Bayer CropScience

Document Title

Summary of the toxicological studies
Diflufenican + Flurtamone SC 350 (100+250 g/L)

Data Requirements

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According to the guidance document, SANCO/10181/2013, for preparing dossiers for the approval of a chemical active substance

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Author(s)

[redacted]

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Version history

Date	Data points containing amendments or additions[1] and brief description	Document identifier and version number

[1] It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4 How to revise an Assessment Report

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

INTRODUCTION

DFF+FLT SC 350 (internal code AE F088657 01 SC31 A2 alias EXP 30930) is a suspension concentrate containing 100 g/L diflufenican and 250 g/L flurtamone.
A dermal absorption study was conducted which is summarized here, otherwise no new studies were conducted since inclusion into Annex I of Directive 91/414 in 2003 (Directive 2003/84/EC, dated 25th of September 2003, Entry into Force 1st of January 2004.
This document summarizes the information related to the new dermal absorption study for the plant protection product diflufenican + **flurtamone** SC 350 (also known as DFF+FLT SC 350, DFF+FLT SC 100+250, Bacara, Carat or Dolmen) which contains the active substances diflufenican and **flurtamone**.

CP 7.1 Acute toxicity

No new studies were conducted since inclusion into Annex I of Directive 91/414 in 2003.

CP 7.1.1 Oral toxicity

The acute oral LD_{50} of the EXP 30930 formulation in rats was greater than 2000 mg/kg.

CP 7.1.2 Dermal toxicity

The dermal LD_{50} of the EXP 30930 formulation was greater than 2000 mg/kg in rats.

CP 7.1.3 Inhalation toxicity

The neat formulation will not be used in a manner that is expected to pose any acute inhalation hazard. With respect to 94/79/EEC, testing for the acute inhalation toxicity of DFF + FLT SC 350 was not triggered and, thus, not conducted.

CP 7.1.4 Skin irritation

The formulation EXP 30930 was not irritating to skin.

CP 7.1.5 Eye irritation

The formulation EXP 30930 was not irritating to eyes.

CP 7.1.6 Skin sensitization

In a modified Local Lymph Node Assay (IMDS) in NMRI mice of the strain Hsd Win:NMRI (6 animals/test item group and 6 control animals) to determine if there is any specific (sensitizing) or non-specific (irritant) stimulating potential of the test item DFF+FLT SC 350 (100+250) G no evidence of a sensitizing potential was detected.
Also in a Buehler study the formulation EXP 30930 was not a skin sensitizer.

CP 7.1.7 Supplementary studies on the plant protection product

No supplementary studies were performed.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No supplementary studies for combinations of plant protection products were conducted since the formulation is not recommended to be combined with other plant protection products.

CP 7.2 Data on exposure

DFF+FLT SC 350 is a suspension concentrate containing 100 g/L of diflufenican and 250 g/L of **flurtamone**. The proposed use is as a herbicide in spring (barley, wheat) and winter (barley, oats, rye, spelt, triticale and wheat) cereals during pre or post-emergence period. Application of DFF+FLT SC 350 will be achieved via field crop sprayer. The application parameters, with usage information are summarized in **Table 7.2-1**.
Since the following Risk Assessment conclusions are present to support only **flurtamone** Annex I Renewal no conclusions will be made for diflufenican.

Table 7.2-1. Application parameters for DFF+FLT SC 350

Crop(s)	Product Name	F/G	Application	Growth stage BBCH	N° of applications	Maximum Application rate		Spray volume (L/ha)	PHI
						(L product/ha)	(kg FLT*/ha)		
Spring Cereals: Barley, Wheat	Bacara, Carat or Dolmen	F	FCS	00-09 (Pre-emergence)	1	0.5	0.125	200-400	NA **
Winter Cereals: Barley, Oats, Rye, Spelt, Triticale, Wheat.				10-29 (Post-emergence)					

* FLT: **flurtamone**, F: Field use, FCS: Field crop sprayer, NA: Not applicable. **: The pre-harvest interval is covered by the growing period remaining between the envisaged application and harvest.

CP 7.2.1 Operator exposure

Consideration on estimation of operator exposure
Operator exposures to DFF+FLT SC 350 are estimated using the German model[1] and the UK-POEM[2] with the relevant scenario "Tractor-mounted/trailed boom sprayer: hydraulic nozzles" for cereals. Exposure calculations are performed without and with protective equipment.

It should be noted that "no PPE" is equivalent to a typical work wear (e.g. trousers and a long shirt) as well as sturdy foot wear for both models. The "with PPE" condition comprises the use of protective gloves worn during mixing and loading as well as when handling contaminated surfaces along with usual clothing. Both models allow estimates for protected operators wearing additional PPE, if necessary.

It should be noted that this selection of protective measures is not intended to be a recommendation for the minimum PPE necessary when handling DFF+FLT SC 350. It does not consider specific

[1] Lundehn, J.-R.; Westphal, D.; Kieczka, H.; Krebs, B.; Löcher-Bolz, S.; Maasfeld, W.; Pick, E.-D. (1992): Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protections); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, no 277, 1 - 112 (1992); (M-001230-02-1)

[2] Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel., Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM) – A User's Guide (UK MAFF); 1992, revised model 2007

requirements, which may exist in individual Member States. Additional PPE can be used to further reduce the exposure of the operator.

Dermal absorption

Dermal absorption data are available for **flurtamone** from an *in vitro* study with human/rat skin. Details regarding how the dermal absorption values were derived are provided in **Section 7.3**. The values used in the following risk assessments were:

Flurtamone:

Concentrate: 0.3 %.
Spray dilution: 8 %.

The proposed AOEL for **flurtamone** was derived from the 1-year dog study NOAEL of 5.6 mg/kg bw/day and a Safety Factor (SF) of 100. Available studies indicate that **flurtamone** was rapidly absorbed and extensively metabolised by rats following oral administration by gavage. Results of a bile excretion study showed that at 5 mg/kg bw more than 90 % of the administered dose was absorbed. In addition, as the liver is the target organ no adjustment for oral absorption is considered necessary when calculating systemic AOEL.
Based on **flurtamone** toxicological profile, i.e. on the absence of carcinogenic, mutagenic or teratogenic potential, the current conventional (EU) Uncertainty Factor (UF) of 100 is considered to be appropriate for setting AOEL.

Therefore, the new **AOEL will be 0.056 mg/kg bw/day**.

The results of the exposure calculations for operators are summarized in **Table 7.2.1-1**.

Table 7.2.1-1. Predicted systemic operator exposure as a proportion of the AOEL

Substance	PPE	Total systemic exposure (mg/kg bw/day)	% of AOEL *
German model Field crop sprayer application to cereals, 20 ha/day at a rate of 0.5 L product/ha, 70 kg operator			
Flurtamone	No PPE 1)	0.00018	3.21
	With PPE 2)	0.00155	2.77
UK-POEM Field crop sprayer application to cereals, 50 ha/day at a rate of 0.5 L product/ha, 60 kg operator			
Flurtamone	No PPE 1)	0.0384	68.6
	With PPE 2)	0.0356	63.6

* **Flurtamone**: AOEL = 0.056 mg/kg bw/day
1) No PPE: one layer of typical work wear (e.g. trousers and a long sleeved shirt) as well as sturdy foot wear
2) With PPE: In addition to typical work wear (see 1) protective gloves are worn during mixing and loading as well as when handling contaminated surfaces.

German Model

For **Flurtamone**, predicted systemic operator exposure accounts for 3.21 % of the systemic AOEL (0.056 mg/kg bw/day) without PPE and to 2.77 % when PPE is worn.

UK-POEM

For **Flurtamone**, predicted systemic operator exposure accounts for 68.6 % of the proposed systemic AOEL even if no PPE is considered. Assuming that in addition to the typical work wear protective gloves are worn when handling the concentrate and contaminated surfaces the corresponding exposure estimate for **Flurtamone** accounts for 63.6 % of the respective systemic AOEL.

Assessment

Based on these favourable exposure estimates there is no unacceptable risk anticipated for the operator with the intended use of DFF+FLT SC 350 if adequate work clothing is worn and, in addition, protective gloves during mixing/loading and when handling contaminated surfaces.

CP 7.2.1.1 Estimation of operator exposure

Operator exposure to DFF+FLT SC 350 is estimated using the German Model, as well as the UK-POEM for Tractor-mounted/trailed boom sprayer, hydraulic nozzles. In the following the assumptions used for the calculations are summarised.

German Model

Treated area: 20 ha/day
Max. dose rate: 0.5 L product/ha, i.e.:
- **Flurtamone**: 0.125 kg as/ha
Operator body weight: 70 kg
Clothing: One layer of typical work wear (e.g. trousers and a long sleeved shirt) and sturdy foot wear
Dermal absorption:
- **Flurtamone**: 0.3 % for the concentrate and 8 % for the in-use dilution

Personal protective equipment (PPE):
No PPE: No additional PPE is worn during mixing/loading and application
With PPE: Gloves are worn during mixing/loading and when handling contaminated surfaces

Detailed calculations with the BBA model are presented in **Table 7.2.1.1-1**.

Table 7.2.1.1-1. Predicted systemic exposure to Flurtamone according to the German model/no PPE and with PPE

Operator exposure estimate: German model. Tractor-mounted/trailed boom sprayer: hydraulic nozzles					
Product:	Bacara, Carat or Dolmen				
Active substance:	Flurtamone		a.s. concentration:	250	[g/l or kg]
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None
Dose [l or kg/ha]:	0.5			Hands:	Gloves
Work rate [ha/day]:	20		PPE during application:	Respiration:	None
Body weight [kg]:	70			Hands:	None
Inhalation absorption [%]	100			Head:	None
Dermal absorption [%]	0.3	(concentrate)		Body:	Standard protective overall
	8.0	(dilution)			

Calculation of route exposure:

Route	Specific exposure [mg/kg a.s.]	a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day] No PPE	Reduction factor	with PPE	
I_M =	0.0006	2.5	0.000021	1.0	0.000021	I = Inhalation
$D_{M(H)}$ =	2.4	2.5	0.0857	0.01	0.000857	D = Dermal
I_A =	0.001	2.5	0.000036	1.0	0.000036	M = Mix/Loading
$D_{A(C)}$ =	0.06	2.5	0.0021	1.0	0.002143	A = Application
$D_{A(H)}$ =	0.38	2.5	0.0136	1.0	0.013571	H = Hands
$D_{A(B)}$ =	1.6	2.5	0.0029	0.01	0.002857	C = Head
						B = Body

Absorbed dose:

Route		Absorption [%]	**No PPE** Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	**With PPE** Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.3	0.085714	0.000257	0.000857	0.000003
	Application	8.0	0.018571	0.001486	0.018571	0.001486
Inhalation:	Mix/Loading	100	0.000021	0.000021	0.000021	0.000021
	Application	100	0.000036	0.000036	0.000036	0.000036
		Total =		**0.0018**		**0.00155**

UK-POEM

Treated area: 50 ha/day
Max. dose rate: 0.5 L product/ha, i.e.;
- **Flurtamone**: 0.125 kg a.s./ha

Min. spray volume: 200 L/ha
Max. spray concentration
- **Flurtamone**: 0.625 mg/mL

Work duration: 6 hours/day
Operator body weight: 60 kg
Dermal absorption:
- **Flurtamone**: 0.3 % for the concentrate and 8% for the in-use dilution

Personal protective equipment (PPE):

No PPE: No additional PPE is worn during mixing/loading and application

With PPE: Gloves are worn during mixing/loading and when handling contaminated surfaces

Detailed calculations with the UK POEM are presented in **Table 7.2.1.1-2**.

Table 7.2.1.1-2. Predicted systemic exposure to Flurtamone according to the UK-POEM/no PPE and with PPE

Application method	**Tractor-mounted/trailed boom sprayer: hydraulic nozzles**		
Product	**Bacara, Carat or Dolmen**	Active substance	**Flurtamone**
Formulation type	**water-based**	a.s. concentration	**250** mg/ml
Dermal absorption from product	**0.3** %	Dermal absorption from spray	**8** %
Container	**1 litre any closure**		
PPE during mix/loading	**Gloves**	PPE during application	**None**
Dose	**0.5** l/ha	Work rate/day	**50** ha
Application volume	**200** l/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING

Container size	1	litres		
Hand contamination/operation	0.01	ml		
Application dose	0.5	litres product/ha		
Work rate	50	ha/day		
Number of operations	25	/day		
Hand contamination	0.25	ml/day		
Protective clothing	None		Gloves	
Transmission to skin	100	%	5	%
Dermal exposure to formulation	0.250	ml/day	0.0125	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	200	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65 %	10 %	25 %	
Clothing	None	Permeable	Permeable	
Penetration	100 %	5 %	15 %	
Dermal exposure	6.5	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	41.550	ml/day		

ABSORBED DERMAL DOSE

	Mix/load	Application		Mix/load	Application	
Dermal exposure	0.250	41.550	ml/day	0.013	41.550	ml/day
Concen. of a.s. product or spray	250	0.625	mg/ml	250	0.625	mg/ml
Dermal exposure to a.s.	62.500	25.969	mg/day	3.125	25.969	mg/day
Percent absorbed	0.3	8		0.3	8	%
Absorbed dose	0.188	2.078	mg/day	0.009	2.078	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0.625	mg/ml
Inhalation exposure to a.s.	0.0375	mg/day
Percent absorbed	100	%
Absorbed dose	0.0375	mg/day

PREDICTED EXPOSURE	No PPE		With PPE	
Total absorbed dose	2.3025	mg/day	2.1244	mg/day
Operator body weight	60	kg	60	kg
Operator exposure	0.0384	mg/kg bw/day	0.0354	mg/kg bw/day

CP 7.2.1.2 Measurement of operator exposure

Since the risk assessment carried out indicated that the acceptable operator exposure level (AOEL) for **flurtamone** was not be exceeded under practical conditions of use, a study to provide a measure of operator exposure under field conditions was not necessary and was therefore not carried out.

CP 7.2.2 Bystander and resident exposure

Risk assessment for bystander and resident

Currently no official and implemented EU model is available for calculation of bystander or residential exposure.

Therefore, as long as there is no official guidance on how to estimate bystander exposure an approach is presented in this document that considers both dermal exposure – derived from available drift data – and inhalation exposure – derived from an operator exposure model simulating a bystander who is exposed in a similar way as an unprotected operator spraying in the field. Additionally, exposure to residents is assessed as well.

This approach is following a guidance of the German Federal Institute for Risk Assessment (BfR)[3] and is in line with what has been published by US EPA and PSD recently. All technical details with regard to figures and assumptions are provided in this guidance.

Exposure estimates and proportions of the systemic AOELs accounted for by the estimates are summarized in the following table.

Table 7.2.2-1: Predicted systemic exposures to bystanders as a proportion of the AOEL

Substance	Scenario	Total systemic exposure* (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
Bystander Exposure				
Flurtamone	Bystander: adult	0.0000489	0.056	**0.0873**
	Bystander: child	0.0000389		**0.0695**
Residential Exposure				
Flurtamone	Resident: adult	0.00000353	0.056	**0.0063**
	Resident: child	0.0000103		**0.0184**

* Assumes a 60 kg bystander for an adult and 16.15 kg for a child.
* Dermal absorption value of 8 % for **flurtamone**. Oral and inhalation absorption were taken as 100 %.

Assessment

The results of the calculations reveal that the situation with respect to bystander and resident exposure is favorable for the intended use of DFF+FLT SC 350.

[3] Martin, S., Westphal, D., Erdtmann-Vourliotis, M., Dechet, F., Schulze-Rosario, C., Stauber, F., Wicke, H. and Chester, G.; Guidance for Exposure and Risk Evaluation for Bystanders and Residents exposed to Plant Protection Products during and after Application, Journal für Verbraucherschutz und Lebensmittelsicherheit *Journal of Consumer Protection and Food Safety* (2008, in preparation)

CP 7.2.2.1 Estimation of bystander and resident exposure

The following definitions and assumptions for bystanders and residents may be applied.

Bystanders and residents are not involved in application or handling plant protection products or the professional handling of treated crops. The question arises whether it is necessary to distinguish between bystanders and residents in terms of the potential for exposure and health risks. However, because the circumstances of this exposure could differ with respect to amount, frequency and duration, this seems to be reasonable.

Bystanders may inadvertently be present within or directly adjacent to an area for a short period of time, typically a matter of minutes, where application of a plant protection product is in progress or has recently taken place. They may be exposed to plant protection products mainly *via* the dermal route from spray drift and by inhalation of drifting spray droplets. Hand held application is considered to be worse case compared to field crop sprayer.

Residents may live or work near areas of the application of plant protection products (e.g. standing, working or sitting in a garden in the vicinity of the application). They may be exposed to 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 substance). For infants and toddlers exposure might also occur orally (e.g. through hand-to-mouth transfer and/or object-to-mouth transfer).

Table CP 7.2.2.1-1: Percent Drift Values for Different Crops (Rautmann *et al.* 2001, current version 27.03.2006) – 1 application only

Crop, Distance 10 m	Percent Drift (1 application) (90th percentile values)
Field crops	0.29
Fruit crops, early	11.81
Fruit crops, late	3.60
Grapes	1.23
Hops	5.77
Vegetables, ornamentals & small fruit:	
< 50 cm	0.29
> 50 cm	1.23

Exposure calculations are performed according to the following equations:

a) Bystander exposure to flurtamone

Dermal exposure due to spray drift following 1 low crop application using a tractor mounted sprayer

$SDE_B = (AR \times D \times BSA \times DA) / BW$

Where:

SDE_B	*= Systemic Exposure of Bystanders via the Dermal Route (mg/kg bw/day)*	
AR	*= Application Rate (mg/m²)*	*0.125 kg a.s./ha = 12.5 mg/m²*
D	*= Drift (%)*	*0.29 % (10 m distance) for 1 application*
BSA	*= Exposed Body Surface Area (m²)*	*1 m² (adult), 0.21 m² (child)*
DA	*= Dermal Absorption (%)*	*8 %*
BW	*= Body Weight (kg/person)*	*60 kg (adult), 16.15 kg (child)*

Inhalation exposure due to spray drift

$SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$

Where:

SIE_B	*= Systemic Exposure of Bystanders via the Inhalation Route (mg/kg bw/day).*	
I_A^*	*= Specific Inhalation Exposure (mg/kg a.s. handled per day)*	*0.001 mg/kg a.s. (FCS).*
AR	*= Application Rate (kg a.s./ha)*	*0.125 kg a.s./ha.*
A	*= Area Treated (ha/day)*	*20 ha (field crop sprayer).*
T	*= Time [Duration] (min)*	*5 min.*
IA	*= Inhalation Absorption (%)*	*100 %.*
BW	*= Body Weight (kg/person)*	*60 kg (adult), 16.15 kg (child).*

Total Systemic Exposure of Bystanders

Adults and Children: $SE_B = SDE_B + SIE_B$ (mg/kg bw/day)

Where:

SE_B	*= Systemic Exposure of Bystanders (mg/kg bw/day).*
SDE_B	*= Systemic Dermal Exposure of Bystanders (mg/kg bw/day).*
SIE_B	*= Systemic Inhalation Exposure of Bystanders (mg/kg bw/day).*

Table CP 7.2.2.1-2. Detailed calculations of bystander exposure to Flurtamone, absorbed dose and % of AOEL

Adults			**Children**		
Bystander of Field Crop, tractor mounted/trailed					
Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (12.5 x 0.29 % x 1 x 8 %) / 60			Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (12.5 x 0.29 % x 0.21 x 8 %) / 16.15		
Absorbed dose:	0.0004833	mg/kg bw/day	Absorbed dose:	0.00003771	mg/kg bw/day
Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.001 x 0.125 x 20 x 5/360 x 100 %) / 60			Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.001/1.74 x 0.125 x 20 x 5/360 x 100 %) / 16.15		
Absorbed dose:	0.0000005787	mg/kg bw/day	Absorbed dose:	0.000001236	mg/kg bw/day
Total systemic exposure: **$SE_B = SDE_B + SIE_B$**			**Total systemic exposure:** **$SE_B = SDE_B + SIE_B$**		
Total absorbed dose:	**0.0000489**	**mg/kg bw/day**	**Total absorbed dose:**	**0.0000389**	**mg/kg bw/day**
% of AOEL:	**0.0873**		**% of AOEL:**	**0.0695**	

b) Residential exposure to flurtamone

Dermal exposure *via* deposits caused by spray drift

$SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$

Where:

SDE_R	*= Systemic Exposure of Residents via the Dermal Route (mg/kg bw/day).*	
AR	*= Application Rate (mg/cm^2)*	*0.125 kg a.s./ha = 0.00125 mg/cm^2.*
D	*= Drift (%)*	*0.29 % (10 m distance) for 1 application.*
TTR	*= Turf Transferable Residues (%)*	*5 %*
TC	*= Transfer Coefficient (cm^2/hour)*	*7300 cm^2/h (adult), 2600 cm^2/h (child).*
H	*= Exposure Duration (hours)*	*2 h.*
DA	*= Dermal Absorption (%)*	*8 %.*
BW	*= Body Weight (kg/person)*	*60 kg (adult), 16.15 kg (child).*

Inhalation exposure due to vapour drift.

$SIE_R = (AC_V \times IR \times IA) / BW$

Where:

SIE_R	*= Systemic Exposure of Residents via the Inhalation Route (mg/kg bw/day)*	
AC_V	*= Airborne Concentration of Vapour (mg/m^3): 0 mg/m^3 (vapour pressure of a.s. < 10^{-5} Pa).*	
IR	*= Inhalation Rate (m^3/day)*	*10.57 m^3/day (adult), 8.31 m^3/day (child).*
IA	*= Inhalation Absorption (%)*	*100 %*
BW	*= Body Weight (kg/person)*	*60 kg (adult), 16.15 kg (child).*

As the vapour pressure of **flurtamone** is 7.0×10^{-6} Pa @ 20 °C and 2.0×10^{-9} Pa @ 25 °C the product is considered as non-volatile and therefore $AC_V = 0$ and $SIE_R = 0$. In addition, oral exposure of children is estimated as well by the following equations.

Children's hand-to-mouth transfer

$SOE_H = (AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA) / BW$

Where:

SOE_H	*= Systemic Oral Exposure via the Hand to Mouth Route (mg/kg bw/day).*	
AR	*= Application Rate (mg/cm)*	*0.125 kg a.s./ha = 0.00125 mg/cm^2.*
D	*= Drift (%)*	*0.29 % (10 m) for 1 application.*
TTR	*= Turf Transferable Residues (%)*	*5 %.*
SE	*= Saliva Extraction Factor (%)*	*50 % (EPA default value).*
SA	*= Surface Area of Hands (cm^2)*	*20 cm^2.*
Freq	*= Frequency of Hand to Mouth (events/hour)*	*20 events/h.*
H	*= Exposure Duration (hours)*	*2 h.*
OA	*= Oral Absorption (%)*	*100 %*
BW	*= Body Weight (kg/person)*	*16.15 kg (child).*

Children's object-to-mouth transfer

$SOE_O = (AR \times D \times DFR \times IgR \times OA) / BW$

Where:

SOE_O	*= Systemic Oral Exposure via the Object to Mouth Route (mg/kg bw/day).*	
AR	*= Application Rate (mg/cm²)*	*0.125 kg a.s./ha = 0.00125 mg/cm².*
D	*= Drift (%)*	*0.29 % (10 m) for 1 application.*
DFR	*= Dislodgeable Foliar Residues (%)*	*20 %.*
IgR	*= Ingestion Rate for Mouthing of Grass/Day (cm²)*	*25 cm²/day.*
OA	*= Oral Absorption (%)*	*100 %*
BW	*= Body Weight (kg/person)*	*16.15 kg (child).*

Total systemic exposure of residents is then estimated for

Adults: $SE_R = SDE_R + SIE_R$ (mg/kg bw/day)
Children: $SE_R = SDE_R + SIE_R + SOE_H + SOE_O$ (mg/kg bw/day)

Where:

SE_R	*= Systemic Exposure of Residents (mg/kg bw/day)*
SDE_R	*= Systemic Dermal Exposure of Residents (mg/kg bw/day)*
SIE_R	*= Systemic Inhalation Exposure of Residents (mg/kg bw/day)*
SOE_H	*= Systemic Oral Exposure via the Hand to Mouth Route (mg/kg bw/day)*
SOE_O	*= Systemic Oral Exposure via the Object to Mouth Route (mg/kg bw/day)*

Table CP 7.2.2.1-3. Detailed calculations of bystander exposure to Flurtamone, absorbed dose and % of AOEL

Adults	Children
Resident: Exposure after application with Field Crop, tractor mounted/trailed	
Dermal exposure: $SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$ (0.00125 x 0.29 % x 5 % x 7300 x 2 x 8 %) / 60 Absorbed dose: 0.000003528 mg/kg bw/d	Dermal exposure: $SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$ (0.00125 x 0.29 % x 5 % x 2600 x 2 x 8 %) / 16.15 Absorbed dose: 0.000004669 mg/kg bw/d
Inhalation exposure: $SIE_R = (AC_V \times IR \times IA) / 1000 \times BW$ (0 x 16.57 x 100 %) / 60 Absorbed dose: 0.0 mg/kg bw/d	Inhalation exposure: $SIE_R = (AC_V \times IR \times IA) / BW$ (0 x 8.31 x 100 %) / 16.15 Absorbed dose: 0.0 mg/kg bw/d
	Oral exposure (hand-to-mouth transfer): $SOE_H = (AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA) / BW$ (0.00125 x 0.29 % x 5 % x 50 % x 20 x 20 x 2 x 100 %) / 16.15 Absorbed dose 0.000004489 mg/kg bw/d
	Oral exposure (object-to-mouth transfer): $SOE_O = (AR \times D \times DFR \times IgR \times OA) / BW$ (0.00125 x 0.29 % x 20 % x 25 x 100 %) / 16.15 Absorbed dose 0.000001122 mg/kg bw/d
Total systemic exposure:	**Total systemic exposure:**
$SE_R = SDE_R + SIE_R$	**$SE_R = SDE_R + SIE_R + SOE_H + SOE_O$**
Total absorbed dose: 0.00000353 mg/kg bw/d	**Total absorbed dose: 0.0000103 mg/kg bw/d**
% of AOEL: 0.0063	**% of AOEL: 0.0184**

CP 7.2.2.2 Measurement of bystander and resident exposure

Since the exposure estimate carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under practical conditions of use, a study to provide a measure of bystander exposure was not necessary and was therefore not carried out.

CP 7.2.3 Worker exposure

According to the use pattern the product is applied in the EU at BBCH growth stage 00-09 (pre-emergence) or 10-29 (post-emergence). Therefore it is reasonable to conclude that there is either no need for farmers to re-enter the treated cereal fields and to come into contact with the crop or that any contact is going to be negligible. The control of the crops shortly after spray application ("scouting") can be performed visually, i.e. without having contact to the treated weeds which would not normally be expected to lead to exposure. However, in order to demonstrate that even if the farmer were to touch the crop there would be no unacceptable levels of exposure a risk assessment for scouting is provided.

CP 7.2.3.1 Estimation of worker exposure

The greatest potential for worker exposure following re-entry will be contamination *via* the skin. Risk of inhalation exposure during re-entry is generally confined to a brief period after application, while the product is drying, which will be rapid under outdoor conditions and would generally be avoided according to good agricultural practices. Exposure to workers entering treated areas are predicted using an exposure model proposed by Hoernicke *et al*,[4] (1998) and Krebs *et al.* [5](2001). The following assumptions are made:

- Re-entry exposure is predominantly *via* the dermal route (contact with the foliage)
- Residues on the foliage depend on:
i) application rate
ii) extent of remaining residues from previous applications
iii) the Leaf Area Index (LAI) [total size of foliage compared to surface area]
- Transfer of residues from foliage to the clothes or skin of workers depends mainly on the intensity of contact with the foliage.
- Activities with a similar pattern can be grouped and a generic Transfer Coefficient (TC) applied
- Dislodgeable Foliar Residues (DFR) are calculated using a default value of 3 µg as/cm² per kg as/ha as proposed by EUROPOEM II.
- Workers re-enter the treated culture shortly after the spray has dried on plant surfaces, nevertheless it is now recommended to use the higher dermal absorption values amongst neat and diluted values (8 % for **flurtamone**).

[4] Hoernicke, E.; Nolting, H.G.; Westphal, D.: Label instructions for the protection of workers re-entering crop growing areas after application of plant protection products; Nachrichtenbl. Deut. Pflanzenschutzd. 50 (10), (1998), 267 - 269 (document no. M-107544-01-1)

[5] Krebs, B., Maasfeld, W., Schrader, J., Wolf, R., Hoernicke, E., Nolting, H-G., Backhaus, G.F. and Westphal, D. (2001) Uniform principles for safeguarding the health of workers re-entering crop growing areas after application of plant-protection products, Worker exposure to agrochemicals, Ed. R.C. Honeycutt and E.W. Day, chapter 8, 107- 117, CRC Press (2001), (document no.: M-209388-01-1)

The Dermal Exposure **(D)** calculation is performed according to the following equation:

$$D = (DFR \times TC \times WR \times AR \times P)/BW$$

Where,

DFR: Dislodgeable foliar residues [µg a.s./cm²]
TC : Transfer Coefficient [cm²/ h]
WR: Work rate [hours/day]
AR: Application rate [kg a.s./ha]
P: Protection factor for PPE (P = 1 no PPE)
BW: Body weight [kg]

The Systemic Exposure **(S)** calculation is performed according to the following equation:

$$S = D \times DA$$

Where,

D: Dermal Exposure [mg a.s./kg bw/day]
DA : Dermal Absorption [%]

DFR levels:
A single application is considered in this risk assessment resulting in an assumed DFR of 3 µg a.s./cm² per kg a.s./ha.

Transfer Coefficients:
As no specific TCs are available in Europe to assess re-entry activities performed in cereals a reasonable value of 2500 cm²/h has been used in this risk assessment. This value was obtained from the Europoem II data for handling vegetables and is considered to be conservative with regards to inspection/scouting activities.

Working Hours:
A period of 2 hours per day is considered reasonable for crop inspection/scouting.

Body Weight:
A body weight of 60 kg is assumed for the re-entry worker.

Predicted exposures are compared with the AOEL of **flurtamone**. Systemic exposure values assume the highest dermal absorption values. Exposure estimates based proportions of the systemic AOELs accounted for by the estimates are summarized in the **Table 7.2.3.1-1**.

Table CP 7.2.3.1-1. Summary of predicted worker exposures arising from the use of DFF+FLT SC 350 and comparison with the AOEL

Active substance	Systemic exposure (mg a.s./kg bw/day)	AOEL (mg a.s./kg bw/day)	% of AOEL
Flurtamone	0.0025	0.056	4.46

*Dermal absorption value of 8 % for **Flurtamone**; Inhalation absorption was taken as 100 %.

Assessment

The exposure of workers entering treated areas is well within acceptable limits for DFF+FLT SC 350.

Detailed calculations of worker exposure during re-entry are presented below:

D	=	DFR	x	TC	x	WR	x	AR	x	P	÷	BW
		µg a.s./cm²		*cm²/h*		*h/day*		*kg/ha*				*kg*
D	=	3	x	2500	x	2	x	0.125	x	1	÷	60
D	=	31.25 µg a.s./day/kg bw										
						÷ 1000 µg/mg						
D	**=**	**0.0313 mg a.s./kg bw/day**										
								x DA (8 %, highest dermal absorption value)				
S	**=**	**0.0025 mg a.s./kg bw/day**										

CP 7.2.3.2 Measurement of worker exposure

Since the exposure estimate carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under practical conditions of use, a study to provide a measure of worker exposure was not necessary and was therefore not carried out.

CP 7.3 Dermal adsorption

Summary and conclusion on dermal absorption

Flurtamone
The extent of dermal absorption of **flurtamone** formulated as an SC 350 formulation, containing **flurtamone** at a concentration of 250 g/L and diflufenican at a concentration of 100 g/L, was investigated *in vitro* using human and rat skin. A summary of the study is given in the following section. A conclusion and recommendation regarding the dermal absorption of **flurtamone** in the DFF+FFA SC 350 formulation is given below.

The *in vitro* study results indicated that the mean percentage of [^{14}C]-**flurtamone** considered to be potentially absorbable over a period of 24 hours for the neat formulation was 0.34 % and 2.9 % for the human and rat skin, respectively. The mean percentage of [^{14}C]-**flurtamone** considered to be potentially absorbable at the low dose was 5.1 % and 19.4 % for the human and rat skin respectively.

In the absence of an appropriate *in vivo* rat study the *in vitro* human skin values were used alone.

According to the new EFSA guidance[6] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75 % of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were met for high dose group in this study. There is also the provision that a standard deviation equal to or larger than 25 % of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Albeit that the notifier considers that the value of 25 % for the standard deviation limit to be too conservative, the

[6] EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665.

application of the guidance results in the following values for [^{14}C]-**flurtamone** in the Diflufenican + **Flurtamone** SC 100+250 formulation:

- **0.3 % for the neat formulation (250 g/L)**
- **8 % for the low dose (0.25 g/L).**

CP 7.3.1 Dermal absorption, *in vivo*

No study available with the appropriate formulation.

CP 7.3.2 Comparative dermal absorption, *in vitro* using rat and human skin

Report:	**CP 7.3**
Title:	Bacara [^{14}C]-**Flurtamone**: Comparative *In Vitro* Dermal Absorption Study using Human and Rat skin.
Document N°:	M-261476-01-1
Guidelines:	O.E.C.D. guideline for the testing of chemicals, skin absorption: *in vitro* Method 428 (April 2004), O.E.C.D. Environmental health and safety publications series on testing and assessment N°28, Guidance document for the conduct of skin absorption studies (March 2004), European Commission guidance document on dermal absorption-Sanco/222/2000 rev.7, (March 2004).
GLP	Yes

Material and methods

Rat skin:

Species, strain: Rat, Sprague-Dawley: Crl:CD (SD).
Source: [redacted] (France).
Sex: Male.
Number: 13.
Anatomical site: Dorsal
Rat Skin Preparation: Each animal was killed by cervical dislocation. After sacrifice the skin was clipped and removed for use in the study. The dorsal skin was dermatomed by use of a mini-dermatome to obtain samples of *ca* 480 to 600 µm in thickness.

Human skin: Source: [redacted]s, France.
Number and sex: 10 donors, female.
Anatomical region: Abdomen.
Thickness: 475 to 678 µm.

Test Material:

Non-radiolabelled: Batch: DP639D.
Purity = 99.5 %.
Radiolabelled: [phenyl-UL-^{14}C]-**flurtamone**
Batch: SEL/1199.
Specific activity: 3.73 MBq/mg.
Radiopurity of the formulation: 99 %.

Formulation: The formulation used in this experiment was the Bacara SC 350 formulation containing **flurtamone** (250 g/L) and diflufenican (100 g/L). It was used at two nominal concentrations of **flurtamone**: neat, 250 g **flurtamone**/L and 0.25 g **flurtamone**/L.

Test system: A flow-through diffusion cell system (Franz's cell modified, Gallas, France) was used to study the absorption of the test substance (exposure area of 1 cm^2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid was Eagle's medium supplemented with 5 % bovine serum albumin and gentamycin (50 mg/L) at a pH of 7.4. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2 °C (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.

Skin integrity: Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Dermalab, Cortex Technology, Denmark) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 40 g/hm² were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

Treatment: The dose preparation was applied to the split-thickness skin sample with a pipette at the rate of approximately 10 µL/cm^2 exposed skin. The dose preparations were assayed for radioactivity content (by LSC) by using dose checks (surrogate dose) taken before, during and after the dosing process.

Sampling: The receptor fluid passing through the receptor chamber was collected in glass vials held in a fraction collector. The fraction collector was started after dose application. Samples were then collected hourly for the duration of the experiment (24 hours). At 8 hours post-application, the skin was swabbed with freshly prepared 1 % v/v Tween 80 in PBS (phosphate buffer saline) using natural sponge swabs, in order to remove and retain the non-absorbed dose, until no radioactivity was detected with a Geiger-Müller monitor. At the end of the study (24 hours after application), the treated skin and the skin adjacent to the treatment site (surrounding swabs) were swabbed. Each skin sample was tape-stripped to remove the stratum corneum. This involved the application of Monaderm adhesive tape (Monaderm, Monaco) for 5 seconds before the tape was carefully removed against the direction of hair growth. This procedure was continued until a 'shiny' appearance of the epidermis was evident, which indicated that the stratum corneum had been removed. The tape-strips were collected into scintillation vials for analysis. The skin surrounding the application site (surrounding skin) was separated from the treated skin. Both surrounding skin and tape-stripped treated skin were retained for analysis.

Radioassay: The amounts of radioactivity in the various samples were determined by liquid scintillation counting (LSC). Samples were counted for 10 minutes or for 2 sigma % in an appropriate scintillation cocktail using a Packard 1900 TR counter with on-line computing facilities. Quenching effects were determined using an external standard and spectral quench parameter (tSIE) method. Efficiency correlation curves were prepared for each scintillation cocktail and were regularly checked by the use of [^{14}C-n-hexadecane standards. The scintillation counter was recalibrated when a deviation of greater than 2 % was observed when counting quality control standards. The

limit of detection was taken to be twice the background values for blank samples in appropriate scintillation cocktails.

Findings:
Flurtamone was demonstrated to be soluble in the receptor fluid at the concentration of 0.3 mg/mL of receptor fluid which was approximately 948 times the maximal concentration of **flurtamone** in the receptor fluid. Therefore the solubility in the receptor fluid was deemed to be sufficient to avoid any risk of back diffusion.

Measurements of the homogeneity of the three concentrations of formulation applied indicated that it was acceptable.

Good recovery data were obtained, with mean total recoveries of radioactivity in the range of 97.7 % to 100.2 % of the applied dose.

These study results are presented in **Table 7.3.2-1**

Table 7.3.2-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]-flurtamone in the DFF+FFA SC 350 formulation at the rates of 250 g/L and 0.25 g/L to human and rat skin samples.

Results expressed in terms of percentage of applied radioactivity.

Dose Levels	Distribution of radioactivity (% dose)							
	Neat formulation: High dose (SYP12772, 250 g/L)				Dilution: Low dose (SYP12778, 0.25 g/L)			
Species	Human (n=6)		Rat (n=5)		Human (n=9)		Rat (n=7)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT								
Skin swabs (8h)	99.18	0.62	89.22	4.58	89.35	7.93	70.25	15.50
Skin swabs (24h)	0.19	0.40	0.31	0.30	1.06	0.65	3.15	2.07
Surface Dose (tape-strips 1&2)	0.30	0.43	2.13	2.10	1.748	1.512	3.789	2.229
Donor chamber	0.23	0.49	0.30	0.58	1.318	2.408	1.091	1.572
Total % non-absorbed	**99.89**	**0.29**	**95.96**	**5.00**	**93.48**	**5.26**	**78.28**	**14.01**
SKIN COMPARTMENT								
Skin [a]	0.06	0.04	0.28	0.41	1.19	1.46	1.68	1.72
Stratum corneum [b]	0.17	0.33	2.43	1.25	1.46	1.43	12.26	9.03
Total % at dose site	**0.23**	**0.36**	**2.72**	**1.40**	**2.65**	**2.63**	**13.94**	**10.38**
RECEPTOR COMPARTMENT								
Receptor fluid (0-24h)	0.12	0.08	0.13	0.02	2.39	1.28	5.12	4.37
Receptor fluid terminal	n.d.	n.a.	0.006	0.002	0.09	0.13	0.38	0.39
Receptor chamber	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Total % directly absorbed [c]	**0.12**	**0.08**	**0.13**	**0.02**	**2.477**	**1.274**	**5.496**	**4.751**
Total % Potentially Absorbable [d]	**0.34**	0.37	**2.85**	**1.39**	**5.12**	2.94	**19.44**	14.11
TOTAL % RECOVERY	**100.24**	**6.47**	**98.80**	**5.05**	**98.60**	**4.06**	**97.72**	**2.70**

[a]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[b]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[c]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[d]: total % directly absorbed + total % at dose site
SD: standard deviation
n.d.: not detected (below the limit of detection)
n.a. : not applicable
n: number of skin cells used for calculation
In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

Conclusion

The dermal penetration of [^{14}C]-**flurtamone** through human and rat dermatomed skin using the DFF+FFA SC 350 formulation was investigated at two concentrations corresponding to the neat product (250 g /L) and to a representative dilution (0.25 g/L), respectively.

The mean percentage of **flurtamone** in the SC 350 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 0.34 % and 2.9 % for the human and rat skin, respectively.

The mean percentage of **flurtamone** in the SC 350 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 5.1 % and 19.4 % for the human and rat skin respectively.

According to the new EFSA guidance[7] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75 % of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were met for high dose group in this study. There is also the provision that a standard deviation equal to or larger than 25 % of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Albeit that the notifier considers that the value of 25 % for the standard deviation limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-**flurtamone** in the + Diflufenican + **Flurtamone** SC 100+250 formulation.

- **0.3 % for the neat formulation (250 g/L).**
- **8 % for the low dose (0.25 g/L).**

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information -data provided separately (Document J)

[7] EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665.