Document Title

Summary of the toxicological studies for Fosetyl-aluminium WG 80 (800 g/kg)

Data Requirements

EU Regulation 1107/2009 & EU Regulation 284/2013
Document MCP
Section 7: Toxicological studies

According to the Guidance Document SANCO/10181/2013 for preparing dossiers for the approval of a chemical active substance

Date

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Bayer CropScience

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Version history

Date (yyyy-mm-dd)	Data points containing amendments or additions[1] and brief description	Document identifier and version number
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2016-05-03	Dossier update according to "Request for additional information on the supplementary dossier submitted by Bayer CropScience for the approval renewal of the active substance Fosetyl (2015-5865)" by RMS France on 2016-04-04: - The evaluation of the exposure of bystanders and residents using the new EFSA calculator has been added to chapters CP 7.2.2 and CP 7.2.2.1 and as Table 7.2.2-2 and Table 7.2.2.1-4.	M-533242-02-1

[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

Fosetyl was included in Annex I to Directive 91/414/EEC in 2006 (Directive 2006/64/CE of 18 July 2006, Entry into Force on 1 May 2007). This Supplementary Dossier contains only data which were not submitted at the time of the Annex I inclusion of fosetyl under Directive 91/414/EEC and which were therefore not evaluated during the first EU review. All data which were already submitted by Bayer CropScience (BCS) for the Annex I inclusion under Directive 91/414/EEC are contained in the DAR, its Addenda and are included in the Baseline Dossier provided by BCS. These data are only mentioned in the Supplementary Dossier for the sake of completeness and only general information (e.g. author, reference etc.) is available for these data. In order to facilitate discrimination between new data and data submitted during the Annex I inclusion process under Directive 91/414/EEC, the old data are written in grey typeface. For all new studies, detailed summaries are provided within this Supplementary Dossier. However, for a better understanding of the toxicological behaviour of fosetyl-aluminium (fosetyl-Al) WG 80, short summaries including the results of all studies are given at the beginning of the relevant sections. Additional information requested by the RMS France on 2016-04-04 during the evaluation of the Supplementary Dossier is highlighted in yellow.

Fosetyl is the ISO common name for ethyl hydrogen phosphonate (IUPAC) but the aluminium salt fosetyl-Al, a variant of fosetyl, is used in the formulated product.

The formulation Fosetyl-Al WG 80 is a water dispersible granule (WG) formulation containing 800 g/kg of fosetyl-Al. This formulation is registered throughout Europe on a wide range of crops under trade names such as Aliette. Fosetyl-Al WG 80 was already a representative formulation of BCS for the Annex I inclusion of fosetyl under Directive 91/414/EEC.

CP 7.1 Acute toxicity

Fosetyl-Al WG 80 (FEA WG 80) has a very low acute oral and percutaneous toxicity in male and female rats.
An acute inhalation study has previously not been required for products containing only non-volatile active substances if they are not dusty with a significant proportion of inhalable particles or applied by spraying generating inhalable particles. Thus, no acute inhalation study has been conducted using the current recipe of FEA WG 80. The current data requirements for plant protection products, however, stipulate that acute inhalation studies should be performed with all products that are applied by spraying, such as FEA WG 80. Such a test has been performed using an earlier recipe named "Aliette 80WDG". The main difference between the previous formulation and the current formulation is the replacement of ethoxylated nonylphenol (NPE) dispersing agents by more environmental friendly ingredients.
FEA WG 80 is irritating to eyes but not to skin. It has no skin-sensitizing potential (see Table 7.1- 1).

Table 7.1- 1: Acute toxicity studies with fosetyl-Al WG 80

Study Type	Species	Results	Reference
Acute oral toxicity	Rat	LD_{50} > 2000 mg/kg bw (♂+♀)	[redacted].; 1999; M-199989-01-1
Acute dermal toxicity		LD_{50} > 2000 mg/kg bw (♂+♀)	[redacted].; 1999; M-200031-01-1
Acute inhalation toxicity		LC_{50} > 5.02 mg/L air (4 h, ♂+♀)	[redacted]; 1990; M-163218-01-1
Skin irritation	Rabbit	Non irritating	[redacted].; 1999; M-200020-01-1
Eye irritation		Eye irritant (reversible effects), Eye Irrit. 2, H319	[redacted]B; 1999; M-199998-01-1
Skin sensitization (Modified Buehler Test, nine induction applications)	Guinea pig	Not sensitizing	[redacted].; 1999; M-200010-01-1

CP 7.1.1 Oral toxicity

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fosetyl under Directive 91/414/EEC. Please refer to the DAR and the Baseline Dossier of fosetyl. A short overall summary of these studies is provided in Section CP 7.1.

CP 7.1.2 Dermal toxicity

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fosetyl under Directive 91/414/EEC. Please refer to the DAR and the Baseline Dossier of fosetyl. A short overall summary of these studies is provided in Section CP 7.1.

CP 7.1.3 Inhalation

No inhalation test has been conducted with the current recipe of Fosetyl-Al WG 80 (Specification No. 102000024225-02). As a surrogate, the classification of the product is based on a test ([redacted]F; 1990; M-163218-01-1) conducted with a previous recipe of Fosetyl-Al WG 80 (EXP02329B). The main difference between the previous formulation and the current formulation is the replacement of ethoxylated nonylphenol (NPE) dispersing agents by more environmental friendly ingredients. None of the new ingredients in the current recipe is classified for acute inhalation toxicity; therefore no additional contribution to inhalation toxicity is expected. A detailed rationale for bridging between the two recipes ([redacted]; [redacted]; 2015; M-521768-01-1) can be found in the respective CONFIDENTIAL part (Document JCP).

Report:	KCP 7.1.3/01 [redacted],; 1990; M-163218-01-1
Title:	Aliette 80WDG pulverized: Acute inhalation toxicity study in rats
Report No.:	R002726
Document No.:	M-163218-01-1
Guideline(s):	USEPA (=EPA): 81-3
Guideline deviation(s):	The relative humidity during exposure was >70% in the high concentration group.
GLP/GEP:	**yes**

Executive Summary
The inhalation toxicity of Aliette 80 WDG (FEA WG 80) was determined in male and female Sprague-Dawley rats by exposure to an undiluted powder aerosol. The aerosol was generated using a Gem T Trost Air Mill coupled with a motor-driven revolving disc delivery system. Two groups of 5 rats per sex were exposed for 4 h to concentrations of 2.17 or 5.02 mg test item/L (actual concentrations). The post treatment observation period was 14 days.
The aerosol sampled from the inhalation chamber showed an MMAD of 1.320 µm (GSD 3.628) and 4.967 µm (GSD 1.860) in the low and high concentration group, respectively.
The dust in the low-concentration group was highly respirable with 84% of the particles being smaller than 4.79 µm. The aerosol in the high concentration group had a coarser particle-size distribution with 50% of particle diameters below 4.96 µm.
Prominent in-life observations included activity decrease, chromodacryorrhea, dilated pupils, gasping, lacrimation, nasal discharge, piloerection, polyuria, respiratory gurgle, salivation and withdrawn testes. All animals were free of any signs by Day 5 of the study.
Two females of the high concentration group died during Day 1 of the study. Upon necropsy, no abnormality was detected in surviving rats. Decedents showed signs of nasal discharge, salivation, chromodacryorrhea and polyuria; lungs dark red and swollen with red fluid.
The 4-h LC_{50} value of fosetyl-Al WG 80 is greater than 5.02 mg/L in both sexes. Based on this result, FEA WG 80 is not classified for acute inhalation toxicity according to the criteria of Regulation 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Name:	Aliette 80 WG (FEA WG 80)
Description:	Fine, off-white powder
Batch / Lot No.:	REF.# 212-DAL-88 014677-A Pulverized
Purity:	80% a.s. (w/w)
Stability of test compound:	Not reported
2. Vehicle:	Not applicable

3. Test animals

Species:	Rat
Strain:	Sprague-Dawley (HSD:(SD) BR)
Sex:	Males and females
Age:	Young adult
Weight when tested:	Males : 202-288 g Females : 195-235 g
Source:	[redacted], USA
Acclimatisation period:	6 days (♂), 1 day (♀)
Diet:	Purina Formula Chow #5008, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	1-3 per cage (males separate from females); one per cage during exposure period; Suspended, wire bottom, stainless steel cages

Environmental conditions:

Temperature:	Not reported
Humidity:	Not reported
Air changes:	Not reported
Photoperiod:	Not reported

B. STUDY DESIGN AND METHODS

1. In life dates: 1990-01-17 to 1990-02-14

2. Animal assignment and treatment

Test concentrations:	2.17, 5.02 mg/L (actual) 14.6, 82.4 mg/L (nominal)
Application route:	Inhalation, powder aerosol. Not reported whether full-body or nose-only exposure was employed.
Group size:	5 rats/sex/group
Exposure duration:	4 h
Post-treatment observation period:	14 days
Observations:	Clinical signs, mortality, body weight, gross necropsy

3. Generation of test atmosphere

Exposure apparatus:	500-L New York University design, stainless steel, dynamic flow inhalation chamber.
Flow rate:	2.17 mg/L: 95.7 L/min 5.02 mg/L: 97.1 L/min
System of generating aerosols:	Gem T Trost Air Mill coupled with a motor-driven revolving disc delivery system.
Method of particle size determination:	Gravimetrically via cascade impactor

4. Test atmosphere

Temperature and humidity in air chamber:	21-22°C 2.17 mg/L: 69-71% 5.02 mg/L: 91-95%
Particle size distribution:	2.17 mg/L: 84% of particles were < 4.79 µm 5.02 mg/L: 50% of particles were < 4.96 µm
MMAD (GSD)	2.17 mg/L: 1.320 µm (3.628) 5.02 mg/L: 4.967 µm (1.860)

II. RESULTS AND DISCUSSION

A. MORTALITY

Two females of the high concentration group died (see Table 7.1.3- 1).

B. CLINICAL OBSERVATIONS

Prominent in-life observations included activity decrease, chromodacryorrhea, dilated pupils, gasping, lacrimation, nasal discharge, piloerection, polyuria, respiratory gurgle, salivation and withdrawn testes. All animals were free of any signs by Day 5 of the study.

C. BODY WEIGHT

The body weights of all surviving rats increased throughout the observation period.

D. NECROPSY

There were no abnormalities observed at necropsy of survivors. Decedents showed signs of nasal discharge, salivation, chromodacryorrhea and polyuria; lungs dark red and swollen with red fluid.

Table 7.1.3- 1: Results of the acute inhalation test with FEA WG 80

Concentration (mg/L)	Toxicological result*			Onset and duration of signs#	Onset of death	Mortality (%)
Male rats						
2.17	0	5	5	4.5 h – 6 h	–	0
5.02	0	5	5	4.5 h – Day 4	–	0
Female rats						
2.17	0	5	5	4.5 h – 6 h	–	0
5.02	2	4	5	4.5 h – Day 3	4.5 h, Day 1	40
LC_{50}: >5.02 mg/L (males + females)						

* 1st number = number of dead animals, 2nd number = number of animals with toxic signs, 3rd number = number of animals used

Due to test material covering observation windows, animals could not be observed during the exposure period.

III. CONCLUSION

The 4-h LC_{50} of FEA WG 80 is greater than 5.02 mg/L in both male and female Sprague-Dawley rats. Thus, FEA WG 80 is not classified for acute inhalation toxicity according to the criteria of Regulation 1272/2008.

CP 7.1.4 Skin irritation

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fosetyl under Directive 91/414/EEC. Please refer to the DAR and the Baseline Dossier of fosetyl. A short overall summary of these studies is provided in Section CP 7.1.

CP 7.1.5 Eye irritation

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fosetyl under Directive 91/414/EEC. Please refer to the DAR and the Baseline Dossier of fosetyl. A short overall summary of these studies is provided in Section CP 7.1.

CP 7.1.6 Skin sensitization

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fosetyl under Directive 91/414/EEC. Please refer to the DAR and the Baseline Dossier of fosetyl. A short overall summary of these studies is provided in Section CP 7.1.

CP 7.1.7 Supplementary studies on the plant protection product

No such studies are necessary since there are no concerns arising, e.g., from potential synergistic or additive effects exerted by the active substance or other components in the plant protection product that would require further investigations.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No such studies are necessary since fosetyl-aluminium WG 80 is not intended for use in combination with other plant protection products.

CP 7.2 Data on exposure

Evaluations of the exposure of operators, bystanders, residents and re-entry workers to fosetyl-aluminium (fosetyl-Al) when used in the Fosetyl-Al WG 80 (FEA WG 80) formulation are provided in the following sections.

CP 7.2.1 Operator exposure

FEA WG 80 is a water dispersible granule containing 800 g/kg fosetyl-Al. The proposed representative use is as a fungicide and bactericide on pome fruit. Applications of FEA WG 80 will be achieved via broadcast air assisted sprayers. Water will be the diluent/carrier in all situations. The full representative GAP information is given in document D1 and is summarised in Table 7.2.1- 1.

Table 7.2.1- 1: Application parameters for FEA WG 80.

Application technique	Crop(s)	Growth stage	For G	Maximum dose rate		Spray volume (L/ha)	Max N° of treat-ments	Spray Interval (day)	PHI (day)
				kg/ha product	kg/ha fosetyl-Al				
BAA	Pome fruits	55-85	F	4.5	3.6	300-1500	3	7-10	28

BAA = Broadcast air assisted sprayer. F = Field use, G = Greenhouse use

Dermal absorption:

The following dermal absorption values for fosetyl-Al are used in the present risk assessment (for details see Section CP 7.3):

- 1% for the concentrate (measured at 500 g/L) and 3% (measured at 1 g/L with a predicted lowest in-use concentration of 2.4 g/L) for the spray dilution.

Acceptable Operator Exposure Level AOEL:

An AOEL of **5 mg/kg bw/day** is established for fosetyl-Al[1] based on the NOAEL of 500 mg/kg bw/day obtained in a 90-day mechanistic rat study using a safety factor of 100 with no adjustment for oral absorption being necessary (see also Document MCA, Section 5).

[1] Fosetyl, EFSA Scientific Report (2005) 54, 1-79, Conclusion of the peer review.

Operator exposure estimates

Operator exposures to FEA WG 80 are estimated using the German model[2], the UK-POEM[3] and the new EFSA calculator[4] (although not implemented at the time of writing) with the relevant scenario "Tractor-mounted/trailed broadcast air assisted sprayer". Details are given in Section CP 7.2.1.1 and in Table 7.2.1.1- 1 to Table 7.2.1.1- 3.

The results of the exposure calculations are summarized in Table 7.2.1- 2.

Table 7.2.1- 2: Predicted systemic exposure as a proportion of the AOEL

Substance	**PPE**	**Total systemic exposure (mg/kg bw/day)***	**% of AOEL#**
German model Tractor-mounted/trailed broadcast air assisted sprayer: hydraulic nozzles. **8 ha**			
Fosetyl-Al	No PPE 1)	0.16087	3
	With PPE 2)	0.04016	0.8
UK-POEM Tractor-mounted/trailed broadcast air assisted sprayer: hydraulic nozzles, **15 ha**			
Fosety-Al	No PPE 3)	0.870900	17
	With PPE 4)	0.819935	16
EFSA Calculator Tractor-mounted/trailed broadcast air assisted sprayer: hydraulic nozzles, **10 ha**			
Fosety-Al	No PPE 5)	0.2256	5
	With PPE 6)	0.0632	1

\# Fosetyl-Al: AOEL = 5 mg/kg bw/day
1) Lightly dressed operator, wearing a short sleeved T-Shirt, shorts and shoes.
2) Gloves during mixing/loading and a standard coverall during application.
3) One layer of typical work wear (e.g. trousers and a long sleeved shirt) as well as sturdy foot wear
4) In addition to typical work wear (see 3) protective gloves are worn during mixing and loading and when handling contaminated surfaces.
5) Potential exposure without RPE/PPE.
6) In addition to typical work wear (see 3) protective gloves are worn during mixing and loading and when handling contaminated surfaces.

Overall assessment

Exposure estimates predict no unacceptable risk. Operators using FEA WG 80 for the representative use on pome fruit should wear adequate work clothing (e.g. a long sleeved shirt, trousers and sturdy foot wear). All three models predict that the product is safe to use without additional PPE. However, the notifier recommends that they also wear protective gloves as a good farming practice during mixing/loading and when handling contaminated surfaces.

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2 [redacted]. (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).

3 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.

4 EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874.: Version 30/03/2015.

CP 7.2.1.1 Estimation of operator exposure

Operator exposure to fosetyl-Al in the FEA WG 80 formulation is estimated using the German Model, as well as the UK-POEM and the soon to be implemented EFSA calculator for tractor-mounted/trailed broadcast air assisted sprayer.

In the following paragraphs the assumptions used for the calculations are summarised.

German Model

Treated area:	8 ha/day.
Max. dose rate:	4.5 kg product/ha, i.e.,
- FEA:	3.6 kg a.s./ha.
Body weight:	70 kg.

UK-POEM

Treated area:	15 ha/day.
Max. dose rate:	4.5 kg product/ha, i.e.,
- FEA:	3.6 kg a.s./ha.
Min. spray volume:	300 L/ha.
Work duration:	6 hours/day.
Body weight:	60 kg.

EFSA Calculator

Treated area:	10 ha/day.
Max. dose rate:	4.5 kg product/ha, i.e.,
- FEA:	3.6 kg a.s./ha.
Min. spray volume:	300 L/ha.
Season:	Early (worst case).
Work duration:	6 hours/day.
Body weight:	60 kg.

Dermal absorption:

- FEA: 1% for the concentrate and 3% 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.

Table 7.2.1.1- 1: Predicted systemic exposure to fosetyl-Al according to the German model/no PPE and with PPE

Operator exposure estimate: German model. Tractor-mounted/trailed broadcast air-assisted sprayer

Product:	FEA WG 80				
Active substance:	FEA	a.s. concentration:	800	[g/l or kg]	
Formulation:	WG	PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	4.5		Hands:	Gloves	
Work rate [ha/day]:	8	PPE during application:	Respiration:	None	
Body weight [kg]:	70		Hands:	None	
Inhalation absorption [%]	100		Head:	None	
Dermal absorption [%]	1.0 (concentrate)		Body:	Standard protective coverall	
	3.0 (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 =	0.008	28.8	0.003291	1.0	0.003291	I = Inhalation
$D_{M(H)}$ =	2.0	28.8	0.8229	0.01	0.008229	D = Dermal
I_A =	0.018	28.8	0.007406	1.0	0.007406	M = Mix/loading
$D_{A(C)}$ =	1.2	28.8	0.4937	1.0	0.493714	A = Application
$D_{A(H)}$ =	0.7	28.8	0.288	1.0	0.288	H = Hands
$D_{A(B)}$ =	9.6	28.8	3.9497	0.05	0.197486	C = Head
						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	1.0	0.823857	0.008229	0.008229	0.000082
	Application	3.0	4.731429	0.141943	0.9792	0.029376
Inhalation:	Mix/Loading	100	0.003291	0.003291	0.003291	0.003291
	Application	100	0.007406	0.007406	0.007406	0.007406
		Total =		**0.160869**		**0.040155**

Table 7.2.1.1- 2: Predicted systemic exposure to fosetyl-Al according to the UK POEM/no PPE and with PPE

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha			
Product	**FEA WG 80**	Active substance	**FEA**	
Formulation type	WG or SG	a.s. concentration	**800**	mg/g
Dermal absorption from product	**1** %	Dermal absorption from spray	**3**	%
PPE during mix/loading	Gloves	PPE during application	None	
Dose	**4.5** kg product/ha	Work rate/day	**15**	ha
Application volume	**300** L/ha	Duration of spraying	**6**	h

DERMAL EXPOSURE DURING MIXING AND LOADING				
Hand contamination/kg a.s.	5.72	mg/kg a.s.		
Hand contamination/day	308.88	mg/day		
Protective clothing	None		Gloves	
Transmission to skin	100	%	1	%
Dermal exposure to a.s.	308.88	mg/day	3.0888	mg/day
INHALATION EXPOSURE DURING MIXING AND LOADING				
Inhalation exposure/kg a.s.	0.0358	mg/kg a.s.		
Inhalation exposure/day	1.9332	mg/day		
RPE	None		None	
Transmission through RPE	100	%	100	%
Inhalation exposure to a.s.	1.9332	mg/day	1.93320	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION								
Application technique	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha							
Application volume	300	spray/ha						
Volume of surface contamination	400	ml/h						
Distribution	Hands		Trunk		Legs			
	10%		65%		25%			
Clothing	None	Permeable		Permeable		None	Permeable	Permeable
Penetration	100%			5%		100%	2%	5%
Dermal exposure	10	5.2		5	ml/h	10	5.2	5 ml/h
Duration of exposure	6	h						
Total dermal exposure to spray	121.2	ml/day				121.2	ml/day	
Concentration of a.s. in spray solution	12	mg/ml				12	mg/ml	
Dermal exposure to a.s.	1454.4	mg/day				1454.4000	mg/day	

INHALATION EXPOSURE DURING SPRAYING		
Inhalation exposure to spray	0.05	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	12	mg/ml
Inhalation exposure to a.s.	3.6	mg/day
Percent absorbed	100	%
Absorbed dose	3.6	mg/day

ABSORBED DOSE	No PPE				PPE (if used)			
	Mix/load		Application		Mix/load		Application	
Dermal exposure to a.s.	308.88	mg/day	1454.4	mg/day	3.0888	mg/day	1454.4	mg/day
Percent absorbed	2	%	3	%	1	%	3	%
Absorbed dose (dermal route)	3.0888	mg/day	43.632	mg/day	0.030888	mg/day	43.632	mg/day
Inhalation exposure to a.s.	1.9332	mg/day	3.6	mg/day	1.9332	mg/day	3.6	mg/day
Absorbed dose	5.022	mg/day	47.232	mg/day	1.96409	mg/day	47.232	mg/day

PREDICTED EXPOSURE				
Total absorbed dose	52.254	mg/day	49.196088	mg/day
Operator body weight	60	kg	60	kg
Operator exposure	0.8709	mg/kg bw/day	0.8199348	mg/kg bw/day
AOEL	5	mg/kg bw/day		
%AOEL	17.4 %		16.4 %	

Table 7.2.1.1- 3: Predicted systemic exposure to fosetyl-Al according to the EFSA Calculator/no PPE and with PPE

Exposure assessment

Substance	fosetyl Al	Formulation = Wettable granules, soluble granules	Application rate-3.6 kg a.s. /ha	Spray dilution = 12 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Pome fruit early (without leaves) / Outdoor / Upward spraying / Vehicle-mounted			Buffer = 5	Number applications = 3, Application interval = 7 days
Percentage Absoprtion	Dermal for product = 1	Dermal for in use dilution = 3	Oral = 100	Inhalation = 100	
RVNAS	5 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.2268	% of RVNAS	4.51%
	Acute systemic exposure mg/kg bw/day		0.7451	% of RVAAS	
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0632	% of RVNAS	1.26%
	Acute systemic exposure mg/kg bw/day		0.2997	% of RVAAS	

CP 7.2.1.2 Measurement of operator exposure

Not required as assessments demonstrated safe use using the accepted models.

CP 7.2.2 Bystander and resident exposure

No EU-wide validated and accepted official model is currently available for estimation of bystander and residential 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)[5] and is in line with what has been published by US EPA and UK CRD recently. All technical details with regard to figures and assumptions are provided in this guidance.

At the request of the RMS resident exposure using the new EFSA calculator is also presented in this chapter.

5 [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).

No acute non-dietary risk assessment is included in this submission. Lack of scientific guidance or methodology is an acceptable reason for waiving according to Guidance of the European Commission[6]. The absence of such guidance on derivation of an appropriate reference dose ("AAOEL") was recognized by

- the European Food Safety Authority[7], and
- the European Commission Standing Committee[8].

Therefore, this waiver is presented in line with the Guidance of the European Commission.

However as the residential estimates cover an average exposure over a longer duration it is likely that the residential calculations adequately cover bystander safety.

Exposure estimates and proportions of the systemic AOELs accounted for by the estimates are summarised in the following Table 7.2.2- 1 and Table 7.2.2- 2. Detailed information and calculations are presented in Section CP 7.2.2.1.

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

Substance	Scenario	Total systemic exposure* (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
Bystander of high crop application (tractor-mounted)				
	Bystander: adult	0.022698		0.454
	Bystander: child	0.019660	5	0.393
Resident exposure after high crop application (tractor-mounted)				
	Resident: adult	0.0025255		0.0505
	Resident: child	0.0140526	5	0.2811

* Assumes a 60 kg bystander for an adult and 16.15 kg for a child.
Dermal absorption value of 3% was used. Inhalation absorption was taken as 100% for both compounds.

Table 7.2.2- 2: Predicted systemic exposures as a proportion of the AOEL using the EFSA calculator

Substance	Scenario	Total systemic exposure* (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
Resident exposure after high crop application (tractor-mounted)				
	Resident: adult	0.0434		0.87
Fosetyl-Al	Resident: child	0.0970	5	1.94

* Assumes a 60 kg bystander for an adult and 10 kg for a child.
Dermal absorption value of 3% was used. Inhalation absorption was taken as 100% for both compounds.

6 Guidance Document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013, SANCO/10181/2013, May 2013.

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

8 Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. SANTE-10832-2015.

Assessment
The results of the calculations reveal that the situation with respect to bystander and resident exposure is favourable for the intended use of FEA WG 80.

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 7.2.2.1- 1: Percent Drift Values for Different Crops ([redacted] *et al.* 2001, current version 22.03.2006) – 2 applications.

Crop, Distance 10 m	Percent Drift (2 applications) (82nd percentile values)
Field crops	0.24
Fruit crops, early	9.61
Fruit crops, late	3.11
Grapes	1.07
Hops	4.18
Vegetables, ornamentals & small fruit:	
< 50 cm	0.24
> 50 cm	1.07

Exposure calculations are performed according to the following equations:

a) Bystander exposure to fosetyl-Al in the FEA WG 80 formulation.

Dermal exposure due to spray drift following 2 high crop applications using a tractor mounted field 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/m^2)	7.2 kg a.s./ha = 720 mg/m^2
D	= Drift (%)	11.81% (10 m distance) for 2 applications.
BSA	= Exposed Body Surface Area (m^2)	1 m^2 (adult), 0.21 m^2 (child).
DA	= Dermal Absorption (%)	3%
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)	0.018 mg/kg a.s. (high crop tractor sprayer).
AR	= Application Rate (kg a.s./ha)	7.2 kg a.s./ha.
A	= Area Treated (ha/day)	8 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 7.2.2.1- 2: Calculations for bystander exposure to fosetyl-Al in FEA WG 80

Adults	Children
Bystander of high crop application (tractor-mounted)	
Dermal Exposure SDE_B = (AR x D x BSA x DA)/BW SDE_B = (360 x 0.1181 x 1 x 0.03) / 60 SDE_B = 0.021258 mg/kg/day	Dermal Exposure SDE_B = (AR x D x BSA x DA)/BW SDE_B = (360 x 0.1181 x 0.21 x 0.03) / 16.15 SDE_B = 0.016585 mg/kg/day
Inhalation Expsoure SIE_B = (I_A* x AR x A x T x IA)/BW SIE_B = (0.018 x 3.6 x 8 x 0.1667 x 1.00) / 60 SIE_B = 0.00144000 mg/kg/day	Inhalation Exposure SIE_B = (I_A* x AR x A x T x IA)/BW SIE_B = (0.010345 x 3.6 x 8 x 0.1667 x 1.00) / 16.15 SIE_B = 0.00307462 mg/kg/day
Total Sytemic Exposure $SE_B = SDE_B + SIE_B$ = 0.022698 mg/kg/day	Total Sytemic Exposure $SE_B = SDE_B + SIE_B$ = 0.019660 mg/kg/day
%AOEL = 0.4540	**%AOEL = 0.3932**

b) Residential exposure to fosetyl-Al in the FEA WG 80 formulation.

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/cm²)	7.2 kg a.s./ha = 0.072 mg/cm².
D	= Drift (%)	9.61 % (10 m distance) for 2 applications.
TTR	= Turf Transferable Residues (%)	5%.
TC	= Transfer Coefficient (cm²/hour)	7300 cm²/h (adult), 2600 cm²/h (child).
H	= Exposure Duration (hours)	2 h.
DA	= Dermal Absorption (%)	3%.
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/m³): 0 mg/m³ (vapour pressure of a.s. < 10^{-5} Pa).	
IR	= Inhalation Rate (m³/day)	16.57 m³/day (adult), 8.31 m³/day (child).
IA	= Inhalation Absorption (%)	100%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

As the vapour pressure of fosetyl-Al is <10^{-7} Pa at 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 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/cm²)	7.2 kg a.s./ha = 0.072 mg/cm².
D	= Drift (%)	9.61% (10 m distance) for 2 applns.
TTR	= Turf Transferable Residues (%)	5%.
SE	= Saliva Extraction Factor (%)	50% (EPA default value).
SA	= Surface Area of Hands (cm²)	20 cm².
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)	7.2 kg a.s./ha = 0.072 mg/cm².
D	= Drift (%)	9.61% (10 m distance) for 2 applns.
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 7.2.2.1- 3: Calculations for resident exposure to fosetyl-Al in FEA WG 80.

Adults			Children		
Resident: Exposure after application with Field Crop, tractor mounted/trailed broadcast air assisted sprayer					
Dermal exposure:			Dermal exposure:		
$SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$			$SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$		
(0.0720 x 0.0961 x 0.05 x 7300 x 2 x 0.03) / 60			(0.0720 x 0.0961 x 0.05 x 2600 x 2 x 0.03) / 16.15		
Absorbed dose:	0.00252551	mg/kg bw/d	Absorbed dose:	0.00334178	mg/kg bw/d
Inhalation exposure:			Inhalation exposure:		
$SIE_R = (AC_V \times IR \times IA) / 1000 \times BW$			$SIE_R = (AC_V \times IR \times IA) / BW$		
(0 x 16.57 x 100%) / 60			(0 x 8.31 x 100%) / 16.15		
Absorbed dose:	0.0	mg/kg bw/d	Absorbed dose:	0.0	mg/kg bw/d
			Oral exposure (hand-to-mouth transfer):		
			$SOE_H = (AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA) / BW$		
			(0.0720 x 0.0961 x 0.05 x 0.5 x 20 x 20 x 2 x 1) / 16.15		
			Absorbed dose	0.00856867	mg/kg bw/d
			Oral exposure (object-to-mouth transfer):		
			$SOE_O = (AR \times D \times DFR \times IgR \times OA) / BW$		
			(0.072 x 0.0961 x 0.2 x 25 x 1) / 16.15		
			Absorbed dose	0.00214217	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:	**0.00252551**	mg/kg bw/d	**Total absorbed dose:**	**0.01405262**	mg/kg bw/d
% of AOEL:	**0.051**		**% of AOEL:**	**0.281**	

Resident exposure using the EFSA calculator:

Bystander and resident exposure to fosetyl-Al during and following the use of the FEA WG 80 formulation is estimated using the EFSA calculator and the scenario "Upward spraying, Vehicle-mounted".
Four pathways of exposure are considered (EFSA PPR Panel, 2010):

- spray drift (at the time of application)
- vapour (may occur after the PPP has been applied)
- surface deposits
- entry into treated crops

75th percentiles are considered for the single pathways and the total exposure from all pathways is calculated as mean value. A summary of the exposure calculations using the EFSA calculator for the critical GAP (see Table 7.2.1- 1) is presented below.

Table 7.2.2.1- 4: Resident exposure calculation (using the EFSA calculator)

Substance	Fosetyl-Al	Formulation = Wettable granules, soluble granules	Application rate 3.6 kg a.s. /ha	Spray dilution = 12 g a.s./L	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Pome fruit / Outdoor / Upward spraying / Vehicle-mounted			Buffer = 5	Number applications = 3; Application interval = 7 days
Percentage Absoprtion	Dermal for product = 1	Dermal for in use dilution = 3	Oral = 100	Inhalation = 100	
RVNAS	5 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0518	% of RVNAS	1.04%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.02%
	Surface deposits (75th percentile) mg/kg bw/day	0.0326	% of RVNAS	0.65%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0469	% of RVNAS	0.94%
	All pathways (mean) mg/kg bw/day	0.0970	% of RVNAS	1.94%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0281	% of RVNAS	0.56%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.00%
	Surface deposits (75th percentile) mg/kg bw/day	0.0053	% of RVNAS	0.11%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0261	% of RVNAS	0.52%
	All pathways (mean) mg/kg bw/day	0.0434	% of RVNAS	0.87%

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

The worker re-entry exposure has been calculated for fosetyl-Al following application of the fosetyl-Al WG 80 (FEA WG 80) formulation for the representative use on pome fruit. The estimation 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.*[9] (1998) and [redacted] *et al.*[10] (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 Brouwer *et al.*[11] (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).
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).

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9 [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.

10 [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).

11 [redacted]: (2001); Modeling re-entry exposure estimates: techniques and application rates; Worker exposure to agrochemicals, [redacted] chapter 9, 119- 138, CRC Press (2001).

DFR values:

A maximum of 3 applications is considered in this risk assessment resulting in an estimated worst case DFR of 9 µg as/cm² per kg as/ha for the EUROPOEM II assessment whilst a default half-life of 30 days was applied when using the EFSA calculator.

Transfer Coefficient values:

A TC value of 4500 cm²/person/h has been used in this risk assessment. This value was obtained from the Europoem II data for fruit trees and is also used in the new EFSA calculator.

Predicted exposures are compared with the AOEL of fosetyl-Al. Systemic exposure values assume the highest measured dermal absorption value for fosetyl-Al in the FEA WG 80 formulation (3%). A body weight of 60 kg is assumed for the re-entry worker. Exposure estimates based proportions of the systemic AOELs accounted for by the estimates are summarised in the following Table 7.2.3.1-1. Detailed calculations are presented on the following pages.

Table 7.2.3.1- 1: Summary of predicted fosetyl-Al worker exposures (no PPE) arising from the use of FEA WG 80 and comparison with the respective AOEL

Active substance	Model	Systemic exposure* (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
Fosetyl-Al	Europoem	0.583200	5	12
	EFSA	0.500444		10

*3% dermal absorption, 60 kg worker.

Assessment

The exposure of workers to fosetyl-Al when entering treated areas is well within acceptable levels following application of FEA WG 80 to pome fruits.

Detailed calculations of worker exposure during re-entry:

Europoem II:

Product Name: FEA WG 80

Active substance: FEA

D	=	DFR	x	TC	x	WR	x	AR	x	P
		µg/cm²		cm²/pers/h		hrs/day		kg/ha		
D	=	9	x	4500	x	8	x	3.6	x	1

D = 1166400 µg a.s./pers/day

= 1166.4 mg a.s./pers/day

= 19.44 mg/kg bw/day

using 3.00% dermal absorption (highest value)

S = 19.44 x 0.0300

= 0.583200 mg/kg bw/day

EFSA Calculator:

Worker exposure from residues on foliage for Aliette WG 80		
Crop type	Pome fruit	
Indoor or outdoor	Outdoor	
Application method	Upward spraying	
Application equipment	Vehicle-mounted	
Worker's task	Searching, reaching, picking	
Main body parts in contact with foliage	Hand and body	
Application rate of active substance	3.6	kg a.s./ha
Number of applications	3	
Interval between multiple applications	7	days
Half-life of active substance	30	days
Multiple application factor	2.4	
Dermal absorption of the product	100%	
Dermal absorption of the in-use dilution	3.00%	
Dislodgeable foliar residue (i_AppRate*i_DFR)	10.8	kg a.s./cm^2
Working hours	8	hr
Dermal transfer coefficient - Total potential exposure	2250	cm^2/hr
Dermal transfer coefficient - arms, body and legs covered	2250	cm^2/hr
Dermal transfer coefficient - hands, arms, body and legs covered	2250	cm^2/hr
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves
Total systemic exposure (mg a.s./day)	150.1332798	30.0266560	15.0133280
Total systemic exposure per kg body weight (mg/kg bw/day)	2.5022213	0.5004443	0.2502221
% of RVNAS	50.04%	10.01%	5.00%

CP 7.2.3.2 Measurement of worker exposure

Not considered to be necessary as a safe use was predicted in the previous section.

CP 7.3 Dermal absorption

The extent of dermal absorption of fosetyl-aluminium (fosetyl-Al) formulated as a WG (fosetyl-Al WG 80 or FEA WG 80) formulation was investigated *in vitro* using human and rat epidermal membranes ([redacted],; 2000; M-206372-01-1). A summary of the study is given below along with the mean values based on the study results and following application of the new EFSA[12] guidance rules. A conclusion and recommendation regarding the dermal absorption of fosetyl-Al formulated as the FEA WG 80 is given below.

The mean percentage of fosetyl-Al in the FEA WG 80 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for higher concentration dilution of 500 g/L was 0.70% for the human epidermal membranes and 4% for the rat epidermal membranes. Applying the new EFSA guidance (albeit without the possibility of removing the stratum corneum values as the stratum corneum was not sampled separately) these values adjust to 1 and 6% for the human and rat, respectively.

The mean percentage of fosetyl-Al in the FEA WG 80 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for lower concentration dilution of 1 g/L was 1.3% for the human epidermal membranes and 22.8% for the rat epidermal membranes. Applying the new EFSA guidance (albeit without the possibility of removing the stratum corneum values as the stratum corneum was not sampled separately) these values adjust to 3 and 25% for the human and rat, respectively.

According to the new EFSA guidance there is 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. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-fosetyl-Al in the FEA WG 80 formulation:

<u>Human Skin</u>	<u>Rat Skin</u>
• 1% @ 500 g/L. • 3% @ 1 g/L.	• 6% @ 500 g/L. • 25% @ 1 g/L.

It is worth noting that these values are conservative in that the exposure period was 24 hours and that the whole skin has been included in the absorbed fraction in addition to the normalisation where the recovery was less than 95% and the addition of the standard deviation to the mean values. Furthermore the high dose was a water dilution of the granule formulation resulting in a lower concentration of 500 g/L compared to a nominal 800 g/kg for the neat formulation.

12 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.

Report:	KCP 7.3/01; cfy.W B, s,; 2000; M-206372-01-1
Title:	In vitro absorption from a 800 g/kg WG formulation through human and rat epidermis Fosetyl-AL
Report No.:	C014312
Document No.:	M-206372-01-1
Guideline(s):	Draft OECD guideline for the testing of chemicals; skin absorption: in vitro method 428 (1996)
Guideline deviation(s):	none-
GLP/GEP:	**yes**

Material and methods

Human skin: Number: minimum of 2 donors per dose level.
Anatomical region: Abdomen, back and buttocks.
Preparation: Extraneous tissue was removed from human whole skin samples obtained *post mortem*. The skin samples were immersed in water at 60°C for 40-45 seconds and the epidermis teased away from the dermis. Each epidermal membrane was given an identifying number and stored frozen on aluminium foil until required for use.

Rat skin: Source: [redacted] UK.
Strain: Wistar.
Age: 28 ± 7 days.
Sex: Male.
Number: minimum of 2 donors per dose level.
Anatomical region: Dorsal and flank.
Preparation: The skins were soaked for approximately 20 hours in 1.5M sodium bromide then rinsed in distilled water. The epidermis was carefully peeled from the dermis. Each epidermal membrane was given an identifying number and stored frozen on aluminium foil until required for use.

Test Material:

Non-radiolabelled: Batch: GELL 605.278-1.
Purity = 98.9%.

Radiolabelled: [2-^{14}C]-fosetyl-Al
Batch: GHS1015.1.
Specific activity: 2.17 MBq/mg.
Radiopurity of the formulation: 99%.

Formulation: The formulation used in this experiment was the fosetyl-Al WG 80 (Aliette) formulation (specification number 102000001579) containing fosetyl-Al at a nominal concentration of 800 g/kg (actual 794 g/kg). It was used at two nominal concentrations of fosetyl-Al: 500 g/L and 1 g/L.

Test system: The type of static glass diffusion cell used in this study has an exposed skin surface area of 2.54 cm^2 and a receptor volume of approximately 4.5 mL. Discs of approximately 3 cm diameter of prepared skin were mounted, dermal side down, in diffusion cells held together with individually numbered clamps and placed in a water bath maintained at 32 ± 1 °C. Fosetyl-Al has a water solubility of 3 g/L which is sufficient to avoid complications from back diffusion. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 1 °C (close to the normal skin temperature).

Skin integrity: Skin integrity was determined by measurement of the electrical resistance across the sample. Skin with a measured resistance of <10 kΩ (human) or <2.5 kΩ (rat) were regarded as having a lower integrity than normal and not used for exposure to the test materials, due to the possibility of compromised barrier function.

Treatment: The receptor chambers of the cells containing small magnetic stirrer bars were filled with a recorded volume of receptor fluid physiological saline). A pre-treatment sample (0.1 mL) was taken from each receptor chamber for analysis by LSC. An equal volume of fresh receptor fluid was added to each receptor chamber to replace the volume removed. Both doses were applied at the rate of 10 µL/cm². After dosing, the cells were replaced in a water bath maintained at 32 ± 1 °C. The diffusion cells remained unoccluded for the duration of the experimental period (24 hours).

Sampling: For all cells, 0.1 mL samples of receptor fluid were taken using an autosampler pre-treatment and at 1, 2, 3, 4, 6, 8, 10, and 24 hours after application for analysis by LSC. The volume of fluid in the receptor chamber was maintained by the replacement of a volume of receptor fluid, equal to the sample volume immediately after each sample was taken.

After the 24 hour sample had been taken, the skin was washed by gently swabbing with a series of natural sponges (approximately 1 cm³) pre-wetted with 3% Teepol® L in water to terminate the exposure. Another two sponges, pre-wetted with water, were used to further swab the surface.

Decontamination was shown to be complete following assessment of residual radioactivity levels on the skin surface/sponges with a Geiger counter. All the sponges were combined and digested in Soluene® 350. After the final receptor fluid sample had been taken at the end of the experiment, the remaining fluid in the receptor chamber was discarded and the chamber rinsed with fresh receptor fluid which was also discarded.

The donor chamber was carefully removed and the underside wiped with a single sponge pre-wetted with 3%Teepol® L in water which was added to the wash sponges (below). The donor chamber was washed with methanol and the sample analysed for fosetyl-Al by LSC.

The epidermal surface of the skin was decontaminated by gently swabbing the application site with natural sponges pre-wetted with 3% Teepol® L, and with further sponges pre-wetted with water. Decontamination was shown to be complete following assessment of residual radioactivity levels on the skin surface/sponges with a Geiger counter. The sponges were digested in Soluene® 350 and made up to a recorded volume. A sample was taken for analysis.

Radioassay: The [^{14}C]-fosetyl-Al test preparations and samples collected during this study were analysed by Liquid Scintillation Counting (LSC). The limit of quantification (LOQ) using the above procedure was set at 3.9 µg/mL (human) and 2.0 µg/mL (rat) for the 500 g/L dilution applications and 0.006 µg/mL (human) and 0.003ng/ml (rat) for the l g/L dilution applications. The LOQ values for the formulation concentrate and aqueous dilution were different due to different ratios of [^{14}C]-fosetyl-Al to unlabelled fosetyl-Al

Findings:

<u>Human</u>

No absorption of fosetyl-Al from the 500 g/L dilution was detected (<7.0 µg/cm²; <0.14% of the applied dose) through human epidermis throughout the entire 24 h period of exposure. From the l g/L dilution, fosetyl-Al absorption was essentially constant over the whole of the 24 h exposure period (0.002 µg/cm²/h), although an initial higher rate (0.013 µg/cm²/h) was noted during the first hour of contact.

The results for the proportion of the applied dose absorbed have been recalculated from Table 3 presented in the report on page 27. The results for the 500 g/L group were calculated using the four cells that presented total recoveries >90% (i.e. cells 32 and 52 were excluded). The results for the 1 g/L group were calculated using the 5 cells presented in the report (see Table 7.3- 1).

Rat

From the 500 g/L dilution, an initial absorption rate of 2.60 µg/cm^2/h measured during the first hour of contact, was followed by a slower rate of 0.368 µg/cm^2/h up to 24h. Over the entire 24 h exposure period, the average absorption rate was 0.407 µg/cm^2/h. In terms of the proportion of the applied dose absorbed, fosetyl-Al absorption increased from 5.41 µg/cm^2 (0.11%) at 6 h to 7.47 µg/cm^2 (0.15%) at 10h, with 12.0 µg/cm^2 (0.24%) being absorbed by 24 h. Similarly, from the 1 g/L dilution, the fastest rate of absorption (0.131 µg/cm^2/h) was measured during the first hour of contact and was followed by a slower rate of 0.007 µg/cm^2/h up to 24 h. Over the entire 24 h exposure period, the average absorption rate was 0.009 µg/cm^2/h.

The results for the proportion of the applied dose absorbed have been recalculated from Table 4 presented in the report on page 28. The results for the 500 g/L group were calculated using all five of the cells that are presented in the report. The results for the 1 g/L group were calculated using the four cells that presented total recoveries >85% (i.e. cell 14 was excluded, see Table 7.3- 2).

Table 7.3- 1: Mean Distribution of Radioactivity at 24 Hours after Dose Application of [^{14}C]-Fosetyl-Al in a WG 80 Formulation to Human Epidermal Skin Samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)			
Dose levels	**Concentrate: High dose (500 g/L)**		**Dilution: Low dose (1 g/L)**	
Species (n)	**Human (4)**		**Human (5)**	
	Mean	**SD**	**Mean**	**SD**
SURFACE COMPARTMENT				
Skin washes [a]	77.14	15.97	86.98	22.31
Spreaders	2.43	0.81	0.42	0.12
Donor chamber	13.81	11.31	11.05	19.27
Total % non-absorbed	**93.39**	**3.99**	**98.45**	**3.25**
SKIN COMPARTMENT				
Skin	***0.55***	***0.55***	***1.02***	***1.30***
RECEPTOR COMPARTMENT				
Total % directly absorbed [b]	***0.14***	***0.00***	***0.28***	***0.42***
Total % Potentially Absorbable [c]	0.69	0.55	1.30	1.72
TOTAL % RECOVERY	**94.08**	**3.52**	**99.75**	**1.68**
Evaluation according to EFSA Guidance				
Standard deviation >25%?	Yes		Yes	
Recovery <95%?	Yes		No	
Adjusted Total % Potentially Absorbable [d]	**1**		**3**	

[a]: sum of radioactivity found in wash sponges at 24 hours.
[b]: sum of radioactivity found in receptor fluid (0-24 hours) taking the LOQ of 0.14%.
[c]: total % directly absorbed + total % at dose site.
[d] : values considered for the adjusted Total % Potentially Absorbable according to EFSA are in ***bold Italics***
SD: standard deviation
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.

Table 7.3- 2: Mean Distribution of Radioactivity at 24 Hours after Dose Application of [^{14}C]-Fosetyl-Al in a WG 80 Formulation to Rat Epidermal Skin Samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)			
Dose levels	Concentrate: High dose (500 g/L)		Dilution: Low dose (1 g/L)	
Species (n)	Rat (5)		Rat (5)	
	Mean	SD	Mean	SD
SURFACE COMPARTMENT				
Skin washes [a]	95.62	2.80	66.43	5.81
Spreaders	1.76	0.38	1.04	0.35
Donor chamber	2.38	1.90	1.97	0.25
Total % non-absorbed	**99.76**	**3.98**	**69.44**	**7.87**
SKIN COMPARTMENT				
Skin	3.76	1.80	***23.71***	***5.20***
RECEPTOR COMPARTMENT				
Total % directly absorbed [b]	***0.24***	***0.08***	***3.33***	***1.90***
Total % Potentially Absorbable [c]	4.00	1.85	27.83	4.83
TOTAL % RECOVERY	**103.76**	**2.34**	**92.26**	**3.09**
Evaluation according to EFSA Guidance				
Standard deviation >25%?	Yes			
Recovery <95%?	No		No	
Adjusted Total % Potentially Absorbable [d]			***25***	

[a]: sum of radioactivity found in wash spinnes at 24 hours.
[b]: sum of radioactivity found in receptor fluid (at 24 hours) taking the LOQ of 0.14%.
[c]: total % directly absorbed + total % at dose site.
[d]: values considered for the adjusted Total % Potentially Absorbable according to EFSA are in ***bold Italics***
SD: standard deviation
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 through human and rat epidermal membranes of [^{14}C]-fosetyl-Al in the FEA WG 80 formulation was investigated at the two concentrations of 500 and 1 g/L.

The mean percentage of fosetyl-Al in the FEA WG 80 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for higher concentration dilution of 500 g/L was 0.7% for the human epidermal membranes and 4% for the rat epidermal membranes. Applying the new EFSA guidance (albeit without the possibility of removing the stratum corneum values as the stratum corneum was not sampled separately) these values adjust to 1 and 6% for the human and rat respectively.

The mean percentage of fosetyl-Al in the FEA WG 80 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for lower concentration dilution of 1 g/L was 1.3% for the human epidermal membranes and 22.8% for the rat epidermal membranes. Applying the new EFSA guidance (albeit without the possibility of removing the stratum corneum values as the stratum corneum was not sampled separately) these values adjust to 3 and 25% for the human and rat, respectively.

According to the new EFSA guidance[13] there is 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. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-fosetyl-Al in the WG 80 formulation:

Human Skin	Rat Skin
• 1% @ 500 g/L.	• 6% @ 500 g/L.
• 3% @ 1 g/L.	• 25% @ 1 g/L.

It is worth noting that these values are conservative in that the exposure period was 10 hours and that the whole skin has been included in the absorbed fraction in addition to the normalisation where the recovery was less than 95% and the addition of the standard deviation to the mean values. . Furthermore the high dose was a greater dilution of the granule formulation resulting in a lower concentration of 500 g/L compared to a nominal 800 g/kg for the neat formulation.

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information, please refer to the respective Document JCP.

[13] 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.