Bayer CropScience

Document Title

Summary of the toxicological studies foramsulfuron + isoxadifen-ethyl OD 45 (22.5+22.5 g/L)

PUBLIC VERSION

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Section 7: Toxicological studies

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

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Bayer CropScience

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Version history

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

[1] Changes will be presented according to the 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

Comments with respect to the Annex I renewal of approval process

This dossier contains study reports already submitted by Bayer CropScience for the Annex I inclusion of foramsulfuron, as well as new data, not yet evaluated at EU level and that was considered by the applicant to be necessary for the renewal of approval of foramsulfuron. In order to distinguish these reference to studies in the original dossier are depicted in grey.

For summaries of studies submitted during the frame of the first Annex I inclusion please refer to the corresponding section in the Monograph. Copies of the study reports are provided in the baseline dossier provided by Bayer CropScience. Additional studies which were not submitted during the Annex I inclusion process are provided in the dossier and summarized in this document.

Foramsulfuron + isoxadifen-ethyl OD 45 (also called Equip OD®) is an Oil Dispersible (OD) formulation containing the herbicide foramsulfuron (22.5 g/L) and the safener isoxadifen-ethyl (22.5 g/L). This formulation is applied in various in Europe on various crops, notably in corn fields.

CP 7.1 Acute toxicity

Equip OD® has a low acute toxicity. It is an irritant for skin but not a skin sensitizer. The toxicity data package that was submitted for the first European approval was conducted with Equip OD® (batch coded AE F130360 01 1K05 A5). Since the first approval of the formulation at European level there have been changes in the composition of the formulation. A bridging document has been included in the confidential section (J-CP) of the dossier and it demonstrates that the differences are not significant and do not justify the repetition of animal studies.

Type of study	Species	Sex	Result	Reference
Acute oral toxicity	Rat	Male & Female	> 5000 mg/kg	M-192928-01-1 (1999) XXXXXX KCP 7.1.1/01
Acute dermal toxicity	Rat	Male & Female	5000 mg/kg	M-192930-01-1 (2000) XXXXXX KCP 7.1.2/01
Acute inhalation toxicity	Rat	Male & Female	LC50 > 5.25 mg/L	M-192640-01-1 (1999) XXXXXX KCP 7.1.3/01
Skin irritancy	Rabbit	Male	Moderate and reversible irritant, Xi, R38	M-192932-01-1 (1999) XXXXXX KCP 7.1.4/01
Eye irritancy	Rabbit	Male	Slight reversible irritant, but not labelled	M-192934-01-1 (2000) XXXXXX KCP 7.1.5/01
Acute sensitization (3 induction Buehler assay)	Guinea pig	Female	Not sensitizer	M-193056-01-1 (1999) XXXXXX KCP 7.1.6/01
Acute sensitization (9 induction Buehler assay)	Guinea pig	Female	Not sensitizer	M-202547-01-1 (2001) XXXXXX KCP 7.1.6/02

Type of study	Species	Sex	Result	Reference
Acute sensitization (LLNA)	Mouse	Female	Not sensitizer	M-226970-01-1 (2004) **XXXXXX** KCP 7.1.6/03

Therefore, according to the EC classification criteria the formulation Equip OD® is labelled as follows:

- **EC classification criteria (2001/59/EC):**
  Acute dermal irritancy: Xi/R38 "irritating to skin"

- **GHS (rev.4) 2011:**
  Dermal irritancy: Category 3: WARNING, H316 "Cause mild skin irritation"

- **Regulation (EC) No 1272/2008 (CLP):**
  Dermal irritancy: Category 2: WARNING, H315 "Cause skin irritation"

CP 7.1.1 Oral toxicity

Report:	K[redacted]v;[redacted];1999;M-192928-01
Title:	Rat acute oral toxicity AE F130360 + AE F122006 oil dispersable 22.5 + 22.5 g/l Code: AE F160360 01 1K05 A3
Report No:	C005915
Document No(s):	Report includes Trial Nos.: TOX95126 M-192928-01-1
Guidelines:	**EU (=EEC): 92/69/EEC, B.1; SMAF: 4200; OECD: 401; USEPA (=EPA): OPPTS.870.1100; Deviation not specified**
GLP/GEP:	**yes**

The acute oral LD_{50} for AE F130360 01 1K05 A304 in both male and female Sprague Dawley rats was >5000 mg/kg body weight, the highest international limit dose.

According to the EC classification criteria this formulation is labelled as follows:

- **EC classification criteria (2001/59/EC): None**
- **GHS (rev.4) 2011: None**
- **Regulation (EC) No 1272/2008 (CLP): None**

CP 7.1.2 Dermal toxicity

Report:	K[redacted]k;[redacted];;2000;M-192930-01
Title:	Rat acute dermal toxicity AE F130360 + AE F122006 oil flowable 22.5 + 22.5 g/l Code: AE F130360 01 1K05 A3
Report No:	C005916
Document No(s):	Report includes Trial Nos.: TOX95127 M-192930-01-1
Guidelines:	**EU (=EEC): 92/69/EEC, B, B.1; JMAF: 4200; OECD: 402; USEPA (=EPA): OPPTS 870.1200;Deviation not specified**
GLP/GEP:	**yes**

The acute dermal LD_{50} value in Sprague Dawley rats of AE F130360 01 1K05 A304 was >5000 mg/kg body weight, the highest international regulatory limit dose.

According to the EC classification criteria this formulation is labelled as follows:

- **EC classification criteria (2001/59/EC): None**
- **GHS (rev.4) 2011: None**
- **Regulation (EC) No 1272/2008 (CLP): None**

CP 7.1.3 Inhalation toxicity

Report:	K[redacted]k;[redacted];1999;M-192640-01
Title:	Rat acute inhalation toxicity AE F130360 + AE F122006 22.5 + 22.5 g/l oil flowable Code: AE F130360 01 1R05 A3
Report No:	C005886
Document No(s):	Report includes Trial Nos.: TOX/99207 M-192640-01-1
Guidelines:	**EU (=EEC): 92/69/EEC B2; JMAF: 4200; OECD: 403; USEPA (=EPA): OPPTS 870.1300;Deviation not specified**
GLP/GEP:	**yes**

The 4-hour acute inhalation median lethal concentration (LC_{50}) of AE F130360 01 1K05 A304 to Sprague Dawley rats was >5.25 mg/L, which did not cause mortality and was the highest achievable concentration.

According to the EC classification criteria this formulation is labelled as follows:

- **EC classification criteria (2001/59/EC): None**
- **GHS (rev.4) 2011: None**
- **Regulation (EC) No 1272/2008 (CLP): None**

CP 7.1.4 Skin irritation

Report:	K[redacted]x;[redacted];;1999;M-192932-01
Title:	Rabbit skin irritancy AE F130360 + AE F122006 22.5 + 22.5 g/l, oil flowable Code: AE F130360 01 1K05 A3
Report No:	C005917
Document No(s):	Report includes Trial Nos.: TOX95128 M-192932-01-1
Guidelines:	**EU (=EEC): 92/69/EEC, B, B.5; JMAF: 4200; OECD: 404; USEPA (=EPA): OPPTS 870.2500;Deviation not specified**
GLP/GEP:	**yes**

AE F130360 01 1K05 A304 was moderately and reversibly irritating to rabbit skin and moderately irritating according to the Primary Irritancy Index.

According to the EC classification criteria this formulation is labelled as follows:

- **EC classification criteria (2001/59/EC):**
  Acute dermal irritancy: Xi/R38 "irritating to skin"
- **GHS (rev.4) 2011:**
  Dermal irritancy: Category 3: WARNING, H316 "Cause mild skin irritation "
- **Regulation (EC) No 1272/2008 (CLP):**
  Dermal irritancy: Category 2, WARNING, H315 "Cause skin irritation"

CP 7.1.5 Eye irritation

Report:	K[redacted]x;[redacted];;2000;M-192934-01
Title:	Rabbit eye irritancy AE F130360 + AE F122006 22.5 + 22.5 g/l oil flowable Code: AE F130360 01 1K05 A3
Report No:	C005918
Document No(s):	Report includes Trial Nos.: TOX95129 M-192934-01-1
Guidelines:	**EU (=EEC): 92/69/EEC, B, B.5; JMAF: 4200; OECD: 405; USEPA (=EPA): OPPTS 870.2400;Deviation not specified**
GLP/GEP:	**yes**

AE F130360 01 1K05 A304 was slightly and reversibly irritating to the rabbit eye and slightly irritating according to the Primary Irritancy Index.

According to the EC classification criteria this formulation is labelled as follows:

- **EC classification criteria (2001/59/EC): None**
- **GHS (rev.4) 2011: None**
- **Regulation (EC) No 1272/2008 (CLP): None**

CP 7.1.6 Skin sensitization

In the original submission for the approval of foramsulfuron and the formulation EQUIP OD at European level a skin sensitisation study was submitted according to the 3-induction Buehler test.

Report:	K[redacted]n;[redacted];;1999;M-193056-01
Title:	Guinea pig skin sensitisation (3-induction Buehler test) AE F130360 + AE F122006 22.5 + 22.5 g/l, oil flowable Code: AE F130360 01 1K05 A3
Report No:	C005974
Document No(s):	Report includes Trial Nos.: TOX95130 M-193056-01-1
Guidelines:	**EU (=EEC): 96/54/EC, B.6; OECD: 406; USEPA (=EPA): OPPTS 870.2600;Deviation not specified**
GLP/GEP:	**yes**

In the study it was shown that the formulation, AE F130360 01 1K05 A304, was not a skin sensitiser according to the 3-induction guinea pig Buehler test.

According to the EC classification criteria this formulation is labelled as follows:

- **EC classification criteria (2001/59/EC): None**
- **GHS (rev.4) 2011: None**
- **Regulation (EC) No 1272/2008 (CLP): None**

New data
Two additional studies are presented in this document, that were not previously reviewed at European level – an additional Buehler test (with 9 induction applications) and an LLNA study (KCA 7.1.6/02 and 7.1.6/03 respectively). The original Buehler test submitted for the first review was a three-induction test which today is not considered to be sufficient to prove the non-sensitizing properties of a formulation.The additional Buehler test was performed with 9 induction applications and is included in the summary for completeness. However, since the formulation contains the safener, isoxadifen-ethyl, which is classified as H317 (may cause an allergic skin reaction) an LLNA study was performed to confirm the results of the Buehler test (non-sensitising). It should also be noted that the LLNA was performed using the formulation AE F130360 01 1K05 A901 which is equivalent to the formulation currently sold (see Doc J-CP for detailed information on the composition of the formulation).

Additional Buehler x 9 sensitization test

Report:	K[redacted]n;[redacted];;2001;M-202547-01
Title:	EQUIP (AE F130360 01 1K05 A3xx) - Sensitizing potential in the guinea-pig - modified Buehler Test (9 induction applications)
Report No:	C016513
Document No(s):	Report includes Trial Nos.: 198/131 M-202547-01-1
Guidelines:	**EU (=EEC): 92/69, V, B6; OECD: 406; USEPA (=EPA): 798.4100;Deviation not specified**
GLP/GEP:	**yes**

Material and Methods:
The formulation AE F130360 01 1K05 A3, a light beige liquid formulation (batch number: KD945/990301) contained the active ingredients foramsulfuron (AE F130360) at the nominal concentration of 22.5 g/L (2.42%w/w certified by analysis) and isoxadifen-ethyl (AE F122006) at the nominal concentration of 22.5g/L (2.44 %w/w certified by analysis).

Thirty female Dunkin/Hartley guinea pigs were used. They were approximately 6 weeks old at arrival, housed in groups of 5, were acclimatised for 5 days and weighed 250-550 g at the start of treatment. Four extra animals were used for preliminary dose ranging investigations. Ten control and 20 test animals were used for the main study.

Preliminary study: The topical irritancy of a range of concentrations (10% w/w to undiluted compound) in sterile water was evaluated to identify where possible, a) a concentration that would produce irritation suitable for the induction phase of the main study and b) a maximum non-irritant concentration for the challenge phase.

Main study: Based on the results of the preliminary study, the following concentrations were used:

> Induction phase topical applications: 50% v/v in sterile water, which was the minimally irritant concentration
>
> Challenge phase topical applications: 10% v/v in sterile water, which was the highest concentration that did not produce irritancy

i) Induction phase:
Ten animals were allocated to a control group (induction : vehicle – challenge : test article) and twenty animals to the treated group (induction and challenge : test article).

Application area: one clipped and shaved area on the left lateral abdominal region
Time of administration ; day 0, 2, 4, 7, 9, 11, 14, 16 and 18

Method of application : the test article was applied (0.5 ml, 50% solution in water for injection) under an occlusive dressing composed of Codex hydrophilic gauze 20 x 20 mm, maintained in contact with the skin using an occlusive and hypo-allergenic patch. The position of this patch was maintained by an additional dressing.

Exposure : 6 hours
Rest period : days 18 to 28

ii) Challenge phase:
Ten days after the last induction application all the test and control guinea pigs were challenged topically. A topical 6-hour challenge of a 10% v/v dilution of the test material in sterile water on a 20 x 20 mm gauze patch was applied to area of the shaved skin of the right flank.

Skin responses at the challenge sites were evaluated 24 and 48 hours after removal of the dressing. The cutaneous macroscopic examinations were performed according to Draize scale to the challenge application site, 24 and 48h after removal of the occlusive dressing.

The criteria chosen to consider the doubtful reactions as positive or negative were modified as follows: non persistent (at 24 hours and not at 48 hours) reactions were considered as negative.

All animals were observed twice daily - at the beginning and end of the working day - for signs of ill-health or toxicity. Body weights were recorded on Study Day 0 (the first day of topical application) and

on the last day observations of dermal responses were made (Day 29).

Findings:
Main study: There was no mortality. Body weight changes in the treated animals were not influenced by treatment when compared to controls.

i) Induction phase:
Slight to moderate erythema and slight oedema was observed in all test animals following the induction applications. No dermal reactions were seen in any control animal during this period.

ii) Challenge phase:
After the challenge, the macroscopic examinations did not reveal any lesion of delayed hypersensitivity in the 20 guinea-pigs of the treated group. No cutaneous abnormality was noted in the 10 guinea-pigs of the control group.

Conclusion:
Under the experimental conditions of the study and according to the modified method established by Buehler, a challenge application with the test article at a concentration of 10% (v/v) did not provoke any reaction of cutaneous sensitisation.

According to the EC classification criteria (2001/59/EC Directive), this formulation is labelled as follows:

- **EC classification criteria (2001/59/EC Directive: None**
- **GHS (rev.4) 2011: None**
- **Regulation (EC) No 1272/2008 (CLP): None**

Report:	K[redacted]6; [redacted];2004;M-226970-01
Title:	AE F130360 – Evaluation of potential dermal sensitization in the local lymph node assay (LLNA)
Report No:	C039527
Document No:	M-226970-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**yes**

Material and Methods:
The dermal contact sensitization potential of AE F130360 00 1K05 A9, an agrochemical formulation containing the active ingredient foramsulfuron (AE F130360) (nominal 22.5 g/L) and the safener isoxadifen-ethyl (nominal 22.5 g/L), was tested using the murine Local Lymph Node Assay. Sixteen female CBA mice were allocated to 4 groups of four animals each:

- three groups received the test substance at a concentration of **20, 10 or 5%** in DMF,
- one control group received the vehicle DMF.

The test substance or the vehicle were applied on external surfaces of each ear (50 µl/ animal) for three consecutive days (Days 0, 1 and 2) at the appropriate concentrations. On Day 5, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated thymidine and the obtained values were used to calculate proliferation indices.

Findings:

Table 7.1.6-1

Group Number	Test Group Name	Mean DPM	Proliferation Index
1	control DMF	3784	-
2	AE F130360 01 1K05 A9 5% DMF	9546	2.5
3	AE F130360 01 1K05 A9 10% DMF	8441	2.2
4	AE F130360 01 1K05 A9 20% DMF	9998	2.6

Negative lymphoproliferative responses (PI < 3) were noted at all tested concentrations

- No mortality and no clinical signs were observed during the study.
- No cutaneous reactions were observed in the vehicle, reference control or treated groups.
- Negative lymphoproliferative responses (PI < 3) were noted at all tested concentrations.

Conclusion

AE F130360 01 1K05 A9 showed no potential for sensitization under the conditions of the Local Lymph Node Assay.

According to the EC classification criteria (2001/59/EC Directive), this formulation is labelled as follows:

- **EC classification criteria (2001/59/EC Directive: None**
- **GHS (rev.4) 2011: None**
- **Regulation (EC) No 1272/2008 (CLP): None**

CP 7.1.7 Supplementary studies on the plant protection product

Not relevant: the formulation is not recommended to be combined with other plant protection products.

CP 7.1.8 Supplementary studies for combinations of plant protection products

Not required by EU Regulation 1107/2009 & EU Regulation 284/2013.

CP 7.2 Data on exposure

CP 7.2.1 Operator exposure

AE F130360 01 1K05 A9 (also called Equip OD®) is an oil dispersion (OD) formulation containing the herbicide foramsulfuron (22.5 g/L) and the safener isoxadifen-ethyl (22.5 g/L). The proposed use is as an herbicide on grass and dicot weeds in corn fields. The product is to be packaged in wide neck bottles/containers of varying sizes depending on the country (0.25-10L). Applications of Equip OD® will be achieved via a field crop sprayer (tractor mounted ground boom sprayer). Water will be the diluent/carrier in all situations. Usage information pertinent to operator exposure is summarised in Table 7.2.1-1.

Table 7.2.1-1: Application parameters for Equip OD®

Application technique	Crop	Country	Maximum dose rate			Spray volume (L/ha)	No of appl.	Interval between appl. (days)	PHI (days)
			(L/ha product)	(g as/ha)					
				Foramsulfuron	Isoxadifen ethyl				
FCS	Corn	Europe	2.667*	60*	60*	100* to 400	1**	-	#
			1.33	30	30		2	7-14	

FCS = Field Crop Sprayer. Appl. = application
PHI = Pre Harvest Interval.
#: covered by normal vegetation period between last application and harvest
* = worst case used for calculations
**= Single application of Equip OD® at the maximum product rate of 2.6 L/ha

Operator exposure estimates are calculated using both the German model[1] ([redacted] *et al.*, 1992) and the UK-POEM[2] (PSD, 1992). Exposure calculations are performed without and with protective equipment.

Consideration on acceptable operator exposure level (AOEL)

Foramsulfuron : Considering the proposed use pattern of Equip OD®, it is appropriate to compare predicted exposures to an AOEL derived from sub-chronic dosing studies. An Acceptable Operator Exposure Level (AOEL) of 0.1 mg/kg bw/day is established for foramsulfuron from a rabbit

[1] 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 Forstwirschaft, Berlin-Dahlem, n° 277, 1992.

[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) (UK MAFF) 1992, revised model 2003

developmental study - lowest NOAEL: 50 mg/kg bw/day adjusted to 10 mg/kg bw/day for 20% oral absorption and a safety factor of 100.

Isoxadifen-ethyl : as it is a safener, has not been evaluated in this dossier. Isoxadifen-ethyl will be addressed at Member State level where required.

Consideration on dermal absorption

No data are available on the current Equip OD formulation. As the oral absorption of foramsulfuron is 20% (as used to define the AOEL), the notifier used this value for the dermal penetration of both the concentrate and the spray dilution. In the original dossier the study submitted for dermal absorption (KCA 7.3/01) was an *in vivo* rat dermal absorption study for the active substance in a previous version of the formulation that varies from the current formulation by more than the 25% permitted by the latest EFSA guidance on dermal absorption[3]. The data do suggest however that the value of 20% is a reasonable one for human skin given that 20% was achieved with the spray dilution on rat skin (generally more permeable than human skin) and approximately 7% for the concentrate.

Consideration on estimation of operator exposure

- No unacceptable risk is predicted with German model even when no PPE are worn during mixing loading and application.
- UK POEM predicts acceptable exposure if gloves are worn during mixing loading.
- Additional PPE can be used to further reduce the exposure of the operator.

It should be noted that "no PPE" in the German Model considers a lightly dressed operator, wearing a short sleeved T-Shirt, shorts and shoes. Such an unprotected operator should never handle plant protection products as this clothing is not in accordance with good occupational practice. Therefore, a coverall or alternatively, work trousers, a work jacket and sturdy footwear should be regarded as basic working clothing for operators handling plant protection products. This scenario is in line with the UK POEM, if "no PPE" is considered (i.e. an operator wearing typical (long sleeved) working clothing). Both models allow estimates for protected operators wearing additional PPE, if necessary.

A comparison of the corresponding exposure estimate with the proposed AOEL (in terms of percentage of the AOEL) is presented in table 7.2.1-2. Detailed assumptions and considerations as well as exposure calculations are presented in point 7.2.1.1.

[3] 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.

Table 7.2.1-2: Comparison of estimated systemic operator exposure to foramsulfuron [mg/kg bw/day] with the proposed AOEL

Application type	Crop	PPE	Total systemic exposure foramsulfuron [mg/kg bw/day]	% of AOEL IPV [0.1 mg/kg bw/day]
Field crop sprayer	Corn	**Field uses, German model (70 kg operator)**		
		No PPE 1)	0.0153	**15**
		With PPE 2)	0.0071	**68**
		Field uses, UK POEM (60 kg operator)		
		No PPE 1)	0.184	**184**
		With PPE 2)	0.094	**94**

1) Short trousers and a short sleeved shirt
2) One layer of typical work wear (e.g. trousers and a long sleeved shirt) as well as sturdy foot wear and protective gloves during mixing/loading

The both models estimates predict that Equip OD® can be used safely with field crop sprayers when gloves are worn during mixing/loading. As a good practice when handling pesticides, wearing gloves during spraying would reduce the exposure. The detailed calculations are presented in the Tables 7.2.1.1-1 & 2.

CP 7.2.1.1 Estimation of operator exposure

a) Estimation according to the German model

Exposure is calculated for field application technique with the maximum dose rate. Lower dose rates will be covered by this calculation and separate evaluations are not made. The following assumptions are made:

Field crop sprayer
- Treated area: 20 ha/day
- Max. dose rate: 2.667 L/ha Equip OD ® corresponding to 0.06 kg/ha foramsulfuron

Dermal absorption: 20% for diluted and concentrate product.

Operator body weight: 70 kg

Taking into account these parameters the exposure is estimated as follows.

Table 7.2.1.1-1 Calculation of operator exposure to foramsulfuron using field crop sprayers (German model, without and with PPE)

Operator exposure estimate: German model. Tractor-mounted/trailed boom sprayer: hydraulic nozzles

Product:	Equip OD					
Active substance:	Foramsulfuron		a.s. concentration:		23	[g/l or kg]
Formulation:	Liquid		PPE during mix/loading:	Respiration:		None
Dose [l or kg/ha]:	2.667			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 [%]	20.0	(concentrate)		Body:		None
	20.0	(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 = Inhalation
I_M =	0.0006	1.2002	0.00001	1.0	0.00001	D = Dermal
$D_{M(H)}$ =	2.4	1.2002	0.0411	0.01	0.000411	M = Mix/Loading
I_A =	0.001	1.2002	0.000017	1.0	0.000017	A = Application
$D_{A(C)}$ =	0.06	1.2002	0.001	1.0	0.001029	H = Hands
$D_{A(H)}$ =	0.38	1.2002	0.0065	1.0	0.006515	C = Head
$D_{A(B)}$ =	1.6	1.2002	0.0274	1.0	0.027432	B = Body

Absorbed dose:

Route		Absorption [%]	No PPE: Estimated route exposure [mg/kg bw/day]	No PPE: Systemic exposure [mg/kg bw/day]	With PPE: Estimated route exposure [mg/kg bw/day]	With PPE: Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	20.0	0.041148	0.00823	0.000411	0.000082
	Application	20.0	0.034976	0.006995	0.034976	0.006995
Inhalation:	Mix/Loading	100	0.00001	0.00001	0.00001	0.00001
	Application	100	0.000017	0.000017	0.000017	0.000017
		Total =		**0.015252**		**0.007105**

b) Estimation according to the UK-POEM

For comparison with the above German model estimates, the UK POEM is also used to estimate the exposure. Using the UK-POEM, the highest exposure for each application type is calculated if the maximum dose rates and the minimum spray volumes are used. Lower dose rates and higher spray volume will be covered by this calculation and separate evaluations are not made. For modelling purpose with the UK POEM, OD will be considered as an Emulsion Concentrate formulation (EC).

Taking into account the more realistic parameters, the following assumptions are made:

Treated area: 50 ha/6 hours per day
Volume applied: 100 L/ha as a worst case
Container size: 1L as a worst case
Max. dose rate: 0.06 kg as/ha foramsulfuron

Exposure estimates based on UK-POEM and proportions of the systemic AOEL accounted for by the estimates are summarised in the following table. Detailed calculations are presented in the table 7.2.1.1-2.

Table 7.2.1.1-2 Calculation of operator exposure to foramsulfuron using field crop sprayers (UKPOEM, without and with PPE)

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**Equip OD**	Active substance	**foramsulfuron**
Formulation type	organic solvent-based	a.s. concentration	**22.5** mg/ml
Dermal absorption from product	**20** %	Dermal absorption from spray	**20** %
Container	1 litre any closure		
PPE during mix/loading	Gloves	PPE during application	None
Dose	**2.667** l/ha	Work rate/day	**50** ha
Application volume	**100** l/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING

Container size	1	litres	
Hand contamination/operation	0.01	ml	
Application dose	2.667	litres product/ha	
Work rate	50	ha/day	
Number of operations	134	/day	
Hand contamination	1.34	ml/day	
Protective clothing	None		Gloves
Transmission to skin	100	%	10 %
Dermal exposure to formulation	1.340	ml/day	0.134 ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer/hydraulic nozzles			
Application volume	100	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	1.340	41.550	ml/day	0.134	41.550	ml/day
Concen. of a.s. product or spray	22.5	0.600075	mg/ml	22.5	0.600075	mg/ml
Dermal exposure to a.s.	30.150	24.933	mg/day	3.015	24.933	mg/day
Percent absorbed	20	20	%	20	20	%
Absorbed dose	6.030	4.987	mg/day	0.603	4.987	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0.600075	mg/ml
Inhalation exposure to a.s.	0.0360045	mg/day
Percent absorbed	100	%
Absorbed dose	0.0360045	mg/day

PREDICTED EXPOSURE	No PPE		With PPE	
Total absorbed dose	11.0536	mg/day	5.6256	mg/day
Operator body weight	60	kg	60	kg
Operator exposure	0.1842	mg/kg bw/day	0.0938	mg/kg bw/day

CP 7.2.1.2 Measurement of operator exposure

Estimations of operator exposure using PPE are performed with the respective exposure model. Detailed calculations and summaries are presented in CP 7.2.1.1.

CP 7.2.2 Bystander and resident exposure

There is no official model available to calculate the exposure of bystanders. Some proposals were given by the EUROPOEM Bystander Working Group but the report is still a draft and not officially published because slight changes may still be accepted following comments provided by the members of the working group. Therefore, as long as there is no official guidance on how to calculate bystander exposure an approach is presented in this document that considers both dermal exposure - derived from available drift data - and inhalation exposure - derived from the operator exposure models 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)[4] and is in line with what has been published by US EPA and CRD 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 summarised in the following table. Detailed information and calculations are presented in chapter CP 7.2.2.1.

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

Substance	Person	Total systemic exposure (mg/kg bw/day)*	AOEL mg/kg bw/day	% of AOEL
Exposure of bystanders to field crop sprayer drift				
Foramsulfuron	Bystander: adult	0.00000583	**0.1**	**0.0058**
	Bystander: child	0.00000458		**0.0046**
Exposure of residents close to field crop sprayer drift				
Foramsulfuron	Resident: adult	0.00000035	**0.1**	**0.0004**
	Resident: child	0.000000508		**0.0005**

* Assumes a 60 kg bodyweight for an adult and 16.15 kg for a child
Foramsulfuron dermal penetration of 20% for the diluted spray and 100 % absorption *via* the inhalation route.

Assessment
The result of the calculations, reveals that the situation with respect to bystander and resident exposure is favourable for the intended uses of Equip OD®. Bystanders and residents will not be exposed to critical levels of foramsulfuron during spray application of Equip OD® in the fields.

[4] [redacted]
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.

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).
According to [redacted] *et al* are presented hereafter the drift values used to run calculations for both bystanders and residents.

Table 7.2.2.1-1: Percent Drift Values for Different Crops ([redacted] et al. 2001, current version 27.03.2006)

Crop, Distance 10 m	Percent Drift (1 application) (90^{th} percentile values)	Percent Drift (2 application) (82^{th} percentile values)
Field crops	**0.29**	**0.24**
Fruit crops, early	10.81	9.61
Fruit crops, late	3.60	3.11
Grapes	1.23	1.07
Hops	3.77	4.18
Vegetables, ornamentals & small fruit: < 50 cm > 50 cm	 0.29 1.23	 0.24 1.07

For the current risk assessment the worst case with drifts for application on field crops are considered. A drift value of **0.29%** was used for bystanders (present for just one application) and **0.24%** for residents (possibly submitted to 2 applications).

Exposure calculations are performed according to the following equations:

a) Bystander exposure

Foramsulfuron
Dermal exposure due to spray drift following low crop application using field crop 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) 0.006 kg a.s./ha = 0.60 mg/m².
D = Drift (%) 0.29%.
BSA = Exposed Body Surface Area (m²) 1 m² (adult), 0.21 m² (child).
DA = Dermal Absorption (%) 20%.
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. (field crop sprayer).
AR = Application Rate (kg a.s./ha) 0.0060 kg a.s./ha.
A = Area Treated (ha/day) 50 ha (tractor).
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 7.2.2.1-2: Calculations for bystander exposure to foramsulfuron

Adults	Children
Bystander of Field Crop, tractor mounted/trailed	
Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (0.6 x 0.29% x 1 x 20 %) / 60 Absorbed dose: 0.0000058 mg/kg bw/day	Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (0.6 x 0.29% x 0.21 x 20 %) / 16.15 Absorbed dose: 0.000004525 mg/kg bw/day
Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.001 x 0.006 x 20 x 5/360 x 100%) / 60 Absorbed dose: 0.0000000278 mg/kg bw/day	Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.001/1.74 x 0.006 x 20 x 5/360 x 100%) / 16.15 Absorbed dose: 0.0000000593 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: 0.00000583 mg/kg bw/day	**Total absorbed dose: 0.00000458 mg/kg bw/day**
% of AOEL: 0.0058	**% of AOEL: 0.0046**

* based on children's inhalation rate of 1.0 m³/h for moderate activity (US EPA 2001, therefore ratio between children's and adults' inhalation rate: 1.0/1.74)

b) Residential exposure

Foramsulfuron

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) x 2 (for no. of applications >2). Foramsulfuron: 0.003 kg a.s./ha x 2 = 0.00012 mg/cm^2.
D	= Drift (%)		0.24%.
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 (%)		20%.
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 foramsulfuron = 4.2×10^{-11} Pa at 20°C and 25°C = non volatile).	
IR	= Inhalation Rate (m^3/day)	16.57 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).

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^2) x 2 (for no of applications >2). Foramsulfuron: 0.003 kg a.s./ha x 2 = 0.00012 mg/cm^2.	
D	= Drift (%)	0.24%.
TTR	= Turf Transferable Residues (%)	5%.
SE	= Saliva Extraction Factor (%)	50%.
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/cm^2) x 2 (for no. of applications >2).
Foramsulfuron: 0.003 kg a.s./ha x 2 = 0.00012 mg/cm^2.
D = Drift (%) 0.24%.
DFR = Dislodgeable Foliar Residues (%) 20%.
IgR = Ingestion Rate for Mouthing of Grass/Day (cm^2) 25 cm^2/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 7.2.2.1-3: Calculations for resident exposure to foramsulfuron

Adults	Children
Resident, Exposure after application with Field Crop, tractor mounted/trailed	
Dermal exposure: $SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$ (0.00006 x 0.24% x 5% x 7300 x 2 x 20%) / 60 Absorbed dose: 0.0000003504 mg/kg bw/d	Dermal exposure: $SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$ (0.00006 x 0.24% x 5% x 2600 x 2 x 20%) / 16.15 Absorbed dose: 0.0000004637 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): $SOE_H = (AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA) / BW$ (0.00006 x 0.24% x 5% x 50% x 20 x 20 x 2 x 20%) / 16.15 Absorbed dose 0.0000000357 mg/kg bw/d
	Oral exposure (object-to-mouth transfer): $SOE_O = (AR \times D \times DFR \times IgR \times OA) / BW$ (0.00006 x 0.24% x 20% x 25 x 20%) / 16.15 Absorbed dose 0.0000000089 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: 0.00000035 mg/kg bw/d	**Total absorbed dose: 0.000000508 mg/kg bw/d**
% of AOEL: 0.0004	**% of AOEL: 0.00051**

CP 7.2.2.2 Measurement of bystander and resident exposure

Since the risk assessment carried out indicated that the health-based limit values (AOEL) for the active substance foramsulfuron will not be exceeded under practical conditions of use, a study to provide a measure of bystander exposure to the formulated product Equip OD® under field conditions was not necessary and therefore was not carried out.

CP 7.2.3 Worker exposure

According to the application parameters of Equip OD® the only intended use is spray application to corn at early growth stages (BBCH 12-16). At these growth stages no re-entry exposure would be expected due to the relative height of the crop. However, the potential exposure due to scouting procedures is provided in the following section.

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 [redacted] *et al*,[5] (1998) and [redacted] *et al.* [6](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 Residue (DFR) is calculated using a default value of 3 µg as/cm² per kg as/ha. This figure is based [redacted] *et al.*[7] (2001)
- 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.

The dermal exposure calculation is performed according to the following equation:

$$D = DFR \times TC \times WR \times AR \times P.$$

Where:

DFR = Dislodgeable foliar residues (µg as/ cm²).

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[5] [redacted].: 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)

[6] [redacted]. (2001) Uniform principles for safeguarding the health of workers re-entering crop growing areas after application of plant-protection products, Worker exposure to agrochemicals, [redacted], chapter 8, 107- 117, CRC Press (2001), (document no.: M-209388-01-1)

[7] [redacted] Modeling re-entry exposure estimates: techniques and application rates; Worker exposure to agrochemicals, [redacted], chapter 9, 119- 138, CRC Press (2001), (document no.: M-128767-01-1)

TC = Transfer Coefficient (cm²/person/h).
WR = Work rate (hours/day).
AR = Application rate (kg as/ha).
P = Protection factor for PPE (P = 1 no PPE, just a long sleeved shirt, or 0.1 when adequate clothing and gloves are worn).

DFR values:

A single application is considered in this risk assessment resulting in an estimated worst case DFR of 3 µg as/cm² per kg as/ha.

Transfer Coefficient values:

[redacted] et al (1998) propose that a transfer coefficient (TC) of 30,000 (cm²/person/h) be used for the transfer of residues from foliage to the clothes or skin of a worker in initial estimates of exposure. This value is considered to represent a worst case for worker exposure, being derived from tasks requiring intensive contact with foliage and representing an unprotected worker.

As no specific TCs are available in Europe to assess re-entry activities performed in cereals a conservative value of 2500 cm²/person/h has been used in this risk assessment. This value was obtained from the Europoem II data for vegetables which are believed to be the most reasonable surrogate from the available data for scouting activities in young cereal crops.

Predicted exposures are compared with the AOEL of foramsulfuron. Systemic exposure values assume the a dermal absorption value of 20%. A body weight of 60 kg is assumed for the re-entry worker. Exposure estimates based on proportions of the systemic AOEL accounted for by the estimates are summarised in the following Table. Detailed calculations are presented on the following pages.

Table 7.2.3.1-1: Summary of predicted worker exposures arising from the use of Equip OD® and comparison with the AOEL

Active substance	**Systemic exposure*** (mg/kg bw/day)	**AOEL** (mg/kg bw/day)	**% of AOEL**
Foramsulfuron	0.0003	0.1	0.3

*20% dermal absorption. 60 kg worker.

Assessment

The exposure of workers entering treated areas is well within acceptable levels following application of Equip OD®.

Detailed calculations of worker exposure during re-entry:

Re-entry exposure to foramsulfuron:

Product Name: Equip OD
Active substance: Foramsulfuron

D	=	DFR	x	TC	x	WR	x	AR	x	P
		µg/cm²		cm²/pers/h		hrs/day		kg/ha		
D	=	3	x	2500	x	2	x	0.006	x	1

D	=	90	µg a.s./pers/day
	=	0.09	mg a.s./pers/day
	=	0.0015	mg/kg bw/day
using	20.00%	dermal absorption (highest value)	
S	=	0.0015	x 0.2000
	=	0.000300	mg/kg bw/day

CP 7.2.3.2 Measurement of worker exposure

Not relevant

CP 7.3 Dermal adsorption

Report:	K[redacted]0; [redacted]1999;M-193881-01
Title:	In vivo dermal absorption study in the male rat [14C]-AE F130360 (code: AE F130360 01, R05 A)
Report No:	C006428
Document No(s):	Report includes trial No.: Tox98102 M-193881-01-1
Guidelines:	**OECD: 417;Deviation not specified**
GLP/GEP:	**yes**

In the original dossier the study submitted for dermal absorption (KCA 7.3/01) was an *in vivo* rat dermal absorption study for the active substance in a previous version of the formulation that varies from the current formulation by more than the 25% permitted by the latest EFSA guidance on dermal absorption[8]. The data do suggest however that the value of 20% is a reasonable one for human skin given that 20% was achieved with the spray dilution on rat skin (generally more permeable than human skin) and approximately 7% for the concentrate.

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document J).

[8] 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.