Bayer CropScience

Document Title

Tier 2 Summary of the Toxicological Studies and Exposure Data and Information on the Plant Protection Product for Iprovalicarb + folpet WG 65.3

Specification No: 102000011659-04

Substance(s)

IPROVALICARB
(Annex I Renewal)

Data Requirements

Regulation EC/1141/2010
on the renewal of the inclusion of AIR2 active substances

in conjunction with

Directive 91/414/EEC and Regulation EC/1107/2009

According to OECD format guidance for industry data submissions (SANCO/10387/2010 rev. 8 - on the renewal of active substances included in Annex I)

Annex IIIA
Section 3, Point 7
Document M

According to OECD format guidance for industry data submissions on plant protection products and their active substances

Date

2012-05-22

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M-431209-01-5

OWNERSHIP STATEMENT

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IIIA1 7 Toxicological Studies and Exposure Data and Information on the Plant Protection Product

IIIA1 7.1 Acute toxicity

Iprovalicarb is not acutely toxic via oral, dermal or inhalation route. It is not irritating to skin or eyes and was not a skin sensitizer in the Magnusson-Kligmann test.
The acute toxicity studies on the representative formulation IPV+FLP WG 65.3 were carried out after the first inclusion of iprovalicarb. IPV+FLP WG 65.3 is not acutely toxic via the oral and the dermal routes. It is moderately irritating to skin and severely irritating to the eyes. This product was not submitted to a skin sensitizing assay such as Buehler or Magnusson-Kligmann assays, since the concentration of folpet contained in the product will anyway lead to a sensitizing positive response.
The toxicity data package has been conducted on the formulated product iprovalicarb + folpet WG 65.3 with the composition code UVP 05539447. This formulation had a composition slightly different (inerts) from the formulation iprovalicarb + folpet WG 65.3 (composition code UVP 06361579 which is commercialized. The differences, however, are without toxicological relevance as demonstrated in the bridging document (N°: M-246642-03-1). Therefore the data package is fully representative for iprovalicarb + folpet WG 65.3.

Type of study/species	**Result**	**Reference**
Acute oral /rat	LD_{50} > 2500 mg/kg	[redacted](2000) M-026075-01-1
Acute dermal / rat	LD_{50} > 2000 mg/kg	[redacted](2000) M-026071-01-1
Skin irritancy / rabbit	Moderately irritant	[redacted](2000) M-021579-02-1
Eye irritancy / rabbit	Irritant	[redacted](2000) M-021570-02-1
Acute sensitization	Assumed sensitizer due to high content of folpet which is a known skin sensitizer.	-

Separate testing for inhalation toxicity was not conducted, because it was not triggered according to the criteria of Directive 94/79/EEC due the results obtained during the characterization study of this WG formulation by [redacted][1].

Therefore, the following classification/labelling is proposed for iprovalicarb + folpet WG 65.3:
- EU directive 1999/45/EC:

    Xi Irritant,
    R41 : "May cause severe damage to eyes"
    R43 : "May cause sensitization by skin contact"

[1] [redacted]: " Physical, chemical and technical properties of iprovalicarb + folpet WG 65.3", January 2005, doc. M-244466-01-1

- GHS (rev.4) 2011:

Eye irritation: Category 1: DANGER, H318, causes severe eye damage
Skin sensitization: Category 1: WARNING, H317, may cause an allergic skin reaction

- Regulation (EC) No 1272/2008 (CLP):
Eye irritation: Category 1: DANGER, H318, causes severe eye damage
Skin sensitization: Category 1: WARNING, H317, may cause an allergic skin reaction

IIIA1 7.1.1 Acute oral toxicity

Report:	**KIIIA1 7.1.1/01; [redacted] 2000**
Title:	SZX 0722 9 WG + Folpet 56.3 (c.n. Iprovalicarb; Folpet) - Study for acute oral toxicity in rats.
Document No	M-026075-01-1
Guidelines:	OECD Guidelines N° 423 (2001) EC 67/54/548/EEC (1967) EPA OPPTS 870.1100
GLP	Yes

Material and methods:
SZX 0722 9 WG + folpet 56.3, (formulation 07373/0048(0046), development number 3000244654) contained the active ingredients iprovalicarb (9.7%) and folpet (56.9%) and was formulated in demineralised water with Cremophor EL® 2 %. The test substance was administered in a single dose by stomach tube to fasted male and female rats. The application volume was 10 ml/kg bw. The post-treatment observation period was 14 days.

Findings**:**

Dose mg/kg b.w.	Toxicological result *	Duration of signs	Time of death	Mortality [%]
males				
2000	0/3/3	40 m – 6 h	--	0
females				
2000	0/3/3	1 h – 2 d	-	0
oral LD_{50} > 2500 mg/kg bw				

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

Clinical signs: Piloerection, decreased motility and reactivity, spastic gait, laboured breathing and diarrhoea in males and females at 2000 mg/kg bw; additional constipation and light-coloured faeces in females.

Body weights: No toxicological effects on body weights or body weight gain.

Gross necropsy: No significant findings.

Conclusion**:**

SZX 0722 + Folpet WG 65.3 is not acutely toxic to rats following oral administration.
According to the criteria for classification in Commission Directive 2001/59/EC, this formulation is not classified.
According to GHS (rev.4) 2011 this formulation is not classified.
According to Regulation (EC) No 1272/2008 (CLP) this formulation is not classified.

IIIA1 7.1.2 Acute percutaneous (dermal) toxicity

Report:	**KIIIA1 7.1.2/01; [redacted] 2000**
Title:	SZX 0722 9 WG + Folpet 56.3 (c.n.: Iprovalicarb + Folpet) - Study for acute dermal toxicity in rats.
Document No	M-026071-01-1
Guidelines:	OECD Guidelines N° 402 EEC B.3. EPA OPPTS 870.1200
GLP	Yes

Material and methods:

SZX 0722 9 WG + folpet 56.3, (formulation 07373/0048(0046), development number 3000244654), contained the active ingredients iprovalicarb (9.7%) and folpet (56.9%). The test substance was pulverised and placed on the shorn back of males and female rats. The exposure time was 24 hours. The post-treatment observation period was 14 days.

Findings:

Dose mg/kg b.w.	Toxicological result *	Duration of signs #	Time of death	Mortality [%]
males				
2000	0/0/5		--	0
females				
2000	0/3[#]/5	5 d – 6 d	--	0
dermal LD_{50} > 2000 mg/kg bw				

* 1st number = number of dead animals 2nd number = number of animals with toxic signs
3rd number = number of animals used [#] only local effects

Clinical signs: None.

Gross necropsy: No pathological changes.

Local findings: Reddening of treatment area observed in females from day 5 to day 6.

Conclusion**:**

SZX 0722 + folpet WG 65.3 is not toxic to rats following acute dermal application.

According to the criteria for classification in Commission Directive 2001/59/EC, this formulation is not classified.

According to GHS (rev.4) 2011 this formulation is not classified.

According to Regulation (EC) No 1272/2008 (CLP) this formulation is not classified.

IIIA1 7.1.3 Acute inhalation toxicity to rats

Since iprovalicarb + folpet WG 65.3 is commercialized in the form of a Wettable Granule formulation which is a solid and is practically dust free, no acute inhalation study is required. The neat formulation will not be used in a manner that is expected to pose any acute inhalation hazard.
With respect to 94/79/EEC, testing for the acute inhalation toxicity of iprovalicarb + folpet WG 65.3 is not triggered because it:

- is not a gas or liquefied gas,
- is not a smoke generating formulation or fumigant,
- is not to be used with fogging equipment,
- is not a vapour releasing preparation,
- is not an aerosol,
- is not a powder, is dust-free, and hence does not contain a significant proportion of particles of diameter < 50 µm (> 1 % on a weight basis), as has been clearly demonstrated by [redacted][2] in an attrition test where most of the particles after attrition were >125 µm. SZX 0722 + folpet WG 65.3 contains only 0.15 % of particles with diameter < 50 µm on a weight basis.
- is not to be applied from aircraft and
- does not contain active substances with a vapour pressure > 1×10^{-2} Pa and
- is not to be used in a manner which generates a significant proportion of particles or droplets of diameter < 50 µm (<1% on a weight basis).,

Table 7.3.1-1: Result of the particle size determination according to CIPAC MT 170*

Sieve	Mass (g)	Residue (%)	Sum of residues (%)
1000 µm	0.39	0.39	0.39
800 µm	1.41	1.39	1.78
500 µm	14.25	14.10	15.88
250 µm	46.24	45.75	61.63
125 µm	30.65	30.32	91.95
75 µm	7.40	7.32	99.27
50 µm	0.72	0.71	99.98
pan	0.15	0.15	100.13
	Sum : 101.21		

* Automatic sieving with Laboratorsiebmaschine Typ VS 1000 fa. Retsch, weight of formulation 101.08 g, sieving time of 5 minutes.

Conclusion:
In the absence of the need to perform an acute inhalation toxicity study the iprovalicarb + folpet WG 65.3 formulation need not be classified.

According to the criteria for classification in Commission Directive 2001/59/EC, this formulation is not classified.

According to GHS (rev.4) 2011 this formulation is not classified.

According to Regulation (EC) No 1272/2008 (CLP) this formulation is not classified.

[2] [redacted]: " Physical, chemical and technical properties of iprovalicarb + folpet WG 62,25", January 2005, doc. M-244466-01-1

IIIA1 7.1.4 Skin irritation

Report:	**KIIIA1 7.1.4/01; [redacted] 2000**
Title:	Acute skin irritation test (patch test) of SZX 0722 9 WG + Folpet 56.3 in rabbits
Document No	M-021579-02-1
Guidelines:	OECD Guidelines N° 404. EEC B.4. EPA OPPTS 870.1200
GLP	Yes

Material and methods:

SZX 0722 9 WG + folpet 56.3, (formulation 07373/0048(0046), development number 3000244654) contained the active ingredient iprovalicarb (9.7%) and folpet (56.9%) and was moistened with water. 500 mg of test substance was applied to the shaved dorsal skin of male rabbits. The exposure time was four hours. Scores were taken 1, 24, 48 and 72 hours and 4 to 8 days after patch removal.

Findings:

Table 7.1.4-1: Irritant Effects on the skin (Exposure: 4 hours)

Animal no.	1 h		24 h		48 h		72 h		4 d		5 d		6 d		7 d		8 d	
	E	O	E	O	E	O	E	O	E	O	E	O	E	O	E	O	E	O
1	1	0	1	1	1	1	1	0#	1	0#	1	0#	0	0##	0	0*	0	0
2	1	0	1	1	1	1	1	0#	1	0#	1	0#	1	0##	1	0*	0	0
3	1	1	1	2	1	2	1	1#	1	1#	1	1##	1	0*	1	0*	0	0

abbreviation: 0 = no pathological findings; E = Erythema and eschar formation; O = Oedema formation
induration of the skin; ## laceration of the skin; * peeling of the skin

Table 7.1.4-2: Mean scores

Animal		24 hours	48 hours	72 hours	Mean scores	Response	Reversible (days)
1	Erythema (redness) and Eschar formation	1	1	1	1.0	-	7
	Oedema Formation	1	1	0#	0.7	-	8
2	Erythema (redness) and Eschar formation	1	1	1	1.0	-	8
	Oedema Formation	1	1	0#	0.7	-	8
3	Erythema (redness) and Eschar formation	2	2	1	1.7	-	8
	Oedema Formation	2	2	1#	1.7	-	8

Abbreviations: No positive response: mean scores < 2 = -
Positive response: mean scores ≥ 2 = +

An **erythema** (grade 1) was observed in all three animals 1 hour to 5 days after patch removal and in animal N°s 2 and 3 up to 7 days after patch removal. All animals showed an **oedema**: animal N°s 1 and 2 (grade 1) 24 and 48 hours after patch removal; animal N° 3 1 hour (grade 1), 24 hours and 48

hours (grade 2), 72 hours to 5 days (grade 1) after patch removal. Induration of the skin was seen in all animals between 72 hours and 5 days. Laceration of the skin was observed in all animals between 5 and 6 days after patch removal. Peeling of the skin was observed in all animals between 6 and 7 days after patch removal.

There were no systemic intolerance reactions.

Conclusion:
SZX 0722 + folpet WG 65.3 was found to be moderately irritating to the skin with full reversibility within 8 days.

According to the criteria for classification in Commission Directive 2001/59/EC, this formulation is not classified.
According to GHS (rev.4) 2011 this formulation is not classified.
According to Regulation (EC) No 1272/2008 (CLP) this formulation is not classified.

IIIA1 7.1.5 Eye Irritation

Report:	**KIIIA1 7.1.5/01; [redacted] 2000**
Title:	Acute eye irritation study of SZX 0722 9 WG + folpet 56.3 by instillation into the conjunctival sac of rabbits
Document No	M-021570-02-1
Guidelines:	OECD Guidelines N° 405. EEC B.5.
GLP	Yes

Material and methods:
SZX 0722 9 WG + folpet 56.3, (formulation 07373/0048(0046), development number 3000244654) contained the active ingredient iprovalicarb (9.7 %) and folpet (56.9 %) and was moistened with water One single dose of 100 mg test substance was administered into the right eye of male rabbits. Examination time was 1, 24, 48, 72 hours and 4 to 21 days after administration.

Findings:

Table 7.1.5-1: Irritant Effects on the eye

Time after administration	Cornea Opacity	Iris	Conjunctivae Redness	Conjunctivae Chemosis
		Animal no.: 1/2/3		
1 h	0/0/0	0/0/0	1#/1#/1#	2/2/2
24 hrs	1/1/2	1/1/1	2#/2##/2##	3/3/3
48 hrs	1/1/2	1/1/1	2##/2##/2##	2/3/3
72 hrs	1/1/2	1/1/1	2/2/2	2/2/2
4 days	1/1/2	1/1/1	2/2/2	2/2/2
5 days	1/1/2	0/0/1	1/1/2	1/1/1
6 days	0/1/2	0/0/1	1/0/2	1/0/1
7 days	0/1/2	0/0/1	1/0/2	1/0/1
8 days	0/1/2	0/0/1	1/0/1	1/0/1
9 days	0/1/2	0/0/0	1/0/1	1/0/1
10 days	0/1/2	0/0/0	0/0/1*	0/0/1
11 days	0/0/1	0/0/0	0/0/1*	0/0/1
12 days	-/-/1	-/-/0	-/-/1*	-/-/1
13 days	-/-/1	-/-/0	-/-/0*	-/-/0
14 days	-/-/1	-/-/0	-/-/0	-/-/0
15 days	-/-/1	-/-/0	-/-/0	-/-/0
16 days	-/-/1	-/-/0	-/-/0	-/-/0
17 days	-/-/1	-/-/0	-/-/0	-/-/0
18 days	-/-/1	-/-/0	-/-/0	-/-/0
19 days	-/-/1	-/-/0	-/-/0	-/-/0
20 days	-/-/1	-/-/0	-/-/0	-/-/0
21 days	-/-/1	-/-/0	-/-/0	-/-/0

deposits of test substance in the conjunctival sac;
whitish deposits in the conjunctival sac (probably plus);
* loss of hair (lower lid)

Corneal opacity (grade 1) was observed in animal N°s 1 and 2 from 24 hours to 5 days, in animal N°. 2 up to 10 days after instillation. Corneal opacity was observed in animal N°. 3 from 24 hours to 10 days (grade 2) and 11 to 21 days after instillation (grade 1).

The fluorescein test was performed

- after 24 hours revealed corneal staining in animal N° 1 (3/4 of the corneal surface) and animal N°s. 2 and 3 (whole surface);
- after 7 day revealed corneal staining in animal N° 2 and 3 (1/2 of the corneal surface);
- after 14 days revealed corneal staining in animal N° 3 (1/4 of the corneal surface);
- after 21 days revealed corneal staining in animal N° 3 (1/4 of the corneal surface).

An irritation of the **iris** (grade 1) was observed in all three animals 24 hours to 4 days, in animal N°. three until 8 days after instillation.

Conjunctival redness was observed in all three animals 1 hour (grade 1) and 24 hours to 4 days (grade 2), in animal N° 3 up to 7 days after instillation. Corneal opacity (again grade 1) was observed

in animal N° 1 from 5 to 9 days, in animal N° 2 at 5 days and in animal N° 3 from 8 to 12 days after instillation.

Conjunctival chemosis (of grade 1 to 3) was observed in all three animals 1 hour to 5 days after instillation, in animal N° 1 from 9 days and in animal N° 3 up to 12 days after instillation.

Deposits of the test substance in the conjunctival sac were observed in all three animals 1 hour after instillation. Whitish deposits were noted in all three animals 24 and 48 hours after instillation. Loss of hair at the lower lid was observed in animal no. three 10 to 13 days after instillation.

There were no systemic intolerance reactions.

Conclusion:
SZX 0722 + folpet WG 65.3 was found to cause serious damage to eyes.

According to the EC classification criteria (2001/59/EC Directive), this formulation is classified Xi /R41 Irritant, may cause severe damage to eyes.
According to GHS (rev.4) 2011 this formulation is classified Category 1, DANGER, H318, causes severe eye damage.
According to Regulation (EC) No 1272/2008 (CLP) this formulation is classified: Category 1, DANGER, H318, causes severe eye damage.

IIIA1 7.1.6 Skin sensitization

Because of the known skin sensitising properties of the active ingredient folpet (guaranteed content: 563 g/kg) and positive results observed in sensitising tests with other formulations containing folpet, a sensitising potential of the formulation iprovalicarb + folpet WG 65.3 was assumed.

According to the EC classification criteria (2001/59/EC Directive), this formulation is classified Xi/R43, irritant/may cause sensitization by skin contact.
According to GHS (rev.4) 2011 this formulation is classified: Category 1, DANGER, H317, may cause an allergic skin reaction.
According to Regulation (EC) No 1272/2008 (CLP) this formulation is classified: Category 1, DANGER, H317, may cause an allergic skin reaction.

IIIA1 7.1.7 Supplementary studies for combinations of plant protection products

Not relevant: iprovalicarb + folpet WG 65. 3 is not recommended to be combined with other plant protection products.

IIIA1 7.2 Short-term toxicity studies

Not required by Directive 91/414/EEC

IIIA1 7.3 Operator exposure

Iprovalicarb + folpet WG 65.3 is a water dispersible granule formulation containing 90 g/kg of iprovalicarb and 563 g/kg of folpet. The proposed use is as a fungicide on grapes. Iprovalicarb + folpet WG 65.3 will be applied to vines via broadcast air assisted sprayers and hand-held sprayers. Water will be the diluent/carrier in all situations. Usage information pertinent to operator exposure is summarised in Table 7.3-1.

Access to Folpet data ;

The representative formulation in the application for Annex I Renewal of iprovalicarb is a combination with folpet, which – from a Bayer perspective - is a 3rd party substance, procured from [redacted]. ([redacted]). Bayer CropScience AG has the right of reference to files, data, studies, summaries and assessments owned by [redacted] which were submitted in the EU for the support of the registration of the active substance folpet and the representative formulation Folpan 80 WDG. The right to references of Bayer CropScience AG extends to all EU countries. A separate Letter of Access is included in this supplementary dossier (M-428625-01-1).

Bayer CropScience AG is using a risk envelope approach for the risk assessment of the representative formulation. Within the scope of this supplementary dossier, up to 4 applications at 1.35 kg/ha folpet are proposed as a safe use in grapes. This is much below the critical GAP that [redacted] currently defends in this crop in the EU, where 10 applications of up to 1.6 kg/ha have been approved, with all other parameters such as interval between applications or pre-harvest interval being identical or very similar. Therefore, Bayer CropScience AG considers it justified to refer to folpet data owned by [redacted] wherever appropriate. A folpet-specific risk assessment is not considered necessary to defend the Annex I listing of iprovalicarb.

Table 7.3-1: Application parameters for iprovalicarb + folpet WG 65.3

Crop	Application technique	F / G	Maximum application rate (kg/ha)	Minimum amount water (L/ha)	Max. number of treatments	Interval between treatments (days)	PHI (days)
Grapes	BAA	F	PPP 2.4 IPV 0.216 FLP 1.3512	400	4	10-14	28
	HHS						

BAA = Broadcast air assisted sprayer, Appl. = application, PHI = Pre Harvest Interval
F = Field use, G = Greenhouse use PPP = plant protection product, IPV = iprovalicarb, FLP = folpet

Consideration on acceptable operator exposure level (AOEL)

Iprovalicarb: finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 26 February 2002 in view of the inclusion of iprovalicarb in Annex I of Directive 91/414/EEC a

systemic AOEL of 0.015 mg/kg bw/day was proposed for iprovalicarb based on a 53 week dog study and a safety factor of 200 (European Commission - SANCO/2034/2000-FINAL – 02 July 2002).

Folpet: refer to folpet-specific risk assessment of [redacted]. ([redacted]).

Consideration on dermal absorption

Iprovalicarb: dermal absorption data are available from an *in vivo* study in rats and an *in vitro* study with human/rat skin for iprovalicarb. Derived from the results of these studies it is proposed to use **1% (concentrate) and 16.3% (diluted)** to calculate systemic exposures.

Folpet: refer to folpet-specific risk assessment of [redacted]. ([redacted]).

For details please see point IIIA1 7.6.

Consideration on estimation of operator exposure

With respect to the outdoor uses operator exposure estimates are calculated using the German model only, the UK POEM not offering scenarios for grapes. Exposure calculations are performed without and with protective equipment.
It should be noted that this selection of protective measures is not intended to be a recommendation for the minimum PPE necessary when handling iprovalicarb + folpet WG 65.3. It does not consider specific requirements, which may exist in individual Member States. Additional PPE can be used to further reduce the exposure of the operator.

It has to be pointed out that "no PPE" in the German Model considers a lightly dressed operator, wearing a short sleeved T-Shirt, shorts and shoes. Such an unprotected professional 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. The model allows 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 7.3-2. Detailed assumptions and considerations as well as exposure calculations are presented in chapter IIIA1 7.3.1.

T**able 7.3-2: Comparison of estimated systemic operator exposure to iprovalicarb (IPV) [mg/kg bw/day] with the proposed AOEL**

Application type	Crop	PPE	Total systemic exposure IPV [mg/kg bw/day]	% of AOEL IPV (0.015 mg/kg bw/day]
Field uses, German model (70 kg operator)				
Broadcast air assisted sprayer	Grapes	No PPE [1)]	0.0414	280
		With PPE [2)]	0.0102	68
Hand-held sprayer		No PPE [1)]	0.0220	147
		With PPE [2)]	0.0094	63

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 German model estimates predict that iprovalicarb + folpet WG 65.3 can be used safely with broadcast air-assisted sprayers or hand-held sprayers when gloves are worn during mixing loading and a standard protective overall during application. As a good practice when handling pesticides, wearing gloves during hand-held spraying would reduce the exposure.

The detailed calculations are presented in the Tables 7.3.1-1 & 2.

IIIA1 7.3.1 Estimation of operator exposure without personal protective equipment

a) Estimation according to the German model

Exposure is calculated for each 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:

Broadcast air assisted sprayer

Treated area: 8 ha/day

Max. dose rate: 2.4 L/ha iprovalicarb + folpet WG 65.3 corresponding to 0.216 kg/ha iprovalicarb and 1.3512 kg/ha folpet

Hand-held sprayer

Treated area: 1 ha/day

Max. dose rate: 2.4 L/ha iprovalicarb + folpet WG 65.3 corresponding to 0.216 kg/ha iprovalicarb and 1.3512 kg/ha folpet

Dermal absorption: IPV 1% (concentrate) and 16.3% (in use dilution)
FLP 10% (both concentrate and in use dilution)
(see IIIA1 7.6)

Operator body weight: 70 kg

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

Table 7.3.1-1 Calculation of operator exposure to iprovalicarb using tractor-mounted/trailed broadcast air-assisted sprayers (German model, without and with PPE)

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

Product:	Iprovalicarb + folpet WG 65.3					
Active substance:	iprovalicarb		a.s. concentration:	90	[g/l or kg]	
Formulation:	WG		PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	2.4			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	
	16.3	(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 =	0.008	1.728	0.000197	1.0	0.000197	D = Dermal
$D_{M(H)}$ =	2.0	1.728	0.0494	0.01	0.000494	M = Mix/Loading
I_A =	0.018	1.728	0.000444	1.0	0.000444	A = Application
$D_{A(H)}$ =	1.2	1.728	0.0296	1.0	0.029623	H = Hands
$D_{A(H)}$ =	0.7	1.728	0.0173	1.0	0.01728	C = Head
$D_{A(B)}$ =	9.6	1.728	0.237	0.05	0.011849	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	1.00	0.049371	0.000494	0.000494	0.000005
	Application	16.3	0.283886	0.046273	0.058752	0.009577
Inhalation:	Mix/Loading	100	0.000197	0.000197	0.000197	0.000197
	Application	100	0.000444	0.000444	0.000444	0.000444
		Total =		**0.0474**		**0.0102**

Table 7.3.1-2 Calculation of operator exposure to iprovalicarb using hand-held sprayers (German model, without and with PPE)

Operator exposure estimate: German model. Hand-held sprayer: hydraulic nozzles. Outdoor, high level target						
Product:	Iprovalicarb + folpet WG 65.3					
Active substance:	folpet		a.s. concentration:	563	[g/l or kg]	
Formulation:	WG		PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	2.4			Hands:	Gloves	
Work rate [ha/day]:	1		PPE during application:	Respiration:	None	
Body weight [kg]:	70			Hands:	None	
Inhalation absorption [%]	100			Head:	None	
Dermal absorption [%]	10.0	(concentrate)		Body:	Standard protective coverall	
	10.0	(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 =	0.02	1.3512	0.000386	1.0	0.000386	D = Dermal
$D_{M(H)}$ =	21.0	1.3512	0.04054	0.01	0.004054	M = Mix/Loading
I_A =	0.3	1.3512	0.005791	1.0	0.005791	A = Application
$D_{A(C)}$ =	4.8	1.3512	0.0927	1.0	0.092654	H = Hands
$D_{A(H)}$ =	10.6	1.3512	0.2046	1.0	0.20461	C = Head
$D_{A(B)}$ =	25.0	1.3512	0.4826	0.05	0.024129	B = Body

Absorbed dose:

Route		Absorption [%]	**No PPE** Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	**With PPE** Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	10.0	0.40536	0.040536	0.004054	0.000405
	Application	10.0	0.779835	0.077984	0.321393	0.032139
Inhalation:	Mix/Loading	100	0.000386	0.000386	0.000386	0.000386
	Application	100	0.005791	0.005791	0.005791	0.005791
		Total=		**0.1247**		**0.03872**

IIIA1 7.3.2 Estimation of operator exposure using personal protective equipment

Estimations of professional operator exposure using PPE are performed with the respective exposure model. Detailed calculations and summaries are presented in IIIA1 7.3.1.

IIIA1 7.3.3 Measurement of operator exposure

Since the risk assessment carried out indicated that the acceptable operator exposure level (AOEL) for iprovalicarb + folpet WG 65.3 will not be exceeded under practical conditions of use, a study to provide a measure of operator exposure under field conditions was not necessary and was therefore not carried out.

IIIA1 7.4 Bystander exposure

No EU-wide accepted official model is available for estimation of bystander exposure. Some proposals were given by the EUROPOEM Bystander Working Group but the report is still a draft and not officially published. Therefore as long as there is no official EU-wide guidance on how to estimate bystander exposure an approach is presented in this document that considers both dermal exposure – derived from available drift data – and inhalation exposure – derived from an operator exposure model simulating a bystander who is exposed in a similar way as an unprotected operator.
This approach follows a guidance of the German Federal Institute for Risk Assessment (BfR)[3] and is in line with what has been published by US EPA and CRD recently. All technical details with regard to figures and assumptions are provided in this guidance.

A comparison of the exposure estimates with the proposed AOEL (in terms of percentage of the AOEL) is presented in table 7.4-1. For details see chapter IIIA1 7.4.1

[3] Martin, S., Westphal, D., Erdtmann-Vourliotis, M., Dechet, F., Schulze-Rosario, C., Stauber, F., Wicke, H. and Chester, G. (2008): Guidance for Exposure and Risk Evaluation for Bystanders and Residents exposed to Plant Protection Products during and after Application;. J. Verbr. Lebensm.1661-5751/00/000001-10 DOI 10.1007/s00003-008-0361-5

Table 7.4-1: Comparison of estimated systemic bystander/resident exposure to iprovalicarb (IPV) [mg/kg bw/day] with the proposed AOEL

Scenario	Application technique	Person	Systemic exposure* IPV [mg/kg bw/day]	% of AOEL# IPV
Bystander	BAA	Adult	0.000729	4.9
		Child	0.000578	3.9
Resident	BAA	Adult	0.0000917	0.6
		Child	0.000193	1.3

BAA = Broadcast air assisted sprayer
* Considers 60 kg adult and 16.15 kg child
# AOEL= 0.015 mg/kg bw/day (IPV)

Based on these results there is no unacceptable risk anticipated for the bystander/resident with the intended professional uses of iprovalicarb + folpet WG 65.3.

IIIA1 7.4.1 Estimation of bystander exposure without personal protective equipment

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. For infants and toddlers exposure might also occur orally (e.g. through hand-to-mouth transfer and/or object-to-mouth transfer). For large scale applications performed in the field in addition exposure by inhalation of vapour drift (depending on the vapour pressure of the active substance) is considered.

Bystander/resident exposure may occur following foliar spray application outdoors. Bystander/resident exposure is calculated regarding the application scenario leading to the highest drift value. Application scenarios causing lower spray drift will be covered by this calculation and separate evaluations are not made. Exposure is calculated for adult and child bystanders as well as adult and child residents.

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

Table 7.4.1-1: Percent Drift Values (Rautmann *et al.* 2001, current version 27.03.2006)

Crop, Distance 10 m	Percent Drift (1 application) (90^{th} percentile values)	Percent Drift (2 applications) (82^{th} percentile values)
Grapes	1.23	1.07

Corresponding exposure estimates are presented in the following.

A. Bystander exposure to IPV

Exposure calculations are performed according to the following equations:

Dermal exposure due to spray drift

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

Where:

SDE_B = Systemic Exposure of Bystanders via the Dermal Route (mg/kg bw/day)
AR = max. Application Rate (grapes = 21.6 mg IPV/m²)
D = Drift (1.23% for use in grapes; a bystander is supposed to be submitted only once to the drift)
BSA = Exposed Body Surface Area (1 m²: adult, 0.21 m²: child)
DA = Dermal Absorption (16.3% IPV, 10% FLP)
BW = Body Weight (60 kg: adult, 16.15 kg: child)

Inhalation exposure due to spray drift

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

Where:

SIE_B = Systemic Exposure of Bystanders via the Inhalation Route (mg/kg bw/day)
I_A = Specific Inhalation Exposure (0.018 mg/kg a.s. handled per day)
AR = Application Rate (grapes = 0.216 kg IPV/ha)
A = Area Treated (grapes = 8 ha)
IA = Inhalation Absorption (100%)
BW = Body Weight (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)

Detailed exposure calculations are presented in the following tables.

Table 7.4.1-2: Calculations for bystander exposure to iprovalicarb when applied via broadcast air assisted sprayer (use in grapes)

Adults	Children
Bystander of High Crop, tractor mounted/trailed	
Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (21.6 x 1.23% x 1 x 16.3 %) / 60 Absorbed dose: 0.0007218 mg/kg bw/day	Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (21.6 x 1.23% x 0.21 x 16.3 %) / 16.15 Absorbed dose: 0.0005631 mg/kg bw/day
Inhalation exposure: $SIE_B = (I_A * \times AR \times A \times T \times IA) / BW$ (0.018 x 0.216 x 8 x 5/360 x 100%) / 60 Absorbed dose: 0.0000072 mg/kg bw/day	Inhalation exposure: $SIE_B = (I_A * \times AR \times A \times T \times IA) / BW$ (0.018/1.74 x 0.216 x 8 x 5/360 x 100%) / 16.15 Absorbed dose: 0.0000157 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: 0.000729 mg/kg bw/day	**Total absorbed dose: 0.000578 mg/kg bw/day**
% of AOEL: 4.86	**% of AOEL: 3.85**

B. Resident exposure to IPV

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 (grapes: 2 x 0.000216 mg IPV/cm² = 0.000432 mg IPV /cm²)

D = Drift (1.07% for use in grapes – a resident may be possibly submitted twice to the drift)

TTR = Turf Transferable Residues (5%)

TC = Transfer Coefficient (adult = 7300 cm²/h, child = 2600 cm²/h)

H = Exposure Duration (2 hours)

DA = Dermal Absorption (16.3% IPV, 10% FLP)

BW = Body Weight (60 kg: adult, 16.15 kg: child)

Inhalation Exposure (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): vapour pressure of iprovalicarb is 7.7 x 10^{-8} Pa at 20°C. According to guideline this compound is non volatile substance (vapour pressure <1 x 10^{-5} Pa at 20°C). Thus, resident inhalation exposure can be estimated as negligible (i.e. airborne conc. of 0 mg/m^3).

IR = Inhalation Rate (m^3/day): 16.57 (adult), 8.31 (child)

IA = Inhalation Absorption (%): 100

BW = Body Weight (kg/person): 60 (adult), 16.15 (child)

In addition, oral exposure of children is estimated as well by the following equations.

Children's hand-to-mouth transfer

$SOE_H = (2 \times AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA) / BW$

Where:

SOE_H = Systemic Oral Exposure via the Hand to Mouth Route (mg/kg bw/day)

AR = Application Rate (grapes: 2 x 0.000216 mg IPV/cm^2 = 0.000432 mg IPV /cm^2)

D = Drift (1.07% for use in grapes)

TTR = Turf Transferable Residues (5%)

SE = Saliva Extraction Factor (50%)

SA = Surface Area of Hands (20 cm^2)

Freq = Frequency of Hand to Mouth (20 events/hour)

H = Exposure Duration (2 hours)

OA = Oral Absorption (100%)

BW = Body Weight (child = 16.15 kg)

Children's object-to-mouth transfer

$SOE_O = (2 \times AR \times D \times DFR \times IgR \times OA) / BW$

Where:

SOE_O = Systemic Oral Exposure via the Object to Mouth Route (mg/kg bw/day)

AR = Application Rate (grapes: 2 x 0.000216 mg IPV/cm^2 = 0.000432 mg IPV /cm^2)

D = Drift (1.07% for use in grapes)

DFR = Dislodgeable Foliar Residues (20%)

IgR = Ingestion Rate for Mouthing of Grass/Day (25 cm^2)

OA = Oral Absorption (100%)

BW = Body Weight (child = 16.15 kg)

Total systemic exposure of residents is then estimated for

Adults: $SE_R = SDE_R$ (mg/kg bw/day)

Children: $SE_R = SDE_R + SOE_H + SOE_O$ (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)

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)

Detailed exposure calculations are presented in the following table.

Table 7.4.1-3: Calculations for resident exposure to iprovalicarb when applied via broadcast air assisted sprayer (use in grapes)

Adults	Children
Resident: Exposure after application with High Crop, tractor mounted/trailed	
Dermal exposure: $SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$ (0.00432 x 1.07% x 5% x 7300 x 2 x 16.3%) / 60 Absorbed dose: 0.00009167 mg/kg bw/d	Dermal exposure: $SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$ (0.00432 x 1.07% x 5% x 2600 x 2 x 16.3%) / 16.15 Absorbed dose: 0.000123 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): $SOE_H = (AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA) / BW$ (0.00432 x 1.07% x 5% x 50% x 20 x 20 x 2 x 100%) / 16.15 Absorbed dose 0.00005724 mg/kg bw/d
	Oral exposure (object-to-mouth transfer): $SOE_O = (AR \times D \times DFR \times IgR \times OA) / BW$ (0.00432 x 1.07% x 20% x 25 x 100%) / 16.15 Absorbed dose 0.00001431 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: 0.0000917 mg/kg bw/d	**Total absorbed dose: 0.000193 mg/kg bw/d**
% of AOEL: 0.611	**% of AOEL: 1.29**

IIIA1 7.4.2 Measurement of bystander exposure

The predicted systemic bystander/resident exposure is always well below the proposed systemic AOELs. Therefore, a study to provide a measure of bystander exposure under field conditions was not necessary and was therefore not carried out. For details see IIIA1 7.4 and IIIA1 7.4.1.

IIIA1 7.5 Worker exposure

Iprovalicarb + folpet WG 65.3 is intended for the spray treatment in grapes. In grapes work activities are tasks like pruning/thinning/harvesting which are done by farmers usually throughout the growing season.

A comparison of the corresponding exposure estimates with the proposed AOEL (in terms of percentage of the AOEL) is presented in table 7.5-1. Detailed calculations are presented in chapter IIIA1 7.5.1.

Table 7.5-1: Comparison of estimated systemic worker exposure to iprovalicarb [mg/kg bw/day] with the proposed AOEL

Crop	Protection	Systemic exposure IPV [mg/kg bw/day]*	% of AOEL IPV (0.015 mg/kg bw/day)
Grapes	No PPE (P = 1)	0.11883	792
	Gloves (P = 0.1)	0.01188	79
	No PPE (P=1) DFR study	0.014154	94

* Assumes a 60 kg worker. Dermal absorption of IPV of 16.3% (max value)

Overall assessment of worker exposure to iprovalicarb + folpet WG 65.3 when harvesting grapes:
Calculations of worker exposure show that exposure of workers harvesting grape without protective gloves is not acceptable.
Therefore, it is necessary for workers to wear protective gloves (90% protection) for harvesting operations in treated grapes as it is clearly recommended on labels.

Calculations of worker exposure based on the results of a specific DFR study run in 2011 (see chapter 7.5.2) in Germany show that exposure of workers harvesting grape without protective gloves is acceptable. Nevertheless as recommended on the labels it is of good practice to wear gloves for operations on treated grapes.

Based on this exposure estimates there is no unacceptable risk anticipated for the worker with the intended uses of iprovalicarb + folpet WG 65.3 especially when gloves are worn.

IIIA1 7.5.1 Estimation of worker exposure without personal protective equipment

Calculations are performed according to the following equation:

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

where
E = *systemic exposure (mg/kg bw/day)*
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*
DA = *Dermal absorption (%)*
BW = *Body weight (kg/person)*

The basis for the dermal exposure assessment related to the relevant scenario is formed by a multiplication of DFR, TC, duration of the work and application rate. Work rates are considered with a maximum of 8 hours for maintenance work and hand harvesting. The maximum dose rate is always

applied. 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. A calculation for protective equipment is not made in a first tiered approach and P is set to 1. Calculation for workers with PPE are also run with a P value set at 0.1 (90% protection), see chapter 7.5.2.

Considerations on DFR:

Where experimental DFR data are not available an estimation of the amount of DFR immediately after application can be made taking into account the application rate, the crop habitat (leaf area index: LAI) and the (possible) extent of residues remaining on foliage from previous applications (a possible default value for the LAI is no larger than 2). In other cases, a highly conservative default value for the DFR may be taken as 3 µg/cm² for a standardised application rate of 1 kg/ha. In a Tier 1 approach this value is used without further consideration of crop specific LAI.

The following scenario has been taken into account:

- workers in vineyards (4 applications max at 0.216 kg IPV/ha, interval 10-14 days, PHI of 28 days)

Farmers will only do consecutive treatments if the efficacy of the previous treatment is no longer sufficient. Low efficacy is mainly caused by a decline of residues. Therefore, accumulations of residues on plant surfaces after repeated applications will only occur to a small extent depending on the degree of decline. It is only reasonable to expect some residue decay would occur during the required minimum interval between two applications. Otherwise it would be highly unconceivable for growers to repeat any application when the active substance dislodgeable residues on the foliage could be preserved completely from a single application.

Where no DFR or residue data are available it may be assumed that residues will decline by 50% from the total deposit of the previous application.

An example demonstrates that with this assumption, DFRs will reach an upper maximum level that will not be exceeded.

It may be assumed that:

after the first application DFR will be 3 µg/cm² with a following decrease (50%) to 1.5 µg/cm² after a spray interval

after the 2nd application DFR will be 1.5 + 3 = 4.5 µg/cm² with a following decrease to 2.25 µg/cm²

after the 3rd application DFR will be 2.25 + 3 = 5.25 µg/cm² with a following decrease to 2.625 µg/cm²

directly after the 4th application DFR will be 2.625 + 3 = 5.625 µg/cm²

directly after the xth application DFR would be 3 + 3 = 6 µg/cm²

With these assumptions, DFRs will not exceed a maximum of 5.625 µg/cm² /kg as handled after the 4th application.

Considerations on Transfer Coefficients (TC)

In a Tier 1 assessment, the TCs used in this risk assessment are taken from the EUROPOEM II report[4]. The following TC values were used.

Table 7.5.1-1: Transfer coefficients based on EUROPOEM II

Crop	Transfer Coefficients [cm^2/hr]
Grapes (as for fruit trees)	4500

Detailed calculations of worker exposure during re-entry in vegetables fields (or greenhouse) and vineyards are presented below (Tables 7.5.1-2 to 5):

Table 7.5.1-2: Rentry exposure to iprovalicarb in grapes (4 applications at 0.216 kg IPV/ha):

Product Name	iprovalicarb + folpet WG 65.3									
Active substance	iprovalicarb									
	D	=	DFR	x	TC	x	WR	X	AR	x P
			µg/cm^2		cm^2/pers/h		hrs/day		kg/ha	
			5.625	x	4500	x	8	x	0.216	x 1
		=	43740 µg a.s./pers/day							
		=	43.74 mg a.s./pers/day							
		=	0.729 mg a.s./kg bw/day (x		60	kg person)				
and under consideration of 16.30% dermal absorption (for a dried foliar residue)										
	S		0.729 x		0.1630					
		=	0.11883 mg a.s./kg bw/day							

IIIA1 7.5.2 Estimation of worker exposure using personal protective equipment

Calculations being performed according to the following equation:

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

The exposure of workers wearing gloves is simply divided by a factor of 10, the value of P decreasing from 1 to 0.1. Therefore no detailed calculations are presented herein and the estimates are presented in table 7.5-1.

IIIA1 7.5.3 Estimation of worker exposure using data on dislogeable residues

In 2011 was run a specific DFR study on vine leaves.

[4] Post application exposure of workers to pesticides in agriculture (Dec 2002); Re-entry working group EUROPOEM II project – FAIR3 – CT96-1406.

Report:	**KIIIA1 7.5.3/01, [redacted] 2011**
Title:	Determination of the dislodgeable foliar residues (DFR) of iprovalicarb in/on grapes after spraying of SZX 0722 & Folpet WG 65.3 in the field in Germany
Document No:	M-431156-01-1
Guidelines:	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K- Reentry Protection, Series 132-1 (a))
GLP	Yes

(SZX 0722 & Folpet WG 65.3 is one of the previous denomination for iprovalicarb + folpet WG 65.3)

The purpose of the study 11-2913 was to determine the magnitude of the dislodgeable foliar residues of iprovalicarb (comprising total residue of iprovalicarb as sum of its S,R- and S,S-diastereomers and SZX 0722 S,R-diastereomer and SZX 0722 S,S-diastereomer individual) on grapes leaf foliage after each of four spraying applications with SZX 0722 & Folpet WG 65.3, a WG formulation containing 56.3% folpet and 9% iprovalicarb.

The study included one supervised residue trial conducted in the field in Northern Europe (Germany) during the 2011 season.

The actual application data are presented in the following table. These data reflect the intended application scheme, or, if minor deviations occurred, these were within the acceptable range.

Table 7.5.3-1: Application Summary

Trial no. Country	Formulation	Appl. mode	Application							
			No. of appl.	Interval (days)	Growth stage (BBCH code)	DBH PHI	Test item rate (kg/ha)	Water rate (L/ha)	a.s.	Appl. rate (kg a.s./ha)
11-2913-01 Germany	SZX 0722 & Folpet WG 65.3	SPI	4	10	77 - 85	28 - 58 / 28	2.4	800	folpet	1.3512
									iprovalicarb	0.216

a.s.: Active substance
Appl.: Application
SPI: Spraying
DBH: Days before harvest
PHI: Pre-harvest interval

The analyses were conducted according to the following analytical method:

Table 7.5.3- 2: Analytical Method Used

Active substance	Analyte	Method Number	Limit of Quantification*			Sample Material	Measurement Principle
			[µg/L]	[mg/kg]	[µg/cm²]		
iprovalicarb	1. S,R-Diastereomer 2. S,S-Diastereomer 3. Sum of Diastereomers calc.	01318	20	0.02	0.01	washings	HPLC-MS/MS

* Limit of Quantification is given as the sum of the S,S- and S,R-diastereomer

Analyte	Final determination as:	Residues calculated as:
Iprovalicarb S,R-Diastereomer	Iprovalicarb S,R-Diastereomer	iprovalicarb
Iprovalicarb S,S-Diastereomer	Iprovalicarb S,S-Diastereomer	iprovalicarb

Analyte	Final determination as:	Residues calculated as:
Sum of Diastereomers		Sum of both diastereomers

The average field recoveries (as sum of the S,R- and S,S-diastereomer) were within the range of 91 - 100% with an overall average of 98% and an overall relative standard deviation of 3.7%.
The average laboratory recoveries for the S,R-diastereomer were within the acceptable range of 98 – 102% with an overall average of 101%, relative standard deviations ranged from 8.1% – 13.7% with an overall relative standard deviation of 10.5%.
The average laboratory recoveries for the S,S-diastereomer were within the acceptable range of 100 – 102% with an overall average of 101%, relative standard deviations ranged from 9.9% – 14.4% with an overall relative standard deviation of 11.3%.
No residues above the LOQ were found in the control samples. Results were not corrected for field recoveries.

The analytical results for iprovalicarb (individual diastereomers and the sum of the diastereomers) and the ratio of the diastereomers in washings from grape leaf punches averaged for sub-plots 1-3 are summarized in Table 7.5.3 **3**.

Table 7.5.3 3: Residue Summary on Grapes/Leaf Foliage

Trial No. Country	Sample Material Analysed	DA1. T	Average Residues [µg/cm²]			Ration S,R/S,S
			S,R-Diast.	S,S-Diast.	Iprovali-carb*	
11-2913-01 Germany	Grape, leaf punch washings	- 0	< 0.01	< 0.01	< 0.01	--
	Grape, leaf punch washings	0	0.164	0.176	0.340	0.93
	Grape, leaf punch washings	3	0.085	0.092	0.176	0.93
	Grape, leaf punch washings	7	0.070	0.077	0.146	0.91
	Grape, leaf punch washings	10	0.068	0.074	0.142	0.91
	Grape, leaf punch washings	10	0.193	0.205	0.397	0.94
	Grape, leaf punch washings	13	0.151	0.161	0.312	0.95
	Grape, leaf punch washings	17	0.167	0.185	0.353	0.90
	Grape, leaf punch washings	20	0.110	0.119	0.228	0.92
	Grape, leaf punch washings	20	0.229	0.241	0.470	0.95
	Grape, leaf punch washings	23	0.135	0.148	0.284	0.91
	Grape, leaf punch washings	27	0.161	0.172	0.333	0.93
	Grape, leaf punch washings	30	0.163	0.179	0.342	0.91
	Grape, leaf punch washings	30	0.307	0.317	0.624	0.97
	Grape, leaf punch washings	**33**	0.327	0.343	**0.670**	0.95
	Grape, leaf punch washings	37	0.199	0.208	0.407	0.95
	Grape, leaf punch washings	44	0.140	0.156	0.297	0.90
	Grape, leaf punch washings	51	0.148	0.158	0.305	0.94
	Grape, leaf punch washings	58	0.126	0.136	0.262	0.93
	Grape, leaf punch washings	65	0.148	0.162	0.310	0.91

* iprovalicarb as sum of S,R- and S,S-diastereomer

Results were evaluated with Microsoft Excel®. Rounding errors may occur when evaluating the presented data with only the three given significant digits

DA1.T: days after first treatment " - " = before respective treatment
Bold values: day(s) of respective treatment(s)

Conclusion:
the study shows:
- a clear decline of residues after each application
- a DFR_0 after the first application of 0.34 µg/cm²
- a DFR_0 after the forth application of 0.624 µg/cm²
- a DFR of 0.67 µg/cm² 3 days after the forth application (max value)

For worker exposure calculation, the notifier used the worst case residue value found during this study (0.64 µg/cm²) which was found 3 days after the 4th (and last) application and which is clearly lower than the default value of 3 µg/cm² and far lower than the 5.625 µg/cm² used in the first tiered approach in above chapter 7.5.1.

Table 7.5.3-4: Re-entry exposure to iprovalicarb in grapes (4 applications at 0.216 kg IPV/ha):

Product Name: iprovalicarb + folpet WG 65.3
Active substance: iprovalicarb

D	=	DFR	x	TC	x	WR	x	AR	x	P
		µg/cm²		cm²/pers/h		hrs/day		kg/ha		
D		0.67	x	4500	x	8	x	0.216	x	1

D = 5209.92 µg a.s./pers/day
= 5.20992 mg a.s./pers/day
= 0.086832 mg/kg bw/day
using 16.30% dermal absorption (for a dried foliar residue)
S = 0.086832 x 0.1630
= 0.014154 mg/kg bw/day

IIIA1 7.5.4 Measurement of worker exposure

Since the exposure estimate carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under practical conditions of use, a study to provide a measure of worker exposure was not necessary and was therefore not carried out. For details see IIIA1 7.5 and IIIA1 7.5.1.

IIIA1 7.6 Dermal absorption

The dermal penetration studies on iprovalicarb (IPV) were carried out after the first inclusion of iprovalicarb in which a 10% default value was used. These studies were realized in 2003 using a WG formulation (84 g IPV/kg) comparable to the current representative WG formulation (90 g IPV/kg). Two dose levels were tested: a concentrate formulation (9.43 g IPV/L formulation) and a diluted formulation corresponding to the application phase (0.12 g IPV/L formulation). Taking into account the fact that generally the higher the dilution the higher the dermal penetration, these concentrations cover those encountered with the GAPs of the new representative formulation iprovalicarb + folpet WG 65.3 (granulate at 90 g IPV/kg for mixing loading and a diluted spray at 216 g IPV/400 L water = 0.54 g IPV/L).
Folpet: refer to folpet-specific risk assessment of [redacted].

IIIA1 7.6.1 Dermal absorption *in vivo* in the rat

Iprovalicarb

Report:	**KIIIA1 7.6.1; [redacted] (2003)**
Title:	Iprovalicarb & Copper WG 8.4 + 40.6 formulation – *In vivo* dermal absorption study in the male rat.
Report No & Document No	SA 03186 M-104491-01-1
Guidelines:	OECD Guidelines N° 417 (April 1997 OECD Guideline for "Testing of chemicals" New Draft Guideline 427. Dec. 2000. Directive 1999/11/EC EPA 40 CFR 160 (FIFRA) Japanese Min. of Agriculture, Forestry and Fisheries (JMAFF) notification 11 Nousan 6283 Oct 01. 1999 modified by 12 Nousan 8628. Dec 06. 2000
GLP	Yes

Material and method:

The extent of absorption of radioactive material was investigated following topical application of the iprovalicarb & Copper WG 8.4 + 40.6 formulation containing [^{14}C]-iprovalicarb as the active ingredient to male Sprague-Dawley CD strain rats at two dose levels: concentrate formulation corresponding to the mixing and loading phase (9.43 mg iprovalicarb/ml formulation) and a diluted formulation corresponding to the application phase (0.12 mg iprovalicarb/ml formulation). For technical reasons, the liquid formulation was prepared by diluting the WG 8.4 + 40.6 wettable granules in water.

A preliminary study was conducted on three groups of 2 male rats for each dose treatment, with an exposure time of 8 hours (analogous to the normal working day) and sacrifice times at 24, 72 and 144 hours after dose application, to obtain an indication of the proportion of the test substance absorbed through the skin, excreted, and that retained in the skin or remaining upon the skin surface. The results from the preliminary study were used to determine the sacrifice times in the main study, the need to investigate the material remaining in the skin and its localisation (by tape stripping procedure) and any

requirement to examine the tissue distribution of the radioactivity.
The main study consisted of four groups of five animals for each treatment level, which were exposed to the test product for 8 hours.
Based on results from the preliminary study the sacrifice times employed in the main study were 8, 24, 72 and 144 hours. The tape stripping procedure was included in the main study to determine the distribution of the radioactivity through the skin. Since the levels of radiolabelled material absorbed into the animal were low, there was no need to investigate the tissue distribution of the radioactivity.

Findings:
After a single application of the two iprovalicarb & Copper WG 8.4 + 40.6 formulations, the mean total recoveries of radioactivity were in the range of 92.28 – 104.04% and 91.38 – 101.52% for the diluted and concentrate formulation groups, respectively.

The results of the definitive study can be summarized as follows (expressed as mean percentages of the applied dose):

	Diluted concentration SYP12409				Concentrate concentration SYP12408			
Group Number Sacrifice times	8 8 h	9 24 h	10 72 h	11 144 h	4 8 h	5 24 h	6 72 h	7 144 h
SURFACE COMPARTMENT								
Dose site swabs 8h	81,669	78,903	75,755	79,149	74,468	68,937	84,999	78,259
Dose site swabs (terminal)	N.A.	4,452	6,263	4,070	N.A.	11,806	9,563	6,905
Surface dose**	1,475	0,561	0,246	0,604	2,275	1,066	0,421	0,979
Dressing	0,725	1,610	0,818	2,761	0,985	2,571	1,181	1,328
Fur (dose site)	N.A.	N.A.	N.A.	1,204	N.A.	N.A.	N.A.	0,320
Total non-absorbed	**83,870**	**85,526**	**83,082**	**87,306**	**77,728**	**85,911**	**96,164**	**87,791**
SKIN COMPARTMENT								
Stratum corneum*	6,662	4,127	1,155	2,329	7,964	4,718	1,230	3,666
Treated skin[a]	2,521	1,478	0,296	0,613	1,366	0,704	0,230	0,512
Total at dose site	**9,183**	**5,605**	**1,452**	**2,942**	**9,330**	**5,422**	**1,461**	**4,178**
SYSTEMIC COMPARTMENT								
Excreta	0,460	2,893	4,047	9,523	0,049	0,271	1,203	2,151
Tissues	6,484	4,795	3,270	3,847	2,371	3,671	1,845	1,351
Total direct absorption	**6,944**	**7,688**	**7,317**	**13,370**	**2,420**	**4,233**	**3,048**	**3,502**
Total amount absorbed* **	**16,127**	**13,293**	**8,769**	**16,312**	**11,750**	**9,655**	**4,508**	**7,680**

Dose site = treated skin + stratum corneum (% recoveries recalculated for the whole site of application 12 cm^2)

[a]: following tape-stripping procedure, N.A. : not applicable
*: excluding tape strips 1 & 2 which are considered to be non-absorbed surface dose
**: surface dose corresponds to tape-strips 1 & 2.
***: Total amount absorbed = total direct absorption + total at dose site
h: hours

In both groups, the vast majority of the applied radioactivity was removed from the skin by swabbing (swabs, surface dose, dressing and fur at dose site). This accounted for 83.08% to 87.31% and 77.73% to 96.16% of the applied dose in the diluted and concentrate formulation groups, respectively. The amount of radioactivity detected in the dressing appeared to be highest for the diluted treatment group and stable over time in the concentrate treatment groups. Therefore, a part of the test chemical may have been lost by desquamation.

The fraction of test chemical present in the stratum corneum for both diluted and concentrate treatment groups was highest at 8 hours, and lower at 24, 72 and 144 hours post-application, respectively.
The fraction of test chemical present in the treated skin following the tape-stripping for both diluted and concentrate treatment groups was highest at 8 hours and lower at 24, 72 and 144 hours post-application, respectively.

After taking account of numeric differences between groups, the examination of the ratios of percentages in the stratum corneum and the systemic compartment between 8 hours and 72 hours post-application seems to show that a part of the test chemical applied may have been dynamic and therefore may be susceptible to move from the stratum corneum into the animal. Therefore, in order to be conservative the amounts of radioactivity recovered in the stratum corneum and the treated skin can be allocated to the systemic compartment.

The maximum amount of test chemical recovered in excreta (urine, faeces and cage wash) at 144 hours post-application was 9.523% and 2.151% in the diluted and concentrate formulation groups, respectively. The daily excretion in each group tended to increase from the first day until termination.
The percentages of radioactivity found in the carcass remained constant from 8 hours to 144 hours for both the diluted and concentrate formulations. In addition, the percentages of radioactivity found in the surrounding skin was almost equivalent to those found in the application site. Therefore, in order to be conservative, these tissue fractions were included in the systemic compartment.

The amount in the systemic compartment (excreta & tissues) corresponding to the total amount of test chemical directly absorbed was 13.37% and 3.502% of the dose applied, for the diluted and concentrate formulation groups, respectively.

Results showed that residual chemical in the stratum corneum and in the treated skin may possibly become available systemically after 8 hours. Therefore, taking a conservative approach, the total amount of [^{14}C]-iprovalicarb absorbed can be calculated as the sum of percentages of radioactivity recovered in the excreta, the tissues (+ all non-treatment site skin), the stratum corneum and the treated skin, and were approximately 16.31% and 7.680% at 144 hours post-application for the diluted and concentrate formulation groups, respectively.

Conclusion

In conclusion, the total amount of applied radiolabelled [^{14}C]-iprovalicarb absorbed was 16.31% and 7.680% at 144 hours post application for the diluted and concentrate formulations, respectively.

IIIA1 7.6.2 Comparative dermal absorption, *in vitro* using rat and human skin

Iprovalicarb

Report:	**KIIIA1 7.6.2; [redacted] (2003)**
Title:	Iprovalicarb & Copper WG 8.4 + 40.6 formulation – Comparative *in vitro* dermal absorption study using human and rat skin.
Report No & Document No	SA 03187 M-104497-01-1
Guidelines:	OECD Guidelines N° 428 "Testing of chemicals" adopted Dec. 2000. Directive 1999/11/EC EPA 40 CFR 160 (FIFRA)
GLP	Yes

Material and method:

The comparative *in vitro* dermal penetration of radioactivity following a single topical application of [^{14}C]-iprovalicarb in a liquid suspension of iprovalicarb & Copper WG 8.4 + 40.6 formulation to rat and human dermatomed skin was evaluated. For technical reasons, the liquid formulation was prepared by diluting the WG 8.4 + 40.6 wettable granules in water. The liquid formulation was tested at two dose levels corresponding to the mixing and loading phase (9.43 mg iprovalicarb/ml formulation) and a diluted formulation corresponding to the application phase (0.12 mg iprovalicarb/ml formulation).
Eight and ten flow-through diffusion cells were prepared for human and rat skin, respectively and were exposed to the concentrate formulation.

Six flow-through diffusion cells were prepared for each skin type and were exposed to the diluted formulation. Dermatomed membranes were maintained in the cells at approximately 32°C. The integrity of the membranes was first tested by the TEWL method (Trans-Epidermal Water Loss method). The [^{14}C]-iprovalicarb in the two formulations was applied to the unoccluded skin samples at a rate of 10 µl/cm^2.

The skin samples were exposed to the test material for 8 hours, after which time the remaining dose was washed off the skin with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffered saline) using natural sponge swabs. Receptor fluid samples were collected at hourly intervals for the duration of the study (24 hours). The solubility of iprovalicarb in the receptor fluid was demonstrated to be sufficient for the study. At the end of the study (24 hours) the skin samples were tape stripped to remove residual surface dose and the stratum corneum.

Findings:

The group mean distribution of radioactivity (expressed as mean % of applied radioactivity) are summarised in the following table:

Dose levels	Concentrate formulation		Diluted formulation	
Group	1	2	3	4
Species	Human skin	Rat skin	Human skin	Rat skin
SURFACE COMPARTMENT				
Surface dose*	2.563	11.094	3.602	4.053
Skin swabs	84.672	64.190	79.951	78.694
Donor chamber	2.204	1.155	1.168	0.883
Total % non-absorbed	*89.439*	*76.439*	*84.721*	*83.630*
SKIN COMPARTMENT				
Skin	0.654	5.850	1.571	2.830
Stratum corneum**	1.120	9.439	1.172	7.085
Total % at dose site	*1.774*	*15.289*	*2.743*	*9.915*
SYSTEMIC COMPARTMENT				
Total % directly absorbed : Receptor fluid (including receptor fluid at termination & receptor chamber)	*0.323*	*0.781*	*8.825*	*5.842*
*Total % absorbable***	*2.097*	*16.070*	*11.568*	*15.757*
Total % recovery	*91.535*	*92.509*	*96.289*	*99.388*

* : surface dose = tape strips 1 & 2
** : excluding tape strips 1 & 2 which are considered to be non-absorbed dose
*** total % absorbable = total % absorbed + total % at dose site

Conclusion

Following the application of [^{14}C]-iprovalicarb at a concentrate dose level which corresponds to the mixing and loading phase, the dermal absorption was 7.7 times greater in rat skin than in human skin, accounting for 16.07% and 2.097% of the applied dose, respectively.
Following the application of [^{14}C]-iprovalicarb at a diluted dose level which corresponds to the application phase, the dermal absorption was 1.4 times greater in rat skin than in human skin. accounting for 15.76 % and 11.57% of the applied dose, respectively. This difference was not considered sufficient to correct *in vivo* data.
In summary, the notifier will use dermal penetration factors of **1% (concentrate)** and **16.3% (diluted)**.

Folpet

Folpet: refer to folpet-specific risk assessment of [redacted]. ([redacted])

IIIA1 7.7 Dislogeable residues

IIIA1 7.7.1 Dislogeable residues - foliar

Not required by Directive 91/414/EEC.

IIIA1 7.7.2 Dislogeable residues - soil

Not required by Directive 91/414/EEC.

IIIA1 7.7.3 Dislogeable residues - indoor surface re-volatization

Not required by Directive 91/414/EEC.

IIIA1 7.8 Epidemiology

Not required by Directive 91/414/EEC.

IIIA1 7.9 Data on formulants

IIIA1 7.9.1 Material safety data sheet for each formulant

Safety data sheet for each formulant is provided in document H

IIIA1 7.9.2 Available toxicological data for each formulant

The available toxicological data for each formulant is provided with the MSDS provided in Document H

IIIA1 7.10 Domestic animal/livestock safety

Not required by Directive 91/414/EEC.

IIIA1 7.11 Other/special studies

None.