Metiram negligible exposure dossier – human non-dietary exposure assessment

[redacted]

BASF SE
Environmental health and safety
Product Safety (FEP)
[redacted]

Date: May 21st, 2019
BASF DocID 2019/1075961

Inhaltsverzeichnis

List of Tables

1 Introduction

EFSA has concluded that the scientific criteria for the determination of endocrine disrupting (ED) properties are met for metiram. As such, information is requested to demonstrate that metiram may be used such that estimated human exposure is negligible, and/or documentary evidence for the application of the derogation under Art. 4(7)2 of Regulation (EC) No. 1107/2009

The Commission Regulation (EC) No. 1107/2009 (Annex II, 3.6.5) states, that

"An active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, including a review of the scientific literature, reviewed by the Authority, it not considered to have endocrine disrupting properties that may cause adverse effect in humans, unless the exposure of humans to that 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 cloded systems or in other conditions excluding contact with humans and where residued of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005."

With regard to negligible exposure, the recommendations given in the Sanco Draft Guidance, 2015 (https://ec.europa.eu/food/sites/food/files/safety/docs/adv-grp_wg_20150625_tech-guidance.pdf) were consulted and a negligible exposure with regard to dietary exposure is considered, if the residues are below 0.01 mg/kg. For non-dietary exposure, a margin of exposure of ≥ 1000 is considered to represent a negligible exposure situation, if shown for operators, workers, bystander and residents. The following reference values have been used for metiram and the relevant metabolite ETU:

Table 1: Agreed reference values of metiram and ETU (taken from the List of endpoints RAR Italy (October 2017))

Compounds	ADI	ARfD	AOEL
Metiram	0.03 mg/kg bw	0.4 mg/kg bw	0.016 mg/kg bw
ETU	0.002 mg/kg bw	0.05 mg/kg bw	0.005 mg/kg bw

The following assessment addresses the following areas:

I Comments on the ED Assessment of metiram with regard to human health
II Dermal absorption of metiram
III Dermal absorption of ETU
IV Demonstration of negligible exposure to metiram and ETU conducting non-dietary exposure assessment

The demonstration of negligible exposure to metiram and ETU conducting dietary exposure assessment had been conducted in a separate updated dossier (BASF DocID 2019/1075956), which will be submitted together with this document and a negligible exposure document with regard to non-target organisms.

The GAP considered is for use of polyram (BAS 222 28 F) on potato only, at up to three applications of 1.26 kg a.s./ha, at BBCH 21 to 89.

2 Comments on the ED Assessment of metiram with regard to human health

In the Peer Review Meeting the experts agreed on the endocrine disrupting properties of metiram with regard to human health as follows:

"*Experts agree that completeness of the dataset is sufficient for the assessment of all the modalities. Metiram is considered not to meet the criteria of EAS mediated adversity. However, adverse effects (T-mediated) on thyroid weight and/or histopathology were observed in several species (rat, mouse and dog), incidence in thyroid tumours in rat study. Furthermore, changes in thyroid hormones levels in blood were observed in rat and dog.*
These effects were observed below MTD. The endocrine mode of action (MoA) is postulated as follows: decreased production of thyroid hormones (T4, T3), increased TSH levels, thyroid follicular cell hypertrophy, increased thyroid weight, thyroid follicular cell hyperplasia, tumours of the thyroid gland (adenomas and carcinomas)."

Thyroid changes (weights, histopathology, blood hormones) are seen after metiram treatment in rats and dogs, at higher doses also thyroid weight and histopathological changes in mice. The observed thyroid tumour incidences seen in rat carcinogenicity study are not considered treatment-related, as they were within HCDs. There is no evidence for thyroid tumors in mice. A CLH intention on zinc ammoniate ethylenebis(dithiocarbamate)-poly[ethylenebis(thiuramdisulfide)]; metiram has been send from Italy to ECHA, however a final decision on treatment relationship of the effects and the classification on carcinogenicity has not been taken yet. There are no conclusive ED mode of action studies available on metiram. For one of the rat metabolites of metiram (ETU), ED mode of action studies are available, with evidence for reversible TPO (thyroid peroxidase) inhibition.

According to the ECHA/EFSA Guidance Document, 2018, thyroid effects seen in animal studies shall be further assessed following the Appendix A of the document. Considering adverse outcome pathways of thyroid (-related) effects, two adverse outcomes are of relevance: 1. Thyroid tumors (which are not clearly induced by metiram) and 2. Adverse neurodevelopment, (for which no indication is seen in the available animal studies). Furthermore, there are known physiological differences between animal species and humans with regard to thyroid hormone homeostasis (e.g. binding to transport proteins, T4-half-lives are much faster in rats and dogs compared to humans (Janssen & Janssen, 2017)). These pharmacokinetic and pharmacodynamic differences are also observed, when internal thyroid hormones are measured in rats and humans after treatment with propyl thiouracil (Kampmann and Molholm Hansen, 1981 and Francis and Rennert, 1980)

Thus, - based on the absence of clear evidence for metiram-induced thyroid tumors or adverse neurodevelopment, and lacking ED mode of action studies for metiram - it is inappropriate to conclude on endocrine disrupting properties of metiram relevant to humans, based on the available data.

3 Dermal absorption of metiram

Metiram is a polymer and as such not assumed to be readily absorbable through the skin. A new *in vitro* dermal penetration had been conducted with radioactive metiram in metiram technical (= BAS 222 29 F), as aqueous preparation through human skin. The data from the in vitro dermal penetration, which had been conducted in 2018 were evaluated according to the new EFSA guidance 2017 and revealed values of 0.064% and 0.3% dermal absorption for the concentrate and the dilution respectively (Fabian & Landsiedel, 2018, BASF DocID 2018/1048747).

Metiram technical (= BAS 222 29 F) is essentially similar to the solo formulation BAS 222 28 F. A detailed comparison is provided in the table below:

Table 2: Comparison between BAS 222 29 F and BAS 222 28 F

Chemical name	**Cas.No.**	**% w/w BAS 222 29 F**	**% w/w BAS 222 28 F**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted] is an inert polymer and thereby not contributing to dermal absorption of metiram. The minor amounts of [redacted] and [redacted] in BAS 222 28 F, are also not assumed to contribute to dermal penetration of metiram, especially when considering the dilution factor used for spray dilutions in the field, which are mimicked by dermal penetration studies (factors of 1:1 aqueous dilutions used for the concentrate and 1:300 – 1:700 for the spray dilution).

Skin irritation studies of BAS 222 29 F and BAS 222 28 F did not qualify for labelling. Furthermore, Assessint the early timepoints of the in vivo skin irritation study, conducted with BAS 222 28 F, in the 1 h or 4 h timepoint after application of the pure formulation to rabbit´s skin, grade 1 erythema were seen in the BAS 222 28 F study only, but no edema, which might contribute to increased dermal penetrations.

More generally, dermal penetration of polymers (MW > 500 Da; topological surfaces > 120 Angstrom) is not assumable and analytical investigations conducted in the dermal penetration study (2018/1048747) gave evidence, that the polymer was stable in the aqueous application solution with only <2% degradation to smaller molecules occurring.

For the purpose of this negligible exposure document, the dermal penetration values of **0.064 and 0.3% of metiram in BAS 222 28 F** are used. For further clarification of the values a further dermal penetration study of metiram in BAS 222 28 F is currently conducted. The experiment starts in calender week 21 and the first results will be available at the end of June 2019.

4 Dermal penetration of ETU

Dermal penetration values of 12 and 17% were derived for the in vitro dermal penetration study of ETU, when the study results were assessed according to EFSA Guidance 2012. When a re-assessment is done following the EFSA Guidance 2017, the same values are found. Thus, dermal penetration values of 12% and 17% are used for the non-dietary risk assessment of ETU in this negligible exposure dossier.

5 Demonstration of negligible exposure to metiram and ETU conducting non-dietary exposure assessment

Exposure assessments and risk evaluations to demonstrate negligible exposure for operators, workers, bystanders and residents are presented below for the representative formulation BAS 222 28 F, when applied in potatoes, based on the current exposure models and higher tier study data where applicable.

Note: Besides to metiram operators, bystander, residents and re-entry worker are expected to be exposed to a certain extend to the contained impurity and degradation product ethylenethiourea [ETU, Imidazolidine-2-thione (IUPC), CAS 96-45-7] as well.
Exposure and risk evaluations are thus shown for metiram and ETU.

The toxicological reference value (Acceptable Operator Exposure Level) for metiram and dermal absorption values appropriate for BAS 222 28 F, which were used in the non-dietary risk assessment are shown in Table 3 below.

Table 3: Endpoints for metiram used in non-dietary risk assessment

Endpoint		**Value**	**Reference**
Metiram	Dermal penetration - Concentrate - Spray dilutions	0.064% 0.3%	See section 3 above
	AOEL	0.016 mg/kg bw/day	SANCO/4059/2001. Rev. 3.3.2005 and List of endpoints RAR metiram, (October 2017)

The toxicological reference values (Acceptable Operator Exposure Level) for the metabolite and dermal absorption values appropriate for exposure assessment after application of BAS 222 28 F are shown in Table 4.

Table 4: Endpoints for metabolites ETU used in non-dietary risk assessment

		Value	**Reference**
ETU	Dermal penetration - Concentrate - Spray dilutions	 12% 17%	See section 4 above
	AOEL	0.005 mg/kg bw/day	See List of Endpoints RAR metiram (October 2017)

In the following a negligible exposure assessment for the derogation assessment of metiram is provided. The plant protection product BAS 222 28 F is assessed for the already registered use as fungicide in potatoes using broadcast ground boom application. Information on the critical use pattern relevant for operator exposure is summarised in Table 5.

Table 5: Summary of critical use pattern

Crop (indoor / field)	**Application rate** (g as/ha)		**Spray dilution** (L/ha)	**Application equipment**	**Number of applications**
Potatoes (field)	metiram	1260	100 (up to 1000)	Tractor mounted/drawn groundboom sprayer	3

Negligible exposure for all relevant exposure groups i.e. operator, resident and bystander as well as re-entry worker could be demonstrated considering exposure to metiram and ETU from the use of BAS 222 28 F in potatoes

5.1 Operator exposure

Estimation of potential operator exposure is shown below for BAS 222 28 F considering the intended use and the following predictive models:

- EFSA guidance: European Food Safety Authority (2014) Guidance on the Assessment of Exposure for Operators, Workers, Residents and Bystanders in Risk Assessment for Plant Protection Products EFSA Journal 2014;12(10):3874 [55 pp.]. doi:10.2903/j.efsa.2014.3874 .

Risk assessment for operator

The estimated operator exposure to metiram for the use of BAS 222 28 F in potatoes is shown in Table 6 below.

Table 6: Estimated operator exposure to metiram in BAS 222 28 F

Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)[1]	% of AOEL[2]
Outdoor tractor operated sprayer application to low field crops – potatoes 1.8 kg BAS 222 28 F/ha corresponding to 1260 g metiram per ha			
AOEM - 50 ha/day - 60 kg operator	Gloves and coverall during all operations, respiratory PPE (FP1, P1 and similar) during mixing/loading	0.00069	4.3

[1] systemic exposure based on dermal absorption of 0.064% for mixing/loading and 0.3% for application
[2] based on a systemic AOEL of 0.016 mg/kg bw/day

Operators may also experience co-exposure to the metabolite ETU. Additional exposure and risk evaluations for the metabolite ETU were performed based on tier 1 model of the EFSA guidance. On the condition of operators wearing no PPE safe uses could be shown. Results are presented in the table below.

Table 7: Estimated operator exposure to ETU in BAS 222 28 F

Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)[1]	% of AOEL
Outdoor tractor operated sprayer application to low field crops – potatoes 1.8 kg BAS 222 28 F/ha corresponding to 1260 g metiram per ha			
AOEM - 50 ha/day - 60 kg operator	None	0.00022	**4.3**

[1] systemic exposure based on dermal absorption of 12% for mixing/loading and 17% for application
[2] based on the proposed AOEL of 0.005 mg/kg bw/day

5.1.1 Estimation of operator exposure

BAS 222 28 F is applied in field crops (potatoes), which is professional uses only. The relevant application scenario is outdoor tractor operated groundboom application systems. Risk assessments are based on the EFSA guidance model with consideration of the following input parameters. As this assessment aims to demonstrate use conditions of negligible exposure only the exposure scenario that fulfils the criteria is shown here.

Table 8: AOEM input parameters for tractor operated sprayer application

Application rate of active substance	1.26	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	63	kg a.s./day	*i_AmountAS*
Dermal absorption of the product	0.06%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	0.30%		*i_Absorbure*
Formulation type	Wettable granules, soluble granules		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted-Drift Reduction		
Season	not relevant		

	Exposure value	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	31825	157427	AOEM	
	Body	22725	53553	AOEM	
	Head	409	5641	AOEM	
	Protected hands (glover)	245	1983	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	732	3920	AOEM	
	Protected head (hood and face shield)	7	319	AOEM	
	Inhalation	128	286	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Glover	Yes		incl. in AOEM model	
	Clothing	workwear - arms, body and legs covered		incl. in AOEM model	
	Head and respiratory PPE	FP1, P1 and similar		0.5	0.25
	Water soluble bag	No		1	

	Exposure value	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	3954	11661	AOEM	
	Body	812	825	AOEM	
	Head	32	69	AOEM	
	Protected hands (glover)	31	87	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	28	32	AOEM	
	Inhalation	8	15	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Glover	Yes		incl. in AOEM model	
	Clothing	workwear - arms, body and legs covered		incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted	

Estimation of operator exposure without personal protective equipment

While for metiram personal protective equipment is required when applied in BAS 222 28 F to potatoes to demonstrate negligible exposure, co-exposure to the metabolite ETU fulfils the negligible exposure criteria less than 10% of the AOEL already with the worst-case scenario of potential exposure as demonstrated in the Table 9 below.

Table 9: Estimated operator exposure to ETU in BAS 222 28 F without using PPE

	Operation	Route of exposure	Metiram Actual exposure (mg/day)	ETU Adjustment factor*	ETU % absorption	ETU Predicted systemic exposure (mg/day)	ETU % AOEL
AOEM **Crop:** potatoes **Source of metiram data: Appendix 8. 1**	**Mixing loading**	**Inhalation**	**0.1281**	**0.001**	**100**	**0.00013**	**0.04**
		Dermal	54.96	0.001	12	0.00659	2.20
	Application	Inhalation	0.0081	0.0075	100	0.00006	0.02
		Dermal	4.79	0.0075	17	0.00010	2.04
Total exposure (all routes for mixing/loading and application combined)						**0.00022**	**4.30**

Without PPE, longer term assessment based on the ETU AOEL of 0.005 mg/kg bw/ predict safe use for the AOEM.

Estimation of operator exposure with personal protective equipment

Exposure predictions for operators using protective equipment (PPE) are summarized in Table 10.

Table 10: Estimated operator exposure to metiram in BAS 222 28 F using PPE

Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)[1]	% of AOEL[2]	Reference in Appendix
Outdoor tractor operated sprayer application to low crops – potatoes 1.8 kg BAS 222 28 F/ha corresponding to 1260 g metiram per ha				
AOEM - 50 ha/day - 60 kg operator	Gloves and coverall during mixing/loading and application, RPE (FP1, P1 or similar) during mixing/loading	0.00069	4.3	Appendix 8. 2

[1] systemic exposure based on dermal absorption of 0.064% for mixing/loading and 0.3% for application
[2] based on a systemic AOEL of 0.016 mg/kg bw/day

Estimation of operator exposure to ETU

Additional estimation of operator exposure to the metabolite ETU if protective equipment as required for metiram i.e. protective gloves and RPE is considered is presented in the Table 11 below.

Table 11: Estimated operator exposure to ETU in BAS 222 28 F using PPE

	Operation	Route of exposure	Metiram Actual exposure (mg/day)	ETU Adjust-ment factor*	ETU % absorption	ETU Predicted systemic exposure (mg/day)	ETU % AOEL
AOEM Crop: **potatoes** Source of metiram data: Appendix 8. 2	Mixing loading	Inhalation	0.1281	0.001	100	0.00013	0.04
		Dermal	1.3859	0.001	12	0.00017	0.06
	Application	Inhalation	0.0081	0.0075	100	0.00006	0.02
		Dermal	0.0923	0.0075	17	0.00012	0.04
Total exposure (all routes for mixing/loading and application combined)						0.00047	**0.16**

*Derived from 0.1% ETU relative to metiram contained in the undiluted preparation and 0.75% (maximum estimate) contained in the spray dilute
²AOEL proposed for ETU: 0.005 mg/kg bw

Exposure assessments to metiram
With PPE, model assessments (AOEM) showed a safe use according to the criteria of negligible exposure of metiram when applied in BAS 222 28 F under the condition wearing gloves and long-sleeved clothing during mixing/loading and application and applying respiratory protective equipment (FP1, P1 or similar) during mixing/loading. Predicted exposure levels are 4.3% of the proposed AOEL (0.016 mg/kg bw/day).

Exposure assessments to ETU
Without consideration of PPE the exposure assessment to ETU gave already acceptable risk for potatoes based on the AOEM. Applying the PPE and RPE recommended for metiram the estimated exposure is 0.16% of the AOEL for ETU.

In conclusion for operators applying the active substance metiram in the preparation BAS 222 28 F to potatoes, safe use according to the negligible exposure criteria can be demonstrated if protective clothing (gloves) is worn during mixing/loading and application and in addition respiratory protective equipment is applied during mixing/loading.
Under the same condition negligible can also be demonstrated for ETU.

5.1.2 Measurement of operator exposure

Since a negligible exposure of the operator could be demonstrated applying the standard model according to EFSA guidance no higher tier assessment und thus no measurement of operator exposure was considered necessary.

5.2 Bystander and resident exposure

The plant protection product BAS 222 28 F is already registered for the use as fungicide in potatoes. The critical GAP is summarised in Table 5.

At EU level the EFSA guidance model for bystander and resident exposure assessment is in place as tier 1 approach.

- Guidance for the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products
  EFSA Journal 2014;12(10):3874

For compounds that have no acute risk and thus no AAOEL is derived the resident exposure assessment is considered to cover exposure of bystander as well given the shorter duration of exposure. Residents may be in addition be exposed to the relevant degradation product ETU. Exposure assessments following the principles of the model used for metiram were performed.
Exposure assessments and risk evaluations for residents for the representative formulation BAS 222 28 F are presented below.

Risk assessment for bystander and resident

A summary of the risk assessment for residents is provided in Table 12 for metiram and Table 13 for ETU.

Table 12: Summary of resident exposure following application of BAS 222 28 F in potatoes

EFSA model approach with 10 m drift estimates, drift reduction nozzles [see Appendix 8. 3]				
	Adults		**Children**	
	Predicted systemic exposure (mg/kg bw/day	**% proposed AOEL²**	**Predicted systemic exposure (mg/kg bw/day**	**% proposed AOEL²**
Spray drift	0.000031	0.19%	0.00018	1.1%
Vapour	0.00023	1.4%	0.0011	6.7%
Surface deposits	0.0000077	0.048%	0.00020	1.2%
Entry treated crops	0.00091	5.7%	0.0016	10%
All pathways (mean)	0.0010	6.1%	0.0026	17%
EFSA refined approach based on product specific DFR of 0.74 µg/cm² and foliar DT_{50} of 7 days with 10 m drift estimates, drift reduction nozzles [see Appendix 8. 4]				
	Adults		**Children**	
	Predicted systemic exposure (mg/kg bw/day	**% proposed AOEL²**	**Predicted systemic exposure (mg/kg bw/day**	**% proposed AOEL²**
Spray drift	0.000031	0.19%	0.00018	1.1%
Vapour	0.00023	1.4%	0.0011	6.7%
Surface deposits	0.0000052	0.033%	0.00014	0.85%
Entry treated crops	0.00015	1.0%	0.00028	1.7%
All pathways (mean)	0.00037	2.3%	0.0015	9.4%

[1] According to the EFSA guidance resident exposure model
[2] Based on a systemic AOEL of 0.016 mg/kg bw/day for metiram.

For ETU a negligible exposure is demonstrated based on the refined EFSA approach applied for metiram as summarized in Table 13 below.

Table 13: Summary of resident exposure to ETU and % of the AOEL following the application of BAS 222 28 F in potatoes

Exposure group	Pathway of exposure	ETU Predicted systemic exposure (mg/kg bw/day)	ETU % AOEL
Adult	Spray drift	0.000011	0.22
	Vapour	0.0000017	0.035
	Surface deposits	0.0000022	0.044
	Entry treated crops	0.000065	1.3
	All pathways (mean)	0.000061	1.2
Child	Spray drift	0.000059	1.2
	Vapour	0.0000080	0.16
	Surface deposits	0.0000054	0.11
	Entry treated crops	0.00012	2.3
	All pathways (mean)	0.00034	6.8

[1] Proposed AOEL of ETU = 0.005 mg/kg bw/day i.e. 5 µg/kg bw/day

Assessment
When considering individual exposure pathways the assessment for metiram demonstrates the negligible exposure. There, is however a somewhat higher exposure notable for children when considering a combined exposure by all pathways. Applying product specific information on dislodgeable foliar residue and residue decline negligible exposure can be demonstrated for both metiram and the metabolite ETU.
Since no AAOEL is considered necessary for metiram and thus no risk from acute exposure is assumed the bystander is covered by the resident exposure assessment provided.

Conclusion
In conclusion accidental exposure of residents and bystanders to metiram and ETU due to the use of BAS 222 28 F in potatoes is considered negligible.

5.2.1 Estimation of bystander and resident exposure

Bystanders and residents are not involved in application or handling of plant protection products or the professional handling of treated crops. Therefore, exposure differs significantly from operator or worker exposure levels. The exposure assessment presented for metiram and ETU below is based on the EFSA guidance model.

A. Resident exposure

Residents are persons who live, work or attend any institution adjacent to an area that has been treated with a plant protection product. Possible situations are persons who are standing, working, or sitting in a garden in the vicinity of the application. They may be exposed to the plant protection products mainly via the dermal route from spray drift deposits and by inhalation of vapour drift

depending on the vapour pressure of the active substances. Furthermore, they may unintendedly enter treated crops after treatment or may come into contact with surface deposits of the plant protection product that have drifted off. For infants and toddlers oral exposure via hand-to-mouth transfer or object-to-mouse transfer has to be considered, too.
It can be assumed that residents are unlikely to take actions to avoid or control exposure, and they wear only light clothing and no protective equipment. In addition, as conservative approach it is assumed that residents are located directly downwind of the centre of the treatment area from the point of spray emission caused by professional agricultural uses.

It can be assumed that the exposure duration of residents being in a garden is longer than the exposure duration of bystanders who just pass by the treated area for some minutes. Therefore, the default exposure duration of 2 hours is adopted for risk evaluations and exposure to vapour is considered for a whole day.

The parameters applied in the EFSA guidance model are summarized below:

Table 14: Parameters for EFSA guidance assessment of residential exposure for metiram when applied in BAS 222 28 F

Resident exposure for BAS 222 28 F / Polyram DF				
Croptype	Root and tuber vegetables			
Application method	Downward spraying			
Application equipment	Vehicle-mounted-Drift Reduction			i_AppEquip
Formulation type	Wettable granules, soluble granules			i_FormTyp
Buffer strip	10	m		i_Buffer
Application rate of the product	1.26	kg a.s./ha		i_AppRate
Concentration of active substance (in-use dilution for liquid applications)	6.3	g a.s./l		d_ConcAS
Dermal absorption of product	0.1%			i_AbsorpProduct
Dermal absorption of in-use dilution	0.30%			i_Absorpinuse
Oral absorption	60%			i_AbsorpOralInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	3.78	µg a.s./cm²		d_DFR
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa	Pa		i_Volat
Concentration in air	0.001	mg/m³		d_AirCon
Resident dermal spray drift exposure 75th percentile - adult	0.20385	ml spray dilution/person		
Resident dermal spray drift exposure 75th percentile - child	0.17965	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - adult	0.00009	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - child	0.00013	ml spray dilution/person		
Resident dermal spray drift exposure mean - adult	0.10973	ml spray dilution/person		
Resident dermal spray drift exposure mean - child	0.1	ml spray dilution/person		
Resident inhal. spray drift exposure mean - adult	0.00007	ml spray dilution/person		
Resident inhal. spray drift exposure mean - child	0.00011	ml spray dilution/person		
Exposure duration dermal	2	hours		d_ReExpDur
Exposure duration inhalation	24	hours		d_ReExpDurInhal
Exposure duration entry into treated crops	0.25	hours		d_ExpDurTreatCrop
Light clothing adjustment factor	18.0%			d_ClothAF
Breathing rate adult	0.23	m³/day/kg		d_BreathRAd
Breathing rate child (1-3 year old)	1.07	m³/day/kg		d_BreathRCh
Drift percentage on surface (75th percentile)	1.30%			
Drift percentage on surface (mean)	1.00%			
Turf transferable residues percentage	5.00%			d_Turf
Transfer coeff. of surface deposits-adult	7300	cm²/hour		d_ReTCAd
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm²/hour		d_ReTCCh
Saliva extraction percentage	50.00%			d_SalExt
Surface area of hands mouthed	20	cm²		d_AreaHM
Frequency of hand to mouth activity	9.5	events/hour		d_ReFreqHM
Ingestion rate for mouthing of grass per day	25	cm²		d_MouthGrass
Dislodgeable residues percentage transferability for object to mouth	20.00%			d_DRP
Transfer coefficient for entry into treated crops (75th percentil	7500	cm²/h		d_TcEntryAd
Transfer coefficient for entry into treated crops (75th percentil	2250	cm²/h		d_TcEntryCh
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm²/h		d_TcEntryAd
Transfer coefficient for entry into treated crops (mean) - child	1794	cm²/h		d_TcEntryCh
d_MAF	Multiple application factor		2.57	

For the refined assessment the following adoption of the parameters were made:

Table 15: Refined parameters for EFSA guidance assessment of residential exposure for metiram when applied in BAS 222 28 F

Dislodgeable foliar residue (i_AppRate*i_DFR)		0.9324	µg a.s./cm²	*d_DFR*
d_MAF	Multiple application factor		1.75	

The predicted exposures are summarised in the following.

Assessment

The results of the resident exposure calculations for metiram following the EFSA approach are summarised in Table 16 below.

Table 16: Estimated resident exposure to metiram and % of the AOEL (EFSA approach)

1.1 1-3 year old child

Pathway of exposure	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)	0.0018	0.011	0.0020	0.016	0.026
Total systemic exposure per kg body weight (mg/kg bw/day)	0.00018	0.0011	0.00020	0.0016	0.0026
% of RVNAS	1.1%	6.7%	1.2%	10%	17%

1.2 Adult

Pathway of exposure	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0019	0.014	0.00046	0.055	0.059
Total systemic exposure per kg body weight (mg/kg bw/day)	0.000031	0.00023	0.0000077	0.00091	0.00098
% of RVNAS	0.19%	1.4%	0.048%	5.7%	6.1%

[2] Based on a systemic AOEL of 0.016 mg/kg bw/day for metiram.

As evident from the individual exposure pathways the main contributor is the entry into the treated field. This contribution is impacted by 2 default assumptions that are likely not met by metiram based on the evidence provided in the re-entry exposure study conducted in grapes. The EFSA guidance model assumes a DFR default of 3 µg/cm² / kg a.i. and thus for metiram based on the application rate of 1.26 kg a.i./ha a DFR value of 1.26 x 3 = 3.78 µg/cm². Instead the DFR values obtained for BAS 222 28 F when applied in grapes at an even higher application rate of 1.4 kg a.i./ha where at maximum 0.74 µg/cm². Furthermore, the default foliar DT_{50} of 30 days is also not reflected by the study data. Instead a DT_{50} of less than 7 days is considered more realistic but still a worst case. The DFR values measured do not provide any indication for accumulation of metiram by repeated application. Therefore, a refined assessment based on the available product specific DFR data and foliar DT_{50} is provided in Table 17 which shows a negligible exposure also for the exposure of children even when considering combined exposure to all pathways. The robust study summary of this field exposure and dislogdeable foliar residue study is provided in the RAR of RMS Italy of Oct. 2017 a summary of the DFR data is provided below.

Table 17: Estimated resident exposure to metiram and % of the AOEL (refined EFSA approach)

1.1 1-3 year old child

Pathway of exposure	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)	**0.0018**	**0.0107**	**0.0014**	**0.0028**	**0.0151**
Total systemic exposure per kg body weight (mg/kg bw/day)	**0.00018**	**0.0011**	**0.00014**	**0.00028**	**0.0015**
% of RVNAS	**1.1%**	**6.7%**	**0.85%**	**1.7%**	**9.4%**

1.2 Adult

Pathway of exposure	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	**0.0019**	**0.0138**	**0.00031**	**0.0092**	**0.0224**
Total systemic exposure per kg body weight (mg/kg bw/day)	**0.000031**	**0.00023**	**0.0000052**	**0.00015**	**0.00037**
% of RVNAS	**0.19%**	**1.4%**	**0.033%**	**1.0%**	**2.3%**

Estimation of resident exposure to ETU

Resident exposure to ETU may occur following drift-off events of the spray and subsequent degradation of metiram to metabolites. The standardised model assessment as presented for metiram, however, is not transferable to ETU as relevant information on the input factors to be used is lacking. This especially applies to application rates to consider as the occurrence of environmental exposure to ETU is mainly the consequence of degradation of the parent compound rather than the application of these compounds via the spray. The same applies for the assessment of inhalation exposure of residents. Thus, the assessment was conducted based on the metiram external assessment applying the already presented ETU adjustment factor and ETU specific dermal and oral absorption estimates.

The estimates based on the refined metiram approach are provided in Table 18 for the individual pathways of exposure and for the all pathway exposure scenario.

In conclusion accidental exposure of residents to metiram and ETU due to the use of BAS 222 28 F in potatoes is considered negligible.

Table 18: Estimated resident exposure to ETU and % of the AOEL following the application of BAS 222 28 F in potatoes based on the standard approach for metiram

Subject	Pathway of exposure	Route of exposure	Metiram		ETU adjustment factor **	ETU				
			actual exposure per route	Formula used for calculation of external exposure		% absorption	Predicted systemic exposure per route	Predicted systemic exposure per scenario	Proposed AOEL	% proposed AOEL***
			(mg/kg bw/day)				(mg/kg bw/day)			
Individual exposure scenarios (75th percentile data)										
Adult	Spray drift	dermal	0.0088	(C15*(1-d_ClothAF)*d_ConcAS) /d_BwAdult*0.5 (drift-reduction factor)	0.0075	17	0.000011	0.000011	0.005	**0.22**
		inhalation	0.0000047	(C17*d_ConcAS)/d_BwAdult*0.5 (drift reduction factor)	0.0075	100	0.000000035			
	Vapour	inhalation	0.00023	d_AirCon *d_BreathRAd	0.0075	100	0.0000017	0.0000017	0.005	**0.035**
	Surface deposits	dermal	0.0017	(i_AppRate/100)*C29 *d_Turf*d_ReTCAd *d_ReExpDur*d_MAF /d_BwAdult *0.5 (drift reduction factor)	0.0075	17	0.0000022	0.0000022	0.005	**0.044**
	Entry treated crops	dermal	0.0510	(d_TcEntryAd*0.25*d_DFR*d_MAF)/1000/d_BwAdult	0.0075	17	0.000065	0.0000650	0.005	**1.3**

Subject	Pathway of exposure	Route of exposure	Metiram		ETU adjustment factor **	ETU				
			actual exposure per route	Formula used for calculation of external exposure		% absorption	Predicted systemic exposure per route	Predicted systemic exposure per scenario	Proposed AOEL	% proposed AOEL***
			(mg/kg bw/day)				(mg/kg bw/day)			
Individual exposure scenarios (75th percentile data)										
Child	Spray drift	dermal	0.046	(C16*(1-d_ClothAF) *d_ConcAS)/d_BwChild *0.5 (drift-reduction factor)	0.0075	17	0.000059	0.000059	0.005	**1.2**
		inhalation	0.000041	(C18*d_ConcAS)/d_BwChild*0.5 (drift reduction factor)	0.0075	100	0.00000031			
	Vapour	inhalation	0.0011	d_AirCon *d_BreathRCh	0.0075	100	0.0000080	0.0000080	0.005	**0.16**
	Surface deposits	dermal	0.0037	(i_AppRate/100)*C29 *d_Turf*d_ReTCCh *d_ReExpDur *d_MAF/d_BwChild *0.5 (drift reduction factor)	0.0075	17	0.0000048	0.0000054	0.005	**0.11**
		hand-to mouth	0.000014	(i_AppRate/100)*C29*d_Turf*d_SalExt*d_AreaHM *d_ReFreqHM*d_ReExpDur *d_MAF /d_BwChild*0.5 (drift reduction factor)	0.0075	100	0.00000011			
		object to mouth	0.000072	(i_AppRate/100)*C29*d_DRP*d_MouthGrass*d_MAF/d_BwChild *0.5 (drift reduction factor)	0.0075	100	0.00000054			
	Entry treated crops	dermal	0.0918	(d_TcEntryCh*0.25*d_DFR*d_MAF)/1000/d_BwChild	0.0075	17	0.0001170	0.00012	0.005	**2.4**

Subject	Pathway of exposure	Route of exposure	Metiram		ETU adjustment factor **	ETU				
			actual exposure per route	Formula used for calculation of external exposure		% absorption	Predicted systemic exposure per route	Predicted systemic exposure per scenario	Proposed AOEL	% proposed AOEL***
			(mg/kg bw/day)				(mg/kg bw/day)			
All pathways (mean data)										
Adult	Spray drift	dermal	0.0088	(C15*(1-d_ClothAF)*d_ConcAS) /d_BwAdult*0.5 (drift-reduction factor)	0.0075	17	0.000011189	0.000011	0.005	**0.22**
		inhalation	0.0000047	(C17*d_ConcAS)/d_BwAdult* 0.5 (drift reduction factor)	0.0075	100	0.000000035			
	Vapour	inhalation	0.00023	d_AirCon *d_BreathRAd	0.0075	100	0.0000017	0.0000017	0.005	**0.035**
	Surface deposits	dermal	0.0017	(i_AppRate/100)*C29 *d_Turf*d_ReTCAd *d_ReExpDur*d_MAF /d_BwAdult *0.5 (drift reduction factor)	0.0075	17	0.000002223	0.0000022	0.005	**0.044**
	Entry treated crops	dermal	0.0510	(d_TcEntryAd*0.25*d_DFR*d_MAF)/1000/d_BwAdult	0.0075	17	0.0000650	0.0000650	0.005	**1.3**
	All pathways		**0.0470**		**0.0075**		**0.000061**	**0.000061**	**0.005**	**1.2**

Subject	Pathway of exposure	Route of exposure	Metiram		ETU adjustment factor **	ETU				
			actual exposure per route	Formula used for calculation of external exposure		% absorption	Predicted systemic exposure per route	Predicted systemic exposure per scenario	Proposed AOEL	% proposed AOEL***
			(mg/kg bw/day)				(mg/kg bw/day)			
All pathways (mean data)										
Child	Spray drift	dermal	0.046	(C16*(1-d_ClothAF) *d_ConcAS)/d_BwChild *0.5 (drift-reduction factor)	0.0075	17	0.000059	0.000059	0.005	**1.2**
		inhalation	0.000041	(C18*d_ConcAS)/d_BwChild*0.5 (drift reduction factor)	0.0075	100	0.00000031			
	Vapour	inhalation	0.0011	d_AirCon *d_BreathRCh	0.0075	100	0.0000080	0.0000080	0.005	**0.16**
	Surface deposits	dermal	0.0037	(i_AppRate/100)*C29 *d_Turf*d_ReTCCh *d_ReExpDur *d_MAF/d_BwChild *0.5 (drift reduction factor)	0.0075	17	0.0000048	0.0000054	0.005	**0.11**
		hand-to mouth	0.000014	(i_AppRate/100)*C29*d_Turf*d_SalExt*d_AreaHM *d_ReFreqHM*d_ReExpDur *d_MAF /d_BwChild*0.5 (drift reduction factor)	0.0075	100	0.00000011			
		object to mouth	0.000072	(i_AppRate/100)*C29*d_DRP*d_MouthGrass*d_MAF/d_BwChild *0.5 (drift reduction factor)	0.0075	100	0.00000054			
	Entry treated crops	dermal	0.092	(d_TcEntryCh*0.25*d_DFR*d_MAF)/1000/d_BwChild	0.0075	17	0.00012	0.00012	0.005	**2.3**
	All pathways		**0.262**		**0.0075**		**0.00034**	**0.00034**	**0.005**	**6.8**

*Calculated based on EFSA Guidance formula

**Derived from 0.75% ETU relative to metiram contained in the spray dilute

***AOEL proposed for ETU: 0.005 mg/kg bw

Dislodgeable foliar residues

The robust study summary of the study referred to is provided in the RAR of the RMS Italy of October 2017 [B.6.4.3.1 report CP 7.3.2.2/1, BASF DocID 2015/1020152]. The results of the measurements of dislodgeable foliar residues (DFR) at the selected days after the first treatment until day 14 post terminal treatment are shown in Table 19 below.

Table 19: DFR measurements in grape vineyards following three sequential applications of BAS 222 28 F with an application rate of 1.4 kg a.i./ha

Sampling occasion	Metiram		ETU	
	(µg)	(µg/cm²)[1]	(µg)	(µg/cm²)[1]
Spain				
Pre-applic 1	15.464	0.039	4.494	0.011
Post-applic 1	240.242	0.601	5.246	0.013
Pre-applic 2	23.330	0.058	4.494	0.011
Post-applic 2	155.557	0.389	5.418	0.014
Pre-applic 3	162.830	0.407	19.713	0.049
Post-applic 3	293.820	0.735	13.838	0.035
1 DALA	37.151	0.093	23.463	0.059
2 DALA	36.574	0.091	21.102	0.053
3 DALA	37.490	0.094	7.058	0.018
5 DALA	5.497	0.014	5.021	0.013
7 DALA	14.343	0.036	5.021	0.013
14 DALA	53.801	0.135	6.635	0.017
Germany				
Pre-applic 1	2.308	0.006	6.522	0.016
Post-applic 1	49.538	0.124	6.522	0.016
Pre-applic 2	33.988	0.085	6.522	0.016
Post-applic 2	28.025	0.070	6.522	0.016
Pre-applic 3	3.706	0.009	6.522	0.016
Post-applic 3	11.234	0.028	6.522	0.016
1 DALA	16.941	0.042	5.634	0.014
2 DALA	7.933	0.020	6.678	0.017
3 DALA	10.293	0.026	5.634	0.014
5 DALA	12.867	0.032	11.048	0.028
7 DALA	10.833	0.027	5.634	0.014
14 DALA	16.729	0.042	5.085	0.013

DALA = Day After Last Application

[1] Based on total leaf disc area rounded to 400 cm² (two-sided surface); Application rate: 1.4 kg metiram/ha.

DFR sampling at pre-application times were performed shortly before application, DFR sampling at post-application times were performed within 3 hours following application once the spray had dried on the foliage. The values were corrected for field recoveries and show the means of the respective subplots A, B, C, D and F sampled.

In conclusion DFR measurements for metiram gave values of 0.093 µg/cm² for the Spanish field site and 0.042 µg/cm² for the German field site at the day or re-entry (1 DALA). For ETU dislodgeable foliar residues were less with 0.059 µg/cm² in Spain and 0.014 µg/cm² in Germany.

Since re-entry by residents may occur at any time further consideration of resident exposure in the light of the DFR values as investigated over the application period is needed. The analysis of how the DFR data at the day after last application compare to those at the other sampling dates is presented in the Table 20 below.

Table 20: DFR statistical analysis

	Metiram		**ETU**	
Sampling occasion	(µg/cm²)[1]		(µg/cm²)[1]	
Spain				
Post-applic 1	0.601		0.013	
Pre-applic 2	0.058		0.011	
Post-applic 2	0.389		0.014	
Pre-applic 3	0.407		0.049	
Post-applic 3	0.735		0.035	
1 DALA	0.093	**40th perc**	0.059	**max val**
2 DALA	0.091		0.053	
3 DALA	0.094		0.018	
5 DALA	0.014		0.013	
7 DALA	0.036		0.013	
14 DALA	0.135		0.017	
Min	0.014		0.011	
Max	0.735		0.059	
Geomean	0.132		0.022	
75 percentile	0.398		0.042	
Germany				
Post-applic 1	0.124		0.016	
Pre-applic 2	0.085		0.016	
Post-applic 2	0.070		0.016	
Pre-applic 3	0.009		0.016	
Post-applic 3	0.028		0.016	
1 DALA	0.042	**60th perc**	0.014	**30th perc**
2 DALA	0.020		0.017	
3 DALA	0.026		0.014	
5 DALA	0.032		0.028	
7 DALA	0.027		0.014	
14 DALA	0.042		0.013	
Min	0.009		0.013	
Max	0.124		0.028	
Geomean	0.036		0.016	
75 percentile	0.056		0.016	

With regard to metiram, the DFR values as generated for the day of re-entry (1 DALA) may not be considered as being representative for the whole of the application period of BAS 222 28 F because the values correspond to the 40th percentile estimate for the field site in Spain and the 60th percentile estimate for the field site in Germany. In order to decrease the level of uncertainty in the assessment made the maximum estimates of metiram DFR data could be used instead as alternative approach. This would correspond to a DFR of 0.74 µg/cm².

Overall to conduct a refined risk assessment for the resident the maximum DFR for metiram of 0.74 µg/cm² is applied as a reasonable worst case.

When assessing the decline behavior of metiram there is no indication for accumulation after repeated application. The DFR values immediately after the individual application at both study sites stay at a comparable level. Thus, assuming a foliar DT_{50} of 7 days (i.e. the inter-application interval) is considered a reasonable worst case for the resident. By this a multiapplication factor of 1.75 is derived.

A. Bystander exposure

For compounds that have no acute risk and thus no AAOEL is derived the resident exposure assessment is considered sufficiently conservative to cover exposure of bystander as well given the assumed shorter duration of exposure.

In conclusion, based on the resident exposure assessment provided above the accidental exposure of bystanders to metiram and ETU under the use conditions of BAS 222 28 F in potatoes is considered negligible.

5.2.2 Measurement of bystander and resident exposure

Since the risk assessment performed indicates that the health-based limit values (AOEL) will not be exceeded under practical conditions of use, studies to provide field data on bystander or residential exposure to BAS 222 28 F were not considered necessary and were thus not performed.

5.3 Worker exposure

The plant protection product BAS 222 28 F is already registered for the use as fungicide in potatoes. Information on the formulation and the critical use pattern relevant for the re-entry worker risk assessment can be found in Table 5.

Exposure assessments and risk evaluations for re-entry workers for the representative formulation BAS 222 28 F are presented below. Estimations of potential worker exposure have been undertaken applying the following guidance for exposure prediction:

- EFSA guidance: European Food Safety Authority (2014) Guidance on the Assessment of Exposure for Operators, Workers, Residents and Bystanders in Risk Assessment for Plant Protection Products EFSA Journal 2014;12(10):3874 [55 pp.]. doi:10.2903/j.efsa.2014.3874

Risk assessment for worker

A summary of the worker risk assessment is provided Table 21.

Table 21: Summary of re-entry workers exposure following application of BAS 222 28 F without and with protective equipment

	Potential exposure	Work wear - arms, body and legs covered
Total systemic exposure (mg a.s./day)	**0.730**	**0.082**
Total systemic exposure per kg body weight (mg/kg bw/day)	**0.012**	**0.0014**
% of RVNAS	**76%**	**8.5%**

[1] based on a systemic AOEL of 0.016 mg/kg bw/day for metiram

For workers entering a treated potato field after application of BAS 222 28 F the predicted exposure for a worker wearing normal working clothing is negligible.

Applying the same approach as done for operators and residents the worker exposure to ETU was estimated. However, with the standard assessment the 10% AOEL consumption is slightly exceeded as shown in Table 22. However, the refined assessment based on product specific DFR and foliar decline data results in 1.9% AOEL consumption.

Table 22: Summary of worker exposure to ETU and % of the AOEL following the application of BAS 222 28 F in potatoes

Predicted systemic exposure	Proposed AOEL	% proposed AOEL***
mg/kg bw/day		
Standard EFSA approach		
0.00058	0.005	12
Refined EFSA approach		
0.00010	0.005	1.9

Conclusion

It is concluded that the risk for worker wearing adequate working clothing when re-entering potatoes treated with BAS 222 28 F after the spray dilute has dried is negligible.

5.3.1 Estimation of worker exposure

Worker exposure to metiram from the product BAS 222 28 F

BAS 222 28 F will be used as a fungicide in potatoes during growth stages 21-89 for potatoes with a maximum of 3 applications per season. Thus, the considered reasonable worst case for the maximum applied amount of product per season is 1.26 kg/ha metiram in potatoes.

Hand operations in potatoes, which may result in relevant re-entry exposure do not belong to standard growing procedures after the application of the product. Exposure scenarios one may think of as a worst case may be scouting and crop inspection. These operations are considered to be of limited duration and of limited direct contact to the treated plants. For these operations a working period of 2 hours per day is considered a reasonable approach.

For the re-entry worker assessment according to EFSA guidance model the following parameter were taken into account:

Table 23: Parameters used in EFSA guidance model for metiram when applied in BAS 222 28 F

Crop type	**Root and tuber vegetables**		
Indoor or outdoor	**Outdoor**		
Application method	**Downward spraying**		
Application equipment	**Vehicle-mounted-Drift Reduction**		
Worker's task	**Inspection, irrigation**		
Main body parts in contact with foliage	**Hand and body**		
Application rate of active substance	**1.26**	kg a.s./ha	*i_AppRate*
Number of applications	**3**		*i_AppNo*
Interval between multiple applications	**7**	days	*i_AppInt*
Half-life of active substance	**30**	days	*d_HalflifeAS*
Multiple application factor	**2.6**		*d_MAF*
Dermal absorption of the product	**0.1%**		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	**0%**		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	**3.78**	µg a.s./cm^2	*d_DFR*
Working hours	**2**	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	**12500**	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	**1400**	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	**no TC available for this assessment**	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	**NA**	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	**NA**	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	**NA**	ha/hr*10^(-3)	*d_InhalTcSort*

Estimation of worker exposure with personal protective equipment

The results of the re-entry worker risk assessment without PPE is provided in Table 24 below,

Table 24: Estimated worker exposure to metiram and % of the AOEL (EFSA approach and refined approach)

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves
EFSA guidance approach			
Total systemic exposure (mg a.s./day)	**0.730**	**0.082**	**no TC available for this assessment**
Total systemic exposure per kg body weight (mg/kg bw/day)	**0.012**	**0.0014**	
% of RVNAS	**76%**	**8.5%**	
EFSA guidance refined approach Product specific DFR of 0.74 µg/cm² and foliar DT_{50} of 7 days			
Total systemic exposure (mg a.s./day)	**0.12**	**0.014**	**no TC available for this assessment**
Total systemic exposure per kg body weight (mg/kg bw/day)	**0.0020**	**0.00023**	
% of RVNAS	**13%**	**1.4%**	

With regard to ETU the following estimates are made:

Table 25: Estimated worker exposure to ETU and % of the AOEL following the application of BAS 222 28 F in potatoes

Metiram		**ETU**				
External dermal exposure	**Formula used for calculation of external exposure**	**adjustment factor ****	**% absorption**	**Predicted systemic exposure**	**AOEL**	**% AOEL*****
mg/kg bw/day				**mg/kg bw/day**		
EFSA guidance assessment						
0.454	d_DermTcCV1*d_WorkHr *d_DFR*d_MAF/1000 /d_Bw_Adult	0.0075	17	0.000579	0.005	12
EFSA refined assessment Product specific DFR of 0.74 µg/cm² and foliar DT_{50} of 7 days						
0.076	d_DermTcCV1*d_WorkHr *d_DFR*d_MAF/1000 /d_Bw_Adult	0.0075	17	0.00010	0.005	1.9

In conclusion the risk for re-entry worker coming into contact with treated canopy after application of BAS 222 28 F is negligible for both exposure to metiram and ETU.

5.3.2 Measurement of worker exposure

Since the risk assessment performed indicates that the health-based limit values (AOEL) will not be exceeded under practical conditions of use, studies to provide field data in potatoes on worker exposure to BAS 222 28 F were not considered necessary and were thus not performed.

6 References

BASF DocID 2019/1075956 Metiram Amendment to the AIR dossier – Negligible exposure assessment; Residues in or on treated products, food and feed and plant metabolism, 20th May, 2019

Draft Renewal Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009 Metiram RMS Italy, October 2017.

Fabian E, Landsiedel R (2018) 14C-BAS 222 F in aqueous preparation – Study of penetration through human skin in vitro, BASF DocID 2018/1048747, unpublished

Fabian E, Landsiedel R (2015) 14C-Reg.No. 146099 (metabolite of BAS 222 (Metiram), BF 222-ETU; CAS No. 96-47-7) in aqueous vehicle – Study of penetration through human skin in vitro; BASF DocID 2015/1110140, unpublished

Francis GL, Rennert OM (1980) Correlation of Plasma Propylthiouracil levels with inhibition of thyroid hormone synthesis in the rat, 29(5), 410 - 414

Janssen ST, Janssen OE (2017) Directional thyroid hormone distribution via the blood stream to target sites. Molecular and Cellular Endocrinology 458, 16 – 21.

Kampmann JP, Molholm Hansen JE (1981) Correlation between antithyroid effect and serum concentrations of propylthiouracil in patients with hyperthyroidism, Br J Clin Pharmac, 12, 681 – 686

Sanco-2014-12096 (2015) Draft Commission Notice Technical guidance on the interpretation of points 3.6.3 to 3.6.5, and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, in particular regarding the assessment of negligible exposure to an active substance in a plant protection product under realistic conditions of use, Draft – May 2015; https://ec.europa.eu/food/sites/food/files/safety/docs/adv-grp_wg_20150625_tech-guidance.pdf

[redacted] (2015) Determination of worker re-entry exposure (combined with dislodgeable foliar residues) associated to typical crop maintenance activites in grape vineyards following treatment with BAS 222 28 F in Germany and Spain, 2013; BASF DocID 2015/1020152 Unpublished

7 Appendices

Appendix 8. 1: EFSA guidance operator exposure assessment for metiram applied in BAS 222 28 F to potatoes without PPE

2.1 Mixing and loading

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	**20.368**	**0.339**	*D15*i_AbsorpProduct*
Body	**14.544**	**0.242**	*D16*i_AbsorpProduct*
Head	**0.262**	**0.004**	*D17*i_AbsorpProduct*
Inhalation	**128.137**	**2.136**	*D21*i_AbsorpInhalation*
Sum	**163.310**	**2.722**	
With RPE/PPE (as selected above)			
Hands	**20.368**	**0.339**	*D18*i_AbsorpProduct*
Body	**0.468**	**0.008**	*D19*i_AbsorpProduct or D15*i_AbsorpProduct*F24*
Head	**0.262**	**0.004**	*D20*i_AbsorpProduct or D17*i_AbsorpProduct*F25*
Inhalation	**128.137**	**2.136**	*D21*i_AbsorpInhalation*G25*
Sum	**149.235**	**2.487**	
Water soluble bag	**149.235**	**2.487**	*C70*F26*

2.2 Application

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	**11.862**	**0.198**	*D30*i_AbsorpInuse*
Body	**2.436**	**0.041**	*D31*i_AbsorpInuse*
Head	**0.097**	**0.002**	*D32*i_AbsorpInuse*
Inhalation	**8.128**	**0.135**	*D35*i_AbsorpInhalation*
Sum	**22.523**	**0.375**	
With RPE/PPE (as selected above)			
Hands	**11.862**	**0.198**	*D33*i_AbsorpInuse*
Body	**0.085**	**0.001**	*D34*i_AbsorpInuse or D31*i_AbsorpInuse*F38*
Head	**0.097**	**0.002**	*D32*i_AbsorpInuse*F39*
Inhalation	**8.128**	**0.135**	*D35*i_AbsorpInuse*G39*
Sum	**20.173**	**0.336**	

Appendix 8. 2: EFSA guidance operator exposure assessment for metiram applied in BAS 222 28 F to potatoes with PPE

2.1 Mixing and loading

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	**20.4**	**0.34**	*D15*i_AbsorpProduct*
Body	**14.5**	**0.24**	*D16*i_AbsorpProduct*
Head	**0.262**	**0.00**	*D17*i_AbsorpProduct*
Inhalation	**128.137**	**2.14**	*D21*i_AbsorpInhalation*
Sum	**163.3**	**2.72**	
With RPE/PPE (as selected above)			
Hands	**0.157**	**0.003**	*D18*i_AbsorpProduct*
Body	**0.468**	**0.008**	*D19*i_AbsorpProduct or D15*i_AbsorpProduct*F24*
Head	**0.209**	**0.003**	*D20*i_AbsorpProduct or D17*i_AbsorpProduct*F25*
Inhalation	**32.034**	**0.534**	*D21*i_AbsorpInhalation*G25*
Sum	**32.87**	**0.548**	
Water soluble bag	**32.87**	**0.548**	*C70*F26*

2.2 Application

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	**11.862**	**0.198**	*D30*i_AbsorpInuse*
Body	**2.436**	**0.041**	*D31*i_AbsorpInuse*
Head	**0.097**	**0.002**	*D32*i_AbsorpInuse*
Inhalation	**8.128**	**0.135**	*D35*i_AbsorpInhalation*
Sum	**22.523**	**0.375**	
With RPE/PPE (as selected above)			
Hands	**0.094**	**0.002**	*D33*i_AbsorpInuse*
Body	**0.085**	**0.001**	*D34*i_AbsorpInuse or D31*i_AbsorpInuse*F38*
Head	**0.097**	**0.002**	*D32*i_AbsorpInuse*F39*
Inhalation	**8.128**	**0.135**	*D35*i_AbsorpInuse*G39*
Sum	**8.405**	**0.140**	

Appendix 8. 3: EFSA guidance resident exposure assessment for metiram applied in BAS 222 28 F to potatoes (standard assessment)

2. Resident exposure 75th Percentile

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0018	0.00018	*((C16*i_AbsorpInuse*(1-d_ClothAF))+C18)*d_ConcAS*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107	0.00107	*d_AirCon*d_BreathRCh*d_BwChild*	
Surface deposits				
Dermal	0.0002	0.00002	*(i_AppRate/100)*C29*d_Turf*d_ReTCCh*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1))*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0012	0.00012	*(i_AppRate/100)*C29*d_Turf*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0006	0.00006	*(i_AppRate/100)*C29*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0164	0.00164	*(d_TcEntryCh*0.25*d_DFR*d_MAF)/1000 *MAX(i_AbsorpProduct,i_AbsorpInuse)*	
Hand to mouth			*(i_AppRate/100)*d_Turf*d_MAF*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			*(i_AppRate/100)*d_DRP*d_MouthGrass* i_AbsorpOralInuse*d_MAF*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0019	0.00003	*(C15*i_AbsorpInuse*(1-d_ClothAF))+C17)*d_ConcAS*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138	0.00023	*d_AirCon*d_BreathRAd*d_BwAdult*	
Surface deposits (dermal)	0.0005	0.00001	*(i_AppRate/100)*C30*d_Turf*d_ReTCAd*d_ReExpDur*i_AbsorpInuse*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.0547	0.00091	*(d_TcEntryAd*0.25*d_DFR*d_MAF)/1000 *MAX(i_AbsorpProduct,i_AbsorpInuse)*	

3. Summing of exposure pathways mean

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0011	0.000112	*((C20*i_AbsorpInuse*(1-d_ClothAF))+C22)*d_ConcAS*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107	0.001070	*d_AirCon*d_BreathRCh*d_BwChild*	
Surface deposits				
Dermal	0.0001	0.000013	*(i_AppRate/100)*C30*d_Turf*d_ReTCCh*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1))*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0009	0.000092	*(i_AppRate/100)*C30*d_Turf*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0005	0.000049	*(i_AppRate/100)*C30*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0131	0.001309	*(d_TcEntryMeanCh*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse))*	
Hand to mouth			*(i_AppRate/100)*1*d_Turf*d_MAF*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			*(i_AppRate/100)*1*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0011	0.00002	*"(C19*i_AbsorpInuse*(1-d_ClothAF))+C21)*d_ConcAS"*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138	0.00023	*d_AirCon*d_BreathRAd*d_BwAdult*	
Surface deposits (dermal)	0.0004	0.00001	*(i_AppRate/100)*C30*d_Turf*d_ReTCAd*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1)*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.0436	0.00073	*(d_TcEntryMeanAd*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)*	

Appendix 8. 4: EFSA guidance resident exposure assessment for metiram applied in BAS 222 28 F to potatoes (refined assessment)

2. Resident exposure 75th Percentile

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0018	0.00018	*((C16*i_AbsorpInuse*(1-d_ClothAF))+C18)*d_ConcAS*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107	0.00107	*d_AirCon*d_BreathRCh*d_BwChild*	
Surface deposits				
Dermal	0.0001	0.00001	*(i_AppRate/100)*C29*d_Turf*d_ReTCCh*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1))*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0008	0.00008	*(i_AppRate/100)*C29*d_Turf*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0004	0.00004	*(i_AppRate/100)*C29*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0028	0.00028	*(d_TcEntryCh*0.25*d_DFR*d_MAF)/1000 *MAX(i_AbsorpProduct,i_AbsorpInuse)*	
Hand to mouth			*(i_AppRate/100)*d_Turf*d_MAF*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			*(i_AppRate/100)*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0019	0.00003	*(C15*i_AbsorpInuse*(1-d_ClothAF))+C17)*d_ConcAS*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138	0.00023	*d_AirCon*d_BreathRAd*d_BwAdult*	
Surface deposits (dermal)	0.0003	0.00001	*(i_AppRate/100)*C30*d_Turf*d_ReTCAd*d_ReExpDur*i_AbsorpInuse*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.0092	0.00015	*(d_TcEntryAd*0.25*d_DFR*d_MAF)/1000 *MAX(i_AbsorpProduct,i_AbsorpInuse)*	

3. Summing of exposure pathways mean

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0011	0.000112	*((C20*i_AbsorpInuse*(1-d_ClothAF))+C22)*d_ConcAS*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107	0.001070	*d_AirCon*d_BreathRCh*d_BwChild*	
Surface deposits				
Dermal	0.0001	0.000009	*(i_AppRate/100)*C30*d_Turf*d_ReTCCh*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1))*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0006	0.000063	*(i_AppRate/100)*C30*d_Turf*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0003	0.000033	*(i_AppRate/100)*C30*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0022	0.000220	*(d_TcEntryMeanCh*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse))*	
Hand to mouth			*(i_AppRate/100)*1*d_Turf*d_MAF*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			*(i_AppRate/100)*1*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0011	0.00002	*"(C19*i_AbsorpInuse*(1-d_ClothAF))+C21)*d_ConcAS"*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138	0.00023	*d_AirCon*d_BreathRAd*d_BwAdult*	
Surface deposits (dermal)	0.0002	0.00000	*(i_AppRate/100)*C30*d_Turf*d_ReTCAd*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1)*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.0073	0.00012	*(d_TcEntryMeanAd*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)*	