

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 3 – B.6 (PPP) – Miravis Plus

Toxicology, Metabolism Data & Assessment of Risks for Humans

Great Britain

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B.6. TOXICOLOGY AND METABOLISM DATA AND ASSESSMENT OF RISKS FOR HUMANS

Miravis Plus (A21857B) is the representative formulation for the approval of the new active substance pydiflumetofen. Miravis Plus (A21857B) is an emulsifiable concentrate formulation containing 62.5 g/L pydiflumetofen. This document reviews the toxicology, including human health hazard and classification and the dermal absorption of A21857B.

B.6.1. ACUTE TOXICITY OF THE PLANT PROTECTION PRODUCT

The acute toxicity of A21857B has been assessed by application of the calculation method according to Regulation 1272/2008 (CLP). The outcome of the classification for human health effects is summarised in Table B.6.1-1.

Based on the calculation method of CLP, A21857B is calculated to be of low acute oral, dermal and inhalation toxicity, not meeting the criteria for classification for acute toxicity via any route. A21857B is not irritating to the skin but requires classification for serious eye damage in Category 1 (H318). A21857B is not a skin sensitiser. In addition, A21857B is classified for carcinogenicity and reproductive toxicity, both in Category 2 (H351 and H361f).

Table B.6.1-1: Summary of toxicity assessment of A21857B

Human Health Hazard	Toxicological assessment and conclusion on human health classification
Acute oral toxicity	Calculation method: No relevant ingredients for calculation CLP classification: Not Classified
Acute dermal toxicity	Calculation method: No relevant ingredients for calculation CLP classification: Not Classified
Acute inhalation toxicity	Calculation method: No relevant ingredients for calculation CLP classification: Not Classified
Skin irritation	Calculation method: No relevant ingredients for calculation CLP classification: Not Classified
Eye irritation	Calculation method: Contains 5.5% components classified in Category 1, above the generic concentration limit for classification for serious eye damage in Category 1. CLP classification: Serious Eye Damage Category 1- H318
Skin sensitisation	Calculation method: No relevant ingredients for calculation CLP classification: Not Classified
Other human health hazards	Calculation method: Contains 5.7% of the active substance which is classified in Category 2, for carcinogenicity (H351) and reproductive toxicity (H361f). The concentration of the active substance in the product is above the generic concentration limits (1% and 3% respectively) which trigger classification of the mixture. CLP classification: Carcinogenicity Category 2- H351 Reproductive toxicity Category 2- H361f

B.6.1.1. Oral

The acute oral toxicity of A21857B has been assessed by application of the calculation method (Regulation 1272/2008). See Volume 4 Confidential Information for more details.

The product does not contain any components classified for acute oral toxicity. Therefore, A21857B does not require classification for acute oral toxicity based on the calculation method, in accordance with Regulation 1272/2008.

Overall, no classification for acute oral toxicity is required for A21857B, in accordance with Regulation 1272/2008.

B.6.1.2. Dermal

The acute dermal toxicity of A21857B has been assessed by application of the calculation method (Regulation 1272/2008). See Volume 4 Confidential Information for more details.

The product does not contain any components classified for acute dermal toxicity. Therefore, A21857B does not require classification for acute dermal toxicity based on the calculation method, in accordance with Regulation 1272/2008.

Overall, no classification for acute dermal toxicity is required for A21857B, in accordance with Regulation 1272/2008.

B.6.1.3. Inhalation

The acute inhalation toxicity of A21857B has been assessed by application of the calculation method (Regulation 1272/2008). See Volume 4 Confidential Information for more details.

The product does not contain any components classified for acute inhalation toxicity. Therefore, A21857B does not require classification for acute inhalation toxicity based on the calculation method, in accordance with Regulation 1272/2008.

Overall, no classification for acute inhalation toxicity is required for A21857B, in accordance with Regulation 1272/2008.

B.6.1.4. Skin irritation

The skin irritation potential of A21857B has been assessed by application of the calculation method (Regulation 1272/2008). See Volume 4 Confidential Information for more details.

Based on the concentration of ingredients and calculation method of CLP, A21857B does not require classification for skin corrosion or skin irritation, in accordance with Regulation 1272/2008.

Overall, no classification for skin irritation is required for A21857B, in accordance with Regulation 1272/2008.

B.6.1.5. Eye irritation

The eye irritation potential of A21857B has been assessed by application of the calculation method (Regulation 1272/2008). The sum of relevant ingredients classified for serious eye damage in Category 1 is 5.50 %, which exceeds the generic concentration limit for classification of a mixture in Category 1 of $\geq 3\%$. See Volume 4 Confidential Information for more details.

Based on the concentration of ingredients in the formulated product that are classified for serious eye damage, A21857B requires classification for serious eye damage in Category 1 (H318), in accordance with Regulation No. 1272/2008.

Overall, A21857B is classified in Category 1 for serious eye damage in accordance with Regulation 1272/2008.

B.6.1.6. Skin sensitization

The skin sensitisation potential of A21857B has been assessed by application of the calculation method (Regulation 1272/2008). See Volume 4 Confidential Information for more details.

The product does not contain any components classified for skin sensitisation. Therefore, A21857B does not require classification for skin sensitisation based on the calculation method, in accordance with Regulation 1272/2008.

Overall, no classification for skin sensitisation is required for A21857B, in accordance with Regulation 1272/2008.

B.6.1.7. Assessment of other toxicological hazards

Based on the toxicological information available on the active substance (classified with H351 and H361f) and its concentration at 5.7%, A21857B meets the criteria for classification for carcinogenicity in Category 2 (H351) and reproductive toxicity (fertility) in Category 2 (H361f) in accordance with Regulation 1272/2008. See Volume 4 Confidential Information for details.

B.6.1.8. Supplementary studies on the plant protection product

Not available and not required.

B.6.1.9. Supplementary studies for combinations of plant protection products

Not available and not required.

B.6.2. DERMAL ABSORPTION

The in vitro dermal penetration of pydiflumetofen formulated as Pydiflumetofen EC (A21857B) through human skin has been investigated in a study conducted in accordance with OECD test guideline 428. The available study was interpreted in accordance with the EFSA Guidance on Dermal Absorption (2017).

Table B.6.2.1 Summary of *in vitro* dermal penetration studyTable 6.2-1. Summary of *in vitro* dermal penetration study

Method, guideline, GLP status, reference	Species	Test substance, dose levels, duration of exposure	Results
<i>In vitro</i> dermal penetration OECD 428 (2004) GLP Compliant ██████ & ██████, 2017 (Report No. 37801, Study No. 798908)	Human (female) abdominal or breast skin, dermatomed (split thickness), thickness of 380-400 µm 4 donors Receptor fluid: Phosphate buffered saline containing polyoxyethylene 20 oleyl ether (PEG, ca 6%, w/v), sodium azide (ca 0.01%, w/v), streptomycin (ca 0.1 mg/mL) and penicillin (ca 100 units/mL) Washing solution: Simple Antibacterial Hand wash/ultrapure water, 2% (v/v)	[phenyl-U- ¹⁴ C]-Pydiflumetofen, radiochemical purity 99.1% Formulation concentrate: 64.2g/L; nominal dose 10.00 µL/cm ² (642µg ai/cm ²), 8 valid diffusion cells Spray dilution I: 2g/L; nominal dose 10.00 µL/cm ² (20.0µg ai/cm ²), 8 valid diffusion cells Spray dilution II : 0.60g/L; nominal dose 10.00 µL/cm ² (5.96µg ai/cm ²), 8 valid diffusion cells Duration of exposure = 6 hours Duration of experiment = 24 hours	High dose concentrate = 0.4% Mid dose: Spray dilution I = 7.3% Low dose: Spray dilution II = 11%

Material and methods

In an *in vitro* experiment, the dermal penetration of pydiflumetofen formulated as A21857B through human skin was investigated. The formulation concentrate (64.2g/L / 642µg ai/cm²), Spray dilution I (2g/L / 20.0µg ai/cm²) or Spray dilution II (0.60g/L / 5.96µg ai/cm²), were applied to human dermatomed skin at a rate of 10 µL/cm². The skin was mounted into a static diffusion cell system. The static diffusion cells were placed in a steel manifold on a magnetic stirrer plate heated via a circulating water bath to maintain the skin surface temperature at 32°C ± 1°C. The surface area of exposed skin within the cells was 0.64 cm². The receptor chamber volume was nominally 5 mL. The exposure of the skin to the test material lasted 6 hours under unoccluded conditions; thereafter the skin was thoroughly washed. Samples of the receptor fluid were taken in 2-hour intervals from 0 to 8 hours and twice more at 12 and 24 hours after the start of the exposure. All receptor fluid samples were analysed by liquid scintillation counting. Dermal absorption estimates were derived in accordance with the EFSA guidance on dermal absorption (2017).

Prior to the experiment, the skin sample integrity was determined by a barrier integrity assessment. Electrical resistance of skin samples was measured and any skin sample exhibiting a resistance less than 10.9 kΩ was excluded from subsequent absorption measurements. At the end of the experiment, cells were assessed to be valid if total recoveries fulfilled guideline requirements (a total recovery per membrane of 100 ± 10%).

Following termination of the experiment, the stratum corneum was removed with (up to) 20 successive tape strips. Each tape strip was then individually analysed by liquid scintillation counting.

Results

The mean recoveries of radioactivity from the different experimental compartments are presented in Table 6.2-2. Eight diffusion cells were used for each tested concentration, all of which were accepted in the final results.

Table 6.2-2. *In-vitro* dermal penetration of [phenyl-U-¹⁴C]-Pydiflumetofen formulated as A21857B through human skin – Recovery data

Dose group	High dose		Mid dose		Low dose	
	(Formulation concentrate)		(Spray dilution I)		(Spray dilution II)	
Target concentration [mg/mL]	62.5		2		0.55	
Target dose [µg/cm ²]	625		20		6	
Mean actual applied dose [µg/cm ²]	642		20		5.96	
Number of cells used/Valid cells	8/8		8/8		8/8	
	Recovery [%]		Recovery [%]		Recovery [%]	
	Mean	SD	Mean	SD	Mean	SD
Dislodgeable dose						
Dislodgeable Dose 6 h*	100.42	-	86.27	-	78.00	-
Total Dislodgeable Dose**	100.68	-	93.23	-	88.86	-
Donor chamber wash	0.04	0.03	1.35	1.54	1.70	3.53
Dose associated to skin						
Tape strips: 1 st sample, strips 1 - 2	0.03	0.03	1.52	0.95	1.12	0.57
Tape strips: 2 nd sample, strips 3 - 20	0.07	0.04	2.14	0.86	2.65	1.27
Skin preparation	0.09	0.09	2.22	1.61	3.51	2.40
Absorbed dose						
Sum receptor samples incl. wash out	0.00	0.00	0.00	0.00	0.00	0.00
Receptor fluid	0.08	0.05	0.97	0.23	2.06	0.63
Receptor chamber wash	0.01	0.0	0.11	0.06	0.31	0.14
Total recovery	100.96	0.67	100.18	1.21	98.49	0.95
Absorption complete? (>75% absorption within half the study duration)	No		No		No	
Absorption estimates when absorption not essentially completed (= absorbed dose + dose associated to skin + tape strips sample 2)^a	Yes		Yes		Yes	
Measure absorption (= absorbed dose + dose associated to skin)	0.25	0.18	5.43	2.22	8.52	3.07
Absorption estimate normalised^b	n/a		n/a		n/a	
Relevant absorption estimate^c	0.401		7.295		11.098	
Absorption estimates used for risk assessment^c	0.4 %		7.3%		11 %	

* Dislodgeable Dose 6 h = Skin Wash 6 h + Tissue Swab 6 h + Pipette Tip 6 h

** Total Dislodgeable Dose = Dislodgeable Dose 6 h + Skin Wash 24 h + Tissue Swab 24 h + Pipette Tip 24 h + Donor Chamber Wash

a In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the radioactivity in the second tape-strip pool (3rd to 6th tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study. Finally, the skin preparation is also considered potentially absorbable.

b Cells with insufficient recovery (<95%) were corrected by normalization of absorption estimate to 100% recovery if mean recovery was <95%.

c In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) to address variability between replicates, a multiple of the standard deviation should be added to the mean dermal absorption value. This value was then rounded to the required number of significant figures.

n/a not applicable

The amount of [¹⁴C]-Pydiflumetofen absorbed through human split-thickness skin membranes over 24 h from the formulation concentrate (62.5 g/L) and the intended in-use concentrations, 2 g/L and 0.55 g/L was 0.09%, 1.08% and 2.36% of the applied dose, respectively, as measured in the receptor fluid and receptor chamber wash.

For every concentration the absorption at 12h was < 75% of the total amount absorbed, therefore absorption was not recorded as complete. Hence the amount of test substance contained in the tape strips (excluding tape strips 1 and 2) was not excluded from the absorption estimates. Only one tape strip (tape strip 15) of cell 20 was excluded from the tape strip pool and assigned to the exposed skin, as it contained trace amounts of epidermis. As the total recovery for all cells across the three tested dilutions was > 95%, no absorption estimates were normalised in accordance with EFSA Guidance on dermal absorption 2017. In accordance with EFSA guidance, the relevant absorption estimate was calculated with a multiplication factor to treat the variability within the results.

Conclusion

In conclusion, *in vitro* dermal absorption of [phenyl-¹⁴C]-Pydiflumetofen formulated as A21857B through human skin is low. The human dermal absorption estimates of pydiflumetofen in A21857B (Miravis Plus) were 0.25 ± 0.18 % for the formulation concentrate (62.5 mg a.s./mL), 5.43 ± 2.22 % for the spray dilution I (2.0 mg a.s./mL), and 8.52 ± 3.07 % of the spray dilution II (0.55 mg a.s./mL).

The human dermal penetration estimates of pydiflumetofen in A21857B (Miravis Plus) to be used for risk assessment were calculated to be **0.4 %** for the concentrate (**62.5 g/L**), **7.3%** for spray dilution I (**2 g/L**) and **11%** for spray dilution II (**0.55 g/L**) of A21857B.

B.6.3. AVAILABLE TOXICOLOGICAL DATA RELATING TO CO-FORMULANTS

Safety Data Sheet for the co-formulants have been provided and have been taken into account in the assessment of the hazard classification of the product.

B.6.4. EXPOSURE DATA

‘Miravis Plus’ is the representative formulation for the approval of the active substance pydiflumetofen. A summary of the application parameters pertinent to the operator, bystander, resident and worker exposure assessment for ‘Miravis Plus’ are presented below.

Table B.6.4-1: Summary of ‘Miravis Plus’ application parameters pertinent to the operator, bystander, resident and worker exposure assessment.

‘Miravis Plus’ (A21857B)	
Formulation type	Emulsifiable concentrate (EC)
Use	For use as a professional fungicide on winter and spring cereals, winter and spring oilseed rape
Active substance concentration	62.5 g/L pydiflumetofen (Code: SYN545974)
Application method	Vehicle mounted boom sprayer
Maximum individual dose	3.2 L product/ha equivalent to 0.2 kg a.s./ha
Application volume	100 – 300 L/ha
Spray concentration range	Including lower application rate of 2.65 L product/ha (equivalent to 0.166 kg a.s./ha): 0.553 – 2.00 g a.s./L
Maximum number of applications per year	1 per year
Interval between applications	365 days
Latest time of application	BBCH 69
Classification	H318: Causes serious eye damage H351: Suspected of causing cancer H361f: Suspected of damaging fertility
Packaging	1 L HDPE or PE/PA bottle 5, 10, 20 L HDPE or f-HDPE canister

Systemic AOEL	0.05 mg/kg bw/day
Systemic AAOEL	0.15 mg/kg bw/day
Oral absorption	50%
Dermal absorption	Concentrate: 0.4% Dilution (2 g/L): 7.3% Dilution (0.55 g/L): 11%
Vapour pressure	0.0184 µPa at 20°C (99.5%) According to DAR 04 Volume 3CA Section B2

Estimates of operator, worker, bystander and resident exposure have been conducted in line with the 2014 EFSA guidance¹ and the respective calculator (hereafter referred to as EFSA Calculator). Considering the proposed uses of the representative product, the maximum application rate of 3.2 L product/ha intended for spring and winter cereals and oilseed rape is the critical GAP for operator, bystander, resident and worker exposure. This use is considered for this assessment and covers uses for winter and spring cereals with the lower application rate of 2.65 L product/ha.

B.6.4.1. Operator exposure

A Tier 1 estimate of operator exposure is presented based on the highest application rate and the highest dermal absorption values (worst-case scenario). A summary of the estimated longer term operator exposure to pydiflumetofen for the proposed uses of 'Miravis Plus' is provided in the following table. Outputs of the EFSA Calculator are presented in Appendix 1 (Estimate 1).

Table B.6.4.1-1: Estimated longer term operator exposure to pydiflumetofen during the application of 'Miravis Plus' and comparison with AOEL

Model: EFSA Calculator version 30/03/2015

		Pydiflumetofen	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL (0.05 mg/kg bw/day)
Scenario: Cereals / Outdoor / Downward spraying / Vehicle-mounted Formulation type: Emulsifiable Concentrate Work rate: 50 ha Season: Not relevant			
Application rate		0.2 kg a.s./ha	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) mixing/loading and application	0.0050	10

Based on the EFSA Calculator, the predicted longer term operator exposure is equivalent to 10% of the systemic AOEL of pydiflumetofen for an operator applying the product via vehicle mounted boom sprayer to low crops and using no PPE. The predicted operator exposure is within acceptable levels and no further risk assessment is required.

A summary of the estimated acute operator exposure to pydiflumetofen for the proposed uses of 'Miravis Plus' is provided in the following table. Outputs of the EFSA Calculator are presented in Appendix 1 (Estimate 1).

Table B.6.4.1-2: Estimated acute operator exposure to pydiflumetofen during the application of 'Miravis Plus' and comparison with AAOEL

¹ European Food Safety Authority (2014). Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, EFSA Journal 2014;12(10):3874.

Model: EFSA Calculator version 30/03/2015

		Pydiflumetofen	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AAOEL (0.15 mg/kg bw/day)
Scenario: Cereals / Outdoor / Downward spraying / Vehicle-mounted Formulation type: Emulsifiable Concentrate Work rate: 50 ha Season: Not relevant			
Application rate		0.2 kg a.s./ha	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) mixing/loading and application	0.0311	21

Based on the EFSA Calculator, the predicted acute level of operator exposure is equivalent to 21% of the AAOEL of pydiflumetofen for an operator applying the product via vehicle mounted boom sprayer to low crops and using no PPE. The predicted acute operator exposure is within acceptable levels and no further risk assessment is required.

Classification of 'Miravis Plus'

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.

B.6.4.2. Bystander and resident exposure

A Tier 1 longer term resident and bystander exposure assessment is presented based on the highest application rate, the minimum proposed water volume and the highest dermal absorption values (worst-case scenario). For exposure of residents and bystanders to vapour the EFSA Guidance specifies default values for the average concentration of active substance in the air 24 hours after application of the product. These values are based on the volatility of the active substance (preferably at 25 °C):

Substances with low volatility having a vapour pressure of $< 5 \times 10^{-3}$ Pa (the default average concentration in air in the 24 hours after application is 1 µg/m³). Moderately volatile substances with a vapour pressure between 5×10^{-3} Pa and 10^{-2} Pa (the default average concentration in air in the 24 hours after application is 15 µg/m³).

Pydiflumetofen has a vapour pressure of 0.0184 µPa according to DAR 04 Volume 3CA Section B2. The vapour pressure of pydiflumetofen is therefore within the specified range for low volatility substances at 20 °C.

Exposure to bystanders and residents has been calculated using the EFSA Calculator. A summary of the estimated longer term resident exposure to pydiflumetofen for the proposed uses of 'Miravis Plus' is provided in the following table. Outputs of the EFSA Calculator are presented in Appendix 1 (Estimate 2).

Table B.6.4.2-1: Estimated resident (longer term) exposure to pydiflumetofen from the uses of 'Miravis Plus' and comparison with AOEL

Model: EFSA Calculator version 30/03/2015

		Pydiflumetofen	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL (0.05 mg/kg bw/day)
Vehicle mounted boom spray application outdoors to cereals Buffer zone: 2-3 (m) Drift reduction technology: No DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 365 days			
Number of applications and application rate		1 x 0.2 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.0059	12
	Vapour (75 th perc.)	0.0011	2
	Deposits (75 th perc.)	0.0004	1
	Re-entry (75 th perc.)	0.0037	7
	Sum (mean)	0.0076	15
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0014	3
	Vapour (75 th perc.)	0.0002	<1
	Deposits (75 th perc.)	0.0001	<1
	Re-entry (75 th perc.)	0.0021	4
	Sum (mean)	0.0027	5

For the proposed uses of 'Miravis Plus', the predicted longer term exposures to a child and adult resident are within acceptable limits for all exposure pathways, with the sum of 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.

A summary of the estimated bystander (acute) exposure to pydiflumetofen for the proposed uses of 'Miravis Plus' is provided in the following table. Outputs of the EFSA Calculator are presented in Appendix 1 (Estimate 3).

Table B.6.4.2-2: Estimated bystander (acute) exposure to pydiflumetofen from the uses of 'Miravis Plus' and comparison with AAOEL

Model: EFSA Calculator version 30/03/2015

		Pydiflumetofen	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AAOEL (0.15 mg/kg bw/day)
Vehicle mounted boom spray application outdoors to cereals Buffer zone: 2-3 (m) Drift reduction technology: No DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 365 days			
Number of applications and application rate		1 x 0.2 kg a.s./ha	
Resident child	Drift (75 th perc.)	0.0136	9

Body weight: 10 kg	Vapour (75 th perc.)	0.0011	1
	Deposits (75 th perc.)	0.0012	1
	Re-entry (75 th perc.)	0.0037	2
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0037	2
	Vapour (75 th perc.)	0.0002	<1
	Deposits (75 th perc.)	0.0005	<1
	Re-entry (75 th perc.)	0.0021	1

For the proposed uses of 'Miravis Plus', the predicted acute exposure of a child and adult bystander 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.

B.6.4.3. Worker exposure

A Tier 1 estimate of worker exposure is presented based on the highest application rate and the highest dermal absorption values (worst-case scenario). A summary of the estimated longer term worker exposure to pydiflumetofen for the proposed uses of 'Miravis Plus' is provided in the following table. Outputs of the EFSA Calculator are presented in Appendix 1 (Estimate 4).

Note: It is not possible to provide an assessment of acute exposure to workers using the EFSA calculator as available data are not reliable enough (for example the transfer coefficient and dislodgeable foliar residues input parameters).

Table B.6.4.3-1: Estimated longer term worker exposure to pydiflumetofen from the uses of 'Miravis Plus' and comparison with AOEL

Model: EFSA Calculator version 30/03/2015

		Pydiflumetofen	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL (0.05 mg/kg bw/day)
Inspection/irrigation Outdoor Work rate: 2 hours/day DT50: 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 365 days			
Application rate		1 x 0.2 kg a.s./ha	
Body weight: 60 kg	Work wear (arms, body and legs covered) TC: 1400 cm ² /person/h	0.0031	6

Based on the EFSA Calculator, the predicted longer term systemic exposure for a worker undertaking inspection/irrigation activities is calculated to be equivalent to 6% of the AOEL of pydiflumetofen for a worker wearing normal workwear (arms, legs and body covered). The predicted worker exposure is within acceptable levels and no further risk assessment is required.

B.6.5. EXPOSURE AND RISK ASSESSMENT

B.6.5.1. 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.

B.6.5.2. 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.

B.6.5.3. 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).

B.6.6. REFERENCES RELIED ON

Data Point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCP 7.3	██████ ██████ ██████	05/01/ 2017	Pydiflumetofen EC (A21857B) - The In Vitro Percutaneous Absorption of Radiolabelled Pydiflumetofen in Concentrate Formulation and Two In Use Dilutions Through Human Split Thickness Skin Report No. 37801 Document No. VV-466646 , A21857B_10002 Test Facility Charles River Laboratories GLP Unpublished	N	Y	Data/study report never submitted before to this country	SYN	N

B.6.7. REFERENCE LIST

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.

APPENDIX 1: EXPOSURE CALCULATIONS

Estimate 1: EFSA Calculator estimate of exposure for operators applying 'Miravis Plus': vehicle mounted boom sprayer; no PPE

Model input

Substance name	Pydiflumetofen
Product name	Miravis Plus'
Reference value non acutely toxic active substance (RVNAS)	0.05 mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)	0.15 mg/kg bw/day
Crop type	Cereals
Substance properties	
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.
Minimum volume water for application (liquids)	100 L/ha
Maximum application rate of active substance	0.2 kg a.s. /ha
50% Dissipation Time DT50	30 days
Initial Dislodgeable Foliar Residue	3 µg/cm ² of foliage/kg a.s. applied/ha
Dermal absorption of product	0.40%
Dermal absorption of in-use dilution	11.00%
Oral absorption of active substance	50.00%
Inhalation absorption of active substance	100.00%
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10 ⁻³ Pa
Scenario	
Indoor or Outdoor application	Outdoor
Application method	Downward spraying
Application equipment	Vehicle-mounted
Buffer strip	2-3 m
Number of applications	1
Interval between multiple applications	365 days
Season (upward spraying orchards only)	not relevant

Operator exposure for Miravis Plus' outdoor spray applications

Application rate of active substance	0.2 kg a.s./ha	<i>i_AppRate</i>
Assumed area treated	50 ha/day	<i>d_AreaTreated</i>
Amount of active substance applied	10 kg a.s./day	<i>i_AmountAS</i>
Dermal absorption of the product	0.40%	<i>i_AbsorpProduct</i>
Dermal absorption of in-use dilution	11.00%	<i>i_AbsorInuse</i>
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Season	not relevant	

Mixing and loading	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75 th centile	95 th centile		
	Hands	28588	106902	AOEM	
	Body	17999	140606	AOEM	
	Head	519	2846	AOEM	
	Protected hands (gloves)	154	1981	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	183	1463	AOEM	
	Protected head (hood and face shield)	8	161	AOEM	
	Inhalation	7	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
Application	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	
	Exposure values	µg exposure/day applied		Reference	Comment
		75 th centile	95 th centile		
	Hands	1483	12376	AOEM	
	Body	829	4275	AOEM	
	Head	39	118	AOEM	
	Protected hands (gloves)	148	4360	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	23	56	AOEM	
	Inhalation	3	11	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE
Longer term		
Total systemic exposure from mixing, loading and application (mg a.s./day)	0.4577478	0.2977582
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0076291	0.0049626
% of RVNAS	15.26%	9.93%
Acute		
Total systemic exposure from mixing, loading and application (mg a.s./day)	2.8872756	1.8665737
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0481213	0.0311096
% of RVAAS	32.08%	20.74%

Estimate 2: EFSA Calculator – Child and Adult Resident (longer term) exposure for vehicle mounted outdoor boom spray application

Resident exposure for Miravis Plus'					
Croptype			Cereals		
Application method			Downward spraying		
Application equipment			Vehicle-mounted		<i>l_AppEquip</i>
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.				<i>i_FormVal</i>
Buffer strip			2-3 m		<i>i_Buffer</i>
Application rate of the product			0.2 kg a.s./ha		<i>i_AppRate</i>
Concentration of active substance (in-use dilution for liquid applications)			2 g a.s./l		<i>d_ConcAS</i>
Dermal absorption of product			0.40%		<i>l_AbsorpProduct</i>
Dermal absorption of in-use dilution			11.00%		<i>l_AbsorpInuse</i>
Oral absorption			50.00%		<i>l_AbsorpOrallnuse</i>
Dislodgeable foliar residue (<i>i_AppRate</i> * <i>i_DFR</i>)			0.6 µg a.s./cm ²		<i>d_DFR</i>
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa		Pa		<i>l_Volat</i>
Concentration in air			0.001 mg/m ³		<i>d_AirCon</i>
Resident dermal spray drift exposure 75th percentile - adult			0.47 ml spray dilution/person		
Resident dermal spray drift exposure 75th percentile - child			0.327 ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - adult			0.00010 ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - child			0.00022 ml spray dilution/person		
Resident dermal spray drift exposure mean - adult			0.22318 ml spray dilution/person		
Resident dermal spray drift exposure mean - child			0.18 ml spray dilution/person		
Resident inhal. spray drift exposure mean - adult			0.00009 ml spray dilution/person		
Resident inhal. spray drift exposure mean - child			0.00017 ml spray dilution/person		
Exposure duration dermal			2 hours		<i>d_ReExpDur</i>
Exposure duration inhalation			24 hours		<i>d_ReExpDurInhal</i>
Exposure duration entry into treated crops			0.25 hours		<i>d_ExpDurTreatCrop</i>
Light clothing adjustment factor			18.0%		<i>d_ClothAF</i>
Breathing rate adult			0.23 m ³ /day/kg		<i>d_BreathRAD</i>
Breathing rate child (1-3 year old)			1.07 m ³ /day/kg		<i>d_BreathRCh</i>
Drift percentage on surface (75th percentile)			5.60%		
Drift percentage on surface (mean)			4.10%		
Turf transferable residues percentage			5.00%		<i>d_Turf</i>
Transfer coeff. of surface deposits-adult			7300 cm ² /hour		<i>d_ReTCAd</i>
Transfer coeff. of surface deposits-child (1-3 year old)			2600 cm ² /hour		<i>d_ReTCCh</i>
Saliva extraction percentage			50.00%		<i>d_SalExt</i>
Surface area of hands mouthed			20 cm ²		<i>d_AreaHIM</i>
Frequency of hand to mouth activity			9.5 events/hour		<i>d_ReFreqHM</i>
Ingestion rate for mouthing of grass per day			25 cm ²		<i>d_MouthGrass</i>
Dislodgeable residues percentage transferability for object to mouth			20.00%		<i>d_DRP</i>
Transfer coefficient for entry into treated crops (75th percentile) - ad			7500 cm ² /h		<i>d_TcEntryAd</i>
Transfer coefficient for entry into treated crops (75th percentile) - chi			2250 cm ² /h		<i>d_TcEntryCh</i>
Transfer coefficient for entry into treated crops (mean) - adult			5980 cm ² /h		<i>d_TcEntryAd</i>
Transfer coefficient for entry into treated crops (mean) - child			1794 cm ² /h		<i>d_TcEntryCh</i>
1. Total					
1.1 1-3 year old child					
Spray drift (75th percentile)		Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0594308	0.0107000	0.0040152	0.0371250	0.0760527
Total systemic exposure per kg body weight (mg a.s./day/kg)	0.0059431	0.0010700	0.0004015	0.0037125	0.0076053
% of RVNAS	11.89%	2.14%	0.80%	7.43%	15.21%
1.2 Adult					
Spray drift		Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0849880	0.0138000	0.0089936	0.1237500	0.1594963
Total systemic exposure per kg body weight (mg a.s./day/kg)	0.0014165	0.0002300	0.0001499	0.0020625	0.0026583
% of RVNAS	2.83%	0.46%	0.30%	4.13%	5.32%

Estimate 3: EFSA Calculator – Child and Adult Bystander (acute) exposure for vehicle mounted outdoor boom spray application

Bystander exposure for Miravis Plus ¹				
Croptype	Cereals			
Application method	Downward spraying			
Application equipment	Vehicle-mounted			i_AppEquip
Formulation type	soluble concentrates, emulsifiable concentrate, etc.			
Application rate of the product	0.2 kg a.s./ha			i_AppRate
Buffer strip	2-3 m			i_Buffer
Concentration of active substance (in-use dilution for liquid applications)	2 g a.s./l			d_ConcAS
Dermal absorption of product	0.40%			i_AbsorpProduct
Dermal absorption of in-use dilution	11.00%			i_AbsorpInuse
Oral absorption	50.00%			i_AbsorpOrallnuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.6 µg a.s./cm ²			d_DFR
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10 ⁻³ Pa			i_Volat
Concentration in air	0.001 mg/m ³			d_AirCon
Bystander dermal spray drift exposure - adult	1.21 ml spray dilution/person			
Bystander dermal spray drift exposure - child	0.74 ml spray dilution/person			
Bystander inhal. spray drift exposure - adult	0.00050 ml spray dilution/person			
Bystander inhal. spray drift exposure - child	0.00112 ml spray dilution/person			
Exposure duration	2 hours			d_ByExpDur
Exposure duration entry into treated crops	0.25 hours			d_ExpDurTreatCrap
Light clothing adjustment factor	18.0%			d_ClothAF
Breathing rate adult	0.23 m ³ /kg bw/day			d_BreathRAd
Breathing rate child (1-3 year old)	1.07 m ³ /kg bw/day			d_BreathRCh
Drift percentage on surface (90th percentile)	8.50%			
Turf transferable residues percentage	5.00%			d_Turf
Transfer coeff. of surface deposits-adult	14500 cm ² /hour			d_ByTCAd
Transfer coeff. of surface deposits-child (1-3 year old)	5200 cm ² /hour			d_ByTCCh
Saliva extraction percentage	50.00%			d_SalExt
Surface area of hands mouthed	20 cm ²			d_AreaHM
Frequency of hand to mouth activity	20 events/hour			d_ByFreqHM
Ingestion rate for mouthing of grass per day	25 cm ²			d_MouthGrass
Dislodgeable residues percentage transferability for object to mouth	20.00%			d_DRP
Transfer coefficient for entry into treated crops - adult	7500 cm ² /h			d_TcEntryAd
Transfer coefficient for entry into treated crops - child	2250 cm ² /h			d_TcEntryCh
1. Total				
1.1 1-3 year old child				
	Spray drift	Vapour	Surface deposits	Entry into treated crops
Total systemic exposure (mg a.s./day)	0.1357360	0.0107000	0.0118490	0.0371250
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0135736	0.0010700	0.0011849	0.0037125
% of RVAAS	9.05%	0.71%	0.79%	2.48%
1.2 Adult				
	Spray drift	Vapour	Surface deposits	Entry into treated crops
Total systemic exposure (mg a.s./day)	0.2192840	0.0138000	0.0271150	0.1237500
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0036547	0.0002300	0.0004519	0.0020625
% of RVAAS	2.44%	0.15%	0.30%	1.38%

Estimate 4: EFSA Calculator – Worker (longer term) exposure for inspection/irrigation activities

Worker exposure from residues on foliage for Miravis Plus'			
Crop type	Cereals		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Inspection, irrigation		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.2 kg a.s./ha		
Number of applications	1		
Interval between multiple applications	365 days		
Half-life of active substance	30 days		
Multiple application factor	1.0		
Dermal absorption of the product	0.40%		
Dermal absorption of the in-use dilution	11.00%		
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.6 µg a.s./cm ²		
Working hours	2 hr		
Dermal transfer coefficient - Total potential exposure	12500 cm ² /hr		
Dermal transfer coefficient - arms, body and legs covered	1400 cm ² /hr		
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment	cm ² /hr	
Inhalation transfer coefficient for automated applications	NA ha/hr*10 ^{^(-3)}		
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10 ^{^(-3)}		
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10 ^{^(-3)}		
1. Total			
	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves
Total systemic exposure (mg a.s./day)	1.6500000	0.1848000	no TC available for this assessment
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0275000	0.0030800	
% of RVNAS	55.00%	6.16%	