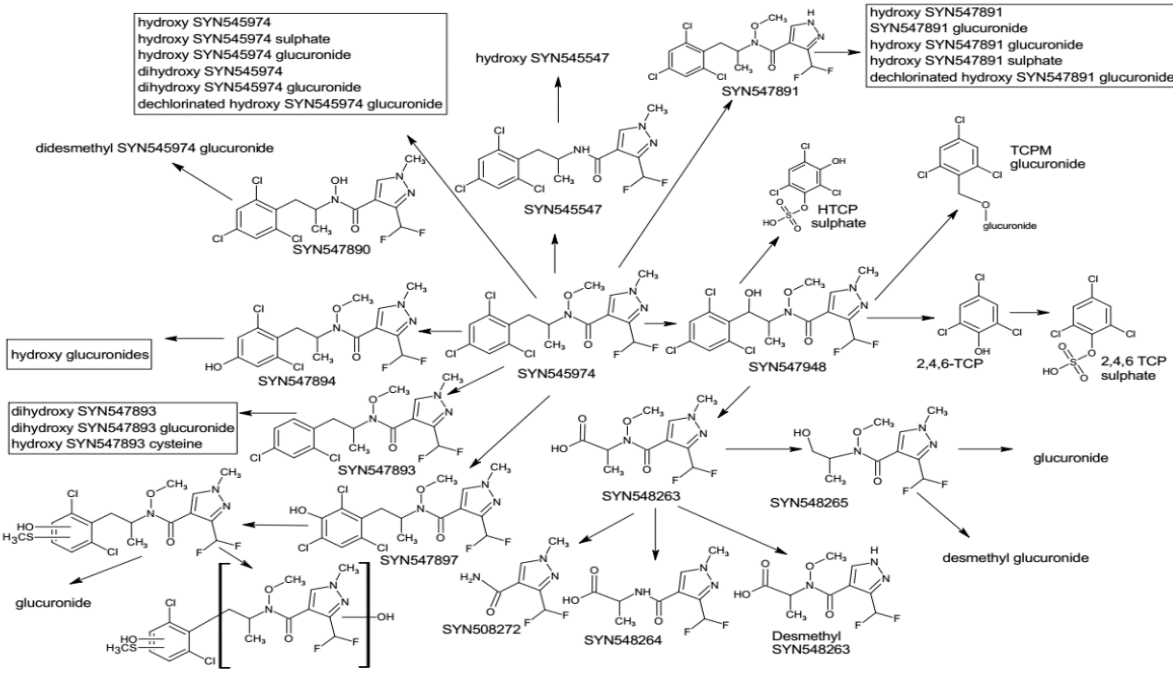
Tissue distribution after a single oral dose of pydiflumetofen (5, 100 and 300 mg/kg bw) was similar, irrespective of radiolabel ([^{14}C]-phenyl or pyrazole), sex or dose. The highest levels of radioactivity were observed in the liver, kidneys, adrenals and renal fat. After seven days, levels of radioactivity were only higher in the liver and kidneys compared to blood. The depletion profile of all tissues appeared to be similar to that of blood/plasma. No plateaus were observed in any tissue, suggesting that accumulation in tissues is unlikely. At termination, total tissue and carcass residues accounted for ≤ 3.0% of the administered dose.

Metabolism

After a single oral low dose of 5 mg/kg bw, pydiflumetofen was extensively metabolised (> 95% of administered dose) in the rat mainly via first pass metabolism. Generally, metabolite profiles were similar irrespective of radiolabel apart from a few radiolabel-specific metabolites, dose (except for faeces) or sex. At 5 mg/kg bw, unchanged pydiflumetofen was a minor component only present in faeces up to 3.9% of the administered dose. However, at the higher doses (100-300 mg/kg bw) unchanged pydiflumetofen was a major component in faeces present up to 48.2% of the administered dose.

Only two metabolites (2,4,6 TCP sulphate in urine and plasma and SYN548272 in plasma) individually accounted for >10% of the administered dose. Numerous other metabolites were detected as cleavage products and as molecules that retained both the phenyl and pyrazole ring moieties. The intact metabolites detected were qualitatively and quantitatively similar between the two labels. The cleavage of the parent molecule occurred following hydroxylation of pydiflumetofen on the carbon adjacent to the trichlorophenyl ring to give SYN547948. This then cleaved to yield the 2,4,6 trichlorophenol (2,4,6-TCP) and SYN548263. 2,4,6-TCP was then sulphated, which accounted for the largest % of dose excreted at up to 14.9% of the administered dose. Other metabolites that retained the phenyl ring were hydroxyl 2,4,6-TCP (HTCP) sulphate and 2,4,6-TCP methanol (TCPM) glucuronide. SYN548263 was further metabolised by demethoxylation to SYN548264 and by N-demethylation. Amide hydrolysis of the pyrazole half molecules gave the pyrazole amide, SYN508272. Reduction of SYN548263 yielded the alcohol SYN548265. SYN548265 was further metabolised via demethylation and glucuronidation.

Numerous metabolites that retained both the phenyl and pyrazole moieties were observed. The primary metabolic routes for these metabolites included demethoxylation to SYN545547, N-dealkylation to SYN547891, single and di-hydroxylation, O-demethylation to SYN547890, oxidative dechlorination to SYN547894 and reductive dechlorination to SYN547893. The majority of these metabolites were also mono and di-hydroxylated and in many cases conjugated with glucuronide or in the case of SYN547894, glutathione. The proposed metabolic pathway of pydiflumetofen in the rat is shown below:



In the mouse, no major urinary metabolites (>10% of the administered dose) were identified. However, the most abundant metabolites in the mouse were qualitatively similar to those in the rat suggesting metabolism is similar between the two species.

In a GLP in vitro comparative metabolism study using human and rat liver microsomes, pydiflumetofen was metabolised into 14 different metabolites (P1-14). Metabolites were qualitatively similar between human and male rat microsomes. Fewer metabolites and higher levels of unchanged pydiflumetofen (P15) in female rat microsomes suggested metabolism occurred at a slower rate in the female rat. Some quantitative differences in metabolites were observed between human and rat microsomes which suggests the rates of metabolism may be different between the two species; however no unique human metabolites were observed.

Excretion

Irrespective of radiolabel, dose or sex, following a single oral administration of [^{14}C]-pydiflumetofen in rats, the majority of the radioactivity (> 91%) was eliminated by 48 hours post dose and excretion was essentially complete by 168 h (as indicated by the low levels of radioactivity in the carcass). Absorption was limited by dose. The majority of the absorbed dose was excreted in faeces via bile elimination.

The main route of excretion was in the faeces via the bile; urinary excretion was a minor route. After an oral dose of 5 mg/kg bw, 81% of the administered dose was excreted via bile compared to 15% via the faeces. However at higher doses, excretion decreased in bile to 41% of the administered dose at 100 mg/kg bw (females) and 18% at 300 mg/kg bw (males) but increased in faeces.

After a single oral dose in the mouse, excretion was essentially complete after 7 days. The major route of excretion was via faeces (bile duct cannulated mice were not investigated); urinary excretion was a minor route. Approximately 63-79% of the administered dose was excreted via faeces at 10 mg/kg bw; however this increased to 76-94% at 300 mg/kg bw suggesting oral absorption may also be limited by dose in mice.

Pharmacokinetics

Parent and metabolites (total radioactivity)

In the rat, after a single oral dose of 5 mg/kg bw, blood/plasma C_{max} was reached from 0.5-2 h post dose, whereas at higher doses (100 or 300 mg/kg bw), C_{max} was reached at 8 h. Systemic exposure was comparable between blood and plasma, irrespective of dose or radiolabel. After a single oral exposure, systemic exposure increased in a sub-proportional manner between 5 and 300 mg/kg bw. Additional pharmacokinetic parameters for total radioactivity in the rat are presented in the table below.

	Pharmacokinetic parameters for total radioactivity in rat plasma after oral administration with pyrazole-labelled pydiflumetofen			
	5 mg/kg bw		**300 mg/kg bw**	**100 mg/kg bw**
	Male	**Female**	**Male**	**Female**
C_{max} (µg	0.49	0.67	7.1	3.1
C_{max}/D	0.0969	0.131	0.0259	0.0365
t_{max} (hours)[1]	2	0.5	8	2
$t_{1/2}$ (hours)	56.6*	30.4*	18.6*	10.6
$AUC_{(0-t)}$ (µg equiv.h/mL)	6.43	5.37	195	55.9
$AUC_{(0-t)}$/D	1.26	1.05	0.705	0.653
$AUC_{(0-inf)}$ (µg equiv.h/mL)	7.45*	5.81*	197*	56.2
$AUC_{(0-inf)}$/D	1.47*	1.13*	0.712*	0.658
AUC % Extrap	13.7*	7.56*	1.02*	0.678

** = Coefficient of determination was less than 0.800 and/or the extrapolation of the AUC to infinity represents more than 20% of the total area.*

[1] = Median reported for t_{max}

Parent only (non-radiolabelled)

In the rat, systemic exposure to pydiflumetofen after repeat oral dosing increased in a proportional manner from 3 to 10 mg/kg bw/d, however became sub-proportional at concentrations above 300 and 100 mg/kg bw/d in males

and females respectively. Systemic exposure was higher in females compared to male rats. Linearity for males below 30 mg/kg bw/d could not be determined due to low systemic exposure. HSE notes that although non-linear kinetics were observed in the rat from approximately 300 mg/kg bw/d in males and from 100 mg/kg bw/d in females, systemic exposure continued to increase and no plateau was observed up to the highest dose of 1000 mg/kg bw/d.

In the mouse, after repeat oral dosing, systemic exposure (AUC) increased sub-proportionally in relation to dose above 100 mg/kg bw/d. HSE notes that although non-linear kinetics were observed in the mouse from approximately 100 mg/kg bw/d in both sexes, systemic exposure continued to increase and no plateau was observed up to the highest dose of 1000 mg/kg bw/d.

In the pregnant rabbit, after repeat oral dosing from gestation day 6-27, systemic exposure to pydiflumetofen was sub-proportional in relation to dose above 300 mg/kg bw. Inter-individual variability was high between tested animals which decreases the reliability of these findings.

In the dog, after repeat oral dosing of pydiflumetofen for 90-days inter-individual variability was high. However, systemic exposure appeared to increase approximately proportionally (sometimes supra-proportionally) with dose and was generally higher in males compared to females.

HSE notes that no repeat dose ADME studies were conducted using radiolabelled pydiflumetofen. However, an adequate justification was provided by the applicant.

Residue definition for body fluids and tissues

Based on the main ADME studies in the rat, the residue definition for body fluids (blood) and tissues (liver) was set as ~~pydiflumetofen and~~ 2,4,6-TCP (free + conjugates).

2.6.2. Summary of acute toxicity

The acute toxicity of pydiflumetofen was investigated in standard studies conducted via the oral, dermal and inhalation routes. Studies investigating skin and eye irritation/corrosion, as well as skin sensitisation were also conducted. An in vitro 3T3 NRU study was also performed to investigate the potential phototoxicity of pydiflumetofen. As no phototoxic effect was observed, photomutagenicity tests are not required, in accordance with the data requirements of Regulation 283/2013.

Based upon the results of these studies, pydiflumetofen is of low acute toxicity via the oral (LD_{50} >5000 mg/kg bw), dermal (LD_{50} >5000 mg/kg bw) or inhalation (4-hr-LC_{50} aerosol >5.11 mg/mL) routes. Pydiflumetofen was also found to be non-irritating to the skin and eye of rabbits. The in vivo skin and eye irritation studies are regarded by HSE to be in breach of Art 62 of Reg 1107/2009 as in vitro alternatives should have been employed in the first instance. Pydiflumetofen was also non-sensitisting to the skin in a LLNA when tested up to limit of solubility. The *in vitro* phototoxicity study produced a PIF of 1.7, meeting the threshold of non-phototoxicity (< 2), and thus pydiflumetofen is not phototoxic.

The following conclusions have been made in terms of the classification of pydiflumetofen:

- No acute toxicity classification is proposed
- The data requirements of regulation 283/2013 have been met.

The table below summarises the studies carried out as part of the acute toxicity investigations of pydiflumetofen:

Study and *Acceptability*	**Species/ Strain**	**Sex**	**Acceptable**	**Result**	**Classification according to Reg (EC) No. 1272/2008**
Acute oral toxicity study (OECD 425) [redacted], (2012) Batch:	Rat (Wistar)	M & F	Y	LD_{50} >5000 mg/kg bw	No Classification

Study and *Acceptability*	**Species/ Strain**	**Sex**	**Acceptable**	**Result**	**Classification according to Reg (EC) No. 1272/2008**
1228284-64-7 Purity %: 98.5 *Acceptable, relied upon*					
Acute dermal toxicity study (OECD 402) [redacted], (2013) Batch: 1228284-64-7 Purity %: 98.5 *Acceptable, relied upon*	Rat (Wistar)	M & F	Y	LD_{50} >5000 mg/kg bw	No Classification
Acute inhalation toxicity study (OECD 403) [redacted] (2013) Batch: 1228284-64-7 Purity %: 98.5 *Acceptable, relied upon*	Rat (Wistar)	M & F	Y	4hr-LC_{50} > 5.11 mg/L (aerosol)	No Classification
Skin irritation study (OECD 404) [redacted] (2012) Batch: 1228284-64-7 Purity %: 98.5 *Acceptable, relied upon but in breach of Art 62 of Reg 1107/2009*	Rabbit (New Zealand White, NZW)	M	Y	Not Irritating	No Classification
Eye irritation study (OECD 405) [redacted], (2012a) Batch: 1228284-64-7	Rabbit (New Zealand White, NZW)	M	Y	Not Irritating	No Classification

Study and *Acceptability*	**Species/ Strain**	**Sex**	**Acceptable**	**Result**	**Classification according to Reg (EC) No. 1272/2008**
Purity %: 98.5 *Acceptable, relied upon but in breach of Art 62 of Reg 1107/2009*					
Skin Sensitisation study (LLNA) (OECD 429) [redacted], (2013) Batch: 1228284-64-7 Purity %: 98.5 *Acceptable, relied upon*	Mice (CBA/J Rj)	F	Y	Not Sensitising (SI < 3)	No Classification
Phototoxicity study (OECD 432) [redacted], (2015) Batch: 1228284-64-7 Purity %: 98.5 *Acceptable, relied upon*	BALB/c 3T3 Cells	n/a	Y	Not phototoxic (PIF <2)	Not applicable

2.6.3. Summary of short-term toxicity

The short-term toxicity of pydiflumetofen has been investigated via the oral route in GLP and guideline studies for 28 and 90 days in rats and mice and for 90 days and 1 year in dogs; an investigation via the dermal route in rats (28-days) was also provided.

There was no effect in rats when pydiflumetofen was administered dermally.

Rats

When pydiflumetofen was administered orally to rats for 28 days, the liver was identified as the main target organ. Dietary concentrations of 0, 500, 4000, 8000 and 16000 ppm equated to estimated mean achieved doses of 0, 43, 343, and 1322 mg/kg bw/d in males and 0, 40, 322, 619 and 1174 mg/kg bw/d in females. There were no deaths or clinical signs of toxicity and body weight development was affected in males only at the high dose of 1600 ppm (1322 mg/kg bw/d). Liver weights were increased from 4000 ppm by 18% and 20% (absolute) and 21% and 24% (relative) in males and females respectively, associated with centrilobular hypertrophy in both sexes and statistically significantly lower ALT from 8000 ppm in females only. A **NOAEL of 500 ppm (equivalent to 43/40 mg/kg bw/d in males/females)** was therefore identified in rats following 28 days' exposure, based on increased liver weights and hepatocellular hypertrophy at the LOAEL of 4000 ppm (343/322 mg/kg bw/d in males and females).

When pydiflumetofen was administered to rats orally for 90 days, the liver and thyroid were identified as target organs. Dietary concentrations of 0, 250, 1500, 8000 and 16000 ppm equated to mean estimated achieved doses 0, 18.6, 111, 587 and 1187 mg/kg bw/d in males and 0, 21.6, 127, 727 and 1325 mg/kg bw/d in females. There were no deaths or clinical signs of toxicity and body weight development and food consumption were affected in both sexes from 8000 ppm. Liver weights were increased from 1500 ppm by 21% (absolute) and 26% (relative) in males and 16% (absolute) and 18% (relative) in females. Liver weight increases were associated with hepatocellular hypertrophy in males from 1500 ppm (only apparent in females from 8000 ppm) and with reduced ALP in both sexes from 1500 ppm. Follicular cell hypertrophy of the thyroid was noted in males from 1500 ppm (not statistically significant at this dose) and in females from 8000 ppm. **A NOAEL of 250 ppm (equivalent to 18.6 and 21.6 mg/kg bw/d in males and females respectively)** was identified in rats following 90-days' exposure, based on liver weight increases, hepatocellular hypertrophy, reduced ALP, and thyroid follicular cell hypertrophy at the LOAEL of 1500 ppm (111/127 mg/kg bw/d in males and females).

In rats the most sensitive NOAEL was 18.6 mg/kg bw/d, derived from the 90-day study.

Mice

Consistent with the findings in rats, when pydiflumetofen was administered to mice for 28 days, the liver was identified as the main target organ. Dietary concentrations of 0, 500, 1500, 4000 and 7000 ppm equated to estimated achieved doses of 0, 76, 213, 612 and 1115 mg/kg bw/d in males and 0, 96, 266, 701 and 1312 mg/kg bw/d in females. There were no deaths or clinical signs of toxicity. Body weight development was affected in males at all doses, resulting in final body weight gains that were 55% lower than controls at 500 ppm (the lowest tested dose); females were not affected. Liver weights were increased from 500 ppm by 9% (absolute) and 16% (relative) in males and 14% (absolute) and 21% (relative) in females. **A NOAEL could not be identified for mice following 28 days' exposure** as it was less than the lowest dose tested of 500 ppm (equivalent to 76/96 mg/kg bw/d in males/females).

When pydiflumetofen was administered to mice for 90-days, the liver was again identified as the main target organ. Dietary concentrations of 0, 100, 500, 4000 and 7000 ppm equated to estimated achieved doses of 0, 17.5, 81.6, 630 and 1158 mg/kg bw/d in males and 0, 20.4, 106, 846 and 1483 mg/kg bw/d in females. There were no deaths or clinical signs of toxicity. Liver weights were increased from 500 ppm in males by 18% (absolute) and 14% (relative); in females liver weights increases became apparent at 4000 ppm with an increase in absolute weight of 59% and relative weight of 60%. Hepatocellular hypertrophy was noted, reaching statistical significance from 7000 ppm in males and 4000 ppm in females. Clinical chemistry changes, indicative of liver impairment, were noted in both sexes; cholesterol was increased from 500 ppm in males (reaching statistical significance from 4000 ppm) and at 7000 ppm in females, whilst triglyceride concentrations were increased from 4000 ppm in both sexes (reaching statistical significance at 7000 ppm). A **NOAEL of 100 ppm (17.56 mg/kg bw/d) in males and 500 ppm (106 mg/kg bw/d) in females was determined in mice following 90 days' dietary exposure** based on increased liver weights and increased cholesterol at the LOAEL of 500 ppm (106 mg/kg bw/d) in males and increased liver weights, hepatocellular hypertrophy, and increased triglycerides at the LOAEL of 4000 ppm (846 mg/kg bw/d) in females**.**

In mice the most sensitive NOAEL is 17.56 mg/kg bw/d, derived from males in the 90-day study

Dogs

Consistent with the findings in rodents, the liver was identified as a target organ in dogs.

Following 90 days' exposure to pydiflumetofen at doses of 0, 30, 300 and 1000 mg/kg bw/d, body weight gain was reduced in female dogs from 300 mg/kg bw/d, along with liver weight increases and clinical chemistry changes (increased ALP) at the same dose. In males body weight gain was reduced at 1000 mg/kg bw/d, whilst liver weight increases and clinical chemistry changes comprising increases in ALP and triglyceride concentrations were noted from 300 mg/kg bw/d. **A NOAEL of 30 mg/kg bw/d** was therefore identified in male and female dogs following 90 days' exposure, based on reduced body weight gain in females and increased liver weights with associated clinical chemistry changes in both sexes at the LOAEL of 300 mg/kg bw/d.

When the length of exposure was increased to one year in dogs (at doses of 0, 100, 300 & 1000 mg/kg bw/d), there were no treatment related effects on body weight development or food consumption and there were no deaths or clinical signs of toxicity. However, the liver was again identified as a target organ in both sexes. Liver weights were increased from 300 mg/kg bw/d; absolute and relative weights were increased by 24% and 35% in males and 20% and 31% in females. There were no unusual histopathological findings in the liver; however, clinical

chemistry changes, indicative of liver impairment, were noted comprising large increases in ALP (up to 4-fold in males and 3-fold in females). **A NOAEL of 100 mg/kg bw/d** was therefore identified in male and female dogs following 1 year' exposure of pydiflumetofen, based on increased liver weights and concomitant increases in ALP at the LOAEL of 300 mg/kg bw/d.

In dogs, the most sensitive NOAEL is 30 mg/kg bw/d, derived from the 90-day study.

Overall, administration of pydiflumetofen to rats, mice or dogs, results in impaired body weight development. The liver was identified as a target organ in all species, whilst the thyroid was additionally identified as a target organ in rats only. HSE agreed with RAC that no classification for STOT RE was warranted as no effects were observed at doses relevant for classification (see GB MCL Technical Report. for further details).

The most sensitive NOAEL was 17.56 mg/kg bw/d, identified in mice following 90-days' exposure.

The table below summarises the main findings from the repeated-dose toxicity studies:

Study & *Acceptability*	**Test material & Dose levels**	**NOAEL**	**LOAEL**	**Effects at LOAEL**
28-day **rat** dietary study ([redacted], 2012) *Acceptable GLP and guideline study*	Pydiflumetofen 0, 500, 4000, 8000 & 16000 ppm Equivalent to: Males: 0, 43, 343, 677 & 1322 mg/kg bw/d Females: 0, 40, 322, 619 & 1174 mg/kg bw/d in females	500 ppm (43/40 mg/kg bw/d in M/F)	4000 ppm (343/322 mg/kg bw/d in M/F)	↑ Liver weights in M & F ↑ centrilobular hepatocellular hypertrophy in M & F
28-day **mouse** dietary study ([redacted], 2012a) *Acceptable GLP and guideline study*	Pydiflumetofen 0, 500, 1500, 4000 & 7000 ppm Equivalent to: Males: 0, 76, 213, 612 & 1115 mg/kg bw/d Females: 0, 96, 266, 701 & 1312 mg/kg bw/d	< 500 ppm (76/96 mg/kg bw/d in M/F)	500 ppm (76/96 mg/kg bw/d in M/F)	↓ Body weight & Body weight gain in M ↑ Liver weights in M & F
90-day **rat** dietary study ([redacted] & [redacted], 2015) *Acceptable GLP and guideline study*	Pydiflumetofen 0, 250, 1500, 8000 & 16000 ppm Equivalent to: Males: 0, 18.6, 111, 587 & 1187 mg/kg bw/d Females: 0, 21.6, 127, 727 & 1325 mg/kg bw/d	250 ppm (18.6/21.6 mg/kg bw/d in M/F)	1500 ppm (111/127 mg/kg bw/d in M/F)	↑ Liver weights in M & F ↓ ALP in M & F ↑ hepatocellular hypertrophy in M ↑ Thyroid follicular cell hypertrophy in M

Study & *Acceptability*	**Test material & Dose levels**	**NOAEL**	**LOAEL**	**Effects at LOAEL**
90-day **mouse** dietary study ([redacted], 2015) *Acceptable GLP and guideline study*	Pydiflumetofen 0, 100, 500, 4000 & 7000 ppm Equivalent to: Males: 0, 17.5, 81.6, 630 & 1158 mg/kg bw/d Females: 0, 20.4, 106, 846 & 1483 mg/kg bw/d	Males: 100 ppm (17.56 mg/kg bw/d) Females: 500 ppm (106 mg/kg bw/d)	Males: 500 ppm (81.6 mg/kg bw/d) Females: 4000 ppm (846 mg/kg bw/d)	Males: ↑ Liver weights ↑ Cholesterol Females: ↑ Liver weights ↑ Hepatocellular hypertrophy ↑ Triglyceride
90-day **dog** oral (capsule) study ([redacted], 2015) *Acceptable GLP and guideline study*	Pydiflumetofen 0, 30, 300 & 1000 mg/kg bw/d	30 mg/kg bw/d	300 mg/kg bw/d	↓ Body weight gain in F ↑ Liver weights in M & F ↑ ALP in M & F ↑ Triglyceride in M
1-year **do**g oral (capsule) study ([redacted], 2015a) *Acceptable GLP and guideline study*	Pydiflumetofen 0, 30, 100 & 300 mg/kg bw/d	100 mg/kg bw/d	300 mg/kg bw/d	↑ Liver weights in M & F ↑ ALP in M & F ↑ Thyroid weights in M
28-day **rat** dermal study ([redacted], 2013) *Acceptable GLP and guideline study*	Pydiflumetofen 0, 100, 300 & 1000 mg/kg bw/d	1000 mg/kg bw/d	>1000 mg/kg bw/d	No effects up to and including the highest dose tested of 1000 mg/kg bw/d

2.6.4. Summary of genotoxicity

The genotoxic potential of pydiflumetofen was tested in a range of in vitro and in vivo tests.

The in vitro tests included two Ames tests (reverse mutation assay with *Salmonella typhimurium* and *Escherichia coli)*, an in vitro mammalian cell gene mutation assay (in mouse lymphoma L5178Y cells) and an in vitro chromosome aberration test (in human lymphocytes). The two Ames tests were conducted on different batches of pydiflumetofen: one on a standard toxicology batch (SMU2EP12007) and one on a batch spiked with potential impurities (SMU4FL762) to support the technical specification of pydiflumetofen. Both Ames tests and the mammalian cell gene mutation assay gave negative results. The in vitro chromosome aberration test gave a weakly positive/equivocal result, indicative of potential clastogenicity.

The in vivo tests included two mouse bone marrow micronucleus tests and a rat bone marrow chromosome aberration assay. The two mouse bone marrow micronucleus tests were conducted on different batches of pydiflumetofen: one on a standard toxicology batch (SMU2EP12007) and one on a batch spiked with potential impurities (SMU4FL762) to support the technical specification of pydiflumetofen. The in vivo mouse studies gave negative results, meaning the weakly positive/equivocal in vitro clastogenicity finding was not corroborated in vivo. The rat bone marrow chromosome aberration assay was conducted on the same batch (SMU2EP12007) that gave a positive result in the in vitro chromosome aberration test. Pydiflumetofen gave a negative result when tested in this in vivo chromosome aberration test in rats. Therefore, pydiflumetofen is not considered to be genotoxic in vivo. Classification for mutagenicity is not required (see GB MCL Technical Report).

The in vivo bone marrow tests in the rat and mouse did not include assessments of bone marrow exposure to pydiflumetofen. However, in the mouse studies, the observed clinical signs indicated that the test material had been systemically available, reaching the bone marrow. Additionally, pydiflumetofen is known to be systemically available in the mouse and rat after oral gavage dosing, as demonstrated in the ADME studies reported in section 6.1. Therefore, the bone marrow will have been exposed to pydiflumetofen in these in vivo mouse bone marrow micronucleus tests and the in vivo rat bone marrow chromosome aberration assay.

The following table summarises the genotoxicity investigation of pydiflumetofen:

Test system and Acceptability	Concentration/ dose levels	Purity (%)	Result	Reference
In vitro studies				
Bacterial mutation assay (Ames) *S. typhimurium* strains (TA 1535, TA 1537, TA 98 and TA 100). *E. coli* strains (WP2 uvrA pKM101 and WP2 pKM101) +/- S9 *Acceptable modern study*	3, 10, 33, 100, 333, 1000, 2500, 5000 µg/plate Batch: SMU2EP12007	98.5	Negative	[redacted] (2012)
Bacterial mutation assay (Ames) *S. typhimurium* strains (TA 1535, TA 1537, TA 98 and TA 100). *E. coli* strains (WP2 uvrA pKM101 and WP2 pKM101) +/- S9 *Acceptable modern study*	3, 10, 33, 100, 333, 1000, 2500, 5000 µg/plate Batch: SMU4FL762 (spiked with impurities)	96.7	Negative	[redacted] (2014)

In vitro cytogenetics in human lymphocytes +/- S9 *Acceptable modern study*	Exp I (4 hrs, with and without S9): With S9 – 16.1, 28.1, 49.2 µg/mL Without S9 – 16.1, 28.1, 150.8 µg/mL Exp IIA (22 hrs, with and without S9): With S9 – 9.2, 16.1, 2475.4, 4332.0 µg/mL Without S9 – 5.3, 9.2, 16.1 µg/mL Exp IIB (22 hrs, without S9): 3.0, 4.0, 5.0, 6.0, 7.0, 10.0, 15.0, 20.0, 40.0 µg/mL Batch: SMU2EP12007	98.5	Weakly positive/equivocal in absence of metabolic activation	[redacted] (2013)
Mammalian cell mutation assay (mouse lymphoma L5178Y TK +/-) +/- S9 *Acceptable modern study*	Exp I (4 hrs, with and without S9): With S9 – 7.5, 15.0, 30.0, 45.0, 60.0 µg/mL Without S9 – 7.5, 15.0, 22.5, 30.0, 60.0 µg/mL Exp II (4 hrs, with and without S9): With S9 – 7.5, 15.0, 30.0, 60.0, 90.0 µg/mL Without S9 – 7.5, 15.0, 30.0, 45.0, 60.0 µg/mL Exp III (4 hrs, without S9): 40.0, 80.0, 90.0, 100.0, 110.0 µg/mL Batch: SMU2EP12007	98.5	Negative	[redacted].-E. (2013)
In vivo studies				
Micronucleus assay in mouse-bone marrow *Acceptable modern study*	24-hour preparation interval: 500, 1000, and 2000 mg/kg bw. 48-hour preparation interval: 2000 mg/kg bw. Batch: SMU2EP12007	98.5	Negative	[redacted] (2012)
Micronucleus assay in mouse bone marrow *Acceptable modern study*	24-hour preparation interval: 500, 1000, and 2000 mg/kg bw. 48-hour preparation interval: 2000 mg/kg bw. Batch: SMU4FL762 (spiked with impurities	96.7	Negative	[redacted] (2014)
Rat Bone Marrow Chromosome Aberration Assay *Acceptable modern study*	500, 1000 and 2000 mg/kg Batch: SMU2EP12007	98.5	Negative	[redacted] (2017)

2.6.5. Summary of long-term toxicity and carcinogenicity

Pydiflumetofen has been evaluated for chronic toxicity in the rat and for carcinogenic potential in the rat and mouse in GLP and guideline studies.

In the study in rats given doses of 0, 200, 1000 or 6000 ppm to males (9.9, 51, 319 mg/kg bw/d) and doses of 0, 150, 450 or 1500 ppm to females (10.2, 31 and 102 mg/kg bw/d), no tumours were observed in both sexes up to the top dose tested, at which reductions in body weight gain of 22% in males and 13% in females were observed. Although thyroid follicular adenomas were increased in females at the top dose (3/51 (5.9%) vs 1/51 (2%) in controls), the increase was within the laboratory contemporary (5-years) HCD (0 – 5.8%), they were not statistically significant and there was no association with pre-neoplastic lesions. Therefore the NOAEL for carcinogenicity was 6000 ppm (319 mg/kg bw/d) in males and 1500 ppm (102 mg/kg bw/d) in females.

In the study in mice given doses of 0, 75, 375 or 2250 ppm (0, 9.2/9.7, 45.4/48.4, or 288/306 mg/kg bw/d in males/females), there was a dose-related increase in liver adenomas (18% and 44% at mid- and top-dose vs 8% in controls) and carcinomas (8% and 20% at mid- and top-dose vs 4% in controls) in males from the mid dose, which reached statistical significance at the highest dose. The incidences at the top dose were also above the laboratory historical control ranges from 5 studies conducted between 2007-2009 (10-28% for adenoma; 6-10% for carcinoma) and tumour multiplicity was also noted. In addition, pre-neoplastic lesions (eosinophilic foci of cellular alterations: 12.2% and 20% at the mid and top dose respectively vs 2% in controls; above HCD) occurred in males from the mid dose. Overall, pydiflumetofen was clearly carcinogenic in the liver of male mice up to a dose which was not excessively toxic to the animals (7% and 11.6% reduction in terminal body weight in males and females respectively). Therefore the NOAEL for carcinogenicity was 75 ppm (9.2 mg/kg bw/d) in males and the top dose of 2250 ppm (306 mg/kg bw/d) in females. Overall, the most sensitive **carcinogenic NOAEL is 9.2 mg/kg bw**/d in male mice based on liver tumours at the next dose of 45.4 mg/kg bw/d.

Several mechanistic investigations indicated that a CAR-mediated MoA was the most plausible MoA for these liver tumours in male mice. However, the lack of relevance to humans of such MoA was not fully demonstrated. Qualitative differences between humans and rodents, particularly in the ultimate key event of hepatocellular proliferation, were not fully substantiated. The limited *in vitro* study with human hepatocytes showed significant cytotoxicity at concentrations > 10 µM, confounding the interpretation of the absence of proliferation. In addition, cells from only one donor were used and the results cannot be interpreted as being representative from a cross section of the human population. No transgenic knockout animals or humanised receptor models were employed to provide further support for the lack of human relevance.

In addition, alternative MoAs were not fully excluded. Furthermore, an explanation for the differential sensitivity between male and female mice and between rats and mice with respect to the development of liver tumours is lacking. Based on these considerations, HSE agrees with RAC that a potential carcinogenic hazard to humans cannot be excluded and that classification for carcinogenicity in category 2 (H351) is warranted. For further details, see the GB MCL Technical Report.

With regard to chronic toxicity, in rats, pydiflumetofen caused decreases in body weight (10.8%), body weight gain (13%), food consumption and food utilisation, an increase in liver weight (16%) with associated hypertrophy at the mid dose of 1000 ppm in males. These effects became more severe at the top dose of 6000 ppm (e.g. ↓18.2% in body weight; ↓22% body weight gain; ↑36% liver weight) at which an increase in GGT was also seen. In females, adverse effects were only observed at the top dose of 1500 ppm (↓ 9.1 % body weight; ↓ 13% body weight gain, reduced food consumption, ↑15% liver weight; hepatocyte hypertrophy). Therefore a chronic toxicity NOAEL of 200 ppm (9.9 mg/kg bw/d) was identified in males and a chronic toxicity NOAEL of 450 ppm (31 mg/kg bw/d) was identified in females.

In mice, pydiflumetofen caused decreases in terminal body weight (7% and 11.6% in males and females), body weight gain (14% and 24% in males and females) and food consumption at the top dose in both sexes. Food utilisation was also decreased (by 12%) in top dose males. A statistically significant increase in liver weight (by 52% and 17% in males and females respectively) was observed at the top dose in both sexes. In addition, in males, liver weight was increased by 12% at the mid dose. In males, increased liver weight was associated with hepatocyte hypertrophy from the mid dose (6/49 and 18/50 at 375 and 2250 ppm respectively vs 0/50 in controls). Therefore a chronic toxicity NOAEL of 75 ppm (9.2 mg/kg bw/d) was identified in males and a chronic toxicity NOAEL of 375 ppm (48.4 mg/kg bw/d) was identified in females. Overall, the most sensitive **chronic toxicity NOAEL is 9.2 mg/kg bw/d** from the mouse study based on increased liver weight and associated hypertrophy in males at the next dose of 45.4 mg/kg bw/d.

The table below summaries the results of the carcinogenicity studies.

Study & *Acceptability*	**Mode of Dosing**	**Test Material & Dose Levels**	**NOAEL**	**LOAEL**	**Effects at LOAEL**
104 week **rat** carcinogenicity study with a combined 52 week toxicity study ([redacted], 2015) *Modern, valid guideline study*	Dietary	Pydiflumetofen 98.5% Males 0, 200, 1000 & 6000 ppm; Females 0, 150, 450 & 1500 ppm	*Chronic toxicity* Males 200 ppm (9.9 mg/kg bw/d); Females 450 ppm (31 mg/kg bw/d) *Carcinogenicity* Males 6000 ppm (319 mg/kg bw/d) Females 1500 ppm (102 mg/kg bw/d)	*Chronic toxicity* Males 1000 ppm (51 mg/kg bw/d) Females 1500 ppm (102 mg/kg bw/d) *Carcinogenicity* Males >6000 ppm (>319 mg/kg bw/d) Females >1500 ppm (>102 mg/kg bw/d)	*Chronic toxicity* 1000 ppm (mid-dose males): ↓ bw and bwg, food utilization, hepatocyte hypertrophy and ↑liver weight. 1500 ppm (top-dose females): ↓ bw and bwg, food utilization, ↑liver weight associated with minimal hepatocellular hypertrophy *Carcinogenicity* No treatment related neoplastic findings.
80 week **mouse** carcinogenicity study ([redacted], 2015a) *Modern, valid guideline study*	Dietary	Pydiflumetofen 98.5% 0, 75, 375 & 2250 ppm	*Chronic toxicity* Males: 75 ppm (9.2 mg/kg bw/d) Females: 375 ppm (48.4 mg/kg bw/d) *Carcinogenicity* Males: 75 ppm (9.2 mg/kg bw/d) Females: 2250 ppm (306 mg/kg bw/d)	*Chronic toxicity* Males: 375 ppm (45.4 mg/kg bw/d) Females: 2250 ppm (306 mg/kg bw/d) *Carcinogenicity* Males: 375 ppm (45.4 mg/kg bw/d) Females: >2250 ppm (>306 mg/kg bw/d)	*Chronic toxicity* 375 ppm (males): ↑liver weight associated with hepatocellular hypertrophy 2250 ppm (females): ↓ bw and bwg, food consumption, ↑liver weight. *Carcinogenicity* Liver tumours in males from 375 ppm. No tumours in females up to 2250 ppm

2.6.6. Summary of reproductive toxicity

Pydiflumetofen has been evaluated for the potential to cause effects on fertility and reproductive performance in a GLP and guideline multi-generation reproductive toxicity study in the Wistar (Han) rat. The developmental toxicity of pydiflumetofen was also investigated in the (SD) rat and (NZW) rabbit in GLP and guideline compliant studies with preliminary range-finding studies for both.

In the two-generation study, rats were given pydiflumetofen at dietary levels of 0, 150, 450 and 1500 ppm (females, equivalent to 0, 11.9, 36.1 and 116.2 mg/kg bw/d) or 0, 150, 750 and 4500 ppm (males, equivalent to 0, 11.9, 59.1 and 276.6 mg/kg bw/d). The dose levels were selected based on non-proportionality of the kinetics with respect to dose due to dose limited absorption of pydiflumetofen (see ADME section).

Reproductive toxicity

There were no effects on fertility and mating performance or gestation length for either generation at any dietary concentration. Sperm parameters were unaffected. All pregnant females gave birth to live litters with a similar number of pups born, and there was no effect of treatment on the postnatal survival of P or F1 generation litters to Day 21 of age.

The mean length of the oestrous cycle was statistically significantly increased at the top dose (4.05 d vs 3.93 d in controls) in the P generation only. The increase was driven by 2 females with longer cycle length (5 and 4.5 d) and was well within the laboratory historical control data (HCD) mean range (4.0 – 4.3 d) from four studies conducted between 2009 and 2014. Therefore, the effect was considered unrelated to treatment.

A delay in sexual maturation was noted in both sexes at the top dose in the F1 generation. Mean age at preputial separation (PS) was statistically significantly increased by approx. 3 days (45.9 d vs 43.0 in controls). However, when excluding from the analysis a clear outlier, with an age at PS of 57 days, the top dose mean was 45.4 d. This increase was at the upper bound of the laboratory HCD mean range (43.0 – 45.3 d; mean = 44.2 d) from 6 studies conducted between 2008 and 2014. However, when excluding from the HCD 3 studies from 2008 and 2009 (because > 5 years from study's year), the increase (45.4 d) was clearly above the more time-restricted and more relevant HCD mean range (43.0 – 43.5 d). In addition, it is unclear whether the outlier was a spontaneous aberration or was caused by the test substance. It is therefore uncertain whether the very high PS value in one top-dose animal should have been excluded from the analysis.

Mean age at vaginal opening (VO) was statistically significantly increased by approx. 3 days (33.0 d vs 30.3 d in controls). This increase was well within the laboratory HCD mean range (29.3 – 34.1 d; mean = 31.5 d) from 6 studies conducted between 2008 and 2014. However, when excluding from the HCD 3 studies from 2008 and 2009 (because > 5 years from study's year), the increase (33.0 d) was clearly above the more time-restricted and more relevant HCD mean range (29.3 – 31.3 d).

Therefore the delay in PS and VO at the top dose was considered to be treatment related. Pup body weights were statistically significantly reduced at the top dose compared with controls in both sexes of the F1 generation from day 7 to day 21 of lactation (by 10-12%). However, the reduction was within the laboratory HCD range from 6 studies conducted between 2008 and 2014, and more importantly was not replicated in the F2 generation. Therefore, the decrease in pup body weight was unconvincing and hence the delay in sexual maturation could not be considered the secondary unspecific consequence of the reduced pup body weight development.

In agreement with RAC, HSE concludes that although these pups went on to mate and reproduce successfully and despite the absence of endocrine effects and the lack of effects on other developmental landmarks, ano-genital distance and other reproductive parameters and organs, the delay in puberty onset at the top dose was seen in both sexes, was clear (statistically significant and outside time-relevant HCD) and specific (i.e. independent of reductions in pup body weight development). Based on this analysis, HSE agrees that classification of pydiflumetofen for adverse effects on fertility and sexual function in category 2 (H361f) is warranted. For furtrher information on classification, please see the GB MCL Technical Report. A **NOAEL for reproductive toxicity** was therefore set at 450/750 ppm in females/males (equivalent to **36.1 mg/kg bw/d in females and 59.1 mg/kg bw/d in males**) based on a delay in sexual maturation at the top dose of 1500/4500 ppm in females/males (equivalent to 116.2 mg/kg bw/d in females and 276.6 mg/kg bw/d in males).

Parental toxicity

In males, there were decreases in body weight gains (10%) in both generations, reductions in food consumption (8%) in the F1 generation and statistically significant increases in liver and thyroid weights with associated hypertrophy in both generations at the top dose. In top dose females, there was a statistically significant increase in liver weight with associated hypertrophy in both generations. Therefore the **NOAEL for parental toxicity** was set at 450/750 ppm in females/males (equivalent to **36.1 mg/kg bw/d in females and 59.1 mg/kg bw/d in males**).

Offspring toxicity

There were no effects on offspring up to the top dose of 1500/4500 ppm in males/females. Therefore the **NOAEL for offspring toxicity** was set at 1500/4500 ppm (equivalent to **116.2 mg/kg bw/d in females and 276.6 mg/kg bw/d in males**).

Adequacy of top dose

RAC concluded that only minimal parental toxicity was evident at the top dose, especially in females. Therefore RAC agreed that the top dose was inadequate and that the study had not fully investigated the reproductive toxicity potential of pydiflumetofen. HSE considers that the top dose was adequate in males, with decreases in body weight gains (10%) in both generations, reductions in food consumption (8%) in the F1 generation and statistically significant increases in liver and thyroid weights with associated hypertrophy in both generations. The top dose should have been higher in females; however, the Agency notes that the OECD TG (No. 416, 2001) states *'the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering'.* Attainment of the MTD is not specified in the OECD TG. In top dose females, there was a statistically significant increase in liver weight with associated hypertrophy in both generations, which is the most sensitive effect of the toxicity profile of the substance. Hence, target organ toxicity in the liver was induced at the top dose in both generations in females. Therefore, HSE concludes that the requirements of the OECD TG for selection of the top dose in females was also met, as 'toxicity' was induced.

Developmental toxicity

Rat

In the main PNDT study in SD rats given gavage doses of 0, 10, 30 or 100 mg/kg bw/d pydiflumetofen, statistically significant effects on maternal body weight gain (by 18-90%) and food consumption were seen during gestation days 6-10 at the top dose. None of the developmental findings were considered treatment related. A number of malformations (e.g. exencephaly in 2 fœtuses from the same top dose litter) and variations (including ribs with 1 or more absent costal cartilage) observed at 30 and 100 mg/kg bw/d were either not dose-related or within the HCD ranges from animals from the same supplier ([redacted]) and had not been seen in the dose-ranging study up to the much higher dose of 1000 mg/kg bw/d. Overall, there was no developmental toxicity in the rat. A marginal **NOAEL of 30 mg/kg** bw/d was identified for **maternal toxicity** and a **NOAEL of 100 mg/kg bw/d** was identified for **developmental toxicity.**

HSE notes that the top dose caused insufficient maternal toxicity and questions the adequacy of the study. Although kinetic data (see ADME section) had shown that the systemic dose became non-linear at 100 mg/kg/bw/d, it still increased at higher doses. Therefore, a much higher dose should have been employed to ensure a full investigation of the developmental toxicity potential of pydiflumetofen in the rat.

Rabbit

In the main PNDT study in NWZ rabbits given gavage doses of 0, 10, 100 or 500 mg/kg bw/d pydiflumetofen, no maternal toxicity was observed up to the top dose. Therefore, a **NOAEL of 500 mg/kg bw/d** was identified for **maternal toxicity.** The only developmental findings of concern were the presence of one single incidence of diphragmatic hernia (visceral abnormality) at the top dose and the increased litter incidence of a skeletal variant (ribs with 1 or more absent costal cartilage) at 100 and 500 mg/kg bw/d (63% and 47.6% respectively vs 27.3% in controls). The diphragmatic hernia was well within the laboratory HCD ranges from 46 studies performed between 2010 and 2017. Therefore, it was not considered treatment-related. The skeletal varaiant was statistically significant and although not dose-related, was outside the laboratory HCD range (25% - 42.8%) from 54 studies conducted between 2007 and 2017. Relation to treatment could therefore not be excluded and a **NOAEL of 10 mg/kg bw/d** was identified for **developmental toxicity**.

However, this skeletal variant has no impact on normal growth or function; and was not associated with changes in other rib parameters or any retardation in skeletal development. Overall, HSE agrees with RAC that this minor skeletal variation in the rabbit was insufficient to trigger classification for developmental toxicity. For furtrher information on classification, please see the GB MCL Technical Report.

HSE notes that the top dose caused no maternal toxicity and questions the adequacy of the study in fully exploring the developmental toxicity potential of pydiflumetofen in the rabbit.

The most sensitive **maternal NOAEL is 30 mg/kg bw/d in the rat** and the most sensitive **developmental NOAEL is 10 mg/kg bw/d in the rabbit**.

The table below summaries the results of the reproductive toxicity studies.

Study & *Acceptability*	**Mode of Dosing**	**Test material & Dose Levels**	**NO(A)EL (mg/kg bw/day)**	**LOAEL (mg/kg/day)**	**Effects at the LOAEL**
Two generation reproductive toxicity study in the **rat** [redacted], (2015) *Modern, valid, guideline study*	Dietary	Pydiflumetofen 98.5% Males: 0, 150, 750 & 4500 ppm Females: 0, 150, 450 & 1500 ppm	*Parental:* Males 750 ppm ppm (46 mg/kg bw/d) Females 450 ppm (31.6 mg/kg bw/d)	*Parental:* Males 4500 ppm (276.6 mg/kg bw/d) Females: 1500 ppm (116 mg/kg/d)	*Parental:* ↓(10%) bwg in males in P0 and F1; ↓(8%) food con in males in F1; ↑liver wt and associated hypertrophy in males and femelaes in P0 and F1; ↑thyroid wt and associated hypertrophy in males in P0 and F1;
			Reproduction: Males 750 ppm ppm (46 mg/kg bw/d) Females 450 ppm (31.6 mg/kg bw/d)	*Reproduction*: Males 4500 ppm (276.6 mg/kg bw/d) Females: 1500 ppm (116 mg/kg/d)	*Reproduction* Delays in VO and PS in F1 pups
			Offspring: Males: 4500 ppm (276.6 mg/kg bw/d) Females 1500 ppm (116 mg/kg bw/d)	*Offspring*: Males: >4500 ppm (>276.6 mg/kg bw/d) Females >1500 ppm (>116 mg/kg bw/d)	*Offspring* No treatment-related effects
Range-finding Developmental toxicity in the rat. [redacted], (2011) *Supportive study*	Gavage	Pydiflumetofen 99.5% 0, 100, 200, 500 & 1000 mg/kg bw/d	Not applicable – range-finding study	Not applicable – range-finding study	*Maternal*: Transient effect on bwg was seen at 500 and slight body weight loss at 1000 mg/kg bw/day during gestation days 6-9 only. *Developmental*: None.
Main Developmental toxicity in the **rat** [redacted], (2015) *Modern, guideline study but top dose inadequate*	Gavage	Pydiflumetofen 98.5% 0, 10, 30 & 100 mg/kg bw/d	*Maternal*: 30 mg/kg bw/d *Developmental*: 100 mg/kg bw/d	*Maternal*: 100 mg/kg bw/d *Developmental*: >100 mg/kg bw/d	*Maternal*: Marginal effects on bodyweight and food consumption during gestation days 6-9. *Developmental*: None.

Study & *Acceptability*	**Mode of Dosing**	**Test material & Dose Levels**	**NO(A)EL (mg/kg bw/day)**	**LOAEL (mg/kg/day)**	**Effects at the LOAEL**
Range-finding Developmental toxicity in the rabbit [redacted], (2015a) *Supportive study*	Gavage	Pydiflumetofen 99.3% & 98.5% Phase 1: 0, 250, 500 & 1000 mg/kg bw/d Phase 2: 0 & 1000 mg/kg bw/d	Not applicable – range-finding study	Not applicable – range-finding study	*Maternal*: ↓ bwg at 1000 mg/kg bw/d *Developmental*: None.
Developmental toxicity in the **rabbit** [redacted], (2015b) *Modern, guideline study but top dose inadequate*	Gavage	Pydiflumetofen 98.5% 0, 10, 100 & 500 mg/kg bw/d	*Maternal*: 500 mg/kg bw/d *Developmental*: 10 mg/kg bw/d	*Maternal*: >500 mg/kg bw/d *Developmental*: 100 mg/kg bw/d	*Maternal*: None. *Developmental*: Increased incidence of one skeletal variant (rib costal cartilage interrupted) at 100 and 500 mg/kg bw/d without clear dose response but incidence above the HCD

2.6.7. Summary of neurotoxicity

The neurotoxicity of pydiflumetofen has been evaluated in two rat acute neurotoxicity studies and in the 90-day rat study. In an acute oral (gavage) neurotoxicity study in male and female rats, there was no effect on males up to and including the highest dose tested; in females, however, clinical signs of toxicity were noted from 1000 mg/kg bw at both the cage-side observation and the FOB assessment, with one female at 1000 mg/kg bw being sacrificed in extremis. Clinical signs seen within 2-6 hours of dosing (ruffled fur, hunched posture, lateral recumbency, closed eyes, laboured breathing, pale/ruffled fur, repetitive cage chewing and unsteady gate) were transient and indicative of general toxicity, and not a specific neurotoxic effect.

Accompanying the clinical signs from 1000 mg/kg bw were transient signs potentially indicative of neurotoxicity, comprising decreased body temperature and an effect on locomotor activity (decreased mean total distance and mean number of rearings). However, the findings were transient and reversible. No unusual findings were seen at necropsy, particularly on those tissues relating to the central or peripheral nervous system.

Overall, **a NOAEL for acute neurotoxicity of 100 mg/kg bw** was ascertained in females in this study.

In a second oral (gavage) acute neurotoxicity study, conducted in females only, similar transient effects were seen. Clinical signs of toxicity were noted from 100 mg/kg bw during the cage-side observations (within 6-hours post-dose) and from 100 mg/kg bw at the first FOB assessment at 6-hours post-dose only. All effects had reversed by the next examination. Consistent with the findings of the first study, body temperature was statistically significantly reduced on day 1 (6-hours post dose) and an effect on locomotor activity (reduced mean total distance and mean number of rears) was noted from 100 mg/kg bw. No clear dose response was seen between the 100 and 300 mg/kg bw dose groups and the effects were transient and reversible (in all cases they were only observed at the day one measurements).

Overall, the low dose of **100 mg/kg bw was considered the LOAEL for acute neurotoxicity** in this confirmatory study. Taken together, a **LOAEL of 100 mg/kg bw** has been identified for pydiflumetofen **for potential acute neurotoxicity**.

Overall, in two acute neurotoxicity studies, transient effects (day 1 only) were seen in females, comprising clinical signs of toxicity, reduced body temperature and reduced locomotor activity. In a 90-day toxicity study in the rat ([redacted] and [redacted], 2015), no similar effects were seen during detailed clinical examinations, functional

observational battery (FOB) parameters or locomotor activity (LMA) assessments up to and including the highest dose tested of 16000 ppm (1322/1174 mg/kg bw/d in males and females).

Owing to the transient nature of the effects, no classification for STOT SE is warranted for pydiflumetofen. This was confirmed in a recent GB MCL Technical Report. for pydiflumetofen which concluded (in agreement with RAC) that no classification for STOT SE was necessary for pydiflumetofen, owing to the transient and reversible nature of the observed effects.

The table below summarises the main findings in the rat acute neurotoxicity studies.

Study & *Acceptability*	**Test material & Dose levels**	**NOAEL**	**LOAEL**	**Effects at LOAEL**
Acute neurotoxicity study ([redacted], 2015) *Acceptable modern study*	Pydiflumetofen Males: 0, 300, 1000 & 2000 mg/kg bw Females: 0, 100, 1000 & 2000 mg/kg bw	*Neurotoxicity & general toxicity* 100 mg/kg bw in females	*Neurotoxicity & general toxicity* 1000 mg/kg bw in females	1 F sacrificed in extremis Clinical signs on day 1 in F: Ruffled fur, laboured breathing, recumbency, piloerection, reduced muscle tone, reduced activity, abnormal gait, skin cold-to-touch, impaired pupil reflex, and mydriasis ↓ Body temperature ↓Locomotor activity (mean total distance and mean number of rearings)
Acute neurotoxicity study in females only ([redacted], 2015a) *Acceptable modern study*	Pydiflumetofen Females: 0, 100, 300 & 1000 mg/kg bw	*Neurotoxicity & general toxicity* <100 mg/kg bw	*Neurotoxicity & general toxicity* 100 mg/kg bw	Clinical signs on day 1: Ruffled fur, ventral recumbency, piloerection, skin cold-to-touch & impaired extensor thrust reflex, decreased activity, and decreased rearing ↓ Body temperature ↓Locomotor activity (mean total distance and mean number of rearings)

2.6.8. Summary of further toxicological studies on metabolite and the active substance

Summary of immunotoxicity

No specific studies on immunotoxicity are available for pydiflumetofen and none are required.

There were no treatment-related changes indicative of immunotoxic potential in rats, mice or dogs following repeated exposure to pydiflumetofen. There was no effect on haematological (leukocyte/lymphocyte counts) or clinical chemistry (globulin concentration) parameters. There were no unusual macroscopic or microscopic findings related to those tissues of the immune system that were examined (lymph nodes, thymus, spleen, bone marrow and adrenals). Additionally, the spleen, thymus and adrenals were weighed, and no treatment-related changes were seen. Furthermore, pydiflumetofen does not belong to any class of chemicals which are known to have immunotoxic properties (e.g., halogenated aromatic hydrocarbons). Therefore, no studies to further elucidate the immunotoxic potential of pydiflumetofen are required. It can be concluded from the available data that pydiflumetofen has no immunotoxic potential and that further investigation is not required.

Summary of endocrine disrupting properties

Pydiflumetofen did not show a consistent pattern indicative of thyroid adversity across short-term and long-term studies in multiple species (rat, mouse and dog) indicative of T-mediated adversity. Thyroid effects were only observed concomitantly to liver effects. As there was insufficient evidence of thyroid-mediated adverse effects,

HSE concludes that pydiflumetofen does not cause T-mediated adversity and this modality has been sufficiently investigated.

Pydiflumetofen did not cause specific effects on endocrine or reproductive organs in either repeat-dose toxicity or two-generation reproductive toxicity studies. In the two-generation study in rats, both sexes of the F1 generation showed a delay in sexual maturation. However, there were no functional consequences of this delay (ie mating performance and fertility were unaffected), and no changes were observed in other developmental landmarks and reproductive parameters. HSE agrees with the assessment of EFSA and the EU peer-review process that in the absence of other endocrine effects, changes in other developmental landmarks, ano-genital distance and other reproductive parameters and organs, the delay in sexual maturation in F1 pups alone is not sufficient evidence to support a direct effect of the test substance on the endocrine system. HSE concludes that pydiflumetofen does not cause a pattern of EAS-mediated adversity and this modality has been sufficiently investigated.

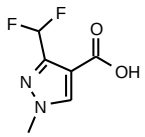
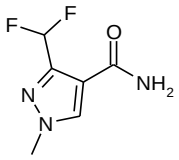
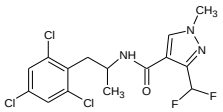
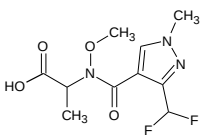
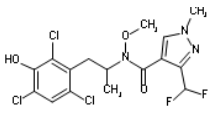
Overall, HSE agrees with the conclusion of EFSA that based on the available evidence, the EATS modalities are considered sufficiently investigated and pydiflumetofen does not cause endocrine-mediated adverse effects. HSE therefore concludes that in accordance with point 3.6.5 of Annex II to Regulation 1107/2009, as amended by Regulation 2018/605, pydiflumetofen is not an endocrine disruptor in humans.

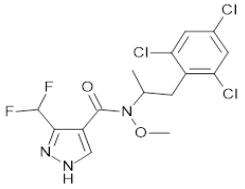
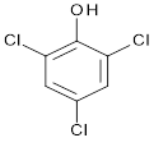
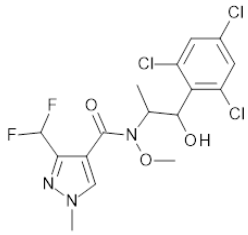
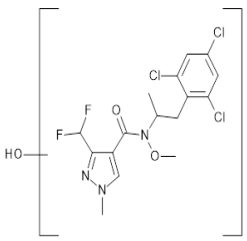
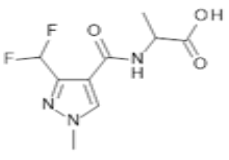
2.6.9. Summary of toxicological data on impurities and metabolites

Dietary metabolites

The table below gives an overview of the toxicological profile, including reference values for a number of pydiflumetofen dietary metabolites and for the parent substance itself.

Metabolite	**Structure of aglycon**	**Detected in rat metabolism Yes/No**	**Avalaible relevant toxicological data**	**Conclusion for dietary risk assessment**
Parent (pydiflumetofen)		Not applicable	- Rat oral LD_{50} > 5000 mg/kg bw - Not genotoxic (negative Ames and MCGM; weakly positive in vitro CA, but negative in vivo MN and CA) - 28D rat: NOAEL = 43/40 mg/kg bw/d (M/F) based on liver effects at 343/342 mg/kg bw/d - 90D rat: NOAEL = 18/6/21.6 mg/kg bw/d (M/F) based on liver and thyroid effects at 111/127 mg/kg bw/d - PNDT, rabbit: NOAELmat = 500 mg/kg bw/d (highest dose); NOAELdev = 10 mg/kg bw/d based on increased incidence of variant at 100 mg/kg bw/d (although no dose-response)	**ADI = 0.09 mg/kg bw/d** (based on NOAEL of 9 mg/kg bw/d from mouse cancer study) **ARfD = 0.3 mg/kg bw** (based on NOAELmat of 30 mg/kg bw/d from rat PNDT study)

Metabolite	**Structure of aglycon**	**Detected in rat metabolism Yes/No**	**Avalaible relevant toxicological data**	**Conclusion for dietary risk assessment**
CSAA798670 glucuronide/sulphate (=NOA449410)		No	- Rat oral LD_{50} > 2000 mg/kg - Not genotoxic (Ames, in vitro CA, MLA TK, in vivo MN) - 28D rat: NOAEL = 1000 mg/kg bw/d (highest dose) - 90D rat: NOAEL = 1000 mg/kg bw/d (highest dose) - PNDT, Rabbit: NOAEL mat/dev = 250 mg/kg bw/d (highest dose)	**Less toxic than parent**; Specific ADI = 0.25 mg/kg bw/d set at EU level, but **parent reference values may be more appropriate**
SYN508272 glucuronide/sulphate		Yes **Major pyrazole specific metabolite** detected for up to 14,8% AUC in rat blood	- Rat oral LD_{50} > 500 < 2000 mg/kg bw./d - Genotox: In vitro: Ames negative, MLA TK negative, CA positive In vivo: MN negative (proof of blood exposure available) => Overall conclusion: not genotoxic - 28D rat: NOAEL =37-42.5 mg/kg bw./d (M-F).	**More toxic than parent**; Hence, specific **ADI = 0.04 mg/kg bw/d** set even though can be considered covered by parent (major rat metabolite) **Could be included in RD-RA with parent using RPF of 2.25**
SYN545547 glucuronide/sulphate		Yes but minor metabolite (<10% AD) Intermediary metabolite (found at 1.3% total excreta)	Genotox: In vitro tests: Ames, MN (human lymphocyte) and MLA Tk (L5178Y cells) were negative. Not genotoxic	Not major rat metabolite. Not genotoxic, hence **TTC CCIII values** (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment
SYN548263 glucuronide/sulphate		Yes but <10% AD Detected at 8.9% in urine and 7% AUC in blood Precursor of SYN508272 found at 14.8% TRA in blood	Genotox: In vitro tests: Ames, MN (human lymphocyte) and MLA Tk (L5178Y cells) were negative. Not genotoxic	Major rat metabolite (as a precursor of a major rat metabolite) Not genotoxic **Covered by parent. Hence, parent reference values** should be used in the risk assessment
SYN547897		Yes but minor (<10% AD)	QSAR and read across analysis (genotoxicity end-point only): no alerts highlighted for both SYN547897 and	Not major rat metabolite. Not genotoxic based on QSAR and read-across,

Metabolite	Structure of aglycon	Detected in rat metabolism Yes/No	Avalaible relevant toxicological data	Conclusion for dietary risk assessment
		Detected at 0.9% in urine and 4.3% TRA in plasma	the parent pydiflumetofen. Not genotoxic	hence **TTC CCIII values** (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment
SYN547891 glucuronide/sulphate		Yes, but minor (<10% AD)	QSAR and read across analysis (genotoxicity end-point only): no alerts highlighted for both SYN547891 and the parent pydiflumetofen. Not genotoxic	Not major rat metabolite. Not genotoxic based on QSAR and read-across, hence **TTC CCIII values** (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment
2,4,6 – TCP sulphate		Yes **Major phenol specific metabolite** detected for up to 44% TRA in plasma (2,4,6-TCP and conjugates)	Toxicity data available from literature and from applicant (full genotoxicity package and 28-day study)	Although major rat metabolite, extensive dataset should take priority. Less toxic than parent. Not genotoxic. Specific ADI = 0.4 mg/kg bw/d Specific ARfD = 1 mg/kg bw. **As less toxic than parent, the parent reference values should be used in the risk assessment**
SYN547948		Yes, but minor (<10% AD)	QSAR and read across analysis (genotoxicity end-point only): no alerts highlighted for both SYN547948 and the parent pydiflumetofen. Not genotoxic.	Not major rat metabolite. Not genotoxic based on QSAR and read-across, hence **TTC CCIII values** (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment
CSCD745176 (hydroxylated parent)		Yes, but minor (<10% AD)	QSAR and read across analysis (genotoxicity end-point only): no alerts highlighted for both CSCD745176 and the parent pydiflumetofen. Not genotoxic.	Not major rat metabolite. Not genotoxic based on QSAR and read-across, hence **TTC CCIII values** (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment
SYN548264 glucuronide/sulphate		Yes, but minor (<10% AD)	QSAR and read across analysis (genotoxicity end-point only): no alerts highlighted for both SYN548264 and metabolite SYN548263 for which there is a	Not major rat metabolite. Not genotoxic based on QSAR and read-across, hence **TTC CCIII values** (1.5 and 5 µg/kg bw/d) could be used in

Metabolite	Structure of aglycon	Detected in rat metabolism Yes/No	Avalaible relevant toxicological data	Conclusion for dietary risk assessment
			negative in vitro genotox package. Not genotoxic.	the dietary risk assessment

CSAA798670 glucuronide/sulphate

CSAA798670 is a common metabolite to a number of SDHI molecules and toxicity studies performed on this metabolite have been assessed during the peer-review of other pyrazole active substances (sedaxane, fluxapyroxade, benzovendiflupyr). Metabolite **CSAA798670 glucuronide/sulphate** is a livestock metabolite of pydiflumetofen. In the human gastro-intestinal tract, the glucuronide and/or sulphate will be easily cleaved, leading to systemic exposure to the aglycon, CSAA798670. Therefore, the toxicological properties determined for the aglycon can be extrapolated to the conjugates. A number of GLP and OECD compliant toxicity studies (acute oral toxicity study, 28-d study, 90-d study, rabbit PNDT study) and standard in vitro genotoxicity assays are available on metabolite CSAA798670. The metabolite did not show any genotoxic potential in the standard three in vitro genotoxicity tests. It was of low acute oral toxicity (LD_{50} > 2000 mg/kg bw) in the rat and did not show any adverse effects up to the limit dose of 1000 mg/kg bw/d in a 28-day and 90-day study in the rat. In addition, no maternal toxicity or developmental toxicity was seen in rabbits up to the top dose of 250 mg/kg bw/d. However, significant maternal toxicity was noted at doses of 500 mg/kg bw/d and above in a range-finding study in pregnant rabbits. In conclusion, **CSAA798670 is of significantly lower toxicity than the parent substance** (parent 28-day rat NOAEL = 43/40 mg/kg bw/d based on liver effects and parent 90-day rat NOAEL = 18.6/21.6 mg/kg bw/d based on liver effects). From a toxicological point of view, CSAA798670 might not be needed to be included in the residue definition for risk assessment (RD-RA). Alternatively, if inclusion is required from a residue perspective, the parent dietary reference values could be used on a conservative basis. At EU level, a specific ADI of 0.25 mg/kg bw/d was derived from the NOAEL of 250 mg/kg bw/d from the rabbit PNDT study with an UF of 1000 (extra assessment factor of 10 to account for the limited database, as no long-term, multigeneration or rat developmental toxicity studies are available). An ARfD was not established, but if required, it could be set at the same level of the ADI. HSE is of the view, that if this metabolite needs to be taken into account in the dietary risk assessment, then it would be more apprropriate to include it in the RD-RA together with the parent (and **applying the parent reference values**) rather than setting a separate RD-RA and applying the metabolite-specific ADI of 0.25 mg/kg bw/d.

SYN508272 glucuronide/sulphate

Metabolite **SYN508272 glucuronide/sulphate** is a livestock metabolite of pydiflumetofen. In the human gastro-intestinal tract, the glucuronide and/or sulphate will be easily cleaved, leading to systemic exposure to the aglycon, SYN508272. Therefore, the toxicological properties determined for the aglycon can be extrapolated to the conjugates. Several GLP and OECD compliant toxicity studies (acute oral toxicity study and 28-d study) and standard in vitro and in vivo genotoxicity assays are available on metabolite **SYN508272**. The metabolite was positive in the in vitro chromosome aberration test, but this result was not confirmed in vivo in a valid rat bone marrow micronucleus study. It was of moderate acute oral toxicity (500 < LD_{50} < 2000 mg/kg bw) in the rat and a NOAEL of 500 ppm (37.4/42.5 mg/kg bw/d in males/females) was identified from a 28-day study in the rat based on effects on body weights and food consumption at the next dose level of 2000/4000 ppm (143.1/243.5 mg/kg bw/d in males/females). In conclusion, **SYN508272 appears of higher toxicity than the parent substance**, with moderate acute oral toxicity compared to the low acute toxicity of the parent (LD_{50} > 5000 mg/kg bw). In the 28-day toxicity study in the rat, reductions in body weight gain and food consumption were observed at 143 mg/kg bw/d (males)/243.5 mg/kg bw/d (females). In comparison, the same effect (decrease BW gains) was observed at 10 fold higher dosage (i.e. 1322 mg/kg bw/d) in the equivalent 28-d study in rat performed with pydiflumetofen. One explanation of these differences may be a higher oral absorption of the metabolite compared to the parent. Indeed, ADME studies demonstrated that oral absorption of pydiflumetofen is limited by the dose level: 19-24% at 300 mg/kg bw in males and 50-55% at 100 mg/kg bw in females. Therefore, from a toxicological point of view, SYN508272 needs to be considered in the residue definition for risk assessment (RD-RA). SYN508272 is a major rat metabolite of pydiflumetofen as it was detected in plasma accounting for up to 14.8% of the total radioactivity AUC (TRA). On this basis, its toxicological profile can be considered covered by that of the parent and the parent dietary reference values could be used in the risk assessment. However, HSE agrees with the EU, that given its higher toxicity potential compared to the parent, it would be more appropriate to set

metabolite specific reference values on the basis of the available data. An **ADI of 0.04 mg/kg bw/d** was set at EU level from the NOAEL of the 28-day study with the application of an UF of 1000 (extra assessment factor of 10 to account for the limited database, as no long-term, multigeneration or developmental toxicity studies are available). The ARfD was set at the same level of the ADI. It should be noted that this metabolite-specific ADI is lower than the parent ADI (0.09 mg/kg bw/d), confirming the relative higher toxicity of the metabolite. If from a residue perspective, a dietary risk assessment is required for this metabolite, **SYN508272 glucuronide/sulphate could be included in the RD-RA together with parent by applying a Relative Potency Factor (RPF) of 2.25.** Alternatively, a separate RD-RA could be set for this metabolite using its specific ADI and ARfD.

SYN545547 glucuronide/sulphate

Metabolite **SYN545547 glucuronide/sulphate** is a livestock metabolite of pydiflumetofen. In the human gastro-intestinal tract, the glucuronide and/or sulphate will be easily cleaved, leading to systemic exposure to the aglycon, SYN545547. Therefore, the toxicological properties determined for the aglycon can be extrapolated to the conjugates. GLP and OECD compliant in vitro genotoxicity assays (supported by a comparative genotoxicity QSAR analysis) are available on metabolite **SYN545547**. The metabolite was negative in the standard battery of 3 in vitro tests and therefore it is considered to be non-genotoxic. It is noted that SYN545547 is only a minor rat metabolite; therefore it is not covered by the parent dataset. However, based on the available data, if a dietary risk assessment were to be required, **the TTC Cramer Class III values (chronic value = 1.5 µg/kg bw/d and acute value = 5 µg/kg bw)** could be used. This is in contrast to the advice given by the EU peer-review process.

SYN548263 glucuronide/sulphate

Metabolite **SYN548263 glucuronide/sulphate** is a livestock metabolite of pydiflumetofen. In the human gastro-intestinal tract, the glucuronide and/or sulphate will be easily cleaved, leading to systemic exposure to the aglycon, SYN548263. Therefore, the toxicological properties determined for the aglycon can be extrapolated to the conjugates. Overall, GLP and OECD compliant in vitro genotoxicity assays are available on metabolite **SYN548263**. The metabolite was negative in the standard battery of 3 in vitro tests and therefore it is considered to be non-genotoxic. It is noted that SYN548263 is only a minor rat metabolite (< 10% AD in urine and plasma); however, it is a direct precursor of SYN508272, which is a major rat metabolite (14.8% TRA in blood). On this basis, it can be assumed that at some point, SYN548263 must have also been present at similar levels in plasma; thus it can be considered a major rat metabolite, **covered by the parent dataset**. Therefore, if a dietary risk assessment were to be required, **the dietary reference values of the parent could be used.** This is in contrast to the advice given by the EU peer-review process.

SYN547897

SYN547897 is not a major rat metabolite; therefore it cannot be considered covered by the parent dataset. However, given the lack of genotoxicity based on a comparative QSAR analysis with the parent, HSE concludes that, if required, the **TTC Cramer Class values (chronic value = 1.5 µg/kg bw/day and acute value = 5 µg/kg bw) can be used in the dietary risk assessment.** This is in contrast to the EU decision not to set a toxicological reference values for SYN547897.

SYN547891 glucuronide/sulphate

Metabolite **SYN547891 glucuronide/sulphate** is a livestock metabolite of pydiflumetofen. In the human gastro-intestinal tract, the glucuronide and/or sulphate will be easily cleaved, leading to systemic exposure to the aglycon, SYN547891. Therefore, the toxicological properties determined for the aglycon can be extrapolated to the conjugates.

SYN547891 is not a major rat metabolite; therefore it cannot be considered covered by the parent dataset. However, given the lack of genotoxicity based on a comparative QSAR analysis with the parent, HSE concludes that, if required, the **TTC Cramer Class values (chronic value = 1.5 µg/kg bw/day and acute value = 5 µg/kg bw) can be used in the dietary risk assessment.**

2,4,6-TCP sulphate

Metabolite **2,4,6-TCP sulphate** is a livestock metabolite. In the human gastro-intestinal tract, the sulphate will be easily cleaved, leading to systemic exposure to the aglycon, 2,4,6-TCP. Therefore, the toxicological properties determined for the aglycon can be extrapolated to the conjugate. In addition, it is noted that 2,4,6-TCP sulphate is a major rat metabolite covered by the parent.

ADME: In rats, oral absorption was very extensive (>90% of the dose). 2,4,6-TCP was rapidly and extensively conjugated and excreted in urine. The highest concentrations of 2,4,6-TCP were found in the kidney, blood and liver.

Acute toxicity: An oral LD50 of 820 mg/kg bw is cited in NCI (1979). No further data were identified in the search of the published literature. However 2,4,6-TCP has the following harmonised EU classification (and GB mandatory classification) entry for acute endpoints: Acute Tox 4 (H302); Skin Irrit 2 (H315) and Eye Irrit. 2 (H319).

Short-term toxicity: The short-term toxicity of pydiflumetofen has been investigated in three publications, a 90-day study in rats and preliminary 7-wk studies in rats and mice. The preliminary studies do not allow the identification of robust NOAELs and hence they are not described further. In addition, as the 90-day study had some limitations, the Applicant recently generated and submitted two regulatory studies, a 14-day range finder and a 28-day study in the rat. In the 90-day study, a LOAEL was identified at 240 mg/kg bw/d for changes in the weights of liver, kidney and adrenals and the **NOAEL was set at 80 mg/kg bw/d**. In the recently submitted GLP and guideline 28-day gavage study adverse effects were seen at the top dose (500 mg/kg bw/d) on the weight of the liver (females), thyroid (males) and uterus (females). Based on these effects a **NOAEL of 250 mg/kg bw/d** could be identified from the study.

Genotoxicity: A wide range of in vitro and in vivo studies were identified in the published literature. These were in the main non-standard studies with several limitations and showing inconsistent results. Following the EU peer-review process, it was concluded that the genotoxic potential of 2,4,6-TCP was inconclusive, based on positive results observed in vitro and inconsistent results observed in vivo, and needed to be clarified. On this basis, Syngenta recently submitted a modern package of three in vitro tests (Ames, micronucleus and mammalian cell gene mutation tests) and an in vivo TGR (Transgenic rodent) assay in rats. These well conducted tests have demonstrated that 2,4,6-TCP is not genotoxic in vitro or in vivo.

Long-term toxicity and carcinogenicity: The chronic toxicity and carcinogenic potential of 2,4,6-TCP was investigated in rats and mice (NCI, 1979). 2,4,6-TCP was carcinogenic in male F344 rats, inducing lymphomas or leukemias from the lowest dose of **258 mg/kg bw/d (LOAEL)**. It was also carcinogenic in both sexes of B6C3F1 mice, inducing liver hepatocellular carcinomas and/or adenomas from the lowest dose of 650 mg/kg bw/d. Based on these findings, 2,4,6-TCP has harmonised classification in the EU and mandatory classification in GB with Carc. Cat 2 (H351).

Reproductive toxicity: The reproductive toxicity potential of 2,4,6-TCP was investigated in two limited rat one-generation studies from the open literature, but only the first one is considered reliable. In a publication from 1986, 2,4,6-TCP had no effect on any sperm parameter or male fertility. Treatment of females with 1000 mg/kg bw/d of 2,4,6-TCP produced maternal toxicity as reflected in increased lethality and decreased weight gain in the dams. However no treatment-related differences were seen in litter sizes or pup survival. Male and female birth weights were significantly depressed in the 500 and 1000 mg/kg bw/d groups; these differences disappeared by Day 4 post-partum suggesting that they were a reflection of maternal toxicity. Overall, in this limited study, the reproductive processes of male and female rats di not appear to be a primary target of 2,4,6-TCP up to the limit dose of 1000 mg/kg bw/d. HSE notes that a **NOAEL of 100 mg/kg bw/d could be identified for generalised offspring toxicity and a NOAEL of 500 mg/kg bw/d could be identified for parental toxicity.**

Dietary reference values: Although 2,4,6-TCP is a major rat metabolite of pydiflumetofen and could be considered 'covered' by the parent, HSE notes that there is a significant dataset on the substance showing that 2,4,6-TCP has a different toxicity profile compared to pydiflumetofen. Therefore, the specific toxicological data on 2,4,6-TCP should take priority and be used to establish specific reference values.The most appropriate POD for the derivation of the ADI is the NOAEL of 80 mg/kg bw/d for effects on organ weights at 240 mg/kg bw/d from the rat 90-day study. By applying the standard default factor of 100 and an additional factor of 2 as tumours were seen at the LOAEL of 258 mg/kg bw/d, and **ADI of 0.4 mg/kg bw/d** is derived. No further assessment factors are required as chronic/carcinogenicity studies and reproductive toxicity studies are available. Considering that 2,4,6-TCP is acutely toxic by the oral route, an ARfD should be derived. An appropriate POD for the ARfD is the offspring NOAEL of 100 mg/kg bw/d for reduced pup body weights at birth in the reproductive toxicity study. By applying the standard default factor of 100, an **ARfD of 1 mg/kg bw** can be established. These reference values compared to those of the parent substance indicate that 2,4,6-TCP **is not more toxic than pydiflumetofen**. Therefore, if 2,4,6-TCP needs to be included in the RD for risk assessment from an exposure perspective, it could

be either added to the parent and **assessed against the parent dietary reference values or a separate and specific RD could be set for it, utilising the specific reference values set for 2,4,6-TCP in the dietary risk assessment.**

SYN547948, CSCD745176 (hydroxylated parent) and SYN548264 glucuronide/sulphate

Metabolite **SYN548264 glucuronide/sulphate** is a livestock metabolite of pydiflumetofen. In the human gastro-intestinal tract, the glucuronide/sulphate will be easily cleaved, leading to systemic exposure to the aglycon, SYN548264. Therefore, the toxicological properties determined for the aglycon can be extrapolated to the conjugates. Metabolites SYN547948, CSCD745176 (hydroxylated parent) and SYN548263 are not genotoxic based on QSAR and read-across analysis. Metabolites SYN547948, CSCD745176 and SYN548264 are not major rat metabolites and hence are not covered by the parent dataset. Based on these considerations, if a dieatry risk assessment were required for **SYN547948, CSCD745176 and SYN548264, the TTC Cramer Class III values** (chronic value = 1.5 µg/kg bw/d and acute value = 5 µg/kg bw) could be used.

Consideration of the need for combined risk assessment for some metabolites assigned the TTC Cramer Class III values

Metabolite SYN545547 and metabolite SYN547891 are significant plant metabolites requiring an exposure and risk assessment. These two metabolites have been assigned the same TTC Cramer Class III values. Therefore, the need for a combined risk assessment should be considered. The structures of these two metabolites are similar; however, there are sufficient differences to justify an independent assessment. Overall a combined risk assessment against the TTC Cramer Class III values for metabolites SYN545547 and SYN547891 is not required.

2.6.10. Summary of medical data and information

No adverse effects have been reported in humans during manufacture of the active substance, formulation of products and conduct of field trials.

2.6.11. Summary table of all studies relevant to the derivation of the reference values

Study & *Acceptability*	**Mode of Dosing**	**Test Material & Dose Levels**	**NOAEL**	**LOAEL**	**Effects at LOAEL**
Acute neurotoxicity study in **rats** ([redacted], 2015) *Acceptable modern study*	Gavage	Pydiflumetofen Males: 0, 300, 1000 & 2000 mg/kg bw Females: 0, 100, 1000 & 2000 mg/kg bw	*Neurotoxicity & general toxicity* 100 mg/kg bw in females	*Neurotoxicity & general toxicity* 1000 mg/kg bw in females	1 F sacrificed in extremis Clinical signs on day 1 in F: Ruffled fur, laboured breathing, recumbency, piloerection, reduced muscle tone, reduced activity, abnormal gait, skin cold-to-touch, impaired pupil reflex, and mydriasis ↓ Body temperature ↓Locomotor activity (mean total distance and mean number of rearings)
Acute neurotoxicity study in female **rats** only ([redacted], 2015a) *Acceptable modern study*	Gavage	Pydiflumetofen Females: 0, 100, 300 & 1000 mg/kg bw	*Neurotoxicity & general toxicity* <100 mg/kg bw	*Neurotoxicity & general toxicity* 100 mg/kg bw	Clinical signs on day 1: Ruffled fur, ventral recumbency, piloerection, skin cold-to-touch & impaired extensor thrust reflex, decreased activity, and decreased rearing ↓ Body temperature

Study & *Acceptability*	**Mode of Dosing**	**Test Material & Dose Levels**	**NOAEL**	**LOAEL**	**Effects at LOAEL**
					↓Locomotor activity (mean total distance and mean number of rearings)
28-day **rat** dietary study ([redacted], 2012) *Acceptable GLP and guideline study*	Dietary	Pydiflumetofen 0, 500, 4000, 8000 & 16000 ppm Equivalent to: Males: 0, 43, 343, 677 & 1322 mg/kg bw/d Females: 0, 40, 322, 619 & 1174 mg/kg bw/d in females	500 ppm (43/40 mg/kg bw/d in M/F)	4000 ppm (343/322 mg/kg bw/d in M/F)	↑ Liver weights in M & F ↑ centrilobular hepatocellular hypertrophy in M & F
28-day **mouse** dietary study ([redacted], 2012a) *Acceptable GLP and guideline study*	Dietary	Pydiflumetofen 0, 500, 1500, 4000 & 7000 ppm Equivalent to: Males: 0, 76, 213, 612 & 1115 mg/kg bw/d Females: 0, 96, 266, 701 & 1312 mg/kg bw/d	< 500 ppm (76/96 mg/kg bw/d in M/F)	500 ppm (76/96 mg/kg bw/d in M/F)	↓ Body weight & Body weight gain in M ↑ Liver weights in M & F
90-day **rat** dietary study ([redacted] & [redacted], 2015) *Acceptable GLP and guideline study*	Dietary	Pydiflumetofen 0, 250, 1500, 8000 & 16000 ppm Equivalent to: Males: 0, 18.6, 111, 587 & 1187 mg/kg bw/d Females: 0, 21.6, 127, 727 & 1325 mg/kg bw/d	250 ppm (18.6/21.6 mg/kg bw/d in M/F)	1500 ppm (111/127 mg/kg bw/d in M/F)	↑ Liver weights in M & F ↓ ALP in M & F ↑ hepatocellular hypertrophy in M ↑ Thyroid follicular cell hypertrophy in M
90-day **mouse** dietary study ([redacted], 2015)	Dietary	Pydiflumetofen 0, 100, 500, 4000 & 7000 ppm	Males: 100 ppm (17.56 mg/kg bw/d)	Males: 500 ppm (81.6 mg/kg bw/d)	Males: ↑ Liver weights ↑ Cholesterol

Study & *Acceptability*	**Mode of Dosing**	**Test Material & Dose Levels**	**NOAEL**	**LOAEL**	**Effects at LOAEL**
Acceptable GLP and guideline study		Equivalent to: Males: 0, 17.5, 81.6, 630 & 1158 mg/kg bw/d Females: 0, 20.4, 106, 846 & 1483 mg/kg bw/d	Females: 500 ppm (106 mg/kg bw/d)	Females: 4000 ppm (846 mg/kg bw/d)	Females: ↑ Liver weights ↑ Hepatocellular hypertrophy ↑ Triglyceride
90-day **dog** oral (capsule) study ([redacted], 2015) *Acceptable GLP and guideline study*	Capsule	Pydiflumetofen 0, 30, 300 & 1000 mg/kg bw/d	30 mg/kg bw/d	300 mg/kg bw/d	↓ Body weight gain in F ↑ Liver weights in M & F ↑ ALP in M & F ↑ Triglyceride in M
1-year **dog** oral (capsule) study ([redacted], 2015a) *Acceptable GLP and guideline study*	Capsule	Pydiflumetofen 0, 30, 100 & 300 mg/kg bw/d	100 mg/kg bw/d	300 mg/kg bw/d	↑ Liver weights in M & F ↑ ALP in M & F ↑ Thyroid weights in M
28-day **rat** dermal study ([redacted], 2013) *Acceptable GLP and guideline study*	Dermal	Pydiflumetofen 0, 100, 300 & 1000 mg/kg bw/d	1000 mg/kg bw/d	>1000 mg/kg bw/d	No effects up to and including the highest dose tested of 1000 mg/kg bw/d
104 week **rat** carcinogenicity study with a combined 52 week toxicity study ([redacted], 2015) *Modern, valid guideline study*	Dietary	Pydiflumetofen 98.5% <u>Males</u> 0, 200, 1000 & 6000 ppm; <u>Females</u> 0, 150, 450 & 1500 ppm	*Chronic toxicity* <u>Males</u> 200 ppm (9.9 mg/kg bw/d); <u>Females</u> 450 ppm (31 mg/kg bw/d) *Carcinogenicity* <u>Males</u> 6000 ppm (319 mg/kg bw/d) <u>Females</u>	*Chronic toxicity* <u>Males</u> 1000 ppm (51 mg/kg bw/d) <u>Females</u> 1500 ppm (102 mg/kg bw/d) *Carcinogenicity* <u>Males</u> >6000 ppm (>319 mg/kg bw/d) <u>Females</u>	*Chronic toxicity* <u>1000 ppm</u> (mid-dose males): ↓ bw and bwg, food utilization, hepatocyte hypertrophy and ↑liver weight. <u>1500 ppm</u> (top-dose females): ↓ bw and bwg, food utilization, ↑liver weight associated with minimal hepatocellular hypertrophy *Carcinogenicity* No treatment related neoplastic findings.

Study & *Acceptability*	**Mode of Dosing**	**Test Material & Dose Levels**	**NOAEL**	**LOAEL**	**Effects at LOAEL**
			1500 ppm (102 mg/kg bw/d)	>1500 ppm (>102 mg/kg bw/d)	
80 week **mouse** carcinogenicity study ([redacted], 2015a) *Modern, valid guideline study*	Dietary	Pydiflumetofen 98.5% 0, 75, 375 & 2250 ppm	*Chronic toxicity* Males: 75 ppm (**9.2 mg/kg bw/d**) Females: 375 ppm (48.4 mg/kg bw/d) *Carcinogenicity* Males: 75 ppm (9.2 mg/kg bw/d) Females: 2250 ppm (306 mg/kg bw/d)	*Chronic toxicity* Males: 375 ppm (45.4 mg/kg bw/d) Females: 2250 ppm (306 mg/kg bw/d) *Carcinogenicity* Males: 375 ppm (45.4 mg/kg bw/d) Females: >2250 ppm (>306 mg/kg bw/d)	*Chronic toxicity* 375 ppm (males): ↑liver weight associated with hepatocellular hypertrophy 2250 ppm (females): ↓ bw and bwg, food consumption, ↑liver weight. *Carcinogenicity* Liver tumours in males from 375 ppm. No tumours in females up to 2250 ppm
Two generation reproductive toxicity study in the **rat** [redacted], (2015) *Modern, valid, guideline study*	Dietary	Pydiflumetofen 98.5% Males: 0, 150, 750 & 4500 ppm Females: 0, 150, 450 & 1500 ppm	*Parental:* Males 750 ppm ppm (46 mg/kg bw/d) Females 450 ppm (31.6 mg/kg bw/d)	*Parental:* Males 4500 ppm (276.6 mg/kg bw/d) Females: 1500 ppm (116 mg/kg/d)	*Parental:* ↓(10%) bwg in males in P0 and F1; ↓(8%) food con in males in F1; ↑liver wt and associated hypertrophy in males and femelaes in P0 and F1; ↑thyroid wt and associated hypertrophy in males in P0 and F1;
			Reproduction: Males 750 ppm ppm (46 mg/kg bw/d) Females 450 ppm (31.6 mg/kg bw/d)	*Reproduction:* Males 4500 ppm (276.6 mg/kg bw/d) Females: 1500 ppm (116 mg/kg/d)	*Reproduction* Delays in VO and PS in F1 pups
			Offspring: Males: 4500 ppm (276.6 mg/kg bw/d) Females 1500 ppm (116 mg/kg bw/d)	*Offspring:* Males: >4500 ppm (>276.6 mg/kg bw/d) Females >1500 ppm (>116 mg/kg bw/d)	*Offspring* No treatment-related effects
Main Developmental toxicity in the **rat** [redacted], (2015)	Gavage	Pydiflumetofen 98.5% 0, 10, 30 & 100 mg/kg bw/d	*Maternal*: **30 mg/kg bw/d** *Developmental*: 100 mg/kg bw/d	*Maternal*: 100 mg/kg bw/d *Developmental*: >100 mg/kg bw/d	*Maternal*: Marginal effects on bodyweight and food consumption during gestation days 6-9. *Developmental*: None.

Study & *Acceptability*	**Mode of Dosing**	**Test Material & Dose Levels**	**NOAEL**	**LOAEL**	**Effects at LOAEL**
Modern, guideline study but top dose inadequate					
Developmental toxicity in the **rabbit** [redacted], (2015b) *Modern, guideline study but top dose inadequate*	Gavage	Pydiflumetofen 98.5% 0, 10, 100 & 500 mg/kg bw/d	*Maternal*: 500 mg/kg bw/d *Developmental*: **10 mg/kg bw/d**	*Maternal*: >500 mg/kg bw/d *Developmental*: 100 mg/kg bw/d	*Maternal*: None. *Developmental*: Increased incidence of one skeletal variant (rib costal cartilage interrupted) at 100 and 500 mg/kg bw/d without clear dose response but incidence above the HCD

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

The acceptable daily intake (ADI) is typically derived from the lowest NOAEL in the most susceptible species in long term toxicity and multi-generation reproduction toxicity studies with the application of an appropriate uncertainty factor. The dietary route of exposure is considered the most relevant for derivation of this dietary reference value.

The lowest NOAEL in the long-term studies was 9.2 mg/kg bw/d from the 80 week mouse carcinogenicity study for liver tumours in males at the LOAEL of 45.4 mg/kg bw/d. An uncertainty factor of 100 is proposed for derivation of the ADI. Although tumours were seen at the LOAEL, these were sex-specific and most likely not relevant to humans. In addition there is a factor of 5 between the NOAEL and the LOAEL. Therefore an additional assessment factor is not required.

ADI = 9.2 mg/kg bw/d /100 = <u>0.09 mg/kg bw/d</u>

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

Establishment of the ARfD, in the absence of a specific study designed to determine this endpoint, is based on a consideration of NOAELs for "acute effects" observed in studies ranging from acute to sub-chronic exposure durations. Relevant NOAELs may be derived from studies involving administration of a single dose or from repeat dose studies in which effects are noted during the initial days of dosing.

In the acute neurotoxicity study, transient clinical signs and effect on body temperature and locomotor activity (LMA) were observed in female rats after a single gavage dose of 1000 mg/kg bw and above. In the modified study (females only) the same effects were observed at ≥ 100 mg/kg bw. All signs of toxicity were resolved by day 2. A LOAEL of 100 mg/kg bw was identified from the study.

However, a lower NOAEL of 30 mg/kg bw/d was identified from the prenatal developmental toxicity study in rats for effects on maternal body weights during the first days of dosage at the LOAEL of 100 mg/kg bw/d. This is an appropriate 'acute' NOAEL for the derivation of the ARfD. Applying an UF of 100, an ARfD of 0.3 mg/kg bw is derived.

ARfD= 30 mg/kg bw/d /100 = <u>0.3 mg/kg bw</u>

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

Considering all available sub-chronic toxicity studies available with pydiflumetofen, the male mouse seems to be the most sensitive species with a NOAEL of 17.5 mg/kg bw/d in the 90-day study for effects on the liver at the LOAEL of 81.6 mg/kg bw/d, although the 90-day study in rat gave a similar NOAEL of 18.6-21.6 mg/kg bw/d (also for effects on the liver). However, as a marginally increased incidence of rib cartilage variant (one or more costal cartilage interrupted) was observed at 100 and 500 mg/kg bw/d (no clear dose-response, but outside historical control data) in the prenatal developmental toxicity in rabbit, it is thus proposed that the AOEL should be based on the NOAEL of 10 mg/kg bw/d from this study in rabbit with an uncertainty factor of 100. As demonstrated by the comparative intravenous and oral absorption study, although oral absorption was 85-90%, the oral bioavailability (F) value was 50% (most likely due to direct excretion of absorbed material into the bile with lack of systemic availability). Therefore a correction is required. It should be noted that this value differs from that established by the EU as oral systemic availability is 50% and correction is required.

AOEL = 10 mg/kg bw/d/100 x 50%= <u>0.05 mg/kg bw/d</u>

The AAOEL can be set using the same NOAEL of 30 mg/kg bw/d used for the ARfD applying an UF of 100 and a correction for 50% oral systemic availability. It should be noted that this value differs from that established by the EU as oral systemic availability is 50% and correction is required.

AAOEL = 30 mg/kg bw/d/100 x 50% = <u>0.15 mg/kg bw</u>

2.6.15. Summary of product exposure and risk assessment

Operator exposure

Estimates of operator exposure using the EFSA calculator predict that the proposed use of 'Miravis Plus' on winter and spring cereals, winter and spring oilseed rape will result in acceptable long-term systemic exposure equal to 10% of the AOEL of pydiflumetofen and an acceptable acute systemic operator exposure equal to 21% of the AAOEL of pydiflumetofen for an operator that applied the product without using PPE.

The product 'Miravis Plus' is classified for human health effects.

- H318: Causes serious eye damage
- H351: Suspected of causing cancer
- H361f: Suspected of damaging fertility

The use of suitable protective gloves and face protection (faceshield) when handling the concentrate is required.

Bystander and resident exposure

Estimates of resident exposure using the EFSA calculator predict that longer term exposure to a child and adult is within acceptable limits for all exposure pathways, with the sum of the mean for all pathways being equal to 15% of the AOEL of pydiflumetofen for a child resident and 5% of the AOEL of pydiflumetofen for an adult resident. The longer term exposure to bystanders is covered by the resident exposure assessment.

Estimates of bystander exposure using the EFSA calculator predict that acute exposure of a child and adult to pydiflumetofen from spray drift, vapour, surface deposits and re-entry into treated crops pathways are all within acceptable limits. The acute exposure to residents is covered by the bystander exposure assessment.

Worker exposure

Estimates of worker exposure using the EFSA calculator predict that the proposed uses of 'Miravis Plus' on winter and spring cereals, and winter and spring oilseed rape will result in acceptable longer term systemic exposure equal

to 6% of the AOEL of pydiflumetofen for a worker undertaking inspection and irrigation activities in treated crops wearing normal work wear (arms, body and legs covered).

2.7. RESIDUE

The representative uses of pydiflumetofen in GB are on cereal crops (wheat, durum wheat, barley, rye, triticale, oat and spelt) and oilseed rape. The representative formulation A21857B is an emulsifiable concentrate (EC) containing 62.5 g/L of the active substance.

MRL work is being conducted in parallel with the new active substance review. As part of this work, a proposed GAP on carrots and associated root crops is being considered as a future GB use. The intended GAPs for carrots and associated root crops are for the formulation A19649H (Suspension Concentrate (SC) formulation containing 200 g/L pydiflumetofen).

The proposed GAPs (and critical GAPs highlighted in bold) are shown in Table 2.7.4.1 in section 2.7.4.

2.7.1. Summary of storage stability of residues

Plant matrices:

Storage stability of parent pydiflumetofen was investigated in the following plant commodities: lettuce head (high water), orange fruit (high acid), wheat grain (high starch), wheat straw (not specified), potato tuber (high starch), oilseed rape seed (high oil) and dried adzuki bean (high protein). All samples are considered stable for at least ~~up to~~ 23 months when stored at ≤ -18 ºC. This accommodates the period that samples were stored for in the supporting residue trials (Volume 3 CA B7, section 7.3, max of 15 months, section 7.5.3, max of 15 months and section 7.6.2, max 16 months).

As samples of pydiflumetofen have been shown to be stable in at least one representative commodity in all five of the commodity categories (high water, high starch, high, acid, high protein, and high oil); it can be assumed that residues are stable in all other commodities for the same period (for at least ~~up to~~ 23 months) when stored frozen at ≤ -18 ºC.

In accordance with OECD 506, as no instability has been observed over the range of crop commodities tested, then this conclusion can be extrapolated to processed commodities, to support the processing studies submitted.

Animal matrices:

The storage stability of pydiflumetofen was investigated in bovine muscle, liver, fat, milk and chicken eggs. The metabolites SYN508272 and SYN548264 were investigated in milk, SYN547897 in bovine liver and kidney and SYN548263 in kidney. 2,4,6 Trichlorophenol was investigated in bovine muscle, liver, kidney, fat, milk and chicken eggs.

Residues of pydiflumetofen were found to be stable in bovine muscle, liver, fat, milk and chicken eggs for at least ~~up to~~ 24 months when stored at -20ºC.

The storage stability studies demonstrated stability of: SYN508272 and SYN548264 in milk for at least ~~up to~~ 12 months; SYN548263 in bovine kidney for at least ~~up to~~ 12 months and 2,4,6 – TCP (free and conjugated) in bovine muscle, liver, kidney, fat, milk and eggs for at least ~~up to~~ 12 months. Stability of SYN547897 was also tested in bovine kidneys and bovine liver for a period of up to 12 months; however there seemed to be some decline towards the end of the trial, and it is concluded that SYN547897 was only sufficiently stable in bovine liver and bovine kidney for up to ~9.5 months and 11 months respectively. All samples testing the metabolites were stored at –18°C.

Stability of pydiflumetofen, 2,4,6 – TCP (free and conjugated), SYN508272, SYN548264, and SYN548263 accommodates the period that the samples are stored in the supporting feeding studies (see Volume 3, Section 7.4.1). There is some uncertainty in the levels SYN547897 determined in the bovine liver (but not kidney) in the first feeding study since the liver and kidney samples were stored for 10.5 months in the freezer before analysis. However a further feeding study specifically tailored to the analysis of SYN547897 in bovine kidney and liver was performed analysing the liver and kidney samples in a quick time frame (within 9 days of frozen storage).

Stability of sample extracts:

No specific study was conducted which investigated the stability of sample extracts of pydiflumetofen (or any of its metabolites). However, extract stability was confirmed within the method validation studies for both plant and animal matrices. The storage conditions of the plant and animal extracts, respectively, were: 5 ± 4 ºC in the dark; and 3 – 8 ºC in the dark. Extract storage stability was also demonstrated within individual studies by the procedural recovery extracts being stored under the same conditions for the same time as the test samples, giving acceptable recoveries. Therefore, all storage of extracts in the studies in Volume 3 CA B7 is sufficiently supported. For more details please refer to section 7.1.3 of Volume 3 CA B7.

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

All of the mg/kg residue amounts stated in this section are mg/kg parent equivalents.

Primary crops

Metabolism in primary crops was investigated using pyrazole and pheny labelled pydiflumetofen (SYN545974). Studies were performed on three plant species: wheat (cereal crop group), tomato (fruit crop group) and oilseed rape (pulses and oilseed crop group). Radiolabelled pydiflumetofen was applied as a post emergence foliar spray to all crops, an additional sub-sample of tomatoes were studied following soil treatment at transplanting. Considering the representative uses are cereals and oilseed rape, the metabolism studies performed on wheat and oilseed rape are underdosed compared to the cGAPs in terms of individual application rate. However, the cGAP for cereals comprises of a single application of 200 g a.s./ha at BBCH 69 – whereas the wheat metabolism study applications were spread over two treatments (2 x 0.63N). The oilseed rape metabolism study was at 0.67- 0.73N (GAP rate is 1 x 200 g as/ha). The tomato metabolism study was conducted at 2 x 200 g as/ha. Nevertheless, a consistent pattern of metabolism was observed and the metabolism studies are considered relevant to the consideration of the residue definition for the uses being assessed. A summary of the available primary crop metabolism studies is presented below in Table 2.7.2.1.

Table 2.7.2.1: Summary of plant metabolism studies

Group	Crop	Label	Application and sampling details				
			Method, F or G[(a)]	**Application rate**	**BBCH growth stage at application**	**Number**	**Sampling (DAT)**
Cereals	Wheat	[phenyl-U-14C] & [pyrazole-5-14C]-SYN545974	Foliar spray application, F	125 g as/ha	BBCH 32-34 and 58	2	Forage : 10d after application 1 Hay : 29d after application 2 Straw and grain: 50d after application 2
Fruits and fruiting vegetables	Tomato	[phenyl-U-14C] & [pyrazole-5-14C]-SYN545974	Foliar spray application, G	200 g as/ha	BBCH 83 and 86	2	1 and 14 days (fruits only)
			Soil application, G	20 mg as/plant	transplanting stage	1	103 days (fruit only)
Oilseeds	Oilseed rape	[phenyl-U-14C] & [pyrazole-5-14C]-SYN545974	Foliar spray application, F	150 g as/ha[(b)]	BBCH 65	1	62 days (seed and trash)

a: Field or Glasshouse
b: 150 g as/ha was the intended rate; the rates achieved were 134.2 g a.s./ha (0.67N) and 146.6 g a.s./ha (0.73N) for the phenyol and pyrazole labels respectively.

The major identified component of the residue was parent pydiflumetofen for all crop matrices. Parent pydiflumetofen accounted for between 30.0-96.6 % TRR (0.007 – 1.167 mg/kg) for the foliar treated samples; and 4.1 % TRR (0.001 mg/kg) for the soil treated tomato sample. Only two metabolites were identified and characterised – these are SYN545547 and SYN547891. These metabolites were identified in all crops; however, SYN545547 and SYN547891 did not individually exceed 10 % of the TRR in any crop matrix. The highest absolute amount of metabolite was identified in wheat straw, pyrazole label - 3.9 % TRR, (0.059 mg/kg) and 4.3 % TRR, (0.065 mg/kg) for SYN545547 and SYN547891, respectively.

Tomato

See the overview of metabolism in ~~wheat~~ tomato in Table 2.7.3.1 in section 2.7.3. Mature fruit was sampled. Results from both foliar application and soil application are presented to show the range of metabolites, although the intended uses are foliar sprays only, the soil application is not directly relevant. The soil application showed significantly less uptake into the plant was observed – although it must be noted that the application rates are not directly comparable between the treatment types. Parent pydiflumetofen was found in very low amounts in soil treated tomato (4.1 % TRR, 0.00~~0~~1 mg/kg. For both labels the TRR in the soil treated mature fruit samples were lower (max. 0.013 mg/kg) compared to the minimum of 0.481 mg/kg in the foliar treated samples. Additionally, a large number of low level unidentified metabolites were observed; up to 25 discrete components of which no single metabolite exceeded 0.002 mg/kg.

Samples were extracted using aqueous acetonitrile (in multiple stages, with the initial extractions at 80 % v/v acetonitrile decreasing to 50 % v/v acetonitrile). Extractable radioactivity inclusive of surface wash and extracted radioactivity quantified from washed fruit was high (> 97%TRR) for both fruits derived from foliar and soil treatments.

For the foliar applications, the overall identification was high with >96% of the TRR being identified. Parent pydiflumetofen was the main component of the residue, found in mature fruit at 91.7 – 96.6% TRR (~~0.477~~ 0.461-0.661 mg/kg). ~~Other~~ Metabolites identified were SYN545547 (accounting for up to 3.6 % TRR, up to 0.021 mg/kg) and SYN547891 (accounting for up to 1.6 % TRR, up to 0.011 mg/kg).

The metabolism in soil treated tomato plants was markedly different to the foliar treated samples. Significantly less uptake into the plant was observed – although it must be noted that the application rates are not directly comparable between the treatment types. For the phenyl label: total TRR in the soil treated sample was 0.007 mg/kg; compared with a minimum of 0.521 mg/kg in foliar treated sample. The same phenomenon was observed for the pyrazole label. Parent pydiflumetofen was found in very low amounts in soil treated tomato (4.1 % TRR, 0.00~~0~~1 mg/kg). In addition to this, a higher degree of metabolisation was observed in soil treated plants. This resulted in a large number of unidentified low level metabolites (together totalling 88.9% 'unidentified' comprising up to 25 discrete components), of which no single metabolite exceeded 0.002 mg/kg. The soil treated sample is not relevant to the proposed representative uses. These findings match with the findings for the rotational crop metabolism study (see below), since a number of low level amounts of unassigned peaks were found in the samples representing uptake of residues from soil in the rotational crop metabolism study.

Wheat

See the overview of metabolism in wheat in Table 2.7.3.2 in section 2.7.3. Forage, hay, straw and grain were sampled. All plant matrices sampled are included to show the range of metabolites and their distribution across the whole crop. As the intended use is not for a forage use, the residues in grain and straw are most important.

Samples were extracted using aqueous acetonitrile (at 80 % v/v acetonitrile). Extractable radioactivity was high, > 85%TRR for grain and >94% for other samples.

The overall identification was sufficient with >76.5% of the TRR being identified. Parent pydiflumetofen was the main component of the residue, found in grain at 81.5 – 81.6 % TRR (0.030 – 0.046 mg/kg) and in straw at 76.4

– 83.6 % TRR (1.075 – 1.167 mg/kg). ~~Other~~ Metabolites identified were SYN545547 (accounting for up to 3.9 % TRR, up to 0.059 mg/kg) and SYN547891 (accounting for up to 8.3 % TRR, up to 0.065 mg/kg). Similar relative levels of parent and metabolites were found in forage and hay.

Oilseed Rape

See the overview of metabolism in oilseed rape in Table 2.7.3.3 in section 2.7.3. Trash and seed were sampled. All plant matrices sampled are included to show the range of metabolites and their distribution across the whole crop. As the intended use is not for a forage use, the residues in seed are most important.

Samples were extracted using aqueous acetonitrile (at 80 % v/v acetonitrile). Seed samples were extracted using a combination of aqueous acetonitrile (80 % v/v) and hexane. Extractable radioactivity was in the range of 72% to 81%TRR.

The overall identification was low with >36.1 ~~63.1~~% (and up to 65.3% in the seed) of the TRR being identified. This is likely due to the low absolute levels found in crop matrices (max. 0.062 mg/kg total TRR). Non-extractable residues in the seed comprising up to 28%TRR accounted for only 0.005 mg/kg. An unassigned component in the seed comprised 0.001 mg/kg (max 6%TRR) and three unassigned components in trash comprised, individually, up to 0.005 mg/kg (max 8.4%TRR). Parent pydiflumetofen was the main component of the residue, found in seeds at 39.2 – 62.6 % TRR (0.007 – 0.012 mg/kg) and in trash at 30.0 – 50.9 % TRR (0.018 to 0.032 ~~ND – 0.002 mg/kg~~). ~~Other~~ Metabolites identified were SYN545547 (accounting for up to 6.1 % TRR, up to 0.002 ~~0.059~~ mg/kg) and SYN547891 (accounting for up to 5.1 % TRR, up to 0.003 mg/kg).

Metabolism of pydiflumetofen in each of the three foliar treated crops was broadly similar, and followed the same metabolic pathway: this was demethylation of the pyrazole ring to produce SYN547891; and reduction of the parent molecule producing SYN545547. Parent pydiflumetofen remained the major component in all samples: tomato fruit (91.7% to 96.6% TRR foliar applied samples and 4.1% TRR for the soil treatment), wheat (70.5% to 91.0% TRR), and oilseed rape (30.0% to 62.6% TRR). Residues of SYN545547 and SYN547891 accounted for a maximum of 6.1% TRR and 8.3% TRR, respectively, across all commodities. All metabolites identified were found in their free non-conjugated form. Extractability was generally high in all samples: tomato fruit (≥ 97 % TRR), wheat (≥84.9 % TRR), and oilseed rape (≥ 71.8 % TRR). Extractability was lowest in oilseed rape seeds; however, overall levels of residue in mg/kg were low (max. 0.015 mg/kg) and the levels of the metabolites in oilsed rape seeds did not exceed 0.001 mg/kg in either label. Therefore, this lower extractability is not considered to impact the validity of the results.

Across each of the primary crop metabolism studies, the degree of identification of residues was generally acceptable when you take account of the low %TRR and mg/kg levels of unassigned peaks in each of the studies. However, considering the degree of identification, it is not ideal that the primary crop metabolism studies most relevant to the representative uses were underdosed. For example the oilseed rape metabolism study was at one application at 0.67- 0.73N. For cereals (wheat), the studies were only underdosed considering the individual rate of application: cGAP is one appplication only. The wheat metabolism study applications represented two applications each at 0.63N (2 x 0.63N).

Please refer to the section on residue definition (section 2.7.3) which also considers a justification for the proposal for primary crops and rotational crops (same residue definition proposal made for primary and rotational crops), also considering the possibility of the proposal being a potential universal residue definition suitable to all crops. The current assessment includes the current primary crop representative uses (cereals and oilseed rape), the additional MRL assessment uses considered here (carrots, parsnips, and parsley roots) in the DAR (alongside the representative uses) and the impacted rotational crops. The available data are suitable to cover the (additional MRL assessment) uses on carrots, parsnips and parsley roots.

Enantiomer composition:

Pydiflumetofen is a racemate. In terms of enantiomeric conversion, the applicant has made the case (document N5 on isomeric composition) that chemically interconversions are not predicted based on mechanistic and structure related grounds. Interconversion of the enantiomers of SYN545974 is not considered feasible by any conventional chemical or biochemical process to which the compound will be exposed.

However, it is possible for differential metabolism of residues of pydiflumetofen to occur. The enantiomeric composition in the spray solution and in primary crop metabolism samples was determined to see whether any change occurred during the metabolism studies. The enantiomeric fraction shifted from 0.5 in the spray solution to a maximum of 0.56 (in oilseed rape seed); the fraction remained at 0.5 in tomato fruits. A quantitiative estimate was not determined for the wheat study; however the enantiomeric peaks looked similar.

Based on these determinations, the % change in enantiomeric excess[5] was estimated for oilseed rape seed (up to 12.4%), oilseed trash (<5%), and tomato fruit (<1%). Whilst there was a range in values determined (wheat not analysed, tomato fruits <1%, surface wash <2%, oilseed 12.4% and trash 4.8%), there was only one primary crop sample, oilseed rape trash, which exceeded a 10% change in enantiomeric excess (by a small amount). HSE is not proposing to consider an assessment factor in the consumer risk assessment to consider the potential changes in isomer ratio/amounts in plants. Some further information on enantiomeric composition of pydiflumetofen in crops based on findings in some published paper is presented at the end of sectin B.7.2.1 which does not impact this conclusion.

Storage stability of residues (in the metabolism context):

OECD Guidelines (501, plant metabolism) indicate that metabolism studies should be completed within an analysis period of six months, or otherwise be appropriately supported by storage stability investigations performed in the context of the metabolism studies.

In terms of primary crops, the tomato metabolism study was completed within an experimental period of around 7 months, the wheat metabolism main analytical work was done within around 10 months, and the oilseed rape metabolism study analytical work was done in around 28 months.

Each of the primary crop metabolism studies led to the identification of only two metabolite peaks (SYN545547 and SYN547891) as well as parent pydiflumetofen. In all of the primary crop metabolism studies, there were some unassigned peaks, which were not identified.

In order to consider storage stability of residues in the metabolism context, representative radio chromatograms (TLC) of plant samples after initial analysis were considered (comparisons between TLC before and after the main storage period) in each of the metabolism studies. These representative TLC chromatograms supporting the storage stability work showed the major ‘spot’ of pydiflumetofen, and then weaker TLC spots for the metabolites SYN545547 and SYN547891. These are sufficient to show that there is no marked qualitative change in the samples over the period of the study, as far as can be seen in the context of the TLC work; these cannot be interpreted quantitatively.

The TLC storage stability results were only able to show the ‘weak’ TLC spots for the metabolites SYN545547 and SYN547891, and did not cover the low level peaks (indicated to be more polar in nature)/components that were unassigned during the HPLC analysis and metabolic profiling.

Only limited information is available on stability of the residues from the investigations conducted on stability in these metabolism studies. Parent pydiflumetofen has been demonstrated as stable for at least up to 23 months over frozen storage in the ‘cold’ non-radiolabelled freezer stability investigations (section 2.7.1). The three TLC spots (parent and the two identified metabolites) were visible on the TLC radiographs for the ‘post storage’ samples. Ideally such storage stability investigations should not be based on TLC alone to support stability over long term storage in metabolism studies (those that take longer than six months).

[5] Enantiomeric excess is explained in the EFSA guidance on stereoisomers (2019, “Guidance of EFSA on risk assessments for active substances of plant protection products that have stereoisomers as components or impurities and for transformation products of active substances that may have stereoisomers”)

Whilst presenting some uncertainty, the data are likely to be sufficient in the context of the conclusions surrounding the proposal for the residue definition for primary crops.

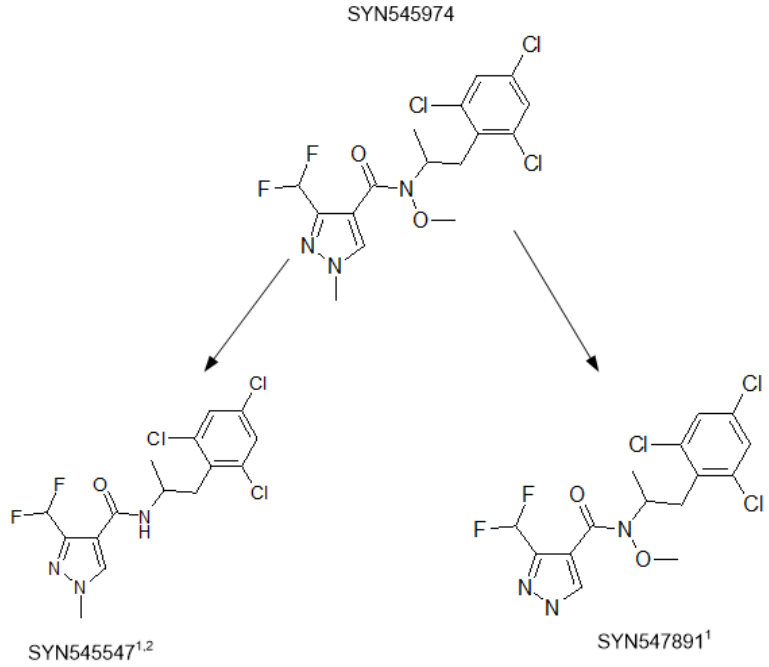
Metabolic pathway

A consistent picture of pydiflumetofen metabolism is observed for both phenyl and pyrazole labels and across 3 crop groups (cereals, oilseeds and fruits & fruiting vegetables).

In plants, the principal biotransformations observed were:

- Demethylation of the pyrazole ring to produce SYN547891.
- Reduction of the parent molecule producing SYN545547.

Figure 2.7.2.1: Proposed metabolic pathway in primary crops.



1. Identified in foliar treated crops.
2. Identified in soil treated crops.

Rotational crops

Metabolism in rotational crops was investigated using pyrazole and phenyl labelled pydiflumetofen (SYN545974). The representative uses (cereals and oilseeds) can be grown in rotation and field soil degradation studies indicate the DT_{90} value for parent pydiflumetofen is significantly greater than 100 days. Therefore, consideration of residues in rotational crops is required. Consideration of soil accumulation has also been made due to the persistent nature of parent pydiflumetofen (see section 2.7.7 on the magnitude of residues in rotational crops). There are no major soil metabolites.

Table 2.7.2.2: Summary of available metabolism studies on rotational crops

Crop group	Crop	Label position	Application and sampling details			
			Method, F or G[a]	Target rate (kg a.s./ha)	Sowing intervals (days)	Harvest time
Leafy vegetables	Lettuce	[phenyl-U-14C] & [pyrazole-5-14C]-SYN545974	Bare soil, F	1 x 0.4	30, 120, 270	growth stage (BBCH 41-43, BBCH 45 for 120DAA lettuce) and at maturity (BBCH 49).
Root and tuber vegetables	Turnip	[phenyl-U-14C] & [pyrazole-5-14C]-SYN545974	Bare soil, F	1 x 0.4	30, 120, 270	BBCH 49
Cereals	Wheat	[phenyl-U-14C] & [pyrazole-5-14C]-SYN545974	Bare soil, F	1 x 0.4	30, 120, 270	Forage (BBCH 15-30), hay (BBCH 49-60) and maturity (BBCH 89) growth stage

a: Field or Glasshouse - (whilst the application was made to the soil outside; the soil was in containers and the containers were moved into the glasshouse part way through the growing period, see the further explanation in Vol 3 Section B.7.6.1).

Metabolism in rotational crops was investigated using pyrazole and pheny labelled pydiflumetofen (SYN545974). Pydiflumetofen was applied at a nominal rate of 400 g a.s./ha via foliar spray application directly to the soil (double, 2N, the maximim seasonal rate of 200 g a.s/ha for the representative uses and 0.63N when considering soil exposures arising from year on year application and accumulation in the soil due the persistence of pydiflumetofen in soil). ~~However, Considering soil accumulation, the trial is underdosed with respect the worst case rotational residue scenario (please refer to section 2.7.7 on the assessment of residues in rotational crops).~~ Lettuce, turnip and wheat were planted 30, 120 and 270 days after application. Immature lettuce, turnip foliage, wheat straw, wheat hay and wheat straw were harvested and analysed. Mature lettuce, turnip roots and wheat grain were also harvested; however, overall levels of TRR were low (<0.01 mg/kg) and no further identification was conducted. Residues in samples of lettuce and turnip replanted at the 120 and 270 day PBIs were also all below 0.01 mg/kg, and so no further analysis was conducted on these samples either.

Extractability was high in all analysed samples (≥83.2 % TRR). Overall levels of TRR were low. Parent pydiflumetofen was the principal residue detected in all samples (18.6 – 77.8 % TRR); the maximum absolute residue of parent pydiflumetofen was 0.063 mg/kg in wheat straw at 120 DALA (pyrazole label). SYN545547 and SYN547891 were detected in each of the samples at lower levels than the parent; found at up to 0.005 mg/kg and 0.012 mg/kg, respectively. Unidentified components were present in all samples, and accounted for between 2.3 and 67.0 % TRR; with the highest level found in 30 DALA wheat straw (0.116 mg/kg, pyrazole label). A larger number of unassigned peaks was found in the rotational crop metabolism samples compared to samples in the primary crop metabolism studies, where there were also some unassigned peaks. No individual unidentified component was present at >0.010 mg/kg (~~6.7~~ 4.6 % TRR, in wheat straw). In turnip foliage there was an estimated highest level of unidentified residue (individual component) of 10.2 % TRR (0.001 mg/kg). Due to the low levels of TRR found, the radioactive peaks were present at low mg/kg amounts, even when at >5%TRR.

The individual level of metabolite SYN547891 exceeded 10 % TRR (max 13.3%TRR) for the following samples: immature lettuce (phenyl label, 30 day PBI); wheat forage (phenyl and pyrazole label, 30 day PBI); and wheat hay (pyrazole label, 270 day PBI). Despite the % TRR exceeding 10 % for the above samples, the total radioactive residue for SYN547891 did not exceed 0.004 mg/kg in commodities for human consumption in any case. SYN547891 was found at up to 0.012 mg/kg in wheat straw. SYN545547 was found at max 5.6%TRR. See a discussion in section 2.7.3 on the consideration for whether to include or exclude the metabolites in the residue definition. See the overview of metabolism in rotational crops in Table 2.7.3.4.

Overall, the residue pattern in rotational crops is considered to be sufficiently similar to that in primary crops, see Figure 2.7.2.1.

In terms of the assessment of the studies, storage stability of residues and enantiomeric composition of residues was considered in full in Section B.7.6.1. A summary is provided below.

Please refer to the section on residue definition (section 2.7.3) which also considers a justification for the proposal for rotational crops.

Enantiomer composition (rotational crop metabolism):

Pydiflumetofen is a racemate. In terms of enantiomeric conversion, the applicant has made the case (document N5 on isomeric composition) that chemically interconversions are not predicted based on mechanistic and structure related grounds. Interconversion of the enantiomers of SYN545974 is not considered feasible by any conventional chemical or biochemical process to which the compound will be exposed.

However, it is possible for differential metabolism of residues of pydiflumetofen to occur. The enantiomeric composition in the spray solution and in straw samples (120 & 270 DALA) was determined to see whether any change occurred during the rotational crop metabolism study. The enantiomeric fraction shifted from 0.5 in the spray solution to a maximum of 0.57 (270 DALA sample). The 'S' enantiomer of pydiflumetofen was more prevalent in the 270 DAA samples and the 'R' enantiomer of pydiflumetofen was more prevalent in the 120 DAA samples.

Based on these determinations, the %change enantiomeric excess[6] was estimated for wheat straw. This was calculated to be ≤10% for the samples at 270 days (DAA). For the 120 DAA sample timing, one of the samples (pyrazole label) indicated a change in enantiomeric excess > 10% (%change EE of 13.4%). The direction of the enantiomer increase was different in the 270 DAA samples compared to the 120 DAA samples. HSE is not proposing to consider an assessment factor in the consumer risk assessment to consider the potential changes in isomer ratio/amounts in rotational crops. Some further information on enantiomeric composition of pydiflumetofen in crops based on findings in some published paper is presented at the end of sectin B.7.2.1 which does not impact this conclusion.

Storage stability of residues (in the rotational crop metabolism context):

OECD Guidelines (502, rotational crop metabolism) indicate that metabolism studies should be completed within an analysis period of six months, or otherwise be appropriately supported by storage stability investigations performed in the context of the metabolism studies.

The length of frozen storage depended on the samples (as there were various replant intervals); this ranged from 1.7 to 2.4 years (up to around 28 months).

The analytical work in this study led to the identification of only two metabolite peaks (SYN545547 and SYN547891) as well as parent pydiflumetofen. There were a number of low level unassigned peaks which were not identified.

In order to consider storage stability of residues in the rotational crop metabolism context, representative radio chromatograms (TLC) of wheat hay & straw, immature lettuce and turnip foliage, 20-29 months (1.7 to 2.4 years) after 'initial analysis' were considered (comparisons between TLC before and after the storage period). These representative TLC chromatograms supporting the storage stability work showed the major 'spot' of pydiflumetofen, and then weaker TLC spots for the metabolites SYN545547 and SYN547891. These are sufficient to show that there is no marked qualitative change in the samples over the period of the study, as far as can be seen in the context of the TLC work; these cannot be interpreted quantitatively.

[6] Enantiomeric excess is explained in the EFSA guidance on stereoisomers (2019, "Guidance of EFSA on risk assessments for active substances of plant protection products that have stereoisomers as components or impurities and for transformation products of active substances that may have stereoisomers")

The TLC storage stability results were only able to show the 'weak' TLC spots for the metabolites SYN545547 and SYN547891, and did not cover the low level peaks (indicated to be more polar in nature)/components that were unassigned during the HPLC analysis and metabolic profiling. The metabolite profiles (HPLC work) were obtained from samples stored for a maximum of 122 days (4 months, 'initial analysis'). Many peaks present in the HPLC work were present at too low levels to enable identification. Only pydiflumetofen (SYN545974, and metabolites SYN545547 and SYN547891 were identified in the rotational crop metabolism study.

Only limited information is available on stability of the residues from the investigations conducted on stability in this study. Parent pydiflumetofen has been demonstrated as stable for at least up to 23 months over frozen storage in the 'cold' non-radiolabelled freezer stability investigations (section 2.7.1). The three TLC spots (parent and the two identified metabolites) were visible on the TLC radiographs for the 'post storage' samples. Ideally such storage stability investigations should not be based on TLC alone to support stability over long term storage in metabolism studies (those that take longer than six months).

Whilst presenting some uncertainty, the data are likely to be sufficient in the context of the conclusions surrounding the proposal for the residue definition for rotational crops.

Animal

Metabolism in livestock was investigated using pydiflumetofen radiolabelled in the phenyl ring or the pyrazole ring. Investigations were done in both laying hens and lactating goats (as well as in rat to support toxicology studies (Vol 3 CA B6, Section 6.1)).

In summary, the major compounds found in products of animal origin were parent (SYN545974), hydroxy SYN545974, 2,4, 6-TCP and its sulphate ester conjugate, alkyl hydroxy metabolite SYN547948, phenolic metabolite SYN547897, N-desmethoxy metabolite SYN545547, pyrazole N-desmethyl metabolite SYN547891, pyrazole amide metabolite SYN508272 and pyrazole carboxylic acid metabolites NOA449410, SYN548263 and SYN548264.

Poultry
Pydiflumetofen was administered orally to twelve hens in two radiolabelled forms (phenyl or pyrazole labels) for fourteen consecutive days (doses of 56.3 and 56.9 mg as equivalents/kg dry matter in the diet respectively corresponding to 3.3 and 3.6 mg as equivalents/kg bodyweight, 73N and 80N ~~43N and 47N for (fate scenario) Tier 1 10 year use and 51N and 55N for (fate scenario) Tier 2 long term use~~.

The N rates cited here (and also in section 2.7.5 feeding studies) take into account all crop residue sources in terms of the livestock anticipated dietary burdens (primary crop for the representative uses, primary crop for the additional MRL assessment uses assessed here (carrots, parsnips, and parsley roots) and the impacted rotational crops).

Approximately 103.4 % and 88.0 % of the administered dose were recovered in total for the phenyl and pyrazole label, respectively. The main fraction was excreted via excreta accounting for approximately 99.1 % (phenyl label) and 84.3 % (pyrazole label). Radioactive residues associated with edible portions (egg and tissues) accounted for up to <0.1% of the administered dose for both labels.

To determine the residues in eggs and identify when a plateau was reached, daily egg samples were obtained on the fourteen consecutive days of the study. For the phenyl label, the level of radioactive residues increased to a plateau concentration of 0.064 mg eq/kg (egg white) and 0.344 mg eq/kg (egg yolk), at 6 and 10 days respectively. For the pyrazole label, a plateau of 0.062 mg eq/kg (egg white) and 0.116 mg eq/kg (egg yolk) was reached after 7 days. ~~The plateau of residues in eggs has been further considered in the feeding study for poultry, [redacted] (2015).~~

Samples of liver, egg yolk, egg white and muscle were extracted with acetonitrile and water. Fat samples were extracted with a mixture of acetonitrile, water and hexane and subsequently with acetonitrile and water. The extractable TRR levels for both labels were generally high, ranging from 87.0 % TRR to 98.8 % TRR, except for egg yolk (pyrazole label; 81.2% TRR) and liver (51.7% TRR and 52.5% TRR for the phenyl and pyrazole labels, respectively). Radioactive residues in the RRR (residual radioactive residue) obtained after the initial extraction

of egg yolk (pyrazole label) and liver (both labels) was 18.7 – 48.3 % TRR, which were further investigated using either the surfactant sodium dodecyl sulphate (SDS) or proteolytic enzyme hydrolysis.

For both labels, unchanged parent (SYN545974) was found in egg yolk, egg white and all tissues at levels ranging from 0.001 mg/kg to 0.025 mg/kg (0.5% TRR to 46.5% TRR). In liver and egg white, parent was the major component. For the phenyl label exclusively, the 2,4,6-TCP sulphate conjugate (egg yolk: 67.8% TRR; 0.242 mg/kg, muscle: 48.4% TRR; 0.013 mg/kg, fat: 26.5% TRR; 0.027 mg/kg, egg white: 14.5% TRR; 0.008 mg/kg) was identified. For the pyrazole label the label specific metabolites, SYN508272 (muscle: 46.3% TRR; 0.010 mg/kg, egg white: 34.3% TRR; 0.018 mg/kg) and NOA449410 (egg white: 15.4% TRR; 0.008 mg/kg) were identified.

The transformation steps in the metabolic pathway identified were:

- N-demethylation of the pyrazole ring
- N-demethoxylation of the amide nitrogen
- monohydroxylation of the benzyl methylene functionality
- monohydroxylation of the trichlorophenyl ring
- cleavage at the benzylic methylene, N-alkyl and amide linkages between the phenyl and pyrazole rings
- conjugation of metabolites to form their glucuronide and/or sulphate ester analogues. In all instances conjugates were characterised as glucuronide/sulphate due to the nature of the enzyme used to hydrolyse them with the exception of the 2,4,6-trichlorophenol sulphate in milk and muscle of the phenyl label experiment which was formally identified.

The metabolic pathway observed in poultry is also observed within the ruminant pathway, with the ruminant pathway containing some additional transformation steps. The overall pathway is presented in Figure 2.7.2.2.

Ruminant

Pydiflumetofen was administered orally to two goats in two radiolabelled forms (phenyl or pyrazole labels) for seven consecutive days (nominal dose of 143.6 and 204.6 mg as equivalents/kg dry matter in the diet respectively corresponding to 4.6 mg as equivalents/kg bodyweight, 55N ~~22N for (fate scenario) 'Tier 1 10 year use' and 28N for (fate scenario) 'Tier 2 long term use'~~.

Approximately 96.0 % and 94.7 % of the administered dose were recovered in total for the phenyl and pyrazole label, respectively. The main fraction was excreted via excreta accounting to approximately 84.2 % (phenyl label) and 76.3 % (pyrazole label). Radioactive residues associated with edible portions (milk and tissues) accounted for <0.1% to 0.4% of the administered dose for both labels.

To determine when a plateau was reached, milk samples were obtained by combining samples over a 24-hr period for 7 consecutive days. For the phenyl label, the level of radioactive residues increased to a plateau after 2 days with a concentration of 0.091 mg eq/kg (by averaging residues for days: 3, 4, 5 and 6). For the pyrazole label, a plateau of 0.138 mg eq/kg was reached after 5 days.

Samples of liver, kidney and muscle were extracted with acetonitrile and water. Fat and milk samples were extracted with a mixture of acetonitrile, water and hexane and subsequently with acetonitrile and water. The extractable TRR levels were generally high, ranging from 83.4 % TRR to 98.8 % TRR, except for liver (50.4% TRR and 47.4% TRR for the phenyl and pyrazole labels, respectively). Radioactive residues in the RRR (residual radioactive residue) obtained after the initial extraction of liver and kidney was 9.2 – 52.6 % TRR, which were further investigated using either SDS or proteolytic enzyme hydrolysis.

For both labels, unchanged parent (SYN545974) was found in milk and all tissues at levels ranging from 0.011 mg/kg to 0.570 mg/kg (0.5% TRR to 73.8% TRR). In fat, parent was the major component. The metabolite hydroxy SYN545974 (phenyl - fat: 8.6% TRR; 0.019 mg/kg, pyrazole - fat: ≤10.2% TRR; ≤0.028 mg/kg) was identified for both labels. For the phenyl label exclusively, the 2,4,6-TCP sulphate conjugate (milk: 42.2% TRR; 0.051 mg/kg) was identified. For the pyrazole label the label specific metabolites, SYN548263 (kidney: 16.6% TRR; 0.389 mg/kg, milk: 14.2% TRR; 0.019 mg/kg), SYN548264 (milk: 28.7% TRR; 0.038 mg/kg), SYN508272 (muscle: 17.7% TRR; 0.024 mg/kg, milk: 11.0%TRR; 0.014 mg/kg) and NOA449410 (kidney: 11.7 % TRR; 0.275 mg/kg) were identified.

The transformation steps in the metabolic pathway identified were:

- N-demethylation of the pyrazole ring
- N-demethoxylation of the amide nitrogen
- monohydroxylation of the benzyl methylene functionality
- monohydroxylation of the trichlorophenyl ring
- cleavage at the benzylic methylene, N-alkyl and amide linkages between the phenyl and pyrazole rings
- Conjugation of metabolites to form their glucuronide and/or sulphate ester analogues (all except hydroxy SYN545974). In all instances conjugates were characterised as glucuronide/sulphate due to the nature of the enzyme used to hydrolyse them with the exception of the 2,4,6-trichlorophenol sulphate in milk and muscle of the phenyl label experiment which was formally identified.

The metabolic pathway observed in ruminants (which includes all the pathway observed in hens as well) is presented in Figure 2.7.2.2.

Assessment remarks in regard of both ruminant and poultry metabolism studies:

Enantiomer composition

In terms of enantiomeric conversion, the applicant has made the case (document N5 on isomeric composition) that chemically interconversions are not predicted based on mechanistic and structure related grounds. Interconversion of the enantiomers of SYN545974 is not considered feasible by any conventional chemical or biochemical process to which the compound will be exposed.

In animal metabolism studies (including in the rat), no analytical determination of enantiomers were included to consider the potential for differential metabolism of residues of pydiflumetofen to occur. As a precautionary measure, it is proposed that an assessment factor is used (x 2) applied to all residue levels in animal products, to account for the possibility of any differential metabolism in livestock commodites. Some further information on enantiomeric composition of pydiflumetofen in rat liver microsomes (*in vitro* investigation) based on findings in some published paper is presented at the end of sectin B.7.2.1 which does not impact this conclusion. This factor has been applied to the livestock residues in the consumer risk assessments undertaken in section 2.7.9 [this factor has not been applied to the ~~TTC~~ exposure assessment for the livestock metabolite SYN 547897 compared to the TTC undertaken in section 2.7.3].

Storage stability of residues (in the metabolism context):

OECD Guidelines (503, livestock metabolism) indicate that metabolism studies should be completed within an analysis period of six months, or otherwise be appropriately supported by storage stability investigations performed in the context of the metabolism studies.

Both of the poultry and ruiminant metabolism studies were conducted over the long term, involving storing the samples over a period of 2.5 years. When samples were not being worked on, they were kept in frozen storage. Initial HPLC metabolic profiling was done, after the samples had been extracted after 4 months of frozen storage. The samples were all initially analysed within 6 months of necroscopy. The assessment of chromatograms supplied to compare extracts analysed initially with the same extracts analysed at the end of the study were evaluated and are considered in full in sections B.7.2.2 and B.7.2.3. Assessment is challenging as chromatographic peaks were not always resolved or with consistent shape in the comparative chromatograms. Some differences were observed in the ruminant liver that are attributable to the storage stability issues observed in the 'cold' non radiolabelled study for livestock samples (metabolite SYN547897, see below).

In terms of context, the applicant observed that the major residue in both hen and goat studies are parent SYN554974 and the 2,4,6-TCP metabolite, findings also replicated in the 'cold' (non-radiolabelled) ruminant and poultry feeding studies. These residues are covered in the freezer storage stability studies reported (in section B.7.1.2 and in vol 1 2.7.1). In these 'cold' (non-radiolabelled) freezer stability studies, residues of parent pydiflumetofen and 2,4,6 – TCP (free and conjugated) were shown to be stable in various animal matrices over frozen storage for at least 2 years (parent) and at least 1 year (2,4,6 –TCP).

The applicant also noted that additional animal metabolites were also analysed in the ruminant feeding studies in order to demonstrate a thorough investigation of the residue of concern. HSE acknowledges this and also recognises that one of the feeding studies involved a very quick analysis in order to ensure stability of the metabolite SYN547897 in the feeding study in liver/kidney, since the 'cold' (non-radiolabelled) residues stability study had demonstrated some degradation of the metabolite SYN547897 which tested freezer stability for up to a one year period in liver and kidney. This metabolite was only stable in bovine liver up to ~9.5 months and in bovine kidney for up to 11 months. These periods are greatly exceeded by the maximum storage period in the metabolism study for the ruminant study; the metabolite was investigated and analysed particularly quickly in a ruminant feeding study.

The 'cold' (non-radiolabelled) storage stability studies also demonstrated stability of: SYN508272 and SYN548264 in milk for at least a year, and SYN548263 in bovine kidney for at least a year.

Conclusion on storage stability of residues in the metabolism context. It is common for modern metabolism studies, with the detailed analytical approaches, to take place over a period in access of 6 months (often considerably longer). HSE does not regard it as ideal that these livestock samples were not extracted/worked on until a timepoint of 4 months.

The applicant remarked that overall, (aside from the clear differences noted for the ruminant liver), storage stability profiles presented can be considered sufficiently comparable with the caveat that complex samples analysed on different HPLC systems and columns at different time intervals will show some inconsistency in peak resolution and retention time. HSE agrees that is difficult to fully assess when the chromatograms do not show the same peak shape in the 'before' and 'after' chromatograms. HSE considers that there is some uncertainties presented by the data (presented by having samples stored for a long period in the metabolism studies), however aside from the differences observed in liver, and accepting that there is some uncertainty, the data are regarded as acceptable to support the derivation of residue definition in livestock products.

Fat soluble – Yes. Residues were not very high in fat at up to 0.1 mg eq./kg (TRR) in poultry and up to 0.3 mg eq./kg (TRR) in ruminant (TRR residues were much higher in ruminant liver and kidney); however residues of pydiflumetofen were higher in fat compared to muscle. This is not surprising based on the logPow determined for pydiflumetofen (log Pow 3.8 at 25°C, section B.2.7/06). Other logPow values were provided for livestock metabolites based on *in silico* calculation methods (section B.2.7): SYN548263 logPow 0.17 or <0.17 dependent on pH, so not anticipated to be fat-soluble. 2,4,6-trichlorophenol (EXC4915) log Pow 3.6 at pH ≤ 4.59 or <3.6 at pH >4.59, so some possibility of fat solubility. In the ruminant feeding study fat determinations, residues of pydiflumetofen were present at a higher level than residues of 2,4,6-trichlorophenol (which were detectable but only found up to 0.01 mg/kg in fat samples at the highest dosing level).

Pigs

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

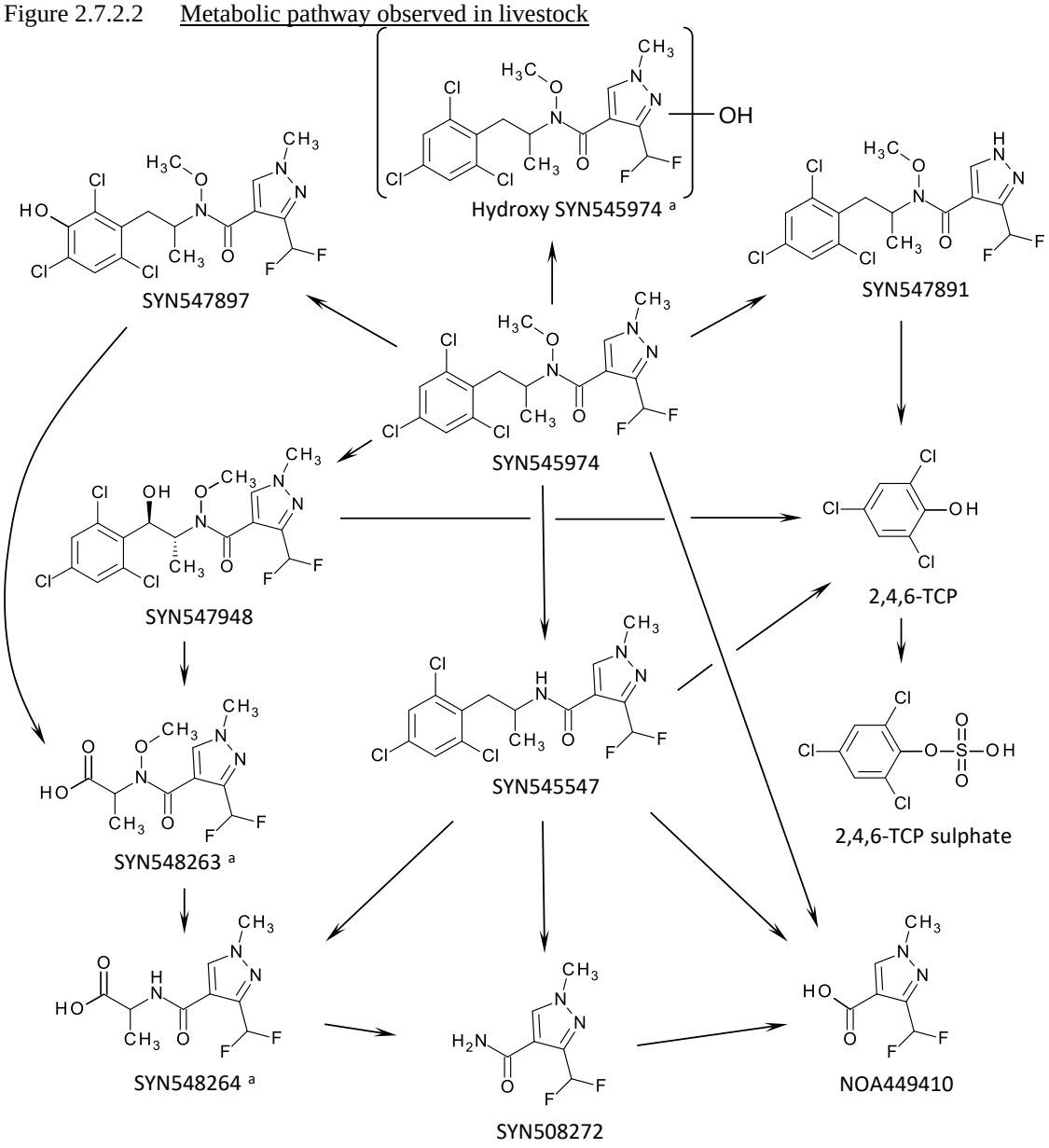
Fish

At present there is no agreed guidance on how to conduct fish metabolism studies to determine the residue definition for risk assessment and enforcement and there are no agreed guidance documents on how then to conduct a fish feeding study. Guidance on residues in fish (metabolism studies and feeding studies) has been under development in the EU. The OECD programme on residue guidelines has not yet considered guidelines applicable to fish.

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

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

Figure 2.7.2.2 Metabolic pathway observed in livestock



2.7.3. Definition of the residue

Plants

The available primary crop metabolism data are for foliar application to wheat, tomato and oilseed rape, and also a soil application to tomatoes. A similar metabolic pathway was observed across all three metabolism studies.

The most relevant metabolism data for the intended uses are the studies on wheat and oilseed rape. The conduct of these studies was broadly reflective of the representative GAPs in terms of timing of application, application method and application rate, however the application rates in the metabolism studies were underdosed (with regard to individual and total application rate for oilseed rape, and with regard to individual application rate for wheat). The oilseed rape metabolism study was at one application at 0.67- 0.73N. For cereals (wheat), the studies were only underdosed considering the individual rate of application: cGAP is one appplication only. The wheat metabolism study applications represented two applications each at 0.63N (2 x 0.63N).

This assessment also considers an MRL application for root crops (carrot, parsley root and parsnip).

Only parent pydiflumetofen was analysed in the field trials supporting the representative uses and carrots, parsley roots and parsnips.

This section also (alongside primary crops) considers rotational crops, as the same two main metabolites (SYN545547 and SYN547891) that were found and identified in primary crops were also the same two main metabolites that were found and identified in rotational crop metabolism study. Therefore the consideration of metabolites for the residue definition proposals for primary crops and rotational crops crops can be taken together.

The overview of metabolism tables below (Table 2.7.3.1 to Table 2.7.3.4) cover the primary crops of tomatoes, wheat and oilseed rape, as well as rotational crops.

Please also refer to the summaries of each of the plant (and rotational crop) metabolism studies in section 2.7.2.

Table 2.7.3.1 Overview of metabolism in tomato

	Tomato (Fruit)					
Outdoor/Indoor	Indoor (glasshouse)					
Type of application	Foliar				Soil Applied	
Method of application	Hand-held sprayer				Drop wise by pipette	
Number treatments	2				1	
Timing of treatments	1) 03/09/2013 2) 10/09/2013				06/06/2013	
g a.s./ha/treatment	[Phenyl-U-14C]-SYN545974 1) 198.28 2) 195.58		[Pyrazole-5-14C]-SYN545974 1) 226.72 2) 173.82		[Phenyl-U-14C]-SYN545974 19.998 (mg as/plant)	[Pyrazole-5-14C]-SYN545974 20.105 (mg as/plant)
Crop growth stage at last application (BBCH GS)	BBCH 86					
PHI (days)	1DAA2	14DAA2	1DAA2	14DAA2	Harvest at maturity - 3 months after application	
	Phenyl		**Pyrazole**		**Phenyl**	**Pyrazole**
Plant part	Mature Fruit	Mature Fruit	Mature Fruit	Mature Fruit	Mature Fruit	Mature Fruit
TRR (mg/kg)	**0.521**	**0.642**	**0.481**	**0.633**	**0.007**	**0.013**
Surface wash extract (% TRR)	96.9	88.9	98.3	94.9	NA	NA
Total extractable residues (% TRR)	100	99.7	98.4	100	NA	97.5
SYN545974 (Parent)	91.7	92.2	95.9	96.6		4.1
SYN547891	1.4	1.6	0.6	1.0		
SYN545547	3.6	3.3	1.8	1.4		0.4
Total identified (% TRR)	96.7	97.1	98.3	99.0	NA	4.4
Unidentified	2.1	3	ND	0.006		88.9[b]
Other fractions[#]	1.2	0.3	ND	0.001	ND	4.9
Total Characterized (%TRR)	3.3	3.3	ND	0.007	NA	94
Uncharacterised	-	-	-	-	-	-
Not analysed fractions	-	-	-	-	-	-

Unresolved	-	-	-	-	-	-
Unextractable radioactive residues(% TRR)	0.1	0.3	1.6	0.001	NA	2.6
Acid/base hydrolysis	-	-	-	-	-	-
Enzymatic hydrolysis	-	-	-	-	-	-
Bound/PES(% TRR)	-	-	-	-	-	-
Accountability (% TRR)[a]	100	100	100	100	NA	100

**Phenyl label: comprising multiple discrete components, no single one of which >0.8% TRR (>0.004 mg/kg)

Fractions produced during processing that were too low for analysis.

NA Not Analysed

[a] Descrepancies due to losses or gains on fractionation

[b] Unassigned radiocomponents comprising at least 25 discrete components, no single one of which >11.9% TRR (>0.002 mg/kg)

metabolites > 10 % TRR < 0.01 mg/kg

metabolites > 10 % TRR > 0.01 mg/kg

Table 2.7.3.1 cont. Residues in terms of mg/kg

	Tomato (Fruit)					
	Phenyl		Pyrazole		Phenyl	Pyrazole
	Mature Fruit	Mature Fruit	Mature Fruit	Mature Fruit	Mature Fruit	Mature Fruit
SYN545974 (Parent)	0.477	0.592	0.461	0.611	NA	0.00
SYN547891	0.007	0.011	0.003	0.006		<0.001
SYN545547	0.019	0.021	0.009	0.009		
Total identified (mg/kg)	0.503	0.624	0.473	0.626	NA	0.001
Unassigned**	0.01	0.015	ND	0.006		0.008
Other fractions[#]	0.007	0.002		0.001		0.001
Total Characterized (mg/kg)	0.017	0.017	ND	0.007	NA	0.009
Not analysed fractions	-	-	-	-	-	-
Unresolved	-	-	-	-	-	-

Uncharacterised	-	-	-	-	-	-

Please see footnote details for Table 2.7.3.1 above.

Table 2.7.3.2 Overview of metabolism in wheat

	Wheat (Cereals/grass crop)							
Outdoor/Indoor	**Outdoor**							
Type of application	**Foliar**							
Method of application	**Hand-held sprayer**							
Number treatments	2							
Timing of treatments	1) 19/07/2012 2) 26/07/2012							
g a.s./ha/treatment	[Phenyl-U-14C]-SYN545974 1) 123.2 2) 129.1	[Pyrazole-5-14C]-SYN545974 1) 124.2 2) 128.1	[Phenyl-U-14C]-SYN545974 1) 123.2 2) 129.1	[Pyrazole-5-14C]-SYN545974 1) 124.2 2) 128.1	[Phenyl-U-14C]-SYN545974 1) 123.2 2) 129.1	[Pyrazole-5-14C]-SYN5459 74 1) 124.2 2) 128.1	[Phenyl-U-14C]-SYN545974 1) 123.2 2) 129.1	[Pyrazole-5-14C]-SYN545974 1) 124.2 2) 128.1
Crop growth stage at last application (BBCH GS)	BBCH 58	BBCH 58	BBCH 58	BBCH 58	BBCH 58	BBCH 58	BBCH 58	BBCH 58
Total seasonal application rate (g a.s./ha)	252.3	252.3	252.3	252.3	252.3	252.3	252.3	252.3
14C labelling	**Phenyl**	**Pyrazole**	**Phenyl**	**Pyrazole**	**Phenyl**	**Pyrazole**	**Phenyl**	**Pyrazole**
Plant part	Forage	Forage	Hay	Hay	Straw	Straw	Grain	Grain
TRR (mg/kg)	**0.338**	**0.465**	**0.977**	**1.391**	**1.286**	**1.527**	**0.037**	**0.057**
Total extractable residues (% TRR)	96.5	95.6	94.2	94.2	95.8	94.5	90.4	84.9
SYN545974 (Parent)	91.0	84.3	84.1	70.5	83.6	76.4	81.5	81.6
SYN547891	1.2	2.4	3.0	3.6	2.4	4.3	8.3	7.8
SYN545547	1.4	2.7	2.4	2.4	2.8	3.9	2.9	2.6
Total identified (% TRR)	93.6	89.4	89.5	76.5	88.8	84.6	92.7	92.0
Unidentified	NA	2.5	4.2	13.8			NA	3.3
Other fractions[#]								
Total Characterized (%TRR)	NA	2.5	4.2	13.8[d]			NA	3.3
Uncharacterised	-	-	-		1.9	1.5	-	-
Not analysed fractions	-	-	-	-	-	-	-	-

Unresolved	-	-	-	-	-	-	-	-
Unextractable radioactive residues(% TRR)	3.5	4.4	5.8	5.7	4.6	6.1	9.6	15.2
Acid/base hydrolysis	-	-	-	-	-	-	-	-
Enzymatic hydrolysis	-	-	-	-	-	-	-	-
Bound/PES(% TRR)	-	-	-	-	-	-	-	-
Accountability (% TRR)[a]	100	100	100	100	100	100	100	100

**Phenyl label: comprising multiple discrete components, no single one of which >0.8% TRR (>0.004 mg/kg)

Fractions produced during processing that were too low for analysis.

NA Not Analysed

[a] Descrepancies due to losses or gains on fractionation

[d] Unassigned radiocomponents comprising at least 12 discrete components, no single one of which >2.6%TRR, (0.036 mg/kg)

metabolites > 10 % TRR < 0.01 mg/kg

metabolites > 10 % TRR > 0.01 mg/kg

Table 2.7.3.2 cont. Residues in terms of mg/kg

	Wheat (Cereals/grass crops)							
	Phenyl Forage	**Pyrazole** Forage	**Phenyl** Hay	**Pyrazole** Hay	**Phenyl** Straw	**Pyrazole** Straw	**Phenyl** Grain	**Pyrazole** Grain
SYN545974 (Parent)	0.307	0.392	0.821	0.981	1.075	1.167	0.030	0.046
SYN547891	0.005	0.012	0.029	0.049	0.036	0.059	0.003	0.004
SYN545547	0.004	0.011	0.023	0.034	0.032	0.065	0.001	0.001
Total identified (mg/kg)	0.316	0.415	0.873	1.064	1.143	1.291	0.034	0.051
Unassigned**	NA	0.012	0.041	0.189	-	-	-	-
Other fractions[#]	-	-	-	-	-	-	-	-
Total Characterized (mg/kg)	NA	0.012	0.041	0.189	-	-	NA	0.002
Not analysed fractions	-	-	-	-	-	-	-	-
Unresolved	-	-	-	-	-	-	-	-

Uncharacterised	-	-	-	-	0.024	0.023	-	-

Please see footnote details for Table 2.7.3.2 above.

Table 2.7.3.3 Overview of metabolism in oilseed rape

	Oil Seed Rape (Pulses/oilseeds)					
Outdoor/Indoor	**Outdoor**					
Type of application	**Foliar**					
Method of application	**Hand-held sprayer**					
Number treatments	1					
Timing of treatments	11/07/2012					
g a.s./ha/treatment	[Phenyl-U-14C]-SYN545974	[Pyrazole-5-14C]-SYN545974	[Phenyl-U-14C]-SYN545974	[Pyrazole-5-14C]-SYN545974	[Phenyl-U-14C]-SYN545974	[Pyrazole-5-14C]-SYN545974
	134.2	146.6	134.2	146.6	134.2	146.6
Crop growth stage at last application (BBCH GS)	BBCH 65	BBCH 65	BBCH 65	BBCH 65	BBCH 65	BBCH 65
Total seasonal application rate (g a.s./ha)	134.2	146.6	134.2	146.6	134.2	146.6
14C labelling	**Phenyl**	**Pyrazole**	**Phenyl**	**Pyrazole**	**Phenyl**	**Pyrazole**
Plant part	Forage	Forage	Trash	Trash	Seeds	Seeds
TRR (mg/kg)	**NA**	**NA**	**0.062**	**0.061**	**0.02**	**0.019**
Total extractable residues (% TRR)	NA	NA	81.3	75.6	74.5	71.8
SYN545974 (Parent)			50.9	30.0	62.6	39.2
SYN547891			5.1	3.3	2.7	ND
SYN545547			3.7	2.8	ND	6.1
Total identified (% TRR)	NA	NA	59.7	36.1	65.3	45.3
Unidentified			6.2	34.9[c]	6.0	8.6
Other fractions[#]			23.7	13.6		
Total Characterized (%TRR)	NA	NA	29.9	48.5	6.0	8.6

Uncharacterised	-	-	-	-	-	-
Not analysed fractions	-	-	-	-	-	-
Unresolved	-	-	-	-	-	-
Unextractable radioactive residues(% TRR)	NA	NA	18.7	24.4	25.5	28.2
Acid/base hydrolysis	-	-	-	-	-	-
Enzymatic hydrolysis	-	-	-	-	-	-
Bound/PES(% TRR)	-	-	-	-	-	-
Accountability (% TRR)[a]	NA	NA	100	100	100	100

**Phenyl label: comprising multiple discrete components, no single one of which >0.8% TRR (>0.004 mg/kg)

Fractions produced during processing that were too low for analysis.

NA Not Analysed

[a] Descrepancies due to losses or gains on fractionation

[c] Unassigned radiocomponents comprising at least 10 discrete components, no single one of which >8.4%TRR, (0.005 mg/kg)

metabolites > 10 % TRR < 0.01 mg/kg

metabolites > 10 % TRR > 0.01 mg/kg

Table 2.7.3.3 cont. Residues in terms of mg/kg

	Oil Seed Rape (Pulses/oilseeds)					
	Phenyl	**Pyrazole**	**Phenyl**	**Pyrazole**	**Phenyl**	**Pyrazole**
	Forage	Forage	Trash	Trash	Seeds	Seeds
SYN545974 (Parent)	NA	NA	0.032	0.018	0.012	0.007
SYN547891			0.003	0.002	0.001	ND
SYN545547			0.002	0.002	ND	0.001
Total identified (mg/kg)	NA	NA	0.037	0.022	0.013	0.008
Unassigned**			0.004	bri	0.001	0.002
Other fractions[#]			0.015	0.008	-	-

Total Characterized (mg/kg)	NA	NA	0.019	0.03	0.001	0.002
Not analysed fractions	-	-	-	-	-	-
Unresolved	-	-	-	-	-	-
Uncharacterised	-	-	-	-	-	-

Please see footnote details for Table 2.7.3.3 above.

Table 2.7.3.4 Overview of metabolism in rotational crops – phenyl label

Outdoor/Indoor	Aged out doors for 28 days after treatment with test item before being brought indoors for all further maintenance																								
Bare soil application: Y/N	Y																								
Plant back interval- application to bare oil	Plantback intervals of 30, 120 and 270 days																								
Dose of application (g a.s./ha)	Phenyl						Pyrazole																		
	388						409																		
Ploughing at 20 cm depth: Y/N	N						N																		
Phytotoxicity observed (Y/N)	Not recorded																								
14C labelling	[Phenyl-U-14C]-SYN545974						[Phenyl-U-14C]-SYN545974												[Phenyl-U-14C]-SYN545974						
Crop	Lettuce (Leafy vegetables)						Wheat (Cereal small grain)												Turnip (Root & tuber vegetables)						
	Immature			Mature																					
Plant back intervals (days)	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	
Plant part	Leaves			Leaves			Forage			Hay			Straw			Grain			Tubers			Foliage			
TRR (mg/kg)[a]	0.012	0.005	0.001	0.001	0.005	0.001	0.03	0.010	0.01	0.06	0.06	0.04	0.17	0.153	0.11	0	0.01	0.003	0.01	0.002	0.002	0.010	0.004	0.004	
Total extractable residues (% TRR)	85.5	NE	NE	NE	NE	NE	96.8	89.2	96.3	91.9	85.2	94.7	86.9	85.9	87.3	NE	NE	NE	NE	NE	NE	93.6	NE	NE	
SYN545974 (Parent)	69.3						77.8	37.3	59.7	50.1	42.9	76.1	30	33.7	37.2							77.2			
SYN547891	11.6						12.0	4.9	7.5	6.2	4.5	9.7	6.1	5.3	5.5							3.9			
SYN545547	4.0						2.2	2.4	3.1	2.5	1.5	3.6	1.8	1.4	2.0							ND			
Total identified (% TRR)	84.9	NE	NE	NE	NE	NE	92.0	44.6	70.3	58.8	48.9	89.4	37.9	40.4	44.7	NE	NE	NE	NE	NE	NE	81.1	NE	NE	
Unidentified[a]	3.4						10.6[k]	33.7[e]	16.8[d]	38.9[e]	28[f]	7.3[e]	43.1[k]	42.8[i]	44.2[i]							10.2[k]			
Total Characterized (%TRR)	3.4						10.6	33.7	16.8	38.9	28.0	7.3	43.1	42.8	44.2							10.2			
Not analysed fractions	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Unresolved	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Unextractable radioactive residues(% TRR)	14.5						3.2	10.7	3.7	8.1	14.8	5.3	12.2	14.1	3.2							6.5			
Acid/base hydrolysis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Enzymatic hydrolysis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Bound/PES(% TRR)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Accountability (% TRR)[l]	100	NE	NE	NE	NE	NE	100	100	100	100	100	100	100	100	100	NE	NE	NE	NE	NE	NE	100	NE	NE	
see footnotes overpage																									

Table 2.7.3.4 cont. Overview of metabolism in rotational crops – phenyl label (mg/kg)

	[Phenyl-U-14C]-SYN545974 Lettuce (Leafy vegetables)						[Phenyl-U-14C]-SYN545974 Wheat (Cereal small grain)												[Phenyl-U-14C]-SYN545974 Turnip (Root & tuber vegetables)					
	Immature			Mature																				
	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270
	Leaves			Leaves			Forage			Hay			Straw			Grain			Tubers			Foliage		
SYN545974 (Parent)	0.009	NE	NE	NE	NE	NE	0.024	0.004	0.008	0.032	0.025	0.030	0.052	0.051	0.037	NE	NE	NE	NE	NE	NE	0.008	NE	NE
SYN547891	0.001						0.004	<0.001	0.001	0.004	0.003	0.004	0.011	0.008	0.006							<0.001		
SYN545547	<0.001						0.001	<0.001	<0.001	0.002	0.001	0.001	0.003	0.002	0.002							ND		
Total identified (% TRR)																								
Unidentified[a]	<0.001						0.005	0.001	0.001	0.025[e]	0.019[g]	0.003	0.076[k]	0.068[l]	0.050[j]							0.001		
Total Characterized (%TRR)																								
Not analysed fractions																								
Unresolved																								

NE - Not extracted
ND - Not detected
metabolites > 10 % TRR < 0.01 mg/kg
metabolites > 10 % TRR > 0.01 mg/kg

[a] Components that have been extracted, concentrated and chromatographed
[c] All residues are from summation except where level were too low to require extraction
[k] Phenyl label: comprising at least 5 individual components none individually exceeding > 2.9% TRR (> 0.001 mg/kg)
[e] Phenyl label: comprising at least 12 individual components none individually exceeding > 5.3% TRR (> 0.001
[d] Phenyl label: comprising at least 6 individual components none individually exceeding > 4.1% TRR (> 0.001
[f] Phenyl label: comprising at least 21 individual components none individually exceeding > 5.0% TRR
[g] Phenyl label: comprising at least 20 individual components none individually exceeding > 4.7% TRR
[h] Phenyl label: comprising at least 2 individual components none individually exceeding > 3.9% TRR (> 0.002
[l] Phenyl label: comprising at least 22 individual components none individually exceeding > 6.9% TRR
[i] Phenyl label: comprising at least 27 discrete components, no single one of which > 6.0% TRR (> 0.009
[j] Phenyl label: comprising at least 17 discrete components, no single one of which > 4.6% TRR (> 0.005
[b] Phenyl label: comprising at least 1 individual component not exceeding 10.2% TRR (0.001 mg/kg)
[m] Descrepancies due to losses or gains on fractionation

Table 2.7.3.4 cont. Overview of metabolism in rotational crops – pyrazole label

14C labelling	[Pyrazole-5-14C]-SYN545974						[Pyrazole-5-14C]-SYN545974												[Pyrazole-5-14C]-SYN545974					
Crop	Lettuce (Leafy vegetables)						Wheat (Cereal small grain)												Turnip (Root & tuber vegetables)					
	Immature			Mature																				
Plant back intervals (days)	**30**	**120**	**270**	**30**	**120**	**270**	**30**	**120**	**270**	**30**	**120**	**270**	**30**	**120**	**270**	**30**	**120**	**270**	**30**	**120**	**270**	**30**	**120**	**270**
Plant part	Leaves			Leaves			Forage			Hay			Straw			Grain			Tubers			Foliage		
TRR (mg/kg)*	0.019	0.004	0.006	0.007	0.004	0.002	0.03	0.027	0.01	0.09	0.11	0.04	0.21	0.219	0.16	0.01	0.01	0.002	0.01	0.003	0.002	0.014	0.007	0.007
Total extractable residues (% TRR)	86.1	NE	NE	NE	NE	NE	96.8	91.1	95.5	90	84.5	93.5	88.2	85.9	83.2	NE	NE	NE	NE	NE	NE	89.6	NE	NE
SYN545974 (Parent)	76.7						59.1	22.5	21.9	23.8	52.2	67.9	26.0	28.7	18.6							44.4		
SYN547891	6.8						13.3	3.0	4.6	3.1	5.5	12.2	5.5	4.4	4.6							4.8		
SYN545547	2.3						3.5	2.3	ND	1.7	2.3	5.6	2.3	2.2	1.5							3.8		
Total identified (% TRR)	85.8	NE	NE	NE	NE	NE	75.9	27.8	26.5	28.6	60.0	85.7	33.8	35.3	24.7	NE	NE	NE	NE	NE	NE	53.0	NE	NE
Unidentified*	3.4						14.3[k]	63.0[e]	62.4[d]	53.8[e]	27.3[f]	9.3[e]	54.3[k]	46.4[i]	67[j]							24.8[k]		
Organosoluble fractions																								
Aqueous soluble fractions																								
Neutral fraction																								
Acidic fraction																								
Polar fraction																								
Total Characterized (%TRR)	14.5						14.3	63.0	62.4	53.8	27.3	9.3	54.3	46.4	67							24.8		
Not analysed fractions																								
Unresolved																								
Unextractable radioactive residues(% TRR)							3.2	8.9	4.5	9.9	15.5	6.5	11.3	14.1	2.9							10.4		
Acid/base hydrolysis																								
Enzymatic hydrolysis																								
Bound/PES(% TRR)																								
Accountability (% TRR)	100	NE	NE	NE	NE	NE	100	100	100	100	100	100	100	100	100	NE	NE	NE	NE	NE	NE	100	NE	NE
see footnotes overpage																								

Table 2.7.3.4 cont. Overview of metabolism in rotational crops – pyrazole label (mg/kg)

	[Pyrazole-5-14C]-SYN545974						[Pyrazole-5-14C]-SYN545974												[Pyrazole-5-14C]-SYN545974					
	Lettuce (Leafy vegetables)						Wheat (Cereal small grain)												Turnip (Root & tuber vegetables)					
	Immature			Mature																				
	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270	30	120	270
	Leaves			Leaves			Forage			Hay			Straw			Grain			Tubers			Foliage		
SYN545974 (Parent)	0.015	NE	NE	NE	NE	NE	0.016	0.006	0.003	0.022	0.056	0.024	0.055	0.063	0.030	NE	NE	NE	NE	NE	NE	0.005	NE	NE
SYN547891	0.001						0.004	0.001	0.001	0.003	0.006	0.004	0.012	0.010	0.008							0.001		
SYN545547	<0.001						0.001	0.001	ND	0.002	0.002	0.002	0.005	0.005	0.002							<0.001		
Total identified (mg/kg)	0.016						0.021	0.008	0.004	0.027	0.064	0.030	0.072	0.078	0.040							0.006		
Unidentified*	<0.001						0.004	0.013	0.009	0.051	0.023	0.003	0.116	0.103	0.107							0.002		
Organosoluble fractions																								
Aqueous soluble fractions																								
Neutral																								
Acidic																								
Polar																								
Total Characterized (mg/kg)	<0.001						0	0.01	0.01	0.05	0.03	0	0.12	0.103	0.11							0.002		
Not analysed fractions																								
Unresolved																								

NE - Not extracted
ND - Not detected — metabolites > 10 % TRR < 0.01 mg/kg
* Components that have been extracted, concentrated and chromatographed — metabolites > 10 % TRR > 0.01 mg/kg
' All residues are from summation except where level were too low to require extraction
[b] Pyrazole label: comprising at least 6 individualcomponents none individually exceeding > 3.5% TRR (> 0.001 mg/kg)
[c] Pyrazole label: comprising at least 29 individual components none individually exceeding > 9.2% TRR
[d] Pyrazole label: comprising at least 15 individual components none individually exceeding > 7.0% TRR
[e] Pyrazole label: comprising at least 30 individual components none individually exceeding > 7.3% TRR
[f] Pyrazole label: comprising at least 17 individual components none individually exceeding > 4.3% TRR
[g] Pyrazole label: comprising at least 2 individual components none individually exceeding > 5.2% TRR
[h] Pyrazole label: comprising at least 38 individual components none individually exceeding > 6.7% TRR
[i] Pyrazole label: comprising at least 33 discrete components, no single one of which > 4.6% TRR (> 0.010
[j] Pyrazole label: comprising at least 19 discrete components, no single one of which > 5.8% TRR (> 0.009
[k] Pyrazole label: comprising at least 5 individual components none individually exceeding > 10.2% TRR

Given that parent pydiflumetofen is found as the major component in the metabolism studies, the parent component seems the most suitable marker residue for the residue definition for enforcement.

The two identified metabolites (SYN545547 and SYN547891) found in primary crops are the same two metabolites identified in the rotational crop metabolism. As per the primary crops, the main component of the residue in rotational crops is parent pydiflumetofen. In primary crops, each of these metabolites was <10%TRR. Despite the % TRR exceeding 10 % for some rotational crop samples (SYN547891 only), the total radioactive residue for SYN547891 did not exceed 0.001 ~~0.004~~ mg/kg in rotational crop commodities for human consumption in any case. SYN547891 was found at up to 0.012 mg/kg in (rotational) wheat straw. See section 2.7.2.

Toxicologically it is concluded that the risk assessment for these metabolites (SYN545547 and SYN547891) is not 'covered' by the reference values for parent pydiflumetofen and specific toxicological data are not available for these. The following conclusions on the toxicology of the two metabolites are discussed in full detail in Volume 3 CA B6 Part II.

Metabolite	Covered by parent	Reference value	Tox. relevant
SYN545547	Found in rat metabolism but minor metabolite (<10%)	Not genotoxic, hence TTC CCIII values (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment	?
SYN547891	Found in rat metabolism but minor metabolite (<10%)	Not genotoxic, hence TTC CCIII values (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment	?

Toxicological advice is that a combined exposure assessment for SYN545547 and SYN547891 is not needed when considering the consumer dietary exposure of these plant metabolites versus the TTCs (Cramer Class III), see section 2.6.9.

The TTC approach outlined above (CCIII) is appropriate when insufficient toxicological studies are available to propose a specific ADI or ARfD but genotoxicity can be excluded (based on QSAR or data). In this case, the TTC approach is used as a screening tool to check if metabolites need additional consideration.

Rotational crop trials on the magnitude of residues were evaluated where residues of parent pydiflumetofen only were analysed (section 2.7.7). Following presentation to the Expert Committee on Pesticides (ECP) in the process of seeking Independent Scientific Advice (ISA), the assessment took account of the highest estimated soil exposures taking account of crop interception (since pydiflumetofen is applied to the primary crop) and considering soil accumulation of residues accounting for year to year use. Considering the highest ratios of the metabolites to parent (see section 2.7.7), and applying these to the highest derived levels of parent pydiflumetofen in all the rotated crops, it is concluded that the metabolites SYN545547 and SYN547891 are not expected at or above 0.01 mg/kg in any rotated food commodity. Therefore the below assessment of estimating exposure for metabolites SYN545547 and SYN547891 and a comparison to TTCs has only considered contribution of primary crop residues. For future uses, if soil exposures are markedly increased then it would be necessary to consider whether rotational crops would need to be included in an estimation of metabolite exposures versus the TTCs.

~~As these~~ The metabolites SYN545547 and SYN547891 were also not analysed for in the primary crop field trials. ~~, in either primary or rotational crops~~Therefore, an estimate of possible residue levels in items consumed directly by humans has been made based on the levels of these metabolites in the metabolism studies, and a consideration of the ratios of metabolite to parent expected to be found in crops.

SYN547891

In primary crop plants: max %TRR was 8.3%TRR in wheat grain

In rotational crops: max %TRR was 13.3%TRR in wheat forage

SYN545547

In primary crop plants: max %TRR was 6.1%TRR in oilseed rape seeds

In rotational crops: max %TRR was 5.6%TRR in wheat hay

The ratios of metabolite: parent as found in the various primary crop metabolism studies (primary and rotational crop) were taken from each of the radiolabelled studies. Focus was kept to when samples applicable to human consumption contained a positive residue of the metabolite (at the same time as a finding of the parent (same sample)). These are outlined in Table 2.7.3.5.

Table 2.7.3.5 Individual M: P ratios (in primary crop plant metabolism studies (PC is primary crop; RC is rotational crop). The M: P ratios are based on relative %TRR levels in the same sample (inclusion of samples where both parent and the metabolite were found).

Study sample	label	comment	M: P SYN547891 (X:1)	M: P SYN545547 (X:1)
Tomato (PC) (foliar application)	Phenyl	Mature fruit 1 DALA	1.4 : 91.7 (0.0153:1)	3.6 : 91.7 (0.0393 : 1)
Tomato (PC) (foliar application)	Phenyl	Mature fruit 14 DALA	1.6 : 92.2 (0.0174:1)	3.3 : 92.2 (0.0358:1)
Tomato (PC) (foliar application)	Pyrazole	Mature fruit 1 DALA	0.6 : 95.9 (0.0063:1)	1.8 : 95.9 (0.0188:1)
Tomato (PC) (foliar application)	Pyrazole	Mature fruit 14 DALA	1.0 : 96.6 (0.0104:1)	1.4 : 96.6 (0.0145:1)
Tomato (PC) (soil application)	Pyrazole	-		0.4 : 4.1 (0.0976:1)
Oilseed rape seed (PC)	Phenyl		2.7 : 62.6 (0.0431:1)	
Oilseed rape seed (PC)	Pyrazole			6.1 : 39.2 **(0.156:1)**
Wheat grain (PC)	Phenyl		8.3 : 81.5 (**0.102:1**)	2.9 : 81.5 (0.0356:1)
Wheat grain (PC)	Pyrazole		7.8 : 81.6 (0.0956:1)	2.6 : 81.6 (0.0319:1)
Immature lettuce (RC))	Phenyl	30 DAT (days after treatment) Plant Back Interval	11.6 : 69.3 (**0.1674:1**)	4.0 : 69.3 (0.0577:1)
Immature lettuce (RC)	Pyrazole	30 DAT (days after treatment) Plant Back Interval	6.8 : 76.7 (0.0887:1)	2.3 : 76.7 (0.030:1)

The M:P ratio values vary across commodities and within studies (same commodities), but there are a number of data points to base a M:P ratio that can be applied to the level of parent determined in the trials. It is proposed to derive an estimate using a worst case estimate of a M:P ratio from the above (the highest ratio in the above tables, which for SYN547891 was found in wheat grain the lettuce rotational crop sample (max 10.2% 16.7% of the amount of parent) and for SYN545547 - max 15.6% of the amount of parent was found in oilseed rape. This approach is considered to be especially conservative for chronic dietary exposure estimation. Given that parent is the main component found in all the metabolism studies, including rotational crops, the M:P ratio is being considered to help determine whether a broad residues definition across various plant commodities might be applicable.

Two options for the consumer risk assessment are being presented (see section 2.7.9) to accommodate different environmental fate approaches to the estimation of exposures relevant to rotational crops A: Tier 1 10 year use assessment and B: Tier2 – long term use, impacting the estimation of levels of the rotational crops themselves.

~~Considering the crop inputs (across the range of primary and rotated crops, and taking account of pydiflumetofen levels that might arise from either of these sources), the estimated levels of parent are:~~

~~STMRs (ranging from 0.03 mg/kg (numerous crops) to 0.13 mg/kg for barley and oat grain in the Tier 1 assessment and ranging from 0.02 mg/kg (numerous crops) to 0.12 mg/kg for barley and oat grain in the Tier 2 assessment) mg/kg; and~~

~~HRs (ranging from 0.03 mg/kg (numerous crops) and 0.133 mg/kg for various vegetable crops, e.g. leafy vegetables in the Tier 1 assessment and ranging from 0.02 mg/kg to 0.096 mg/kg (leafy vegetables) in the Tier 2 assessment).~~

For SYN547891, the maximum prediction based on the ratios would be a level of 10.2% ~~16.7%~~ (of the amount of parent present, expressed as parent). This is based on the highest M:P due to the variation in ratios seen. The lowest ratio represents 0.63% (of the amount of parent present).

For SYN545547, the maximum prediction based on the ratios would be a level of 15.6% (of the amount of parent present, expressed as parent). This is based on the highest M:P due to the variation in ratios seen. The lowest ratio represents 1.45% (of the amount of parent present).

In order to express the results of SYN547891 and SYN545547, from the 'as parent' pydiflumetofen basis expression to the 'mg of metabolite/kg' expression ('metabolite equivalent'), the levels for each of the metabolites 'as parent' need to be multiplied by a molecular weight adjustment factor of x 0.97 for SYN547891 and x 0.93 for SYN545547, due to the lower molecular weights of SYN547891 and SYN545547 respectively compared to parent pydiflumetofen (411.7 g/mol and 396.7 g/mol compared to 426.7 g/mol).

Based on these levels, it is possibly anticipated that some residue findings of either metabolite above 0.01 mg/kg would be found in ~~either rotational or~~ primary crops~~, even taking account of the high predicted levels of soil accumulation of residues (Tier 1 assessment 10 year use)~~. ~~Exceedances of the 0.01 mg/kg level (by either of these metabolites) would be expected to be the minority rather than the 'norm'.~~ An estimated (worst case, since the highest M:P ratios have been used) HR for SYN547891 and SYN545547 could be above 0.01 mg/kg (please see the values for the HR values (STMRs for blended commodities such as barley) applied in the acute exposure estimation for the metabolites in Table 2.7.3.6). However, any values above 0.01 mg/kg would not be expected to be markedly higher than 0.01 mg/kg, ~~be likely to be infrequent. For example, the HR in Table 2.7.3.6 for carrots metabolite SYN545547 is at 0.0119 mg/kg); this has been derived on the basis of the highest M:P ratio applied to the HR for parent in carrots (a median M:P ratio applied to the median for parent in carrots would yield an approximately ten fold lower value of 0.0025 mg/kg).~~

For the purpose of TTC screening to calculate the estimated exposure of the metabolite to see whether the intakes assessed are below the TTC, the worst case ~~of these two scenarios was applied, see Tier 1 10 year use assessment, and the worst case~~ M:P ratios for each metabolite were used. This therefore assumed that each commodity contained SYN547891 at 10.2% ~~16.7%~~ of the level of parent, and for SYN545547 at 15.6% (of the amount of parent present). A combined exposure assessment for the purpose of this TTC (exposure assessment of both SYN547891 and SYN545547 in crops) was not considered necessary (section 2.6.9).

The estimated levels of the metabolites to derive dietary intake values to compare to the TTCs are presented in Table 2.7.3.6 below.

Table 2.7.3.6 Estimated residue levels for each of the metabolites SYN547891 and SYN545547 in primary crops

Primary crop	Residue input scenario	Residue of pydiflumetofen from field trials (mg/kg)	Estimated level of metabolite SYN547891 expressed as parent pydiflumetofen (mg/kg)	Estimated level of metabolite SYN547891 (mg/kg metabolite equivalent basis)	Estimated level of metabolite SYN545547 expressed as parent pydiflumetofen (mg/kg)	Estimated level of metabolite SYN545547 (mg/kg metabolite equivalent basis)

Oilseed rape	STMR (for chronic and acute)	0.01	0.0010	0.0010	0.0016	0.0015
Carrot	STMR (chronic)	0.067	0.0068	0.0066	0.0105	0.0097
Carrot	HR (acute)	0.082	0.0084	0.0081	0.0128	0.0119
Parsley root	STMR (chronic)	0.067	0.0068	0.0066	0.0105	0.0097
Parsley root	HR (acute)	0.082	0.0084	0.0081	0.0128	0.0119
Parsnip	STMR (chronic)	0.067	0.0068	0.0066	0.0105	0.0097
Parsnip	HR (acute)	0.082	0.0084	0.0081	0.0128	0.0119
Barley grain	STMR (for chronic and acute)	0.1	0.0102	0.0099	0.0156	0.0145
Oat grain	STMR (for chronic and acute)	0.1	0.0102	0.0099	0.0156	0.0145
Wheat grain	STMR (for chronic and acute)	0.025	0.0026	0.0025	0.0039	0.0036
Rye grain	STMR (for chronic and acute)	0.025	0.0026	0.0025	0.0039	0.0036

The total chronic dietary risk assessment for crops (~~excluding~~ animal products have been excluded, since these metabolites are not expected to be found in livestock) for pydiflumetofen was considered taking account of estimated residues in primary crops ~~(Tier 1 (10 year use)), as pydiflumetofen was sought and found in primary and rotational rotational crops. The consumer risk assessment has considered the crop inputs from all these sources, see section 2.7.7~~. The application of the highest M:P ratio is likely to be considered a worst case in terms of estimation of the levels of residues of each of the metabolites in various crops.

The ~~TTC~~ estimations of exposure and comparison to the TTC values for each of the metabolites are estimated and presented in Table 2.7.3.7 (chronic) and Table 2.7.3.8 (acute) below. The table for the chronic TTC considers UK and EU total chronic dietary intakes (derived from UK NESTI model and also EU PRIMo v3.1). The table for the acute TTC considers UK NESTI (acute/short term intakes)~~; the highest two and~~ EU IESTI values in PRIMo v3.1 ~~were the same as the UK NESTIs (potatos and carrots, UK infants critical consumer group)).~~ None of the TTC levels are exceeded.

Table 2.7.3.7 ~~TTC~~ Chronic exposure assessment for food directly consumed by humans containing SYN 547891 and SYN545547. The ~~crop~~ estimates are based on dietary intakes of primary crops including the representative uses and the MRL assessment uses. ~~Tier 1/10 year use scenario (see section 2.7.9).~~

As per the dietary risk assessment for residues of pydiflumetofen (section 2.7.9) a PF has not been applied to the residue in oilseed rape. This is uncertain as there is no processing information for the metabolites themselves. The exposure estimates are well below the chronic TTC value (CCIII) of 0.0015 mg/kg bw/day.

	~~Total chronic dietary intake (all crop commodities) for parent (mg/kg bw/day)~~	~~Estimate of possible residue level of the metabolite~~[&]	Total chronic dietary intake (all primary ~~all~~ commodities) for **metabolite** (mg/kg bw/day)[£&]	CCIII TTC of 0.0015 mg/kg bw/day Exceeded ?
UK estimation for SYN547891	~~0.004571 mg/kg bw/day (critical consumer is UK toddler)~~	~~16.2% (16.7 x 0.97) % of level of the 'overall' STMR (PC+RC) levels for parent residue in all crops (see section 2.7.7, 2.7.7.18 and Tables 2.7.7.19)~~	0.000055 mg/kg bw/day (critical consumer is UK toddler)	**No** (4% of the TTC level)
EU PRIMo 3.1 estimation for SYN547891	~~0.00145 mg/kg bw/day (critical consumer is Dutch toddler)~~	~~16.2% (16.7 x 0.97) % of level of the 'overall' STMR (PC+RC) levels for parent residue in all crops (see section 2.7.7, 2.7.7.18 and Tables 2.7.7.19)~~	0.000045 mg/kg bw/day (critical consumer is Danish child)	**No** (3% of the TTC)
UK estimation for SYN545547	~~0.004648 mg/kg bw/day (critical consumer is UK toddler)~~	~~14.5% (15.6 x 0.93) % of level of the 'overall' STMR (PC+RC) levels for parent residue in all crops (see section 2.7.7, 2.7.7.18 and Tables 2.7.7.19)~~	0.000080 mg/kg bw/day (critical consumer is UK toddler)	**No** (5% of the TTC level)
EU PRIMo 3.1 estimation for SYN545547	~~0.00145 mg/kg bw/day (critical consumer is Dutch toddler)~~	~~14.5% (15.6 x 0.93) % of level of the 'overall' STMR (PC+RC) levels for parent residue in all crops (see section 2.7.7, 2.7.7.18 and Tables 2.7.7.19)~~	0.00005 mg/kg bw/day (critical consumer is Danish toddler)	**No** (4% of the TTC level)

[£]the risk assessment model tabular outputs are not included, however the highest total dietary intake estimated for each of the metabolites based on the residue inputs and approaches are explained in this table.

[&] Please note these estimations of the levels of the metabolites on which these exposure calculations are made (versus the TTC) are based on mg metabolite eq./kg amounts. The M:P ratios were based on %TRR levels of each of the parent and metabolite expressed in mg/kg parent equivalents. In order to express these residues in metabolite equivalents, the residues were estimated taking account of the ratio (M:P (e.g. 10.2%) and also the molecular weight adjustment (e.g. 0.97)). The molecular weight adjustment is explained in the text above the table.

Table 2.7.3.8 ~~TTC~~ Acute exposure assessment (UK NESTIs) for crops ~~(PC and RC)~~ directly consumed by humans containing SYN 547891 and SYN545547 ~~– Tier 1 – 10 year use~~. Please note: the highest ~~two~~ IESTI values in PRIMo v3.1 were the same as the UK NESTIs (~~potatoes and~~ carrots, UK infants critical consumer group)).

Please note these estimations of the levels of the metabolites on which these exposure calculations are made (versus the TTC) are based on mg metabolite eq./kg amounts. The M:P ratios were based on %TRR levels of each of the parent and metabolite expressed in mg/kg parent equivalents. In order to express these residues in metabolite equivalents, the residues were estimated taking account of the highest ratio (M:P (e.g. 10.2%) and also the molecular weight adjustment (e.g. 0.97)). The molecular weight adjustment is explained in the text above the table. Where applicable (e.g. blended commodities), the STMR rather than an HR has been used in this acute exposure assessment (for the column titled 'HR').

	SYN547891 Estimated highest NESTI (UK) or IESTI intake (EU PRIMo)	SYN547891 Acute TTC value of 0.005 mg/kg bw/day (for CCIII) Exceeded ?	SYN545547 Estimated highest NESTI (UK) or IESTI intake (EU PRIMo)	SYN545547 Acute TTC value of 0.005 mg/kg bw/day (for CCIII) Exceeded ?
Oilseed rape$	0.0000015 (EU IESTI DE child)	**No** (< 0.1% of the TTC)	0.000002 (EU IESTI DE child)	**No** (< 0.1% of the TTC)
Oilseed rape$	0.000014 (UK NESTI 4-6 year old child)	**No** (0.3% of the TTC)	0.000022 (UK NESTI 4-6 year old child)	**No** (0.4% of the TTC)
Carrots	0.00051 (EU IESTI UK infant) UK NESTI infant	**No** (10% of the TTC)	0.00075 (EU IESTI UK infant) UK NESTI infant	**No** (15% of the TTC)
Parsley roots	0.000035 (EU IESTI DK child)	**No** (0.7% of the TTC)	0.00005 (EU IESTI DK child)	**No** (1% of the TTC)
Parsnips	0.00030 (EU IESTI UK child) UK NESTI infant	**No** (6% of the TTC)	0.00043 (EU IESTI UK child) UK NESTI infant	**No** (9% of the TTC)
Barley grain	0.000050 IESTI UK 7-10 year old) UK NESTI 7-10 year old	**No** (1% of the TTC)	0.000081 IESTI UK 7-10 year old) UK NESTI 7-10 year old	**No** (2% of the TTC)
Oat grain	0.000010 (EU IESTI DE child)	**No** (0.2% of the TTC)	0.000015 (EU IESTI DE child)	**No** (0.3% of the TTC)
Oat grain	0.000031 (UK NESTI infant)	**No** (0.6% of the TTC)	0.000046 (UK NESTI infant)	**No** (1% of the TTC)
Wheat grain	0.000036 (EU IESTI UK 4-6 year old child) UK NESTI 4-6 year old child	**No** (0.7% of the TTC)	0.000052 (EU IESTI UK 4-6 year old child) UK NESTI 4-6 year old child	**No** (1% of the TTC)
Rye grain	0.000016 (EU IESTI UK infant) UK NESTI infant)	**No** (0.3% of the TTC)	0.000023 (EU IESTI UK infant) UK NESTI infant)	**No** (0.5% of the TTC)

$ As per the UK dietary risk assessment for residues of pydiflumetofen (section 2.7.9) a PF has not been applied to the residue in oilseed rape (the UK consumption values are based on RAC expression). The default PF applied in the PRIMo v3.1 acute assessment is similar to that derived from the processing studies for parent. ~~the HR for parent for Oilseeds represents an HR-P of 0.069 (HR of 0.04 and a PF applied of 1.67). This PF is an uncertain estimate for the metabolites as the PF was derived for parent only and because these estimations for metabolites assume the levels of metabolites and M:P ratios based on the ratios found in the plant and rotational crop metabolism studies, whereas~~ There is no processing information for the metabolites themselves, so the assessment wrt processing for the metabolites is uncertain. The ~~estimation is done to take account of possible~~

~~concentration over processing. These~~ exposure estimates are well below the acute TTC value (CCIII) of 0.005 mg/kg bw/day.

~~The TTC estimations of exposure and comparison to the TTC values have focussed on the Tier1/10 year use, soil exposure scenario (which is worst case compared to the Tier 2 /long term use scenario also considered in this residues assessment).~~ As the TTC ~~is~~ values are not exceeded by any of the acute or chronic estimates of exposure, these metabolites do not require inclusion in the residue definition. This is based upon the crops under consideration for the representative uses and the MRL application crops (carrots, parsnip, and parsley roots) ~~and all the rotational crops considered in this assessment~~. The available metabolism data are considered suitable to cover the (additional MRL assessment) uses on carrots, parsnips and parsley roots. Further reconsideration of the residue definition may be required for future uses of pydiflumetofen. However it is noted that the above consideration takes up only a maximum of 5% of the chronic TTC level and 15% of the acute TTC level. The estimated long term (chronic) and short term dietary (acute) intakes are considered to be well within the TTCs and a universal residue definition of parent pydiflumetofen only (for products of plant origin) is proposed ~~for the current time~~. Toxicological data for metabolites SYN545547 and SYN547891 are not a regulatory requirement at this time.

~~It is noted, that only parent pydiflumetofen was analysed for in the rotational crop field trials (see section 2.7.7). Some positive residues of pydiflumetofen were found (<0.01 to 0.05 mg/kg for crops destined for human consumption and up to 0.09 mg/kg in barley straw, however the N rate for the studies leading to these results are estimated to be 0.32 to 0.38N for 'Tier 1 10year use' and 0.44 to 0.53N for 'Tier 2 long term use'). It would not necessarily be expected that residues of the metabolites SYN545547 and SYN547891 would have been found in the trials that have been already conducted (see section 2.7.7), had they included these metabolites as additional analytes that were determined. However, these trials are clearly underdosed (0.3 to 0.5N) with regard to estimated soil exposures (taking account of the soil persistence and potential for accumulation of pydiflumetofen. It is questionable whether these metabolites (SYN545547 and SYN647891) might be found in rotational crops in studies at more appropriate higher dosing levels. For any further rotational crop trials generated, it would be appropriate to include these metabolites.~~

~~Considering the relative levels of SYN545547 and SYN547891 compared to parent in primary and rotational crop samples, and the outcome of the metabolite exposure assessment for SYN545547 and SYN547891 presented above (versus the TTC CCIII), considering residue in primary crops and rotational crops, these metabolites do not require inclusion in the residue definition for risk assessment for either primary crops or rotational crops at this time.~~

~~The current assessment includes the current primary crop representative uses (cereals and oilseed rape), the additional MRL assessment uses considered here (carrots, parsnips, and parsley roots) in the DAR (alongside the representative uses) and the impacted rotational crops. The available metabolism data are suitable to cover the (additional MRL assessment) uses on carrots, parsnips and parsley roots. As noted above, a universal residue definition of parent pydiflumetofen only (for products of plant origin) is proposed for the current time.~~

~~The current exposure assessment (versus the TTC) has already considered the scaled up residues in all the rotational crops (by applying the M:P ratios to the overall estimates of exposure relating to parent pydiflumetofen). Therefore, although it is not currently known whether metabolites could form (in low amounts) in rotational crops at more suitable dosing levels, the TTC exposure assessment (estimated intakes are well below the TTCs for CCIII) has concluded that toxicological data for metabolites SYN545547 and SYN547891 are not a regulatory requirement at this time.~~

For wider future crop uses, the ~~TTC~~ exposure estimation and comparison to the TTC values should be reconsidered to confirm that the metabolite exposures remain below the TTC CCIII levels, also to address the sufficiency of the toxicological data available. Such a future exposure assessment (versus the TTCs) could use the current data on plant M:P ratios in both primary (section 2.7.3) and rotational crops (2.7.7) (if determinable residues are anticipated in rotational crops), utilising the metabolism studies already generated.

Additionally it is considered that parent pydiflumetofen can be considered an adequate residue definition for risk assessment (RD-RA) and residue definition for enforcement (RD-Enf) ~~monitoring (and enforcement)~~ in honey. There is no indication of metabolites being significant enough for inclusion in the RD-RA for plants, so it is expected that only pydiflumetofen residues (parent) might transfer to honey from above ground plant parts. Furthermore, pydiflumetofen has been shown to be stable to hydrolysis (see section 2.7.6).

In summary, parent pydiflumetofen, is the only component proposed for both the enforcement and risk assessment residue definitions, in products of plant origin and also honey.

Livestock

The available livestock metabolism data are summarised in section 2.7.2 and written up in full in section B.7.7.2 (poultry- hens) and B.7.7.3 (ruminant-goat). The studies were suitably dosed with parent pydiflumetofen (phenyl and pyrazole labelled residues investigated).

Pydiflumetofen was more extensively metabolised in the goat and hen studies than in plants. Full details of the amounts of all the metabolites in poultry and goat are presented in the overview of metabolism tables presented below (Table 2.7.3.9 and Table 2.7.3.10).

The **main** metabolite components (any >10%TRR) in livestock (across different matrices) are summarised in Table 2.7.3.11.

Although %TRR of metabolites might be high, corresponding mg/kg amounts in matrices might be low (e.g. in poultry muscle, SYN508272 was found at 46.3% however this was only at a level of 0.01 mg eq./kg in the hen metabolism study). Please see overview of metabolism tables (see Table 2.7.3.9 (ruminants) and Table 2.7.3.10 (poultry)) for amounts, and where >10% represents ≥0.01 mg/kg or < 0.01 mg/kg, and also for further breakdown on components present at <10%TRR.

Table 2.7.3.9 Overview of metabolism in ruminant (goat)

	Animal	**Ruminants**									
	Number of animals	**1 per radiolabel**									
	mg/kg DM basis (nominal)	100									
	Number dosing days	7									
	Time of sacrifice after the final dose (hours)	11									
	Matrix	**Milk**	**Liver**	**Kidney**	**Muscle**	**Fat**	**Milk**	**Liver**	**Kidney**	**Muscle**	**Fat**
	14C labelling	[Phenyl-U-14C]-SYN545974					[Pyrazole-5-14C]-SYN545974				
	Plateau reached in eggs and milk (days)	2					5				
	TRR [mg/kg]	**0.122**	**6.984**	**1.73**	**0.102**	**0.221**	**0.132**	**8.827**	**2.341**	**0.138**	**0.279**
% TRR	Total extractable residues (% TRR)	92.3	50.4	83.4	86.0	98.8	93.9	47.4	90.0	94.3	97.6
	SYN545974 (Parent)	15.7	8.2	0.8	24.4	67.2	8.7	2.0	0.5	13.4	73.8
	2,4,6-TCP (as conjugate)	43.2 (42.2)	0.5 (0.5)	1.2 (1.2)	9.0 (6.1)	-	NA	NA	NA	NA	NA
	SYN547948 (as conjugate)	2.2	2.6 (0.9)	0.9 (ND)	3.8	5.3	0.7	1.9 (ND)	0.7 (ND)	1.1	3.3
	SYN547897 (as conjugate)	-	1.9 (ND)	2.9 (2.9)	1.8	-	-	3.0 (ND)	2.7 (1.9)	1.2	-
	SYN545547 (as conjugate)	-	3.4 (2.7)	7.4 (7.4)	-	-	-	1.8 (1.6)	ND (ND)	-	-
	SYN547891 (as conjugate)	-	1.4 (0.6)	-	-	-	-	0.4 (ND)	-	-	-
	SYN508272 (as conjugate)	NA	-	NA	NA	NA	11.0	-	1.5 (0.7)	17.7	1.0
	NOA449410 (as conjugate)	NA	NA	NA	NA	-	2.6	2.9 (1.7)	11.7 (9.1)	3.6	-
	SYN548263 (as conjugate)	NA	-	NA	NA	NA	14.2	-	16.6 (14.6)	4.9	4.3
	SYN548264 (as conjugate)	NA	-	NA	NA	-	28.7	-	0.8 (0.8)	0.6	-
	Hydroxy SYN547974	-	-	-	-	8.6	-	-	-	-	10.2
	Total identified (% TRR)	61.1	18.0	13.2	39.0	81.1	65.9	12.0	34.5	42.5	92.6
	Unassigned in pre-enzyme hydrolysis - organosoluble fractions	-	3.1[o]	3.9[s]	-	-	-	7.9[o]	5.5[s]	-	-
	Unassigned in post-enzyme hydrolysis - organosoluble fractions	-	10.0[p]	18.9[t]	-	-	-	10.5[p]	16.3[t]	-	-
	Post enzyme hydrolysis - aqueous soluble fractions	-	4.2[q]	15.0[u]	-	-	-	2.4[q]	6.4[u]	-	-
	Unassigned (chromatographed)	16.3[m]	7.0[r]	6.3[v]	39.7[x]	10.9[z1]	18.3[m]	6.5[r]	4.8[v]	36.4[x]	3.4[z1]
	Other Fractions (chromatographed)	-	-	-	-	-	-	-	-	-	-
	Total Characterized (%TRR)	16.3	24.3	44.1	39.7	10.9	18.3	27.3	33.0	36.4	3.4
	Other Fractions (not chromatographed)	6.3[n]	-	2.9[w]	3.0[y]	1.9[z2]	1.7[n]	-	1.2[w]	1.3[y]	2.5[z2]
	Not analysed fractions										
	Unresolved										
	Unextractable radioactive residues(% TRR)	7.7	49.7	16.6	14	1.1	6.1	52.6	9.2	5.7	2.4
	Acid/base hydrolysis										
	Enzymatic hydrolysis										
	Bound/PES(% TRR)										
	Accountability (% TRR)	100.0	100.0	100.0	100	100	100.0	100	100.0	100.0	100.0

Table Footnotes:

NA - Not applicable to that label

ND - not detectable

[a] Phenyl label comprising at least 27 discrete components, no single one of which >2.3% TRR (>0.009 mg/kg).Pyrazole label comprising at least 9 discrete components, no single one of which >2.3% TRR (>0.005 mg/kg).

[b] Phenyl label comprising at least 16 discrete components, no single one of which >1.6% TRR (>0.006 mg/kg).Pyrazole label comprising at least 8 discrete components, no single one of which >1.4% TRR (>0.003 mg/kg).

[c] Phenyl label comprising at least 8 discrete components, no single one of which >1.0%TRR (>0.004 mg/kg).Pyrazole label shown to consist of radioactivity located on the origin, characterised to be similar to that present in the liver debris.

[d] Phenyl label: consists of two fractions no individual one of which accounts for >6.7% TRR (>0.027mg/kg)

(although this particular fraction was not chromatographed, a corresponding fraction from the initial phenyl liver analysis was analysed (acetonitrile:water (1:1, v/v) fraction and shown to consist of radioactivity located on the origin, characterised to be similar to that present in the liver debris).

[g] Extractable residue fractions which were not analysed ([14C] residues too low for analysis). No single fraction comprised ≥ 4.3% TRR (≥0.005 mg/kg) in either radiolabelled experiment.

[h] Phenyl label comprising at least 5 discrete components, no single one of which >3.7% TRR (>0.004 mg/kg). Pyrazole label comprising at least 9 discrete components, no single one of which >6.4% TRR (>0.002 mg/kg).

[i] No single fraction comprised > 6.0% TRR (>0.006 mg/kg) in

[j] Phenyl label comprising at least 7 discrete components, no single one of which >12.3% TRR (>0.006 mg/kg). Pyrazole label comprising at least 3 discrete components, no single one of which >5.0% TRR (>0.003 mg/kg).

[k] Phenyl label comprising at least 4 discrete components, no single one of which >5.0% TRR (>0.001 mg/kg). Pyrazole label comprising at least 6 discrete components, no single one of which >6.0% TRR (>0.001 mg/kg).

[l] no single fraction comprised > 4.2% TRR (>0.001 mg/kg) in either radiolabelled experiment.

[m] Phenyl label comprising at least 7 discrete components, no single one of which >7.4% TRR (>0.009 mg/kg). Pyrazole label comprising at least 7 discrete components, no single one of which >7.1% TRR (>0.009 mg/kg).

[n] No single fraction comprised >3.5% TRR (>0.004 mg/kg) in either radiolabelled experiment.

[o] Phenyl label comprising at least 3 discrete components, no single one of which >2.1% TRR (>0.147 mg/kg). Pyrazole label comprising at least 14 discrete components, no single one of which >1.0% TRR (>0.085 mg/kg).

[p] Phenyl label comprising at least 12 discrete components, no single one of which >2.1% TRR (>0.147 mg/kg). Pyrazole label comprising at least 9 discrete components, no single one of which >2.2% TRR (>0.195 mg/kg).

[q] Phenyl label comprising at least 12 discrete components, no single one of which >0.9% TRR (>0.063 mg/kg). Pyrazole label comprising at least 14 discrete components, no single one of which >0.7% TRR (>0.062 mg/kg).

[r] Phenyl and pyrazole - radioactivity located on the origin

[s] Pyrazole label comprising at least 12 discrete components, no single one of which >0.8% TRR (>0.019 mg/kg).or chromatographed by 1D-TLC solvent system 4. Phenyl label only comprising at least two discrete components, no single one of which >1.0% TRR (>0.017 mg/kg).

[t] Phenyl label comprising at least 10 discrete components, no single one of which >5.6% TRR (>0.098 mg/kg). Pyrazole label comprising at least 11 discrete components, no single one of which >5.4% TRR (>0.126 mg/kg).

[u] Phenyl label analysed by 1D-TLC solvent system 4 comprising and at least 10 discrete components, no single one of which >5.0% TRR (>0.087 mg/kg). Pyrazole label analysed by 1D-TLC solvent system 4 comprising at least 12 discrete components, no single one of which >2.0% TRR (>0.047 mg/kg).

[v] Phenyl and pyrazole labels: radioactivity located on the origin. In both experiments the radioactivity located on the origin was characterised to be similar to that present in the debris.

[w] Extractable residues in 3 fractions (phenyl) and 2 fractions (pyrazole) that were produced during analysis and were individually too low for analysis. No single fraction comprised > 1.6% TRR (≥0.028 mg/kg) in either radiolabelled experiment.

[x] Phenyl label comprising at least 9 discrete components, no single one of which >7.4% TRR (>0.008 mg/kg). Pyrazole label comprising at least 23 discrete components, no single one of which >5.6% TRR (>0.008 mg/kg).

[y] No single fraction comprised >3.0% TRR (>0.003 mg/kg) in either radiolabelled experiment.

[z1] Phenyl label: comprising at least 4 discrete components, no single one of which >3.7% TRR (>0.008 mg/kg). Pyrazole label: comprising at least 2 discrete components, no single one of which >1.9% TRR (>0.005 mg/kg).

[z2] Phenyl label: No single fraction comprised >1.9% TRR (>0.004 mg/kg). Pyrazole label: No single fraction comprised >2.0% TRR (>0.006 mg/kg).

metabolites > 10 % TRR < 0.01 mg/kg

metabolites > 10 % TRR > 0.01 mg/kg

Table 2.7.3.9 Overview of metabolism in ruminant (goat) continued

	Animal	**Ruminants**									
	Number of animals	**1 per radiolabel**									
	mg/kg DM basis (nominal)	100									
	Number dosing days	7									
	Time of sacrifice after the final dose (hours)	11									
	Matrix	**Milk**	**Liver**	**Kidney**	**Muscle**	**Fat**	**Milk**	**Liver**	**Kidney**	**Muscle**	**Fat**
	14C labelling	[Phenyl-U-14C]-SYN545974					[Pyrazole-5-14C]-SYN545974				
	Plateau reached in eggs and milk (days)	2					5				
	TRR [mg/kg]	**0.122**	**6.984**	**1.73**	**0.102**	**0.221**	**0.132**	**8.827**	**2.341**	**0.138**	**0.279**
mg eq./kg	SYN545974 (Parent)	0.019	0.570	0.014	0.025	0.149	0.011	0.179	0.011	0.018	0.206
	2,4,6-TCP (as conjugate)	0.052 (0.051)	0.037 (0.037)	0.021 (0.021)	0.009 (0.006)	-	NA	NA	NA	NA	NA
	SYN547948 (as conjugate)	0.003	0.18 (0.064)	0.016 (ND)	0.004	0.012	0.001	0.170 (ND)	0.016 (ND)	0.002	0.009
	SYN547897 (as conjugate)	-	0.136 (ND)	0.050 (0.050)	0.002	-	-	0.268 (ND)	0.063 (0.045)	0.002	-
	SYN545547 (as conjugate)	-	0.239 (0.188)	0.128 (0.128)	-	-	-	0.160 (0.139)	ND (ND)	-	-
	SYN547891 (as conjugate)	-	0.1 (0.041)	-	-	-	-	0.038 (ND)	-	-	-
	SYN508272 (as conjugate)	NA	-	NA	NA	NA	0.014	-	0.036 (0.017)	0.024	0.003
	NOA449410 (as conjugate)	NA	NA	NA	NA	-	0.003	0.248 (0.146)	0.275 (0.214)	0.005	-
	SYN548263 (as conjugate)	NA	-	NA	NA	NA	0.019	-	0.389 (0.342)	0.007	0.012
	SYN548264 (as conjugate)	NA	-	NA	NA	NA	0.038	-	0.019 (0.019)	0.001	-
	Hydroxy SYN547974	-	-	-	-	0.019	-	-	-	-	0.028
	Total identified (mg/kg)	0.074	1.262	0.229	0.04	0.18	0.086	1.063	0.809	0.058	0.258
	Unassigned in pre-enzyme hydrolysis - organosoluble fractions	-	0.220[o]	0.068[s]	-	-	-	0.678[o]	0.128[s]	-	-
	Unassigned in post-enzyme hydrolysis - organosoluble fractions	-	0.696[p]	0.331[t]	-	-	-	0.925[p]	0.380[t]	-	-
	Post enzyme hydrolysis - aqueous soluble fractions	-	0.293[q]	0.260[u]	-	-	-	0.212[q]	0.150[u]	-	-
	Unassigned (chromatographed)	0.020[m]	0.489[r]	0.109[v]	0.042[x]	0.024[z1]	0.025[m]	0.574[r]	0.112[v]	0.052[x]	0.009[z1]
	Other Fractions (chromatographed)	-	-	-	-						
	Total Characterized (mg/kg)	0.02	1.698	0.768	0.042	0.024	0.025	2.389	0.77	0.052	0.009
	Other Fractions (not chromatographed)	0.008[n]	-	0.050[w]	0.003[y]	0.004[z2]	0.002[n]	-	0.028[w]	0.002[y]	0.007[z2]

See previous page for footnotes

Table 2.7.3.10 Overview of metabolism in poultry (hens) – please see above table on ruminants for the footnotes

	Animal	Poultry									
	Number of animals	6 per radiolabel									
	mg/kg DM basis (nominal)	30									
	Number dosing days	14									
	Time of sacrifice after the final dose (hours)	11									
	Matrix	egg white	egg yolk	muscle	fat	liver	egg white	egg yolk	muscle	fat	liver
	14C labelling	[Phenyl-U-14C]-SYN545974					[Pyrazole-5-14C]-SYN545974				
	Plateau reached in eggs and milk (days)	10					7				
	TRR [mg/kg]	**0.053**	**0.358**	**0.027**	**0.101**	**0.404**	**0.052**	**0.106**	**0.021**	**0.032**	**0.21**
% TRR	Total extractable residues (% TRR)	97.7	87.0	84.2	95.8	51.7	98.8	81.2	90.1	91.5	90.1
	SYN545974 (Parent)	46.5	3.0	8.7	16.6	5.3	26.6	11.0	4.7	30.6	0.5
	2,4,6-TCP (as conjugate)	14.5 (14.5)	67.8 (67.8)	48.4 (48.4)	29.3 (26.5)	-	NA	NA	NA	NA	-
	SYN547948 (as conjugate)	7.1	ND	3.4	3.0	0.7 (ND)	5.5	1.3	1.6	4.1	3.2 (ND)
	SYN547897 (as conjugate)	-	2.3	ND	1.7	2.4 (0.4)	-	6.7	1.1	2.6	0.9 (0.9)
	SYN545547 (as conjugate)	-	ND	-	-	1.2 (0.6)	-	3.9	-	-	3.3 (3.3)
	SYN547891 (as conjugate)	-	ND	-	-	0.2 (0.2)	-	2.5	-	-	ND (ND)
	SYN508272 (as conjugate)	NA	NA	NA	NA	NA	34.3	7.2 (2.6)	46.3	9.6	2.4 (2.4)
	NOA449410 (as conjugate)	NA	NA	-	NA	-	15.4	6.6 (0.8)	-	3.1	-
	SYN548263 (as conjugate)	-	-	-	-	-	-	-	-	-	-
	SYN548264 (as conjugate)	-	-	-	-	-	-	-	-	-	-
	Hydroxy SYN547974	-	-	-	-	-	-	-	-	-	-
	Total identified (% TRR)	68.1	73.1	60.5	50.6	9.8	81.8	39.2	53.7	50.0	10.3
	Unassigned in pre-enzyme hydrolysis - organosoluble fractions	-	NA	-	-	19.4[a]	-	18.7	-	-	11.3[a]
	Unassigned in post-enzyme hydrolysis - organosoluble fractions	-	NA	-	-	6.1[b]	-	6.8	-	-	6.0[b]
	Post enzyme hydrolysis - aqueous soluble fractions	-	-	-	-	4.1[c]	-	-	-	-	4.7[c]
	Unassigned (chromatographed)	24.6[j]	6.6[e]	14.3[k]	13.8[h]	-	10.0[j]	NA	21.3[k]	32.3[h]	-
	Other Fractions (chromatographed)	-	2.6[f]	-	-	-	-	NA	-	-	-
	Total Characterized (%TRR)	24.6	9.2	14.3	13.8	29.6	10.0	25.5	21.3	32.3	22.0
	Other Fractions (not chromatographed)	-	2.2[g]	2.4[l]	20.5[i]	7.4[d]	-	5.5[g]	7.0[l]	2.7[i]	8.6[d]
	Not analysed fractions										
	Unresolved										
	Unextractable radioactive residues(% TRR)	2.3	13.0	15.8	4.3	48.3	1.2	18.7	9.9	8.4	47.5
	Acid/base hydrolysis										
	Enzymatic hydrolysis										
	Bound/PES(% TRR)										
	Accountability (% TRR)	**100**	**100**	**100.0**	**100**	**100**	**100**	**100**	**100.0**	**100.0**	**100**

Table 2.7.3.10 Overview of metabolism in poultry (hens) continued – please see above table on ruminants for the footnotes

	Animal	**Poultry**									
	Number of animals	**6 per radiolabel**									
	mg/kg DM basis (nominal)	30									
	Number dosing days	14									
	Time of sacrifice after the final dose (hours)	11									
	Matrix	**egg white**	**egg yolk**	**muscle**	**fat**	**liver**	**egg white**	**egg yolk**	**muscle**	**fat**	**liver**
	14C labelling	[Phenyl-U-14C]-SYN545974					[Pyrazole-5-14C]-SYN545974				
	Plateau reached in eggs and milk (days)	10					7				
	TRR [mg/kg]	**0.053**	**0.358**	**0.027**	**0.101**	**0.404**	**0.052**	**0.106**	**0.021**	**0.032**	**0.21**
mg eq./kg	SYN545974 (Parent)	0.025	0.011	0.002	0.017	0.021	0.014	0.012	0.001	0.01	0.001
	2,4,6-TCP (as conjugate)	0.008 (0.008)	0.242 (0.242)	0.013 (0.013)	0.030 (0.027)	-	NA	NA	NA	NA	-
	SYN547948 (as conjugate)	0.004	ND	0.001	0.003	0.003 (ND)	0.003	0.001	<0.001	0.001	0.007 (ND)
	SYN547897 (as conjugate)	-	0.008	ND	0.002	0.009 (0.001	-	0.007	<0.001	0.001	0.002 (0.002)
	SYN545547 (as conjugate)	-	ND	-	-	0.005 (0.003)	-	0.004	-	-	0.007 (0.007)
	SYN547891 (as conjugate)	-	ND	-	-	0.001 (0.001)	-	0.003	-	-	ND (ND)
	SYN508272 (as conjugate)	NA	NA	NA	NA	NA	0.018	0.008 (0.003)	0.01	0.003	0.005 (0.005)
	NOA449410 (as conjugate)	NA	NA	-	NA	-	0.008	0.007 (0.001)	-	0.001	-
	SYN548263 (as conjugate)	-	-	-	-	-	-	-	-	-	-
	SYN548264 (as conjugate)	-	-	-	-	-	-	-	-	-	-
	Hydroxy SYN547974	-	-	-	-	-	-	-	-	-	-
	Total identified (mg/kg)	0.037	0.261	0.016	0.052	0.039	0.043	0.042	0.011	0.016	0.022
	Unassigned in pre-enzyme hydrolysis - organosoluble fractions	-	NA	-	-	0.078[a]	-	0.02	-	-	0.023[a]
	Unassigned in post-enzyme hydrolysis - organosoluble fractions	-	NA	-	-	0.023[b]	-	0.008	-	-	0.012[b]
	Post enzyme hydrolysis - aqueous soluble fractions	-	-	-	-	0.017[c]	-	-	-	-	0.01[c]
	Unassigned (chromatographed)	0.013[j]	0.024[e]	0.004[k]	0.015[h]	-	0.006[j]	NA	0.004[k]	0.012[h]	-
	Other Fractions (chromatographed)	-	0.009[f]	-	-	-	-	NA	-	-	-
	Total Characterized (mg/kg)	0.013	0.33	0.004	0.015	0.118	0.006	0.028	0.004	0.012	0.045
	Other Fractions (not chromatographed)	-	0.008[g]	0.001[l]	0.021[i]	0.03[d]	-	0.006[g]	0.002[l]	0.001[i]	0.017[d]

Table 2.7.3.11 Summary of main components in livestock.

Metabolite codes→	parent	2,4,6-TCP	SYN 548264	SYN 508272	SYN 548263	NOA 449410	Hydroxy SYN547974 (hydroxy pydiflumetofen)	SYN 547897*
Conjugated residues ? Free – F Conjugated -C (across all the matrices where found)		Almost all as sulphate conj	F+C	F+C	F+C	F+C	F	F+C
Poultry (73/80N ~~43/47N (Tier 1 10 year use)~~ ~~(51/55N Tier 2 long term use~~)								
Muscle		**X**		**X**				
Fat	**X**	**X**						
Liver								
Egg white	**X**	X		**X**		X		
Egg yolk	X	**X**						
Ruminant (55N ~~22N (Tier 1 10 year use)~~ ~~(28N Tier 2 long term use~~)								
Muscle	**X**			X				
Fat	**X**						X	
Liver								
Kidney					X	X		
Milk	X	**X**	**X**	X	X			

This comparative table only summarises **main metabolite** components (and parent pydiflumetofen).
X denotes 10-<20%TRR.
X (emboldened) represents ≥ 20%
*Although SYN547897 was found at <10%TRR in the metabolism studies, there were some concerns regarding the storage stability of this residue (see section 2.7.1 and 2.7.2) and this metabolite was sought and found in feeding studies in both ruminant liver and ruminant kidney.

The available livestock feeding data are summarised in section 2.7.5 and written up in full in section B.7.4.1 (poultry- hens) and B.7.4.2 (ruminant-cattle). The studies were suitably dosed with parent pydiflumetofen.

Parent and 2,4,6-TCP (free and conjugated) residues were sought in all matrices in the poultry and ruminant feeding studies. In ruminant milk, SYN548264 and SYN508272 were additionally sought. In ruminant liver and kidney SYN548263 and SYN547897 were additionally sought. This represents a good coverage of the metabolites that could be anticipated to be found (as guided by the findings in the livestock metabolism studies) and/or be a potentially toxicological relevant residue. Given the results for parent pydiflumetofen and 2,4,6-TCP in the feeding studies, it is considered that any of the metabolites not looked for in various matrices in the feeding studies would not have been found at determinable levels had they been sought after in these poultry and ruminant metabolism studies.

As can be seen from the above table on main components (Table 2.7.3.11), both parent and 2,4,6-TCP (free and conjugated) are the most prevalent residues when considering the range of the animal matrices.

Considering the residue definition for enforcement (animal products):

With reference to the above tables (Tables 2.7.3.9-2.7.3.11) parent and 2,4,6-TCP seem to be candidates for consideration for inclusion in the enforcement residue definition (RD-enf).

Parent was a main component in most animal matrices. Even in the metabolism studies, where in some matrices it was not present above 10%TRR in the metabolism study, it was still detected in every matrix in the animal metabolism study.

In the feeding studies, the level of finding of pydiflumetofen depended on the dose level of the study (see section 2.7.5). It was also the case in the feeding studies that 2,4,6-TCP was only found at certain doses. At the lowest dose in the hen feeding studies (3.5N ~~2.1N, Tier 1 10 year use~~), pydiflumetofen was not found (<0.01 mg/kg) and 2,4,6-TCP was only found in eggs at a low level. At the higher dosing rates (mid and highest dose) in hens (11.0N and 35.4N ~~6.6N and 21N, Tier 1 10 year use~~) pydiflumetofen was only found in eggs, and 2,4,6-TCP was only found in eggs and kidney. At the lowest dose in the cattle feeding studies (4.1N ~~1.9N, Tier 1 10 year use~~), pydiflumetofen was only found in liver and fat and 2,4,6-TCP was only found in kidney. At the higher dosing rates in cattle (11.1N and 44.1N ~~5.3N and 21N, Tier 1 10 year use~~) pydiflumetofen was found (mid dose, in liver and fat; highest dose, in milk, liver, kidney and fat) only found in eggs, and 2,4,6-TCP (mid and highest dose) was found only in milk, liver and kidney.

It is noted that 2,4,6-TCP is not specific to pydiflumetofen, and could be found in animal products from other sources. Another aspect to consider is that the metabolism data shows that when found, the residues of 2,4,6-TCP are almost exclusively found as the (sulphate) conjugated form. In the feeding studies, the methods of analysis used an enzyme hydrolysis step to release the residues as deconjugated 2,4,6-TCP for analysis. It is not ideal to include conjugated residues in the residue definition applicable to enforcement and residue surveillance monitoring (RD-Enf).

Since parent represents a suitable marker compound, it is proposed that the enforcement residue definition should be parent pydiflumetofen only, and that conversion factors should be derived to be able to convert the level of residue based on RD-Enf to RD-RA.

Considering the residue definition for risk assessment (animal products):

In terms of the metabolites presented above in Table 2.7.3.11, the following toxicological information has been provided (see section 2.6.9):

Metabolite	Whether found in rat metabolism	Reference value/covered by parent(?)	Tox. relevant
2,4,6-TCP	Major in rat	Less toxic than parent; can be regarded as covered by parent Not genotoxic. Specific ADI = 0.4 mg/kg bw/d Specific ARfD = 1 mg/kg bw.	As less toxic than parent, the parent reference values should be used in the risk assessment
SYN548264	Found in rat metabolism but minor metabolite (<10%)	Not covered by parent. Not genotoxic, hence TTC CCIII values (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment	?
SYN508272	Major in rat	Not genotoxic, Data indicates more toxic than parent. Hence, specific ADI = 0.04 mg/kg bw/d set even though can be considered covered by parent (major rat metabolite) Could be included in RD-RA with parent using RPF (relative potency factor) of 2.25	See discussion below (on exposure/prevalence)

Metabolite	Whether found in rat metabolism	Reference value/covered by parent(?)	Tox. relevant
SYN548263	Found in rat metabolism but at <10% AD. Precursor of SYN508272 found at 14.8% TRA in blood	Major rat metabolite (as a precursor of a major rat metabolite) Covered by parent. Hence, parent reference values should be used in the risk assessment	See discussion below (on exposure/prevalence)
NOA449410	No, not found in rat	Less toxic than parent; Specific ADI = 0.25 mg/kg bw/d set at EU level, but parent reference values may be more appropriate	Regarded as less toxic than parent (see discussion below on exposure/prevalence)
Hydroxy SYN547974	Found in rat metabolism but minor metabolite (<10%)	Not genotoxic, hence TTC CCIII values (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment	?
SYN547897	Found in rat metabolism but minor metabolite (<10%)	Not genotoxic, hence TTC CCIII values (1.5 and 5 µg/kg bw/d) could be used in the dietary risk assessment	?

Based on prevalence, pydiflumetofen and 2,4,6-TCP (conjugated and free residues) should be included for dietary risk assessment. Although 2,4,6-TCP is less toxic than parent, the toxicological advice is that it can be included with parent in the RD-RA to be considered from a risk assessment perspective.

In poultry (hen) feeding studies, only residues of pydiflumetofen and 2,4,6-TCP were sought. However given that each of the doses in the feeding studies represents an exaggerated rate (the lowest dose represents 3.5N ~~2.1N Tier 1 10 year use, and 2.5N Tier 2 long term use~~), and residues of either pydiflumetofen and 2,4,6-TCP would not be expected under the anticipated use of pydiflumetofen (based on the uses assessed here), it is not expected that any residues of other metabolites would be found in poultry.

Taking each of the other metabolites found in ruminants in turn:

SYN508272 (more toxic than parent (RPF, relative potency factor, of 2.25)) and SYN548264 (uncertain toxicological relevance, would need to be assessed as CCIII) were sought in milk in the cattle feeding study. SYN508272 was not found at all (<0.01 mg/kg) even at the highest feeding dose rate (regarded as 44.1N ~~21N (Tier 1 10 year use) or 26N (Tier 2 long term use~~)). SYN548264 was only detected (a single detection) at this highest feeding dose at the low level of 0.01 mg/kg, only after 28 days of daily dosing. Both these metabolites do not need to be included in the residue definition for dietary risk, based on not found/very low prevalence.

Hydroxy-pydiflumetofen – (uncertain toxicological relevance, would need to be assessed as CCIII). This was only found in fat and not other matrcies; in fat at 8.6% TRR (phenyl) and 10.2%TRR (pyrazole). It was not found in other matrices. Pydiflumetofen was found in fat at 67.2% TRR (phenyl) and 73.8%TRR (pyrazole). In the feeding study, the range of residues of parent pydiflumetofen found in fat samples was <0.01 to 0.02 mg/kg at the lowest feeding study level (4.1N ~~1.9N Tier 1 10 year use, and 2.4N Tier 2 long term use~~). Given the much lower amounts of the Hydroxy-pydiflumetofen (compared to parent pydiflumetofen), there is not a need to consider inclusion of this hydroxy metabolite of pydiflumetofen in the residue definition for dietary risk, based on it not being expected to be found.

SYN548263 and SYN547897
Both of these metabolites were sought and found in bovine liver and kidney in the feeding study(ies). Due to some concerns with storage stability of residues of SYN547897, the data from the feeding study that was analysed very quickly was used to consider this results of this analyte.

The metabolism study did not determine SYN548263 in liver. This was confirmed in the cattle feeding study where at all doses SYN548263 was sought and the finding was <0.01 mg/kg (all dosing levels).

The relative concentrations of these metabolites in sheep kidney (compared to parent pydiflumetofen and 2,4,6-TCP) are expressed in Table 2.7.3.12 below. The Excel dietary burden calculator was used to predict the expected concentrations at the anticipated exposure levels. This was undertaken, since the toxicological advice was to consider metabolite SYN547897 by conducting a 'screening' exposure assessment versus the TTC (CCIII).

Table 2.3.7.12 Comparative residue levels (mg/kg) estimated in sheep kidney (where the highest kidney residues are anticipated) at the anticipated exposure levels ~~– (Tier 1- 10 year use (fate) scenario)~~

Mg/kg levels expressed as parent	Parent pydiflumetofen	2,4,6-TCP	SYN548263	SYN547897
STMR	<0.01	<0.022 ~~0.009~~	<0.015 ~~0.006~~	0.0096 ~~0.031~~ [A]
HR	<0.01	<0.022 ~~0.011~~	<0.015 ~~0.008~~	0.021 ~~0.045~~ [A]

[A]When expressed on a metabolite equivalent basis, the residue levels for SYN547897 are STMR 0.01 ~~0.032~~ mg/kg and HR 0.022 ~~0.047~~ mg/kg. These metabolite equivalent mg/kg values have fed into calculation of the exposure estimation versus the TTC (CCIII) below.

In kidney, when comparing the cow feeding study SYN548263 levels at the middle dose (where determinable residues were found, 11N) the levels seem to be roughly an 8th ~~5th~~ of the levels of SYN547897, but broadly similar to the level of 2,4,6-TCP in kidney (a little bit lower). In the cow feeding study at the lowest dose (4.1N) residues of SYN548263 in kidney were <LOQ (<0.01 mg/kg) and residues of SYN547897 were found at 0.06 to 0.09 mg/kg. In the ruminant metabolism study the relative findings were: parent and 2,4,6-TCP each around 1% in kidney, and SYN 548263 at 16.6% in kidney (14.6% as conjugate). SYN 547897 was only found in the metabolism study at around 3%, however, there might have been some degradation due to stability issues in this metabolism study.

SYN548263. It is proposed, on a precautionary basis, to include this in the RD-RA for ~~ruminant/~~mammalian kidney only. For kidney, this is proposed based on potential prevalence, also to enable the residue definition for risk assessment to be suitable for future animal dietary burden exposures, since the toxicological advice was to apply the toxicological reference values for parent to the assessment of this metabolite. In the metabolism study, in the ruminant kidney, this metabolite was mostly found in the conjugated form. In the feeding study the metabolite was deconjugated (enzyme hydrolysis step) prior to analysis. Therefore, it should be included in the residue definition (for ~~ruminant/~~mammalian kidney) covering both its free and conjugated form.

SYN547897- screening exposure assessment versus the TTC CCIII.

Using the Excel dietary burden calculator, the following levels of metabolite SYN547897 have been estimated (Table 2.3.7.13). These are residues expressed on a metabolite equivalent basis. The levels found in various animals (kidney) (emboldened value was used in the UK model) were used to screen in the dietary intake calculation of metabolite SYN547897 in foods.

Table 2.3.7.13 Residue levels (mg/kg metabolite equivalents) of SYN547897 estimated in liver and kidney (at the anticipate exposure levels ~~– (Tier 1- 10 year use (fate) scenario)~~.

	Bovine liver	Bovine kidney	Sheep liver	Sheep kidney	Pig liver	Pig kidney
STMR	0.006 ~~0.022~~	0.007 ~~0.028~~	**0.008 ~~0.025~~**	**0.01 ~~0.032~~**	0.002 ~~<0.01~~	0.002 ~~0.011~~
HR	0.01 ~~0.030~~	0.013 ~~0.038~~	**0.017 ~~0.036~~**	**0.022 ~~0.047~~**	0.002 ~~0.011~~	0.003 ~~0.014~~

Chronic exposure assessment (SYN547897):

Based on these commodity inputs (STMR sheep liver and sheep kidney), the highest UK total chronic dietary intake (toddler critical consumer - UK NEDI model) of SNY547897 was estimated as 0.000033 mg/kg bw/day, well below (2% of) the TTC (CCIII) of 0.0015 mg/kg bw/day).

Based on these commodity inputs (STMRs liver and kidney, various species results used), the highest EU PRIMo v3.1 total chronic dietary intake of SNY547897 was estimated as 0.0000015 mg/kg bw/day (critical consumer Irish adult), well below (0.1% of) the TTC (CCIII) of 0.0015 mg/kg bw/day).

Acute Exposure assessment (SYN547897):

In PRIMo v3.1, the highest acute exposure results (critical consumers) were represented by UK consumers:

Liver- Critical consumer acute = 0.00008 mg/kg bw/day (liver- UK infant) 2% of the TTC CCIII (acute) value of 0.005 mg/kg bw/day

Kidney - Critical consumer acute = 0.00005 mg/kg bw/day (kidney-UK toddler) 1% of the TTC CCIII (acute) value of 0.005 mg/kg bw/day

The UK NESTI model estimated these inputs (slightly higher) as:

Highest UK NESTI (Infant critical) for liver 2.7% of the TTC CCIII (acute) value of 0.005 mg/kg bw/day
Highest UK NESTI (Toddler critical) for kidney 1.7% of the TTC CCIII (acute) value of 0.005 mg/kg bw/day

The estimation of exposure of SYN547897 is animal products, indicates that these estimates are all below the respective TTC (chronic and acute vales for CCIII) levels, and it is not necessary to include this metabolite in the residue definition for risk assessment at this time, based on the uses and exposure ~~scenarios (Tier 1 10 year use and Tier 2 long term use)~~ evaluated in this assessment.

NOA449410. This component was not analysed in feeding studies. In the goat metabolism it was only above 10% in ruminant kidney (11.7% TRR, mostly as the conjugated form (9.1%)). In comparison, SYN548263 was found in the metabolism study at 16.6% in kidney (14.6% as conjugate). See Table 2.3.7.12 where it is indicated that SYN548263, if found in kidney, would only be found at very low mg/kg levels (<0.015 mg/kg (mg parent equivalents/kg) and <0.01 metabolite equivelents/kg) in Table 2.3.7.12 ~~considering the Tier 1 10 year use scenario~~). The toxicological advice for NOA449410 was that it is less toxic than parent (specific ADI = 0.25 mg/kg bw/d set at EU level, but parent reference values may be more appropriate). Based on likely low prevalence and that it is of lower toxicity than parent, it is not considered that NOA449410 needs to be further assessed or included in the residue definition for risk assessment.

In summary (livestock), parent is a fat-soluble residue in terms of livestock residues.

Parent pydiflumetofen, is the only component proposed for the enforcement residue definitions, in products of animal origin.

Due to the formation of metabolites in livestock, the following represent the proposed residue definitions for risk assessment: parent pydiflumetofen and 2,4-6, TCP (conjugated and free) expressed as parent. For ~~ruminant/~~mammalian kidney, SYN548263 (free and conjugated) – expressed as parent is additionally included.

Considering that differential metabolism of the pydiflumetofen isomers has not been investigated in livestock or rats, on a precautionary basis an additional assessment factor (of x 2 for the risk assessment) is proposed (applicable to animal product residues only).

Conclusions: Proposals for residue definition

Residue definition for dietary risk assessment (RD-RA) Food of plant origin:

Plants: Pydiflumetofen (sum of isomers)

This proposed residue definition is also suitable for honey.

Conversion factors (between RD-Enf and RD-RA) are not needed for plants; an assessment factor for plants (in consideration of isomer composition is not needed for plants (see section 2.12.5)).

Residue definition for dietary risk assessment (RD-RA) Food of animal origin:

Products of animal origin, except ~~ruminant/~~mammalian kidney: Sum of Pydiflumetofen (sum of isomers) and 2,4,6-trichlorophenol (free and conjugated) expressed as pydiflumetofen.

~~Ruminant/~~mammalian kidney: Sum of Pydiflumetofen (sum of isomers), 2,4,6-trichlorophenol (free and conjugated) and SYN548263 (free and conjugated), expressed as pydiflumetofen.

To bridge between the RD-Enf and RD-RA the following conversion factors are proposed:
All commodities except ~~ruminant/~~mammalian kidney CF= x 3.16 ~~(for both Tier 1 - 10 year use and Tier 2 - long term use)~~
~~Ruminant/~~mammalian kidney CF= x 4.7 ~~(for both Tier 1 - 10 year use and Tier 2 - long term use)~~.

On a precautionary basis, an additional assessment factor of x 2 to apply to the level of animal product residues in the consumer risk assessment is desirable. This is intended to account for possible differential metabolism of the isomers of pydiflumetofen (which is a racemic mixture), since no investigations into the enantiomeric composition of the residues took place in any of the livestock studies. (see section 2.12.5).

Where the methods of analysis converts the livestock product conjugated residues to their free counterparts and the analytes are determined in levels expressed as the free metabolites, the sum of residues, expressed as parent pydiflumetofen, can be calculated as follows, according to the following molecular weights: pydiflumetofen 426.7 g/mol; 2,4,6-trichlorophenol 197.45 g/mol (molecular weight adjustment factor of **x 2.161** (426.7/197.45)); SYN548263 277.2 g/mol (molecular weight adjustment factor of **x 1.539** (426.7/277.2)).

Residue definition for enforcement/monitoring (food of plant and animal origin):

~~Residue definition for risk assessment:~~ pydiflumetofen (sum of isomers)

Fat-soluble

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

The representative uses of pydiflumetofen in GB are on cereal crops (wheat, durum wheat, barley, rye, triticale, oat and spelt) and oilseed rape. The representative formulation A21857B is an emulsifiable concentrate (EC) containing 62.5 g/L of the active substance.

MRL work is being conducted in parallel with the new active substance review. As part of this work, a proposed GAP on carrots and associated root crops is being considered as a future GB use. The intended GAPs for carrots and associated root crops are for the formulation A19649H (Suspension Concentrate (SC) formulation containing 200 g/L pydiflumetofen).

The proposed GAPs are shown in Table 2.7.4.1. The critical GAPs (cGAPs) have been identified and are highlighted in bold.

Table 2.7.4.1 Requested GAPs for GB uses

Crop	Outdoor /protected	Growth stage		Number of applications	Application rate (g a.s./ha)	Water volume (L/ha)	PHI (days)
Representative Uses							
Spring and winter barley	Outdoor	BBCH 30-59 (or 41-59)	Beginning of stem elongation to end of heading. (Or early boot stage to end of heading	1	166	100-300	N/A
Spring and winter barley and oat	**Outdoor**	**BBCH 55-65**	**Middle of heading to full flowering**	**1**	**200**	**100-300**	**N/A**
Spring and winter wheat, durum wheat, spelt, rye and triticale	Outdoor	BBCH 30-59 (or 41-69)	Beginning of stem elongation to end of heading. (Or early boot stage to end of flowering.	1	166	100-300	N/A
Spring and winter wheat, durum wheat, spelt, rye and triticale	**Outdoor**	**BBCH 61-69**	**Beginning of flowering to end of flowering.**	**1**	**200**	**100-300**	**N/A**
Spring and winter oilseed rape (OSR)[(a)]	**Outdoor**	**BBCH 57-69**	**Secondary inflorescences to end of flowering.**	**1**	**200**	**100-300**	**N/A**
MRL Application							
Carrot, parsnip	**Outdoor**	**BBCH 14-49**	**Fourth true leaf unfolded to expansion complete.**	**2 (14-day interval)**	**70**	**300-1000**	**14**
Parsley root	**Outdoor**	**BBCH 21-49**	**After nine or more true leaves unfolded to expansion complete.**	**2 (14-day interval)**	**70**	**200-600**	**14**

N/A – not applicable (PHI is covered by the time remaining between application and harvest).
(a) One application every 3 years.

Barley and oat

The requested GAPs for winter and spring barley and oat are presented in Table 2.7.4.1. Two GAPs have been proposed for winter and spring barley and oats. The cGAP for spring and winter barley and oats consists of one spray application at a rate of 1 x 200 g a.s./ha when the crop has reached the growth stage BBCH 55-65. The cGAP is highlighted in bold.

Residue trial data for barley have been submitted in support of these GAPs. The trials were performed using the representative formulation A21857B.

Barley and oat are major crops. A minimum of eight residue trials that reflect the agronomic and climatic conditions in the UK are required. The applicant has submitted 8 trials on barley that are relevant to the UK. According to SANCO 7525/IV/95 rev 10.3 (June 2017), it is possible to extrapolate residue data from barley (0500010) to oat (0500050), (allowed for applications after the edible part has formed).

The submitted dossier also includes residue trials data from southern Europe. These trials were not evaluated as they do not reflect the agronomic and climatic conditions of the UK and no additional information was provided to support the use of these trials.

Results from trials relevant to the cGAP have been summarised in Table 2.7.4.2. These trials were performed using an application rate of 1 x 200 g a.s./ha applied at BBCH 65.

Residues in barley grain at normal commercial harvest were in the range 0.06 – 0.32 mg/kg. Residues in barley straw at normal commercial harvest (NCH) were in the range 0.27 – 2.72 mg/kg. Residues above the LOQ of 0.01 mg/kg were not found in any control samples of barley fractions grain and straw. Positive residues were observed in samples of whole plant up to 42 days after application. However, given the proposed GAP is a non-forage use, residues in these matrices are not relevant for MRL setting, the animal dietary burden or the consumer risk assessment. On this basis, positive residues in barley whole plant have not been considered further.

The residues in barley grain observed here were typically higher than the pydiflumetofen residues in wheat grain observed in the below summarised trials for the same application rate and timings.

Table 2.7.4.2 Summary of supporting field trials data for barley

Crop	Analyte	Range	STMR (mg/kg)	HR (mg/kg)	MRL (OECD Calculator) (mg/kg) Based on primary crop application only
Barley grain (extrapolated to oat grain)	**RD-RA: pydiflumetofen**	0.06, 2 x 0.08, 2 x 0.10, 0.12, 0.13 0.32	0.1	0.32	-
	RD-Enf: pydiflumetofen	0.06, 2 x 0.08, 2 x 0.10, 0.12, 0.13 0.32	0.1	0.32	0.5
Barley straw (extrapolated to oat straw)	**RD-RA: pydiflumetofen**	0.27, 0.57, 1.13, 1.19, 1.20, 1.27, 1.85, 2.72	1.195	2.72	-
	RD-Enf: pydiflumetofen	0.27, 0.57, 1.13, 1.19, 1.20, 1.27, 1.85, 2.72	1.195	2.72	MRLs not currently set for animal feed items

The samples were analysed for residues of pydiflumetofen using LC-MS/MS method GRM061.03A, quantifying the analyte with a limit of quantification (LOQ) of 0.01 mg/kg. Method validation data are available for cereal grain, wheat straw and cereal forage, please refer to Volume 3 CA, B.5). There are sufficient method validation data to meet the requirements for a reduced validation dataset for barley matrices. Therefore, the method is considered satisfactorily validated for barley matrices in accordance with SANCO 3029/99 rev. 4. Extraction efficiency was satisfactorily addressed for the method.

Wheat and Rye

The requested GAPs for winter and spring wheat, durum wheat, spelt, triticale and rye are presented in Table 2.7.4.1. Two GAPs have been proposed for winter and spring wheat, durum wheat, spelt, triticale and rye. The cGAP consists of one spray application at a rate of 1 x 200 g a.s./ha when the crop has reached the growth stage BBCH 61-69. The cGAP is highlighted in bold.

Residue trial data for wheat have been submitted in support of these GAPs. Eight trials were performed using the representative formulation A21857B. Four trials were performed using formulation A17573A, an EC formulation containing 100 g a.s./L. The differences in the concentration of the active substance in the formulations are not considered to have any impact on the results from the residue trials. This is because the achieved application rate is comparable with the proposed GAP and the difference in formulation is not expected to influence the results at the proposed application timing.

Wheat and rye are major crops. A minimum of eight residue trials that reflect the agronomic and climatic conditions in the UK are required. The applicant has submitted 12 trials on wheat that are relevant to the UK. According to SANCO 7525/IV/95 rev 10.3 (June 2017), it is possible to extrapolate residue data from wheat (0500090) to rye (0500070), (allowed for applications after the edible part has formed). Durum wheat, spelt and triticale are Part 1B commodities on the GB MRL Statutory Register, for which the same MRL applies as wheat (Part 1A commodity). Therefore, these crops are also supported by the submitted residue trials on wheat.

The submitted dossier also includes eight residue trials data from southern Europe. These trials were not evaluated as they do not reflect the agronomic and climatic conditions of the UK and no additional information was provided to support the use of these trials.

Results from trials relevant to the cGAP have been summarised in Table 2.7.4.3. These trials were performed using an application rate of 1 x 200 g a.s/ha applied at BBCH 67-69.

Residues in wheat grain at normal commercial harvest were in the range <0.01 – 0.05 mg/kg. Residues in wheat straw at NCH were in the range 0.28 – 4.0 mg/kg. Residues above the LOQ of 0.01 mg/kg were found in two control samples: one in wheat grain and one in wheat straw at 42 days after last application. Residues were detected at the limit of quantification level of 0.01 mg/kg. No explanation is provided for the origin of pydiflumetofen in these two samples or for how contamination may have occurred. However, the contamination of these control samples is not considered detrimental to the results as no residues were found in any of the other control samples(>LOQ), including control grain or straw samples at NCH. Positive residues were observed in samples of whole plant up to 42 days after application. However, given the proposed GAP is a non-forage use, residues in these matrices are not relevant for MRL setting, the animal dietary burden or the consumer risk assessment. On this basis, positive residues in wheat whole plant have not been considered further.

Table 2.7.4.3 Summary of supporting field trials data for wheat

Crop	Analyte	Range	STMR (mg/kg)	HR (mg/kg)	MRL (OECD Calculator) (mg/kg) Based on primary crop application only
Wheat grain (extrapolated to rye grain)	**RD-RA: pydiflumetofen**	2 x <0.01, 0.01, 3 x 0.02, 3 x 0.03, 2 x 0.04, 0.05	0.025	0.05	-
	RD-Enf: pydiflumetofen	2 x <0.01, 0.01, 3 x 0.02, 3 x 0.03, 2 x 0.04, 0.05	0.025	0.05	0.08
Wheat straw (extrapolated to rye straw)	**RD-RA: pydiflumetofen**	0.28, 0.40, 0.41, 0.84, 0.86, 0.88, 0.94, 1.00, 2.20, 2.39, 3.00, 4.00	0.91	4.0	-
	RD-Enf: pydiflumetofen	0.28, 0.40, 0.41, 0.84, 0.86, 0.88, 0.94, 1.00, 2.20, 2.39, 3.00, 4.00	0.91	4.0	MRLs not currently set for animal feed items

The samples were analysed for residues of pydiflumetofen using LC-MS/MS method GRM061.03A, quantifying the analyte with a limit of quantification (LOQ) of 0.01 mg/kg. Method validation data are available for cereal grain, wheat straw and cereal forage matrices, please refer to Volume 3 CA, B.5. The method is fully validated in accordance with SANCO 3029/99 rev. 4. Extraction efficiency was satisfactorily addressed for the method.

Oilseed rape

The requested GAP for oilseed rape is presented in Table 2.7.4.1. The cGAP consists of one spray application at a rate of 1 x 200 g a.s./ha when the crop has reached the growth stage BBCH 57-69. It is noted that the cGAP for oilseed rape is for one application every three years.

Residue trial data for oilseed rape have been submitted in support of this GAPs. The trials were performed using formulation A19649B, an SC formulation containing 200 g a.s./L. The representative formulation is A21857B, an EC formulation. In accordance with SANCO 7525/VI/95 Rev. 10.3, *'experience shows that EC, WP, WG, and SC formulations usually produce comparable residues (especially if the last application is more than seven days prior to harvest)'*. The proposed GAPs result in an interval between application and harvest that is >7 days. Therefore, it is considered that residue trials conducted with SC and EC formulations are likely to produce comparable residue levels.

Oilseed rape is a major crop. A minimum of eight residue trials that reflect the agronomic and climatic conditions in the UK are required. The applicant has submitted 8 trials on oilseed rape relevant to GB.

The submitted dossier also includes eight residue trials from southern Europe. These trials were not evaluated as they do not reflect the agronomic and climatic conditions of the UK and no additional information was provided to support the use of these trials.

Results from trials relevant to the cGAP have been summarised in Table 2.7.4.4. These trials were performed using an application rate of 1 x 200 g a.s/ha applied at approximately BBCH 69.

Residues in oilseed rape seed at NCH were in the range <0.01 – 0.04 mg/kg. Residues above the LOQ of 0.01 mg/kg were not found in any control samples. Positive residues were observed in samples of whole plant up to 42 days after application. However, given the proposed GAP is a non-forage use, residues in this matrix are not relevant for MRL setting, the animal dietary burden or the consumer risk assessment. On this basis, positive residues in oilseed rape whole plant have not been considered further, although these data are briefly summarised in the section on residues in honey (see section 2.7.8).

Table 2.7.4.4 Summary of supporting field trials data for oilseed rape

Crop	Analyte	Range	STMR (mg/kg)	HR (mg/kg)	MRL (OECD Calculator) (mg/kg) Based on primary crop application only
Oilseed rape (seed)	**RD-RA: pydiflumetofen**	3 x <0.01, 2 x 0.01, 0.02, 0.03, 0.04	0.01	0.04	-
	RD-Enf: pydiflumetofen	3 x <0.01, 2 x 0.01, 0.02, 0.03, 0.04	0.01	0.04	0.07

The samples were analysed for residues of pydiflumetofen using LC-MS/MS method GRM061.03A, quantifying the analyte with a limit of quantification (LOQ) of 0.01 mg/kg. Method validation data are available for oilseed rape (seeds), please refer to Volume 3 CA, B.5. The method is fully validated for oilseed rape seed in accordance with SANCO 3029/99 rev. 4. Extraction efficiency was satisfactorily addressed for the method.

Carrot

MRL work is being conducted in parallel with the new active substance review for pydiflumetofen. As part of this MRL work, a proposed GAP on root crops (carrot, parsley root and parsnip) is being considered as a future GB use. It should be made clear that this proposal for root crops is distinct from the representative uses for pydiflumetofen in GB (cereals and OSR).

The requested GAPs for carrots, parsley roots and parsnips are presented in Table 2.7.4.1. The cGAP consists of two spray applications to root crops at a rate of 2 x 70 g a.s./ha with a 14-day application interval at BBCH 14-49, with a 14-day PHI.

Residue trial data for carrots have been submitted in support of these GAPs. The residue trials were conducted with the formulation A19649B, whereas the intended GAP specifies formulation A19649H. Both formulations are SC formulations containing 200 g/L pydiflumetofen and therefore it is considered that A19649B and A19649H are likely to produce comparable residue levels.

Carrot is a major crop. A minimum of eight residue trials that reflect the agronomic and climatic conditions in the UK are required. The applicant has submitted 8 trials on carrots relevant to the UK. According to SANCO 7525/VI/95 rev. 10.3 (June 2017), it is possible to extrapolate residue data from carrot (213020) to parsnip (213060) and parsley root (213070) for treatments made before and after the formation of the edible portion of the plant. Therefore, it is acceptable to extrapolate carrot residues data to support the proposed GAPs for parsnip and parsley root.

The submitted dossier also includes eight residue trials data from southern Europe. These trials were not evaluated as they do not reflect the agronomic and climatic conditions of the UK and no additional information was provided to support the use of these trials.

Results from trials relevant to the cGAP have been summarised in Table 2.7.4.5. These trials were performed using an application rate of 2 x 70 g a.s./ha (13-14-day application interval), with the final application being made at BBCH 48-49. Residues were determined after a 14-day PHI.

Residues in carrot root at NCH were in the range <0.01 – 0.04 mg/kg. Residues above the LOQ of 0.01 mg/kg were not found in any control samples.

Table 2.7.4.5 Summary of supporting field trials data for carrot

Crop	Analyte	Range	STMR (mg/kg)	HR (mg/kg)	MRL (OECD Calculator) (mg/kg) Based on primary crop application only
Carrot (root) (extrapolated to parsley root and parsnip)	**RD-RA: pydiflumetofen**	<0.01, 3 x 0.02, 2 x 0.03, 2 x 0.04	0.025	0.04	-
	RD-Enf: pydiflumetofen	<0.01, 3 x 0.02, 2 x 0.03, 2 x 0.04	0.025	0.04	**0.08**

The samples were analysed for residues of pydiflumetofen using LC-MS/MS method GRM061.03A, quantifying the analyte with a limit of quantification (LOQ) of 0.01 mg/kg. Method validation data are available for the comparable matrix potato tuber, please refer to Volume 3 CA, B.5. There are sufficient method validation data to meet the requirements for a reduced validation dataset for carrot roots. Therefore, the method is considered satisfactorily validated for carrot roots in accordance with SANCO 3029/99 rev. 4. Extraction efficiency was satisfactorily addressed for the method in carrots.

In this section (2.7.4), summaries of the residues arising from primary crop use have been made.

Please also refer to the overall 'combined residues' summary tables at the end of section 2.7.7 (which brings together the residue contributions (summed) from both primary and rotational crops. See section 2.7.7 Table 2.7.7.5. ~~18 (overview table of combined residues, Tier 1 – 10 year use scenario) and table 2.7.7.19 (overview table of combined residues, Tier 2 – long term use.~~

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

Animal Dietary burden

The median and maximum dietary burden calculation has been performed according to the approach presented in the OECD Guidance document on residues in livestock (series on pesticides No 73, for a total of 9 animal species). All feed items which might be treated with the active substance under evaluation have been considered (Spring and winter barley, spring and winter oats, spring and winter wheat, durum wheat, spelt, rye, triticale and winter and spring oilseed rape and carrot, parsnip and parsley root) as well as rotational crops. Calculations were performed using the Excel calculator proposed by EFSA (pesticides_mrl_guidelines_animal_model_2017). The following assumptions have been made:

1) The highest likely inclusion rate of all crops which may have been treated has been used with the proviso that the aggregate does not exceed 100% diet;
2) All produce eaten which may have been treated, has been treated and contains residues as summarized below;
3) There is no loss of residue during transport, storage, preparation of feed.
4) Where applicable, either processing factors from processing studies have been used (Rape/Canola meal, Brewer's grain (dried) and Wheat gluten (meal)), or the default processing factor values in the Excel calculator have been used, where applicable.

Following presentation to the Expert Committee on Pesticides (ECP) in the process of seeking Independent Scientific Advice (ISA) and taking account of both rotational crop and primary crop residues, the dietary burden has been recalculated according to the revised rotational crop residues assessment in Vol 1 section 2.7.7. The fate parameters (on estimation of residues in soil), affect the rotational crop residues which in turn feed into the animal dietary burden. The revised presentation takes account of ECP ISA on the soil fate parameters and advice to use crop interception rates (this reduces the amount of active substance that impacts the soil), for application made to the primary crop.

The dietary burden considers components of the plant RD-RA (pydiflumetofen only) and residues are calculated using the inputs for the dietary burdens ~~for both Tier 1 10 year use and Tier 2 – long term use scenarios,~~ presented in Table 2.7.5.1 ~~and 2.7.5.2~~. The following estimates includes primary crop (PC) residues of pydiflumetofen in barley, oats, wheat, rye, triticale, oilseed rape (representative uses) and carrot, parsnips, and parsley roots (additional MRL assessment uses) as well as estimated residues in crops grown in rotation (RC). Where crops relevant to the UK GAP can also be grown in rotation, the sum of expected residues (PC + RC) has been used in the calculation where applicable (see section 2.7.7 for further details).

Table 2.7.5.1 Inputs for animal dietary burden ~~– (primary crops and inclusion of rotational crop residues – Tier 1 – 10 year use)~~.

Feed commodity	**Median dietary burden**		**Maximum dietary burden**	
	(mg/kg)	Comment	(mg/kg)	Comment
Primary crop representative uses: oilseed rape, wheat, triticale, rye, barley and oats Primary crop (MRL assessment): carrots **Contributions from both primary and rotational crops were assessed in section 2.7.7, see table 2.7.7.5 for details.**				
Forages				
Alfalfa forage, hay, meal, silage	<0.01	STMR	0.025	HR
Barley forage, silage	<0.01		0.025	
Barley straw	1.195		2.72	

Feed commodity	**Median dietary burden**		**Maximum dietary burden**	
	(mg/kg)	Comment	(mg/kg)	Comment
Bean vines	<0.01		<0.01	
Beet, mangel fodder	<0.01		0.053	
Beet, sugar (tops)	<0.01		0.053	
Cabbage heads, leaves	<0.01		<0.01	
Clover forage, hay, silage	<0.01		0.025	
Corn, field, forage/silage	<0.01		0.025	
Corn, field (maize), pop, stover	0.032		0.114	
Cowpea, forage, hay	<0.01		0.025	
Grass, forage (fresh), hay, silage	<0.01		0.025	
Kale, leaves	<0.01		<0.01	
Lespedeza, forage, hay	<0.01		0.025	
Millet, forage	<0.01		0.025	
Millet, straw	0.032		0.114	
Oat forage, hay	<0.01		0.025	
Oat straw	1.195		2.72	
Pea vines, hay, silage	<0.01		<0.01	
Rape forage	<0.01		0.025	
Rye forage	<0.01		0.025	
Rye straw	0.91		4.0	
Sorghum forage, silage	<0.01		0.025	
Sorghum (grain), stover	0.032		0.114	
Soybean forage, hay, silage	<0.01		0.025	
Trefoil forage	<0.01		0.025	
Triticale forage, hay	<0.01		0.025	
Triticale, straw	0.91		4.0	
Turnip tops, leaves	<0.01		0.053	
Vetch forage, hay	<0.01		0.025	
Wheat forage, hay	<0.01		0.025	
Wheat straw	0.91		4.0	
Roots and Tubers				
Carrot culls	0.067	STMR	0.082	HR

Feed commodity	**Median dietary burden**		**Maximum dietary burden**	
	(mg/kg)	Comment	(mg/kg)	Comment
Cassava/tapioca roots	<0.01		0.042	
Potato culls	<0.01		0.042	
Swede roots	<0.01		0.042	
Turnip roots	<0.01		0.042	
Cereal grains/Crop seeds				
Barley grain	0.1	STMR	0.1	STMR
Bean, dry seed	<0.01		<0.01	
Corn, field (maize), pop, grain	<0.01		<0.01	
Cotton seed (undelinted)	<0.01		<0.01	
Cowpea seed	<0.01		<0.01	
Lupin seed	<0.01		<0.01	
Millet grain	<0.01		<0.01	
Oat grain	0.1		0.1	
Pea (field), dry seed	<0.01		<0.01	
Rye grain	0.025		0.025	
Sorghum grain	<0.01		<0.01	
Soybean seed	<0.01		<0.01	
Triticale grain	0.025		0.025	
Wheat grain	0.025		0.025	
By-products^				
Sugar beet (pulp)	<0.01	STMR	<0.01	STMR
Flaxseed/Linseed (meal)	<0.01	STMR	<0.01	STMR
Rape/Canola meal	<0.01	STMR	<0.01	STMR
Safflower meal	<0.01	STMR	<0.01	STMR
Brewer's grain (dried)	0.194	STMR (barley grain) x calculated PF (1.94)	0.194	STMR (barley grain) x calculated PF (1.94)
Wheat gluten (meal)	0.0053	STMR (wheat grain) x calculated PF (0.21)	0.0053	STMR (wheat grain) x calculated PF (0.21)

^ Relevant by-products not included in the above table are included in the assessment e.g. distillers grain (dried) and wheat (milled by products) - default PFs in the animal dietary burden calculator apply, as specific processing data are not available for these. The approach populates the entries with the relevant residues from the relevant grains/seeds with the above raw commodity inputs inserted accordingly).

The results of the animal dietary burden assessments are is presented below (for Tier 1 -10 year use and Tier 2 -long term use).

Table 2.7.5.2 Option 1 - Median and Maximum dietary burden in livestock-covering PC and RC with the Rotational crop scenario - Tier 1 -10 year use

New data requirements	Regulation (EU) No 283/2013)							
Relevant groups	**Dietary burden expressed in**				**Most critical diet (a)**	**Most critical commodity (b)**		Trigger exceeded (Yes/No)
	mg/kg bw per day		mg/kg DM					0.004
	Median	Maximum	Median	Maximum				mg/kg bw
Cattle (all diets)	0.039	0.060	1.17	1.71	Dairy cattle	Barley	straw	Yes
Cattle (dairy only)	0.039	0.060	1.01	1.55	Dairy cattle	Barley	straw	Yes
Sheep (all diets)	0.053	0.098	1.47	2.50	Lamb	Barley	straw	Yes
Sheep (ewe only)	0.049	0.083	1.47	2.50	Ram/Ewe	Barley	straw	Yes
Swine (all diets)	0.012	0.014	0.54	0.60	Swine (breeding)	Potato	process waste	Yes
Poultry (all diets)	0.020	0.045	0.30	0.66	Poultry layer	Wheat	straw	Yes
Poultry (layer only)	0.020	0.045	0.30	0.66	Poultry layer	Wheat	straw	Yes
(a): When several diets are relevant (e.g. cattle, sheep and poultry "all diets"), the most critical diet is identified from the maximum dietary burdens expressed as "mg/kg								
(b): The most critical commodity is the major contributor identified from the maximum dietary burden expressed as "mg/kg bw per day".								

The resulting maximum dietary burdens for Tier 1 - 10 year use are 0.207 is 0.098 mg/kg bw/d for ruminants and 0.045 0.076 mg/kg bw/d for poultry. For Tier 2 long term use , the resulting maximum dietary burdens are 0.166 mg/kg bw/d for ruminants and 0.065 mg/kg bw/d for poultry. For both ruminants and poultry, for both (fate) Tier assessments, the trigger of 0.004 mg/kg bw/d is exceeded and therefore feeding studies are required for ruminants and poultry, pigs and or fish; feeding studies for ruminants (lactating bovine) and poultry (laying hens) have been submitted. An overview of these studies is presented below (in this section 2.7.5). The detailed evaluation of these studies is in section B.7.4.

In view of these animal dietary burdens the following N rates for the livestock and metabolism feeding studies are estimated (see Table 2.7.5.3). These are based on the maximum dietary burdens expressed on a mg/kg bw/day basis.

Table 2.7.5.3 Consideration of the degree of exaggeration of the livestock studies, considering the dose rates in comparison to the anticipated dietary burdens for the assessed uses.

Study	Actual dosing rates (mg/kg/bw/day)	Maximum dietary burden ~~(Tier 1 10 year use)~~	N rate of study ~~(Tier 1 10 year use)~~ [considering worst case animal exposures according to the various species]	~~Maximum dietary burden (Tier 2 long term use)~~	~~N rate of study (Tier 2 long term use) [considering worst case animal exposures according to the various species]~~
Hen metabolism	3.3 3.6	0.045 ~~0.076~~	73N ~~43N~~ 80N ~~47N~~	~~0.065~~	~~51N~~ ~~55N~~
Goat metabolism	4.6	0.098 sheep 0.083 sheep (ewe only) ~~0.207~~	47N 55N ~~22N~~	~~0.166~~	~~28N~~
Hen feeding 'lowest dose'	0.16	0.045 ~~0.076~~	3.5N ~~2.1N~~	~~0.065~~	~~2.5N~~
Hen feeding 'mid dose'	0.50	0.045 ~~0.076~~	11.0N ~~6.6N~~	~~0.065~~	~~7.7N~~
Hen feeding 'high dose'	1.6	0.045 ~~0.076~~	35.4N ~~21N~~	~~0.065~~	~~25N~~
Cattle feeding [A] 'low dose'	0.40	0.098 ~~0.207~~	4.1N ~~1.9N~~	~~0.166~~	~~2.4N~~
Cattle feeding [A] 'mid dose'	1.09	0.098 ~~0.207~~	11.1N ~~5.3N~~	~~0.166~~	~~6.6N~~
Cattle feeding [A] 'high dose'	4.32	0.098 ~~0.207~~	44.1N ~~21N~~	~~0.166~~	~~26N~~
Cattle feeding [B] 'low dose'	0.40	0.098 ~~0.207~~	4.1N ~~1.9N~~	~~0.166~~	~~2.4N~~
Cattle feeding [B] 'mid dose'	1.10	0.098 ~~0.207~~	11.2N ~~5.3N~~	~~0.166~~	~~6.6N~~
Cattle feeding [B] 'high dose'	3.40	0.098 ~~0.207~~	34.7N ~~16N~~	~~0.166~~	~~20N~~

[A] Cattle feeding study A was used for the determination of all residues except SYN547897

[B] Cattle feeding study B was used only for the determination of SYN547897 in liver and kidney (the samples were analysed quickly to circumvent any issues with stability of these residues).

Overview of feeding studies provided:

Magnitude of residues in livestock was investigated following the administration of pydiflumetofen either through diet or via gelatine capsules at three dosing levels for a period of 28 days. Investigations were done in both laying hens and lactating cattle. Feeding study data are not available or required for pigs or fish (see section 2.7.2).

Poultry

Laying hens were fed pydiflumetofen treated feed at three dosing levels of approximately 3 ppm, 9 ppm and 30 ppm (mg per kg) of dry matter (DM) feed. The 40 hens being fed with treated feed were split into a total of 4 dosing groups: 3 mg pydiflumetofen /kg DM (Group 2, low dose rate), 9 mg pydiflumetofen /kg DM (Group 3, mid dose rate), and 30 mg pydiflumetofen /kg DM (Group 4 and 5, high dose rate). In terms of N rate, these studies equate to high dose rate [35.4N ~~21N Tier 1 10 year use and 25N Tier 2 long term use~~], mid dose rate [11.0N ~~6.6N Tier 1 10 year use and 7.7N Tier 2 long term use~~] and low dose [3.5N ~~2.1N Tier 1 10 year use and 2.5N Tier 2 long term use~~] rate).

Samples were analysed for pydiflumetofen and 2,4,6-TCP (free and conjugated). It is anticipated (from the poultry metabolism data) that the residues analysed as 2,4,6-TCP, were most likely exclusively present as the sulphate conjugate of 2,4,6-TCP. For all matrices, the samples from the high dose rate group were analysed first and if

residues above LOQ (0.01 mg/kg) were found, samples from the mid dose rate group for that matrix were analysed. The same was done for the low dose rate group if the mid dose group showed residues >LOQ.

Parent was found in whole eggs (whites and yolks), egg whites, and egg yolks, at the highest dose and at the mid dose feeding level for both whole eggs and egg whites. For these samples, no residues >LOQ were identified at the low dose rate feeding level. Residues of 2,4,6-TCP were found in whole eggs (white and yolk) and egg yolk at the highest dose and mid dose levels. Residues were still present in the yolk samples at the lowest dose level. In kidney tissues, residues of 2,4,6-TCP >LOQ were identified in the high and mid dose feeding groups.

Residue data indicated that pydiflumetofen residues achieved a plateau level in whole eggs at study day 3. In comparison, data indicates that 2,4,6-TCP residues reached a plateau level in whole eggs slightly later than for pydiflumetofen at ~day 7 of the study.

Ruminant

In both studies into the magnitude of residues in lactating ruminants, lactating dairy cattle were fed gelatine capsules containing pydiflumetofen at three dosing levels of approximately 15 ppm, 45 ppm and 150 ppm per kg of dry matter (DM) feed. The 9 cows being given gelatine capsules containing pydiflumetofen were split into a total of 3 dosing groups: 15 mg pydiflumetofen /kg DM (Group 2, low dose rate), 45 mg pydiflumetofen /kg DM (Group 3, mid dose rate), and 150 mg pydiflumetofen /kg DM (Group 4, high dose rate). In terms of N rate, these studies equate to high dose rate [44.1N ~~21N Tier 1 10 year use and 26N Tier 2 long term use~~], mid dose rate [11.1N ~~5.3N Tier 1 10 year use and 6.6N Tier 2 long term use~~] and low dose [4.1N ~~1.9N Tier 1 10 year use and 2.4N Tier 2 long term use~~] rate). In the second study outlined below the N rates of the low and mid dose rates were the same; in the second study the high dose represented 34.7N ~~16N Tier 1 10 year use and 20N Tier 2 long term use~~.

In the first study all samples (liver, muscle, kidney, fat and milk) were analysed for pydiflumetofen and 2,4,6-TCP. Samples of milk were analysed for SYN548264 and SYN508272 and samples of liver and kidney for SYN548263 and SYN547897.

Positive residues of pydiflumetofen were found in the commodities; whole milk, cream, liver, kidney and fat (subcutaneous, perirenal and mesenterial) at the highest dose level. Residues of pydiflumetofen were found at levels <LOQ (0.01 mg/kg) in skimmed milk and muscle at the highest dose level and in muscle, kidney and whole milk at the mid dose rate level. Residues ≥LOQ were found in cream, liver and subcutaneous, perirenal and mesenterial fat at the mid dose rate and low dose rate feeding levels.

Residues of pydiflumetofen reached a plateau concentration in whole milk at approximately 3 days after dosing began.

Positive residues of 2,4,6-Trichlorophenol were found in the commodities; whole milk, skimmed milk, cream, liver, kidney and perirenal fat at the highest dose level and the mid dose rate level. It is anticipated (from the ruminant metabolism data) that the residues analysed as 2,4,6-TCP, were most likely exclusively present as the sulphate conjugate of 2,4,6-TCP. Residues of 2,4,6-Trichlorophenol were found at levels <LOQ (0.01 mg/kg) in muscle and subcutaneous and mesenterial fat at the highest dose level. At the lowest dose feeding level, residues ≥LOQ (0.01 mg/kg) were found in cream and kidney. The remaining samples which were analysed (residues at higher feeding level ≥LOQ) were <LOQ.

Residues of 2,4,6-trichlorophenol reached a plateau concentration in whole milk at approximately 3-5 days after dosing began.

Highest residues of SYN548264 were found at 0.01 mg/kg in whole milk and skimmed milk at the highest dose level. Whole milk and cream were not analysed at the mid and low dose rate levels. In skimmed milk, residues were <LOQ (<0.01 mg/kg) and not detectable (< 0.00250 mg/kg) at the mid and low dose rate respectively.

At the highest dose rate level, residues of SYN508272 were found at <LOQ (<0.01 mg/kg) in whole milk and skimmed milk and were not detected (< 0.00250 mg/kg) in cream.

At all three dose rates tested, residues of SYN547897 were found at >LOQ (>0.01 mg/kg) in liver and kidney tissue samples.

At the high and mid dose level, residues of SYN548263 were found at >LOQ (>0.01 mg/kg) in kidney tissue samples. Residues were <LOQ in liver at the highest dose rate and in kidney at the lowest dose rate group.

In the second study, residues of the pydiflumetofen metabolite SYN547897 in ruminant tissue (liver and kidney) was investigated. Residues of SYN547897 had been evaluated in the first feeding study, but the second study aimed to analyse samples far quickly due to possible storage stability concerns (for when samples were stored frozen for a significant period of storage.

For liver, mean SYN547897 levels were 0.60 mg/kg in the highest dose group, 0.25 mg/kg in the mid dose group and 0.06 mg/kg in the lowest dose group. The maximum residues were 1.00 mg/kg in the high dose group, 0.33 mg/kg in the mid dose group and 0.07 mg/kg in the low dose group.

For kidney, mean residues of SYN547897 were 0.44 mg/kg in the highest dose group, 0.17 mg/kg in the mid dose group and 0.08 mg/kg in the lowest dose group. Maximum residues were 0.49 mg/kg in the high dose group, 0.19 mg/kg in the mid dose group and 0.09 mg/kg in the low dose group.

The results for the residue levels of SYN547897 in the second study (liver and kidney samples) analysed relatively quickly were fairly similar to the results obtained in the first feeding study.

Derivation of anticipated residues in the livestock products: 'STMR', HR and MRL proposal output tables (taken from 'Excel calculator')

The resultant residues from feeding studies have been used to calculate chronic input ('STMR'), acute input 'HR'and MRL values for animal commodities. Livestock feeding studies were undertaken in lactating cows (ruminants) and laying hens (poultry) and are discussed in section 2.7.5.

To determine the MRLs in animal commodities, the residues in accordance with the residue definition for enforcement were input into the calculator. The residue definition for enforcement is parent only.

To determine the 'STMR' and HR for products of animal origin (POAO) for input into the consumer risk assessment, residues in accordance with the residue definition for risk assessment were input into the calculator. For further discussion of the determination of the residue definition for risk assessment, see section 2.13. The residue definition for risk assessment for ~~ruminant/~~mammalian and poultry, except ~~ruminant/~~mammalian kidney is:

Sum of Pydiflumetofen (sum of isomers) and 2,4,6-trichlorophenol (free and conjugated) expressed as pydiflumetofen

Due to the presence of the metabolite SYN548263 in ruminant kidneys in the feeding studies, the residue definition for risk assessment for ~~ruminant/~~mammalian kidneys only is:

Sum of Pydiflumetofen (sum of isomers), 2,4,6-trichlorophenol (free and conjugated) and SYN548263 (free and conjugated), expressed as pydiflumetofen

As the input residues for bovine automatically populate sheep and swine inputs - and as the metabolic pathway in livestock and rats was similar - the residues of bovine kidney in accordance with the residue definition for risk assessment are applicable to ruminants and swine. As discussed in section B.5, methods GRM061.07A and GRM061.09A have been demonstrated to release 2,4,6-trichlorophenol and SYN548263 from their conjugated form, so results of 2,4,6-trichlorophenol and SYN548263 are expected to include previously conjugated residues (i.e., sum of free and conjugated).

As discussed in EFSA 2015 "Estimation of animal intakes and HR, STMR and MRL calculations for products of animal origin", 'HRs' and MRLs for POAO are derived by considering the highest residue levels for all other commodities and mean residue level for milk, at the different feeding levels as well as the maximum dietary burden values. An MRL is proposed based on the resultant 'HR' value. 'STMRs' are derived considering the mean residue

levels in each commodity at the different feeding levels and the median dietary burdens.

In accordance with the residue definition for risk assessment, residues needed to be given as either the sum of parent and 2,4,6-trichlorophenol (free and conjugated), expressed as parent or sum of parent, 2,4,6-trichlorophenol (free and conjugated) and SYN548263 (free and conjugated), expressed as parent. This meant performing a molecular weight conversion on the results of the feeding study for the two metabolites before summing with parent. An example calculation for each of the two proposed residue definitions for risk assessment are shown below.

RD RA for all commodities excluding ~~ruminant~~ mammalian kidney = SYN545974 + 2,4,6-TCP

1) Molecular weight conversion

To calculate the residues for input into the dietary burden calculator, the molecular weight conversion was determined (given below) that would give residues of 2,4,6-TCP expressed as SYN545974.

$$Molecular\ weight\ conversion = \frac{Molecular\ weight\ of\ SYN545974}{Molecular\ weight\ of\ 2{,}4{,}6-TCP} = \frac{426.7}{197.45} = 2.16$$

2) Using the molecular weight conversion to calculate sum of SYN545974 + 2,4,6-TCP (expressed as parent)

For example, the results for ruminant liver at dose rate 45 (highest dose rate) were 0.05 mg/kg for SYN545974 and 0.03 mg/kg for 2,4,6-TCP. The molecular weight conversion was used to express residues of 2,4,6-TCP as SYN545974, and residues of SYN545974 and 2,4,6-TCP were then summed:

SYN545974 + 2,4,6-TCP = 0.05 + (0.03 x 2.16) = **0.115**

RD RA for ~~ruminant~~ mammalian kidney only = SYN545974 + 2,4,6-TCP + SYN548263

1) Molecular weight conversion

To calculate the residues for input into the dietary burden calculator, molecular weight conversions were determined that would give residues of 2,4,6-TCP expressed as SYN545974 (given in the example above) and to give residues of SYN548263 expressed as SYN545974 (given below).

$$Molecular\ weight\ conversion = \frac{Molecular\ weight\ of\ SYN545974}{Molecular\ weight\ of\ SYN547263} = \frac{426.7}{277.2} = 1.54$$

2) Using the molecular weight conversions to calculate sum of SYN545974 + 2,4,6-TCP (expressed as parent) + SYN548263 (expressed as parent)

At dose rate 45 (highest dose rate), results for ruminant kidney at were 0.01* mg/kg for SYN545974, 0.05 mg/kg for 2,4,6-TCP and 0.02 mg/kg for SYN548263. The molecular weight conversions were used to express residues of 2,4,6-TCP and SYN548263 as SYN545974, before all components of the residue definition were summed, as shown below:

SYN545974 + 2,4,6-TCP + SYN548263 = 0.01* + (0.05 x 2.16) + (0.02 x 1.54) = **0.149**

Inputs for residues in accordance with the definition for enforcement (pydiflumetofen only)

Table 2.7.5.4 Inputs for residues in accordance with the definition for enforcement (pydiflumetofen only) - Ruminant

Ruminant

Dose Rate (mg SYN545974/kg feed)		Dose Rate SYN545974 (mg/kg body weight/day)	Animal	RD Enforcement = SYN545974							
Target	Actual	Actual		Muscle (mg/kg)	Fat (mg/kg)	Fat Per. (mg/kg)	Fat Sub. (mg/kg)	Fat Mes. (mg/kg)	Liver (mg/kg)	Kidney (mg/kg)	Milk (mg/kg)
15	15.7	0.40	2	<0.010	0.010	0.010	<0.010	0.010	0.010	<0.010	<0.010
			3	<0.010	0.010	0.010	<0.010	0.010	0.020	<0.010	<0.010
			4	<0.010	0.020	0.010	0.020	0.020	0.010	<0.010	<0.010
45	47.2	1.09	5	<0.010	0.060	0.060	<0.010	0.060	0.050	<0.010	<0.010
			6	<0.010	0.040	0.040	0.040	0.040	0.040	<0.010	<0.010
			7	<0.010	0.040	0.040	0.030	0.050	0.030	<0.010	<0.010
150	152.5	4.32	8	<0.010	0.110	0.110	0.110	0.170	0.090	0.030	0.012
			9	<0.010	0.070	0.070	0.030	0.070	0.120	0.020	0.010
			10	<0.010	0.050	0.050	<0.010	0.050	0.070	0.010	0.011

[1] to determine the value for fat for input into the dietary burden calculator, the residues for mesenterial fat were taken forward as the representative type of fat. All residues observed in the different types of fat were of a similar magnitude at each dose level.
[2] the value for milk was determined by taking the mean residue over the plateau period as recommended in OECD 505. The plateau period occurred from day three onwards in the feeding studies for SYN545974.

Table 2.7.5.5 Inputs for residues in accordance with the definition for enforcement (pydiflumetofen only) - Poultry

Poultry

Dose Rate (mg SYN545974/kg feed)		Dose Rate SYN545974 (mg/kg body weight/day)	Animal	RD Enforcement = SYN545974				
Target	Actual	Actual		Muscle (mg/kg)	Fat (mg/kg)	Liver (mg/kg)	Kidney (mg/kg)	Eggs (mg/kg)
3	3.3	0.16	2A	<0.010	<0.010	<0.010	<0.010	<0.010

			2B	<0.010	<0.010	<0.010	<0.010	<0.010
			2C	<0.010	<0.010	<0.010	<0.010	<0.010
9	9.9	0.50	3A	<0.010	<0.010	<0.010	<0.010	0.010
			3B	<0.010	<0.010	<0.010	<0.010	<0.010
			3C	<0.010	<0.010	<0.010	<0.010	<0.010
10	33	1.6	4A	<0.010	<0.010	<0.010	<0.010	0.020
			4B	<0.010	<0.010	<0.010	<0.010	0.025
			4C	<0.010	<0.010	<0.010	<0.010	0.022
		1.5	5A	-	-	<0.010	-	0.020
			5B	-	-	<0.010	-	0.019
			5C	-	-	<0.010	-	0.022

[1] the value for eggs was determined by taking the mean residue over the plateau period as recommended in OECD 505. In the feeding studies, the plateau period occurred from day three onwards for SYN545974. The value was for whole eggs (egg white + yolk).

Inputs for residues in accordance with the definitions for risk assessment

Table 2.7.5.6 Inputs for residues in accordance with the definition for risk assessment - Ruminant

Ruminant

Dose Rate (mg SYN545974/kg feed)		Dose Rate SYN545974 (mg/kg body weight/day)	Animal	RD RA = SYN545974 + 2,4,6-TCP (free and conjugated), expressed as parent							RD RA = SYN545974 + 2,4,6-TCP (free and conjugated) + SYN548263 (free and conjugated), expressed as parent
Target	Actual	Actual		Muscle (mg/kg)	Fat (mg/kg)	Fat Per. (mg/kg)	Fat Sub. (mg/kg)	Fat Mes. (mg/kg)	Liver (mg/kg)	Milk (mg/kg)	Kidney (mg/kg)
15	15.7	0.40	2	0.032	0.032	0.032	0.032	0.032	0.032	0.032	0.047
			3	0.032	0.032	0.032	0.032	0.032	0.042	0.032	0.047
			4	0.032	0.042	0.032	0.042	0.042	0.032	0.032	0.047
45	47.2	1.09	5	0.032	0.082	0.082	0.032	0.082	0.115	0.051	0.149
			6	0.032	0.062	0.062	0.062	0.062	0.083	0.039	0.149

			7	0.032	0.072	0.062	0.052	0.072	0.095	0.032	0.127
150	152.5	4.32	8	0.032	0.192	0.132	0.132	0.192	0.220	0.202	0.440
			9	0.032	0.092	0.092	0.052	0.092	0.293	0.197	0.628
			10	0.032	0.072	0.072	0.032	0.072	0.243	0.179	0.485

[1] to determine the value for fat for input into the dietary burden calculator, the residues for mesenterial fat were taken forward as the representative type of fat. All residues observed in the different types of fat were of a similar magnitude at each dose level (see section B.7.4.2).
[2] the value for milk was determined by taking the mean residue over the plateau period as recommended in OECD 505. The plateau period occurred from day three onwards in the feeding studies for both SYN545974 and 2,4,6-TCP.

Table 2.7.5.7 Inputs for residues in accordance with the definition for risk assessment - Poultry

Poultry

Dose Rate (mg SYN545974/kg feed)		Dose Rate SYN545974 (mg/kg body weight/day)	Animal	RD RA = SYN545974 + 2,4,6-TCP (free and conjugated), expressed as parent				
Target	Actual	Actual		Muscle (mg/kg)	Fat (mg/kg)	Liver (mg/kg)	Kidney (mg/kg)	Eggs (mg/kg)
3	3.3	0.16	2A	0.032	0.032	0.032	0.032	0.032
			2B	0.032	0.032	0.032	0.032	0.032
			2C	0.032	0.032	0.032	0.032	0.032
9	9.9	0.50	3A	0.032	0.032	0.032	0.049	0.033
			3B	0.032	0.032	0.032	0.038	0.032
			3C	0.032	0.032	0.032	0.051	0.035
10	33	1.6	4A	0.032	0.032	0.032	0.118	0.092
			4B	0.032	0.032	0.032	0.090	0.070
			4C	0.032	0.032	0.032	0.116	0.078
		1.5	5A	-	-	0.032	-	0.105
			5B	-	-	0.032	-	0.095
			5C	-	-	0.032	-	0.083

[1] the value for eggs was determined by taking the mean residue over the plateau period as recommended in OECD 505. In the feeding studies, the plateau period occurred from day three onwards for SYN545974 and day seven onwards for 2,4,6-TCP. The value was for whole eggs (egg white + yolk).

'STMR', HR and MRL proposal output tables

The following output tables were produced using the excel calculator proposed by EFSA (pesticides_mrl_guidelines_animal_model_2017) are reported below ~~for the (fate) Tier 1 10 year use and Tier 2 long term use scenarios (see section 2.7.7 for further details)~~. As well as the MRL proposal (based on the RD-Enf of pydiflumetofen only) applicable to each species based on the anticipated dietary burden level, the tables also provide an 'STMR' value and an 'HR' value for each livestock product/each species to provide risk assessment residue end-points relevant to the anticipated dietary burden level. This in turn enables a conversion factor to be proposed (to bridge between RD-enf and RD-RA) and these CF are also derived by the 'Excel calculator' and provided in these output tables.

Table 2.7.5.8 Residue outputs – ~~Tier 1 10 year use~~ All commodities, except ~~ruminant/~~mammalian kidney

Animal commodity	**Residues at the closet feeding level** (mg/kg)		**Estimated value at 1N level**		**MRL proposal** (mg/kg)	**CF**	**STMR** (mg/kg)	**HR** (mg/kg)
	Mean	Highest	$STMR_{Enf}$ (mg/kg)	HR_{Enf} (mg/kg)				
Cattle (all diets) Closest feeding level[a]:	0.4	mg/kg bw	6.7	N Dairy cattle (highest diet)				
Meat	-	-	-	-	-	-	0.03	0.03
Muscle	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03
Fat	0.01	0.02	0.001	0.003	**0.01***	3.2	0.003	0.01
Liver	0.01	0.02	0.001	0.003	**0.01***	3.2	0.003	0.01
Kidney	-	-	-	-	-	-	-	-
Fat Per.	0.01	0.01	0.001	0.001	**0.01***	3.2	0.003	0.003
Fat Sub.	0.01	0.02	0.001	0.003	**0.01***	3.2	0.003	0.01
Fat Mes.	0.01	0.02	0.001	0.003	**0.01***	3.2	0.003	0.01
Cattle (dairy only) Closest feeding level[a]:	0.4	mg/kg bw	6.7	N Dairy cattle				
Milk[b]	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03
Sheep (all diets) Closest feeding level[a]:	0.4	mg/kg bw	4.1	N Lamb (highest diet)				
Meat	-	-	-	-	-	-	0.03	0.03
Muscle	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03
Fat	0.01	0.02	0.002	0.005	**0.01***	3.2	0.01	0.02
Liver	0.01	0.02	0.002	0.005	**0.01***	3.2	0.01	0.02
Kidney	-	-	-	-	-	-	-	-

Fat Per.	0.01	0.01	0.001	0.002	**0.01***	3.2	0.003	0.01
Fat Sub.	0.01	0.02	0.002	0.005	**0.01***	3.2	0.01	0.02
Fat Mes.	0.01	0.02	0.002	0.005	**0.01***	3.2	0.01	0.02
Sheep (dairy only)								
Closest feeding level[a]:	0.4	mg/kg bw	4.8	N Ewe				
Milk[b]	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03
Swine								
Closest feeding level[a]:	0.4	mg/kg bw	28.8	N Breeding (highest diet)				
Meat	-	-	-	-	-	-	0.03	0.03
Muscle	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03
Fat	0.01	0.02	<0.001	0.001	**0.01***	3.2	0.003	0.003
Liver	0.01	0.02	<0.001	0.001	**0.01***	3.2	0.003	0.003
Kidney	-	-	-	-	-	-	-	-
Fat Per.	0.01	0.01	<0.001	<0.001	**0.01***	3.2	0.003	0.003
Fat Sub.	0.01	0.02	<0.001	0.001	**0.01***	3.2	0.003	0.003
Fat Mes.	0.01	0.02	<0.001	0.001	**0.01***	3.2	0.003	0.003
Poultry (all diets)								
Closest feeding level[a]:	0.16	mg/kg bw	3.5	N Layer (highest diet)				
Meat	-	-	-	-	-	-	0.03	0.03
Muscle	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03
Fat	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03
Liver	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03
Kidney	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03
Poultry (layer only)								
Closest feeding level[a]:	0.16	mg/kg bw	3.5	N Layer				
Eggs[c]	0.01	0.01	<0.01	<0.01	**0.01***	3.2	0.03	0.03

(a): Closest feeding level and N dose rate related to the maximum dietary burden.

(b): Highest residue level from day D1 to day D2 (daily mean of 9 cows).

(c): Highest residue level from day D1 to day D2 (daily mean of 40 laying hens).

Table 2.7.5.9 Residue outputs – ~~Tier 1 10 year use~~ ~~ruminant~~ mammalian kidney

Animal commodity	Residues at the closet feeding level (mg/kg)		Estimated value at 1N level		MRL proposal (mg/kg)	CF	STMR (mg/kg)	HR (mg/kg)
	Mean	Highest	$STMR_{Enf}$ (mg/kg)	HR_{Enf} (mg/kg)				
Cattle (all diets) Closest feeding level[(a)]:	0.4	mg/kg bw	6.7	N Dairy cattle (highest diet)				
Kidney	0.01	0.01	<0.01	<0.01	**0.01***	4.7	0.05	0.05
Sheep (all diets) Closest feeding level[(a)]:	0.4	mg/kg bw	4.1	N Lamb (highest diet)				
Kidney	0.01	0.01	<0.01	<0.01	**0.01***	4.7	0.05	0.05
Swine Closest feeding level[(a)]:	0.4	mg/kg bw	28.8	N Breeding (highest diet)				
Kidney	0.01	0.01	<0.01	<0.01	**0.01***	4.7	0.05	0.05

(a): Closest feeding level and N dose rate related to the maximum dietary burden.

Conversion factors

Conversion factors for enforcement to risk assessment, estimated at the different feeding levels, are presented below in Table 2.7.5.10 ~~for Tier 1 10 year use~~. These have been taken directly from the Excel dietary burden calculator ~~– Tier 1 scenario~~. The conversion factor for ~~ruminant~~ mammalian kidneys are for the conversion of Pydiflumetofen to 'Sum of Pydiflumetofen (sum of isomers), 2,4,6-trichlorophenol (free and conjugated) and SYN548263 (free and conjugated), expressed as pydiflumetofen'. The conversion factors for the remaining commodities are for Pydiflumetofen to 'Sum of Pydiflumetofen (sum of isomers) and 2,4,6-trichlorophenol (free and conjugated) expressed as pydiflumetofen'.

Table 2.7.5.10 Conversion factors ~~– Tier 1 10 year use~~

Animal	**Bovine**				**Poultry**			
N Rate level	**6.7**	**18.3**	**72.6**		**3.5**	**11.0**	**35.4**	
Muscle	3.2	3.2	3.2		3.2	3.2	3.2	
Fat	3.2	1.4	1.3		3.2	3.2	3.2	
Liver	3.2	2.3	2.4		3.2	3.2	3.2	
Kidney	4.7	14.9	31.4		3.2	4.9	11.6	
Milk	3.2	3.9	16.8					
Eggs					3.2	3.3	4.2	
Fat Per./	3.2	1.5	1.3					
Fat Sub./	3.2	1.7	1.7					
Fat Mes./	3.2	1.4	1.3					
Animal	**Sheep**				**Swine**			
N Rate level	**4.1**	**11.1**	**44.1**		**28.8**	**78.4**	**310.6**	
Muscle	3.2	3.2	3.2		3.2	3.2	3.2	
Fat	3.2	1.4	1.3		3.2	1.4	1.3	
Liver	3.2	2.3	2.4		3.2	2.3	2.4	
Kidney	4.7	14.9	31.4		4.7	14.9	31.4	
Milk	3.2	3.9	16.8					
Fat Per./Fat Per.	3.2	1.5	1.3		3.2	1.5	1.3	
Fat Sub./Fat Sub.	3.2	1.7	1.7		3.2	1.7	1.7	
Fat Mes./Fat Mes.	3.2	1.4	1.3		3.2	1.4	1.3	

CFs selected for STMR and HR calculations are highlighted in red.

Inputs for the consumer risk assessment

As a precautionary measure, it was proposed (see discussion in section 2.7.2) that an assessment factor (x 2) is applied to all residue levels in animal products, to account for the possibility of any differential metabolism of isomers of pydiflumetofen residues in livestock commodites. This factor has been applied in the table below to give the inputs of animal products for the consumer risk assessment, taking into consideration the enantiomeric composition assessment factor (See section 2.7.9 for consumer risk assessments).

Table 2.7.5.11. A summary of the livestock residue values in mg/kg (based on RD-RA) to feed into the human dietary risk assessment **(emboldened values used).**

Livestcok product	Without enantiomeric composition assessment factor		**With enantiomeric composition assessment factor**	
	STMR	HR	**STMR x 2**	**HR x 2**
Swine: Muscle/meat	0.03	0.03	**0.06**	**0.06**
Swine: Fat tissue	0.003	0.003	**0.006**	**0.006**
Swine: Liver	0.003	0.003	**0.006**	**0.006**
Swine: Kidney	0.05	0.05	**0.1**	**0.1**
Bovine: Muscle/meat	0.03	0.03	**0.06**	**0.06**
Bovine: Fat tissue	0.003	0.01	**0.006**	**0.02**
Bovine: Liver	0.003	0.01	**0.006**	**0.02**
Bovine: Kidney	0.05	0.05	**0.1**	**0.1**
Sheep: Muscle/meat	0.03	0.03	**0.06**	**0.06**
Sheep: Fat tissue	0.01	0.02	**0.02**	**0.04**
Sheep: Liver	0.01	0.02	**0.02**	**0.04**
Sheep: Kidney	0.05	0.05	**0.1**	**0.1**
Goat: Muscle/meat	0.03	0.03	**0.06**	**0.06**
Goat: Fat tissue	0.01	0.02	**0.02**	**0.04**
Goat: Liver	0.01	0.02	**0.02**	**0.04**
Goat: Kidney	0.05	0.05	**0.1**	**0.1**
Equine: Muscle/meat	0.03	0.03	**0.06**	**0.06**
Equine: Fat tissue	0.003	0.01	**0.006**	**0.02**
Equine: Liver	0.003	0.01	**0.006**	**0.02**
Equine: Kidney	0.05	0.05	**0.1**	**0.1**
Poultry: Muscle/meat	0.03	0.03	**0.06**	**0.06**
Poultry: Fat tissue	0.03	0.03	**0.06**	**0.06**
Poultry: Liver	0.03	0.03	**0.06**	**0.06**
Poultry: Kidney	0.03	0.03	**0.06**	**0.06**
Other farmed animals: Muscle/meat	0.03	0.03	**0.06**	**0.06**

Other farmed animals: Fat tissue	0.003	0.01	**0.006**	**0.02**
Other farmed animals: Liver	0.003	0.01	**0.006**	**0.02**
Other farmed animals: Kidney	0.05	0.05	**0.1**	**0.1**
Milk: Cattle	0.03	0.03	**0.06**	**0.06**
Milk: Sheep	0.03	0.03	**0.06**	**0.06**
Milk: Goat	0.03	0.03	**0.06**	**0.06**
Milk: Horse	0.03	0.03	**0.06**	**0.06**
Milk: Others	0.03	0.03	**0.06**	**0.06**
Eggs: Chicken	0.03	0.03	**0.06**	**0.06**
Eggs: Duck	0.03	0.03	**0.06**	**0.06**
Eggs: Goose	0.03	0.03	**0.06**	**0.06**
Eggs: Quail	0.03	0.03	**0.06**	**0.06**
Eggs: Others	0.03	0.03	**0.06**	**0.06**

2.7.6. Summary of effects of processing

Nature of the residue

The effect of processing on the nature of the residues of pydiflumetofen was investigated using the active substance radiolabelled in the Pyrazole-5-^{14}C position. The labelling position is considered appropriate to provide sufficient information. The study simulated pasteurisation, baking/boiling/brewing and sterilisation conditions. Pydiflumetofen was observed to be stable upon processing under all 3 representative conditions.

Pydiflumetofen is a racemate. In terms of enantiomeric conversion, the applicant has made the case (document N5 on isomeric composition) that chemically interconversions are not predicted based on mechanistic and structure related grounds. Interconversion of the enantiomers of SYN545974 is not considered feasible by any conventional chemical or biochemical process to which the compound will be exposed, although differential metabolism of residues could occur (as discussed in section 2.7.2). HSE is not proposing to consider an assessment factor in the consumer risk assessment to consider the potential changes in isomer ratio/amounts in plants, including processed commodities.

The residue definition for processed commodities is proposed to be the same as for the raw agricultural commodity (RAC): pydiflumetofen.

Magnitude of the residue

According to the data requirements of Regulation (EC) No 283/2013, studies investigating the magnitude of residues in processed commodities is required as residues in the RAC are >0.1 mg/kg.

Concerning the representative uses on cereals and oilseed rape, based on the residues trials available (see section 2.7.4) residues above 0.1 mg/kg are anticipated for barley and oats, whereas for wheat (and durum wheat, rye, triticale, oat and spelt) and oilseed rape, whilst positive residues were observed in grain/seed, the residue levels observed in these crops were <0.1 mg/kg. Even so, magnitude of the residues studies over processing have been submitted and evaluated for each of wheat, barley and oilseed rape.

Concerning the MRL evaluation work, being considered here in parallel with the representative uses, for carrot and root crops (residues trials for carrots are summarised in section B.7.3.4). As part of this MRL work, a proposed GAP on root crops (carrot, parsley root and parsnip) is being considered as a future GB use. Trials data in line with the requested uses on carrots (which can be extrapolated to parsnip and parsley root), indicate residues in carrots as a result of primary crop application would be 0.01 to 0.04 mg/kg as a result of the intended uses. Residues in carrots arising as uptake of residues in rotational crops indicate a similar highest residue (0.042 mg/kg) when considering the contribution from the rotational crop exposure. ~~An HR for rotational crop residue in carrots of 0.11 (Tier 1 10 year use) or 0.08 (Tier 2 long term use) has been estimated.~~

Specific cooking data have not been supplied for root or tuber crops. However, HSE notes that some (magnitude of residues) processing data are available for the following crops which have not yet been fully evaluated at the current time: grapes (not a rotated crop), apple/pear (not a rotated crop), tomatoes and peppers, and kale (cooking). For the latter crop commodities, tomatoes/peppers/kale (that can be rotated crops), from a brief consideration of the study reports (not full evaluation of the studies) it is noted that a concentration in residues was only observed for sundried tomatoes (x 10 (due to dehydration)) and cooked kale (for the process of cooking kale in water for 15 minutes at 100°C) (a median PF of 1.24 indicating a small possible concentration of the residues over cooking- this is likely due to the reported lower weights of the cooked kale commodity compared to the weight pre-cooking, as it wouldn't be expected that the overall absolute amount of residue could increase in the cooked commodity; the residues in the washing water were not assessed). These studies will be evaluated in full by HSE at the time of a future (GB) MRL assessment. However for the current time, these processing factors do not need to be applied in the risk assessment, as the consumption data sets used are for fresh raw tomatoes and raw vegetables (RAC expression of the consumption data), and as HSE is applying the raw fresh weight residues data for crops such as tomatoes and carrots to RAC consumption data in the consumer risk assessment, it is not anticipated that this additional information (on PFs for apple, grape, tomato and kale) would impact the current consumer risk assessment.

For the representative uses, processing data on the magnitude of residues are available for the following number of independent field trials: barley (2), wheat (2) and oilseed rape (2).

A number of studies were submitted that used field trial derived residues (field incurred residues). The processing operations followed detailed simulated industrial practices and full details of the processes were provided.

Note that at each trial site, there were two trials (described by the applicant in the wheat and barley trials as a balance trial and a follow up trial). Each trial has independently gone through the same processing and analysis. The only difference between these two trials was that, in some cases (wheat and barley) not all the matrices analysed in the first trial were analysed in the second trial. The second trials focussed on processed commodities that are consumed (by humans or livestock animals). In the oilseed rape trials, both trials looked at all of the commodities (consumed items)

The processing factor (for RD-RA) is calculated as shown below:

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

Barley

Two independent field residue trials were conducted in NEU in 2013. Barley was treated at a growth stage of BBCH 57-61 and BBCH 75 with an exaggerated dose (nominally 375 g as/ha and a later final growth stage) to attempt to generate a commodity with quantifiable residues.

Barley grain was processed to obtain cleaned grain, pearl barley offal, pearl barley abrasion dust (rub off), pearl barley, bran, pearl barley flour, pot barley abrasion dust (rub off), pot barley, pot barley bran, pot barley flour, cleaned grain for beer, beer offal, malt with sprouts, malt spouts, cleaned malt, malt directly before brewing, spent grain (brewing grain), dried brewing grain, wort before cooking, wort after cooking, spent hops (flocs), spent yeast, young beer beer. Processing factors are given below.

Some processing factors shows a large difference (>50%) between trials (based on both the individual values from the balance and follow up trials and their mean values) so in principle a third trial should be performed and the median value reported. This was not considered necessary due to the data supplied from the follow up trials giving, in many cases, a total of four separate values from two independent trial sites.

Note that the values given below show data from trials at two independent test sites (and some commodities have results for both balance and follow up studies). As the follow up studies have independently gone through the same processing as the balance trials and as the difference between the trials are not irreconcilable (10 fold different according to OECD 508) the median transfer factor was considered most appropriate and has been calculated.

Table 2.7.6.1 Summary of barley processing factors

Crop (RAC)/Processed product	**Number of studies**[(a)]	**Processing Factor** (PF)	
		Individual values	Median PF
Barley/Cleaned grain	2 (4)	0.73, 0.76, 0.82, 0.82	0.79
Barley/Pearl barley offal (impurities)	2	3.27, 4.12	3.71
Barley/Pearl barley abrasion dust (rub off)	2	2.64, 3.65	3.15
Barley/Pearl barley	2 (4)	0.05, 0.06, 0.12, 0.14	0.09
Barley/ Pearl barley bran	2 (4)	0.13, 0.14, 0.16, 0.18	0.15
Barley/Pearl barley flour	2 (4)	1.82, 2.39, 3.12, 3.20	2.76 ~~2.78~~
Barley/Pot barley abrasion dust (rub off)	2 (4)	3.55, 3.74, 3.74, 5.06	3.74
Barley/Pot barley	2 (4)	0.06, 0.06, 0.12, 0.19	0.09
Barley/Pot barley bran	2 (4)	0.15, 0.16. 0.19, 0.21	0.18
Barley/Pot barley flour	2 (4)	~~2.32,~~ 2.61, 2.82, 3.03, 3.32	2.93
Barley/Cleaned grain for beer	2	0.73, 0.88	0.81

Crop (RAC)/Processed product	**Number of studies**[a]	**Processing Factor** (PF)	
		Individual values	Median PF
Barley/Offal for beer	2	3.08, 6.88	4.98
Barley/Malt with sprouts	2	0.23, 0.28	0.26
Barley/Malt sprouts	2 (4)	0.54, 0.56, 0.69, 0.73	0.63
Barley/Cleaned malt	2 (4)	0.30, 0.31, 0.33, 0.54	0.32
Barley/Malt directly before brewing	2 (4)	0.22, 0.28, 0.30, 0.42	0.29
Barley/Spent grain (brewing grain)	2	0.25, 0.28	0.27
Barely/Dried brewers grain	2 (4)	1.5, 1.87, 2, 2.77	1.94
BarleyWort before cooking	2	<0.01, <0.01	<0.01
Barley/Wort after cooking	2	<0.01, <0.01	<0.01
Barley/Spent hops (flocs)	2	0.23, 0.27	0.25
Barley/Spent yeast	2 (4)	0.02, 0.02, 0.02, 0.03	0.02
BarleyYoung beer	2	<0.01, <0.01	<0.01
Barley/Beer	2 (4)	< 0.01, < 0.01, < 0.01, < 0.01	< 0.01

[a] Number of studies signifies number of independent trials. Figure in brackets gives the number of individual processed fractions assessed across both trials

Residues above LOQ (0.01 mg.kg) were observed in the untreated control plot of trial S13-02518-01 for straw at 41 DALA. The applicant contended that contamination may have occurred through spray drift from earlier applications

Residues in untreated processed specimens were below LOQ (0.01 mg/kg) with the exception of the samples described below:

- Residues of pydiflumetofen in the untreated offal samples S13-02518-01-023A-B1-A-003 and S13-02518-01-023C-B1-C-015 were 0.01 mg/kg.
- Residues of pydiflumetofen in the untreated abrasion dust (rub off) samples S13-02518-01-023B-B1-B-009, S13-02518-02-023A-B3-A-081, S13-02518-02-023B-B3-B-086 were in the range of 0.01 to 0.17 mg/kg (mean of two determinations).
- Residues of pydiflumetofen in the untreated bran samples S13-02518-02-023A-B3-A-083 and S13-02518-02-023B-B3-B-088 were 0.11 and 0.05 mg/kg (mean of two determinations).
- Residues of pydiflumetofen in the untreated flour samples S13-02518-02-023A-B3-A-084 and S13-02518-02-023B-B3-B-089 were 0.14 and 0.06 mg/kg (mean of two determinations).

The applicant contended that potential residues in untreated processed specimens may have been from treated grain being processed prior to untreated grain.

Processed fractions were stored for a maximum of 9 months from sampling to analysis. These storage periods are covered by storage stability trials summarised in section B.7.1, which shows stability in all matrices for 23 months.

The results indicate that residues of pydiflumetofen do not concentrate in the processing of barley into pearl barley, pot barley or beer (processing factor <0.01 to 0.11) but do concentrate in the processing of barley into flour (in both pearl and pot barley – processing factor 2.78-2.93), abrasion dust (PF 3.15-3.74), offal (PF 4.98) and dried brewers grain (PF 1.94).

Wheat

Two independent field residue trials were conducted in NEU in 2012-2013. Wheat was treated at a growth stage of BBCH 69 and BBCH 77-79 with an exaggerated dose nominally 375 g as/ha for the first application and 450 g as/ha for the second application and application at a later final growth stage) to attempt to generate a commodity with quantifiable residues.

Wheat grain was processed to obtain flour (type 550), type 550 and wholemeal - aspitated grain fraction (offal), Aspirated grain (cleaned grain), grain (after conditioning), straight flour, fine bran, coarse bran, mixed bran, total bran and low grade meal. Also obtained were whole meal flour, dough, whole meal bread, wheat germ- aspirated grain (offal), aspirated grain, grain, bruised grain (400-1000 µm), bruised grain (>1000 µm), bruised grain (<400 µm), middlings/germ mixture, bran, flour, bran/germ fraction, fine bran/germ fraction, coarse bran/germ fraction, remaining bran and wheat germs. For starch and gluten the processed fractions were aspirated grain (offal), aspirated grain (cleaned grain), grain (after conditioning), flour, fine bran, coarse bran, wet starch A and B, starch A and B, Starch (mean of starch A and starch B), dried fibre, wet gluten, gluten and gluten feed meal. Processing factors are given below.

Some processing factors shows a large difference (>50%) between trials (based on both the individual values from the balance and follow up trials and their mean values) so in principle a third trial should be performed and the median value reported. This was not considered necessary due to the data supplied from the follow up trials giving, in many cases, a total of four separate values from two independent trial sites.

Note that the values given below show data from trials at two independent test sites (and some commodities have results for both balance and follow up studies). As the follow up studies have independently gone through the same processing as the balance trials and as the difference between the trials are not irreconcilable (10 fold different according to OECD 508) the median transfer factor was considered most appropriate and has been calculated.

Table 2.7.6.2 Summary of wheat processing factors

Crop (RAC)/Processed product	**Number of studies[(a)]**	**Processing Factor (PF)**	
		Individual values	Median PF
Flour (type 550)			
Wheat/Aspirated grain fraction (offal)	2 (4)	2.08, 2.44, 2.83, 3.24	2.64
Wheat/Aspirated grain (cleaned grain)	2 (4)	0.38, 0.78. 0.87, 1.00	0.83
Wheat/Grain (after conditioning)	2	0.61, 0.78	0.70
Wheat/Straight flour	2	<0.11, 0.13	0.12 (best estimate)
Wheat/Middlings (fine bran)	2	2.00, 2.83	2.42
Wheat/Bran (coarse bran)	2	2.78, 3.00	2.89
Wheat/Mixed bran	2	3.09, 3.26	3.18
Wheat/Shorts (total bran)	2 (4)	2.88, 3.13, 3.77, 4.22	3.45
Wheat/Low grade meal (toppings)	2	0.44, 1.74	1.09
Wheat/Flour (type 550)	2 (4)	0.11, 0.15, 0.17, 0.24	0.16
Whole meal flour and wholemeal bread			
Wheat/Aspirated grain fraction (offal)	2	2.25, 4.11	3.18
Wheat/Aspirated grain (cleaned grain)	2	0.34, 0.78	0.56
Wheat/Grain (after conditioning)	2	0.78,1.11	0.95
Wheat/Straight flour	2	0.09, 0.11	0.10
Wheat/Middlings (fine bran)	2	1.56, 2.22	1.89
Wheat/Bran (coarse bran)	2	2.00, 2.89	2.45
Wheat/Mixed bran	2	4.22, 5.00	4.61
Wheat/Shorts (total bran)	2	3.22, 3.75	3.49

Wheat/Low grade meal (toppings)	2	1.66, 2.56	2.11
Wheat/Whole meal flour	2 (4)	0.33, 0.39, 0.42, 0.47	0.41
Wheat/Dough	2	0.33, 0.38	0.36
Wheat/Whole meal bread	2 (4)	0.48, 0.50, 0.53, 0.56	0.52
Wheat germs			
Wheat/Aspirated grain fraction (offal)	2	2.32, 20.00	11.16
Wheat/Aspirated grain (cleaned grain)	2	0.48, 1.00	0.74
Wheat/Grain (after conditioning)	2	0.40, 1.00	0.70
Wheat/Bruised grain (400-1000 μm)	2	0.32, 0.63	0.47
Wheat/Bruised grain (>1000 μm)	2	1.60, 2.13	1.87
Wheat/Bruised grain (<400 μm)	2	0.08, 0.38	0.23
Wheat/Middlings/germ mixture	2	0.32, 0.88	0.6
Wheat/Bran	2	0.64, 1.63	1.14
Wheat/Flour	2	0.20, 0.38	0.29
Wheat/Bran/germ fraction	2	0.76, 1.25	1.01
Wheat/Fine bran/germ fraction	2	0.88, 1.38	1.13
Wheat/Coarse bran/germ fraction	2	1.00, 1.04	1.02
Wheat/Remaining bran	2	0.84, 1.25	1.05
Wheat/Wheat germs	2 (4)	0.63, 0.73, 0.92, 1.00	0.83
Starch and gluten			
Wheat/Aspirated grain fraction (offal)	2	4.32, 22.00	13.16
Wheat/Aspirated grain (cleaned grain)	2	0.46, 1.60	1.03
Wheat/Grain (after conditioning)	2	0.3, 1.40	0.85
Wheat/Straight flour	2	0.14, 0.2	0.17
Wheat/Middlings (fine bran)	2	1.95, 4.80	3.38
Wheat/Bran (coarse bran)	2	2.70, 5.40	4.05
Wheat/Wet starch A	2	<0.03, <0.2	<0. 2 best estimate
Wheat/Starch A	2 (4)	<0.03, <0.03, <0.11, <0.2	<0.11 best estimate
Wheat/Wet starch B	2	<0.03, <0.2	<0.2 best estimate
Wheat/Starch B	2 (4)	<0.03, <0.03, <0.11, 0.2	<0.11 best estimate
Wheat/Starch**	2 (4)	<0.03, <0.03, <0.11, <0.2	<0.11 best estimate
Wheat/Dried fibre	2	0.05, 0.2	1.03

Wheat/Wet gluten	2	0.19, 0.4	0.30
Wheat/Gluten	2 (4)	0.48, 0.59, 1.2, 1.22	0.90
Wheat/Gluten feed meal	2 (4)	0.16, 0.2, 0.22, 0.22	0.21

[a] Number of studies signifies number of independent trials. Figure in brackets gives the number of individual processed fractions assessed across both trials
** Mean of PF for starch A and starch B.

No residues of pydiflumetofen at or above the LOQ (0.01 mg/kg) were found in any of the untreated wheat samples taken at 0 DBLA (whole plant), at 42-46 DALA (grain and straw) and at NCH (grain and straw), with the exception of the wheat grain and straw samples S13-02516-01-019 and -021 at 42 DALA where residues of 0.01 mg/kg were found for pydiflumetofen in both samples. Because of the very low level of residues found in the control samples compared to the treated samples and the fact that no residues were found at NCH in neither grain or straw control samples, this contamination has no impact on the level of residues found in the treated samples and consequently no impact on the study.
Note that the applicant contended that contamination may have occurred through spray drift from earlier applications

Processed fractions were stored for a maximum of 10 months from sampling to analysis. These storage periods are covered by storage stability stability trials summarised in section B.7.1, which shows stability in all matrices for 23 months

The results of the study indicate that residues of pydiflumetofen do not concentrate in the processing of wheat into grain after conditioning, straight flour, Flour (type 550), aspirated grain, whole meal flour, dough and whole meal bread, wheat germs, starch or gluten (processing factors between 0.11 and 0.95) but does concentrate in offal, fine bran, coarse bran, mixed bran, total bran and toppings (PF between 1.01 and 13.16)

Oilseed rape

Two independent field residue trials were conducted in NEU in 2013-2014. Oilseed rape was treated at a growth stage of BBCH 73-75 with an exaggerated dose (nominally 400 g as/ha for the first application and 450 g as/ha for the second application and application at a later final growth stage) to attempt to generate a commodity with quantifiable residues.

Oilseed rape was processed to obtain pressed crude oil (after filtration), pressed crude oil (before filtration), refined pressed oil (after filtration), extracted crude oil (after filtration), extracted presscake (after solvent extraction) and refined extracted oil (after filtration). Processing factors are given below.

Some processing factors shows a large difference (>50%) between trials (based on both the individual values from each independent field trial and the individual values from each field site), in principle a third trial should be performed and the median value reported. This was not considered necessary due to the data supplied from the two trials at each independent trial site, giving a total of four separate values.

Note that the values given below show data from trials at two independent test sites, with two trials at each site. As all the trials have independently gone through the same processing and as the difference between the trials are not irreconcilable (10 fold different) according to OECD 508 the median transfer factor was considered most appropriate and has been calculated.

Table 2.7.6.3 Summary of oilseed rape processing factors

Crop (RAC)/Processed product	**Number of studies[(a)]**	**Processing Factor** (PF)	
		Individual values	Median PF
Oilseed rape/ Pressed crude oil	2 (4)	0.62, 1.22, 1.75, 2.00	1.49

Oilseed rape/ Pressed presscake	2 (4)	0.08, 0.22, 0.25, <0.50	0.24
Oilseed rape/ Refined pressed oil	2 (4)	0.69, 1.22, 1.75, 2.50	1.49
Oilseed rape/ Extracted crude oil	2 (4)	1.09, 1.22, 1.67, 2.00	1.45
Oilseed rape/ Extracted presscake	2 (4)	<0.09, <0.11, <0.33, <0.33	<0.22 (best estimate)
Oilseed rape/ Refined extracted oil	2 (4)	1.09, 1.33, 2.00, 2.33	1.67

[a] Number of studies signifies number of independent trials. Figure in brackets gives the number of individual processed fractions assessed across both trials

Calculation performed using unrounded values.

Processed fractions were stored frozen for a maximum of 183 days from asampling to analysis. These storage periods are covered by storage stability trials summarised in B.7.1, which shows stability in all matrices for 23 months.

The results of the study indicate that residues of pydiflumetofen do not concentrate in the processing of oilseed rape into pressed presscake and extracted presscake (processing factors of 0.26 and 0.22 respectively). Residues of pydiflumetofen do concentrate in the processing of oilseed rape to pressed crude oil, pressed oil, extracted crude oil and refined extracted oil (processing factors of 1.40, 1.54, 1.50 and 1.69 respectively)

Summary

The available data on the magnitude of residues on processing (studies on wheat, barley and oilseed rape) are acceptable to allow processing factors to be determined for pydiflumetofen, based on the levels of residues that are expected to arise following the currently proposed uses in cereals and oilseed rape.

2.7.7. Summary of residues in rotational crops

The following section has been re-drafted following ECP ISA. The revised presentation takes account of ECP ISA on the soil fate parameters to use crop interception rates (this reduces the amount of active substance that impacts the soil), for application made to the primary crop.

The representative uses (cereals and oilseeds), and the uses assessed for MRL purposes (carrots, parsnips and parsley root), can be grown in rotation. Field soil degradation studies indicate the DT_{90} value for parent pydiflumetofen is significantly greater than 100 days – a DT_{50} of 1310 days was derived based on the grass covered soil degradation field studies (see section B.8.2.2 in the Volume 3, CP B.8 document for details). Therefore, consideration of residues in rotational crops is required; in addition, consideration of soil accumulation has also been made, due to the persistent nature of parent pydiflumetofen.

There are no major soil metabolites for pydiflumetofen and no potential for accumulation of soil metabolites over multiple years of use.

The persistence of pydiflumetofen in soil is highly complex. Full details are presented in the environmental fate and behaviour evaluation (B.8.2.2 in the Volume 3, CP B.8). There were initially two possible options for the DT50 value; this was due to differences in the calculation of the field dissipation. The longer dissipation rate used in the soil exposure calculations was recorded in a field dissipation study where the treated bare soil plots were covered with a thin layer of sand immediately after application to prevent losses such as volatilisation and soil surface photolysis; in addition the plots were maintained vegetation-free. As such this represents a conservative dissipation rate. The shorter dissipation rate was obtained from a field dissipation study which used bare soil plots at the time of applications but were not covered with sand after application. As such, these plots may have been subject to natural dissipation losses of pydiflumetofen via volatilisation and soil surface photolysis. In addition, the plots had been sown with grass seed and a coverage of grass was allowed to develop following application. This may have allowed further dissipation of pydiflumetofen from soil via root uptake into the grass plants. As

such the shorter dissipation rate was obtained from a situation similar, but not identical, to the situation in which pydiflumetofen is proposed for use in, i.e. post-emergence application to crops.

Following presentation to the ECP in the process of seeking ISA, the ECP advised that the refinement of the longest non-normalised dissipation DT50 and DT90 from the four grassed sites (SFO DT50 1310 days) could be used in the PECsoil calculations. This was due to the grassed sites having a closer reflection of the intended use to environmental conditions.

The impact of accumulation must be addressed for parent pydiflumetofen (OECD Guidance on Residues in Rotational Crops, 2018). The A_{total} has been derived based on long term use, with crop failure. A_{total} is explained further in OECD, 2018 – in this context, 'long term use' means consecutive yearly applications for an extended period, until a soil plateau concentration is reached. Crop interception has been considered for the derivation of the A_{total}. The GAP which results in the maximum soil exposure is the GAP considered as part of the MRL application for carrots. Despite a higher total application rate (in terms of g a.s./ha) being applied to cereals and oilseed rape, the impact of crop interception results in carrots and parsnips having the highest soil exposure of pydiflumetofen, when considering long term use. In terms of rotational crops, carrots and parsnips have been assessed as the worst case GAP.

The GAP on carrots and parsnips represents 2 x 70 g as/ha (total – 140 g as/ha);an interception rate of 25% has been applied in the assessment in line with FOCUS Groundwater guidance on crop interception values to be used for use on carrot. Further explanation as to the use of carrots as a representative worst case is provided in section B.8.2.2 in the Volume 3, CP B.8 document.

It is typical to include the possibility of crop failure in the assessment, especially for cereal uses for which application could take place early in the crop season. The total soil residues (A_{total}) available for uptake after multiple years of application and crop failure after application to target crop are calculated as a sum of the total seasonal application rate to target crop (g as/ha) and the application rate corresponding to residual residues in the soil from long term use of the product (g as/ha). Crop interception has been included as a refinement of the A_{total} – this was included following ISA provided by the ECP on the rotational crop residues assessment. It is considered that this approach more closely mimics the in-field use of pydiflumetofen. As crop failure is included, the A_{total} is considered to be sufficiently worst case and representative of anticipated soil exposure and will cover the majority of in field scenarios for rotational crops.

Following the OECD Guidance scaling 'rules', the scaling factors must be applied to trials within the range 0.3x – 4x the GAP rate. The possible A_{total} scaling factors were estimated following the fate and behaviour evaluation and are shown below in Table 2.7.7.1.

As discussed above, the scenario which includes crop failure has been used to conduct the risk assessment; this is detailed below.

Table 2.7.7.1 Summary of scaling factors for field rotational crop trials, based on worst case A_{total}

DT50:	**1310 days**		**N rate (lowest dosed rotational trial - ~500 g/ha)**	**N rate (highest dosed rotational trial - ~600 g/ha)**
Continuous use (years)	**Crop failure (Y/N)**	**A total (g a.s. /ha)**		
long term	**Y**	**632.9**	**0.790** (representing a residue upscaling factor of x 1.266)	**0.948** (representing a residue upscaling factor of x 1.055)

The scaling factors must be applied to trials within the range 0.3x – 4x the GAP rate (or equivalent to scaling factors themselves representing up to 3.33 x (for upscaling underdosed trials) or scaling factors representing down to 0.25 X (for downscaling of overdosed trials).

Nature of the residue

The nature of the residue has been addressed in Section 2.7.2 above. A similar metabolic pathway is observed in rotational crops to primary crops, and the same residue definitions for primary crops apply (parent pydiflumetofen for risk assessment and enforcement). The same two plant metabolites identified in the rotational crop metabolism and the primary crop metabolism were SYN545547 and SYN54789.

See section 2.7.2 and section B.7.6.1 which summarises the levels (%TRR and mg/kg levels found) of the residues of pydiflumetofen, and SYN545547 and SYN54789 in rotational crops. As per the primary crops, the main component of the residue in rotational crops is parent pydiflumetofen. SYN547891 exceeded 10 % TRR in some rotational crop metabolism samples (max 13.3%TRR) and SYN545547 did not exceed 10%TRR in rotational crop metabolism samples. Despite this, the total radioactive residue for SYN547891 did not exceed 0.004 mg/kg in commodities for human consumption and SYN547891 was found at up to 0.012 mg/kg in wheat straw.

Considering the potential for soil accumulation, the trials are underdosed (0.63 N). As such it is possible that metabolites may be expected at higher levels than the levels observed in the existing metabolism study.

It is observed that the rotational crop metabolism studies were done as confined studies where the soil was contained within containers (which were moved into the glasshouse part way through the growing cycle). It can be the case, that such studies lead to higher residues than observed in the field studies. However, the following summary and comparative information based on highest residues seen in studies indicates that the metabolism and field studies are not far different in terms of residue levels.

The highest residue of pydiflumetofen observed in barley straw from the field trials (500 g as/ha) was 0.09 mg/kg. The highest residue of pydiflumetofen observed in wheat straw from the metabolism trial (400 g as/ha) was 0.063 mg/kg. The highest residue of pydiflumetofen observed in immature spinach in the field trials (500 g and 600 as/ha) was 0.02 mg/kg. The highest residue of pydiflumetofen observed in immature lettuce from the metabolism trial (400 g as/ha) was 0.015 mg/kg.

In order to further consider the potential for metabolites to be expected in rotational crops, the levels of residues of pydiflumetofen found at determinable levels in the rotational crop field trials (scaled to the anticipated maximum soil exposure levels) have been considered (please see below section on 'magnitude of the residue') taking into account estimated metabolite: parent ratios observed in the rotational crop metabolism studies for SYN545547 and SYN54789. It is also observed that the metabolites SYN545547 and SYN547891 were generally more prevalent in the rotational crop metabolism study than other unidentified metabolites (see the Table 2.7.3.4 in section 2.7.3). It is not expected that residues of any metabolite would be found at determinable levels in any rotated food commodity.

In section 2.7.3, the same residue definition for primary crops and rotational crops is proposed (parent pydiflumetofen only for primary and rotational crops).

Pyrazole derived metabolites

Pydiflumetofen is a pyrazole pesticide. It is common for pyrazole pesticides to break down to form common metabolites such as pyrazole acid and N-desmethylpyrazole-acid. These potentially common pyrazole metabolites were not sought in the rotational crop metabolism study or any of the field rotational crop trials.

However, the level of unidentified metabolite from pyrazole labelled pydiflumetofen did not exceed 10 %TRR for any crop fraction at any PBI in the metabolism study (except for turnip foliage, however the corresponding level was 0.001 mg/kg). The absolute level of unidentified pyrazole metabolite was <0.01 mg/kg in all cases, except for wheat straw at a 30 day PBI (0.014 mg/kg).

In addition, it is stated in section 2.8.2 (fate and behaviour in soil) that for pydiflumetofen: 'levels of metabolite formation were low; HSE consider on the basis of the results that no metabolites formed in soil formally trigger inclusion in risk assessment'.

Therefore, it may be considered that, based on the available data, pyrazole derived metabolites are not expected to be formed in quantifiable amounts following application at the proposed GAPs.

However, the long term persistence of pydiflumetofen means that some uncertainty remains regarding the long term behaviour of metabolites in the soil. A soil monitoring programme is expected to feature as a condition of the approval, this programme will allow the long term metabolite profile in the soil to be more clearly understood. If the monitoring programme highlights that pydiflumetofen may be expected to generate quantifiable amounts of pyrazole derived metabolites, this may require further consideration.

Magnitude of the residue

Eight field trials have been conducted to investigate the magnitude of pydiflumetofen residues in succeeding crops, four trials in NEU/UK and four in SEU. Trials performed in these geographic locations can be used to consider possible residues in rotational crops, in line with OECD 504 which states that trials should be from two diverse geographic locations. In each trial a single application was made to bare soil using A19649B (an SC formulation) at a nominal rate of 500 – 600 g a.s./ha. In the first two studies (four trials), nine representative rotated crops (kale, tomato, maize, soybean, fresh bean, strawberry, spinach, carrot, radish) were planted at nominal intervals of 30, 120, 270 and 330 days. In the last two studies (four trials), three representative rotated crops (spinach, carrot and barley) were planted back into the treated plots at nominal intervals of 30, 60 and 365 days. Considering the potential for soil accumulation, the trials are marginally underdosed with respect to the worst case scenario (0.79 – 0.948 N). The trials are within the standard ±25 %. However, as these values may be used to set MRLs, the possible impact of systemic bias has been considered as whilst there is underdosing, none of the rotational crop trials are overdosed. As such, the positive residue values determined in the trials have been scaled to match the estimated soil exposure, according to the scaling factors in table 2.7.7.1- <LOQ residues have not been scaled.

The results of the residue trials are summarised in Table 2.7.7.2 and Table 2.7.7.3.

With regard to metabolites, metabolites SYN545547 and SYN547891 were identified in the rotational crop metabolism study, and there were other unidentified peaks (please refer back to section 2.7.2 and section 2.7.3 for a summary). Based on the ratios of parent: individual metabolites it would not be expected that the residues of any metabolites would have been found at or above 0.01 mg/kg in the rotational crop field trials conducted at application rates (to bare soil) of 500 g a.s./ha and 600 g a.s./ha (as per the studies available in the submitted rotational crop residue field studies). The rotational crop field studies are underdosed, when considering the potential for accumulation of pydiflumetofen in soils (0.79 – 0.948 N). Based on the co-presence of parent and metabolites in rotational crop metabolism samples[7]: the highest metabolite:parent ratio was 0.1674:1, for immature lettuce (SYN547891). From table 2.7.7.3, the highest residue in a rotated food commodity is 0.0528 mg/kg in mature spinach at a 30 day PBI. The expected worst case metabolite level in food commodities is therefore <0.01 mg/kg. Therefore, it is acceptable to conclude on the basis of the available data that the metabolites SYN545547 and SYN547891 are not expected at or above 0.01 mg/kg in any rotated food commodity.

If, for future extensions of uses, higher application rate rotational crop field trials are generated, this would provide the opportunity for metabolites SYN545547 and SYN547891 to be included as analytes to determine whether these might be found as positive residues when a higher application regime is followed.

[7] Immature lettuce (rotational crop metabolism 30 DAT (days after treatment) Plant Back Intervals:
phenyl sample: M: P SYN547891 (X:1) = 11.6 : 69.3 (**0.1674:1**)
pyrazole sample: M: P SYN547891 (X:1) = 6.8 : 76.7 (0.0887:1)
phenyl sample: M: P SYN545547 (X:1) = 4.0 : 69.3 (0.0577:1)
pyrazole sample: M: P SYN545547 (X:1) = 2.3 : 76.7 (0.030:1)

Table 2.7.7.2 Residues of pydiflumetofen found in field rotational crop studies

Crop group	Crop Part	Plant back interval (nominal in days)	Pydiflumetofen residue found (mg/kg)							
			Northern France (S16-04583-01)	Germany (S16-04583-02)	Southern France (S16-04584-01)	Spain (S16-04584-02)	United Kingdom (S13-01022-01)	Germany (S13-01022-02)	Southern France (S13-01023-01)	Italy (S13-01023-02)
			Application rate ~600 g a.s./ha				Application rate ~500 g a.s./ha			
Leafy crops	Kale leaves (BBCH 49 – NCH)	30	<0.01	<0.01	<0.01	<0.01 [a]	-	-	-	-
		120	<0.01	<0.01	<0.01	-	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01 [a]	-	-	-	-
		330	<0.01	<0.01	<0.01	-	-	-	-	-
	Bean -Whole plant [c] (BBCH 74-75)	30	<0.01	-	-	-	-	-	-	-
		120	<0.01	-	-	-	-	-	-	-
		270	<0.01	-	-	-	-	-	-	-
		330	<0.01	-	-	-	-	-	-	-
	Spinach (BBCH 43)[d]	30	**0.01**	<0.01	<0.01	<0.01 [a]	<0.01	<0.01	**0.01**	<0.01
		60	-	-	-	-	<0.01	<0.01	**0.02**	<0.01
		120	<0.01	<0.01	<0.01	-	-	-	-	-
		270	<0.01	**0.02**	<0.01	<0.01 [a]	-	-	-	-
		330	<0.01	<0.01	<0.01	-	-	-	-	-
		365	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	Spinach (BBCH 49, NCH)	30	**0.05**	<0.01	<0.01	<0.01 [a]	-	<0.01	<0.01	<0.01
		60	-	-	-	-	-	<0.01	<0.01	<0.01
		120	**0.01**	**0.02**	<0.01	-	-	-	-	-
		270	**0.01**	**0.03**	<0.01	<0.01 [a]	-	-	-	-
		330	**0.01**	<0.01	<0.01	-	-	-	-	-
		365	-	-	-	-	-	<0.01	<0.01	<0.01
Leafy crops/root crop based forage crops	Carrot tops with foliage (BBCH 49 – NCH)	30	**0.01**	**0.01**	**0.01**	-	<0.01	<0.01	<0.01	<0.01
		60	-	-	-	-	<0.01	<0.01	**0.01**	<0.01
		120	<0.01	<0.01	**0.01**	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	NS	-	-	-	-
		330	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		365	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	Radish tops with foliage (BBCH 49 – NCH)	30	**0.03**	<0.01	**0.02**	<0.01	-	-	-	-
		120	<0.01	<0.01	**0.01**	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		330	<0.01	<0.01	<0.01	<0.01	-	-	-	-

	Soybean forage (BBCH 73-81)	30	**0.01**	-	<0.01	-	-	-	-	-
		120	**0.01**	-	<0.01	<0.01	-	-	-	-
		270	**0.01**	-	<0.01	-	-	-	-	-
		330	**0.01**	-	<0.01	<0.01	-	-	-	-
	Bean - remaining plant (BBCH 79 – NCH)	30	-	<0.01	<0.01	<0.01	-	-	-	-
		120	-	<0.01	<0.01	<0.01	-	-	-	-
		270	-	<0.01	<0.01	<0.01	-	-	-	-
		330	-	<0.01	<0.01	<0.01	-	-	-	-
	Barley (immature whole plant) (BBCH 41)	30	-	-	-	-	<0.01	<0.01	<0.01	**0.02**
		60	-	-	-	-	<0.01	<0.01	<0.01	<0.01
		365	-	-	-	-	<0.01	<0.01	<0.01 [e]	<0.01
Straw and fodder	Maize remaining plant (BBCH 89 – NCH)	30	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		120	**0.02**	<0.01	<0.01	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		330	**0.01**	<0.01	<0.01	<0.01	-	-	-	-
	Barley Straw (BBCH 89 – NCH)	30	-	-	-	-	**0.02**	<0.01	**0.06**	**0.02**
		60	-	-	-	-	**0.03**	<0.01	**0.09**	**0.02**
		365	-	-	-	-	**0.01**	<0.01	**0.01** [e]	**0.01**
Root and tuber crops	Carrot roots (BBCH 49 – NCH)	30	**0.02**	<0.01	**0.02**	-	<0.01	<0.01	**0.02**	<0.01
		60	-	-	-	-	<0.01	<0.01	**0.02**	**0.02**
		120	**0.02**	<0.01	**0.03**	<0.01	-	-	-	-
		270	**0.02**	<0.01	**0.01**	-	-	-	-	-
		330	**0.01**	<0.01	**0.02**	<0.01	-	-	-	-
		365	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	Radish roots (BBCH 49 – NCH)	30	**0.04**	<0.01	**0.03**	<0.01	-	-	-	-
		120	**0.01**	<0.01	**0.01**	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		330	<0.01	<0.01	<0.01	<0.01	-	-	-	-
Cereal grain/oilseeds and pulses	Soybean seed (BBCH 89 – NCH)	30	-	-	<0.01	- [b]	-	-	-	-
		120	-	-	<0.01	- [b]	-	-	-	-
		270	-	-	<0.01	- [b]	-	-	-	-
		330	-	-	<0.01	- [b]	-	-	-	-
	Bean – dry seed	30	-	<0.01	<0.01	<0.01	-	-	-	-
		120	-	<0.01	<0.01	<0.01	-	-	-	-
		270	-	<0.01	<0.01	<0.01	-	-	-	-

	(BBCH 89 – NCH)	330	-	<0.01	<0.01	<0.01	-	-	-	-
	Barley grain (BBCH 89 – NCH)	30	-	-	-	-	<0.01	<0.01	<0.01	<0.01
		60	-	-	-	-	<0.01	<0.01	<0.01	<0.01
		365	-	-	-	-	<0.01	<0.01	<0.01 [e]	<0.01
Fruits and fruiting vegetables	Strawberry (BBCH 87-89 – NCH)	30	<0.01	<0.01	<0.01	-	-	-	-	-
		120	<0.01	<0.01	<0.01	-	-	-	-	-
		270	<0.01	<0.01	<0.01	-	-	-	-	-
		330	<0.01	<0.01	<0.01	-	-	-	-	-
	Tomato (BBCH 89 – NCH)	30	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		120	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		330	<0.01	<0.01	<0.01	<0.01	-	-	-	-
Other	Maize whole cobs (BBCH 89 – NCH)	30	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		120	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		330	<0.01	<0.01	<0.01	<0.01	-	-	-	-
	Bean – fresh seed (BBCH 79 – NCH)	30	-	<0.01	<0.01	<0.01	-	-	-	-
		120	-	<0.01	<0.01	<0.01	-	-	-	-
		270	-	<0.01	<0.01	<0.01	-	-	-	-
		330	-	<0.01	<0.01	<0.01	-	-	-	-

'-' Not sampled for this time interval, in this study.
NCH – normal crop harvest
a: No control sample available.
b: Insufficient sample size.
c: The crop did not develop sufficiently to obtain usable seed samples in trial S16-04583-01; hence only whole plant was collected.
d: For trial S13-01022-01, this is BBCH 14-18, crop is sufficiently representative of immature spinach leaves.
e: Crop re-drilled after a succeeding crop had already been grown (60 day samples planted and harvested before this crop was sown).

Significant residues (i.e. residues >LOQ) are observed in carrot roots, radish roots, barley straw, soybean forage, carrot tops, radish tops, barley immature whole plants, maize remaining plant and spinach leaves at the dose rate tested during these field trials (500-600 g a.s./ha). This is overdosed considering the maximum total seasonal application rate (200 g a.s./ha).

Without considering accumulation of pydiflumetofen in the soil: If results were down-scaled to this seasonal application rate, positive residues would only be expected in barley straw and radish root. The levels expected in barley straw (up to ~0.04 mg/kg) would be significantly less than the residues expected in cereal crops grown as primary crops (up to 4 mg/kg). For radish root, the expected residue would be only slightly above 0.01 mg/kg (approx. 0.013 mg/kg).

With a consideration of possible accumulation of pydiflumetofen in the soil: These studies are underdosed considering the possible soil accumulation. An estimate of the possible residues expected, based on scaling up positive residues only (as explained in the first paragraph of this section (on magnitude of residues)) is given in Table 2.7.7.3. Only positive residues have been scaled, as <LOQ results cannot be reliably scaled up. The original result is reported in bold text and the scaled result in bold text with square brackets [].

Table 2.7.7.3 Residues of pydiflumetofen found in field rotational crop studies (**scaled**)

Crop group	Crop Part	Plant back interval (nominal in days)	Pydiflumetofen residue found (mg/kg) **[scaled residue (mg/kg)]** The original result is reported in bold text and the scaled result in bold text with square brackets []							
			Northern France (S16-04583-01)	Germany (S16-04583-02)	Southern France (S16-04584-01)	Spain (S16-04584-02)	United Kingdom (S13-01022-01)	Germany (S13-01022-02)	Southern France (S13-01023-01)	Italy (S13-01023-02)
			Application rate ~600 g a.s./ha [f]				Application rate ~500 g a.s./ha [g]			
Leafy crops	Kale leaves (BBCH 49 – NCH)	30	<0.01	<0.01	<0.01	<0.01 [a]	-	-	-	-
		120	<0.01	<0.01	<0.01	-	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01 [a]	-	-	-	-
		330	<0.01	<0.01	<0.01	-	-	-	-	-
	Bean -Whole plant [c] (BBCH 74-75)	30	<0.01	-	-	-	-	-	-	-
		120	<0.01	-	-	-	-	-	-	-
		270	<0.01	-	-	-	-	-	-	-
		330	<0.01	-	-	-	-	-	-	-
	Spinach (BBCH 43)[d]	30	**0.01 [0.0106]**	<0.01	<0.01	<0.01 [a]	<0.01	<0.01	**0.01 [0.0127]**	<0.01
		60	-	-	-	-	<0.01	<0.01	**0.02 [0.0253]**	<0.01
		120	<0.01	<0.01	<0.01	-	-	-	-	-
		270	<0.01	**0.02 [0.0211]**	<0.01	<0.01 [a]	-	-	-	-
		330	<0.01	<0.01	<0.01	-	-	-	-	-
		365	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	Spinach (BBCH 49, NCH)	30	**0.05 [0.0528]**	<0.01	<0.01	<0.01 [a]	-	<0.01	<0.01	<0.01
		60	-	-	-	-	-	<0.01	<0.01	<0.01
		120	**0.01 [0.0106]**	**0.02 [0.0211]**	<0.01	-	-	-	-	-
		270	**0.01 [0.0106]**	**0.03 [0.0317]**	<0.01	<0.01 [a]	-	-	-	-
		330	**0.01 [0.0106]**	<0.01	<0.01	-	-	-	-	-
		365	-	-	-	-	-	<0.01	<0.01	<0.01
Leafy crops/root crop based forage crops	Carrot tops with foliage (BBCH 49 – NCH)	30	**0.01 [0.0106]**	**0.01 [0.0106]**	**0.01 [0.0106]**	-	<0.01	<0.01	<0.01	<0.01
		60	-	-	-	-	<0.01	<0.01	**0.01 [0.0127]**	<0.01

		120	<0.01	<0.01	**0.01 [0.0106]**	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	NS	-	-	-	-
		330	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		365	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	Radish tops with foliage (BBCH 49 – NCH)	30	**0.03 [0.0317]**	<0.01	**0.02 [0.0211]**	<0.01	-	-	-	-
		120	<0.01	<0.01	**0.01 [0.0106]**	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		330	<0.01	<0.01	<0.01	<0.01	-	-	-	-
	Soybean forage (BBCH 73-81)	30	**0.01 [0.0106]**	-	<0.01	-	-	-	-	-
		120	**0.01 [0.0106]**	-	<0.01	<0.01	-	-	-	-
		270	**0.01 [0.0106]**	-	<0.01	-	-	-	-	-
		330	**0.01 [0.0106]**	-	<0.01	<0.01	-	-	-	-
	Bean - remaining plant (BBCH 79 – NCH)	30	-	<0.01	<0.01	<0.01	-	-	-	-
		120	-	<0.01	<0.01	<0.01	-	-	-	-
		270	-	<0.01	<0.01	<0.01	-	-	-	-
		330	-	<0.01	<0.01	<0.01	-	-	-	-
	Barley (immature whole plant) (BBCH 41)	30	-	-	-	-	<0.01	<0.01	<0.01	**0.02 [0.0253]**
		60	-	-	-	-	<0.01	<0.01	<0.01	<0.01
		365	-	-	-	-	<0.01	<0.01	<0.01 [e]	<0.01
Straw and fodder	Maize remaining plant (BBCH 89 – NCH)	30	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		120	**0.02 [0.0211]**	<0.01	<0.01	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		330	**0.01 [0.0106]**	<0.01	<0.01	<0.01	-	-	-	-
	Barley Straw (BBCH 89 – NCH)	30	-	-	-	-	**0.02 [0.0253]**	<0.01	**0.06 [0.0760]**	**0.02 [0.0253]**
		60	-	-	-	-	**0.03 [0.0380]**	<0.01	**0.09 [0.1139]**	**0.02 [0.0253]**
		365	-	-	-	-	**0.01 [0.0127]**	<0.01	**0.01 [e] [0.0127]**	**0.01 [0.0127]**
Root and tuber crops	Carrot roots	30	**0.02 [0.0211]**	<0.01	**0.02 [0.0211]**	-	<0.01	<0.01	**0.02 [0.0253]**	<0.01

	(BBCH 49 – NCH)	60	-	-	-	-	<0.01	<0.01	**0.02 [0.0253]**	**0.02 [0.0253]**
		120	**0.02 [0.0211]**	<0.01	**0.03 [0.0317]**	<0.01	-	-	-	-
		270	**0.02 [0.0211]**	<0.01	**0.01 [0.0106]**	-	-	-	-	-
		330	**0.01 [0.0106]**	<0.01	**0.02 [0.0211]**	<0.01	-	-	-	-
		365	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	Radish roots (BBCH 49 – NCH)	30	**0.04 [0.0422]**	<0.01	**0.03 [0.0317]**	<0.01	-	-	-	-
		120	**0.01 [0.0106]**	<0.01	**0.01 [0.0106]**	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		330	<0.01	<0.01	<0.01	<0.01	-	-	-	-
Cereal grain/oilseeds and pulses	Soybean seed (BBCH 89 – NCH)	30	-	-	<0.01	- [b]	-	-	-	-
		120	-	-	<0.01	- [b]	-	-	-	-
		270	-	-	<0.01	- [b]	-	-	-	-
		330	-	-	<0.01	- [b]	-	-	-	-
	Bean – dry seed (BBCH 89 – NCH)	30	-	<0.01	<0.01	<0.01	-	-	-	-
		120	-	<0.01	<0.01	<0.01	-	-	-	-
		270	-	<0.01	<0.01	<0.01	-	-	-	-
		330	-	<0.01	<0.01	<0.01	-	-	-	-
	Barley grain (BBCH 89 – NCH)	30	-	-	-	-	<0.01	<0.01	<0.01	<0.01
		60	-	-	-	-	<0.01	<0.01	<0.01	<0.01
		365	-	-	-	-	<0.01	<0.01	<0.01 [e]	<0.01
Fruits and fruiting vegetables	Strawberry (BBCH 87-89 – NCH)	30	<0.01	<0.01	<0.01	-	-	-	-	-
		120	<0.01	<0.01	<0.01	-	-	-	-	-
		270	<0.01	<0.01	<0.01	-	-	-	-	-
		330	<0.01	<0.01	<0.01	-	-	-	-	-
	Tomato (BBCH 89 – NCH)	30	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		120	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		330	<0.01	<0.01	<0.01	<0.01	-	-	-	-
Other	Maize whole cobs	30	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		120	<0.01	<0.01	<0.01	<0.01	-	-	-	-
		270	<0.01	<0.01	<0.01	<0.01	-	-	-	-

	(BBCH 89 – NCH)	330	<0.01	<0.01	<0.01	<0.01	-	-	-	-
	Bean – fresh seed (BBCH 79 – NCH)	30	-	<0.01	<0.01	<0.01	-	-	-	-
		120	-	<0.01	<0.01	<0.01	-	-	-	-
		270	-	<0.01	<0.01	<0.01	-	-	-	-
		330	-	<0.01	<0.01	<0.01	-	-	-	-

'-' Not sampled for this time interval, in this study.
NCH – normal crop harvest
a: No control sample available.
b: Insufficient sample size.
c: The crop did not develop sufficiently to obtain usable seed samples in trial S16-04583-01; hence only whole plant was collected.
d: For trial S13-01022-01, this is BBCH 14-18, crop is sufficiently representative of immature spinach leaves.
e: Crop re-drilled after a succeeding crop had already been grown (60 day samples planted and harvested before this crop was sown).
f: Actual application rates ranged from 528 – 643 g/ha; however, the actual application rates at the 30 and 60 PBIs varied by less than 5 % compared to the nominal, as these PBIs have been considered for risk assessment and MRL setting, the scaling has not accounted for the actual application rate in the trial.
g: Actual application rates ranged from 459 – 515 g/ha, ; however, the actual application rates at the 30 and 60 PBIs varied by less than 5 % compared to the nominal, as these PBIs have been considered for risk assessment and MRL setting, the scaling has not accounted for the actual application rate in the trial.

As significant residues in crops grown in rotation cannot be ruled out, there are two options; setting a plant back restriction or setting MRLs based on the available data to accommodate these possible residues.

Positive residues were still predicted at a PBI of 330 days (for root, leafy and forage crops) and for 365 days for cereal straw. It is not possible to conclude, based on the positive residues still observed at 330 days that residues would be not expected after 365 days. Based on the rotational crop residues data sets it is impractical to consider setting a plant back interval that would result in all <LOQ residues. The persistence of pydiflumetofen also makes plant back restrictions unfeasible. Based on the consumer risk assessment of the level of residues identified in the above tables, these residues arising in rotational crops can be included in the risk assessment that supports the active substance (see CRA in section 2.7.9).

As set out in the OECD guidance document on rotational crops, when significant residues >LOQ are expected in rotational crops, MRLs may be set on rotated commodities. This can account for possible uptake in rotated commodities following lawful treatment of a primary crop with a particular active substance. The number of available trials covering the 'super groups' (OECD 2018 Guidance on Residues in Rotational Crops) is laid out below in Table 2.7.7.4. At least one crop should be tested from each subgroup. MRLs are not currently set on animal feed commodities; the impact of rotational residues in feed commodities has been assessed by inclusion of the relevant residues in the dietary burden calculation.

Table 2.7.7.4 MRL setting crop groups for rotational crops

Super crop group	**Sub group**	**Trials required**[8]	**Trials available**	**>LOQ residues?** [a]
Root and tuber	Carrots/radishes/sugar beets/other beets	4	12	Y
	Potatoes (optional)	4	0	-
Bulb and stem vegetables	Leek/celery	4	0	-
Cereals	Wheat/barley/triticale/oats/rye	8	4	N
	Maize/other cereals/sugar cane	8	4	N
Leafy vegetables and brassicas	Lettuce/spinach	4	8	Y
	Head cabbage/kale	4	4	N
	Broccoli/cauliflower	4	0	-
Oilseeds/pulses	Oilseed rape/soybeans	8	1	N
	Dried beans/dried peas	4	3	N
Fruits and fruiting vegetables	Strawberry	4	3	N
	Cucumber/tomato etc.	4	4	N

a: Animal feed commodities not included, MRLs are not currently set on animal feed commodities in GB.

For a number of crop groups (super and/or sub groups) the number of trials available, was less than that set out in the OECD (2018) guidance. However in the commodity groups, where >LOQ residues were estimated, there are a higher number of trials available than requested in the guidance (e.g. 12 for root crops, versus 4 trials required; 8 trials for lettuce and spinach, versus 4 trials required).

HSEs scientific evaluation considers that the available rotational crop field trials data are likely sufficient to propose MRLs, and to not include any replant restrictions on the pesticide labels.

The MRLs have been estimated based on representative crops according to the super groups detailed in table 2.7.7.4 – these super groups have been used to populate the respective MRL crop categories. This is based on the 'super' group approach – as standard, 60 trials are the maximum number of individual trials required for the

[8] OECD 2018 Guidance on Residues in Rotational Crops

'super' group approach (OECD, 2018). Only 43 trials are available; however the vast majority of these show <LOQ residues. For crop groups with n≥4, an MRL has been estimated using the OECD MRL calculator. Furthermore, the OECD (2018) Guidance states that some trials might be waived depending on results of metabolism (OECD 502) and limited field trials (OECD 504) design trials. For example, the level of residue found in cereal grain in the rotational metabolism study was very low (<0.008 mg/kg) – this provides additional reassurance that, as all residues observed in the field trials are also <0.01 mg/kg, a reduced data set is acceptable for the cereal super group.

HSE considers the data sets as sufficient to propose MRL levels.

The table below details the STMR, HR and MRL proposals for rotational crops and primary crops. As set out in the OECD 2018 guidance document for rotational crops, if the contribution of the residue in rotational crops is <25 % of the residue in primary crops, then it is not necessary to combine the primary and rotational residues. This is taken to refer to the HR value; therefore, where the HR for the rotational residue is >25 % of the primary crop, the rotational HR residue is added to each individual primary crop residue to produce an adjusted data set. The combined data set is then used to propose the STMR, HR and MRL.

Rotational residue levels are taken from the two shortest PBIs, 30 days and 60 days – the data sets from these PBIs have been combined in order to have more robust data sets with which to derive end-points for the risk assessment and for MRL setting. The data for these PHIs are considered sufficiently similar, and in practice cover a similar replant situation.

No trials data is available for potatoes, bulb vegetables, stem vegetables or flowering brassica. Data on root and tuber vegetables has been extrapolated to cover bulb vegetables and potatoes – bulb vegetables and potatoes fall into the root and tuber metabolism group – therefore, this is considered an appropriate extrapolation. Stem vegetables and flowering brassica have been supported by the data on leafy vegetables; similarly, stem vegetables and flowering brassica are considered to fall into the leafy vegetable metabolism group.

The STMR and HR proposed in table 2.7.7.5 below are the values that have been used to assess consumer risk.

Table 2.7.7.5 Combined residues considering primary crop (PC) and rotational crop (RC) residues

Crop/crop group	**PC (mg/kg)**			**RC (mg/kg)†**			RC HR >25% of the PC?	Combined adjusted residues* (mg/kg)	Overall (combined PC + RC where needed) residue levels end-points				remark
	Summary of residues	STMR	HR	Summary of residues	STMR	HR			STMR [2] (mg/kg)	HR [1] (mg/kg)	OECD MRL unrounded (mg/kg)	OECD MRL Rounded (mg/kg)	
Commodities under consideration:													
Barley grain → oat grain	0.06, 2x0.08, 2x0.10, 0.12, 0.13 0.32	0.1	0.32	8 x <0.01	<0.01	<0.01	No	N/A	0.1	0.32	0.454	0.5	PC only
Wheat grain → rye grain, triticale grain	2x<0.01, 0.01, 3x0.02, 3 x 0.03, 2 x 0.04, 0.05	0.025	0.05	8 x <0.01	<0.01	<0.01	No	N/A	0.025	0.05	0.078	0.08	PC only
Oilseed rape seed	3x<0.01, 2 x 0.01, 0.02, 0.03, 0.04	0.01	0.04	<0.01	<0.01	<0.01	No	N/A	0.01	0.04	0.064	0.07	PC only
Carrots, parsley root and parsnip (MRL application)	<0.01, 3 x 0.02, 2 x 0.03, 2 x 0.04	0.025	0.04	8x<0.01, 2x0.021, 3x0.025, 0.032, 0.042	<0.01	0.0422	Yes	0.052, 3x0.062, 2x0.072, 2x0.082	0.067	0.082	0.205	0.2	PC + RC
Rotational commodities:													
Strawberries	-	-	-	3 x<0.01	<0.01	<0.01	N/A	N/A	<0.01	<0.01	<0.01	0.01*	RC – only Based on data on strawberries
Potatoes	-	-	-	8x<0.01, 2x0.021, 3x0.025, 0.032, 0.042	<0.01	0.0422	N/A	N/A	<0.01	0.0422	0.059	0.06	RC only – extrapolated from data on root and tuber veg

Root crops (other than carrots/parsnip and parsley root), including sugar beet	-	-	-	8x<0.01, 2x0.021, 3x0.025, 0.032, 0.042	<0.01	0.0422	N/A	N/A	<0.01	0.0422	0.059	0.06	RC only – extrapolated from data on root and tuber veg
Bulb vegetables	-	-	-	8x<0.01, 2x0.021, 3x0.025, 0.032, 0.042	<0.01	0.0422	N/A	N/A	<0.01	0.0422	0.059	0.06	RC only – extrapolated from data on root and tuber veg
Fruit and Fruiting vegetables	-	-	-	4 x<0.01	<0.01	<0.01	N/A	N/A	<0.01	<0.01	<0.01	0.01*	RC only – data from tomatoes
Flowering brassica, kohlrabis	-	-	-	27x<0.01, 4 x 0.011, 2 x 0.013, 0.021, 0.025, 0.032, 0.053	<0.01	0.053	N/A	N/A	<0.01	0.053	0.053	0.06	RC only – data from immature and mature spinach, radish and carrot tops
Head brassicas and leafy brassica [3]	-	-	-	4x<0.01	<0.01	<0.01	N/A	N/A	<0.01	<0.01	<0.01	0.01*	RC only – data from kale
Leaf vegetables, herbs and edible flowers	-	-	-	27x<0.01, 4 x 0.011, 2 x 0.013, 0.021, 0.025, 0.032, 0.053	<0.01	0.053	N/A	N/A	<0.01	0.053	0.053	0.06	RC only – data from immature and mature spinach, radish and carrot tops
Legume vegetables	-	-	-	3 x <0.01	<0.01	<0.01	N/A	N/A	<0.01	<0.01	<0.01	0.01*	RC only – data from bean (seeds)
Stem vegetables	-	-	-	27x<0.01, 4 x 0.011, 2 x 0.013, 0.021,	<0.01	0.053	N/A	N/A	<0.01	0.053	0.053	0.06	RC only – data from immature and mature

				0.025, 0.032, 0.053									spinach, radish and carrot tops
Pulses [4]	-	-	-	4 x <0.01	<0.01	<0.01	N/A	N/A	<0.01	<0.01	<0.01	0.01*	RC only – data from bean and soybean (seeds)
Oilseeds except oilseed rape [4]	-	-	-	4 x <0.01	<0.01	<0.01	N/A	N/A	<0.01	<0.01	<0.01	0.01*	RC only – data from bean and soybean (seeds)
Cereal grains, except barley, oats, rice, wheat, triticale and rye	-	-	-	8 x <0.01	<0.01	<0.01	N/A	N/A	<0.01	<0.01	<0.01	0.01*	RC only – data from barley grain
Honey ‡	3 x <0.01	<0.01	<0.01	<0.01	<0.01	<0.01	‡	3 x<0.02	<0.02	<0.02	<0.02	0.05*	PC +RC ‡
Feed commodities:													
Root and tuber tops	-	-	-	27x<0.01, 4 x 0.011, 2 x 0.013, 0.021, 0.025, 0.032, 0.053	<0.01	0.053	N/A	N/A	<0.01	0.053	N/A	N/A	RC only – data from immature and mature spinach, radish and carrot tops
Barley straw → oat straw	0.27, 0.57, 1.13, 1.19, 1.20, 1.27, 1.85, 2.72	1.195	2.72	2x <0.01 3x 0.025 0.038 0.076 0.114	0.025	0.114	No	N/A	1.195	2.72	N/A	N/A	PC only
Wheat straw → rye straw, triticale straw	0.28, 0.40, 0.41, 0.84, 0.86, 0.88, 0.94, 1.00,	0.91	4.0	2x <0.01 3x 0.025 0.038 0.076 0.114	0.025	0.114	No	N/A	0.91	4.0	N/A	N/A	PC only

	2.20, 2.39, 3.00, 4.00												
Straw – other	-	-	-	2x <0.01 3x 0.025 0.038 0.076 0.114	0.025	0.114	N/A	N/A	0.032	0.114	N/A	N/A	RC only – data from barley straw
Pea/bean vines	-	-	-	3 x <0.01	<0.01	<0.01	N/A	N/A	<0.01	<0.01	N/A	N/A	RC only – data from bean vines
Forage	-	-	-	12x<0.01, 0.011, 0.025	<0.01	0.025	N/A	N/A	<0.01	0.025	N/A	N/A	RC only – data from Maize remaining plant, barley forage, soybean forage

(1): H**R**: Highest residue. When residue definition for enforcement and risk assessment differs, HR according to residue definition for enforcement reported in brackets (HR_{Enf}).
(2): **STMR:** Supervised Trials Median Residue. When residue definition for enforcement and risk assessment differs, STMR according to definition for enforcement reported in brackets ($STMR_{Enf}$).
(3): Sufficient data is available for head cabbage and kale, in line with the sub groups laid out in the 'super' crop group approach. All residues in kale were <LOQ.
(4): One trial on oilseeds, three on pulses – for a total of four trials <LOQ, this is sufficient to support the pulses and oilseeds 'super group'.
(†): Rotational residues selected from the 30 and 60 day PBIs.
(‡): No specific rotational crop data is available on flowers. However, the available data on crop fractions which are produced via flowering (beans, barley grain, maize whole cobs, tomatoes and strawberries) demonstrate <LOQ residues in all cases (<0.01 mg/kg). To account for the uncertainty, the <LOQ results for primary crops have been combined with <0.01, to give an STMR of <0.02 mg/kg. The default honey MRL of 0.05* mg/kg is considered appropriate.

Table 2.7.7.6 MRL estimates considering PC and RC residues

Crop group	MRL category	MRL subcategory (if applicable)	MRL proposal	Comment
Fruits, Fresh or Frozen; Tree nuts	Citrus fruits	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
	Tree nuts	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
	Pome fruits	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
	Stone fruits	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
	Berries and small fruits	Grapes	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
		Strawberries	0.01*	Based on rotational trials data (n=3) and no primary crop use
		Cane fruits	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
		Other small fruit and berries	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
	Miscellaneous fruits with	Edible peel	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
		Inedible peel, small		
		Inedible peel, large		
Vegetables, Fresh or Frozen	Root and tuber vegetables	**Carrot**	**0.2**	See footnote a (PC+RC)
		Parsnip	**0.2**	
		Parsley root	**0.2**	
		Potatoes	0.06	Based on rotational trials data n=15
		Tropical root and tuber vegetables		
		Other root and tuber vegetables except sugar beets (and carrot, parsnip and parsley root)		
	Bulb vegetables	n/a	0.06	Based on rotational trials data, n=15
	Fruiting vegetables	Solanaceae and Malvaceae	0.01*	Based on rotational trials data n=4 (RC only)
		Cucurbits with edible peel		
		Sweet corn		
		Other fruiting vegetables		
	Brassica vegetables(excluding brassica roots and brassica baby leaf crops)	Leafy brassica	0.01*	Based on rotational trials data (n=4) (RC only)
		Head brassica	0.01*	
		Flowering brassica	0.06	Based on rotational trials data n=37 (RC only)
		lettuces and salad plants		

	Leaf vegetables, herbs and edible flowers	Spinaches and similar leaves		
		Grape leaves and similar species		
		Watercresses		
		Witloofs/Belgian endives		
		Herbs and edible flowers		
	Legume vegetables	n/a	0.01*	Based on rotational trials data n=3 (RC only)
	Stem vegetables	n/a	0.06	Based on rotational trials data n=37 (RC only)
	Fungi, mosses and lichens	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
	Algae and prokaryotes organisms	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
Pulses	Pulses	n/a	0.01*	Based on rotational trials data n=4[b] (RC only)[d]
Oilseeds and oil fruits	Oil seeds	**Rapeseeds/canola seeds**	**0.07**	Based on primary crop data n= 8 (PC only)
		All other oilseeds	0.01*	Based on rotational trials data n=4[b] (RC only)[d]
	Oil fruit	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
Cereals	Cereals	**Barley**	**0.5**	Based on primary crop data n=8 (PC only)
		Oat		
		Wheat	**0.08**	Based on primary crop data n=12 (PC only)
		Rye		
		All other cereals	0.01*	Based on rotational trials data n=8 (RC only)
Teas, coffee, herbal infusions, cocoa and carobs	Teas	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
	Coffee beans	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
	Herbal infusions	Flowers	0.01*	No data - default
		Leaves and herbs	0.01*	No data - default
		Roots	0.01*	No data - default
		Any other parts of the plant	0.01*	No data - default
	Cocoa beans	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
	Carobs/Saint John's breads	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)

Hops	Hops	n/a	0.01*	Not grown in rotation and no primary crop use (default 0.01* MRL level)
Spices	Seed spices	n/a	0.01*	No data - default
	Fruit spices			
	Bark spices	n/a	0.01*	No data - default
	Root and rhizome spices	n/a	0.01*	No data - default
	Bud spices	n/a	0.01*	No data - default
	Flower pistil spices	n/a	0.01*	No data - default
	Aril spices	n/a	0.01*	No data - default
Sugar Plants	Sugar plants	Sugar beet roots	0.06	Based on rotational trials data n=15 (RC only)
		Sugar canes	0.01*	No data - default
		Chicory roots	0.06	Based on rotational trials data n=15 (RC only)
		Others	0.01*	No data - default
Honey and other apiculture products	Honey and other apiculture products	Honey	0.05*	See footnote c

Crops under consideration (i.e. with a specific requested GAP) are denoted **in bold.**
a. See table 2.7.7.5 for derivation of rotational MRL.
b. Pulses/oilseeds are a 'super group' n=4, this is sufficient to support an MRL.
c. No specific rotational crop data is available on flowers. To account for the uncertainty, the default honey MRL of 0.05* mg/kg is considered appropriate.
d. One trial on oilseeds, three on pulses – for a total of four trials <LOQ, this is sufficient to support the pulses and oilseeds 'super group'.

2.7.8. Summary of other studies

Literature studies:

Regarding the literature search undertaken by the applicant, it is considered that the search is acceptable in terms of databases searched and the search criteria applied when considering the residues and dietary exposure areas.

The original data submission (July 2020) literature review included searches done for parent and metabolites in November 2015, so the years leading up to submission to HSE (July 2020) had not been included.

The original search did not reveal any references of relevance to this residues risk assessment.

In the latter stages of HSE's evaluation (2022), the applicant supplied an updated literature review to complete the literature review to cover the years up to the time of submission and more recent studies. For this update, parent pydiflumetofen ~~was~~ and metabolites were included in the searches ~~(the original searches in 2015 for metabolites had yielded a very large number of papers that were not relevant)~~.

The updated literature review (dated 2022), yielded six papers of potential relevance in the areas of residues and metabolism. HSE considered that two of these were of potential interest for HSE to consider the full publications, and a summary of these papers (on enantiomeric composition) is summarised at the end of section B.7.2.1, together with a summary of another paper on enantiomeric composition that was included with the toxicology literature papers.

Residue levels in pollen and bee products:

The proposed uses of the representative product are on cereal and oilseed rape crops. According to the guidance document, SANTE/11956/2016 rev. 9, cereals (wheat, barley, oats, rye, durum wheat, spelt and triticale) are

considered non-melliferous. Therefore, residue uptake in honey is unlikely to occur directly following treatment of the target cereal crops. However, oilseed rape is considered to be melliferous, and the proposed GAP includes application at the BBCH growth stages where flowering is likely to occur, therefore, consideration is required. Additionally, considering the persistent, and systemic, nature of the active, residues may be present in succeeding, melliferous crops.

The MRL assessment additional uses considered here (in this assessment report, alongside the cereals and oilseed rape representative uses) are carrots, parsley root and parnsips. Carrot and parsnips are not considered to be melliferous crops, although parsley root is considered to be melliferous. However the assessment conducted here for oilseed rape is expected to be 'worst case' in terms of assessment of potential residues in honey.

The residue definition for risk assessment must be considered for residues in honey. In the absence of a specific metabolism studies, consideration must be given to existing studies. The most critical information to consider is the nature of the residue in primary crops, rotational crops and the stability of the active under representative pasteurisation conditions. Parent pydiflumetofen is proposed as the residue definition for risk assessment in crops (see Vol 1 section 2.7.3); it was also found to be stable under all representative processing conditions. The same applies for the enforcement residue definition. This is the same enforcement definition proposed as for plants. It is noted that an analytical method for the determination of pydiflumetofen in honey is available (see Volume 3, CA B5).

Therefore, parent pydiflumetofen can be considered an adequate residue definition proposal for risk assessment and enforcement in honey.

There is no data available on residues specifically in the aerial parts of oilseed rape crops (e.g. flowers) following treatment with pydiflumetofen. The available data cover residues in oilseed rape seed, indicating residues in the range of <0.01 to 0.04 mg/kg in the seed; whole plant (oil seed rape) data showed high residues in whole plants (up to 3.53 mg/kg) on the day of application, which declined (to up to 2.1 mg/kg 7 or 14 days after application; up to 1.1 mg/kg 21 days after application and up to 0.48 mg/kg 42 days after application). The applicant has supported their submission with bee tunnel trials. Four trials are required to set MRLs, as outlined in SANTE/11956/2016 rev. 9.

A study containing three tunnel trials was evaluated. At the time the study was conducted (completed : 18/01/2017) ; there was no agreed EU or GB guidance document or test methods to address the data requirements. Technical guidelines for determining the magnitude of pesticide residues in honey and setting Maximum Residue Levels in honey (SANTE/11956/2016 rev. 9) have been now been implemented, and were in place prior to the submission of this application. The study was completed in accordance with draft guidance. Although the guidance document was not applicable at the time the study was conducted; the study complied with the guidance document to a satisfactory extent. It can be concluded that the study was conducted in line with the guidance.

The trials were conducted on flowering oilseed rape at a rate of 200 g a.s./ha. This is considered to be representative of the worst case GAP, with respect to the proposed uses of the representative product. Residues of pydiflumetofen were below LOQ (<0.01 mg/kg) in all samples. Therefore, no detectable residues are expected in honey following primary crop use of the representative product in line with the proposed GAPs.

~~As discussed in the section on rotational crops (section 2.7.7), residues might also occur in oilseed rape (aerial parts) arsing from uptake of soil residues of pydiflumetofen.~~

~~When considering the above tunnel trials (1 x 200 g as/ha), these trials do not take account of possible uptake of residues from the soil into the crop.~~

~~However the rotational crop trials are underdosed when considering field uptake into crops. An 'upper' estimation of residues in the aerial parts of oilseed rape arising from the rotational crop residue would be 0.03 mg/kg (Tier 1 10 year use) or 0.02 mg/kg (Tier 2 long term use); see section 2.7.2.~~

~~Taking the data from the tunnel trials (<0.01 mg/kg) and assuming transfer of rotational crop residues (from the aerial plant parts; a 1:1 transfer to honey is broadly assumed) into honey, these data are sufficient to support an MRL of 0.05* mg/kg in honey.~~

The available data suggests that rotational residues (section 2.7.7) will not be present in significant amounts in the aerial parts of crops. Therefore, a full consideration of possible uptake from rotational crops has not been made for honey. Although 4 trials are normally required to support an MRL, given that the residues found are <LOQ, a reduced dataset can be accepted. In this case three trials are considered sufficient to indicate that residues arising in honey following primary crop application using pydiflumetofen will be <LOQ. Given potential uncertainty arising from rotational crops, the default MRL of 0.05* mg/kg is proposed for honey.

2.7.9. Estimation of the potential and actual exposure through diet and other sources

The following section has been re-drafted following ECP ISA. The revised presentation takes account of ECP ISA on the soil fate parameters and the application of crop interception rates (this reduces the amount of active substance that impacts the soil), for application made to the primary crop.

~~Consumer risk has been assessed for the two possible options for the DT_{50} value (Tier 1 10 year use and Tier 2 long term use, see section 2.7.7). Residues in primary crops and rotational crops have been included in the risk assessment based on the level of parent pydiflumetofen predicted. Exposure from animal commodities has been assessed based on predicted levels of pydiflumetofen and the metabolites included in the livestock products RD-RA (residues expressed as parent, as per the RD-RA). Two sets of dietary burdens were conducted, one for each DT_{50} (Tier 1 10 year use and Tier 2 long term use), see section 2.7.5.~~

Chronic (long term) dietary intake estimates

Chronic exposure was estimated twice using two different models. The first of these approaches utilises the UK national calculator and considers a diverse range of consumer groups relevant to the UK. The second uses the EFSA PRIMo version 3.1 calculator to predict the dietary intakes for consumer groups across the EU. Each assessment has been performed using a combined residue input covering both the primary crop uses and considering the possible residues in rotational crops.

The following toxicological reference values have been used in the consumer risk assessments:

ADI (mg/kg bw/day)	0.09
ARfD (mg/kg bw)	0.3

For a full consideration of the plant metabolites SYN545547 and SYN547891 and the livestock metabolite SYN547897 (livestock metabolite) in an exposure assessment versus the TTC , please refer to section 2.7.3.

The following estimates consider the proposed uses on oilseed rape, wheat, rye, oat and barley; as well as the MRL application for carrots, parsnip and parsley root. The risk assessment includes the rotational crop residue inputs (see section 2.7.7) supporting the proposal for the MRLs.

Chronic (long term) UK dietary intake estimates – UK NTMDI and NEDIs

The UK NEDIs for the active and commodities listed below have been calculated for ten consumer groups as detailed in the Regulatory Update 21/2005. The following assumptions have been made:

a) Upper range of normal (97.5th percentile) consumption of each individual crop which may have been treated.

b) All produce eaten which may have been treated has been treated and contains residues at the MRL (NTMDI) or median residue (STMR) (NEDI) found in the trials to support the GAP, as given below.

c) There is no loss of residue during transport or storage, or processing of foods prior to consumption. Although a concentration of residues of pydiflumetofen into oil was observed, a processing factor has not been applied to oilseeds (RD-RA is pydiflumetofen only and the UK consumption values are as per the RAC expression).

d) The STMR values used in the NEDI estimation are based on RD-RA. The TMDI has used the MRL (RD-Enf) and for livestock products the CF applied (RD-enf to RD-RA) and an additional x 2 (enantiomer

assessment factor, see end of section 2.7.7).

Chronic (long term) UK inputs - NEDI

Commodity	*NEDI* STMR (mg/kg)	
Strawberries	<0.01	STMR (see section 2.7.7 for details)
Potatoes (tuber)	<0.01	
Root crops excluding carrot, parsnip and parsley root (root)	<0.01	
Sugar beet (root)	<0.01	
Bulb vegetables	<0.01	
Fruiting vegetables	<0.01	
Flowering brassica	<0.01	
Kohlrabi	<0.01	
Head brassica	<0.01	
Leafy brassica	<0.01	
Leaf vegetables, herbs and edible flowers	<0.01	
Legume vegetables	<0.01	
Stem vegetables	<0.01	
Pulses	<0.01	
Oilseeds excluding oilseed rape	<0.01	
Cereal grains (excluding barley, oats, rice, wheat, rye)	<0.01	
Barley grain	0.1	
Oat grain	0.1	
Wheat grain	0.025	
Rye grain	0.025	
Oilseed rape seed	0.01	
Carrot	0.067	
Parsnip	0.067	
Parsley root†	-	
All other crops	<0.01	
Poultry§	0.06	
Meat fat§	0.06	
Meat excluding poultry and offal§	0.06	
All types of kidney§	0.1	
All types of liver§	0.06	
Other types of offal§	0.06	
Eggs§	0.06	
Milk§	0.06	
Honey$	-	

$ Honey is not a commodity that can be input into the UK consumer risk assessment models.
† Parsley root cannot be input into the UK consumer risk assessment models, the intake is covered by the input for parsnip
§ Residues of pydiflumetofen in animal commodities have been doubled to account for the lack of information on the enantiomer ratio. This is likely to be highly conservative.

Chronic (long term) UK inputs – UK NTMDI

Commodity	*UK NTMDI* MRL (mg/kg)	
Strawberries	0.01*	MRL (See section 2.7.7 for further details)
Potatoes (tuber)	0.06	
Root crops excluding carrot, parsnip and parsley root (root)	0.06	
Sugar beet (root)	0.06	
Bulb vegetables	0.06	
Fruiting vegetables	0.01*	
Flowering brassica	0.06	
Kohlrabi	0.06	
Head brassica	0.01*	
Leafy brassica	0.01*	
Leaf vegetables, herbs and edible flowers	0.06	
Legume vegetables	0.01*	
Stem vegetables	0.06	
Pulses	0.01*	
Oilseeds excluding oilseed rape	0.01*	
Cereal grains (excluding barley, oats, rice, wheat, rye)	0.01*	
Barley grain	0.5	
Oat grain	0.5	
Wheat grain	0.08	
Rye grain	0.08	
Oilseed rape seed	0.07	
Carrot	0.2	
Parsnip	0.2	
Parsley root†	-	
All other crops	0.01*	
Poultry	0.06	Calculated MRL (as RD-Enf) * cf (4.7 for kidney, 3.2 for remaining matrices) * 2 §
Meat fat	0.06	
Meat excluding poultry and offal	0.06	
All types of kidney	0.1	
All types of liver	0.06	
Other types of offal	0.06	
Eggs	0.06	
Milk	0.06	
Honey$	-	-

$ Honey is not a commodity that can be input into the UK consumer risk assessment models.
† Parsley root cannot be input into the UK consumer risk assessment models, the intake is covered by the input for parsnip
§ MRLs for pydiflumetofen in animal commodities were estimated based on the RD-Enf, for the purposes of the TMDI calculation, a conversion factor has been applied (4.7 for kidney (except poultry kidney), and 3.2 for all other matrices (including poultry kidney)). As above, residues have also been doubled to account for the lack of information on the enantiomer ratio. This is likely to be highly conservative.

The relevant intakes are presented in Tables 2.7.9.1 and Table 2.7.9.2

Results

For the NTMDI, chronic intakes for all consumer groups are below the ADI of 0.09 mg/kg bw/day, UK total dietary intakes across all commodities estimated as up to 10 % of the ADI (critical consumer group toddlers). For the NEDI, total dietary (chronic) intakes across all commodities for all consumer groups are below the ADI of 0.09 mg/kg; all

consumer groups have intakes of up to 7 % ADI (critical consumer group infants). Therefore, no health effects due to chronic exposure are expected.

Table 2.7.9. 1 UK NTMDI for 10 consumer groups (calculated using chronic consumer version 1.1) for pydiflumetofen

Active substance: pydiflumetofen **ADI:** 0.09mg/kg bw/day **Source:** dDAR

		TOTAL INTAKE based on 97.5th percentile									
		ADULT	INFANT	TODDLER	4-6 YEARS	7-10 YEARS	11-14 YEARS	15-18 YEARS	VEGETARIAN	ELDERLY (OWN HOME)	ELDERLY (RESIDENTIAL)
mg/kg bw/day		0.00179	0.00891	0.00768	0.00480	0.00378	0.00248	0.00222	0.00180	0.00152	0.00209
% of ADI		2%	10%	9%	5%	4%	3%	2%	2%	2%	2%

	STMR	P	COMMODITY INTAKES									
Commodity	(mg/kg)		(mg/kg bw/day)									
Grapefruit	0.01		0.00002	0.00002	0.00006	0.00005	0.00012	0.00002	0.00001	0.00002	0.00002	0.00002
Lemons	0.01		0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Limes	0.01		0.00000	L/C	0.00002	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001
Mandarins	0.01		0.00001	L/C	0.00006	0.00004	0.00003	0.00002	0.00002	0.00001	0.00002	0.00001
Oranges	0.01		0.00004	0.00011	0.00016	0.00011	0.00008	0.00008	0.00007	0.00005	0.00004	0.00003
Almonds	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Brazil nuts	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
Cashew nuts	0.01		0.00000	L/C	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Chestnuts	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	0.00000	0.00000	0.00000	L/C
Coconuts	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Hazelnuts	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Pecan nuts	0.01		0.00000	L/C	0.00000	L/C	0.00000	0.00000	L/C	0.00000	0.00000	L/C
Pistachios	0.01		0.00000	L/C	0.00000	L/C	0.00000	L/C	L/C	0.00000	L/C	L/C
Walnuts	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Peanuts	0.01		0.00000	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000
Apples	0.01		0.00003	0.00008	0.00015	0.00009	0.00008	0.00004	0.00004	0.00003	0.00002	0.00001

Pears	0.01	0.00001	0.00003	0.00007	0.00004	0.00002	0.00002	0.00001	0.00002	0.00002	0.00001
Apricots	0.01	0.00000	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Peaches	0.01	0.00001	0.00001	0.00003	0.00002	0.00001	0.00001	0.00000	0.00001	0.00001	0.00000
Plums	0.01	0.00001	0.00000	0.00002	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Cherries	0.01	0.00000	0.00001	0.00001	0.00002	0.00001	0.00001	0.00001	0.00001	0.00000	0.00000
Table grapes	0.01	0.00001	0.00002	0.00005	0.00002	0.00003	0.00001	0.00001	0.00002	0.00001	0.00000
Wine grapes	0.01	0.00010	0.00001	0.00001	0.00001	0.00000	0.00001	0.00004	0.00010	0.00007	0.00001
Strawberries	0.01	0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Blackberries	0.01	0.00000	L/C	0.00002	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Loganberries	0.01	0.00000	0.00001	0.00001	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000
Raspberries	0.01	0.00000	L/C	0.00002	0.00001	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000
Gooseberries	0.01	0.00000	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	0.00001	0.00000
Blackcurrants	0.01	0.00001	0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00000	0.00001	0.00000
Red currants	0.01	0.00000	L/C	0.00001	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
White currants	0.01	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Avocados	0.01	0.00001	L/C	0.00001	L/C	L/C	L/C	0.00000	0.00001	0.00001	L/C
Bananas	0.01	0.00002	0.00007	0.00007	0.00004	0.00003	0.00002	0.00001	0.00002	0.00002	0.00002
Dates	0.01	0.00000	L/C	0.00000	0.00000	0.00000	0.00000	L/C	0.00000	0.00001	0.00000
Figs	0.01	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Kiwi fruit	0.01	0.00001	L/C	0.00002	0.00002	0.00001	0.00001	0.00002	0.00001	0.00001	0.00000
Lychees	0.01	0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Mangoes	0.01	0.00001	L/C	0.00002	0.00001	0.00002	0.00001	0.00004	0.00001	0.00000	L/C
Olives	0.01	0.00000	L/C	0.00001	0.00001	L/C	0.00000	L/C	0.00000	0.00000	L/C
Passion fruit	0.01	0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C	L/C
Pineapples	0.01	0.00001	0.00005	0.00005	0.00007	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001
Pomegranates	0.01	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00000	0.00001	0.00001	0.00001
Beetroot	0.06	0.00002	L/C	0.00009	0.00002	0.00002	0.00002	0.00001	0.00003	0.00003	0.00001

Carrots	0.2	0.00014	0.00070	0.00049	0.00038	0.00025	0.00017	0.00020	0.00018	0.00019	0.00015
Celeriac	0.06	0.00002	L/C	L/C	0.00000	0.00000	L/C	L/C	L/C	L/C	L/C
Horseradish	0.06	0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C
Jerusalem artichokes	0.06	0.00001	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Parsnips	0.2	0.00006	0.00018	0.00024	0.00014	0.00010	0.00008	0.00005	0.00008	0.00012	0.00006
Radishes	0.06	0.00002	L/C	0.00006	L/C	0.00001	0.00001	0.00001	0.00002	0.00001	0.00001
Salsify	0.06	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Swedes	0.06	0.00003	0.00017	0.00010	0.00004	0.00005	0.00004	0.00003	0.00003	0.00004	0.00003
Turnips	0.06	0.00002	L/C	0.00006	0.00005	0.00003	0.00003	0.00002	0.00001	0.00004	0.00002
Yam	0.06	0.00018	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Garlic	0.06	0.00000	L/C	0.00000	0.00001	0.00001	0.00000	0.00001	0.00001	0.00001	L/C
Onions	0.06	0.00003	0.00007	0.00007	0.00006	0.00005	0.00004	0.00003	0.00004	0.00003	0.00002
Spring onions	0.06	0.00002	L/C	0.00001	0.00004	0.00001	0.00001	0.00001	0.00002	0.00002	0.00001
Tomatoes	0.01	0.00001	0.00002	0.00003	0.00002	0.00002	0.00001	0.00001	0.00002	0.00001	0.00001
Peppers	0.01	0.00000	L/C	0.00001	0.00000	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Aubergines	0.01	0.00000	L/C	0.00002	0.00001	0.00000	0.00001	0.00000	0.00001	0.00000	L/C
Marrows	0.01	0.00001	L/C	0.00002	0.00000	0.00001	0.00001	0.00000	0.00001	0.00001	0.00001
Cucumbers	0.01	0.00000	0.00000	0.00002	0.00002	0.00001	0.00001	0.00000	0.00001	0.00000	0.00000
Gourd	0.01	0.00001	L/C	L/C	L/C	L/C	0.00000	L/C	0.00000	L/C	L/C
Courgettes	0.01	0.00000	0.00001	0.00002	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Melons	0.01	0.00002	0.00003	0.00005	0.00004	0.00003	0.00002	0.00003	0.00003	0.00003	0.00001
Sweet corn	0.01	0.00001	0.00001	0.00002	0.00001	0.00001	0.00000	0.00001	0.00001	0.00001	0.00000
Broccoli	0.06	0.00004	0.00007	0.00010	0.00007	0.00006	0.00004	0.00004	0.00004	0.00006	0.00002
Cauliflower	0.06	0.00005	0.00019	0.00013	0.00010	0.00005	0.00004	0.00005	0.00007	0.00007	0.00004
Brussels sprouts	0.01	0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
Head cabbage	0.01	0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Chinese cabbage	0.01	0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00001	0.00000	L/C

Kohl Rabi	0.06		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Cress	0.06		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000
Lettuce	0.06		0.00004	0.00002	0.00005	0.00004	0.00004	0.00002	0.00003	0.00004	0.00003	0.00002
Spinach	0.06		0.00003	0.00006	0.00009	0.00005	0.00005	0.00004	0.00002	0.00004	0.00003	0.00002
Watercress	0.06		0.00001	L/C	L/C	0.00000	0.00000	0.00001	L/C	0.00001	0.00002	L/C
Chicory	0.06		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C	L/C
Parsley	0.06		0.00001	L/C	0.00001	L/C	0.00001	0.00000	0.00000	0.00001	0.00001	0.00002
Beans with pods	0.01		0.00001	0.00001	0.00002	0.00001	0.00001	0.00000	0.00001	0.00000	0.00001	0.00000
Runner Beans	0.01		0.00001	L/C	0.00001	0.00000	0.00001	0.00001	0.00000	0.00002	0.00001	0.00001
Beans without pods	0.01		0.00000	0.00001	0.00002	0.00000	0.00001	0.00000	0.00000	0.00001	0.00001	0.00001
Peas with pods	0.01		0.00000	L/C	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	L/C
Peas without pods	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Beansprouts	0.01		0.00000	L/C	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000
Asparagus	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	0.00000	0.00001	0.00000	L/C
Bamboo shoots	0.01		0.00000	L/C	0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
Celery	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Fennel	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Globe artichokes	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C	L/C
Leeks	0.01		0.00000	L/C	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000
Rhubarb	0.01		0.00000	0.00001	0.00001	0.00000	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000
Cultivated mushrooms	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Beans	0.01		0.00002	0.00006	0.00005	0.00003	0.00003	0.00002	0.00002	0.00002	0.00001	0.00001
Lentils	0.01		0.00001	0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
dried Peas	0.01		0.00001	L/C	0.00002	0.00000	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Oilseeds	0.07		0.00022	0.00044	0.00051	0.00050	0.00039	0.00028	0.00025	0.00033	0.00022	0.00027
Potatoes	0.01		0.00003	0.00011	0.00009	0.00008	0.00007	0.00005	0.00005	0.00004	0.00003	0.00003
Tea (dried leaves)	0.01		0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000

Hops (dried 0.25% of beer)	0.01	0.00000	L/C	L/C	L/C	L/C	0.00000	0.00000	0.00000	0.00000	0.00000
Oats	0.5	0.00018	0.00110	0.00061	0.00038	0.00023	0.00018	0.00032	0.00032	0.00026	0.00028
Barley	0.5	0.00012	L/C	0.00017	0.00017	0.00040	0.00010	0.00011	0.00013	0.00013	0.00007
Millet	0.01	L/C	L/C	0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Buckwheat	0.01	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Maize	0.01	0.00000	0.00005	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Wheat	0.08	0.00029	0.00022	0.00068	0.00071	0.00054	0.00040	0.00032	0.00034	0.00026	0.00028
Rice	0.01	0.00002	0.00003	0.00005	0.00004	0.00005	0.00004	0.00003	0.00002	0.00001	0.00000
Rye	0.08	0.00004	0.00011	0.00003	0.00004	0.00004	0.00002	0.00001	0.00005	0.00004	0.00001
Poultry	0.06	0.00010	0.00010	0.00018	0.00017	0.00011	0.00009	0.00009	0.00010	0.00010	0.00005
Meat fat	0.06	0.00001	0.00003	0.00004	0.00003	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001
Meat excl. poultry & offal	0.06	0.00011	0.00024	0.00025	0.00021	0.00018	0.00012	0.00013	0.00002	0.00011	0.00010
All types of kidney	0.1	0.00003	0.00004	0.00014	0.00004	0.00002	0.00002	0.00003	L/C	0.00005	0.00003
All types of Liver	0.06	0.00003	0.00013	0.00014	0.00002	0.00003	0.00004	0.00002	L/C	0.00004	0.00003
Other types of offal	0.06	0.00004	0.00009	0.00013	0.00007	0.00006	0.00006	0.00003	0.00001	0.00005	0.00004
Eggs	0.06	0.00006	0.00028	0.00021	0.00014	0.00010	0.00009	0.00006	0.00006	0.00006	0.00008
Milk	0.06	0.00049	0.00585	0.00335	0.00177	0.00109	0.00071	0.00056	0.00058	0.00052	0.00071
Sugar beet	0.06	0.00084	0.00200	0.00334	0.00202	0.00189	0.00120	0.00116	0.00072	0.00064	0.00091

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

L/C Low consumption (<0.1 g/day) or low number of consumers (<4)

Table 2.7.9. 2 UK NEDI for 10 consumer groups (calculated using chronic consumer version 1.1) for pydiflumetofen

Active substance: pydiflumetofen **ADI:** 0.09 mg/kg bw/day **Source:** dDAR

			TOTAL INTAKE based on 97.5th percentile									
			ADULT	INFANT	TODDLER	4-6 YEARS	7-10 YEARS	11-14 YEARS	15-18 YEARS	VEGETARIAN	ELDERLY (OWN HOME)	ELDERLY (RESIDENTIAL)
mg/kg bw/day			0.00086	0.00671	0.00438	0.00258	0.00178	0.00118	0.00099	0.00090	0.00081	0.00106
% of ADI			<1%	7%	5%	3%	2%	1%	1%	<1%	<1%	1%
	STMR	P	COMMODITY INTAKES									
Commodity	(mg/kg)		(mg/kg bw/day)									
Grapefruit	0.01		0.00002	0.00002	0.00006	0.00005	0.00012	0.00002	0.00001	0.00002	0.00002	0.00002
Lemons	0.01		0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Limes	0.01		0.00000	L/C	0.00002	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001
Mandarins	0.01		0.00001	L/C	0.00006	0.00004	0.00003	0.00002	0.00002	0.00001	0.00002	0.00001
Oranges	0.01		0.00004	0.00011	0.00016	0.00011	0.00008	0.00008	0.00007	0.00005	0.00004	0.00003
Almonds	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Brazil nuts	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
Cashew nuts	0.01		0.00000	L/C	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Chestnuts	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	0.00000	0.00000	0.00000	L/C
Coconuts	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Hazelnuts	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Pecan nuts	0.01		0.00000	L/C	0.00000	L/C	0.00000	0.00000	L/C	0.00000	0.00000	L/C
Pistachios	0.01		0.00000	L/C	0.00000	L/C	0.00000	L/C	L/C	0.00000	L/C	L/C
Walnuts	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Peanuts	0.01		0.00000	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000
Apples	0.01		0.00003	0.00008	0.00015	0.00009	0.00008	0.00004	0.00004	0.00003	0.00002	0.00001
Pears	0.01		0.00001	0.00003	0.00007	0.00004	0.00002	0.00002	0.00001	0.00002	0.00002	0.00001

Apricots	0.01		0.00000	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Peaches	0.01		0.00001	0.00001	0.00003	0.00002	0.00001	0.00001	0.00000	0.00001	0.00001	0.00000
Plums	0.01		0.00001	0.00000	0.00002	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Cherries	0.01		0.00000	0.00001	0.00001	0.00002	0.00001	0.00001	0.00001	0.00001	0.00000	0.00000
Table grapes	0.01		0.00001	0.00002	0.00005	0.00002	0.00003	0.00001	0.00001	0.00002	0.00001	0.00000
Wine grapes	0.01		0.00010	0.00001	0.00001	0.00001	0.00000	0.00001	0.00004	0.00010	0.00007	0.00001
Strawberries	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Blackberries	0.01		0.00000	L/C	0.00002	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Loganberries	0.01		0.00000	0.00001	0.00001	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000
Raspberries	0.01		0.00000	L/C	0.00002	0.00001	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000
Gooseberries	0.01		0.00000	0.00001	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	0.00001	0.00000
Blackcurrants	0.01		0.00001	0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00000	0.00001	0.00000
Red currants	0.01		0.00000	L/C	0.00001	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
White currants	0.01		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Avocados	0.01		0.00001	L/C	0.00001	L/C	L/C	L/C	0.00000	0.00001	0.00001	L/C
Bananas	0.01		0.00002	0.00007	0.00007	0.00004	0.00003	0.00002	0.00001	0.00002	0.00002	0.00002
Dates	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	L/C	0.00000	0.00001	0.00000
Figs	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Kiwi fruit	0.01		0.00001	L/C	0.00002	0.00002	0.00001	0.00001	0.00002	0.00001	0.00001	0.00000
Lychees	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Mangoes	0.01		0.00001	L/C	0.00002	0.00001	0.00002	0.00001	0.00004	0.00001	0.00000	L/C
Olives	0.01		0.00000	L/C	0.00001	0.00001	L/C	0.00000	L/C	0.00000	0.00000	L/C
Passion fruit	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C	L/C
Pineapples	0.01		0.00001	0.00005	0.00005	0.00007	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001
Pomegranates	0.01		0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00000	0.00001	0.00001	0.00001
Beetroot	0.01		0.00000	L/C	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Carrots	0.067		0.00005	0.00024	0.00017	0.00013	0.00008	0.00006	0.00007	0.00006	0.00006	0.00005

Celeriac	0.01		0.00000	L/C	L/C	0.00000	0.00000	L/C	L/C	L/C	L/C	L/C
Horseradish	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C
Jerusalem artichokes	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Parsnips	0.067		0.00002	0.00006	0.00008	0.00005	0.00003	0.00003	0.00002	0.00003	0.00004	0.00002
Radishes	0.01		0.00000	L/C	0.00001	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Salsify	0.01		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Swedes	0.01		0.00000	0.00003	0.00002	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00000
Turnips	0.01		0.00000	L/C	0.00001	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00000
Yam	0.01		0.00003	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Garlic	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
Onions	0.01		0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
Spring onions	0.01		0.00000	L/C	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Tomatoes	0.01		0.00001	0.00002	0.00003	0.00002	0.00002	0.00001	0.00001	0.00002	0.00001	0.00001
Peppers	0.01		0.00000	L/C	0.00001	0.00000	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Aubergines	0.01		0.00000	L/C	0.00002	0.00001	0.00000	0.00001	0.00000	0.00001	0.00000	L/C
Marrows	0.01		0.00001	L/C	0.00002	0.00000	0.00001	0.00001	0.00000	0.00001	0.00001	0.00001
Cucumbers	0.01		0.00000	0.00000	0.00002	0.00002	0.00001	0.00001	0.00000	0.00001	0.00000	0.00000
Gourd	0.01		0.00001	L/C	L/C	L/C	L/C	0.00000	L/C	0.00000	L/C	L/C
Courgettes	0.01		0.00000	0.00001	0.00002	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Melons	0.01		0.00002	0.00003	0.00005	0.00004	0.00003	0.00002	0.00003	0.00003	0.00003	0.00001
Sweet corn	0.01		0.00001	0.00001	0.00002	0.00001	0.00001	0.00000	0.00001	0.00001	0.00001	0.00000
Broccoli	0.01		0.00001	0.00001	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
Cauliflower	0.01		0.00001	0.00003	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Brussels sprouts	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
Head cabbage	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Chinese cabbage	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00001	0.00000	L/C
Kohl Rabi	0.01		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C

Cress	0.01		0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Lettuce	0.01		0.00001	0.00000	0.00001	0.00001	0.00001	0.00000	0.00000	0.00001	0.00001	0.00000
Spinach	0.01		0.00001	0.00001	0.00002	0.00001	0.00001	0.00001	0.00000	0.00001	0.00001	0.00000
Watercress	0.01		0.00000	L/C	L/C	0.00000	0.00000	0.00000	L/C	0.00000	0.00000	L/C
Chicory	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C	L/C
Parsley	0.01		0.00000	L/C	0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Beans with pods	0.01		0.00001	0.00001	0.00002	0.00001	0.00001	0.00000	0.00001	0.00000	0.00001	0.00000
Runner Beans	0.01		0.00001	L/C	0.00001	0.00000	0.00001	0.00001	0.00000	0.00002	0.00001	0.00001
Beans without pods	0.01		0.00000	0.00001	0.00002	0.00000	0.00001	0.00000	0.00000	0.00001	0.00001	0.00001
Peas with pods	0.01		0.00000	L/C	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	L/C
Peas without pods	0.01		0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Beansprouts	0.01		0.00000	L/C	0.00001	0.00001	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000
Asparagus	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	0.00000	0.00001	0.00000	L/C
Bamboo shoots	0.01		0.00000	L/C	0.00000	L/C	0.00000	0.00000	0.00000	0.00000	0.00000	L/C
Celery	0.01		0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Fennel	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Globe artichokes	0.01		0.00000	L/C	L/C	L/C	L/C	L/C	L/C	0.00000	L/C	L/C
Leeks	0.01		0.00000	L/C	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000
Rhubarb	0.01		0.00000	0.00001	0.00001	0.00000	0.00001	0.00000	0.00000	0.00000	0.00001	0.00000
Cultivated mushrooms	0.01		0.00000	0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000
Beans	0.01		0.00002	0.00006	0.00005	0.00003	0.00003	0.00002	0.00002	0.00002	0.00001	0.00001
Lentils	0.01		0.00001	0.00001	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001	0.00001	0.00000
dried Peas	0.01		0.00001	L/C	0.00002	0.00000	0.00001	0.00001	0.00001	0.00001	0.00001	0.00001
Oilseeds	0.01		0.00003	0.00006	0.00007	0.00007	0.00006	0.00004	0.00004	0.00005	0.00003	0.00004
Potatoes	0.01		0.00003	0.00011	0.00009	0.00008	0.00007	0.00005	0.00005	0.00004	0.00003	0.00003
Tea (dried leaves)	0.01		0.00000	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Hops (dried 0.25% of beer)	0.01		0.00000	L/C	L/C	L/C	L/C	0.00000	0.00000	0.00000	0.00000	0.00000

Oats	0.1		0.00004	0.00022	0.00012	0.00008	0.00005	0.00004	0.00006	0.00006	0.00005	0.00006
Barley	0.1		0.00002	L/C	0.00003	0.00003	0.00008	0.00002	0.00002	0.00003	0.00003	0.00001
Millet	0.01		L/C	L/C	0.00000	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Buckwheat	0.01		L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C	L/C
Maize	0.01		0.00000	0.00005	0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Wheat	0.025		0.00009	0.00007	0.00021	0.00022	0.00017	0.00012	0.00010	0.00011	0.00008	0.00009
Rice	0.01		0.00002	0.00003	0.00005	0.00004	0.00005	0.00004	0.00003	0.00002	0.00001	0.00000
Rye	0.025		0.00001	0.00003	0.00001	0.00001	0.00001	0.00001	0.00000	0.00001	0.00001	0.00000
Poultry	0.06		0.00010	0.00010	0.00018	0.00017	0.00011	0.00009	0.00009	0.00010	0.00010	0.00005
Meat fat	0.06		0.00001	0.00003	0.00004	0.00003	0.00002	0.00002	0.00001	0.00001	0.00001	0.00001
Meat excl. poultry & offal	0.06		0.00011	0.00024	0.00025	0.00021	0.00018	0.00012	0.00013	0.00002	0.00011	0.00010
All types of kidney	0.1		0.00003	0.00004	0.00014	0.00004	0.00002	0.00002	0.00003	L/C	0.00005	0.00003
All types of Liver	0.06		0.00003	0.00013	0.00014	0.00002	0.00003	0.00004	0.00002	L/C	0.00004	0.00003
Other types of offal	0.06		0.00004	0.00009	0.00013	0.00007	0.00006	0.00006	0.00003	0.00001	0.00005	0.00004
Eggs	0.06		0.00006	0.00028	0.00021	0.00014	0.00010	0.00009	0.00006	0.00006	0.00006	0.00008
Milk	0.06		0.00049	0.00585	0.00335	0.00177	0.00109	0.00071	0.00056	0.00058	0.00052	0.00071
Sugar beet	0.01		0.00014	0.00033	0.00056	0.00034	0.00031	0.00020	0.00019	0.00012	0.00011	0.00015

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

L/C Low consumption (<0.1 g/day) or low number of consumers (<4)

Acute (short term) UK dietary intake estimates – UK NESTIs

The UK NESTIs for the active and commodities listed below have been calculated for ten consumer groups as detailed in the Regulatory Update 21/2005. The following assumptions have been made:

1) Upper range of normal (97.5th percentile) consumption of each individual crop which may have been treated.
2) All produce eaten which may have been treated has been treated and contains residues at the highest residue (based on RD-RA) found in the trials considered to support GAP, as given below. The HR values applicable to products of animal origin at the anticipated exposure levels are outlined in section 2.7.7 and are as given below. They include an additional x 2 (enantiomer assessment factor, see end of section 2.7.7).
3) There is no loss of residue during transport or storage, or processing of foods prior to consumption. Processing factors have been applied to wheat bran and barley flour (where the PF indicate a concentration and some additional UK consumption data are available for wheat bran and flour); these are tailored additional calculations for wheat bran and barley flour and these are presented at the end of the main NESTI tables. Although a concentration of residues of pydiflumetofen into oil was observed, a processing factor has not been applied to oilseeds (RD-RA is pydiflumetofen only and the UK consumption values are as per the RAC expression).

Acute (short term) UK inputs.

Commodity	***NESTI* HR (mg/kg)**	
Strawberries	<0.01	HR (see section 2.7.7 for details)
Potatoes (tuber)	0.0422	
Root crops excluding carrot, parsnip and parsley root (root)	0.0422	
Sugar beet (root)	0.0422	
Bulb vegetables	0.0422	
Fruiting vegetables	<0.01	
Flowering brassica	0.053	
Kohlrabi	0.053	
Head brassica	<0.01	
Leafy brassica	<0.01	
Leaf vegetables, herbs and edible flowers	0.053	
Legume vegetables	<0.01	
Stem vegetables	0.053	
Pulses	<0.01	
Oilseeds excluding oilseed rape	<0.01	
Cereal grains (excluding barley, oats, rice, wheat, rye)	<0.01	
Barley grain	0.1	STMR (see section 2.7.7 for details)
Oat grain	0.1	
Wheat grain	0.025	
Rye grain	0.025	
Oilseed rape seed	0.01	
Carrot	0.082	HR (see section 2.7.7 for details)
Parsnip	0.082	
Parsley root[†]	-	-
Poultry	0.06	HR (see section 2.7.7 for details) [§]
Meat fat	0.06	
Meat excluding poultry and offal	0.06	
All types of kidney	0.1	
All types of liver	0.06	
Other types of offal	0.06	
Eggs	0.06	
Milk	0.06	

Honey[$]	-	-
Barley flour‡	0.1 (and PF of 2.93)	STMR x PF for barley flour
Wheat bran‡	0.05 (and PF of 4.61)	STMR x PF for wheat bran

[$] Honey is not a commodity that can be input into the UK consumer risk assessment models.
† Parsley root cannot be input into the UK consumer risk assessment models, the intake is covered by the input for parsnip
[§] Residues of pydiflumetofen in animal commodities have been doubled to account for the lack of information on the enantiomer ratio. This is likely to be highly conservative.
‡ Processed fractions (wheat bran and barley flour) were considered separately to the UK consumer model, specific UK consumption data was used – the results are presented at the end of each of the main tables 2.7.9.3.

The relevant intake assessment is presented in Table 2.7.9.3.

Results

Acute intakes for all consumer groups are below the ARfD of 0.3 mg/kg bw. The most critical group are infants consuming milk with an estimated consumption of 2.5 % ArfD. Therefore, no health effects due to acute exposure are expected.

Table 2.7.9. 3 UK NESTI for 10 consumer groups (calculated using acute consumer version 1.2) for pydiflumetofen

Acute Intakes (97.5th percentiles)

			adult		infant		toddler		4-6 year old child		7-10 year old child	
commodity	HR	P	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
Oilseeds	0.01		0.00006	0.0	0.00012	0.0	0.00013	0.0	0.00014	0.0	0.00011	0.0
Potatoes	0.04		0.00101	0.3	0.00649	2.2	0.00449	1.5	0.00338	1.1	0.00232	0.8
Strawberries	0.01		0.00003	0.0	0.00004	0.0	0.00005	0.0	0.00007	0.0	0.00005	0.0
Beetroot	0.04		0.00034	0.1	0.00000	0.0	0.00089	0.3	0.00058	0.2	0.00063	0.2
Carrots	0.08		0.00071	0.2	0.00520	1.7	0.00322	1.1	0.00242	0.8	0.00157	0.5
Celeriac	0.04		0.00050	0.2	0.00000	0.0	0.00006	0.0	0.00007	0.0	0.00009	0.0
Horseradish	0.04		0.00002	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Jerusalem artichoke	0.04		0.00018	0.1	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Parsnips	0.08		0.00098	0.3	0.00296	1.0	0.00223	0.7	0.00241	0.8	0.00195	0.6
Radishes	0.04		0.00004	0.0	0.00000	0.0	0.00013	0.0	0.00005	0.0	0.00004	0.0
Salsify	0.04		0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Swedes	0.04		0.00056	0.2	0.00218	0.7	0.00128	0.4	0.00101	0.3	0.00061	0.2
Turnips	0.04		0.00044	0.1	0.00000	0.0	0.00117	0.4	0.00152	0.5	0.00071	0.2
Yam	0.04		0.00092	0.3	0.00000	0.0	0.00184	0.6	0.00079	0.3	0.00000	0.0
Broccoli	0.05		0.00068	0.2	0.00109	0.4	0.00111	0.4	0.00131	0.4	0.00119	0.4
Cauliflower	0.05		0.00082	0.3	0.00307	1.0	0.00176	0.6	0.00184	0.6	0.00104	0.3
Brussels sprouts	0.01		0.00003	0.0	0.00007	0.0	0.00005	0.0	0.00007	0.0	0.00004	0.0
Head cabbage	0.01		0.00012	0.0	0.00043	0.1	0.00025	0.1	0.00032	0.1	0.00018	0.1
Chinese cabbage	0.01		0.00015	0.1	0.00000	0.0	0.00011	0.0	0.00000	0.0	0.00022	0.1
Kohl Rabi	0.05		0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Cress	0.05		0.00001	0.0	0.00000	0.0	0.00002	0.0	0.00002	0.0	0.00001	0.0
Lettuce	0.05		0.00052	0.2	0.00067	0.2	0.00064	0.2	0.00094	0.3	0.00071	0.2
Spinach	0.05		0.00013	0.0	0.00028	0.1	0.00021	0.1	0.00030	0.1	0.00017	0.1
Watercress	0.05		0.00003	0.0	0.00000	0.0	0.00001	0.0	0.00002	0.0	0.00002	0.0
Chicory	0.05		0.00020	0.1	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00052	0.2
Parsley	0.05		0.00003	0.0	0.00000	0.0	0.00002	0.0	0.00002	0.0	0.00006	0.0
Beans with pods	0.01		0.00002	0.0	0.00005	0.0	0.00005	0.0	0.00004	0.0	0.00002	0.0
Runner Beans	0.01		0.00002	0.0	0.00000	0.0	0.00004	0.0	0.00003	0.0	0.00003	0.0
Peas with pods	0.01		0.00002	0.0	0.00000	0.0	0.00002	0.0	0.00003	0.0	0.00002	0.0

Beansprouts	0.01		0.00002	0.0	0.00001	0.0	0.00003	0.0	0.00004	0.0	0.00004	0.0
Peas without pods	0.01		0.00003	0.0	0.00008	0.0	0.00005	0.0	0.00006	0.0	0.00004	0.0
Beans without pods	0.01		0.00002	0.0	0.00004	0.0	0.00007	0.0	0.00003	0.0	0.00007	0.0
Asparagus	0.05		0.00013	0.0	0.00000	0.0	0.00024	0.1	0.00009	0.0	0.00004	0.0
Bamboo shoots	0.05		0.00005	0.0	0.00000	0.0	0.00005	0.0	0.00001	0.0	0.00002	0.0
Celery	0.05		0.00031	0.1	0.00036	0.1	0.00031	0.1	0.00028	0.1	0.00022	0.1
Fennel	0.05		0.00076	0.3	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Globe artichokes	0.05		0.00045	0.2	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00022	0.1
Leeks	0.05		0.00069	0.2	0.00000	0.0	0.00106	0.4	0.00084	0.3	0.00059	0.2
Rhubarb	0.05		0.00041	0.1	0.00180	0.6	0.00197	0.7	0.00062	0.2	0.00090	0.3
Beans	0.01		0.00006	0.0	0.00018	0.1	0.00012	0.0	0.00012	0.0	0.00008	0.0
Lentils	0.01		0.00002	0.0	0.00006	0.0	0.00005	0.0	0.00006	0.0	0.00004	0.0
dried Peas	0.01		0.00003	0.0	0.00000	0.0	0.00004	0.0	0.00003	0.0	0.00003	0.0
Oats	0.10		0.00009	0.0	0.00032	0.1	0.00031	0.1	0.00018	0.1	0.00021	0.1
Barley	0.10		0.00007	0.0	0.00000	0.0	0.00007	0.0	0.00018	0.1	0.00056	0.2
Millet	0.01		0.00000	0.0	0.00000	0.0	0.00001	0.0	0.00000	0.0	0.00000	0.0
Buckwheat	0.01		0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Maize	0.01		0.00000	0.0	0.00007	0.0	0.00004	0.0	0.00002	0.0	0.00001	0.0
Wheat	0.03		0.00015	0.1	0.00032	0.1	0.00033	0.1	0.00036	0.1	0.00027	0.1
Rice	0.01		0.00006	0.0	0.00006	0.0	0.00013	0.0	0.00011	0.0	0.00011	0.0
Rye	0.03		0.00003	0.0	0.00016	0.1	0.00003	0.0	0.00005	0.0	0.00004	0.0
Poultry	0.06		0.00033	0.1	0.00041	0.1	0.00052	0.2	0.00057	0.2	0.00042	0.1
Meat fat	0.06		0.00004	0.0	0.00012	0.0	0.00011	0.0	0.00012	0.0	0.00008	0.0
Meat excl.poultry & offal	0.06		0.00030	0.1	0.00071	0.2	0.00061	0.2	0.00054	0.2	0.00047	0.2
All types of kidney	0.10		0.00017	0.1	0.00024	0.1	0.00038	0.1	0.00024	0.1	0.00016	0.1
All types of liver	0.06		0.00016	0.1	0.00048	0.2	0.00040	0.1	0.00011	0.0	0.00015	0.1
Other types of offal	0.06		0.00018	0.1	0.00044	0.1	0.00043	0.1	0.00034	0.1	0.00033	0.1
Eggs	0.06		0.00017	0.1	0.00074	0.2	0.00047	0.2	0.00040	0.1	0.00029	0.1
Milk	0.06		0.00078	0.3	0.00745	2.5	0.00440	1.5	0.00280	0.9	0.00179	0.6
Sugar Beet	0.04		0.00109	0.4	0.00235	0.8	0.00328	1.1	0.00269	0.9	0.00221	0.7

			11-14 year old child		15-18 year old child		vegetarian		Elderly - own home		Elderly - residential	
commodity	HR	P	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
Oilseeds	0.01		0.00008	0.0	0.00007	0.0	0.00010	0.0	0.00005	0.0	0.00005	0.0
Potatoes	0.04		0.00164	0.5	0.00123	0.4	0.00126	0.4	0.00100	0.3	0.00110	0.4
Strawberries	0.01		0.00003	0.0	0.00002	0.0	0.00003	0.0	0.00003	0.0	0.00001	0.0
Beetroot	0.04		0.00046	0.2	0.00027	0.1	0.00038	0.1	0.00037	0.1	0.00020	0.1
Carrots	0.08		0.00105	0.3	0.00086	0.3	0.00081	0.3	0.00073	0.2	0.00077	0.3
Celeriac	0.04		0.00005	0.0	0.00003	0.0	0.00036	0.1	0.00000	0.0	0.00000	0.0
Horseradish	0.04		0.00002	0.0	0.00001	0.0	0.00002	0.0	0.00002	0.0	0.00001	0.0
Jerusalem artichoke	0.04		0.00000	0.0	0.00000	0.0	0.00024	0.1	0.00000	0.0	0.00000	0.0
Parsnips	0.08		0.00145	0.5	0.00082	0.3	0.00115	0.4	0.00104	0.3	0.00064	0.2
Radishes	0.04		0.00003	0.0	0.00003	0.0	0.00005	0.0	0.00004	0.0	0.00001	0.0
Salsify	0.04		0.00000	0.0	0.00000	0.0	0.00045	0.2	0.00000	0.0	0.00000	0.0
Swedes	0.04		0.00075	0.3	0.00055	0.2	0.00052	0.2	0.00042	0.1	0.00038	0.1
Turnips	0.04		0.00074	0.2	0.00042	0.1	0.00029	0.1	0.00047	0.2	0.00035	0.1
Yam	0.04		0.00096	0.3	0.00039	0.1	0.00000	0.0	0.00000	0.0	0.00000	0.0
Broccoli	0.05		0.00083	0.3	0.00074	0.2	0.00089	0.3	0.00068	0.2	0.00037	0.1
Cauliflower	0.05		0.00088	0.3	0.00081	0.3	0.00123	0.4	0.00080	0.3	0.00054	0.2
Brussels sprouts	0.01		0.00003	0.0	0.00003	0.0	0.00004	0.0	0.00002	0.0	0.00002	0.0
Head cabbage	0.01		0.00017	0.1	0.00012	0.0	0.00017	0.1	0.00013	0.0	0.00010	0.0
Chinese cabbage	0.01		0.00002	0.0	0.00025	0.1	0.00009	0.0	0.00004	0.0	0.00000	0.0
Kohl Rabi	0.05		0.00071	0.2	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Cress	0.05		0.00001	0.0	0.00001	0.0	0.00002	0.0	0.00001	0.0	0.00001	0.0
Lettuce	0.05		0.00044	0.1	0.00043	0.1	0.00058	0.2	0.00037	0.1	0.00021	0.1
Spinach	0.05		0.00016	0.1	0.00009	0.0	0.00019	0.1	0.00011	0.0	0.00007	0.0
Watercress	0.05		0.00002	0.0	0.00002	0.0	0.00006	0.0	0.00004	0.0	0.00000	0.0
Chicory	0.05		0.00000	0.0	0.00073	0.2	0.00011	0.0	0.00000	0.0	0.00000	0.0
Parsley	0.05		0.00002	0.0	0.00001	0.0	0.00006	0.0	0.00002	0.0	0.00002	0.0
Beans with pods	0.01		0.00002	0.0	0.00003	0.0	0.00003	0.0	0.00002	0.0	0.00001	0.0
Runner Beans	0.01		0.00003	0.0	0.00003	0.0	0.00004	0.0	0.00002	0.0	0.00002	0.0
Peas with pods	0.01		0.00001	0.0	0.00001	0.0	0.00001	0.0	0.00001	0.0	0.00000	0.0
Beansprouts	0.01		0.00002	0.0	0.00002	0.0	0.00003	0.0	0.00002	0.0	0.00001	0.0

Peas without pods	0.01		0.00003	0.0	0.00003	0.0	0.00003	0.0	0.00002	0.0	0.00002	0.0
Beans without pods	0.01		0.00001	0.0	0.00003	0.0	0.00004	0.0	0.00003	0.0	0.00002	0.0
Asparagus	0.05		0.00003	0.0	0.00008	0.0	0.00020	0.1	0.00009	0.0	0.00005	0.0
Bamboo shoots	0.05		0.00009	0.0	0.00002	0.0	0.00007	0.0	0.00002	0.0	0.00001	0.0
Celery	0.05		0.00030	0.1	0.00022	0.1	0.00044	0.1	0.00034	0.1	0.00011	0.0
Fennel	0.05		0.00000	0.0	0.00000	0.0	0.00099	0.3	0.00055	0.2	0.00000	0.0
Globe artichokes	0.05		0.00000	0.0	0.00000	0.0	0.00033	0.1	0.00000	0.0	0.00000	0.0
Leeks	0.05		0.00072	0.2	0.00057	0.2	0.00081	0.3	0.00074	0.2	0.00039	0.1
Rhubarb	0.05		0.00033	0.1	0.00042	0.1	0.00049	0.2	0.00042	0.1	0.00047	0.2
Beans	0.01		0.00007	0.0	0.00007	0.0	0.00006	0.0	0.00003	0.0	0.00003	0.0
Lentils	0.01		0.00007	0.0	0.00003	0.0	0.00003	0.0	0.00002	0.0	0.00001	0.0
dried Peas	0.01		0.00007	0.0	0.00002	0.0	0.00003	0.0	0.00003	0.0	0.00001	0.0
Oats	0.10		0.00009	0.0	0.00015	0.0	0.00012	0.0	0.00007	0.0	0.00007	0.0
Barley	0.10		0.00004	0.0	0.00006	0.0	0.00007	0.0	0.00005	0.0	0.00003	0.0
Millet	0.01		0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Buckwheat	0.01		0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0	0.00000	0.0
Maize	0.01		0.00001	0.0	0.00001	0.0	0.00002	0.0	0.00000	0.0	0.00000	0.0
Wheat	0.03		0.00022	0.1	0.00021	0.1	0.00020	0.1	0.00011	0.0	0.00011	0.0
Rice	0.01		0.00008	0.0	0.00009	0.0	0.00008	0.0	0.00004	0.0	0.00002	0.0
Rye	0.03		0.00002	0.0	0.00002	0.0	0.00004	0.0	0.00002	0.0	0.00001	0.0
Poultry	0.06		0.00035	0.1	0.00032	0.1	0.00070	0.2	0.00028	0.1	0.00015	0.1
Meat fat	0.06		0.00006	0.0	0.00006	0.0	0.00003	0.0	0.00003	0.0	0.00003	0.0
Meat excl.poultry & offal	0.06		0.00034	0.1	0.00034	0.1	0.00016	0.1	0.00022	0.1	0.00019	0.1
All types of kidney	0.10		0.00014	0.0	0.00021	0.1	0.00000	0.0	0.00017	0.1	0.00013	0.0
All types of liver	0.06		0.00025	0.1	0.00012	0.0	0.00000	0.0	0.00014	0.0	0.00011	0.0
Other types of offal	0.06		0.00027	0.1	0.00014	0.0	0.00006	0.0	0.00015	0.0	0.00015	0.0
Eggs	0.06		0.00023	0.1	0.00018	0.1	0.00023	0.1	0.00012	0.0	0.00014	0.0
Milk	0.06		0.00124	0.4	0.00105	0.4	0.00089	0.3	0.00066	0.2	0.00086	0.3
Sugar Beet	0.04		0.00165	0.5	0.00152	0.5	0.00088	0.3	0.00059	0.2	0.00080	0.3

	Residue input (mg/kg) (= STMR x PF)	**NESTI (critical consumer) mg/kg bw/day**	**%ARfD (critical consumer)**	**UK acute 97.5th percentile consumption value (critical consumer)**
Barley flour	0.293 (= 0.1 x 2.93)	0.00281 (toddler)	0.94 % (toddler)	0.0096 kg/kgbw/day (toddler)
Wheat Bran	0.230 (= 0.05 x 4.61)	0.0011 (infant)	0.4 % (infant)	0.00486 kg/kg bw/day (infants)

Acute and chronic EU dietary intake estimates

The EU MS national TMDIs, IEDIs and IESTIs for the active and commodities listed below have been calculated using PRIMo - Pesticide Residues Intake Model (revision 3.1).

The following assumptions have been made:

1) All produce eaten which may have been treated, has been treated and contains residues at the proposed MRL (TMDI) or STMR (IEDI) or HR (IESTI), as given below:

2) For most commodities there is no loss of residue during transport or storage, or processing of foods prior to consumption. However some PFs have been used where there are relevant data (see section 2.7.6. These are also as outlined below.

Chronic (long term) and acute (short term) PRIMo inputs.

Commodity	***Chronic (long term) inputs***		***Acute (short term) inputs)***	
	IEDI **STMR (mg/kg)**		***IESTI*** ***HR (mg/kg)***	
Strawberries	<0.01	STMR (see section 2.7.7 for details)	<0.01	HR (see section 2.7.7 for details)
Potatoes (tuber)	<0.01		0.0422	
Root crops excluding carrot, parsnip and parsley root (root)	<0.01		0.0422	
Sugar beet (root)	<0.01		0.0422	
Chicory root	<0.01		0.0422	
Herbal infusions (dried roots)	<0.01		0.0422	
Bulb vegetables	<0.01		0.0422	
Fruiting vegetables	<0.01		<0.01	
Flowering brassica	<0.01		0.053	
Kohlrabi	<0.01		0.053	
Head brassica	<0.01		<0.01	
Leafy brassica	<0.01		<0.01	
Leaf vegetables, herbs and edible flowers	<0.01		0.053	
Legume vegetables	<0.01		<0.01	
Stem vegetables	<0.01		0.053	
Pulses	<0.01		<0.01	
Oilseeds excluding oilseed rape	<0.01		<0.01	STMR (see section 2.7.7 for details)
Cereal grains (excluding barley, oats, rice, wheat, rye)	<0.01		<0.01	
All other commodities	<0.01		-	-
Barley grain	0.1		0.1	STMR (see section 2.7.7 for details)
Oat grain	0.1		0.1	
Wheat grain	0.025		0.025	
Rye grain	0.025		0.025	
Oilseed rape seed	0.01		0.01 (and pf of 1.67) [#]	
Carrot	0.067		0.082	HR (see section 2.7.7 for details)
Parsnip	0.067		0.082	
Parsley root	0.067		0.082	
Swine muscle/meat	0.06		0.06	HR (see section 2.7.7 for details) [$]
Swine fat tissue	0.006		0.006	

Swine liver	0.006			0.006	
Swine kidney	0.1			0.1	
Bovine, equine and other farmed terrestrial animals – muscle/meat	0.06			0.06	
Bovine, equine and other farmed terrestrial animals – fat tissue	0.006			0.02	
Bovine, equine and other farmed terrestrial animals – liver	0.006			0.02	
Bovine, equine and other farmed terrestrial animals - kidney	0.1			0.1	
Sheep and goat– muscle/meat	0.06			0.06	
Sheep and goat – fat tissue	0.02			0.04	
Sheep and goat – liver	0.02			0.04	
Sheep and goat - kidney	0.1			0.1	
Poultry muscle/meat	0.06			0.06	
Poultry fat tissue	0.06			0.06	
Poultry liver	0.06			0.06	
Poultry kidney	0.06			0.06	
Milk (all)	0.06			0.06	
Eggs (all)	0.06			0.06	
Honey	<0.02			<0.02	HR (see section 2.7.8 for details)
Additional processed fractions (see above for oilseed rape)					
Barley / beer	Processing factors only applied to acute assessment			0.1 (and pf of 0.01)	STMR for barley as set out above * pf
Barley / milling (flour)				0.1 (and pf of 2.93)	STMR for barley as set out above * pf
Barley / cooked				0.1 (and pf of 0.09)	STMR for barley as set out above * pf
Rye / milling (wholemeal) – baking				0.05 (and pf of 0.41)	STMR for rye as set out above * pf
Wheat / bread (wholemeal)				0.05 (and pf of 0.52)	STMR for wheat as set out above * pf
Wheat / milling (wholemeal) – baking				0.05 (and pf of 0.41)	STMR for wheat as set out above * pf
Wheat / milling (flour)				0.05 (and pf of 0.41)	STMR for wheat as set out above * pf

§ Residues of pydiflumetofen in animal commodities have been doubled to account for the lack of information on the enantiomer ratio.

‡ The robust processing factor (1.67) for oilseed rape (oil) was applied the acute risk assessment.

Chronic (long term) PRIMo inputs – TMDI

Commodity	***TMDI* MRL(mg/kg)**	
Strawberries	0.01*	MRL (see section 2.7.7 for details)
Potatoes (tuber)	0.06	
Root crops excluding carrot, parsnip and parsley root (root)	0.06	
Sugar beet (root)	0.06	
Bulb vegetables	0.06	
Fruiting vegetables	0.01*	
Flowering brassica	0.06	
Kohlrabi	0.06	
Head brassica	0.01*	
Leafy brassica	0.01*	
Leaf vegetables, herbs and edible flowers	0.06	
Legume vegetables	0.01*	
Stem vegetables	0.06	
Pulses	0.01*	
Oilseeds excluding oilseed rape	0.01*	
Cereal grains (excluding barley, oats, rice, wheat, rye)	0.01*	
Barley grain	0.5	
Oat grain	0.5	
Wheat grain	0.08	
Rye grain	0.08	
Oilseed rape seed[‡]	0.07	
Carrot	0.2	
Parsnip	0.2	
Parsley root	0.2	
All other crops	0.01*	Default MRL
Swine muscle/meat	0.06	Calculated MRL (as RD-Enf) * cf (4.7 for kidney, 3.2 for remaining matrices) * 2 [§]
Swine fat tissue	0.06	
Swine liver	0.06	
Swine kidney	0.1	
Bovine, equine and other farmed terrestrial animals – muscle/meat	0.06	
Bovine, equine and other farmed terrestrial animals – fat tissue	0.06	
Bovine, equine and other farmed terrestrial animals – liver	0.06	
Bovine, equine and other farmed terrestrial animals - kidney	0.1	
Sheep and goat– muscle/meat	0.06	
Sheep and goat – fat tissue	0.06	
Sheep and goat – liver	0.06	
Sheep and goat - kidney	0.1	
Poultry muscle/meat	0.06	
Poultry fat tissue	0.06	
Poultry liver	0.06	
Poultry kidney	0.06	
Milk (all)	0.06	
Eggs (all)	0.06	
Honey	0.05*	MRL (see section 2.7.8 for details)

[§] MRLs for pydiflumetofen in animal commodities were estimated based on the RD-Enf, for the purposes of the TMDI calculation, a conversion factor has been applied (4.7 for kidney (except poultry kidney), and 3.2 for all other

matrices (including poultry kidney)). As above, residues have also been doubled to account for the lack of information on the enantiomer ratio. This is likely to be highly conservative.

A full description of PRIMo and the underlying assumptions is in the document: 'Use of EFSA pesticide residues intake model (EFSA PRIMo revision 3.1)' available at the following link: http://www.efsa.europa.eu/en/applications/pesticides/tools

Information is also included in the PRIMo model in the tab 'Background information'.

The relevant intake estimates for the TMDI is presented in Table 2.7.9.4; the IEDI in Table 2.7.9.5 for and the IESTI in Tables 2.7.9.6.

Results

For the TMDI, chronic intakes for all consumer groups are below the ADI of 0.09 mg/kg bw/day, the critical consumer group is 'NL toddler' with intakes estimated as up to 3 % of the ADI. For the IEDI, chronic intakes for all consumer groups are below the ADI of 0.09 mg/kg bw/day, the critical consumer group are NL toddlers with intakes estimated as up to 5 % of the ADI. Therefore, no health effects due to chronic exposure are expected. Acute intakes for all consumer groups are below the ARfD of 0.3 mg/kg bw. The most critical group are children consuming cattle milk with an estimated consumption of 2 % ARfD. Therefore, no health effects due to acute exposure are expected.

Table 2.7.9. 4 EFSA model (PRIMo) TMDI for chronic risk assessment – rev. 3.1 for pydiflumetofen

European Food Safety Authority

EFSA PRIMo revision 3.1; 2019/03/19

pydiflumetofen

LOQs (mg/kg) range from: **0.01** to: **0.05**

Toxicological reference values

ADI (mg/kg bw/day):	**0.09**	ARfD (mg/kg bw):	**0.3**
Source of ADI:		Source of ARfD:	
Year of evaluation:		Year of evaluation:	

Input values

Details - chronic risk assessment | Supplementary results - chronic risk assessment | Details - acute risk assessment/children | Details - acute risk assessment/adults

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

	Calculated exposure (% of ADI)	MS Diet	Expsoure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	Exposure resulting from MRLs set at the LOQ (in % of ADI)	Exposure resulting from commodities not under assessment (in % of ADI)
TMDI/NEDI/IEDI calculation (based on average food consumption)	3%	NL toddler	2.60	0.7%	Milk: Cattle	0.4%	Wheat	0.3%	Sugar beet roots	0.8%	
	2%	NL child	1.73	0.6%	Sugar beet roots	0.4%	Wheat	0.3%	Milk: Cattle	0.3%	
	2%	DK child	1.70	0.5%	Rye	0.4%	Wheat	0.3%	Carrots	0.2%	
	2%	GEMS/Food G08	1.59	0.5%	Barley	0.4%	Wheat	0.3%	Potatoes	0.2%	
	2%	GEMS/Food G11	1.52	0.4%	Barley	0.3%	Wheat	0.3%	Potatoes	0.2%	
	2%	GEMS/Food G15	1.48	0.4%	Barley	0.4%	Wheat	0.2%	Potatoes	0.2%	
	2%	DE child	1.46	0.4%	Wheat	0.2%	Carrots	0.2%	Milk: Cattle	0.3%	
	2%	UK infant	1.44	0.4%	Milk: Cattle	0.3%	Carrots	0.2%	Wheat	0.5%	
	2%	GEMS/Food G07	1.43	0.4%	Wheat	0.3%	Barley	0.3%	Potatoes	0.2%	
	1%	FR child 3 15 yr	1.32	0.4%	Wheat	0.3%	Milk: Cattle	0.2%	Sugar beet roots	0.4%	
	1%	GEMS/Food G10	1.29	0.3%	Wheat	0.3%	Barley	0.2%	Potatoes	0.2%	
	1%	FR toddler 2 3 yr	1.23	0.3%	Milk: Cattle	0.3%	Wheat	0.2%	Sugar beet roots	0.4%	
	1%	UK toddler	1.22	0.3%	Wheat	0.2%	Potatoes	0.2%	Milk: Cattle	0.3%	
	1%	GEMS/Food G06	1.21	0.6%	Wheat	0.1%	Potatoes	0.1%	Sugar beet roots	0.1%	
	1%	DE general	1.17	0.3%	Barley	0.3%	Sugar beet roots	0.2%	Wheat	0.2%	
	1%	RO general	1.12	0.5%	Wheat	0.2%	Potatoes	0.1%	Milk: Cattle	0.2%	
	1%	SE general	1.10	0.3%	Wheat	0.3%	Potatoes	0.2%	Carrots	0.2%	
	1%	IE adult	1.08	0.2%	Sweet potatoes	0.2%	Wheat	0.2%	Potatoes	0.1%	
	1%	FI 3 yr	1.06	0.3%	Oat	0.3%	Potatoes	0.2%	Carrots	0.0%	
	1%	DE women 14-50 yr	1.05	0.3%	Sugar beet roots	0.2%	Wheat	0.1%	Milk: Cattle	0.2%	
	1%	NL general	0.97	0.2%	Sugar beet roots	0.2%	Wheat	0.2%	Barley	0.1%	
	1%	PT general	0.94	0.4%	Potatoes	0.3%	Wheat	0.1%	Carrots	0.0%	
	0.9%	ES child	0.85	0.4%	Wheat	0.1%	Milk: Cattle	0.1%	Potatoes	0.2%	
	0.9%	FR infant	0.79	0.2%	Carrots	0.2%	Milk: Cattle	0.1%	Potatoes	0.2%	
	0.9%	FI 6 yr	0.77	0.3%	Potatoes	0.2%	Oat	0.1%	Carrots	0.0%	
	0.8%	IT toddler	0.76	0.6%	Wheat	0.1%	Potatoes	0.0%	Carrots	0.0%	
	0.8%	ES adult	0.74	0.3%	Barley	0.2%	Wheat	0.1%	Potatoes	0.1%	
	0.7%	LT adult	0.59	0.2%	Potatoes	0.1%	Rye	0.1%	Wheat	0.1%	
	0.6%	IT adult	0.53	0.4%	Wheat	0.0%	Potatoes	0.0%	Carrots	0.0%	
	0.6%	FR adult	0.52	0.2%	Wheat	0.1%	Sugar beet roots	0.0%	Milk: Cattle	0.1%	
	0.6%	UK vegetarian	0.50	0.2%	Wheat	0.1%	Potatoes	0.1%	Carrots	0.1%	
	0.5%	DK adult	0.46	0.1%	Carrots	0.1%	Wheat	0.1%	Potatoes	0.1%	
	0.5%	UK adult	0.43	0.1%	Wheat	0.1%	Potatoes	0.0%	Carrots	0.1%	
	0.5%	FI adult	0.42	0.1%	Potatoes	0.1%	Oat	0.1%	Carrots	0.1%	
	0.4%	PL general	0.38	0.2%	Potatoes	0.1%	Carrots	0.0%	Apples	0.0%	
	0.3%	IE child	0.24	0.1%	Wheat	0.0%	Potatoes	0.0%	Milk: Cattle	0.1%	

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of pydiflumetofen is unlikely to present a public health concern.

Table 2.7.9. 5 EFSA model (PRIMo) IEDI for chronic risk assessment – rev. 3.1 for pydiflumetofen

European Food Safety Authority

EFSA PRIMo revision 3.1; 2019/03/19

pydiflumetofen			
LOQs (mg/kg) range from:		to:	
Toxicological reference values			
ADI (mg/kg bw/day):	**0.09**	ARfD (mg/kg bw):	**0.3**
Source of ADI:		Source of ARfD:	
Year of evaluation:		Year of evaluation:	

Input values

Details - chronic risk assessment | Supplementary results - chronic risk assessment

Details - acute risk assessment/children | Details - acute risk assessment/adults

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

TMDI/NEDI/IEDI calculation (based on average food consumption)	Calculated exposure (% of ADI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	Exposure resulting from: MRLs set at the LOQ (in % of ADI)	Exposure resulting from: commodities not under assessment (in % of ADI)
	5%	NL toddler	4.63	4%	Milk: Cattle	0.2%	Wheat	0.1%	Apples		5%
	3%	UK infant	2.90	3%	Milk: Cattle	0.1%	Wheat	0.1%	Carrots		3%
	3%	FR toddler 2 3 yr	2.38	2%	Milk: Cattle	0.2%	Wheat	0.1%	Bovine: Muscle/meat		3%
	2%	NL child	2.23	2%	Milk: Cattle	0.2%	Wheat	0.1%	Sugar beet roots		2%
	2%	FR child 3 15 yr	2.16	2%	Milk: Cattle	0.3%	Wheat	0.1%	Bovine: Muscle/meat		2%
	2%	DE child	2.02	1%	Milk: Cattle	0.2%	Wheat	0.1%	Apples		2%
	2%	UK toddler	1.80	1%	Milk: Cattle	0.2%	Wheat	0.1%	Bovine: Muscle/meat		2%
	2%	DK child	1.80	0.8%	Milk: Cattle	0.3%	Rye	0.2%	Wheat		2%
	2%	SE general	1.45	0.8%	Milk: Cattle	0.3%	Bovine: Muscle/meat	0.2%	Wheat		2%
	2%	ES child	1.41	0.8%	Milk: Cattle	0.2%	Wheat	0.1%	Bovine: Muscle/meat		1%
	1%	RO general	1.33	0.8%	Milk: Cattle	0.3%	Wheat	0.1%	Swine: Muscle/meat		1%
	1%	FR infant	1.28	1%	Milk: Cattle	0.1%	Carrots	0.0%	Wheat		1%
	1%	DE general	1.23	0.8%	Milk: Cattle	0.1%	Wheat	0.1%	Swine: Muscle/meat		1%
	1%	DE women 14-50 yr	1.21	0.8%	Milk: Cattle	0.1%	Wheat	0.1%	Swine: Muscle/meat		1%
	1%	GEMS/Food G11	1.19	0.5%	Milk: Cattle	0.2%	Wheat	0.1%	Barley		1%
	1%	GEMS/Food G15	1.17	0.5%	Milk: Cattle	0.3%	Wheat	0.1%	Swine: Muscle/meat		1%
	1%	GEMS/Food G07	1.13	0.4%	Milk: Cattle	0.2%	Wheat	0.1%	Poultry: Muscle/meat		1%
	1%	GEMS/Food G08	1.11	0.4%	Milk: Cattle	0.2%	Wheat	0.1%	Swine: Muscle/meat		1%
	1%	GEMS/Food G10	1.03	0.4%	Milk: Cattle	0.2%	Wheat	0.1%	Poultry: Muscle/meat		1%
	1%	NL general	0.95	0.6%	Milk: Cattle	0.1%	Wheat	0.1%	Swine: Muscle/meat		1.0%
	1.0%	GEMS/Food G06	0.88	0.4%	Wheat	0.2%	Milk: Cattle	0.0%	Tomatoes		0.8%
	0.9%	IE adult	0.77	0.3%	Milk: Cattle	0.1%	Wheat	0.0%	Sweet potatoes		0.7%
	0.8%	ES adult	0.73	0.3%	Milk: Cattle	0.1%	Wheat	0.1%	Barley		0.7%
	0.7%	FR adult	0.63	0.3%	Milk: Cattle	0.1%	Wheat	0.0%	Swine: Muscle/meat		0.6%
	0.7%	DK adult	0.63	0.4%	Milk: Cattle	0.1%	Wheat	0.1%	Swine: Muscle/meat		0.6%
	0.6%	LT adult	0.56	0.3%	Milk: Cattle	0.1%	Swine: Muscle/meat	0.1%	Rye		0.6%
	0.5%	IT toddler	0.44	0.4%	Wheat	0.0%	Other cereals	0.0%	Tomatoes		0.4%
	0.5%	UK adult	0.44	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Bovine: Muscle/meat		0.4%
	0.5%	UK vegetarian	0.43	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Eggs: Chicken		0.4%
	0.5%	PT general	0.41	0.2%	Wheat	0.1%	Potatoes	0.0%	Carrots		0.4%
	0.4%	FI 3 yr	0.35	0.1%	Wheat	0.1%	Oat	0.1%	Carrots		0.3%
	0.4%	IE child	0.35	0.2%	Milk: Cattle	0.1%	Wheat	0.0%	Carrots		0.4%
	0.3%	IT adult	0.30	0.2%	Wheat	0.0%	Tomatoes	0.0%	Carrots		0.3%
	0.3%	FI 6 yr	0.26	0.1%	Wheat	0.0%	Carrots	0.0%	Potatoes		0.2%
	0.2%	FI adult	0.20	0.1%	Coffee beans	0.0%	Rye	0.0%	Carrots		0.1%
	0.1%	PL general	0.12	0.0%	Potatoes	0.0%	Apples	0.0%	Carrots		0.1%

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of pydiflumetofen is unlikely to present a public health concern.

Table 2.7.9. 6 EFSA model (PRIMo) IESTI for acute risk assessment – rev. 3.1 for pydiflumetofen

Acute risk assessment /children	Acute risk assessment / adults / general population
Details - acute risk assessment /children	Details - acute risk assessment/adults

The acute risk assessment is based on the ARfD.
The calculation is based on the large portion of the most critical consumer group.

Show results of IESTI calculation only for crops with GAPs under assessment

Unprocessed commodities

Results for children				**Results for adults**			
No. of commodities for which ARfD/ADI is exceeded (IESTI):			---	No. of commodities for which ARfD/ADI is exceeded (IESTI):			---
IESTI				**IESTI**			
Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
2%	Milk: Cattle	0 / 0.06	7.5	0.8%	Milk: Cattle	0 / 0.06	2.3
2%	Potatoes	0 / 0.04	6.5	0.5%	Carrots	0 / 0.08	1.6
2%	Carrots	0 / 0.08	5.2	0.5%	Swedes/rutabagas	0 / 0.04	1.4
1%	Leeks	0 / 0.05	3.1	0.4%	Broccoli	0 / 0.05	1.3
1%	Cauliflowers	0 / 0.05	3.1	0.4%	Potatoes	0 / 0.04	1.3
1.0%	Parsnips	0 / 0.08	3.0	0.4%	Cauliflowers	0 / 0.05	1.2
0.9%	Kohlrabies	0 / 0.05	2.8	0.4%	Yams	0 / 0.04	1.2
0.8%	Beetroots	0 / 0.04	2.4	0.4%	Parsnips	0 / 0.08	1.2
0.8%	Celeriacs/turnip rooted	0 / 0.04	2.3	0.4%	Milk: Goat	0 / 0.06	1.1
0.7%	Broccoli	0 / 0.05	2.2	0.4%	Escaroles/broad-leaved	0 / 0.05	1.1
0.7%	Swedes/rutabagas	0 / 0.04	2.2	0.3%	Chards/beet leaves	0 / 0.05	1.0
0.7%	Escaroles/broad-leaved	0 / 0.05	2.1	0.3%	Florence fennels	0 / 0.05	0.99
0.7%	Witloofs/Belgian endives	0 / 0.05	2.1	0.3%	Witloofs/Belgian endives	0 / 0.05	0.98
0.7%	Lettuces	0 / 0.05	2.0	0.3%	Beetroots	0 / 0.04	0.97
0.7%	Celeries	0 / 0.05	2.0	0.3%	Milk: Sheep	0 / 0.06	0.91
Expand/collapse list							
Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)							

Processed commodities

Results for children				**Results for adults**			
No of processed commodities for which ARfD/ADI is exceeded (IESTI):			---	No of processed commodities for which ARfD/ADI is exceeded (IESTI):			---
IESTI				**IESTI**			
Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
2%	Witloofs / boiled	0 / 0.05	4.7	0.7%	Cauliflowers / boiled	0 / 0.05	2.2
1%	Broccoli / boiled	0 / 0.05	4.2	0.6%	Celeries / boiled	0 / 0.05	1.8
1%	Parsnips / boiled	0 / 0.08	4.2	0.6%	Parsnips / boiled	0 / 0.08	1.7
1%	Potatoes / fried	0 / 0.04	3.9	0.5%	Beetroots / boiled	0 / 0.04	1.6
1%	Cauliflowers / boiled	0 / 0.05	3.7	0.4%	Broccoli / boiled	0 / 0.05	1.3
1%	Escaroles/broad-leaved er	0 / 0.05	3.5	0.4%	Kohlrabies / boiled	0 / 0.05	1.1
1%	Leeks / boiled	0 / 0.05	3.0	0.4%	Escaroles/broad-leaved	0 / 0.05	1.1
0.8%	Carrots / juice	0 / 0.07	2.4	0.3%	Florence fennels / boiled	0 / 0.05	1.0
0.8%	Florence fennels / boiled	0 / 0.05	2.4	0.3%	Witloofs / boiled	0 / 0.05	0.98
0.7%	Turnips / boiled	0 / 0.04	2.1	0.3%	Leeks / boiled	0 / 0.05	0.92
0.7%	Sweet potatoes / boiled	0 / 0.04	2.1	0.3%	Turnips / boiled	0 / 0.04	0.81
0.7%	Rhubarbs / sauce/puree	0 / 0.05	2.0	0.3%	Cassava roots / boiled	0 / 0.04	0.80
0.6%	Beetroots / boiled	0 / 0.04	1.9	0.3%	Rhubarbs / sauce/puree	0 / 0.05	0.77
0.5%	Chards/beet leaves / boile	0 / 0.05	1.6	0.3%	Celeriacs / boiled	0 / 0.04	0.77
0.4%	Sugar beets (root) / sugar	0 / 0.12	1.1	0.2%	Chards/beet leaves /	0 / 0.05	0.66
Expand/collapse list							

2.7.10. Proposed MRLs and compliance with existing MRLs

To support the GB representative uses of pydiflumetofen on wheat, barley, durum wheat, oat, spelt, rye, triticale and oilseed rape, and the subsequent possible residues in rotational crops, product of animal origin and honey, the MRLs in Table 2.7.10.1 are proposed. The MRL application to have MRLs in place for a future use on carrot, parsnip and parsley root supports the MRLs outlined in Table 2.7.10.1 also. The residue definition for enforcement is proposed as pydiflumetofen.

Since the MRL proposals in crops are based on a combined assessment considering primary crop and rotational crop residue contributions, these MRL levels are proposed while further rotational crop field trials are generated at more appropriate dosing levels to confirm the levels of the residues in following crops (see Vol 1 section 2.7.7 and section 3.1.4).

See section 2.7.11 (reference made to CODEX MRLs).

Table 2.7.10. 1 Proposed MRLs tier 1 10 year use

Code number	**Commodity**	**Proposed MRL (mg/kg)**
Representative uses, and MRL application – primary crops + rotational crops		
0213020	Carrots	0.3
0213060	Parsnips	0.3
0213070	Parsley roots/Hamburg roots parsley	0.3
0401060	Oilseed rape seed	0.1
0500010	Barley	0.5
0500050	Oat	0.5
0500070	Rye	0.15
0500090	Wheat (include triticale, spelt and durum wheat)	0.15
POAO – considering primary and rotational crop intakes		
1011010	Swine – muscle	0.01*
1011020	Swine – Fat	0.01*
1011030	Swine – Liver	0.01*
1011040	Swine – kidney	0.01*
1011050	Swine – edible offals (other than liver and kidney)	0.01*
1012010	Bovine – muscle	0.01*
1012020	Bovine – Fat	0.01*
1012030	Bovine – Liver	0.01*
1012040	Bovine – kidney	0.01*
1012050	Bovine – edible offals (other than liver and kidney)	0.01*
1013010	Sheep – muscle	0.01*
1013020	Sheep – Fat	0.01
1013030	Sheep – Liver	0.01
1013040	Sheep – kidney	0.01*
1013050	Sheep – edible offals (other than liver and kidney)	0.01*
1014010	Goat – muscle	0.01*
1014020	Goat – Fat	0.01
1014030	Goat – Liver	0.01
1014040	Goat – kidney	0.01*
1014050	Goat – edible offals (other than liver and kidney)	0.01*
1015010	Equine – muscle	0.01*
1015020	Equine – Fat	0.01*
1015030	Equine – Liver	0.01*
1015040	Equine – kidney	0.01*
1015050	Equine – edible offals (other than liver and kidney)	0.01*
1016010	Poultry – muscle	0.01*
1016020	Poultry – Fat	0.01*

1016030	Poultry - Liver	0.01*
1016040	Poultry - kidney	0.01*
1016050	Poultry - edible offals (other than liver and kidney)	0.01*
1017010	Other farmed terrestrial animals - muscle	0.01*
1017020	Other farmed terrestrial animals - Fat	0.01*
1017030	Other farmed terrestrial animals - Liver	0.01*
1017040	Other farmed terrestrial animals - kidney	0.01*
1017050	Other farmed terrestrial animals - edible offals (other than liver and kidney)	0.01*
1020010	Cattle - milk	0.01*
1020020	Sheep - milk	0.01*
1020030	Goat - milk	0.01*
1020040	Horse - milk	0.01*
1030010	Chicken - eggs	0.01*
1030020	Duck - eggs	0.01*
1030030	Geese - eggs	0.01*
1030040	Quail - eggs	0.01*
1040000	Honey	0.05*
Rotational crops		
0152000	Strawberries	0.03
0211000	Potatoes	0.2
0212000	Tropical root and tubers	0.2
0212020	Sweet potatoes	0.2
0213010	Beetroots	0.2
0213030	Celeriacs/turnip rooted celeries	0.2
0213040	Horseradishes	0.2
0213050	Jerusalem artichokes	0.2
0213080	Radishes	0.2
0213090	Salsifies	0.2
0213100	Swedes/rutabagas	0.2
0213110	Turnips	0.2
0213990	Root and tuber vegetables (others)	0.2
0220000	Bulb vegetables	0.2
0230000	Fruiting vegetables	0.03
0241000	Flowering brassica	0.2
0242000	Head brassica	0.03
0243000	Leafy brassica	0.03
0244000	Kohlrabis	0.03
0250000	Leaf vegetables, herbs and edible flowers	0.2
0260000	Legume vegetables	0.03
0270000	Stem vegetables	0.2
0300000	Pulses	0.03
0401010	Linseeds	0.03
0401020	Peanuts/groundnuts	0.03
0401030	Poppy seeds	0.03
0401040	Sesame seeds	0.03
0401050	Sunflower seeds	0.03
0401070	Soyabeans	0.03
0401080	Mustard seeds	0.03
0401090	Cotton seeds	0.03
0401100	Pumpkin seeds	0.03
0401110	Safflower seeds	0.03
0401120	Borage seeds	0.03
0401130	Gold of pleasure seeds	0.03
0401140	Hemp seeds	0.03
0401150	Castor beans	0.03
0401990	Oilseeds (others)	0.03

0500020	Buckwheat and other pseudocereals	0.03
0500030	Maize/corn	0.03
0500040	Common millet/proso millet	0.03
0500080	Sorghum	0.03
0500990	Cereals (others)	0.03
0631000	Herbal infusions from flowers	0.2
0632000	Herbal infusions from leaves and herbs	0.2
0633000	Herbal infusions from roots	0.2
0639000	Herbal infusions from any other parts of the plant	0.03
0800000	Spices	0.03
0900010	Sugar beet roots	0.2
All other commodities		
-	Default MRL at LOQ	-

** denotes MRL at the LOQ*

Table 2.7.10. 2 Proposed MRLs – tier 2 – long term continuous use

Code number	**Commodity**	**Proposed MRL (mg/kg)**
Representative uses, and MRL application – primary crops + rotational crops		
0213020	Carrots	0.3
0213060	Parsnips	0.3
0213070	Parsley roots/Hamburg roots parsley	0.3
0401060	Oilseed rape seed	0.1
0500010	Barley	0.5
0500050	Oat	0.5
0500070	Rye	0.1
0500090	Wheat (include triticale, spelt and durum wheat)	0.1
POAO – considering primary and rotational crop intakes		
1011010	Swine – muscle	0.01*
1011020	Swine – Fat	0.01*
1011030	Swine – Liver	0.01*
1011040	Swine – kidney	0.01*
1011050	Swine – edible offals (other than liver and kidney)	0.01*
1012010	Bovine – muscle	0.01*
1012020	Bovine – Fat	0.01*
1012030	Bovine – Liver	0.01*
1012040	Bovine – kidney	0.01*
1012050	Bovine – edible offals (other than liver and kidney)	0.01*
1013010	Sheep – muscle	0.01*
1013020	Sheep – Fat	0.01*
1013030	Sheep – Liver	0.01*
1013040	Sheep – kidney	0.01*
1013050	Sheep – edible offals (other than liver and kidney)	0.01*
1014010	Goat – muscle	0.01*
1014020	Goat – Fat	0.01*
1014030	Goat – Liver	0.01*
1014040	Goat – kidney	0.01*
1014050	Goat – edible offals (other than liver and kidney)	0.01*
1015010	Equine – muscle	0.01*
1015020	Equine – Fat	0.01*
1015030	Equine – Liver	0.01*
1015040	Equine – kidney	0.01*
1015050	Equine – edible offals (other than liver and kidney)	0.01*
1016010	Poultry – muscle	0.01*
1016020	Poultry – Fat	0.01*

1016030	Poultry - Liver	0.01*
1016040	Poultry - kidney	0.01*
1016050	Poultry - edible offals (other than liver and kidney)	0.01*
1017010	Other farmed terrestrial animals - muscle	0.01*
1017020	Other farmed terrestrial animals - Fat	0.01*
1017030	Other farmed terrestrial animals - Liver	0.01*
1017040	Other farmed terrestrial animals - kidney	0.01*
1017050	Other farmed terrestrial animals - edible offals (other than liver and kidney)	0.01*
1020010	Cattle - milk	0.01*
1020020	Sheep - milk	0.01*
1020030	Goat - milk	0.01*
1020040	Horse - milk	0.01*
1030010	Chicken - eggs	0.01*
1030020	Duck - eggs	0.01*
1030030	Geese - eggs	0.01*
1030040	Quail - eggs	0.01*
1040000	Honey	0.05*
Rotational crops		
0152000	Strawberries	0.02
0211000	Potatoes	0.15
0212000	Tropical root and tubers	0.15
0212020	Sweet potatoes	0.15
0213010	Beetroots	0.15
0213030	Celeriacs/turnip rooted celeries	0.15
0213040	Horseradishes	0.15
0213050	Jerusalem artichokes	0.15
0213080	Radishes	0.15
0213090	Salsifies	0.15
0213100	Swedes/rutabagas	0.15
0213110	Turnips	0.15
0213990	Root and tuber vegetables (others)	0.15
0220000	Bulb vegetables	0.15
0230000	Fruiting vegetables	0.02
0241000	Flowering brassica	0.15
0242000	Head brassica	0.02
0243000	Leafy brassica	0.02
0244000	Kohlrabis	0.02
0250000	Leaf vegetables, herbs and edible flowers	0.15
0260000	Legume vegetables	0.02
0270000	Stem vegetables	0.15
0300000	Pulses	0.02
0401010	Linseeds	0.02
0401020	Peanuts/groundnuts	0.02
0401030	Poppy seeds	0.02
0401040	Sesame seeds	0.02
0401050	Sunflower seeds	0.02
0401070	Soyabeans	0.02
0401080	Mustard seeds	0.02
0401090	Cotton seeds	0.02
0401100	Pumpkin seeds	0.02
0401110	Safflower seeds	0.02
0401120	Borage seeds	0.02
0401130	Gold of pleasure seeds	0.02
0401140	Hemp seeds	0.02
0401150	Castor beans	0.02
0401990	Oilseeds (others)	0.02

~~0500020~~	~~Buckwheat and other pseudocereals~~	~~0.02~~
~~0500030~~	~~Maize/corn~~	~~0.02~~
~~0500040~~	~~Common millet/proso millet~~	~~0.02~~
~~0500080~~	~~Sorghum~~	~~0.02~~
~~0500990~~	~~Cereals (others)~~	~~0.02~~
~~0631000~~	~~Herbal infusions from flowers~~	~~0.15~~
~~0632000~~	~~Herbal infusions from leaves and herbs~~	~~0.15~~
~~0633000~~	~~Herbal infusions from roots~~	~~0.15~~
~~0639000~~	~~Herbal infusions from any other parts of the plant~~	~~0.03~~
~~0800000~~	~~Spices~~	~~0.02~~
~~0900010~~	~~Sugar beet roots~~	~~0.15~~
~~All other commodities~~		
~~-~~	~~Default MRL at LOQ~~	~~-~~

~~** denotes MRL at the LOQ*~~

To support the GB representative uses of pydiflumetofen on wheat, barley, durum wheat, oat, spelt, rye, triticale and oilseed rape, and the subsequent possible residues in rotational crops, product of animal origin and honey, the MRLs in Table 2.7.10.1 are proposed. The MRL application to have MRLs in place for a future use on carrot, parsnip and parsley root supports the MRLs outlined in Table 2.7.10.1 also. The residue definition for enforcement is proposed as pydiflumetofen.

The MRL proposals detailed below take into account potential rotational residues from long term use of pydiflumetofen. Following presentation to the Expert Committee on Pesticides (ECP) in the process of seeking Independent Scientific Advice (ISA), the assessment took account of the highest estimated soil exposures taking account of crop interception (since pydiflumetofen is applied to the primary crop) and considering soil accumulation of residues accounting for year to year use. This assessment led to the below MRL proposals. For a detailed consideration of the rotational crop assessment, see section 2.7.7. The derivation of the MRLs for the representative uses and the MRL application is detailed in section 2.7.7.

See section 2.7.11 (reference made to CODEX MRLs).

Table 2.7.10. 3 Proposed MRLs

Code number	**Commodity**	**Proposed MRL (mg/kg)**
Representative uses, and MRL application		
0213020	Carrots	0.2
0213060	Parsnips	0.2
0213070	Parsley roots/Hamburg roots parsley	0.2
0401060	Oilseed rape seed	0.07
0500010	Barley	0.5
0500050	Oat	0.5
0500070	Rye	0.08
0500090	Wheat (include triticale, spelt and durum wheat)	0.08
POAO – considering primary and rotational crop intakes		
1011010	Swine – muscle	0.01*
1011020	Swine – Fat	0.01*
1011030	Swine – Liver	0.01*
1011040	Swine – kidney	0.01*
1011050	Swine – edible offals (other than liver and kidney)	0.01*
1012010	Bovine – muscle	0.01*
1012020	Bovine – Fat	0.01*
1012030	Bovine – Liver	0.01*
1012040	Bovine – kidney	0.01*
1012050	Bovine – edible offals (other than liver and kidney)	0.01*
1013010	Sheep – muscle	0.01*

1013020	Sheep – Fat	0.01*
1013030	Sheep – Liver	0.01*
1013040	Sheep – kidney	0.01*
1013050	Sheep – edible offals (other than liver and kidney)	0.01*
1014010	Goat – muscle	0.01*
1014020	Goat – Fat	0.01*
1014030	Goat – Liver	0.01*
1014040	Goat – kidney	0.01*
1014050	Goat – edible offals (other than liver and kidney)	0.01*
1015010	Equine – muscle	0.01*
1015020	Equine – Fat	0.01*
1015030	Equine – Liver	0.01*
1015040	Equine – kidney	0.01*
1015050	Equine – edible offals (other than liver and kidney)	0.01*
1016010	Poultry – muscle	0.01*
1016020	Poultry – Fat	0.01*
1016030	Poultry – Liver	0.01*
1016040	Poultry – kidney	0.01*
1016050	Poultry – edible offals (other than liver and kidney)	0.01*
1017010	Other farmed terrestrial animals – muscle	0.01*
1017020	Other farmed terrestrial animals – Fat	0.01*
1017030	Other farmed terrestrial animals – Liver	0.01*
1017040	Other farmed terrestrial animals – kidney	0.01*
1017050	Other farmed terrestrial animals – edible offals (other than liver and kidney)	0.01*
1020010	Cattle – milk	0.01*
1020020	Sheep – milk	0.01*
1020030	Goat – milk	0.01*
1020040	Horse – milk	0.01*
1030010	Chicken – eggs	0.01*
1030020	Duck – eggs	0.01*
1030030	Geese – eggs	0.01*
1030040	Quail – eggs	0.01*
1040000	Honey	0.05*
Rotational crops (substantive MRLs only)		
0211000	Potatoes	0.06
0212000	Tropical root and tubers	0.06
0213010	Beetroots	0.06
0213030	Celeriacs/turnip rooted celeries	0.06
0213040	Horseradishes	0.06
0213050	Jerusalem artichokes	0.06
0213080	Radishes	0.06
0213090	Salsifies	0.06
0213100	Swedes/rutabagas	0.06
0213110	Turnips	0.06
0213990	Root and tuber vegetables (others)	0.06
0220000	Bulb vegetables	0.06
0241000	Flowering brassica	0.06
0244000	Kohlrabis	0.06
0250000	Leaf vegetables, herbs and edible flowers	0.06
0270000	Stem vegetables	0.06
0900010	Sugar beet roots	0.06
0900030	Chicory roots	0.06
All other commodities		
-	Default MRL at LOQ	-

** denotes MRL at the LOQ*

2.7.11. Proposed import tolerances and compliance with existing import tolerances

No import tolerances are proposed and there are no existing import tolerances.

This evaluation has only considered a small number of additional MRL uses (GB) and these are included in the overall assessment (and the MRL proposals covering these are included in the above section 2.7.10).

~~There are some~~ CODEX MRLs ~~that~~ were adopted in 2019 and in more recently in 2021 ~~(which are presented below)~~. HSE notes that the CODEX MRLs are not being considered in this active substance assessment, and these CODEX MRLs will be assessed with a more comprehensive evaluation of further uses (further GB MRL assessment uses that HSE needs to consider after the active substance approval). At the time of this further GB MRLs assessment, the additional processing data (only considered briefly in this evaluation) on grapes, apple, tomatoes and kale will need to be evaluated in full.

~~The currently adopted CODEX MRLs are:~~

2.8. FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1. Summary of behaviour of pydiflumetofen enantiometers in the environment

Pydiflumetofen is composed of two enantiomers. The studies were conducted prior to the adoption in GB of the EFSA Stereoisomers guidance but HSE have used the guidance for useful indicators and principles for evaluation that help in this assessment. It is noted that as well as the standard regulatory studies int eh data package, a single published reference was available on enantiomeric behaviour. The amount of information on the degradation and/or dissipation behaviour of the enantiomers in each study was very limited, both in terms of the number of samples analysed to allow any trend in change in ratio to be detected, and in terms of the limited amount of parent degradation that occurred. Both of these aspects make it challenging to conclude definitively on the degradation behaviour of individual enantiomers. In some studies, specifically the aerobic soil degradation, soil photolysis and aerobic mineralisation in surface water studies, the change in enantiomer excess was either greater than the threshold of 10% change or by extrapolation might have exceeded the 10% threshold had the study been allowed to continue to 50% degradation of pydiflumetofen. However in many cases the degree of extrapolation was high due to limited degradation, and the limited number of samples analysed made it more difficult to determine a clear pattern in changing isomer ratios. In the anaerobic soil study, the change in enantiomer excess was smaller and uncertain whether the 10% change threshold would have been exceeded had the study continued to 50% degradation of pydiflumetofen. In the water/sediment study and field dissipation studies where enantiomer ratio was measured, the change in enantiomer excess extrapolated to a point of 50% dissipation was estimated to be less than 10%; again, it should be noted that in most cases the degree of extrapolation to 50% decline was high. The published study had greater measurement of enantiomer concentrations but experimental details were poorly reported and the degradation behaviour was markedly different to that in the standard regulatory studies. HSE considers that the field dissipation studies represent a more realistic environment with respect to degradation and dissipation processes compared to laboratory conditions. The results of the aqueous photolysis study could also be taken into consideration. Whilst this study does not pose what the EFSA Stereoisomer guidance terms an ‘asymmetric environment’, i.e. an environment that could induce a change in enantiomer excess via microbial activity, some change in enantiomer excess was seen. The change was likely to be less than the threshold 10% change in enantiomer excess when the results were extrapolated out to 50% degradation. However this suggests that changes in enantiomer excess seen in other studies with active microbial communities might not have been as a result of the influence of an asymmetric environment but may have been due to experimental variability. HSE considers that there is some uncertainty over the change in enantiomer excess. However, based on the weight of evidence, i.e. the results in the more realistic field dissipation studies and that apparent changes in enantiomer excess could be seen in non-asymmetric environments, no further investigation of stereoisomer issues is required with respect to environmental fate and behaviour. HSE considers that the change in enantiomer ratio is unlikely to be significant in the overall environmental behaviour of pydiflumetofen and does not need to be taken into consideration in the environmental exposure assessment.

2.8.2. Summary of fate and behaviour in soil

In laboratory soil studies pydiflumetofen was slowly degraded with 'trigger' DT50 values in aerobic soils ranging from 398 to 2380 days, and DT_{90} values ranging from 1320 to 7640 days. Slow degradation was also seen in the anaerobic soil.

In the soil photolysis study, pydiflumetofen was observed to degrade more quickly when exposed to light conditions than in the dark with SFO DT50 of 77 – 197 days compared to 369 ->1000 days in the dark controls. When corrected for latitude (30-50°N), the SFO DT50s under light conditions were 154 days in dry soil and 361 days in moist soil. It should be noted that the actual study duration was 14 – 16 days in length and therefore the DT50s are extrapolated well beyond the study duration which in itself leads to some uncertainty over the kinetic parameters.

HSE noted generally for all the laboratory soil studies the DT50 and DT90 values were extrapolated beyond study duration and therefore there is significant uncertainty associated with the values.

Levels of metabolite formation were low; HSE consider on the basis of the results that no metabolites formed in soil formally trigger inclusion in risk assessment. However it must be stressed that at the end of the aerobic soil study there was still 50-84% AR remaining as unchanged pydiflumetofen.

Field soil dissipation studies were performed at ten locations across Northern and Southern Europe. Pydiflumetofen was applied to bare soil. At six of the sites, the treated plots were covered with a thin layer of sand immediately after application to minimise the potential impact of surface processes on dissipation and were also kept vegetation free throughout the trial period. This is in accordance with the DegT50 study design in the EFSA (2014) guidance and the results can more easily be interpreted with regards deriving a long term bulk soil matrix DT50 appropriate for FOCUS groundwater modelling. At a further four sites the treated plots had been previously sown with grass. Consequently, whilst application was made to bare soil, the plots were subsequently allowed to develop grass growth. Such a design is perhaps more in keeping with addressing the regulatory data requirement to address dissipation under field conditions. Information from studies following this type of design may be considered appropriate for use in long term soil exposure assessments.

At the end of the sampling period (approximately two years) in the six 'DegT50' study design sites, total soil residues of pydiflumetofen had dissipated by 38% to 76%, based on the nominal application rate. At the other four sites which were approximately one year duration, 23-69% dissipation had occurred. The 'trigger' endpoints from the field dissipation studies are shown below. The results from the field studies where pydiflumetofen was applied to bare soil which subsequently had grass growth develop suggest that other processes, such as soil surface photolysis or plant uptake, might increase the rate of dissipation. However dissipation was still slow. As with the laboratory studies there is some uncertainty associated with calculated kinetic parameters in the field dissipation studies because the DT50s in nearly all cases and the DT90s in all cases are extrapolated significantly beyond study duration.

Table 2.8.1-01 Field Dissipation DT50 and DT90 – pydiflumetofen – Trigger endpoints

Parent	Aerobic conditions – **Trigger endpoints**							
Soil type.	Location (country or USA state).	pH[a)]	Depth (cm)	Overall DT_{50} (d) actual	Overall DT_{90}(d) actual	St. (χ^2)	Kinetic parameters	Method of calculation
Sandy loam[b]	Germany	5.68	0-20	8540[d]	>10000[d]	6.5	k_1=0.05381 k_2= 0.000043 g=0.2484	DFOP
Clay loam[b]	Italy	7.40	0-100	1110[d]	3680[d]	11.6	-	SFO
Silty clay loam[b]	Northern France	7.52	0-100	4030[d]	>10000[d]	9.7	-	SFO
Sandy loam[b]	Southern France	7.48	0-50	29	1820[d]	13.3	k_1=0.08239 k_2= 0.000842 g=0.5381	DFOP
Sandy loam[b]	Spain	7.27	0.-30	No reliable fit could be obtained				
Loam[b]	UK	6.84	0-30	2810[d]	9350[d]	11.2	-	SFO
Loamy sand[c]	Germany	6.23	0-30	1310[d]	4360[d]	8.7	-	SFO
Silty clay[c]	Northern France	6.13	0-20	639[d]	2120[d]	13.2	-	SFO
Silt loam[c]	Southern France	7.68	0-30	23.4	2130[d]	9.1	k1: 0.07406 k2: 0.000584 g: 0.6006	DFOP
Loamy sand[c]	Portugal	6.23	0-50	227	755[d]	14.5	-	SFO
Maximum for Tier 1 PECsoil calculation				**8540**	**>10000**			**DFOP**
Value proposed for Tier 2 PECsoil calculation				**1310**	**4360**			**SFO**

[a)] Measured in calcium chloride solution
[b)] application to bare soil, DegT50 design
[c)] application to bare soil, grass cover subsequently developed
[d)] DT50 or DT90 extrapolated beyond study duration

A further study resampling five of the ten European field dissipation studies was submitted. Resampling occurred between 3 to 5 years after termination of the original studies. The calculation of persistence and degradation end points from this study is not accepted by HSE due to concerns over the potential for dilution effects, including from cultivation and plant uptake, to have affected the decline in residues.

Study reports from an additional 14 field dissipation sites in North America and Asia were submitted. Current guidance indicates that non-European sites must be shown to be representative of European conditions in terms of both soil and meteorological conditions before they can be used in GB risk assessments. Following such an assessment, none of the sites are considered by HSE to be of representative of European conditions. Consequently the results have not been used in risk assessment.

Pydiflumetofen was relatively strongly adsorbed to soil with Kfoc values ranging from 1165 to 2206 mL/g. There is no indication of a relationship between soil adsorption of pydiflumetofen and soil pH. Using the McCall Classification scale, pydiflumetofen can be classified as having a low to slight potential mobility in soil.

2.8.3. Summary of fate and behaviour in water and sediment

Pydiflumetofen was stable to hydrolysis under acidic, neutral and alkaline conditions at 50°C. It is therefore expected to be stable at 25°C.

Aqueous photolysis of pydiflumetofen was studied in pH7 buffer (direct photolysis) and in natural water (indirect photolysis). Pydiflumetofen was degraded with an estimated DT50 were 93 and 35 days (summer sunlight 30-50°N) in pH 7 buffer and natural water, respectively. Photolysis in natural water led to the formation of SYN548261 at ≥ 5% AR at two consecutive sampling intervals (maximum 7.3% AR after 21 days) and NOA449410 at a maximum level of 5.8% AR by the end of the experimental period (30 days). It is considered that these two metabolites trigger inclusion in the environmental exposure assessment for surface water.

Pydiflumetofen was not readily biodegradable under the conditions of the available test.

The aerobic mineralisation and degradation of pydiflumetofen in surface water was determined in the laboratory under dark conditions and light/dark conditions. No significant degradation of pydiflumetofen was observed throughout the study. Mineralization was low (< 1%) in all systems tested. DT50 were extrapolated beyond the study period in all incubation groups and ranged from 637 to >1000 days for dark incubation and from 402 to 662 days for light/dark incubation.

The rate and route of degradation of [^{14}C]-pydiflumetofen has been investigated in two water-sediment systems under laboratory aerobic and anaerobic conditions in the dark. The results from the aerobic incubation are used as it is generally considered in regulatory assessments that these are the better representation of surface water bodies associated with agricultural systems.

In the aerobic systems 70-74% of applied pydiflumetofen remained in the total systems after 100 days (end of study). Pydiflumetofen dissipated relatively rapidly from the water phase. The main route of dissipation from water was partitioning into sediment with up to 79% AR being observed at day 30. There was no clear decline phase of the residues in sediment. Only one metabolite was observed at levels above 5% AR and this was identified as SYN545547. It increased throughout the duration of the study and accounted for up to 12.3% AR in sediment extracts and 12.8% AR in the total system after 100 days; there was no clear evidence of decline of this metabolite in sediment. Therefore an environmental exposure assessment for this metabolite in sediment is required.

Satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in water when it is abstracted for drinking water. A data gap has been identified.

2.8.4. Summary of fate and behaviour in air

Pydiflumetofen has a vapour pressure of 1.84 x 10^{-7} Pa at 20°C. According to FOCUS Air guidance criteria, pydiflumetofen does not need to be considered for short-range transport.

The estimated half-life (Atkinson method) of pydiflumetofen in the atmosphere is 5.85 hours, based on OH (12h) concentration of 1.5 x 10^6 radicals/cm^3 as recommended in FOCUS Air guidance document. Pydiflumetofen is therefore not expected to be persistent in air and does not meet the 'trigger' value of an atmospheric half-life of 2 days. Therefore pydiflumetofen does not raise concerns relating to long range atmospheric transport.

2.8.5. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

Pydiflumetofen is a new active substance and thus no monitoring data are available.

2.8.6. Definition of the residues in the environment requiring further assessment

The following was identified as the residue definition for risk assessment.

Compartment	Residue definition for risk assessment
Soil	Pydiflumetofen
Groundwater	Pydiflumetofen
Surface water	Pydiflumetofen NOA449410 SYN548261
Sediment	Pydiflumetofen SYN545547
Air	Pydiflumetofen

2.8.7. Summary of exposure calculations and product assessment

PECsoil

PECsoil values have been calculated for three different GAPs as these lead to different levels of soil exposure. The GAPs are summarised below.

Table 2.8.6-01 Summary of requested GAPs for PECsoil calculations

Crop	Cereals	Cereals	Oil Seed Rape
Application rate (g a.s./ha)	166	200	200
Number of applications/interval (d)	1/-	1/-	1/-
Relative application date/BBCH growth stage	-/30	-/55	-/57
Crop interception (%)	80	90	80
Soil loading after interception (g a.s./ha)	33.2	20	40
Depth of soil layer (relevant for $PEC_{S,plateau}$) (cm)	5 cm for 1 year and 20 years 20cm for longer term	5 cm for 1 year and 20 years 20cm for longer term	5 cm for 1 year and 20 years 20cm for longer term
Product dose l/ha	2.65	3.2	3.2
Product dose g/ha[a]	2907	3510.4	3510.4
Models used for calculation	PECsoil spreadsheet	PECsoil spreadsheet	PECsoil spreadsheet

[a] assuming formulation density of 1.097 g/cm^3 (Volume 3, section CP B.2.6, [redacted] 2016)

Pydiflumetofen exhibited slow dissipation in field dissipation studies. As a result of two different field dissipation study designs being used, the CA evaluation proposes two different dissipation rates for use in PECsoil calculation:

- a DFOP DT50 of 8540 days (DT90 >10000 days) (DFOP parameters k1 = 0.05381, k2 = 0.000043, g = 0.2484) as a 1st tier and
- an SFO DT50 of 1310 days as a 2nd tier (potential refinement)

PECsoil values for use inecotoxicological risk assessment are presented below.

Tier 1 - PECsoil with DFOP DT50 of 8540 days (DT90 >10000 days)

Table 2.8.6-02 1st tier PECsoil for use on cereals at BBCH 30, 166 g pydiflumetofen/ha, 80% crop interception

	PECsoil
PECini	0.044
'Steady state' (mg/kg) after 20 years, 5cm depth	0.567
'Peak' (mg/kg) after 20 years (5cm)	**0.611**
'Steady state' (mg/kg) final, 20 cm depth[1]	0.526
'Peak' (mg/kg) final[1] (5 cm)	0.570

[1] Note: final values reflect a plateau reached after more than 100 years

Table 2.8.6-03 1st tier PECsoil for use on cereals at BBCH 55, 200 g pydiflumetofen/ha, 90% crop interception

	PECsoil
PECini	0.027
'Steady state' (mg/kg) after 20 years, 5cm depth	0.341
'Peak' (mg/kg) after 20 years	**0.368**
'Steady state' (mg/kg) final, 20 cm depth[1]	0.317
'Peak' (mg/kg) final[1]	0.344

[1] Note: final values reflect a plateau reached after more than 100 years

Table 2.8.6-04 1st tier PECsoil for use on oilseed rape at BBCH 57, 200 g pydiflumetofen/ha, 80% crop interception

	PECsoil
PECini	0.053
'Steady state' (mg/kg) after 20 years, 5cm depth	0.683
'Peak' (mg/kg) after 20 years	**0.736**
'Steady state' (mg/kg) final, 20 cm depth[1]	0.634
'Peak' (mg/kg) final[1]	0.687

[1] Note: final values reflect a plateau reached after more than 100 years

Tier 2 - PECsoil with SFO DT50 1310 days

Table 2.8.6-05 2nd tier PECsoil for use on cereals at BBCH 30, 166 g pydiflumetofen/ha, 80% crop interception

		TWA
PECINI mg/kg (1st)	0.044	0.044
1	0.044	0.044
2	0.044	0.044
4	0.044	0.044
7	0.044	0.044
14	0.044	0.044
21	0.044	0.044
28	0.044	0.044
48	0.043	0.044
100	0.042	0.043
Accumulated PECsoil after 20 years		
'Steady state' (mg/kg), 5cm depth	0.202	
'Peak' (mg/kg)	**0.247**	
Accumulated PECsoil after 36 years		
'Steady state' (mg/kg), 20 cm depth[1]	0.052	
'Peak' (mg/kg)[1]	0.096	

[1] Note: if final accumulation was calculated over 5cm, steady state would be 0.208 mg/kg and peak 0.252 mg/kg

Table 2.8.6-06 2nd tier PECsoil for use on cereals at BBCH 55, 200 g pydiflumetofen/ha, 90% crop interception

		TWA
PECINI mg/kg (1st)	0.027	0.027
1	0.027	0.027
2	0.027	0.027
4	0.027	0.027
7	0.027	0.027
14	0.026	0.027
21	0.026	0.027
28	0.026	0.026
48	0.026	0.026
100	0.025	0.026
Accumulated PECsoil after 20 years		
'Steady state' (mg/kg), 5cm depth	0.122	
'Peak' (mg/kg)	**0.149**	
Accumulated PECsoil after 32 years		
'Steady state' (mg/kg), 20 cm depth[1]	0.031	
'Peak' (mg/kg)[1]	0.058	

[1] Note: if final accumulation was calculated over 5cm, steady state would be 0.125 mg/kg and peak 0.152 mg/kg

Table 2.8.6-07 2nd tier PECsoil for use on oilseed rape at BBCH 57, 200 g pydiflumetofen/ha, 80% crop interception

		TWA
PECINI mg/kg (1st)	0.053	0.053
1	0.053	0.053
2	0.053	0.053
4	0.053	0.053
7	0.053	0.053
14	0.053	0.053
21	0.053	0.053
28	0.053	0.053
48	0.052	0.053
100	0.051	0.052
Accumulated PECsoil after 20 years (annual application)		
'Steady state' (mg/kg), 5cm depth	0.244	
'Peak' (mg/kg)	**0.297**	
Accumulated PECsoil after 39 years (annual application)		
'Steady state' (mg/kg), 20 cm depth[1]	0.063	
'Peak' (mg/kg)[1]	0.116	
Accumulated PECsoil after 22 years (application every 3rd year)		
'Steady state' (mg/kg), 5cm depth	0.067	
'Peak' (mg/kg)	0.120	
Accumulated PECsoil after 28 years (application every 3rd year)		
'Steady state' (mg/kg), 20 cm depth[2]	0.017	
'Peak' (mg/kg)[2]	0.070	

[1] Note: if final accumulation was calculated over 5cm, steady state would be 0.250 mg/kg and peak 0.304 mg/kg
[2] Note: if final accumulation was calculated over 5cm, steady state would be 0.068 mg/kg and peak 0.121 mg/kg

To summarise, the maximum PECsoil values for pydiflumetofen for the range of GAPs are:

1st tier – 0.736 mg a.s./ha

2nd tier – 0.297 mg a.s./kg

Table 2.8.6-08 PECsoil for the formulation 'Miravis Plus'

Use	**PECsoil (mg formulation/kg)**
Cereals, 2907 g/ha, 80% interception	0.775
Cereals, 3510.4 g/ha, 90% interception	0.468
Oilseed rape, 3510.4 g/ha, 80% interception	0.936

Soil exposure values for use in the assessment of residues in rotational crops have been presented in Level 2, section 2.7.7.

PECgw

PECgw assessment was made for pydiflumetofen only as no soil metabolites triggered inclusion in the assessment.

Standard first tier FOCUSgw assessment for use on winter and spring cereals (annual application) predicted 80th percentile annual average concentrations of <0.001 µg/L. Standard first tier FOCUSgw assessment for use on winter and spring oilseed rape (application one in every three years) predicted 80th percentile triennial average concentrations of up to 0.018 µg/L.

It was noted that the concentrations in the oilseed rape simulations were increasing at the end of the 60 year simulation period. This is because pydiflumetofen shows very slow degradation with the FOCUSgw models predicting slow movement of an accumulating residue to 1 metre soil depth. Consequently, the applicant submitted results of non-standard FOCUSgw modelling based on use in cereals and oilseed rape with annual applications for 60 years.

In these non-standard simulations, the FOCUSgw models predicted that concentrations increased year on year. In simulations on cereals and oilseed rape with the highest amount of soil exposure, concentrations in some GB-relevant scenarios were predicted to exceed 0.1 µg/L at 45-50 years in the 60 year simulation period. At the end of the simulation period, concentrations were still on an upward trend suggesting that concentrations would only start to fall years after application ceased.

A further series of simulations were conducted to explore the effect of a restricted period of use. Non-standard FOCUSgw simulations explored a ten year annual application period for both cereals and oilseed rape, followed by 50 years where there was no application. No simulation predicted annual average concentrations to exceed 0.1 µg/L. However, the peak concentrations were simulated to occur between 50-60 years into the simulation, i.e. 40-50 years after application ceased. There are numerous uncertainties whether FOCUSgw models can simulate the leaching behaviour of such slowly degrading substances. However, taken at face value, the results suggest that leaching concentrations may not peak until many years after application has ceased.

Taking into account the results of the groundwater modelling, it is proposed that pydiflumetofen could be approved for a single approval period. For a 'standard' approval this would be for a period of ten years; this is the basis of the assessment described above. Considering the properties of pydiflumetofen, it is likelythat it meets the criteria to be a candidate for substitution (see Volume 1, Level 3, Section 3.1.2). In this case approval would be for a period of seven years. In order for approval to be extended into a second approval period, irrespective of whether the approval is for seven or ten years, the applicant must address the long term leaching potential of pydiflumetofen. This is because the modelling results would suggest there is the potential for concentrations in groundwater to exceed 0.1 µg/L decades after after 14 – 20 years usage has been completed.

PECsw

PECsw via spray drift was calculated for pydiflumetofen and two aqueous photolysis metabolites, NOA449410 and SYN548261. Formulation PECsw values were also calculated.

The proposed uses of pydiflumetofen use two doses, 166 g a.s./ha nd 200 g a.s./ha; the equivalent product doses are 2907 and 3510.4 g formulation/ha. The following PECsw values were calculated:

Table 2.8.6-09 PECsw via spray drift for 166 g pydiflumetofen/ha at various buffer distances

Distance (m)	PECsw ini (µg/L)
1 m	1.533
5 m	0.315
6 m	0.266
7 m	0.227
8 m	0.199
9 m	0.177
10 m	0.160
11 m	0.149
12 m	0.133
13 m	0.127
14 m	0.116
15 m	0.111
16 m	0.100
17 m	0.094
18 m	0.089
19 m	0.089
20 m	0.083

Table 2.8.6-10 PECsw via spray drift for 200 g pydiflumetofen/ha at various buffer distances

Distance (m)	PECsw ini (µg/L)
1 m	1.847
5 m	0.380
6 m	0.320
7 m	0.273
8 m	0.240
9 m	0.213
10 m	0.193
11 m	0.180
12 m	0.160
13 m	0.153
14 m	0.140
15 m	0.133
16 m	0.120
17 m	0.113
18 m	0.107
19 m	0.107
20 m	0.100

Table 2.8.6-11 PECsw via spray drift for 2907 g 'Miravis Plus'/ha at various buffer distances

Distance (m)	PECsw ini (µg formulation/L)
1 m	26.841
5 m	5.523
6 m	4.651
7 m	3.973
8 m	3.488
9 m	3.101
10 m	2.810
11 m	2.616
12 m	2.326
13 m	2.229
14 m	2.035
15 m	1.938
16 m	1.744
17 m	1.647
18 m	1.550
19 m	1.550
20 m	1.454

Table 2.8.6-12 PECsw via spray drift for 3510.4 g 'Miravis Plus'/ha at various buffer distances

Distance (m)	PECsw ini (µg formulation/L)
1 m	32.413
5 m	6.670
6 m	5.617
7 m	4.798
8 m	4.212
9 m	3.744
10 m	3.393
11 m	3.159
12 m	2.808
13 m	2.691
14 m	2.457
15 m	2.340
16 m	2.106
17 m	1.989
18 m	1.872
19 m	1.872
20 m	1.755

Table 2.8.6-13 PECsw values via spray drift for metabolite NOA449410

GAP	Spray drift buffer (m)	Maximum PECsw, spraydrift (µg/L)
1 x 166 g a.s./ha	1	0.034
1 x 200 g a.s./ha	1	0.041

Table 2.8.6-14 PECsw values via spray drift for metabolite SYN548261

GAP	Spray drift buffer (m)	Maximum PECsw, spraydrift (µg/L)
1 x 166 g a.s./ha	1	0.076
1 x 200 g a.s./ha	1	0.092

PECsw via drainflow was calculated only for pydiflumetofen as no soil metabolites triggered inclusion in aquatic assessment. The following PECsw values were calculated.

Table 2.8.6-15 PECsw via drainflow for pydiflumetofen

Crop	Maximum PECsw,drainflow (µg/L)
Winter/Spring cereals 1 x 166 g a.s./ha, 80% interception	0.051
Winter/Spring cereals 1 x 200 g a.s./ha, 90% interception	0.031
Oil Seed Rape 1 x 200 g a.s./ha, 80% interception	0.062

PECsed

PECsed via spray drift was calculated for pydiflumetofen and one water/sediment metabolite, SYN545547. Accumulated PECsed values were calculated for both pydiflumetofen and SYN545547 as they appear to be persistent in sediment.

Table 2.8.6-16 PECsed via spray drift for pydiflumetofen

Crop	**Spray drift buffer (m)**	**PECsed, spraydrift (µg/kg)**	**Accumulated PECsed, spraydrift (µg/kg)**
1 x 166 g a.s/ha	1	5.589	25.003
1 x 200 g a.s/ha	1	6.733	30.121

Table 2.8.6-17 PECsed values via spray drift for metabolite SYN545547

Crop	**Spray drift buffer (m)**	**PECsed, spraydrift (µg/kg)**	**Accumulated PECsed, spraydrift (µg/kg)**
1 x 166 g a.s./ha	1	0.807	3.610
1 x 200 g a.s./ha	1	0.973	4.353

PECsed via drainflow was calculated only for pydiflumetofen as no soil metabolites triggered inclusion in aquatic assessment. The following PECsed values were calculated.

Table 2.8.6-18 PECsed via drainflow for pydiflumetofen

Crop	**PECsed, drainflow (µg/kg)**	**Accumulated PECsed, drainflow (µg/kg)**
Winter/Spring cereals 1 x 166 g a.s./ha, 80% interception	0.186	0.832
Winter/Spring cereals 1 x 200 g a.s./ha, 90% interception	0.112	0.501
Oil Seed Rape 1 x 200 g a.s./ha, 80% interception	0.224	1.002

PECair

A quatitative PECair value for pydiflumetofen was not calculated.

2.9. EFFECTS ON NON-TARGET SPECIES

2.9.1. Summary of effects on birds and other terrestrial vertebrates

Birds

Toxicity data addressing acute and long term toxicity to birds for the active substance pydiflumetofen has been provided. For further details of the underlying studies see Section B.9 (CA). A full list of available endpoints is provided in the list of endpoints and in the relevant risk assessments for the representative formulation. The following endpoints have been used to perform the risk assessment:

Table 2.9.1-01: Summary of endpoints used to assess risk from SYN545974 to birds

Test substance	Test type	Test Species	Endpoint	Value	Reference (Author, date)
SYN 545974	Acute Oral	Bobwhite quail (*Colinus virginianus*)	$LD_{50\ extrapolated}$	3776 mg a.s./kg bw	[redacted] and [redacted] (2013)
	Dietary reproductive	Bobwhite quail (*Colinus virginianus*)	NOEC	90.1 mg a.s./kg bw/d	[redacted] *et al.* (2015)

Mammals

Toxicitiy data have been provided and considered within the human health assessment (see Section B.6 (CA) for details of the underlying studies). Endpoints for use in the mammalian risk assessment have been established for acute and long-term toxicity. The following endpoints have been used to perform the risk assessment:

Table 2.9.1-02: Summary of endpoints used to assess risk from SYN545974 to mammals

Test substance	Test type	Test Species	Endpoint	Value	Reference (Author, date)
SYN 545974	Acute Oral	Rat	LD_{50}	> 5000 mg a.s./kg bw/d	[redacted] (2012)
	Two generation reproduction	Rat	NOAEL (reproduction)	~~31.6~~ 36.1 mg a.s./kg bw/d	[redacted] (2015)

Endocrine disruption assessment for birds and mammals

When considering reproductive toxicity, treatment related effects were seen in tests which were sensitive to, but not diagnostic of EATS. The lowest effect dose was 5000 ppm, the highest tested dose for both the Bobwhite Quail and Mallard Duck. No treatment related effects were seen in the parameters for systemic toxicity.

In accordance with EFSA/ECHA guidance, the gross pathology findings should be reported. This was the case for both avian studies and no treatment related effects were observed.

Overall, on the basis of the current dataset and EFSA/ECHA 2018 guidance document it is not possible to fully conclude for pydiflumetofen against ED criteria when considering birds.

For wild mammals, the toxicology data and conclusion for endocrine disruption (see section 2.6.8) have been summarised and considered from an ecotoxicology perspective below:

Toxicology concluded that for Estrogen, Androgen, Thyroid and Steriodogenesis (EATS) modalities the endocrine disruption criteria are not met, hence this conclusion also applies to for wild mammals.

Overall conclusions ED:

Overall, HSE concludes that based on current EFSA/ECHA 2018 guidance it is not possible to reach a conclusion regarding pydiflumetofen for birds or reptiles when considering endocrine disruption.

For non-target wild mammals HSE concludes pydiflumetofen does not meet the criteria of being an ED based on EATS modalities based on current EFSA/ECHA 2018 guidance.

2.9.2. Summary of effects on aquatic organisms

Toxicity data to address pydiflumetofen, relevant metabolites and the formulation A21857B (Miravis Plus) have been provided. The tier 1 and tier 2a toxicity data used in the risk assessments are summarised here in table B2.9.2-1. For full details of all the available toxicity data, see the list of endpoints and Volume 3 CA section B.9.2. Formulation toxicity data have also been submitted and evaluated in the Volume 3 CP B.9.

Table B2.9.2-1: Tier 1 and tier 2a toxicity data relevant to the active substance Pydiflumetofen, its metabolites and the representative formulation A21857B (Miravis Plus).

Test substance	Test organism	Test system	Endpoint (mg/L)		Reference
Acute toxicity to fish					
Pydiflumetofen (active substance)	*Oncorhynchus mykiss*	Acute 96 hr (flow-through)	Mortality, LC_{50}	**0.18** **(mm)**	[redacted] (2012)
	Lepomis macrochirus	Acute 96 hr (flow-through)	Mortality, LC_{50}	0.48 (mm)	[redacted] (2014)
	Pimephales promelas	Acute 96 hr (flow-through)	Mortality, LC_{50}	0.35 (mm)	[redacted] (2013)
	Cyprinus carpio	Acute 96 hr (flow-through)	Mortality, LC_{50}	0.33 (mm)	[redacted] (2013a)
	Cyprinodon variegatus	Acute 96 hr (flow-through)	Mortality, LC_{50}	0.66 (mm)	[redacted] (2013b)
Pydiflumetofen (active substance)	Fish, acute	Geometric mean	EC_{50}	**0.366** **(mm)**	
Miravis Plus A21857B	*Oncorhynchus mykiss*	Acute 96 hr (static)	Mortality, LC_{50}	**2.84** (gm) (0.16 mg a.s./$L_{(gm)}$)	[redacted] (2019)
SYN548261	*Oncorhynchus mykiss*	96 hr (static)	Mortality, LC_{50}	> **100** (nom)	[redacted] and [redacted] (2016)
M700F001 (NOA449410)	*Oncorhynchus mykiss*	96 hr (static)	Mortality, LC_{50}	> **100** (nom)	[redacted] (2009)
Long-term toxicity to fish					
Pydiflumetofen (active substance)	*Pimephales promelas*	Chronic 32-day early life stage (flow-through)	EC_{10} (body weight)	**0.13** (mm)	[redacted] (2020)
Biconcentration in fish					

Test substance	Test organism	Test system	Endpoint (mg/L)		Reference
Pydiflumetofen (active substance)	*Lepomis macrohirus*	26-days, flow-through	Lipid normalised steady state bioconcentraiton factor (BCF_{ssl}) whole fish	31.1 L/kg	[redacted] (2017)
Acute toxicity to invertebrates					
Pydiflumetofen (active substance)	*Daphnia magna*	Static, 48-hours	EC_{50}	0.42 (m.m)	[redacted] (2017)
	Chaoborus crystallinius	Static, 48-hours	EC_{50}	2.489 (m.m)	[redacted] (2015)
	Cyclops agilis speratus	Static, 48-hours	EC_{50}	4.168 (m.m)	[redacted] (2015b)
	Asellus aquaticus	Static, 48-hours	EC_{50}	4.209 (m.m.)	[redacted] (2015)
	Crangonyx pseudogracilis	Static, 48-hours	EC_{50}	1.226 (m.m.)	[redacted] (2015b)
	Lumbriculus veriegatus	Static, 48-hours	EC_{50}	4.651 (m.m.)	[redacted] (2015c)
	Chironomus riparius	Static, 48-hours	EC_{50}	0.691 (m.m)	[redacted]. (2015a)
	Hyalella azteca	Static, 48-hours	EC_{50}	**0.12 (m.m)**	[redacted] *et al* (2015)
	Americamysis bahia	Static, 48-hours	EC_{50}	0.16 (m.m)	[redacted] (2016)
Pydiflumetofen (active substance)	Aquatic invertebrate, acute	Geometric mean	EC_{50}	**1.037 (mm)**[1]	
Miravis Plus A21857B	*Daphnia magna*	Static, 48-hours	EC_{50}	**1.9 (mm)**[1] (0.107 mg a.s./L)	[redacted] (2019)
SYN548261	*Daphnia magna*	Semi-static, 48 hour	EC_{50}	> **100 (nom.)**	[redacted] and [redacted] (2016a)
M700F001 (NOA449410)	*Daphnia magna*	Static, 48-hours	EC_{50}	> **100 (nom.)**	[redacted] (2009a)
Long-term toxicity to invertebrates					
Pydiflumetofen (active substance)	*Americamysis bahia*	Flow through, 28-days	NOEC	**0.037 (nom.)**	[redacted] **(2015a)**
Toxicity to sediment dwelling invertebrates					
Pydiflumetofen (active substance)	*Hyalella azteca*	42 days static spiked sediment (with surface water renewal)	NOEC (28, 35 and 42 day survival)	**36 mg a.s./kg sediment (m.m)**	[redacted] (2015a)
SYN545547	*Chironomus riparius*	28-day Static	NOEC (male development)	**7.2 (m.m)**	[redacted] (2015)
Toxicity to algae					

Test substance	Test organism	Test system	Endpoint (mg/L)		Reference
Pydiflumetofen (active substance)	*Navicula pelliculosa*, strain 661	96-hours, Static	72 h E_rC_{50}	**1.6 (m.m.)**	[redacted] (2015)
Miravis Plus A21857B	*Pseudokirchneriella subcapitata*	96-hours, static	72 hr E_rC_{50}	**7.38 (g.m.)** (0.415 mg a.s./L)	[redacted] (2019)
M700F001 (NOA449410)	*Pseudokirchneriella subcapitata*	72-hours, static	72 h E_rC_{50}	**36.31 (nom.)**	[redacted] (2009b)
SYN548261	*Pseudokirchneriella subcapitata*	96-hours, Static	72 h E_rC_{50}	**>100 (nom.)**	[redacted] & [redacted] 2016b)

[1]The active substance invertebrate geomean endpoint was also used to address the formulation risk assessment for aquatic invertebrates, rather than the *Daphnia* endpoint. Please see Vol. 3CP Part B9.4 for further details.

Toxicity to aquatic plants (Pydiflumetofen):

Only one study assessing the toxicity to aquatic macrophytes with the active substance was available, using *Lemna gibba*. This study was not considered suitable for use in risk assessment due to issues with the analytical measurements taken. This will not form a data gap, since, according to EU Regulation 283/2013, laboratory tests with *Lemna* are only required for herbicides, plant growth regulators and where there is evidence from studies with non-target plants that the substance has herbicidal activity. The available data from non-target plants (section B.9.12) do not indicate that Pydiflumetofen has herbicidal activity, therefore the absence of a reliable *Lemna* study does not constitute a data gap.

Endocrine disruption assessment for aquatic organisms:

For the endocrine disruption assessment two studies testing aquatic organisms and measuring endocrine parameters were conducted: A Fish Short Term Reproduction Assay (FSTRA) with the Fathead minnow ([redacted], 2020a) informing the Oestrogen, Androgen and Steroidogenesis (EAS) modalities, and an Amphibian Metamorphosis Assay (AMA) with the African clawed frog ([redacted], 2020) informing the Thyroid (T) modality. The two fish early life stage (ELS) studies were also considered as part of the EAS modality endocrine assessment, one for Fathead minnow ([redacted], 2020) and one for Sheepshead Minnow ([redacted], 2015). The consideration has been carried out according to the EFSA/ECHA guidance document (2018) based on the available data.

Mechanistic endocrine activity of the EAS modalities has been ~~sufficiently~~ investigated through the FSTRA study ([redacted], 2020a). VTG results for males were inconclusive due to wide variation of the data, but there were no other indications of EAS-mediated adverse effects based on the other parameters measured. For females, only the middle test concentration (0.017 mg a.s./L) had a significant decrease in VTG levels; although all treatments were reduced relative to the control.~~, this was not dose responsive and therefore is not indicative of endocrine activity according to EFSA/ECHA guidance (2018).~~

Adversity based on EAS-mediated parameters has been ~~sufficiently~~ investigated through the FSTRA study which monitored Secondary Sex Characteristics (SSCs), gonad histopathology, ovarian stage scores and testicular stage scores. Evidence for parameters sensitive to, but not diagnostic of, EATS modalities, was also monitored in the FSTRA and two further ELS studies, namely: behaviour, body weight and length, reproduction and morphological abnormalities. Some adversity was observed in gonad histopathology, notably severe oocyte atresia at the highest test concentration (0.13 mg a.s./L) which correlated with a significant reduction in egg production (fecundity) at this treatment level. ~~However, based upon liver histopathology findings in the FSTRA study and larval survival in the ELS studies, the weight of evidence does not suggest that the observations in EAS-mediated parameters of the FSTRA study are due to hormonal changes, but are instead a result of low-level systemic toxicity.~~

~~In conclusion, based on submitted studies for EAS modalities, pydiflumetofen is not an endocrine disruptor for aquatic organisms.~~ Independent Scientific Advice (ISA) was sought from the Expert Committee on Pesticides (ECP) regarding the results from the FSTRA and it was concluded that it was uncertain as to whether the observed effects were due to systemic toxicity or endocrine-mediated. As such, a Rapid Androgen Disruption Activity Reporter (RADAR) assay was requested to provide further mechanistic data. ~~This is currently ongoing, therefore it is not possible to conclude at present on the endocrine disrupting potential of pydiflumetofen on Estrogen, Androgen and Steroidogenesis (EAS) modalities for aquatic organisms.~~

The applicant conducted a RADAR assay and a draft report was submitted to HSE for consideration in September 2023. Results from the RADAR assay indicated that no significant increase or decrease in normalised mean fluorescence was observed in the spiked mode of the test in comparison to the 17MT 3 µg/L control. According to the test guideline OECD 251, it can therefore be concluded that pydiflumetofen is inactive in the RADAR assay. However, it is noted that in the unspiked mode, a statistically significant decrease in normalised mean fluorescence was observed at the lowest test concentration (1.3 µg a.s./L) in comparison to the solvent control. GFP was not visible in the kidneys of the solvent control group or test groups. Fluorescence decreases in unspiked mode are not expected as the eleutheroembryos do not synthesise detectable levels of androgen at this developmental stage.

Considering both the results from the RADAR assay and FSTRA together, overall HSE considers that EAS modalities have been sufficiently investigated. There is uncertainty regarding the lowest RADAR assay test concentration due to the significant decrease in fluorescence in the unspiked mode, however in the FSTRA, other than an increase in moderate oocyte atresia compared to the control at the same concentration, there were no clear endocrine mediated effects. No other significant effects were observed at the other tested concentrations in the RADAR assay in unspiked mode, suggesting the concentration range selected was broadly appropriate. As there were no statistically significant increases or decreases in fluorescence in spiked mode at any of the concentrations tested, this indicates that pydiflumetofen is inactive in the RADAR assay. The significant decrease in female VTG in the FSTRA at a concentration of 17 µg a.s./L does not correspond to any significant effects at a similar concentration in the RADAR assay, suggesting the observed decrease is not endocrine-mediated. Whilst there remains some uncertainty with both the results of the FSTRA and the RADAR assay, taken together HSE considers the results support a negative conclusion for EAS modalities. In addition, the conclusion reached for toxicology (noting uncertainty in 'read across' between vertebrates) was that based on the overall weight of evidence, pydiflumetofen does not cause EAS-mediated adversity and that this modality has been sufficiently investigated

(see in the volume 3, CA section 6 dossier part II (B.6.8.3), adding further support to the overall conclusion that there is lack of adversity for EAS modalities. Please refer to the DAR Vol 3 CA Section B.9.2.3 for further consideration.

HSE considers that endocrine activity of the T-modality has been sufficiently investigated in the provided amphibian metamorphosis assay (AMA) study (Full study summary and evaluation available in section B.9.2.3.3 of volume 3CA B9, study reference [redacted], 2020).

For the purposes of this assessment, based on the EFSA/ECHA 'Guidance for the identification of endocrine disruptors in the context of regulations (EU) No 528.2012 and (EC) No 1107.2009', the tested parameters from the AMA study were divided into 'endpoints indicative of thyroid-mediated modality', and 'endpoints sensitive to, but not diagnostic of, the thyroid modality'.

The only significant result from the parameters which are considered indicative of thyroid-mediated modality was an increase in day 7 developmental stage among tadpoles exposed to the 300 µg /L treatment level compared to the control, when the results were analysed using Jonckheere-Terpstra's Step-Down Test. This result was not significant when analysed using the OECD (2009) and U.S. EPA (2009) preferred statistical method of multi-quantal analysis. HSE has assessed these results and agrees that there is no clear treatment-related effect for developmental stage.

Significant results from the parameters which are sensitive to, but not diagnostic of, the thyroid modality include a significant reduction in whole-body wet weight at day 21 among the tadpoles exposed to the 23 and 300 µg/L treatment levels, compared to the control. This was considered not to be treatment-related, as there was no effect at the interim concentration of 100 µg/L, and reductions in wet body weight at the 300 µg/L treatment level were likely to result from systemic toxicity, considering the liver histopathology findings at this treatment level and the behavioural symptoms of toxicity observed in the range-finder. This indicates that this treatment level approached the maximum tolerable concentration (MTC) for pydiflumetofen.

Additionally, there was a very high incidence of spinal deformity (i.e. scoliosis, bent tail) in all conditions. The highest level was observed in the control condition, at 45% of test organisms for the entire exposure period. No clear dose-response relationship was observed, and as such, this was judged to be not treatment-related, and deemed unlikely to impact any endpoint collected for this assay.

Liver histopathology revealed a relatively low-grade reduction in hepatocellular vacuolation (glycogen incorporation) in eight tadpoles at the 300 µg/L treatment level, which is consistent with diminished hepatic glycogen/lipid storage. This non-specific finding suggests that the energy intake in those frogs was insufficient relative to physiological requirements for growth and activity.

Overall, there were no clear treatment related effects on T-mediated parameters in the submitted AMA study up to the MTC. Slight effects on the whole-body wet weight parameter, were likely due to general toxicity, meaning that overall, the case is strong enough to conclude that there is no evidence of treatment-related changes in thyroid activity.

~~**In conclusion, pydiflumetofen is considered not to have endocrine disruption properties, in accordance with EFSA/ECHA 2018 guidance based on available information.**~~

In conclusion, HSE considers that based on the available evidence, the EATS modalities have been sufficiently investigated and pydiflumetofen does not cause endocrine-mediated adverse effects in aquatic organisms. HSE therefore concludes that pydiflumetofen is not an endocrine disruptor in non-target aquatic organisms.

2.9.3. Summary of effects on arthropods

Bees

Studies conducted with the active substance

Acute oral and acute contact studies were submitted for the active substance for honeybees (*Apis mellifera*) and were considered valid after evaluation. A chronic honeybee larvae repeated exposure study (22d) was also submitted for the active substance which was performed as a limit test. There were uncertainties with the larval test but it was considered valid. In addition, a brood colony feeding study under field conditions, broadly based on the 'Oomen method' was submitted, investigating repeated oral exposure (for 9 days) of the technical active substance via diet.

There is currently no GB-adopted guidance for considering chronic studies in bee risk assessment, however, the endpoints and conclusions of such studies were still considered as supporting information. This is in part due to the results of the larval active substance study, which did raise concerns of potential effects at a low dose of the active substance (see table below).

Studies conducted with formulations A19649B ('Miravis') and A21857B ('Miravis Plus')

Data is available for two formulations: A21857B (Miravis Plus), which is the representative product for the GB assessment of this active, and A19649B which was the representative product for the EU assessment of this active. For A21857B, only an adult acute contact and oral study were submitted. Other data are available for the alternative formulation A19649B, including an adult acute oral and contact study, an adult 10-day chronic study, a larval repeat exposure (22d) and a larval repeated exposure test (8d). A further three semi-field bee brood tunnel tests with exposure to sprayed flowering crop were also submitted, which also included residue data.

The two formulations were compared in the confidential section C.1.3.5 of Volume 4 and are not chemically comparable; additionally changes between the two would be defined as a major change according to CRD formulation guidance (2022). However, on the basis of both formulations having low adult acute oral and contact toxicity (see table below), and a ~~comparable~~ low acute risk demonstrated for both formulations at risk assessment, it is proposed that the studies on A19649B can be used to support assessment of A21857B.

Following discussion at the ECP meeting, the ECP advised that it is incorrect to take the view that the two formulations (EU formulation Miravis A19649B and UK formulation Miravis Plus A21857B) are of comparable toxicity based on evidence from unbounded toxicity values, although the Committee agreed that both formulations do not appear to be very toxic based on the acute toxicity dataset. However, it is not possible to determine if one formulation is more or less toxic than the other, based on the data. The Committee accepted the interpretation and use of semi-field data to support the conclusion on honeybee larvae, given the uncertainties in the laboratory dataset for honeybee larvae. The availability of the colony-feeding field study using the technical active substance rather than the EU formulation, adds weight to the conclusion.

The chronic adult study on A19649B was considered valid but uncertainty is present due to lack of measurements for evaporative loss of the test substance, this was because the test was performed to an older version of the guideline. The two larval studies on A19649B were both considered valid, but produced conflicting endpoints with each other and the third larval study on the active substance detailed above. Therefore, as supporting information to the risk assessment, more weight was given to the results of the semi-field studies on A19649B and the colony-feeding study on the active substance.

The toxicity endpoints for bees are summarised in the table below.

Table 2.9.3-1: Effects on bees

Species	Test substance	Time scale/type of endpoint	End point	Toxicity
Apis mellifera	a.s.	Acute (48 h), Adult	Oral toxicity (LD_{50})	>116 µg a.s./$bee_{(con)}$
Apis mellifera	a.s.	Acute (48 h), Adult	Contact toxicity (LD_{50})	>100 µg a.s./bee
Apis mellifera	Preparation 'A19649B'	Acute (48 h), Adult	Oral toxicity (LD_{50})	>1132 µg f.p./$bee_{(con)}$ (equivalent to >211 µg a.s./$bee_{(con)}$)
Apis mellifera	Preparation 'A19649B'	Acute (48 h), Adult	Contact toxicity (LD_{50})	>1000 µg f.p./bee (equivalent to >186 µg a.s./bee)
Apis mellifera	Preparation 'A21857B' (Miravis Plus)	Acute (48 h), Adult	Oral toxicity (LD_{50})	>423 µg f.p./$bee_{(con)}$ (equivalent to >24.07 µg a.s./$bee_{(con)}$)
Apis mellifera	Preparation 'A21857B' (Miravis Plus)	Acute (48 h), Adult	Contact toxicity (LD_{50})	>1000 µg f.p./bee (equivalent to >56.9 µg a.s./bee)
Apis mellifera	Preparation 'A19649B'	Chronic (10 d repeated exposure), Adult	LD_{50}/LD_{20}/LD_{10} [a] LC_{50}/LC_{20}/LC_{10} [a] NOED [a] NOEC [a]	>138.2 µg a.s./bee/$day_{(con)}$ [a] >3854 mg a.s./kg diet [a] 138.2 µg a.s./bee/$day_{(con)}$ [a] 3854 mg a.s./kg diet [a]
Apis mellifera	a.s.	Bee brood development (Larval 22d, repeated exposure, limit test)*	8d LD_{50} & 22d ED_{50} 8d LC_{50} & 22d EC_{50} 8d & 22d NOED [b] 8d & 22d NOEC [b]	>0.014 µg a.s./$larva_{(con)}$ >0.0035 µg a.s./larva/$day_{(con)}$ >0.09 mg a.s./kg $diet_{(mc)}$ <0.014 µg a.s./$larva_{(con)}$ [b] <0.0035 µg a.s./larva/$day_{(con)}$ [b] <0.09 mg a.s./kg $diet_{(mc)}$ [b]
Apis mellifera	Preparation 'A19649B'	Bee brood development (Larval 22d, repeated exposure)*	8d LD_{50} [c] 8d NOED [b] 8d NOEC [b] 8d $LD_{10/20}$ & 22d $ED_{10/20}$ 22d ED_{50} [c] 22d NOED 22d NOEC	45.24 µg a.s./$larva_{(con)}$ 11.31 µg a.s./larva/$day_{(con)}$ <0.06 µg a.s./$larva_{(con)}$ [b] <0.015 µg a.s./larva/$day_{(con)}$ [b] <0.409 mg a.s./kg $diet_{(nc)}$ [b] n.d. 7.64 µg a.s./$larva_{(con)}$ 1.91 µg a.s./larva/$day_{(con)}$ 0.06 µg a.s./$larva_{(con)}$ 0.015 µg a.s./larva/$day_{(con)}$ 0.409 mg a.s./kg/$diet_{(nc)}$

Species	Test substance	Time scale/type of endpoint	End point	Toxicity
Apis mellifera	Preparation 'A19649B'	Larval 8d, repeated exposure*	8d NOED [d]	55 µg a.s./larva [d] 13.75 µg a.s./larva/day [d]
			8d NOEC	347 mg a.s./kg diet$_{(nc)}$
			8d LD/LC$_{10/20}$	n.d.
			8d LD$_{50}$ [e]	>109.9 µg a.s./larva [e] >27.48 µg a.s./larva/day [e]
			8d LC$_{50}$	>695 mg a.s./kg diet$_{(nc)}$
Semi-field/Field studies				
Apis mellifera	a.s.	Chronic brood colony feeding study under field conditions, repeat oral exposure (9 day exposure, 61 day observation)	No adverse effect on colony development and survival, as tested up to 32.0 mg a.s./kg diet.	
Apis mellifera	Preparation 'A19649B'	Chronic, whole brood, semi-field tunnel test, single spray exposure to flowering *Phacelia*	Three separate studies were performed. No significant adverse effects of the test item on the colonies, as tested up to 200 g a.s./ha.	

A19649B: the representative product for the EU assessment of this active.
A21857B (Miravis Plus): the representative product for the GB assessment of this active.
$_{(con)}$ = consumed dose; $_{(mc)}$ = measured concentration; $_{(nc)}$ = nominal concentration; a.s. = active substance; f.p. = formulated preparation/product; n.d.= not possible to determine.
*These three studies with honeybee larvae were considered valid, but the results are contradictory to each other. Whilst these larval endpoints are not currently used in a quantitative manner in risk assessment (due to current lack of noted/agreed guidance), they have been included for further information.
[a] Note there is uncertainty in the reliability of the endpoints from this study, as no analytical measurements were provided and there were no corrections for evaporative loss of the test substance in the diet.
[b] Although an unbounded 'less-than' NOEC would typically be described as an undefined endpoint, the unbounded values are provided for additional information.
[c] There is some uncertainty with these ED/LD$_{50}$ endpoints due to wide confidence intervals. LC and EC$_{10/20}$ were also calculated in the study, but were unreliable due to extrapolation outside tested concentrations and wide confidence intervals
[d] This endpoint does not take into account the actual consumed dose, which may be lower, as left-over food (incdicating repellence/unpalatability) and corresponding reduction in larval development was observed in 21 % of remaining larvae.
[e] This endpoint does not take into account the actual consumed dose, which may be lower, as left-over food (indicating repellence/unpalatability) and corresponding reduction in larval development was observed in 35 % of remaining larvae.

Non-target arthropods other than bees

The toxicity endpoints for non-target arthropods other than bees are summarised in the tables below.

Table 2.9.3-2: Effects on non-target arthropods other than bees

Species	Life stage	Test Substance	Study type	End point	Toxicity (L f.p./ha)
Typhlodromus pyri	Protonymphs	Preparation 'A21857B'	Tier 1 glass plate (2D)	Mortality, LR_{50} Reproduction*	1.667 >1.250
Aphidius rhopalosiphi	Adult	Preparation 'A21857B'	Tier I glass plates (2D)	Mortality, LR_{50} Reproduction*	>0.375 >0.375
Aphidius rhopalosiphi	Adult	Preparation 'A21857B'	Extended laboratory study on sprayed barley plants (3D)	Mortality, LR_{50} Reproduction*	8.087 5.556
Typhlodromus pyri	Protonymphs	Preparation 'A21857B'	Extended laboratory study on sprayed French bean leaf discs (2D)	Mortality, LR_{50} Reproduction*	5.000 5.000
Chrysoperla carnea	First instar larvae	Preparation 'A21857B'	Extended laboratory study on sprayed French bean leaf discs (2D)	Mortality, LR_{50} Reproduction*	>3.200 3.200

*Reproductive endpoint is defined as 'Highest test rate with < 50 % effect on reproduction'.
f.p.: formulated product

2.9.4. Summary of effects on non-target soil meso- and macrofauna

Earthworms

No earthworm studies were carried out using the active substance, only the representative product A21857B (Miravis Plus). In this case, the study carried out using the representative product 'Miravis Plus' was used to fulfil the active substance data requirements. Two risk assessments were carried out, one using the formulated product endpoints and formulation PEC_{Soil} values, and the other using active substance PEC_{Soil} values, and active substance endpoints which were derived from the formulation endpoints, these were calculated based on the analysed content of pydiflumetofen in the formulation (5.62 % w/v, corresponding to 61.7 g a.s. /L). The study which was used in the risk assessment was deemed valid for regulatory purposes with no significant deviations from the study guidelines. The following endpoints were used for the risk assessment:

Table 2.9.4-01: Summary of endpoints used to assess risk from A21857B to earthworms

Test substance	Test type	Test Species	Endpoint	Value	Reference (Author, date)
A21857B (Miravis Plus)	Earthworm reproduction test	*Eisenia foetida*	$EC_{10\ (reproduction)\ CORR}$ [1)]	97 mg A21857B/kg soil d.w. (Equivalent to 5.45 mg a.s./kg soil d.w.) nom.	[redacted] (2017)

[1)]Endpoint corrected by a factor of 2 due to $\log_{Pow} > 2$
nom.: endpoints based on nominal concentrations

Non-target soil meso- and macro-fauna (other than earthworms)

No studies were carried out on non-target soil meso- and macrofauna (other than earthworms) using the active substance pydiflumetofen, studies were only submitted which tested the effects of the representative product A21857B (Miravis Plus). In this case, the studies carried out using the representative product 'Miravis Plus' were used to fulfil the active substance data requirements. Two risk assessments were carried out, one using the formulated product endpoints and formulation PEC_{Soil} values, and the other using active substance PEC_{Soil} values, and active substance endpoints which were derived from the formulation endpoints, these were calculated based on the analysed content of pydiflumetofen in the formulation (5.62 % w/v, corresponding to 61.7 g a.s. /L).
The studies used in the risk assessment were deemed valid for regulatory purposes with no significant deviations from the study guidelines. A summary of the endpoints used in the risk assessment is provided in Table 2.9.4-02 below.

Table 2.9.4-02: Summary of endpoints used to assess risk from A21857B to non-target meso- and macro-fauna (other than earthworms)

Test substance	Test type	Test Species	Endpoint	Value	Reference (Author, date)
A21857B (Miravis Plus)	Predatory mite reproduction test in soil	*Hypoaspis aculeifer*	$NOEC_{CORR}$ [1)] (reproduction and mortality)	≥ 500 mg product /kg soil d.w. (nom); equivalent to 28.1 mg a.s./kg soil d.w.	[redacted] (2017a)
	Collembolan reproduction test in soil	*Folsomia candida*	28-day NOEC (mortality) $_{CORR}$ [1)]	≥ 500 mg product /kg soil d.w. (nom); equivalent to 28.1 mg a.s./kg soil d.w.	[redacted] (2017)

[1)] Endpoints are corrected by a factor of 2 (due to $\log_{Pow} > 2$) for use in the risk assessment.
nom: nominal concentration
Endpoints in terms of the active substance were calculated based on the analysed content of pydiflumetofen in the formulation (5.62 % w/v, corresponding to 61.7 g a.s. /L).

2.9.5. Summary of effects on soil nitrogen transformation

Three soil micro-organism (nitrogen transformation) studies were submitted for assessment, two conducted using the active substance, and one study conducted with the representative product 'Miravis Plus'. The study conducted using 'Miravis Plus' was found to be unsuitable, as although the deviation from the control nitrogen transformation rate for the whole test period was below the < 25 % threshold, the 14–28 day section-by-section nitrogen transformation rate exceeded this threshold, indicating delated effects of the test substance. As a result, the study duration should have been extended (See Section B.9.9. for further details). For this reason, only the two submitted active substance studies were used for the purposes of the risk assessment. Table 2.9.5-01 below displays the available endpoints for the effects of pydiflumetofen and the representative product 'Miravis Plus', on soil nitrogen transformation.

Table 2.9.5-01: Summary of studies submitted for use in the soil micro-organism (nitrogen transformation) risk assessment

Test substance	Test type	Effect	Reference (Author, date)
SYN545974	Nitrogen transformation test	**No effects on nitrogen transformation rate, greater than or equal to 25 %, were observed by day 28 at up to 2.71 mg a.s./kg dry soil.**	[redacted] (2015)
	Nitrogen transformation test	No effects on nitrogen transformation rate, greater than or equal to 25 % compared to control at 13.5 mg active substance/kg dry soil	[redacted] (2017)
A21857B (Miravis Plus)	Nitrogen transformation test	This study will not be considered further as part of the risk assessment.	[redacted] (2017a)

2.9.6. Summary of effects on terrestrial non-target higher plants

No non-target plant active substance studies were submitted for evaluation. One non-target plant screening study was submitted for the representative product 'Miravis Plus' (A21857B). This is considered acceptable, as the active substance is not a herbicide, and does not demonstrate a herbicidal MOA.

Table 2.9.6-01: Summary of non-target plant screening data for 'Miravis Plus' (A21857B)

Test substance	Study type	Assessment type	Test plant		Observed effects	Reference
Miravis Plus (A21857B)	Phytotoxicity to non-target plants - screening test	Seedling emergence	Monocots	*Allium cepa* (onion)	No effects observed at any test concentration.	[redacted], (2017)
				Triticum aestivum (wheat)	No effects observed at any test concentration.	
			Dicots	*Glycine max* (soybean)	No effects observed at any test concentration.	
				Beta vulgaris (sugar beet)	No effects observed at any test concentration.	
				Brassica napus (Oilseed rape)	No effects observed at any test concentration.	
				Cucumis sativus (cucumber)	No effects observed at any test concentration.	
		Vegetative vigour	Monocots	*Allium cepa* (onion)	No effects observed at any test concentration.	
				Triticum aestivum (wheat)	No effects observed at any test concentration.	
			Dicots	*Glycine max* (soybean)	**Slight phytotoxic effects (necrosis) at 3,200 [2]* mL A21857B /ha**	

Test substance	Study type	Assessment type	Test plant		Observed effects	Reference
				Beta vulgaris (sugar beet)	No effects observed at any test concentration.	
				Brassica napus (Oilseed rape)	No effects observed at any test concentration.	
				Cucumis sativus (cucumber)	**Phytotoxic effects (necrosis) at 800 [1]*, 1,600 [2]*, and 3,200 [4]* mL A21857B /ha**	

* numbers in square brackets [#] represent the numerical score assigned as a rating of phytotoxicity. Plants were rated on a scale from 0 to 10, with 0 representing 'Vigorous healthy plants, indistinguishable from the untreated control', and 10 representing 'Complete destruction of plant parts above ground'.

2.9.7. Summary of effects on other terrestrial organisms (flora and fauna)

2.9.8. Summary of effects on biological methods for sewage treatment

The first-tier toxicity data used in the risk assessment is summarised here (Table 2.9.8-1). For full details of all the available toxicity data see the list of endpoints and Volume 3 CA Section B.9.8.

Table 2.9.8: Table of endpoints

Organism	Test substance	Test type	Endpoint	Reference
Activated sludge microorganisms	Pydiflumetofen	OECD 209 (2010)	EC_{50} (3h) > 1.5 mg a.s./L[1]	[redacted] (2013)

[1]Based on the limit of solubility of pydiflumetofen in water

2.9.9. Summary of product exposure and risk assessment

2.9.9.1 *Risk assessment for birds and mammals*

Birds

The results of the risk assessments of the active substance are summarised here. Risk assessments were conducted according to EFSA Bird and Mammal Guidance Document (2009).

Risk assessment for 'SYN545974'

The risk to birds from the active substance was assessed based on the proposed use on cereals and oilseed rape at a single maximum application rate of and 0.2 kg a.s./ha for BBCH ranges of 30 – 69. The shortcut values for cereals and oilseed rape are the same for the screening step according to EFSA (2009), therefore, the assessment for cereals will cover both uses.

The table below summarises the results of the risk assessment:

Table 2.9.9.1-01: Sumary of the risk assessment of SYN545974 to birds

Intended use	Cereals
Active substance	SYN545974
Application rate (kg/ha)	1 × 0.2
Acute toxicity (mg/kg bw)	3776
TER criterion	10

Crop scenario	**Indicator species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_a**
Cereals and Oilseed Rape	Small omnivorous bird	158.8	1	31.76	118.89
Reprod. toxicity (mg/kg bw/d)	90.1				
TER criterion	5				
Crop scenario	**Indicator species**	**SV_m**	**MAF_m × TWA**	**DDD_m (mg/kg bw/d)**	**TER_{lt}**
Cereals and Oilseed Rape	Small omnivorous bird	64.8	1 x 0.53	6.87	13.12

The acute and chronic risk to birds was shown to be acceptable at the screening step, the TER values were higher than the relevant trigger points.

Secondary poisoning

The risk to birds from consuming fish contaminated with pydiflumetofen was acceptable (DDD = 0.0092 mg/kg bw/d, TER = 9793.48).
The risk to birds from consuming earthworms contaminated with pydiflumetofen was acceptable (DDD = 0.073 mg/kg bw/d, TER = 1234.25).

Drinking water

Acceptable acute and chronic risks for exposure of birds to pydiflumetofen via drinking water were established for the puddles scenario. The leaf scenario was not relevant to the proposed crop use.

Metabolite risk assessment

There were no pydiflumetofen metabolites formed in plant metabolism studies at > 10 %.

Isomeric ratio of pydiflumetofen and metabolites (all non-target organism group)

Refer to section 2.12.74 for consideration.

Overall conclusion to the risk to birds from 'SYN545974'

The risk to birds from 'SYN545974' is considered to be acceptable for the proposed use.

Mammals

The risk to mammals from the active substance was assessed based on the proposed use on cereals and oilseed rape at a single maximum application rate of 0.2 kg a.s./ha for BBCH ranges of 30 – 69. The shortcut values for cereals and oilseed rape are the same for the screening step according to EFSA (2009), therefore, the assessment for cereals will cover both uses.

The table below summarises the results of the risk assessment.

Table 2.9.9.1-02: Sumary of the risk assessment of SYN545974 to mammals

Intended use	Cereals				
Active substance	SYN545974				
Application rate (kg/ha)	1 × 0.2				
Acute toxicity (mg/kg bw)	> 5000				
TER criterion	10				
Crop scenario	**Indicator species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_a**
Cereals and Oilseed Rape	Small herbivorous mammal	118.4	1	23.68	211.15
Reprod. toxicity (mg/kg bw/d)	~~31.6~~ 36.1				
TER criterion	5				
Crop scenario	**Indicator species**	**SV_m**	**MAF_m × TWA**	**DDD_m (mg/kg bw/d)**	**TER_{lt}**
Cereals and Oilseed Rape	Small herbivorous mammal	~~48.9~~ 48.3	1 x 0.53	~~5.18~~ 5.12	~~6.1~~ 7.1

The acute and chronic risk to mammals was shown to be acceptable at the screening step, the TER values were higher than the releant trigger points.

Secondary poisoning

The risk to mammals from consuming fish contaminated with pydiflumetofen was acceptable (DDD = 0.0082 mg/kg bw/d, TER = 4402.44).
The risk to mammals from consuming earthworms contaminated with pydiflumetofen was acceptable (DDD = 0.089 mg/kg bw/d, TER = 405.62).

Drinking water

Acceptable acute and chronic risks for exposure of mammals to pydiflumetofen via drinking water were established for the puddle scenario.

Metabolite risk assessment

There were no pydiflumetofen metabolites formed in plant metabolism studies at > 10 %.

Isomeric ratio of pydiflumetofen and metabolites (all non-target organism group)

Refer to section 2.12.74 for consideration.

Overall conclusion to the risk to mammals from 'SYN545974'

The risk to mammals from 'SYN545974' is considered to be acceptable for the proposed use.

2.9.9.2 *Risk assessment for aquatic organisms*

The result of the risk assessment for the active substance, relevant metabolites and representative formulation is summarised here. Risk assessments were conducted according to Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters: EFSA Journal 2013;11(7):3290.

Active substance

Tier 1 aquatic risk assessment for Pydiflumetofen

Table B2.9.9.2-1 shows the aquatic risk assessment for surface water and sediment for the proposed uses of Pydiflumetofen on oilseed rape at 200 g a.s./ha.

Table B2.9.9.2-1 First-tier risk assessment for exposure to the active substance (Pydiflumetofen) due to use on oilseed rape at 200 g a.s./ha

Scenario	PEC (µg/L)	Fish acute	Fish long-term	Aquatic invertebrates acute	Aquatic invertebrates long-term	Algae	PEC sed (µg/L)	Sediment dwelling invertebrate
		O. mykiss	*P. promelas*	*H. azteca*	*A. bahia*	*N. pelliculosa*		*H. azteca*
		RAC (LC_{50})	RAC (EC_{10})	RAC (EC_{50})	RAC (NOEC)	RAC (E_rC_{50})		RAC (NOEC)
		1.8	13	1.2	3.7	160		3600
Spray-drift (1 m)	1.847	**1.026**	0.142	**1.539**	0.499	0.115	30.121	0.0084
Drainflow	0.062	0.034	0.005	0.05	0.017	0.0004	1.002	0.00028

Conclusion: For the proposed use on cereals and oilseed rape at 200 g a.s./ha, there is an unacceptable acute risk to fish and aquatic invertebrates via spraydrift. Therefore, further consideration is required. An acceptable risk from drainflow can be concluded for all organism groups.
Refinement of the risk assessment for these groups is considered in the tier 2 risk assessment.

Tier 2 aquatic risk assessment for Pydiflumetofen

Table B2.9.9.2-2 Refined risk assessment for acute fish and acute aquatic invertebrates using geomean RACs due to use on oilseed rape at 200 g a.s./ha

Scenario	PECsw (µg/L)	Fish acute	Invertebrates acute
		Geomean RAC (LC_{50})	Geomean RAC (EC_{50})
		3.66 µg/L	10.37 µg/L
Spray-drift (1 m)	1.847	0.50	0.18

Conclusion: For the proposed use on cereals and oilseed rape at 200 g a.s./ha, the acute risk to fish and aquatic invertebrates from spray drift has been resolved using the geomean RAC values. No further consideration is required.

Metabolites of Pydiflumetofen

Risk assessments for the metabolites SYN545547, M700F001 (NOA449410) and SYN548261 are summarised for the critical GAP (200 g a.s./ha on oilseed rape) in Tables B2.9.9.2-3 to B2.9.9.2-5 below:

Table B2.9.9.2-3: First tier risk assessment for exposure to SYN545547 due to use on oilseed rape at 200 g a.s./ha

Scenario	PECsed (µg/kg)	Sediment dwelling organisms
		Chironomus riparius[1]
		RAC (NOEC)
		720
Spraydrift (1 m)	4.353	0.006

[1] Spiked sediment study; value is expressed as µg/kg sediment

Table B2.9.9.2-4: First tier risk assessment for exposure to M700F001 (NOA449410) due to use on oilseed rape at 200 g a.s./ha

Scenario	PECsw (µg/L)	Fish acute	Aquatic invertebrates (acute)	Algae
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		RAC (LC_{50})	RAC (EC_{50})	RAC (E_rC_{50})
		1000	1000	3631
Spraydrift (1 m)	0.041	0.000041	0.000041	0.00001

Table B2.9.9.2-5:First tier risk assessment for exposure to SYN548261 due to use on oilseed rape at 200 g a.s./ha

Scenario	PECsw (µg/L)	Fish acute	Aquatic invertebrates (acute)	Algae
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		RAC (LC_{50})	RAC (EC_{50})	RAC (E_rC_{50})
		1000	1000	10,000
Spraydrift (1 m)	0.092	0.000092	0.000092	0.0000092

Conclusion: For the proposed worst-case use on oilseed rape at 200 g a.s./ha, an acceptable risk to aquatic organisms can be concluded for all relevant metabolites of Pydiflumetofen.

Formulation 'Miravis plus'

Risk assessment for the formulation 'Miravis plus' is summarised in Table B2.9.9.2-6. The PEC values used relate to the worst-case GAP use of 'Miravis Plus' on oilseed rape at 200 g a.s./ha. These values are protective of the risk from all other proposed uses.

Table B2.9.9.2-6: First tier risk assessment for exposure to 'Miravis Plus' due to use on oilseed rape at 200 g a.s./ha

Scenario	PEC (µg formulation/L)	Aquatic invertebrates	Algae
		D. magna	*P. subcapitata*
		RAC (EC_{50})	RAC
		19.00 µg/L	738 µg/L
Spraydrift (1 m)	32.413	**1.7**	0.044
Sraydrift (5 m)	6.670	0.35	-

An acceptable risk to algae is concluded at 1 m. When considering formulation data for aquatic invertebrates, an acceptable risk can be concluded providing a 5 m buffer zone is implemented. However, *Daphnia* was not the most sensitive species when considering active substance data. The most sensitive species was *Hyalella* (EC_{50} of 0.12 mg a.s./L vs EC_{50} of 0.42 mg a.s/L for *Daphnia*), however no formulation data was available with this species. This raised concern as to whether the formulation risk assessment is sufficiently protective of the risk to all aquatic invertebrates. In order to address the risk of the formulation to the most sensitive aquatic invertebrate species, HSE has taken into account the multispecies active substance data. For further details see Part B9.4. The refined formulation risk assessment is summarised in Table B2.9.9.2-7.

Table B2.9.9.2-7: Risk assessment for aquatic invertebrates considering active substance multispecies data.

Scenario	PEC (µg a.s./L)	Aquatic invertebrates Multispecies data RAC 2.64 µg/L[1]
Spraydrift (1 m)	1.847	0.70

[1]RAC derived from aquatic invertebrate geomean RAC of 10.37, adjusted by a factor of 3.925 to reflect the increased toxicity of the formulation compared to the active substance. An acceptable risk to aquatic invertebrates can be concluded at 1 m. This approach is considered more suitable than using the *Daphnia* formulation endpoint, since it accounts for a wider range of species sensitivities and can therefore be considered protective of species more sensitive than *Daphnia.* The risk of the formulation to aquatic invertebrates can therefore be resolved at 1 m with no risk mitigation required. See Vol 3CP Part B9.4 for further detail.

Conclusion: An acceptable risk to aquatic organisms can be concluded for the worst-case GAP use of Miravis Plus. No further consideration is required.

2.9.9.3 *Risk assessment for non-target arthropods*

Bees

Risk Assessment for 'A21857B'

Acute Risk

The acute risk to adult honeybees was assessed in accordance with the SANCO Terrestrial guidance document (SANCO/10329/2002). The critical acute contact and oral LD_{50} values were compared with the maximum individual application rate for the representative uses to derive a Hazard Quotient (HQ) for each exposure route. HQ values of ≤ 50 indicate a low acute risk to honeybees. For the proposed use of the representative formulation A21857B, HQs for the formulation and active substance fell well below the trigger of 50, indicating an acceptable acute risk to bees.

For this acute risk assessment, data on the active substance and the data for the representative product A21857B (Miravis Plus) are the key endpoints. In addition to the risk assessment for the a.s. and Miravis Plus, an assessment of the risk from A19649B has been carried out. Whilst Miravis Plus and A19649B are not chemically comparable, there is an argument, see above (section 2.9.3), that ~~they are ecotoxicologically comparable~~ the data can be used to inform the risk assessment. To further advance this argument an acute risk assessment has been carried out using the formulation endpoints. It can be seen that the risk from both formulations is ~~comparable~~ low, further adding to the argument that data on A19649B can be used to determine the risk from the use of Miravis Plus.

The acute contact and oral risk assessments are summarised below:

Table 2.9.9.3-1 HQ calculations for honeybees for proposed use of 'A21857B' (Miravis Plus)

Substance	Endpoint	Application rate (g/ha)	LD_{50} (µg a.s./bee)	Calculated HQ	Acceptable Risk? (Trigger <50)
Pydiflumetofen	Acute oral	200	>116	<1.724	yes
	Acute contact	200	>100	<2.000	yes
Miravis Plus A21857B	Acute oral	200	>24.07	<8.309	yes
	Acute contact	200	>56.9	<3.515	yes
Formulation A19649B	Acute oral	200	>210.6	<0.950	yes
	Acute contact	200	>186	<1.075	yes

Whilst the acute risk is acceptable, HSE has considered the chronic risk and available field studies further.

Chronic Risk

Currently, there is no agreed guidance that can be used to assess the chronic risk to honeybees, hence whilst these data are required for both the active substance and the formulation, it is not possible to undertake a quantitative risk assessment. Chronic risk was therefore considered using a combined approach, with a qualitative consideration of laboratory studies and semi-field studies, and semi-quantitatively with a margin-of-safety calculation from comparing estimated exposure by diet and by daily-dose with the relevant toxicity endpoints from laboratory studies.

To aid discussion of the chronic honeybee data for risk assessment, two approaches are used to consider a margin of safety, noting that there is no agreed trigger value for comparison:

1. **Dietary concentration margin of safety**: a comparison of the larval and adult toxicity endpoints expressed as mg a.s./kg diet with the dietary exposure via residues (from semi-field studies) as concentration of a.s. in food (expressed as nectar and sugar).

2. **Daily-dose margin of safety**: a comparison of larval and adult chronic toxicity endpoints expressed as mg a.s./bee/day or mg a.s./larva/day to estimated daily exposure. The estimated daily exposure is calculated using residue information from semi-field studies and estimates of honeybee sugar consumption values.

The calculated margin-of-safeties are shown in the table below :

Table 2.9.9.3-2 : Margin of safety calculations to aid discussion of risk of 'A21857B' to chronic honeybees

Test substance	End-point Type	Endpoint [mg a.s./kg diet]	Exposure[3] [mg a.s./kg]	Dietary margin of safety[5]	Endpoint [µg a.s./ bee/day]	Exposure[4] [µg a.s./ bee(or larva)/day]	Daily exposure margin of safety[5]
Chronic adult honeybee							
A19649B	10d LD_{50}	>3854	0.352 (nectar) 2.347 (sugar)	>10948 (nectar) >1642 (sugar)	>138.2	0.3004	>460
	10d NOED	3854		10948 (nectar) 1642 (sugar)	138.2		460
Chronic larval honeybee							
a.s., limit test	8d & 22d NOED	<0.09	0.352 (nectar) 2.347 (sugar)	unbound* **<0.256 (nectar)** **<0.038 (sugar)**	<0.0035	0.02788	unbound* **<0.126**
A19649B	8d NOED	<0.409		unbound* <1.16 (nectar) **<0.174 (sugar)**	<0.015		unbound* **<0.538**
	22d NOED	0.409		1.16 (nectar) **0.174 (sugar)**	0.015		**0.538**

Test substance	End-point Type	Endpoint [mg a.s./kg diet]	Exposure[3] [mg a.s./kg]	Dietary margin of safety[5]	Endpoint [µg a.s./ bee/day]	Exposure[4] [µg a.s./ bee(or larva)/day]	Daily exposure margin of safety[5]
A19649B	8d NOED 1)	347		986 (nectar) 148 (sugar)	13.75		493
Chronic whole honeybee colony							
a.s., Colony-feeding field study	No adverse effects 2)	32	0.352 (nectar) 2.347 (sugar)	90.9 (nectar) 13.63 (sugar)	Not possible to determine dose per larvae or adult bee for this study		

*unbound values are not applicable for this type of margin of safety calculation but are included for reference to aid discussion.
a.s. = active substance.
1) There is uncertainty regarding this endpoint as it does not take into consideration the consumed dose.
2) Note there is not a clearly defined endpoint for this type of study, but at this test concentration (highest tested) there were no adverse effects on honeybees.
3) Dietary exposure was estimated from the worst-case residue value in nectar from the three semi-field bee studies. To convert the value of a.s. in nectar to a.s. in sugar, the worst-case nectar sugar-content value of 15 % was used, as stated in Appendix J1 of EFSA (2013) bee guidance (not currently noted or adopted by GB).
4) Worst-case daily-dose exposure use values of honeybee consumption of sugar from appendix Table J1 in EFSA (2013) bee guidance (not currently noted or adopted by GB).
5) Margin of safety = toxicity endpoint / exposure

The chronic risk assessment approach outlined above, yielded a margin of safety for chronic exposure of pydiflumetofen to adult bees on the basis of first-tier data. Additional information from the semi-field studies (noting their shortcomings outlined above) added some weight to this conclusion.

Due to the contradictory nature of the toxicity endpoints of the larval dataset, there was no reliable larval endpoint and therefore this part of the risk assessment has relied on the semi-field studies. It should be noted that an illustrative assessment was carried out using the range of endpoints (table 2.9.9.2-2 above) with the outcome that one larval endpoint indicated a margin of safety, whilst with the others there was no margin of safety. On the basis of the semi-field and colony feeding studies, the following can be concluded: The semi-field and colony feeding studies saw no adverse effects on bee colonies up to the maximum test concentrations of 32 mg a.s./kg diet (colony-feeding study) or 200 g a.s./ha (semi-field tunnel studies).

This is also in-line with the SANCO (2002) guidance on bee risk assessment (this is adopted by GB), which notes that in higher tier risk assessment '*it is important to consider any effects observed in relation to the overall survival and productivity of the hive*'. Although some uncertainties regaring chronic risk have been identified (see volume B9 3CP section B.9.6.1 for details), the absence of adverse effects on the whole colony, which is consistent across multiple separate semi-field studies not just a single study, supports a conclusion that there is an acceptable risk to honeybees across at least one brood cycle and at all life-stages, as tested up to 200 g a.s./ha or 32 mg a.s./kg food.

The advice of the ECP was sought regarding the risk to bees. Overall, based on the evidence put before it, the ECP advised that bees are not driving the risk assessment (bees are not the most sensitive organism group), and that based on the data available, are not a cause for concern.

Conclusion for honeybees

There is an acceptable acute risk of pydiflumetofen to adult honeybees, as assessed using the hazard quotient approach. There is an acceptable acute risk of pydiflumetofen to honeybee larvae, and an acceptable chronic risk to all honeybee life-stages of pydiflumetofen, as concluded from a qualitative assessment of available data, which was carried out in the absence of GB noted/adopted guidance in this area but which requires consideration. Overall, when considering both the lower and higher tier risk assessment, GB (HSE CRD) considers an acceptable risk of A21857B (Miravis Plus) to honeybees can be concluded for the proposed use.

Other non-target arthropods other than bees

Risk assessment for 'A21857B'

The risk assessment for non-target arthropods other than bees was conducted in accordance with ESCORT 2. The proposed uses of 'A21857B' are as a spray treatment in cereal crops and oilseed rape with a worst-case application rate of 1 application of 3.2 L product/ha. The tier 1 endpoints available for *A. rhopalosiphi* and *T. pyri* were used in the first tier in- and off-field risk assessment. All endpoints passed the off-field assessment, but one endpoint from the *A. rhopalosiphi* study failed the in-field assessment and required further data on that and one additional crop-relevant species. The risk assessment is summarised below:

Table 2.9.9.3-3 Tier 1 off-field risk assessment for non-target arthropods exposed to 'A21857B' (Miravis Plus)

Species	LR_{50} [L/ha]	$PER_{off\text{-}field}$ [L/ha]	Correction factor	$HQ_{off\text{-}field}$	Trigger value
Aphidius rhopalosiphi. Tier I, 2D exposure scenario	>0.375	0.008864	10	<0.236	2
Typhlodromus pyri, Tier I, 2D exposure scenario	1.667			0.0531	2

PER = predicted environmental rate.

Table 2.9.9.3-4 Tier 1 in-field risk assessment for non-target arthropods exposed to 'A21857B' (Miravis Plus)

Species	LR_{50} [L/ha]	$PER_{in\text{-}field}$ [L/ha]	$HQ_{in\text{-}field}$	Trigger value
Aphidius rhopalosiphi Tier I, 2D exposure scenario	0.375	3.2	**8.53**	2
Typhlodromus pyri Tier I, 2D exposure scenario	1.667		1.91	2

PER = predicted environmental rate.

The in-field HQ for *A. rhopalosiphi* exceeds the trigger of 2, therefore further consideration was required (see table below) which involved tier II studies with *A. rhopalosiphi*, *T.pyri* and additional species; *Chrysoperla carnea*.

Table 2.9.9.3-5 Lethal and sublethal effect levels for non-target arthropods exposed to A21857B (Miravis Plus) in cereals and oilseed rape (worst case use)

Species	LR_{50} [L A21857B/ha]	Highest rate with < 50 % effect on reproduction [L A21857B/ha]	$PER_{in\text{-}field}$ [L/ha]
Aphidius rhopalosiphi Tier II, 3D exposure scenario	8.087	5.5556	3.2
Typhlodromus pyri Tier II, 2D exposure scenario	5.0	5.0	
Chrysoperla carnea Tier II, 2D exposure scenario	> 3.2	3.2	

PER = predicted environmental rate.

Based on the reported values, the 50 % effect levels for both non-target arthropod species are greater than the in-field PER. It is noted that for the additional species of *Chrysoperla carnea* the 50 % effect and LR_{50} values are either equal to, or are an unbounded value that is equal to the in-field PER, and are therefore close to the trigger value. Examination of the data from the *C. carnea* study (see Volume 3CP B.9.5.2) shows that at the maximum application rate of 3.2 L A21857B/ha there was a control-corrected mortality of 5.6 % and no effects were observed

for reproduction. Therefore, these effects show that the unbounded value safely exceeds the $PER_{in\text{-}field}$ and it is concluded that there is a low in-field risk to non-target arthropods following application of A21857B to cereals and oilseed rape.

Conclusion for non-target arthropods

The in-field and off-field risk for other non-target arthropods from the intended uses of the product A21857B in oilseed rape and cereals is acceptable. The off -field risk is indicated to be acceptable based on the available data without the necessity to account for risk mitigation measures.

2.9.9.4 *Risk assessment for non-target soil meso- and macro-fauna*

Earthworms

The assessment of the chronic risk to earthworms has been conducted according to SANCO/10329/2002 guidance. Risk is assessed in terms of Toxicity Exposure Ratios (TERs), using the endpoints from Table 2.9.4-01 above.

As the log Pow value for pydiflumetofen is > 2, correction of the study endpoints is required to account for differences in the organic matter content of the test soil in comparison to artificial soils.

The resulting TERs for earthworms are summarised in Table 2.9.9.4-01 below.

Table 2.9.9.4-01: TER calculations for earthworms for each GAP use of pydiflumetofen

Compound	Species, study type	Endpoint	GAP uses	PECsoil, max [mg/kg]	TER_{LT}	Trigger
Active substance risk assessment [a]						
A21857B (Miravis Plus)	*Eisenia foetida*, reproduction	5.45 mg a.s./kg	BBCH 30 Cereals 1x 166 g a.s./ha with 80 % interception	0.611	8.9	5
			BBCH 55 Cereals 1x 200 g a.s. /ha with 90 % interception	0.368	14.8	5
			BBCH 57 Oilseed rape 1x 200 g a.s. /ha with 80 % interception	0.736	7.4	5
Formulated product 'Miravis Plus' risk assessment [a]						
A21857B (Miravis Plus)	*Eisenia foetida*, reproduction	97 mg product/kg soil d.w.	BBCH 30 Cereals, 2,907 g/ha, 80% interception	0.775	125.2	5
			BBCH 55 Cereals, 3,510.4 g/ha, 90% interception	0.468	207.3	5
			BBCH 57 Oilseed rape, 3,510.4 g/ha, 80% interception	0.936	103.6	5

[a] Both risk assessments were carried out using the same study - the active substance risk assessment used the study endpoints represented in terms of the active substance content (5.62 % w/v in the formulation) along with the active substance PEC_{soil} values, and the formulated product risk assessment used formulated product endpoints along with the PEC_{soil} values for the formulated product.

Overall conclusion to the risk to earthworms from 'SYN545974'

The risk to earthworms is considered acceptable for the proposed uses.

Non-target soil meso- and macro-fauna (other than earthworms)

In the absence of pydiflumetofen active substance studies, the risk from pydiflumetofen to *Hypoaspis aculeifer* and *Folsomia candida* could not be directly assessed. However, given that the representative product 'Miravis Plus' contains only one active substance, it is likely that the formulation assessment is protective of the risk from the active. The risk assessment was conducted according to the SANCO/10329/2002 guidance on Terrestrial Ecotoxicology for the proposed application rate of pydiflumetofen.

TER values for non-target soil meso- and macro-fauna (other than earthworms) were calculated as above in the earthworm risk assessment. As the log P_{ow} value for pydiflumetofen is > 2, correction of the study endpoints is required to account for differences in the organic matter content of the test soil in comparison to artificial soils.

PEC_{soil} values have been compared to the study endpoints to determine TERs in Table 2.9.9.4-02 below.

Table 2.9.9.4-02: TER calculations for non-target soil meso- and macro-fauna (other than earthworms) for each GAP use of pydiflumetofen

Compound	Species	Endpoint	GAP uses	PECsoil, max* [mg/kg]	TER_{LT}	Trigger
Active substance risk assessment [a]						
A21857B (Miravis Plus)	*Hypoaspis aculeifer*	28.1 mg a.s./kg	BBCH 30 Cereals 1x 166 g a.s./ha with 80 % interception	0.611	46.0	5
			BBCH 55 Cereals 1x 200 g a.s. /ha with 90 % interception	0.368	76.4	
			BBCH 57 Oilseed rape 1x 200 g a.s. /ha with 80 % interception	0.736	38.2	
A21857B (Miravis Plus)	*Folsomia candida*	28.1 mg a.s./kg	BBCH 30 Cereals 1x 166 g a.s./ha with 80 % interception	0.611	46.0	
			BBCH 55 Cereals 1x 200 g a.s. /ha with 90 % interception	0.368	76.4	
			BBCH 57 Oilseed rape 1x 200 g a.s. /ha with 80 % interception	0.736	38.2	
Formulated product 'Miravis Plus' risk assessment [a]						
A21857B (Miravis Plus)	*Hypoaspis aculeifer*	500 mg product/kg soil d.w.	BBCH 30 Cereals, 2,907 g/ha, 80% interception	0.775	645.2	5
			BBCH 55 Cereals, 3,510.4 g/ha, 90% interception	0.468	1068.4	
			BBCH 57 Oilseed rape, 3,510.4 g/ha, 80% interception	0.936	534.2	
A21857B (Miravis Plus)	*Folsomia candida*	500 mg product/kg soil d.w.	BBCH 30 Cereals, 2,907 g/ha, 80% interception	0.775	645.2	
			BBCH 55 Cereals, 3,510.4 g/ha, 90% interception	0.468	1068.4	

			BBCH 57 Oilseed rape, 3,510.4 g/ha, 80% interception	0.936	534.2	

[a] Both risk assessments were carried out using the same two studies - the active substance risk assessment used the study endpoints represented in terms of the active substance content along with the active substance PEC_{soil} values, and the formulated product risk assessment used formulated product endpoints along with the PEC_{soil} values for the formulated product.

Overall conclusion on the risk to non-target soil meso- and macro-fauna (other than earthworms) from 'SYN545974'

The risk to non-target soil meso- and macro-fauna (other than earthworms) is considered acceptable for the proposed uses.

2.9.9.5 *Risk assessment for soil micro-organisms (nitrogen transformation)*

According to the SANCO Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002 rev 2 final), the trigger for acceptable risk is a < 25% difference (increase or decrease) in activity compared to the control treatment. A comparison has been made of the study endpoint and the maximum PEC_{soil} values in Table 2.9.9.5-01 below:

Table 2.9.9.5-01: Risk assessment for pydiflumetofen for soil micro-organisms

Test substance	Species	Endpoint (mg a.s./kg dry soil)	$PEC_{soil\ max}$ (mg/kg)	Refinement required?
Pydiflumetofen	Soil micro-organisms	2.71	0.736	No

Overall conclusion on the risk to soil micro-organisms (nitrogen transformation) from 'SYN545974'

The risk to soil micro-organisms (nitrogen transformation) is considered acceptable for the proposed uses.

2.9.9.6 *Risk assessment for terrestrial non-target higher plants*

It is stated in the SANCO/10329/2002 guidance document that '*The risk should be considered acceptable, if there are no data indicating more than 50 % phytotoxic effects at the maximum application rate. If the results show more than 50 % effect for one species, or clear indications of effects on more than one species, data requirements and assessment move to the next tier.*'. The guidelines to not provide a quantitative measure of what classifies as a 'clear indications of effects'. Phytotoxicity was observed in two species in the vegetative vigour part of the screening assessment, however this was only mild, and no effects exceeded the trigger of 50 % at any tested concentration in the tier 1 screening assessment (See Table 2.9.6-01).

The assertion that an acceptable risk is demonstrated by the screening assessment can be qualitatively supported by conclusions from studies conducted using the EU representative formulation 'Miravis' (A19649B). Although a certain level of uncertainty surrounds the extrapolation of these data, as 'Miravis' and 'Miravis Plus' have been deemed non-comparable (see Volume 4), both contain the same active substance, which was applied at 200 g a.s. /ha in the respective studies, and so it is likely that any effects resulting from exposure to the active substance would be similar in magnitude.

Overall conclusion on the risk to terrestrial non-target higher plants from 'SYN545974'

The risk to terrestrial non-target higher plants is considered acceptable for the proposed uses.

2.9.9.7 *Risk assessment for biological methods of sewage treatment*

Studies are not required for the formulation as only tests conducted with the active substance are considered necessary to assess the potential risk to biological sewage treatment systems.
Table B2.9.9.7-1: Endpoints for activated sludge exposed to pydiflumetofen

Test item	Test system	Endpoint (mg a.s/L)	Reference
Pydiflumetofen	Activated sludge respiration inhibition	EC_{50} (3h) > 1.5[1]	[redacted] (2013)

[1]based on the limit of solubility of pydiflumetofen

Treatment rates up to 1000 mg a.s./L Pydiflumetofen (1.5 mg a.s./L based on the limit of solubility) had no effect on the respiration rate of activated sewage sludge and indicate that microbial activity in these systems is at low risk. The worst-case PEC_{sw} was 0.001847 mg a.s./L which is significantly lower than the EC_{50} value of 1.5 mg a.s./L

2.10. CLASSIFICATION AND LABELLING

Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification 1)	Reason for no classification 2)
2.1.	Explosives				
2.2.	Flammable gases				
2.3.	Flammable aerosols				
2.4.	Oxidising gases				
2.5.	Gases under pressure				
2.6.	Flammable liquids				
2.7.	Flammable solids				
2.8.	Self-reactive substances and mixtures				
2.9.	Pyrophoric liquids				
2.10.	Pyrophoric solids				
2.11.	Self-heating substances and mixtures				
2.12.	Substances and mixtures which in contact with water emit flammable gases				
2.13.	Oxidising liquids				
2.14.	Oxidising solids				
2.15.	Organic peroxides				
2.16.	Substance and mixtures corrosive to metals				
3.1.	Acute toxicity - oral				
	Acute toxicity - dermal				

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
	Acute toxicity - inhalation				
3.2.	Skin corrosion / irritation				
3.3.	Serious eye damage / eye irritation				
3.4.	Respiratory sensitisation				
3.4.	Skin sensitisation				
3.5.	Germ cell mutagenicity				
3.6.	Carcinogenicity	**Carc cat 2; H351**	**None**	**Not available**	**N/A**
3.7.	Reproductive toxicity	**Repr cat 2; H361f**	**None**	**Not available**	**N/A**
3.8.	Specific target organ toxicity –single exposure				
3.9.	Specific target organ toxicity – repeated exposure				
3.10.	Aspiration hazard				
4.1.	Hazardous to the aquatic environment	**Acute category 1** **Chronic category 1**	**Acute = 1** **Chronic = 1**	**Not available**	**N/A**
5.1.	Hazardous to the ozone layer				

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Warning
Hazard statements: H351, H361f, H410
Precautionary statements: P201, P202, P281, P273, P391, P501

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3: None

2.11. RELEVANCE OF METABOLITES IN GROUNDWATER

No soil metabolites triggered inclusion in groundwater assessment. Consequently there are no metabolites which need to be considered for relevance in groundwater.

2.12. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.12.1. Identity and physical chemical properties

The active substance pydiflumetofen consists of two enantiomers in approx. 50:50 ratio, i.e., a racemic mixture. The applicant has provided evidence that the chemical synthesis yields pydiflumetofen as a racemic mixture.

2.12.2. Methods of analysis

Pydiflumetofen is manufactured as a 50:50 racemic enantiomer mixture therefore generally enantiomer specific methods of analysis are not required.

2.12.3. Mammalian toxicity

Pydiflumetofen is a racemic mixture of two enantiomers *SYN546968 and SYN546969.* The ratio of these enantiomers has been examined in samples from a limited number of crop metabolism studies (see Section 1.5). The data from these limited number of studies show that the ratio of the pydiflumetofen enantiomers did not change significantly over the course of these studies. Given the lack of potential for interconversion of the enantiomers and stability in the enantiomer ratios in the samples examined, it is concluded that the enantiomers of pydiflumetofen degrade at similar rates and that there is no preferential metabolism of either enantiomer in plant matrices. Therefore the substance tested in all toxicological studies is a true reflection of the exposure to pydiflumetofen. However, no data are available on the enantiomer ratio in livestock and an adjustment factor of 2 has been proposed for residues in livestock matrices.

2.12.4. Operator, Worker, Bystander and Resident exposure

As stated under Section 2.12.3 above, no significant shifts in the isometric ratios of the enantiomers of pydiflumetofen were observed in crop metabolism studies. It was also determined that '*the substance tested in all toxicological studies is a true reflection of the exposure to pydiflumetofen'.* It is considered that pydiflumetofen does not have any isomeric concerns and therefore would have no significant impact on the operator, worker, bystander and resident exposure risk assessments.

2.12.5. Residues and Consumer risk assessment

In terms of enantiomeric conversion, the applicant has made the case (document N5 on isomeric composition) that chemically interconversions are not predicted based on mechanistic and structure related grounds. Interconversion of the enantiomers of SYN545974 is not considered feasible by any conventional chemical or biochemical process to which the compound will be exposed.

However, it is possible for differential metabolism of residues of pydiflumetofen to occur.

The enantiomeric composition in the spray solution and in some primary and rotational ~~crop~~ crop metabolism samples was determined to see whether any change in the 50:50 entantiomeric composition occurred during the metabolism studies. The enantiomeric fraction shifted from 0.5 in the spray solution to a maximum of 0.56 (in oilseed rape seed [primary crop]) and a maximum of 0.57 [wheat straw 270 DAT sample - rotational crop]; the fraction remained at 0.5 in tomato fruits [primary crop].

Based on these determinations, the % change in enantiomeric excess (%change in EE) [9] was estimated and was found to be oilseed rape seed (primary crop - up to 12.4%), oilseed trash (primary crop - <5%), and tomato fruit (primary crop - <1%).

In the rotational crop samples, %entantiomeric excess was estimated for wheat straw samples. %change in EE was calculated to be ≤10% for the samples at 270 days (DAA). For the 120 DAA sample timing, one of the samples (pyrazole label) indicated a change in enantiomeric excess > 10% (13.4% changein EE).

It was observed that the 'S' enantiomer of pydiflumetofen was more prevalent in the 270 DAA samples and the 'R' enantiomer of pydiflumetofen was more prevalent in the 120 DAA samples.

HSE is not proposing to consider an assessment factor in the consumer risk assessment to consider the potential changes in isomer ratio/amounts in plants.

The enantiomeric composition was not investigated in any of the livestock metabolism studies (or in the rat metabolism). It is proposed to use a x 2 factor in the consumer risk assessment in order to address residues found

[9] Enantiomeric excess is explained in the EFSA guidance on stereoisomers (2019, "Guidance of EFSA on risk assessments for active substances of plant protection products that have stereoisomers as components or impurities and for transformation products of active substances that may have stereoisomers").

in livestock. This is likely to be especially precautionary, but anyhow worst case. Therefore in the consumer risk assessment, see section 2.7.9 and section 2.7.5, residues in animal products were doubled prior to insertion of inputs into the consumer models (in order to compare with the ADI and ARfD for parent pydiflumetofen).

Some published papers which reported on enatiomeric composition regarding residues in crops (and rat liver microsomes) were retrieved in the literature review for pydiflumetofen. Information from these published papers are summarised at the end of section B.7.2.1. They are of interest, but do not impact the proposals made based only on the assessment of the GLP regulatory residues studies submitted. See section B.7.2.1 for further information.

2.12.6. Environmental fate

As explained in section 2.8.1, limited evidence on the enantiomeric ratio of pydiflumetofen was presented in the environmental fate and behaviour studies. Changes in ratio were generally small although the amount of degradation of pydiflumetofen in the studies was usually less than 50%. It is considered that no further data on change in enantiomeric composition in environmental matrices over time is required.

2.12.7. Ecotoxicology

Pydiflumetofen is a racemic mixture of two enantiomers. As detailed in section 2.12.2. pydiflumetofen is manufactured in a ratio of 50:50 racemic enantiomer mixture and specific methods of analysis for individual enantiomers are not required. It should be noted the batches tested in ecotoxicological studies were considered representative of specification (see volume 4, section C.1.4.2).

As detailed by toxicology (section 2.12.3) the crop metabolism studies demonstrated lack of significant changes in ratios concluding that the enantiomers of pydiflumetofen degrade at similar rates and that there is no preferential metabolism of either enantiomer in plant matrices. It is noted that the submitted hen and rat metabolism studies did not consider enantiomer ratios. However, when considering bird and mammal ecotoxicology risk assessments a conservative approach (in-line with EFSA 2019 guidance on stereoisomers) can be taken by applying an uncertainty factor of 2 for dietary assessment. Taking this conservative approach still results in an acceptable risk to birds and mammals, worst case reproductive TER of 6.56 at screening step for birds and TER of 6.87 at first tier for 'small herbivorous mammals' against trigger of 5. It should be noted risk assessments without uncertainty factor were acceptable at screening step for proposed uses (see Volume 3 CP B 9, section B.9.1.1 and B.9.1.2. for dietary risk assessments without uncertainty factor applied).

Environmental fate have concluded that changes in ratio of the two enantiomers are not significant and do not require further investigation, discussed above in 2.12.6. Therefore, further consideration of non-target aquatic and soil organisms is not required.

2.13. RESIDUE DEFINITIONS

2.13.1. Definition of residues for exposure/risk assessment

Food of plant origin:

Plants: Pydiflumetofen (sum of isomers)

This proposed residue definition is also suitable for honey.

Food of animal origin:

Products of animal origin, except ~~ruminant/~~mammalian kidney: Sum of pydiflumetofen (sum of isomers) and 2,4,6-trichlorophenol (free and conjugated) expressed as pydiflumetofen.

~~Ruminant/~~mammalian kidney: Sum of pydiflumetofen (sum of isomers), 2,4,6-trichlorophenol (free and conjugated) and SYN548263 (free and conjugated), expressed as pydiflumetofen.

On a precautionary basis, an additional assessment factor of x 2 to apply to the level of animal product residues in the consumer risk assessment is desirable. This is intended to account for possible differential metabolism of the isomers of pydiflumetofen (which is a racemic mixture), since no investigations into the enantiomeric composition of the residues took place in any of the livestock metabolism studies.

Where the methods of analysis converts the livestock product conjugated residues to their free counterparts and the analytes are determined in levels expressed as the free metabolites, the sum of residues, expressed as parent pydiflumetofen, can be calculated as follows, according to the following molecular weights: pydiflumetofen 426.7 g/mol; 2,4,6-trichlorophenol 197.45 g/mol (molecular weight adjustment factor of **x 2.161** (426.7/197.45)); SYN548263 277.2 g/mol (molecular weight adjustment factor of **x 1.539** (426.7/277.2)).

To bridge between the RD-Enf and RD-RA the following conversion factors are proposed:

All commodities except ~~ruminant/~~mammalian kidney CF= x 3.16 (for both Tier 1- 10 year use and Tier 2 - long term use)

~~Ruminant/~~mammalian kidney CF= x 4.7 (for both Tier 1- 10 year use and Tier 2- long term use).

Soil: Pydiflumetofen

Groundwater: Pydiflumetofen

Surface water: Pydiflumetofen, NOA449410, SYN548261

Sediment: Pydiflumetofen, SYN545547

Air: Pydiflumetofen

2.13.2. Definition of residues for monitoring

:

Food of plant and animal origin:

~~Plants:~~ Pydiflumetofen (sum of isomers)

Fat-soluble

See section 2.13.1 for the conversion factors (CF) for products of animal origin to bridge between the RD-Enforcement and the RD-risk assessment ~~monitoring~~.

Soil: Pydiflumetofen

Groundwater: Pydiflumetofen

Surface water: Pydiflumetofen

Sediment: Pydiflumetofen

Air: Pydiflumetofen

Level 3

PYDIFLUMETOFEN

3. PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1. BACKGROUND TO THE PROPOSED DECISION

3.1.1. Proposal on acceptability against the decision making criteria – Article 4 and annex II of regulation (EC) No 1107/2009

3.1.1.1. Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	Yes		HSE currently consider that Article 4 of retained Regulation (EC) No 1107/2009 may be complied with for pydiflumetofen, for use as a fungicide on winter and spring wheat, durum wheat, spelt, winter and spring barley, winter and spring oats, winter and spring rye, winter and spring triticale, and winter and spring oilseed rape (refer to Level 1, Table 1.5.1 for details of the representative uses).
3.1.1.2. Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	Yes		HSE currently considers that a sufficiently complete dossier has been submitted which may enable a regulatory decision on approval of pydiflumetofen to be made and to establish that the risks are acceptable with no critical areas of concern identified.
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.	Yes		~~Since the MRL proposals in crops are based on a combined assessment considering primary crop and rotational crop residue contributions, these MRL levels are proposed while further rotational crop field trials are generated at more appropriate dosing levels to confirm the levels of the residues in following crops (see Vol 1 section 2.7.7 and section 3.1.4).~~
3.1.1.3. Restrictions on approval				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.	Yes		(a) the minimum degree of purity of the active substance; Minimum purity 980 g/kg (b) the nature and maximum content of certain impurities;

				No impurities are considered of toxicological or ecotoxicological relevance: (c) restrictions arising from the evaluation of the information referred to in Article 8 of 1107/2009 taking account of the agricultural, plant health and environmental, including climatic, conditions in question; Not applicable (d) type of preparation; Not applicable (e) manner and conditions of application;Not applicable (f) submission of further confirmatory information to the Competent Authority, where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge; Not applicable (g) designation of categories of users, such as professional and non-professional; Not applicable (h) designation of areas where the use of plant protection products, including soil treatment products, containing the active substance may not be authorised or where the use may be authorised under specific conditions; Not applicable (i) the need to impose risk mitigation measures and monitoring after use;Not applicable (j) any other particular conditions that result from the evaluation of information made available in the context of Regulation 1107/2009. Not applicable
3.1.1.4. Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	Yes		ADI = 0.09 mg/kg bw/day ARfD = 0.3 mg/kg bw AOEL = 0.05 mg/kg bw/day AAOEL = 0.15 mg/kg bw
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier:	Yes		Data on residues are sufficient for approval of the active substance. ~~Since the MRL proposals in crops are based on a combined assessment considering primary crop and rotational crop residue contributions, these MRL levels are proposed while further rotational crop field trials are~~

	(a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.			~~generated at more appropriate dosing levels to confirm the levels of the residues in following crops (see Vol 1 section 2.7.7 and section 3.1.4).~~ Acceptable data have been submitted to propose residue definitions in plants and animal products, and to predict the levels of residues in primary crop. Some data are available on rotational crop residues, sufficient to propose MRLs for crops and animal products, taking account of both primary and rotational crop residues where necessary. Acceptable data have been provided on residues in primary crops and processing to support the representative uses. Suitable data are available on methods of analysis for the determination of residues of pydiflumetofen both for risk assessment and enforcement purposes. A consumer risk assessment has been concluded on the basis of the residues data supplied.
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.	Yes		Yes for all of the representative uses.
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	Yes		The applicant has satisfactorily addressed all of the Efficacy requirements for a new active substance. Effectiveness against a range of major diseases has been demonstrated for the proposed uses. Crop safety of pydiflumetofen to the proposed crops has been supported. Additionally, the resistance risk has been appropriately addressed. Further information will be examined at the product authorisation stage to ensure that the product itself fully complies with the data requirements for Efficacy.
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	Yes		

Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	Yes		Acceptable data have been submitted to support the manufacturing sites of pydiflumetofen and the proposed specification is considered supported by the available data, based on full scale manufacturing at one site and pilot scale manufacturing at a second site. None of the impurities identified in technical pydiflumetofen are considered to be of toxicological or ecotoxicological relevance. Following scale-up from pilot plant at the second site, data to confirm the commercial scale technical specification must be submitted. In addition, the toxicological significance of any in the impurity profile must be addressed.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	N/A	N/A	There is currently no FAO specification for pydiflumetofen
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted	N/A	N/A	There is currently no FAO specification for pydiflumetofen
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	Yes		Acceptable methods have been submitted for the determination of pydiflumetofen and all significant impurities in the technical material as manufactured. None of the impurities identified in technical pydiflumetofen are considered to be of toxicological or ecotoxicological relevance.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	Yes		Acceptable methods have been submitted for the determination of pydiflumetofen and selected metabolites in various matrices used in support of all areas of the risk assessment. Acceptable methods have been submitted for the determination of pydiflumetofen and selected metabolites in various matrices for use in post-approval monitoring and control to support the representative uses. For the determination of residues in plants, extraction efficiency was not determined for commodities in the high oil crop group.

				For the determination of residues in air the validated LOQ of 30 µg/m3 does not comply with the required LOQ which is calculated using the proposed AOELsystemic.of 0.05 mg/kg bw/day. Therefore, further method validation data is required to support as lower LOQ of 15 µg/m3.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	Yes		
Impact on human health				
Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	Yes		ADI = 0.09 mg/kg bw/day ARfD = 0.3 mg/kg bw AOEL = 0.05 mg/kg bw/day AAOEL = 0.15 mg/kg bw
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		No	Weakly positive for clastogenicity in vitro but not confirmed in vivo.
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**		No	Pydiflumetofen causes liver tumours in the mouse, but classification with category 1A or 1B is not justified.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where			Not relevant

	residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**		No	Pydiflumetofen causes a delay in sexual maturity in rats, but classification with category 1A or 1B is not justified.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not relevant
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties**	Yes		Pydiflumetofen is classified with carc cat 2 and repro cat 2; however, these interim ED criteria no longer apply and a scientific assessment of the ED properties of the substance against the relevant criteria shows that it is not an ED for human health.
ii)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **toxic for reproduction category 2 and** in addition the RMS considers the substance **has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties**		No	Pydiflumetofen is classified with repro cat 2 but does not effects on endocrine organs. In addition, an assessment against the scientific ED criteria shows that the substance is not an ED.
iii)	Linked to either i) or ii) immediately above.			Not relevant

	It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Fate and behaviour in the environment				
Persistent organic pollutant (POP)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		No	Pydiflumetofen meets the POP criterion for persistence in soil (DT50 in soil >6 months) and in sediment (DT50 in sediment >6 months) Pydiflumetofen does not meet the POP criteria for long range atmospheric transport as it has an atmospheric half-life <2 days. Ecotoxicology does not consider pydiflumetofen to meet the criteria for bioaccumulation. The whole fish BCF is 31.1 L/kg, less than 5000 L/kg. Therefore pydiflumetofen does not meet the criteria for being a POP.
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		No	Environmental Fate and Behaviour notes that pydiflumetofen meets the 'P' criterion in soil (DT50 >120 days) and in sediment (half-life in freshwater sediment >120 days). Toxicology notes that the **T** criterion is met as the substance is classified with Repr. Cat 2. Ecotoxicology does not consider pydiflumetofen to fulfill the PBT criteria for bioaccumulation or toxicity. B: whole fish BCF = 31.1 L/kg (< 2000 L/kg) T: fish NOEC = 0.025 mg a.s./L (> 0.01 mg/L) Aquatic invertebrate NOEC = 0.037 mg a.s./L (> 0.01 mg/L)
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		No	Environmental Fate and Behaviour notes that pydiflumetofen meets the 'vP' criterion in soil (DT50 >180 days) and in sediment (half-life in freshwater sediment >180 days). Ecotoxicology does not consider pydiflumetofen to be very bioaccumulative, the whole fish BCF (31.1 L/kg) does not exceded the trigger of 5000.
Ecotoxicology				

		Yes	No	
	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.	Yes		Acceptable risks have been demonstrated for all of the proposed representative uses when considering the worst-case GAP in oilseed rape: **Birds:** Based on the available data an acceptable risk to birds was demonstrated for all the proposed uses (see Section 2.9.9.1). **Mammals:** Based on the available data an acceptable risk to mammals was demonstrated for all the proposed uses (see Section 2.9.9.2). **Aquatic organisms:** Based on the available data an acceptable risk to aquatic organisms was demonstrated for all the proposed uses considering tier 2 (geometric mean) refinement for fish and aquatic invertebrates (see Section 2.9.9.3). **Bees:** Based on the available data an acceptable risk to bees was demonstrated for all the proposed uses, noting formulation data with the EU representative formulation data was considered in the risk assesmsent (see Section 2.9.9.4). **Non-target arthropods (NTAs):** Based on the available data an acceptable risk to NTAs was demonstrated for all proposed uses. **Soil meso- and macro-fauna:** Based on the available data an acceptable risk to earthworms and (other) soil macro-organisms was demonstrated for all the proposed uses; noting that the risk from the active substance was assessed based on the toxicity of the formulated product (see Section 2.9.9.6). **Soil micro-organisms:** Based on the available data an acceptable risk to soil micro-organisms was demonstrated for all the proposed uses, noting that the risk from the formulated product was assessed based on the toxicity of the active substance (see Section 2.9.9.7). **Non-target terrestrial plants (NTTPs):** Acceptable risks have been demonstrated for all proposed uses, noting formulation data with the EU representative formulation data was considered in the risk assesmsent ((see Section 2.9.9.8). **Sewage treatment:** Based on the available data an acceptable risk to activated sludge micro-organisms was demonstrated for all the proposed uses (see Section 2.9.9.9).

	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance **HAS** endocrine		No	<u>Overall HSE ecotoxicology conclusion for birds, reptiles and wild mammals</u>

	disrupting properties that may cause adverse effects on non-target organisms.			Overall, HSE concludes that based on current EFSA/ECHA 2018 guidance it is not possible to reach a conclusion for birds or reptiles when considering endocrine disruption (see Section 2.9.1). For non-target wild mammals HSE concludes pydiflumetofen does not meet the criteria of being an ED based on EAS or T modalities. Therefore, from an ecotoxicology perspective pydiflumetofen is not an endocrine disruptor for wild mammals based on available data/information (see Section 2.9.1). <u>Overall HSE ecotoxicology conclusion for aquatic organisms</u> Overall, HSE concludes that based on current EFSA/ECHA 2018 guidance that pydiflumetofen does not meet the criteria of being an endocrine disruptor (ED) for aquatic organisms when considering EAS and T modalities based on the available information. Some uncertainties regarding the FSTRA results were identified by HSE and ISA sought from the ECP on this. As a result, a Rapid Androgen Disruption Activity Reporter (RADAR) assay was requested to provide further mechanistic data. ~~This is currently ongoing, therefore it is not possible to conclude at present on the endocrine disrupting potential of pydiflumetofen on Estrogen, Androgen and Steroidogenesis (EAS) modalities for aquatic organisms.in regard to study design, however, HSE still considers that pydiflumetofen is not an endocrine disruptor for aquatic organisms when considering the EAS and T modalities~~ A draft study report for the RADAR assay was submitted by the applicant to HSE in September 2023 and whilst noting some uncertainties with the study, it was concluded that pydiflumetofen was inactive in the RADAR assay. Taken together with the results from the FSTRA, HSE considers EAS modalities have been sufficiently investigated and the results support a negative conclusion for EAS modalities (see Section 2.9.2.).

	Linked to the consideration of the endocrine properties immediately above.		No	The proposed uses are not considered likely to result in negligible exposure. However, HSE concluded pydiflumetofen is not an endocrine disruptor as described above.

	It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.			
	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	Yes		Based on the available data an acceptable risk to bees was demonstrated for all the proposed uses (see Section 2.9.9.4).
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	Yes		As detailed in section 2.13, residue definitions: Residue definition for enforcement (plant and animal products) and residue definition for dietary risk assessment (plants, also honey): pydiflumetofen (sum of isomers). Residue definition for dietary risk assessment - livestock products: Products of animal origin, except ~~ruminant/~~mammalian kidney: Sum of pydiflumetofen (sum of isomers) and 2,4,6-trichlorophenol (free and conjugated) expressed as pydiflumetofen. ~~Ruminant/~~mammalian kidney: Sum of pydiflumetofen (sum of isomers), 2,4,6-trichlorophenol (free and conjugated) and SYN548263 (free and conjugated), expressed as pydiflumetofen.
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration	Yes		Refer to Volume 1, Level 2, section 2.8.6 for a summary of the groundwater exposure assessment.

	of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.			It is considered that pydiflumetofen presents a low risk of contamination of groundwater at >0.1 µg/L provided the approval is initially limited to a single approval period. Further information to address the long term risk of groundwater contamination is required for renewal of approval.

3.1.2. Proposal – Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution	Yes		Efficacy data show that both isomers have biological activity and the active substance does not contain a significant portion of non-active isomers. Environmental Fate and Behaviour notes that pydiflumetofen meets the 'P' criterion in soil (DT50 >120 days) and in sediment (half-life in freshwater sediment >120 days). Toxicology notes that pydiflumetofen meets the 'T' crierion as it is classified for human health with Repr. 2 (H361f) under the CLP Regulation. — ***it meets two (P and T) of the criteria to be considered as a PBT substance***

3.1.3. Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.		No	The substance is carcinogenic and toxic to reproduction. The substance is considered to be 'persistent' within the definition of this criterion (i.e. half-life in soil more than 60 days). The substance has the following classification for the environment: Aquatic Acute 1; H400: Very toxic to aquatic life. Acute M-Factor of 1 Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects. Chronic M-Factor of 1

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

Data gap	**Relevance in relation to representative use(s)**	**Study status**		
		No confirmation that study available or on-going.	**Study on-going and anticipated date of completion**	**Study available but not peer-reviewed**
3.1.4.1. Identity of the active substance or formulation				
Following scale-up from pilot plant at the second manufacturing site, new 5-batch analysis supporting the commercial scale technical specification must be submitted. In addition, the toxicological significance of any changes in the impurity profile must be addressed.	Required for all representative uses.	X		
3.1.4.2. Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
Data on physical and chemical compatibility of tank mixes must be submitted to support the label recommendations of the representative product	Relevant to representative product and therefore all representative uses.	X		
3.1.4.3. Data on uses and efficacy				
3.1.4.4. Data on handling, storage, transport, packaging and labelling				

3.1.4.5. Methods of analysis				
Data to address extraction efficiency high oil crops for the QuEChERS monitoring method using acetonitrile/water (50/50, v/v).	Required for all representative uses	X		
Validation data for the method for the monitoring of residues in air to support a lower LOQ of 15 µg/m^3.	Required for all representative uses	X		
3.1.4.6. Toxicology and metabolism				
None				
3.1.4.7. Residue data				
None ~~Further rotational crop residues trials are required to assess the levels of residues of pydiflumetofen (at higher application rates than current studies) to address possible soil exposures due to persistence and accumulation of pydiflumetofen in soil. Consideration should be given to inclusion of metabolites SYN545547 and SYN547891 in these trials.~~	~~Required for all representative uses~~	~~X (confirmation has not been sought)~~		
3.1.4.8. Environmental fate and behaviour				
An assessment of the effect of water treatment processes on the nature of residues present in surface water, when surface water is abstracted for drinking water.	Required for all representative uses.	X		
To extend approval beyond the first approval period, further information to address the long-	Required for all representative uses.	X		

term potential for groundwater contamination from pydiflumetofen must be submitted; for example – soil and groundwater monitoring.				

3.1.4.9. Ecotoxicology				
~~None required~~ Rapid Androgen Disruption Activity Reporter (RADAR) assay (final study report)	Required for all representative uses.		~~X~~October 2023	

3.1.5. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	**Relevance in relation to representative use(s)**
None ~~Residues: different fate options (Tier 1 10 year use and Tier 2 long term use) are presented in the evaluation.~~ ~~Further fate advice is needed to determine the residues end points that apply.~~ ~~(if an alternative fate scenario needs to be considered, then the residues will require further assessment to finalise the residue end points)~~ ~~Endocrine disrupting potential of pydiflumetofen on Estrogen, Androgen and Steroidogenesis (EAS) modalities for aquatic organisms~~	~~All uses~~

3.1.6. Critical areas of concern

An issue is listed as a critical area of concern:
(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

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

Critical area of concern identified	**Relevance in relation to representative use(s)**
None	

~~Endocrine disrupting potential of pydiflumetofen on Estrogen, Androgen and Steroidogenesis (EAS) modalities for aquatic organisms.~~	

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

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)
All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		Use "A" (X^1)	Use "B" (X^1)
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised	~~X (subject to fate advice)~~	~~X (subject to fate advice)~~
Risk to wild non target terrestrial vertebrates	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised		
Risk to aquatic organisms	Risk identified		
	Assessment not finalised	~~X~~	~~X~~
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached		
	Parametric value of 10µg/L[(a)] breached		
	Assessment not finalised		
Comments/Remarks			

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.
(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

3.1.8. Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	**Justification**
Consumer risk assessment: Rotational crop residues.	[This section outlines the Independent Scientific Advice (ISA) sought from the ECP based on the assessment draft dated Oct 2022. Following presentation to the Expert Committee on Pesticides (ECP) in the process of seeking Independent Scientific Advice (ISA), the assessment took account of the highest estimated soil exposures taking account of crop interception (since pydiflumetofen is applied to the primary crop) and considering soil accumulation of residues accounting for year to year use. This new scenario replaced the 'Tier 1-10 year use' and 'Tier 2 long term use' scenarios on which the original ECP advice was sought. Based on the revised assessment the data gap for further rotational crop field trials was no longer considered necessary.] Two fate scenarios are presented in the residues assessment. ' Tier 1-10 year use' and 'Tier 2 long term use'. The fate parameters to feed into this residues evaluation is still subject to advice/confirmation. Due to the persistent nature of soil residues of pydiflumetofen and the potential for accumulation to occur, residues of pydiflumetofen are expected to occur in rotational crops. As outlined in level 2 (section 2.7.7), the evaluation concludes that rotational crop trials data are likely sufficient to propose MRLs, with a data requirement to generate further rotational crop trials data. The current data on rotational crop residues, that inform the level of residues in rotational crops, are currently underdosed (when considering possibility of accumulation in the soil). Some of the rotational crop residues data can be scaled but further rotational crop field trials conducted at higher dose rates (than the current data) are considered necessary. ECP is invited to advise on the proposals
Consumer risk assessment: Residue definitions:	The rationale for the proposals of residue definitions is presented in full in section 2.7.3 (level 2). Since not all of the metabolites discussed in section 2.7.3 have sufficient toxicological databases to establish their general toxicity profile, exposure assessments for some of the metabolites versus TTCs for Cramer Class III (some presumption of serious toxicity) has been conducted as a form of screening assessment. This has concluded that all of the estimated intakes for metabolites assessed in this way were calculated to be well below the respective TTC values (chronic and acute). ECP is invited to advise on the suitability of the residue definitions and the approaches used (e.g. TTC).

Fate and Behaviour in the Environment: Dissipation assumptions used in calculation of accumulated soil residues	The ECP is invited to comment on the HSE decision making process around selection of a 2nd tier SFO DisT50 (the specific value of 1310 days being currently selected) from grassed field dissipation plots for the purposes of a refined soil exposure assessment of pydiflumetofen
Fate and Behaviour in the Environment: Groundwater assessment – risk of long-term leaching	The ECP is invited to comment on the groundwater exposure assessment and on the need for additional information to address the long term leaching potential. ECP advice on the nature of any additional information that would be considered useful, is also requested?
Ecotoxicology: Aquatic risk assessment (see section B9.4)	Regarding the risk to aquatic invertebrates, formulation toxicity data are available for *Daphnia magna* only. When considering active substance data, the most sensitive species is *Hyalella azteca* which has an EC_{50} of 0.12 mg a.s./L, compared to *D. magna* which has an EC_{50} of 0.42 mg a.s./L. This raised concern as to whether the formulation risk assessment is sufficiently protective of the risk to all aquatic invertebrates. In order to address the risk of the formulation to the most sensitive aquatic invertebrate species, HSE has taken into account the multispecies active substance data to derive an additional margin of safety. The ECP is invited to advise

Ecotoxicology: Endocrine disruption assessment – FSTRA (see section B.9.2.3.1).	The ECP is invited to consider whether the VTG data provide evidence supporting an absence of in vivo mechanistic ED activity in males and females, given the uncertainties noted with the data A significant reduction in fecundity was observed among fish exposed to the highest treatment level tested of 130 µg a.s./L and for females there was increased prevalence and severity oocyte atresia in all test concentrations compared to control, but most notably at test concentrations of 1.3 and 130 µg a.s./L Based on the available data, what is the ECP's view on attributing the potential adverse effects on female gonads and reduction in fecundity seen at the highest treatment level in the FSTRA study to a general bodily stress response due to mild toxicity of the test item to the fish? The ECP did not consider the variation in male VTG results to be of concern, however the significant reduction in female VTG together with increased oocyte atresia and decreased fecundity was considered to be of potential concern. The ECP considered the results from the FSTRA to be unclear as to whether they were endocrine-mediated or due to reproductive toxicity, and hence recommended that a further mechanistic assay was conducted. As such, a Rapid Androgen Disruption Activity Reporter (RADAR) assay was requested to provide further mechanistic data. ~~This is currently ongoing, therefore it is not possible to conclude at present on the endocrine disrupting potential of pydiflumetofen on Estrogen, Androgen and Steroidogenesis (EAS) modalities for aquatic organisms~~

Ecotoxicology: Endocrine disruption assessment – AMA (see section B 9.2.3.2).	The ECP is invited to consider whether the applicant's method of 'maximum tolerated concentration' (MTC) selection in the submitted amphibian metamorphosis assay (AMA) study is scientifically sound, and allows for a robust conclusion on pydiflumetofen's effects on endocrine activity to be drawn. The ECP is invited to advise on the potential impact of a reduced feeding rate on the validity of the study. The ECP is invited to consider whether the incidence of spinal deformity impacts on the reliability of the results produced.
Ecotoxicology: Bee risk assessment (see section 9.6.1)	What is the ECP's view on extrapolation of honeybee toxicity data using the EU representative formulation A19649B (Miravis) for use in the risk assessment for the GB representative formulation A21857B (Miravis Plus)? Given the available data on the toxicity of pydiflumetofen and an associated formulation to honey bee larvae, what is the ECP's view on the potential risk to honey bee larvae?

3.2. PROPOSED DECISION

It is proposed that:

Pydiflumetofen (SYN545974) can be approved as a candidate for substitution under Retained Regulation (EC) No 1107/2009

It is considered that it should be specified that conditions of use shall include risk mitigation measures, where appropriate.

Further information to confirm the approval of the substance

It is proposed that the competent authority concerned shall request the submission of confirmatory information:

a) where new data requirements are established during the evaluation process, or
b) as a result of new scientific and technical knowledge, or
c) to increase confidence in the decision

- None

Additional Considerations

1. The GB Competent Authorities may request submission of information to support authorisation of a product, as regards:

- Data to address extraction efficiency high oil crops for the QuEChERS monitoriong method using acetonitrile/water (50/50, v/v)

- Validation data for the method for the monitoring of residues in air to support a lower LOQ of 15 µg/m^3.

- Following scale up from pilot plant at the second manufacturing site to full scale manufacture, new 5 batch analysis supporting the commercial scale technical specification must be submitted. In addition, the toxicological significance of any changes in the impurity profile must be addressed.
-

2. The GB Competent Authorities may request submission of information for the renewal of the active substance, as regards:

- An assessment of the effect of water treatment processes on the nature of residues present in surface water, when surface water is abstracted for drinking water.

- To extend approval beyond the first approval period, further information to address the long-term potential for groundwater contamination from pydiflumetofen must be submitted; for example - soil and groundwater monitoring.

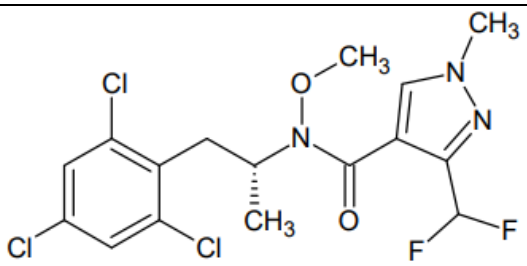
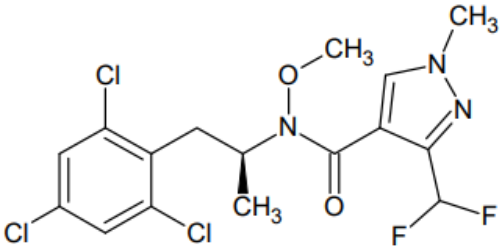
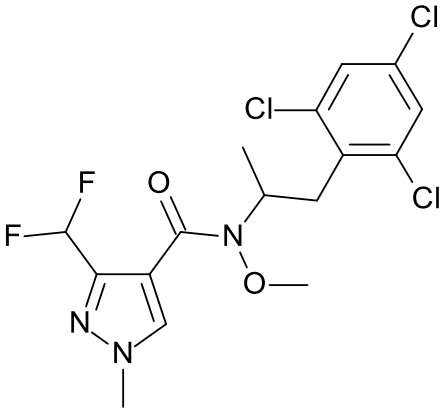
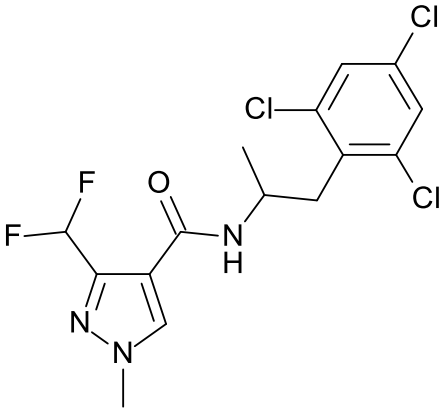
3.3. RATIONALE FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPROVAL OR AUTHORISATION(S), AS APPROPRIATE

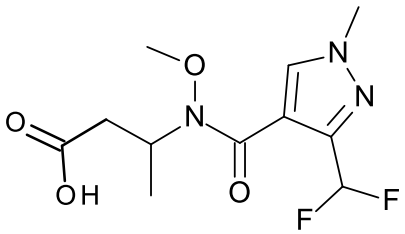
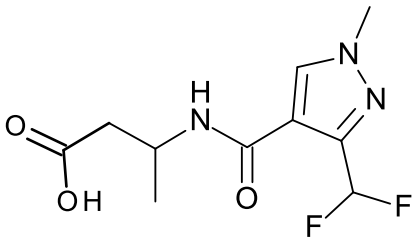
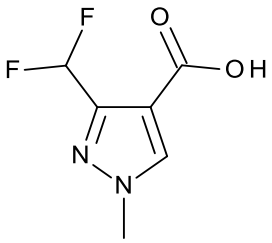
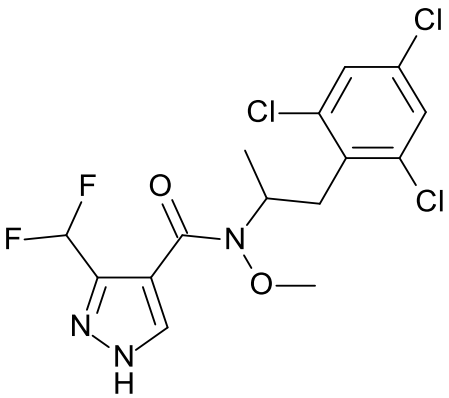
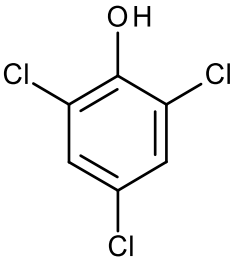
3.3.1. Particular conditions proposed to be taken into account to manage the risks identified

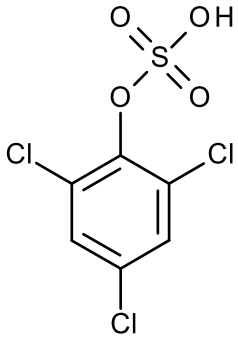
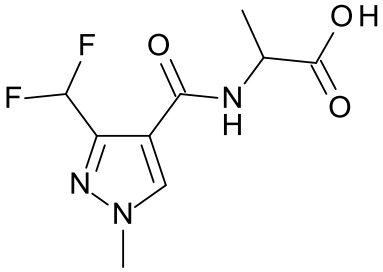
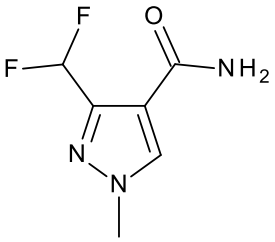
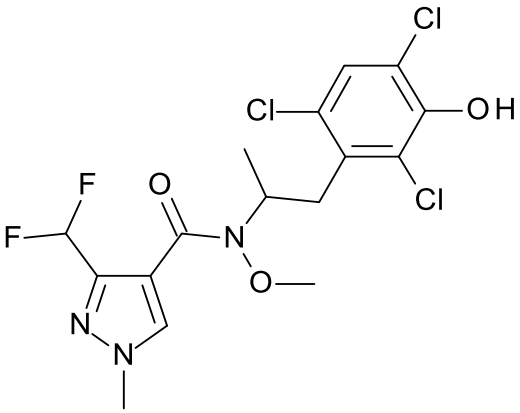
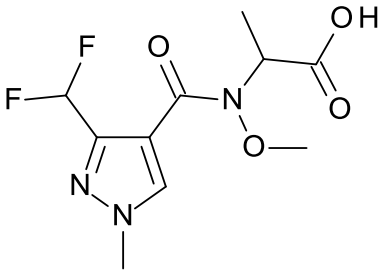
Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
PPE requirements due to classification of product • Protective gloves and face protection (faceshield) when handling the concentrate.	All proposed uses.

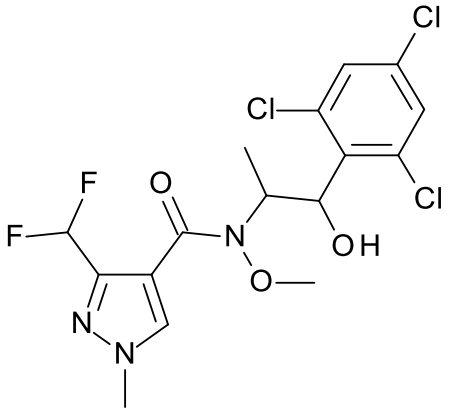
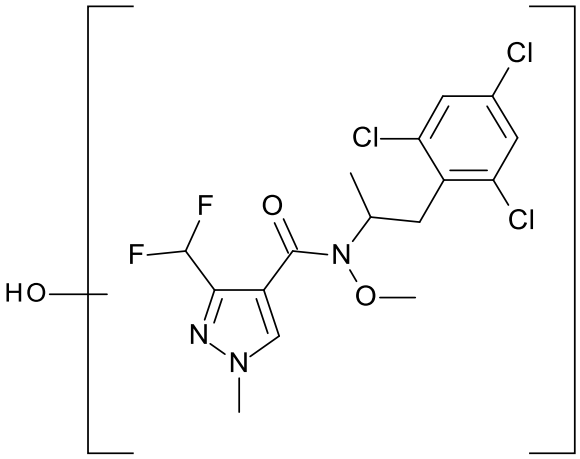
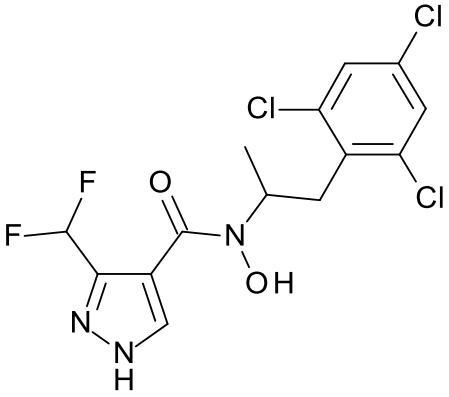
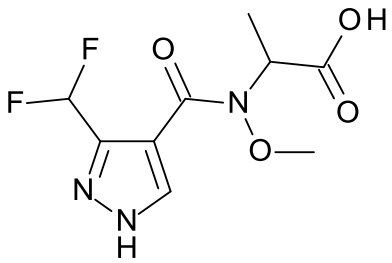
3.4. APPENDICES

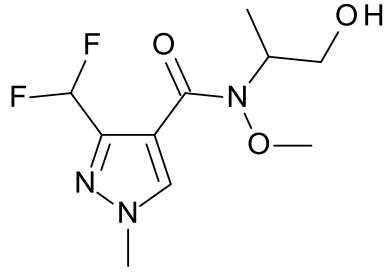
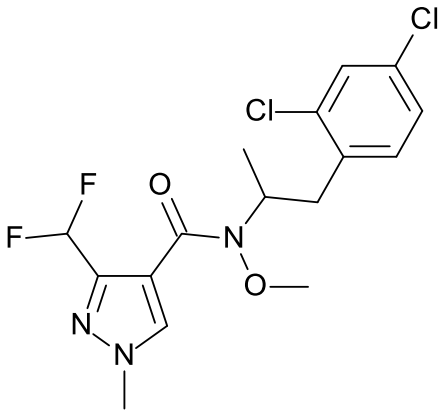
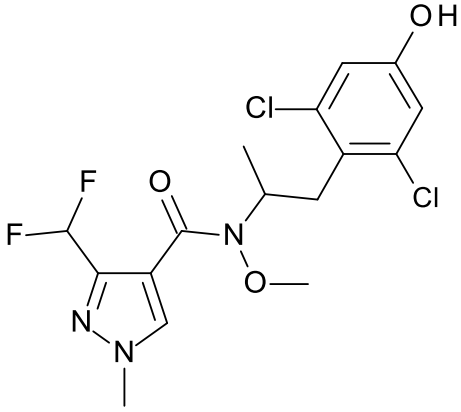
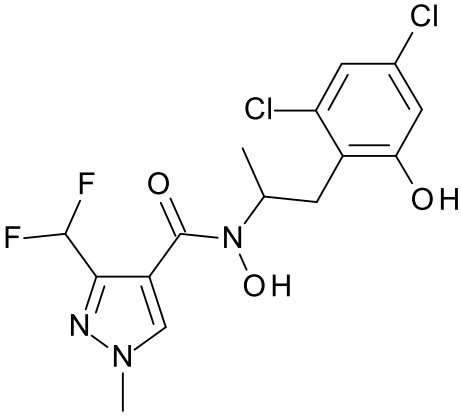
3.4.1. Metabolites and their codes

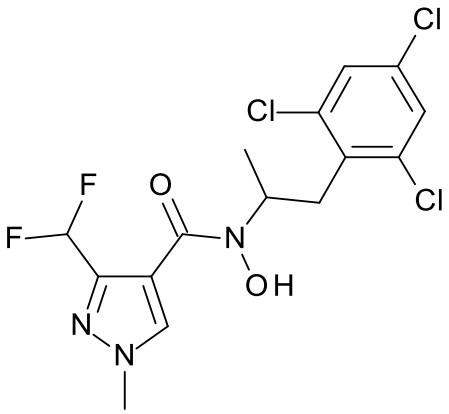
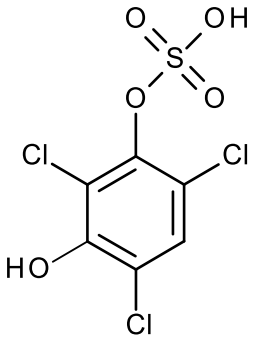
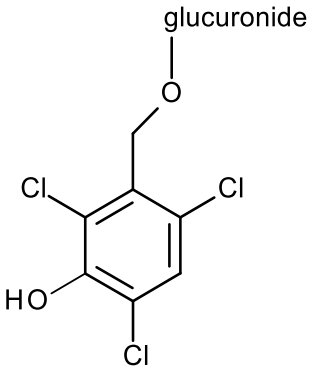
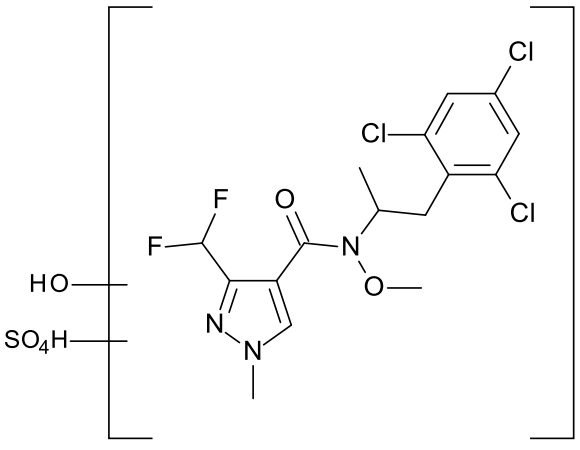
Code Number (Synonyms)	Description	Compound found in:	Structure
SYN546969 CSCD746375	(R)-3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid methoxy-[1-methyl-2-(2,4,6-trichloro-phenyl)-ethyl]-amide	N/A isomer of parent pydiflumetofen	
SYN546968 CSCD746374	(S)-3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid methoxy-[1-methyl-2-(2,4,6-trichloro-phenyl)-ethyl]-amide	N/A isomer of parent pydiflumetofen	
SYN545974 CSCD678790	N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide 1H-Pyrazole-4-carboxamide, 3-(difluoromethyl)-N-methoxy-1-methyl-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-	• Soil (sterile, aerobic, anaerobic, photolysis) • Aqueous photolysis • Water sediment systems • Crop (wheat, oilseed rape, tomato, rotated crops) • Livestock (hen, goat) • Rat	
SYN545547 CSCD550897	3-(difluoromethyl)-1-methyl-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]pyrazole-4-carboxamide	• Soil (sterile, aerobic, anaerobic, photolysis) • Aqueous photolysis • Water sediment systems • Crop (wheat, oilseed rape, tomato, rotated crops) • Livestock (hen, goat) • Rat	

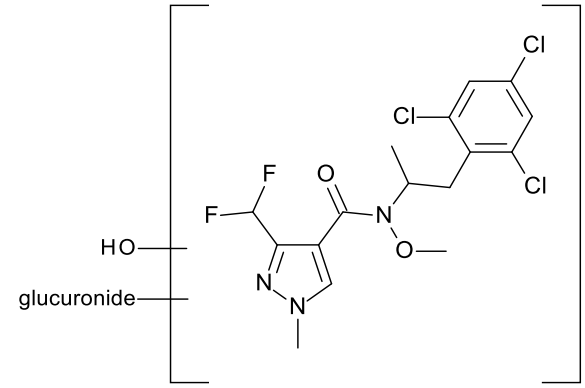
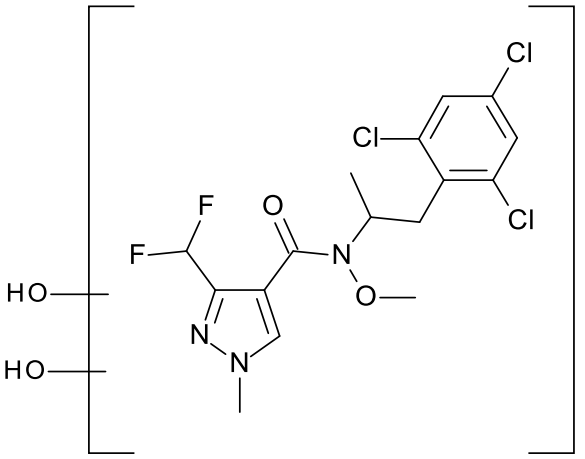
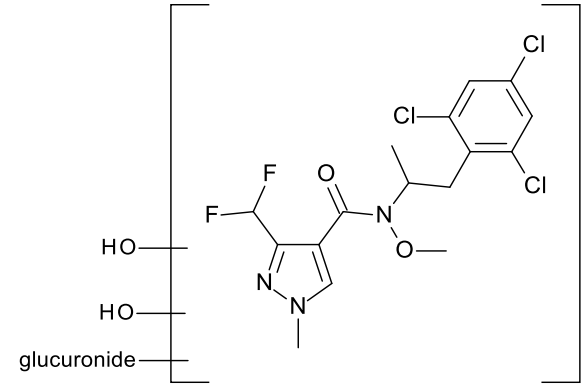
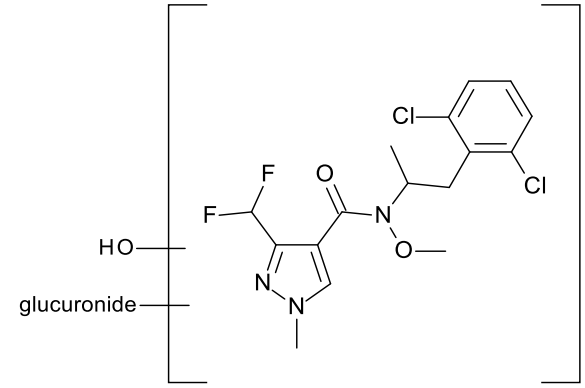
Code Number (Synonyms)	Description	Compound found in:	Structure
SYN548261	3-[[3-(difluoromethyl)-1-methyl-pyrazole-4-carbonyl]-methoxy-amino]butanoic acid	• Aqueous photolysis	
SYN548262	3-[[3-(difluoromethyl)-1-methyl-pyrazole-4-carbonyl]amino]butanoic acid	• Aqueous photolysis	
NOA449410 CSAA798670 R648993	3-(difluoromethyl)-1-methyl-pyrazole-4-carboxylic acid	• Aqueous photolysis • Livestock (hen, goat)	
SYN547891 CSCV764139	3-(difluoromethyl)-N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1H-pyrazole-4-carboxamide	• Crop (wheat, oilseed rape, tomato, wheat, rotated crops) • Livestock (hen, goat) • Rat	
2,4,6-Trichlorophenol 2,4,6-TCP (EXC4915)	2,4,6-trichlorophenol	• Livestock (hen, goat) • Rat	

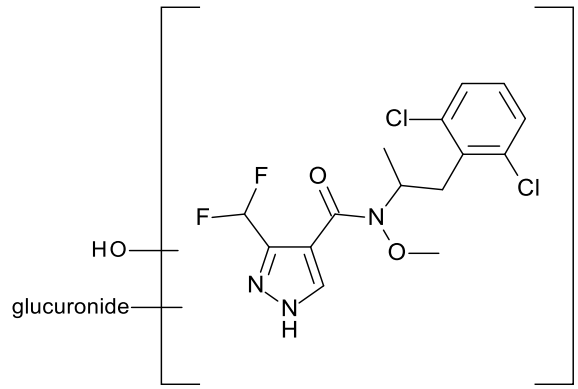
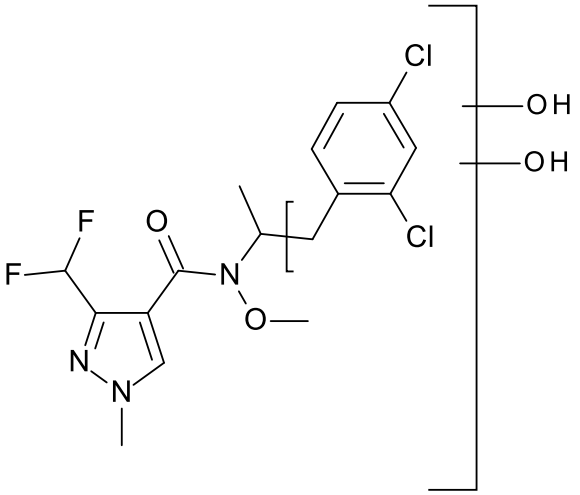
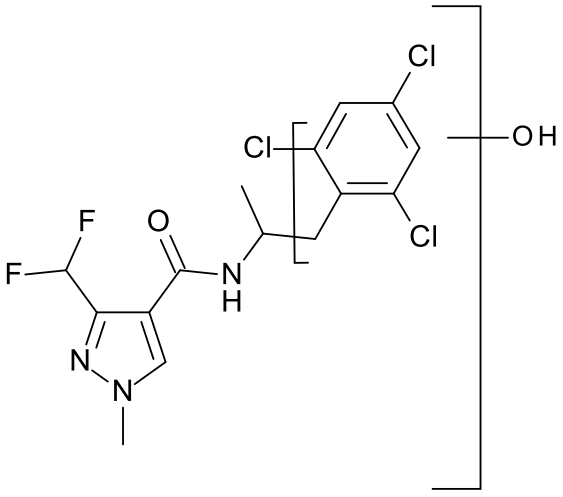
Code Number (Synonyms)	Description	Compound found in:	Structure
Sulphate conjugate of 2,4,6-trichlorophenol	Sulphate conjugate of 2,4,6-trichlorophenol	• Livestock (hen, goat) • Rat	
SYN548264 CSCD548196 N-desmethoxy SYN548263	2-[[3-(difluoromethyl)-1-methyl-pyrazole-4-carbonyl]amino]propanoic acid	• Livestock (goat) • Rat	
SYN508272 CSCC210616 R423363	3-(difluoromethyl)-1-methyl-pyrazole-4-carboxamide	• Livestock (hen, goat) • Rat	
SYN547897 CSCV764146	3-(difluoromethyl)-N-methoxy-1-methyl-N-[1-methyl-2-(2,4,6-trichloro-3-hydroxy-phenyl)ethyl]pyrazole-4-carboxamide	• Livestock (hen, goat) • Rat	
SYN548263 CSCZ159698	2-[[3-(difluoromethyl)-1-methyl-pyrazole-4-carbonyl]-methoxy-amino]propanoic acid	• Livestock (goat) • Rat	

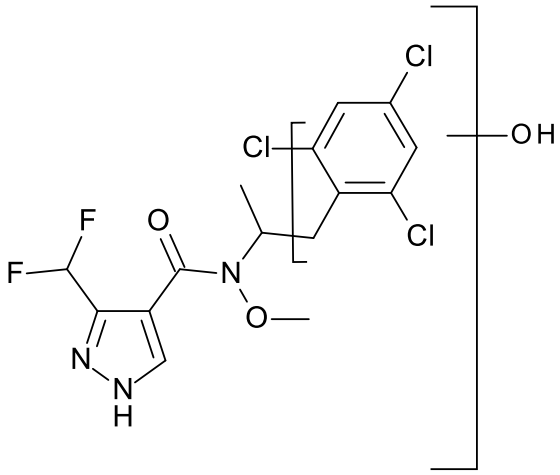
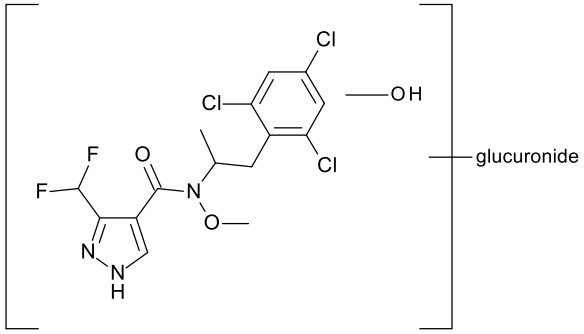
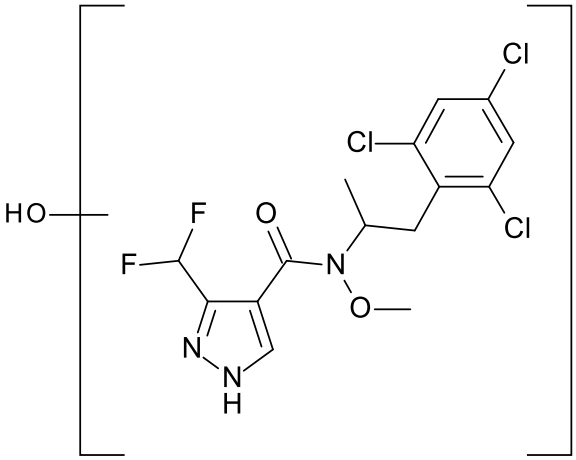
Code Number (Synonyms)	Description	Compound found in:	Structure
SYN547948 CSCY608054	3-(difluoromethyl)-N-[2-hydroxy-1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-N-methoxy-1-methyl-pyrazole-4-carboxamide	• Livestock (hen, goat) • Rat	
Hydroxylated SYN545974	Hydroxylated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide	• Livestock (goat) • Rat	
N-Desmethyl SYN547890	3-(difluoromethyl)-N-hydroxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1H-pyrazole-4-carboxamide	• Rat	
Desmethyl SYN548263 CSCZ159698	Desmethyl 2-[[3-(difluoromethyl)-1-methyl-pyrazole-4-carbonyl]-methoxy-amino]propanoic acid	• Rat	

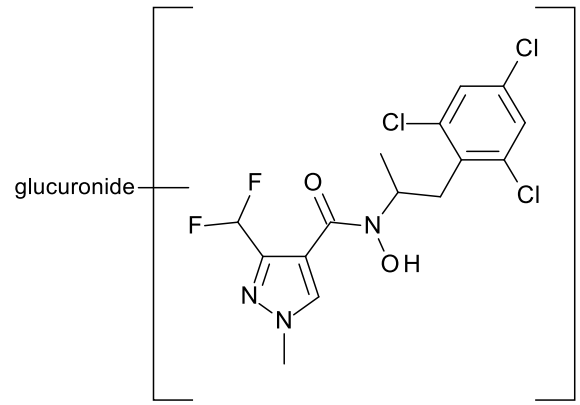
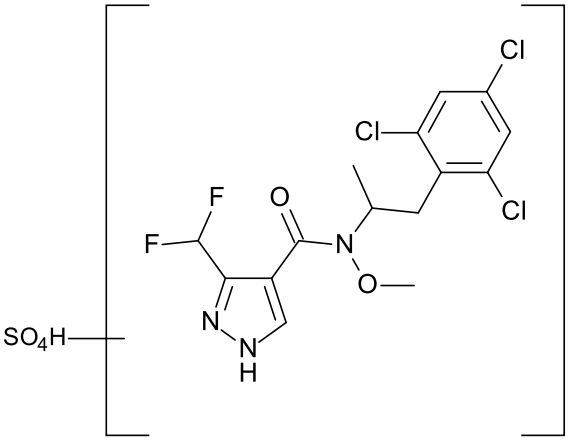
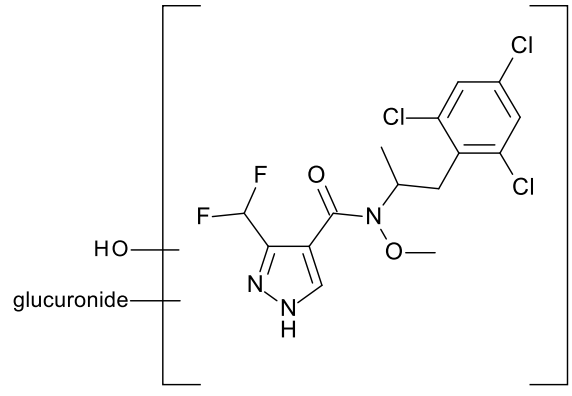
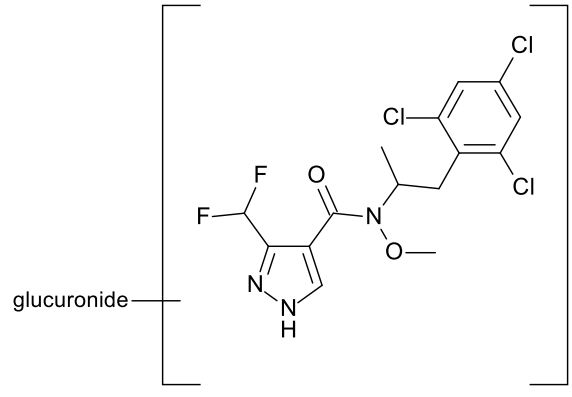
Code Number (Synonyms)	Description	Compound found in:	Structure
SYN548265	3-(difluoromethyl)-N-(2-hydroxy-1-methyl-ethyl)-N-methoxy-1-methyl-pyrazole-4-carboxamide	• Rat	
SYN547893 CSCD677133	N-[2-(2,4-dichlorophenyl)-1-methyl-ethyl]-3-(difluoromethyl)-N-methoxy-1-methyl-pyrazole-4-carboxamide	• Rat	
SYN547894 CSCV764141	N-[2-(2,6-dichloro-4-hydroxy-phenyl)-1-methyl-ethyl]-3-(difluoromethyl)-N-methoxy-1-methyl-pyrazole-4-carboxamide	• Rat	
Dechlorinated hydroxyl SYN545974	N-[2-(2,4-dichloro-6-hydroxy-phenyl)-1-methyl-ethyl]-3-(difluoromethyl)-N-hydroxy-1-methyl-pyrazole-4-carboxamide	• Rat	

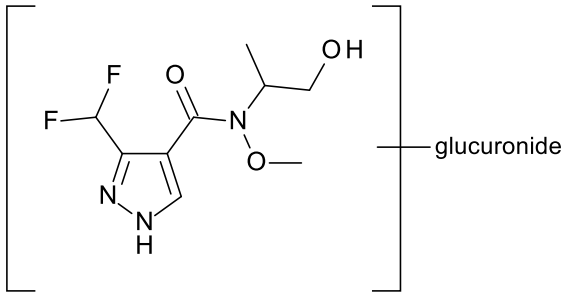
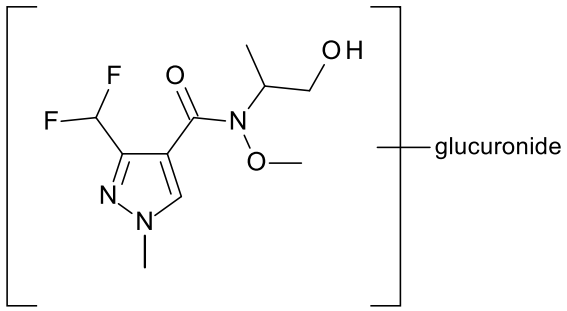
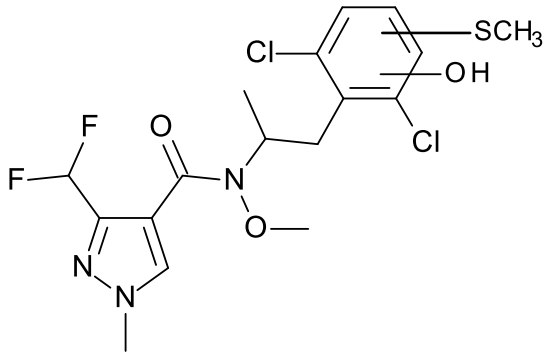
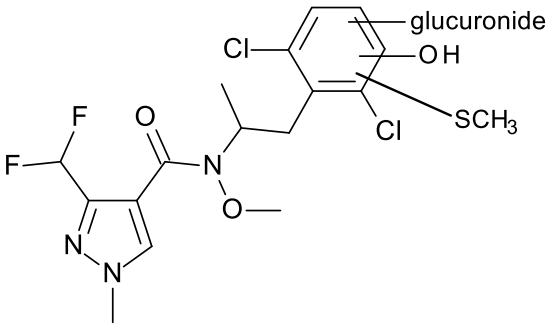
Code Number (Synonyms)	Description	Compound found in:	Structure
SYN547890	3-(difluoromethyl)-N-hydroxy-1-methyl-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]pyrazole-4-carboxamide	• Rat	
Hydroxylated TCP-sulphate HTCP Sulphate	(2,4,6-trichloro-3-hydroxy-phenyl) hydrogen sulfate	• Rat	
TCPM glucuronide	2,4,6-trichloro-3-(methoxymethyl)phenol glucuronide	• Rat	
Hydroxylated SYN545974 Sulphate conjugate	Hydroxylated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide Sulphate conjugate	• Rat	

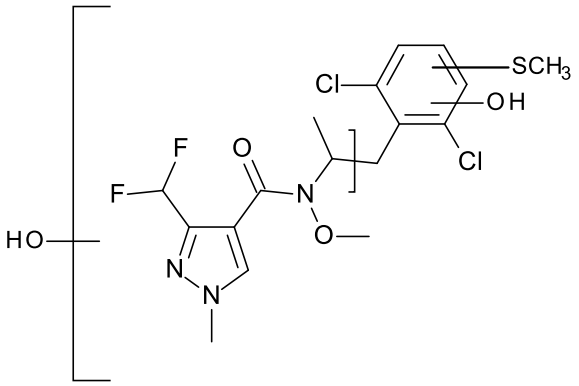
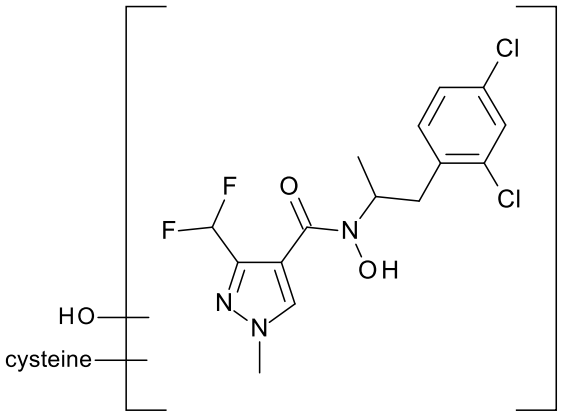
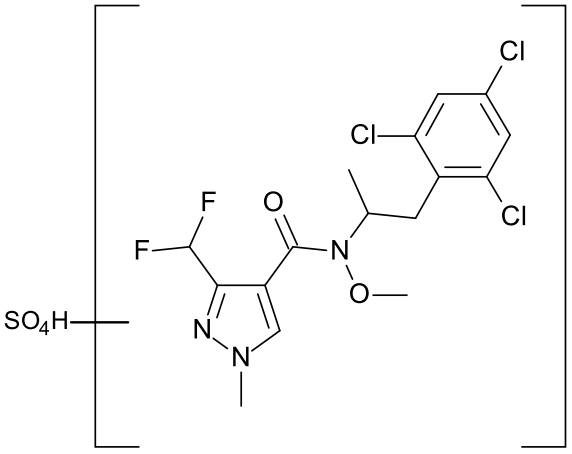
Code Number (Synonyms)	Description	Compound found in:	Structure
Hydroxylated SYN545974 Sulphate conjugate Glucuronide conjugate	Hydroxylated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide Sulphate conjugate Glucuronide conjugate	• Rat	
Dihydroxy SYN545974	Dihydroxylated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide	• Rat	
Dihydroxy SYN545974 Glucuronide conjugate	Dihydroxylated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide Glucuronide conjugate	• Rat	
Dechlorinated hydroxy SYN545974 Glucuronide conjugate	Dechlorinated hydroxylated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide Glucuronide conjugate	• Rat	

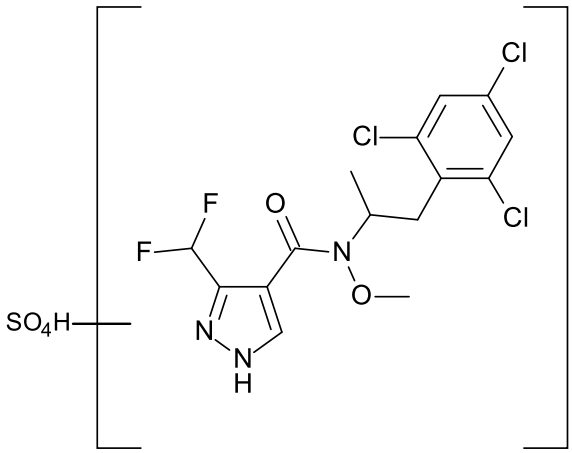
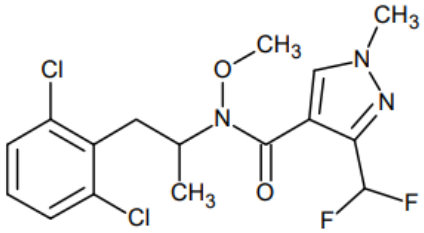
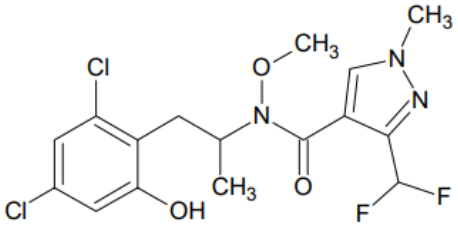
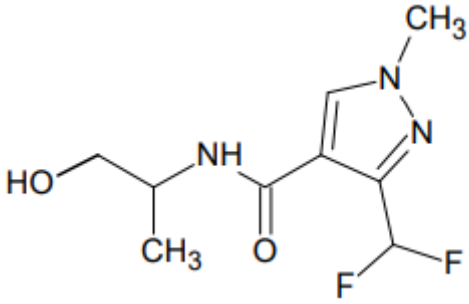
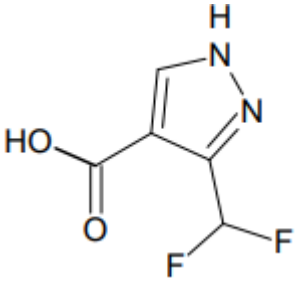
Code Number (Synonyms)	Description	Compound found in:	Structure
Dechlorinated hydroxy desmethyl SYN545974 Glucuronide conjugate	Desmethyl Dechlorinated hydroxylated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide Glucuronide conjugate	• Rat	
Dihydroxy dechlorinatedSYN545974	Dihydroxy dechlorinated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide	• Rat	
Hydroxy SYN545547	Hydroxylated 3-(difluoromethyl)-1-methyl-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]pyrazole-4-carboxamide	• Rat	

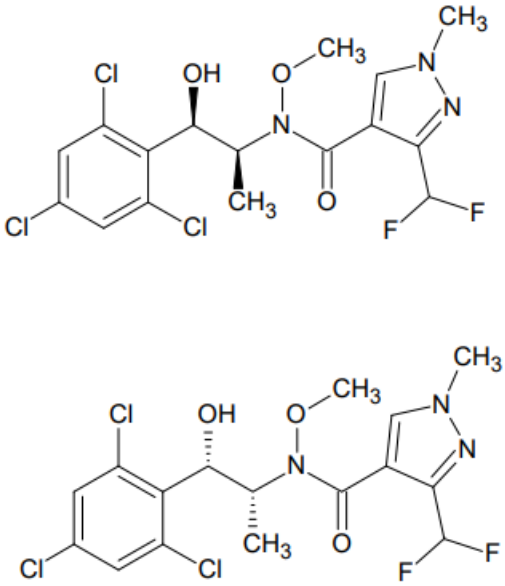
Code Number (Synonyms)	Description	Compound found in:	Structure
Hydroxy SYN547891	Hydroxylated 3-(difluoromethyl)-N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1H-pyrazole-4-carboxamide	• Rat	
SYN547891 Glucuronide conjugate	3-(difluoromethyl)-N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1H-pyrazole-4-carboxamide Glucuronide conjugate	• Rat	
Desmethyl hydroxyl SYN545974	Hydroxylated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide	• Rat	

Code Number (Synonyms)	Description	Compound found in:	Structure
Desmethyl SYN545974 Glucuronide	Desmethyl N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide glucuronide	• Rat	
Desmethyl hydroxy SYN545974 sulphate	3-(difluoromethyl)-N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1H-pyrazole-4-carboxamide Sulphate conjugate	• Rat	
Desmethyl hydroxy SYN545974 glucuronide	Hydroxylated N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide Glucuronide conjugate	• Rat	
Desmethyl SYN545974 glucuronide	3-(difluoromethyl)-N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1H-pyrazole-4-carboxamide Glucuronide conjugate	• Rat	

Code Number (Synonyms)	Description	Compound found in:	Structure
Desmethyl SYN548265 Glucuronide conjugate	Desmethyl 3-(difluoromethyl)-N-(2-hydroxy-1-methyl-ethyl)-N-methoxy-1-methyl-pyrazole-4-carboxamide Glucuronide conjugate	• Rat	
SYN548265 Glucuronide conjugate	3-(difluoromethyl)-N-(2-hydroxy-1-methyl-ethyl)-N-methoxy-1-methyl-pyrazole-4-carboxamide Glucuronide conjugate	• Rat	
Dechlorinated hydroxy thiomethyl SYN545974	Dechlorinated hydroxy thiomethyl N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide	• Rat	
Dechlorinated hydroxy thiomethyl SYN545974 glucuronide	Dechlorinated hydroxy thiomethyl N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide glucuronide conjugate	• Rat	

Code Number (Synonyms)	Description	Compound found in:	Structure
Dechlorinated dihydroxy thiomethyl SYN545974	Dechlorinated dihydroxy thiomethyl N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide glucuronide	• Rat	
Dechlorinated hydroxy SYN545974 cysteine	Dechlorinated hydroxy N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide cysteine	• Rat	
Hydroxy SYN545974 sulphate	Hydroxy N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide sulphate	• Rat	

Code Number (Synonyms)	Description	Compound found in:	Structure
Hydroxy SYN547891 sulphate	Hydroxy 3-(difluoromethyl)-N-methoxy-N-[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1H-pyrazole-4-carboxamide sulphate	• Rat	
SYN547892	Not provided	Analysed for but not found in poultry and ruminant54789	
SYN547895	Not provided	Analysed for but not found in poultry and ruminant	
SYN548266	Not provided	Analysed for but not found in poultry and ruminant	
SYN545720 R958945	Not provided	Analysed for but not found in poultry and ruminant	

Code Number (Synonyms)	Description	Compound found in:	Structure
SYN547949 (two enantiomers of the compound)	Not provided	Analysed for but not found in poultry and ruminant	

3.4.2. GUIDANCE DOCUMENTS USED IN THIS ASSESSMENT

Exposure

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

Residues

- EC (European Commission), 2010. Classes to be used for the setting of EU pesticide Maximum Residue Levels (MRLs). SANCO 10634/2010 Rev. 0, finalized in the Standing Committee on the Food Chain and Animal Health at its meeting of 23-24 March 2010.
- EC (European Commission), 2016. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. 7525/VI/95-rev.10.3.
- FAO (Food and Agriculture Organization of the United Nations), 2009. Submission and evaluation of pesticide residues data for the estimation of Maximum Residue Levels in food and feed. Pesticide Residues. 2nd Ed. FAO Plant Production and Protection Paper 197, 264 pp.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in crops. No. 501, OECD, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in rotational crops. No 502, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in livestock, No. 503, OECD, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Residues in rotational crops (limited field studies). No 504, Paris 2007.
- OECD, 2007, OECD Guidelines for the testing of chemicals – Residues in livestock. No 505, Paris 2007.

- OECD, 2007. OECD Guidelines for the testing of chemicals – Stability of pesticide residues in stored commodities. No 506, OECD, Paris 2007.
- OECD, 2007. OECD Guidelines for the testing of chemicals – Nature of the pesticide residues in processed commodities, high temperature hydrolysis. No 507, Paris 2007.
- OECD, 2008. OECD Guidelines for the testing of chemicals – Magnitude of pesticide residues in processed commodities. No 508, Paris 2008.
- OECD, 2009. OECD Guidelines for the testing of chemicals – Crop field trial. No 509, 2009 and 2021 update.
- OECD, 2009, Guidance document on the definition of residue, (ENV/JM/MONO(2009)30), Series on testing and assessment No. 63 and Series on pesticides No. 31
- OECD, 2008, Guidance document on magnitude of pesticide residues in processed commodities, (ENV/JM/MONO(2008)23), Series on testing and assessment No. 96
- OECD, 2013, Guidance document on residues in livestock, (ENV/JM/MONO(2013)8), Series on pesticides No. 73
- OECD, 2016, Guidance document on crop field trials, (ENV/JM/MONO(2011)50/REV1), Series on testing and assessment No. 164 and Series on pesticides No. 66
- OECD, 2018, Guidance document on residues in rotational crops, (ENV/JM/MONO(2018)9), Series on testing and assessment No. 279 and Series on pesticides No. 97
- Residues trials and MRL calculations, Proposals for a harmonised approach for the selection of the trials and data used for the estimation of MRL, STMR and HR, EFSA, September 2015
- Estimation of animal intakes and HR, STMR and MRL calculations for products of animal origin, EFSA, September 2015
- EFSA guidance on the Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA Journal 2011;9(2):2092)

Ecotoxicology

- General:
  HSE CRD (2022). Formulation studies and combined risk assessment in ecotoxicology. Guidance on the need for studies and their use in risk assessment. Available from:
  https://www.hse.gov.uk/pesticides/resources/E/CRD-Formulation-Guidance-ecotox.pdf
- Birds & Mammals:
  EFSA (2009). Guidance document on risk assessment for birds and mammals. EFSA Journal 2009;7(12):1438
- Aquatic Organisms:
  EFSA (2013). Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290
- Bees/Soil organisms/Non-target plants:
  SANCO/10329/2002 (rev 2 final). Guidance document on terrestrial ecotoxicology under council directive 91/414/EEC.
- Non-target arthropods:

ESCORT 2 (Candolfi *et al.*, 2001). Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods.

3.5. REFERENCE LIST

None

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