Document Title

Tier 2 Summary
of Toxicological Studies and Exposure Data
for the Plant Protection Product Fenhexamid WG 50 (500 g/kg)
(Specification No.: 102000007271)

Substance(s)

FENHEXAMID
(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

Date

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Bayer CropScience

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

IIIA 7.1 Acute toxicity

Most of the toxicological studies (i.e., acute oral and dermal toxicity, skin and eye irritation studies as well as a Buehler Patch Test for skin sensitisation) have been performed with the formulation KBR 2738 WG 50. The composition of this formulation was at that time described by the old company code development no. 30-0170928. Exactly the same formulation composition is now described by the specification no. 102000007271 (Material no. 05419441). Material of this material number has been investigated for skin sensitisation in an additional guinea pig maximization test.

The code KBR 2738 is a synonymous name for the active ingredient fenhexamid. The product names KBR 2738 50 WG or KBR 2738 WG 50 are synonymes for the product Fenhexamid WG 50.

Summary of acute toxicity

Type of study	Vehicle	Results	Report / document no.
acute oral rat	Cremophor EL 2% (v/v) in demineralised water	LD_{50}: >2000 mg/kg bw	24227 M-010213-01-1
acute dermal rat	0.5 mL NaCl solution/g test substance	LD_{50}: >2000 mg/kg bw	24183 M-010215-01-1
skin irritation rabbit	moistened with deionised water	slightly irritating; classification not triggered	24152 M-010162-01-1
eye irritation rabbit	none	slightly irritating; classification not triggered	24152 M-010162-01-1
skin sensitisation guinea pig (Buehler Patch Test)	physiological saline solution	not sensitising	24366 M-010216-02-1
skin sensitisation guinea pig (maximisation test)	physiological saline solution	not sensitising	30066 M-043441-01-1

Fenhexamid WG 50 is of low toxicity to rats after acute oral and dermal application. Due to the physical nature of Fenhexamid WG 50, its intended use and for animal welfare reasons, an inhalation study has not been performed. Fenhexamid WG 50 is only slightly irritating to the skin and eyes of rabbits, so that a classification is not triggered. Furthermore, the product has no skin sensitising potential.
Therefore, the following classification/labelling is proposed for Fenhexamid WG 50:
- EU directive 1999/45/EC: **none**
- Regulation (EC) No 1272/2008 (CLP): **none**

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IIIA 7.1.1 Acute oral toxicity

Report:	**KIIIA 7.1.1/01; [redacted]., 1995**
Title:	KBR 2738 50 WG 04258/0214 - Study for acute oral toxicity in rats
Report No.: Document No.:	24227 **M-010213-01-1**
Dates of work:	1995-03-02 – 1995-03-16
Guidelines:	OECD 401; US-EPA FIFRA 81-1; Directive 67/548/EEC, Annex V, Part B.1. Deviation(s): none
GLP:	yes

I. Materials and methods

A. Materials

1. Test material: KBR 2738 50 WG 04258/0214

Development no.:	30-0170928
Description:	brown granular solid
Lot/Batch no:	0222 based on Fl. no.: 04258/0214
Content:	49.6%
Stability of test compound:	guaranteed for study duration; expiry date: 1996-02-08

2. Vehicle: Cremophor EL 2% (v/v) in demineralised water

3. Test animals:

Species:	Wistar rat (SPF-bred)
Strain:	Hsd.Cpb:WU
Age:	males: approx. 7 - 8 weeks; females: approx. 9 - 10 weeks
Weight at dosing:	males: 167 g – 179 g; females: 164 g – 169 g
Source:	[redacted], [redacted], Germany
Acclimatisation period:	at least 7 days
Diet:	"Altromin® 1324 Diet for Rats and Mice" (composition identical to "Altromin® 1320") ([redacted], Germany), ad libitum
Water:	tap water, ad libitum
Housing:	conventionally in polycarbonate cages type III (5 animals/cage) during acclimatisation and on 1st study day, individually in type IIA cages afterwards bedding: low-dust wood granules type S 8/15 ([redacted] Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose:	2000 mg/kg bw
Application route:	oral (gavage)
Application volume:	10 mL/kg bw
Fasting time:	before administration: approx. 17h + 1h after administration: approx. 2h
Group size:	5 rats/sex/group
Post-treatment observation period:	14 days
Observations:	mortality, clinical signs, body weight, gross necropsy

.

II. Results and discussion

A. Mortality

Table 7.1.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological result*			Occurrence of signs	Time of death	Mortality (%)
Male rats						
2000	0	3	5	5h	--	0
Female rats						
2000	0	3	5	5h	--	0
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

h: hours

B. Clinical observations

At the dose of 2000 mg/kg body weight soft faeces were observed in 3 male and 3 female animals 5 h after administration of the test substance.

C. Body weight

There were no toxicological effects on body weights or on body weight development.

D. Necropsy

At sacrifice at the end of the post-treatment observation period the animals showed no evidence of test-article related macroscopically visible organ lesions.

III. Conclusion

Fenhexamid WG 50 is of low toxicity to rats after acute oral administration.

The study result triggers the following classification/labelling:

- EU directive 1999/45/EC: **none**
- Regulation (EC) No 1272/2008 (CLP): **none**

IIIA 7.1.2 Acute percutaneous (dermal) toxicity

Report:	**IIIA 7.1.2/01; [redacted]., 1995**
Title:	KBR 2738 50 WG 04258/0214 - Study for acute dermal toxicity in rats
Report No.: Document No.:	24183 **M-010215-01-1**
Dates of work:	1995-03-14 to 1995-04-19
Guidelines:	OECD 402; US-EPA FIFRA §81-2; Directive 67/548/EEC, Annex V, Part B.3. Deviation(s): none
GLP:	yes

I. Materials and methods

A. Materials

1. Test material: KBR 2738 50 WG 04258/0214

Development no.:	30-0170928
Description:	brown granular solid
Lot/Batch no:	0222 based on FL no.: 04258/0214
Content:	49.6%
Stability of test compound:	guaranteed for study duration; expiry date: 1996-02-08

2. Vehicle: 0.5 mL NaCl solution/g test substance, mixed to a paste

3. Test animals:

Species:	Wistar rat (SPF-bred)
Strain:	Hsd.Cpb:WU
Age:	males: approx. 11 –12 weeks; females: 16 weeks
Weight at dosing:	males: 270 g – 291 g; females: 225 g – 236 g
Source:	[redacted], [redacted], Germany
Acclimatisation period:	at least 7 days
Diet:	"Altromin® 1324 Diet for Rats and Mice" (composition identical to "Altromin® 1320") ([redacted]), ad libitum
Water:	tap water, ad libitum
Housing:	conventionally in polycarbonate cages type III (5 animals/cage) during acclimatisation, during the test period individually, conventionally in type IIA cages bedding: low-dust wood granules type S 8/15 ([redacted] Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose:	Dose (mg/kg bw)	Surface area (cm²)	Range (mg/cm²)
	males 2000	30	18.5 – 19.4
	females 2000	30	15.0 – 15.7

Application route:	dermal, occlusive dressing
Exposure:	24 hours
Group size:	5 rats/sex/group
Post-treatment observation period:	14 days
Observations:	mortality, clinical signs, skin effects, body weight, gross necropsy

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II. Results and discussion

A. Mortality

Table 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Occurrence of signs	Time of death	Mortality (%)
Male rats						
2000	0	1	5	4d – 4d	-	0
Female rats						
2000	0	5	5	3d – 5d	--	0
LD_{50} > 2000 mg/kg bw						

* 1st number = number of dead animals, 2nd number = number of animals with signs, 3rd number = number of animals in the group

D: day

B. Clinical observations

At 2000 mg/kg body weight decreased motility was observed in one male rat on day 4 of the study. Local skin reactions were recorded in females from day 3 to day 5. They consisted of partial reddening, incrustation, formation of scab and brownish yellow coloured fur.

C. Body weight

There was no treatment-related influence on body weights. In one female rat (rat no. 10, group 2000 mg/kg bw) a transient decrease in body weight development was observed on day 8.

D. Necropsy

Animals sacrificed at the end of the post-treatment observation period showed no evidence of test-article related macroscopically visible organ lesions.

III. Conclusion

Fenhexamid WG 50 is of low systemic toxicity to rats after acute dermal administration.

The study result triggers the following classification/labelling:

- EU directive 1999/45/EC: **none**
- Regulation (EC) No 1272/2008 (CLP): **none**

IIIA 7.1.3 Acute inhalation toxicity to rats

Fenhexamid WG 50 is a wettable granule formulation. Inhalation toxicity testing with Fenhexamid WG 50 is not triggered according to Council Directive 94/79/EEC because the neat product

- is not a gas or liquified gas,
- is not a smoke generating formulation or fumigant,
- is not to be used with fogging equipment,
- is not to be included in a smoke generating aerosol or vapour releasing preparation,
- is not to be applied from aircraft
- does not contain active substances with a vapour pressure > 1 x 10^{-2} Pa and
- the formulation is not a powder, is practically dust-free, and hence does not contain a significant proportion of particles of diameter < 50 µm (> 1 % on a weight basis)

(see [redacted], 2001, BCS document no. M-055003-01-1).

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- Furthermore, Guideline 94/79/EC asks for an inhalation toxicity study only if >1% of the preparation (i.e., the commercial formulation) is inhalable (i.e., particle or droplet size <50 µm) during application.
  - The product Fenhexamid WG 50 is not applied as undiluted product to the fields. Therefore, no particles of respirable size of the neat product can be formed during application.
  - Fenhexamid WG 50 is applied as a highly diluted spray solution. Due to the intended application rates and dilutions the concentration of Fenhexamid WG 50 in spray droplets in general amount to ≤ 1% (corresponding to ≤ 0.5% of the active ingredient fenhexamid in the spray droplets).
  - Applying the logic of the requirement of Guideline 94/79/EC for inhalation toxicity testing to the practical use of Fenhexamid WG 50, the inhalability of Fenhexamid WG 50 amounts to ≤ 1% only due to the dilution of the product in the spray solution. This is below the trigger value for the conduct of an inhalation toxicity study for classification purposes. Furthermore, since it is unrealistic to assume that 100% of the spray droplets are inhalable (requiring solely droplets <50 µm; a value far below 10% can be expected based on measurements of droplet size distribution for standard nozzles), an additional safety factor is given.

Based on these considerations and also on the low inhalation toxicity of the active ingredient fenhexamid (dust: LC_{50} >5057 mg/m³ air or aerosol: LC_{50} >332 mg/m³ air, maximum technically possible concentration) and the fact that none of the other ingredients of the product fenhexamid WG 50 is classified and labelled with regard to health hazards, an acute inhalation toxicity study with fenhexamid WG 50 is not considered to be justified also with respect to animal welfare.

This triggers the following classification/labelling:

- EU directive 1999/45/EC: **none**
- Regulation (EC) No 1272/2008 (CLP): **none**

IIIA 7.1.4 Skin irritation

Report:	**IIIA 7.1.4/01; [redacted] 1995**
Title:	KBR 2738 50 WG 04258/0214 - Study for skin and eye irritation/corrosion in rabbits
Report No.: Document No.:	24152 **M-010162-01-1**
Dates of work:	1995-04-18 to 1995-05-09
Guidelines:	OECD 404; Directive 92/69/EEC, Part B, No. B.4. Deviation(s): none
GLP:	yes

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I. Materials and methods

A. Materials

1. Test material: KBR 2738 50 WG 04258/0214

- Development no.: 30-0170928
- Description: brown powder
- Lot/Batch no: 0222 based on Form. No.: 04258/0214
- Content: 49.6%
- Stability of test compound: guaranteed for study duration; expiry date: 1996-02-08

2. Vehicle: moistened with deionised water

3. Test animals:

- Species: albino rabbit
- Strain: HC:NZW
- Age: adult
- Weight at dosing: 3.9 kg – 4.2 kg
- Source: [redacted], Great Britain
- Acclimatisation period: approx. 1 week
- Diet: standard diet "Ssniff K4" ([redacted], Germany), approximately 100 – 120 g per animal per day, fed once daily in the morning
- Water: tap water, ad libitum
- Housing: individually in stainless steel cages with flat rod bases or plastic cages with perforated bases

B. Study design and methods

1. Animal assignment and treatment:

- Dose: 500 mg/patch
- Application route: dermal, semi-occlusive dressing
- Exposure: 4 hours
- Group size: 3 females
- Observations: clinical signs, skin effects, body weight (at beginning of study)

II. Results and discussion

A. Findings

Exposure of the skin to the test substance resulted in erythematous reactions in all three animals. Additionally, in one rabbit an oedema was observed at the 1 h time point. On day 7 signs of irritation had disappeared in two animals and on day 14 also in the third animal. There were no other lesions or toxic signs.

Table 7.1.4-1 Summary of irritant effects (Score)

Animal	Observation (after patch removal)	24h	48h	72h	Mean scores	Response	Reversible (days)
1	Erythema (redness) and eschar formation*	2	2	1	1.67	--	7
	Oedema formation	0	0	0	0.00	--	na
2	Erythema (redness) and eschar formation*	1	1	1	1.00	--	7
	Oedema formation	0	0	0	0.00	--	na

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3	Erythema (redness) and eschar formation*	2	1	1	1.33	--	14
	Oedema formation	0	0	0	0.00	--	84

na = not applicable *exposed skin areas stained in colour of the test substance, evaluation of erythema possible

Response:	--	= negative for mean scores	<1.5	(GHS)
			<2	(Directive 2001/59/EC)
			<2.3	(Regulation (EC) No 1272/2008)
	(+)	= mild irritant for mean scores	≥1.5 - <2.3	(GHS category 3)
	+	= irritant for mean scores	≥2	(Directive 2001/59/EC)
			≥2.3	(Regulation (EC) No 1272/2008 and GHS category 2)

III. Conclusion

Fenhexamid WG 50 is slightly irritating to the skin of rabbits. Classification is not triggered.

The study result triggers the following classification/labelling:

- EU directive 1999/45/EC: **none**
- Regulation (EC) No 1272/2008 (CLP): **none**

IIIA 7.1.5 Eye irritation

Report:	**IIIA 7.1.5/01; [redacted] 1995**
Title:	KBR 2738 50 WG 04258/0214 - Study for skin and eye irritation/corrosion in rabbits
Report No.:	24152
Document No.:	**M-010162-01-1**
Dates of work:	1995-04-18 to 1995-05-09
Guideline:	OECD 405; Directive 92/69/EEC, Part B, No.B.5. Deviation(s): none
GLP:	yes

I. Materials and methods

A. Materials

1. Test material: KBR 2738 50 WG 04258/0214

Development no.:	730-01/0928
Description:	brown powder
Lot/Batch no.:	0222 based on Form. No.: 04258/0214
Content:	49.6%
Stability of test compound:	guaranteed for study duration; expiry date: 1996-02-08

2. Vehicle: none

3. Test animals

Species:	albino rabbit
Strain:	HC:NZW
Age:	adult
Weight at dosing:	4.0 kg – 4.3 kg
Source:	[redacted], Great Britain
Acclimatisation period:	approx. 1 week

Diet:	standard diet "Ssniff K4" ([redacted], Germany)), approximately 100 – 120 g per animal per day, fed once daily in the morning
Water:	tap water, ad libitum
Housing:	individually in stainless steel cages with flat rod bases or plastic cages with perforated bases

B. Study design and methods

1. Animal assignment and treatment:

Dose:	0.1 mL test substance (equivalent to approx. 61 mg)
Application route:	instillation into the conjunctival sac of one eye
Rinsing:	after 24 hours with normal saline
Group size:	3 females
Observations:	clinical signs, eye effects, body weight (at beginning of study)

II. Results and discussion

A. Findings

Exposure of the eye to the test substance caused in all three animals reactions of the mucous membranes. All these findings proved to be fully reversible within 7 days. Other lesions and toxic signs were not observed.

Table 7.1.5-1 Summary of Irritant Effects (Score)

Animal	Effects	24 h	48 h	72 h	Mean scores	Response	Reversible (days)
1	Corneal opacity	0	0	0	0.00	--	na
	Iritis	0	0	0	0.00	--	na
	Redness conjunctivae	1	1	1	1.00	--	7
	Chemosis conjunctivae	0	0	0	0.00	--	1*
2	Corneal opacity	0	0	0	0.00	--	na
	Iritis	0	0	0	0.00	--	na
	Redness conjunctivae	1	1	1	1.00	--	7
	Chemosis conjunctivae	0	0	0	0.00	--	1*
3	Corneal opacity	0	0	0	0.00	--	na
	Iritis	0	0	0	0.00	--	na
	Redness conjunctivae	0	0	0	0.00	--	1*
	Chemosis conjunctivae	0	0	0	0.00	--	1*

na: not applicable *: with respect to the result 1 hour post application

Response for mean scores:		Corneal opacity	Iritis	Conjunctival redness	Conjunctival oedema	
--	= negative	<1	<1	<2	<2	(Regulation (EC) No. 1272/2008 and GHS)
		<2	<1	<2.5	<2	(Directive 1999/45/EC)
(+)	= mild irritant	≥1 - <3	≥1 - <2	≥2	≥2	(GHS category 2B (effects reversible within 7 days))
+	= irritant	≥1 - <3	≥1 - <2	≥2	≥2	(Regulation (EC) No. 1272/2008 (GHS) category 2)
		≥2 - <3	≥1 - <2	≥2.5	≥2	(Directive 1999/45/EC)
++	= irreversible effects, serious damage	≥3	≥1.5			(Regulation (EC) No. 1272/2008 and GHS category 1)
		≥3	≥2			(Directive 1999/45/EC)

III. Conclusion

Fenhexamid WG 50 is slightly irritating to the eye of rabbits. Classification is not triggered.

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The study result triggers the following classification/labelling:

- EU directive 1999/45/EC: **none**
- Regulation (EC) No 1272/2008 (CLP): **none**

IIIA 7.1.6 Skin sensitization

Report:	**IIIA 7.1.6/01; [redacted], 1995, amended 1995-11-08**
Title:	KBR 2738 50 WG 04258/0214 - Study for skin sensitization effect in guinea pigs (Buehler Patch Test)
Report No.: Document No.:	24366 **M-010216-02-1**
Dates of work:	1995-07-18 to 1995-08-18
Guidelines:	OECD 406; Guideline 92/69/EC, Method B.6, US-EPA FIFRA § 81-6 Deviation(s): none
GLP:	yes

I. Materials and methods

A. Materials

1. Test material: KBR 2738 50 WG 04258/0214

Development no.:	30-0170928
Description:	brownish granules
Lot/Batch no.:	0222 based on 04258/0214
Content:	49.6%
Stability of test compound:	guaranteed for study duration, expiry date: 1996-02-08

2. Vehicle: physiological saline solution

3. Test animals:

Species:	guinea pig (SPF-bred)
Strain:	Hsd:Win:DH (previously termed Bor:DHPW)
Age:	5 – 6 weeks
Weight at dosing-1st application):	262 g – 349 g
Source:	[redacted] Germany
Acclimatisation period:	at least 7 days
Diet:	"Altromin® 3020 - Maintenance Diet for Guinea Pigs" ([redacted], Germany), ad libitum
Water:	tap water, ad libitum
Housing:	conventionally in type IV Makrolon® cages, adaptation: in groups of five per cage, study period: in groups of two or three per cage bedding: low-dust wood shavings ([redacted] Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose

1st – 3rd induction:	paste (1 g test material moistened with 0.5 mL phys. saline solution, concentration approx. 66.67%)
Challenge:	50%
Application route:	dermal, semi-occlusive dressing

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Application volume:	0.5 mL/patch
Exposure:	6 hours per application (induction: 3 times at intervals of 7 days, challenge: 4 weeks after the first induction, 2 weeks after last induction)
Group size:	45 females (controls: 2x10, test item group: 20, range-finding for determination of the induction and challenge concentrations: 5)
Observations:	mortality, clinical signs, skin effects, body weight (at study begin and termination)

II. Results and discussion

A. Findings

The challenge with the 50% test substance formulations led to no skin reactions after 30 and 54 h in the test animals as well as in the control animals. After 78 h a slight skin redness (grade 1) was observed in 2/20 animals of the test substance group and in 1/10 control group animals, indicating that there was no difference in the skin reactions between both groups.

Appearance and behaviour of the animals in test substance group were not different from those of the control group. No mortalities occurred.

By the end of the study the body weight development of the treatment group animals corresponded to that of the control groups.

Table 7.1.6-1 Number of animals exhibiting skin effects

	Test item group (20 animals)							Control group (10 animals)						
	Test item patch				Control patch			Test item patch				Control patch		
Hours	30	54	78	total	30	54	78	30	54	78	total	30	54	78
Challenge 50%	0	0	2	2	0	0	0	0	0	1	1	0	0	0

III. Conclusion

Under the conditions of the Buehler Patch Test and with respect to the evaluation criteria Fenhexamid WG 50 exhibits no skin-sensitization potential.

The study result triggers the following classification/labelling:

- EU directive 1999/45/EC: **none**
- Regulation (EC) No 1272/2008 (CLP): **none**

Report:	**IIIA 7.1.6/02, [redacted], 2000**
Title:	KBR 2738 WG 50 - Study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman)
Report No.: Document No.:	30066 **M-043441-01-1**
Dates of work:	2000-02-01 to 2000-02-25
Guidelines:	OECD 406; Guideline 96/54/EC, Method B.6.; US-EPA 712-C-98-197, OPPTS 870.2600 Deviation(s): The test item contains commercial products known to be stable and homogenous both undiluted and in ready-to-use dilution with water. Therefore, analytical determinations of the stability and homogeneity of the formulations in the physiological saline solution for administration were not performed. These deviations did not limit the assessment of the results.

GLP:	yes

I. Materials and methods

A. Materials

1. Test material: KBR 2738 WG 50
   - Material/Article no.: 00-05419441
   - Description: brown solid
   - Lot/Batch no: 299940019
   - Content: 50.2%
   - Stability of test compound: guaranteed for study duration; expiry date: 2000-12-07

2. Vehicle: sterile physiological saline solution

3. Test animals:
   - Species: guinea pig (SPF-bred)
   - Strain: Hsd Poc:DH
   - Age: 4 – 6 weeks
   - Weight at dosing (1st application): 315 g – 399 g
   - Source: [redacted] Germany
   - Acclimatisation period: at least 7 days
   - Diet: "Altromin®3020 - Maintenance Diet for Guinea Pigs" ([redacted], Germany), ad libitum
   - Water: tap water, ad libitum
   - Housing: conventionally in type IV Makrolon® cages, adaptation: in groups of five animals/cage; study period: in groups of two or three animals/cage bedding: low-dust wood shavings ([redacted], Gemany)

B. Study design and methods

1**. Animal assignment and treatment:**
   - Dose
   - Intradermal induction: 5% (= 20 mg test item/animal)
   - Topical induction: 25% (= 125 mg test item/animal)
   - Challenge: 12% (= 60 mg test item/animal)
   - Application route: intradermal (1st induction), dermal (2nd induction, challenge)
   - Application volume: intradermal induction: 0.1 mL/injection
     topical induction, challenge: 0.5 mL/patch
   - Exposure: intradermal induction,
     1 week later: topical induction: exposure for 48 hours,
     3 weeks after intradermal induction: challenge: exposure for 24 hrs
   - Group size: 37 females (control: 10, test item: 20, range finding:5 for the determination of the induction concentrations, 2 for the determination of the challenge concentration)
   - Observations: mortality, clinical signs, skin effects, body weight (at beginning and termination of study)

II. Results and discussion

A. Findings

After intradermal induction (1st induction) the control group animals showed red wheals or wheals after 48 hours, while the animals in the test item group at the same time presented red wheals, a red injection site, white wheals with red surrounding or a grey wheal with encrustation.
After 7 days encrustations and wheals were recorded at the injection sites in the control group and encrustations in the test item group.
At day 9, immediately after removal of the patch of the second induction, the treatment area of the second induction exhibited skin effects (grade 1) in 3 of 20 animals in the test item group, while there were no skin effects in the control group. The treatment areas of all animals in the test item group were brownish discoloured.
No skin effects, neither in the treatment group nor in the controls, were seen after the challenge using a 12% test item formulation.

Appearance and behaviour of the test item group were not different from the control group.

At the end of the study, the mean body weight of the treatment group animals was in the same range as that of the control group animals.

Table 7.1.6-2 Number of animals exhibiting skin effects

	Test item group (20 animals)					Control group (10 animals)				
	Test item patch			Control patch		Test item patch			Control patch	
Hours	48	72	Total	48	72	48	72	Total	48	72
Challenge 12%	0	0	0	0	0	0	0	0	0	0

III. Conclusion

Under the conditions of the maximization test and with respect to the evaluation criteria fenhexamid WG 50 exhibits no skin-sensitization potential.

The study result triggers the following classification/labelling:

- EU directive 1999/45/EC: **none**
- Regulation (EC) No 1272/2008 (CLP): **none**

IIIA 7.1.7 Supplementary studies for combinations of plant protection products

Not applicable. This plant protection product is not planned to be combined with other plant protection products.

IIIA 7.2 Short-term toxicity studies

Not required by Directive 91/414/EEC or Regulation 1107/2009/EEC.

IIIA 7.3 Operator exposure

Fenhexamid WG 50 is a fungicide intended for outdoor as well as greenhouse spray treatment of various types of low and high growing crops (strawberries, grapes, and tomatoes). The product is formulated as water dispersible granules (WG) and contains as active substance (a.s.) fenhexamid (500 g/kg). Outdoor treatment is conducted by spray application with field crop sprayers or broadcast air assisted sprayers depending on the type of target crop, while applications in the greenhouse are done by handheld equipement. The maximum recommended application rate for outdoor treatment amounts to 1 kg a.s./ha (strawberries). The maximum recommended application rate for treatment in greenhouses amounts to 0.75 kg a.s./ha (strawberries and tomatoes). Water will be the diluent/carrier in all situations. Application parameters are summarised in table 7.3-1.

Table 7.3-1: Application parameters for Fenhexamid WG 50

Crop(s)	Application technique	F / G	Maximum application rate (kg product /ha)	Maximum application rate (kg a.s. /ha)	Minimum amount water (L/ha)	Max. no. of treatments	Min. PHI (days)
Grapes	BAA	F	1.6	0.8	800	2	14
Strawberries	FCS	F	2	1	1000	3	3
	HHS	G	1.5	0.75	300	4	1
Tomatoes	FCS	F	1.5	0.75	300	3	1
	HHS	G	1.5	0.75	300	3	1

FCS = Field crop sprayer, BAA = Broadcast air assisted sprayer, HHS = Hand held sprayer
F = Field use, G = Greenhouse use

<u>Consideration on acceptable operator exposure level (AOEL)</u>

Finalised in the Standing Committee on Plant Health at its meeting on 19 October 2000 in view of the inclusion of fenhexamid in Annex I of Directive 91/414/EEC a systemic AOEL of 0.3 mg/kg bw/day is proposed for fenhexamid based on a NOAEL of 30 mg/kg bw/day established in the 13 week dog study and a safety factor of 100[1].

<u>Consideration on dermal absorption</u>

The extent of dermal absorption of fenhexamid was investigated *in vivo* using the rat and a WP 50 formulation as well as *in vitro* using human and rat skin and a WG 50 formulation. Combining the data from both the *in vivo* and the *in vitro* studies provides the following estimated human *in vivo* absorption values: 500 g/kg = 0.3%, 5 g/L = 3.6%, 0.375 g/L = 8.6%
For details please see point IIIA 7.6.

[1] Fenhexamid 6497/VI/99-rev.2, 19 October 2000

Consideration on estimation of operator exposure

With respect to the outdoor uses operator exposure estimates are calculated using the German model and UK POEM for the respective scenarios. 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 Fenhexamid WG 50. 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.

Neither the German model nor the UK-POEM provides exposure data to evaluate the “hand held application in greenhouses”. Therefore, the exposure of operators during application with hand held sprayers in the greenhouse is evaluated with the Southern European Greenhouse Model. Detailed considerations and calculations as well as a summary of the greenhouse model will be presented under IIIA 7.3.1 (Estimation of operator exposure without personal protective equipment).

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 IIIA 7.3.1.

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Table 7.3-2: Comparison of estimated systemic operator exposure to fenhexamid [mg/kg bw/day] with the proposed AOEL

Application type	Crop	PPE	Total systemic exposure [mg/kg bw/day]	% of AOEL [0.3 mg/kg bw/day]
Field uses, German model*				
Broadcast air assisted sprayer	Grapes	No PPE 1)	0.0934	**31**
		With PPE 2)	0.0211	**7**
Field crop sprayer	Strawberries / Tomatoes	No PPE 1)	0.0544	**18**
		With PPE 2)	0.0154	**5**
Field uses, UK-POEM**				
Field crop sprayer	Strawberries	No PPE 3)	0.1047	**35**
		With PPE 2)	0.0905	**30**
Field crop sprayer	Tomatoes	No PPE 3)	0.1845	**61**
		With PPE 2)	0.1739	**58**
Greenhouse uses				
Hand-held application in greenhouse	Strawberries	No PPE 3)	0.0106	**3.5**
		With PPE 4)	0.0052	**1.7**
Hand-held application in greenhouse	Tomatoes	No PPE 3)	0.0472	**15.7**
		With PPE 4)	0.0239	**8.0**
Hand-held application in greenhouse	Tomatoes (intensive contact)			
		With PPE 5)	0.0129	**4.3**

* Assumes a 70 kg operator, ** assumes a 60 kg amateur operator
1) Short trousers and a short sleeved shirt
2) One layer of typical work wear (e.g. trousers +long sleeved shirt) as well as sturdy foot wear and protective gloves during mixing/loading
3) One layer of typical work wear (e.g. trousers and a long sleeved shirt) and sturdy foot wear during mixing/loading/application
4) Gloves during mixing/loading and application, coverall during application
5) Gloves during mixing/loading and application, impervious clothing during application

IIIA 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. Greenhouse applications are not evaluated with the German model. Exposure for this scenario will be calculated with a separate data set (see IIIA 7.3.3 Measurement of operator exposure). The following assumptions are made for each scenario:

<u>Field crop sprayer</u>

Treated area:	20 ha/day
Max. dose rate:	1.0 kg a.s./ha fenhexamid, (strawberry, covers the use in tomatoes)

<u>Broadcast air assisted sprayer</u>

Treated area:	8 ha/day
Max. dose rate:	0.8 kg a.s./ha fenhexamid (grapes)

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Dermal absorption: 0.3% (concentrate)
8.6% (in use dilution)
(see IIIA 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 fenhexamid using field crop sprayers (German model, without and with PPE)

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

Product:	Teldor				
Active substance:	fenhexamid	a.s. concentration:	500	[g/l or kg]	
Formulation:	WG	PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	2.0		Hands:	Gloves	
Work rate [ha/day]:	20	PPE during application:	Respiration:	None	
Body weight [kg]:	70		Hands:	None	
Inhalation absorption [%]	100		Head:	None	
Dermal absorption [%]	0.3	(concentrate)	Body:	Standard protective coverall	
	8.6	(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	20.0	0.002286	1.0	0.002286	D = Dermal
$D_{M(H)}$ =	2.0	20.0	0.5714	0.01	0.005714	M = Mix/Loading
I_A =	0.001	20.0	0.000286	1.0	0.000286	A = Application
$D_{A(C)}$ =	0.06	20.0	0.0171	1.0	0.017143	H = Hands
$D_{A(H)}$ =	0.38	20.0	0.1086	1.0	0.108571	C = Head
$D_{A(B)}$ =	1.6	20.0	0.4571	0.05	0.022857	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	0.3	0.571429	0.001714	0.005714	0.000017
	Application	8.6	0.582857	0.050126	0.148571	0.012777
Inhalation:	Mix/Loading	100	0.002286	0.002286	0.002286	0.002286
	Application	100	0.000286	0.000286	0.000286	0.000286
		Total =		**0.054411**		**0.015366**

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Table 7.3.1-2: Calculation of operator exposure to fenhexamid 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:	Teldor				
Active substance:	fenhexamid	a.s. concentration:	500	[g/l or kg]	
Formulation:	WG	PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	1.6		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 [%]	0.3	(concentrate)	Body:	Standard protective coverall	
	8.6	(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	6.4	0.000731	1.0	0.000731	I = Inhalation
$D_{M(H)}$ =	2.0	6.4	0.1829	0.01	0.001829	D = Dermal
I_A =	0.018	6.4	0.001646	1.0	0.001646	M = Mix/Loading
$D_{A(C)}$ =	1.2	6.4	0.1097	1.0	0.10971	A = Application
$D_{A(H)}$ =	0.7	6.4	0.064	1.0	0.064	H = Hands
$D_{A(B)}$ =	9.6	6.4	0.8777	0.05	0.043886	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	0.3	0.182857	0.000549	0.001829	0.000005
	Application	8.6	1.051429	0.090423	0.2176	0.018714
Inhalation:	Mix/Loading	100	0.000731	0.000731	0.000731	0.000731
	Application	100	0.001646	0.001646	0.001646	0.001646
		Total =		**0.093349**		**0.021096**

b) Estimation according to the UK-POEM

Using UK-POEM only the application in tomato and strawberry were assessed as the model contains no data for application in grapes. With UK-POEM the highest exposure is calculated by combining the maximum dose rates with the minimum spray volumes. Thus, the following assumptions are made for each scenario:

Field crop sprayer

Treated area:	50 ha/day
Max. dose rate:	1.0 kg a.s./ha fenhexamid (strawberry)
Spray volume:	1000 L/ha
Max. dose rate:	0.75 kg a.s./ha fenhexamid, (tomato)
Spray volume:	300 L/ha
Operator body weight:	60 kg

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

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Table 7.3.1-3: Calculation of operator exposure to fenhexamid using field crop sprayers in strawberry (UK POEM model, without and with PPE)

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

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**Teldor WG 50**	Active substance	**fenhexamid**
Formulation type	WG or SG	a.s. concentration	**500** mg/g
Dermal absorption from product	**0.3** %	Dermal absorption from spray	**8.6** %
PPE during mix/loading	Gloves	PPE during application	None
Dose	**2** kg product/ha	Work rate/day	**50** ha
Application volume	**1000** 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	286 mg/day	
Protective clothing	None	Gloves
Transmission to skin	100 %	1 %
Dermal exposure to a.s.	286.000 mg/day	2.860 mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0.036 mg/kg a.s.
Inhalation exposure/day	1.790 mg/day
RPE	None
Transmission through RPE	100 %
Inhalation exposure to a.s.	1.790 mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Application volume	1000 spray/ha		
Volume of surface contamination	10 ml/h		
Distribution	Hands	Trunk	Legs
	65 %	10 %	25 %
Clothing	None	Permeable	Permeable
Penetration	100 %	5 %	15 %
Dermal exposure	6.5	0.05	0.375 ml/h
Duration of exposure	6 h		
Total dermal exposure to spray	41.55 ml/day		
Conc. of a.s. in spray solution	1 mg/ml		
Dermal exposure to a.s.	41.550 mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0.01 ml/h
Duration of exposure	6 h
Concentration of a.s. in spray	1 mg/ml
Inhalation exposure to a.s.	0.06 mg/day
Percent absorbed	100 %
Absorbed dose	0.06 mg/day

ABSORBED DOSE	No PPE		With PPE	
	Mix/load	Application	Mix/load	Application
Dermal exposure to a.s.	286.000	41.550 mg/day	2.860	41.550 mg/day
Percent absorbed	0.3	8.6 %	0.3	8.6 %
Absorbed dose (dermal route)	0.858	3.573 mg/day	0.009	3.573 mg/day
Inhalation exposure to a.s.	1.790	0.060 mg/day	1.790	0.060 mg/day
Absorbed dose	2.648	3.633 mg/day	1.799	3.633 mg/day

PREDICTED EXPOSURE	No PPE	With PPE
Total absorbed dose	6.2813 mg/day	5.4319 mg/day
Operator body weight	60 kg	60 kg
Operator exposure	0.1047 mg/kg bw/day	0.0905 mg/kg bw/day

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Table 7.3.1-4: Calculation of operator exposure to fenhexamid using field crop sprayers in tomato (UK POEM model, without and with PPE)

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

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**Teldor WG 50**	Active substance	**fenhexamid**
Formulation type	WG or SG	a.s. concentration	**500** g/kg
Dermal absorption from product	**0.3** %	Dermal absorption from spray	**8.6** %
PPE during mix/loading	Gloves	PPE during application	None
Dose	**1.5** kg product/ha	Work rate/day	**50** 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	214.5 mg/day		
Protective clothing	None	Gloves	
Transmission to skin	100 %	1 %	
Dermal exposure to a.s.	214.500 mg/day	2.145 mg/day	

INHALATION EXPOSURE DURING MIXING AND LOADING	
Inhalation exposure/kg a.s.	0.036 mg/kg a.s.
Inhalation exposure/day	1.343 mg/day
RPE	None
Transmission through RPE	100 %
Inhalation exposure to a.s.	1.343 mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION				
Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	300 spray/ha			
Volume of surface contamination	10 ml/h			
Distribution	Hands	Trunk	Legs	
	65 %	10 %	25 %	
Clothing	None	Permeable	Permeable	
Penetration	100 %	5 %	15 %	
Dermal exposure	6.5	0.05	0.375 ml/h	
Duration of exposure	6 h			
Total dermal exposure to spray	41.550 ml/day			
Conc. of a.s. in spray solution	2.5 mg/ml			
Dermal exposure to a.s.	103.875 mg/day			

INHALATION EXPOSURE DURING SPRAYING	
Inhalation exposure to spray	0.01 ml/h
Duration of exposure	6 h
Concentration of a.s. in spray	2.5 mg/ml
Inhalation exposure to a.s.	0.15 mg/day
Percent absorbed	100 %
Absorbed dose	0.15 mg/day

ABSORBED DOSE	No PPE		With PPE	
	Mix/load	Application	Mix/load	Application
Dermal exposure to a.s.	214.500	103.875 mg/day	2.145	103.875 mg/day
Percent absorbed	0.3	8.6 %	0.3	8.6 %
Absorbed dose (dermal route)	0.644	8.933 mg/day	0.006	8.933 mg/day
Inhalation exposure to a.s.	1.343	0.150 mg/day	1.343	0.150 mg/day
Absorbed dose	1.986	9.083 mg/day	1.349	9.083 mg/day

PRELISTED EXPOSURE		
Total absorbed dose	11.0693 mg/day	10.4322 mg/day
Operator body weight	60 kg	60 kg
Operator exposure	0.1845 mg/kg bw/day	0.1739 mg/kg bw/day

c) Estimation according to the Greenhouse Model

Exposure is calculated for spray applications in greenhouse (strawberry, tomato).

To address a data gap for hand-held applications in greenhouses, ECPA conducted seven operator exposure studies during the period of 2002 to 2006. Details of the location and the crop are summarized in the following table.

Table 7.3.1-6: Operator exposure studies in the greenhouse

EOEM Study ID-	Country	Region	Crop	No of Operators	
				Mix/Load	Application
2	**Spain**	**Almeria**	**Peppers**	**10**	**32**
3	**Spain**	**Almeria**	**Cucumber**	**10**	**10**
10	**Italy**	**Tuscany/Veneto**	**Pot Plants**	**10**	**10**
12	**Spain**	**Murcia/Alicante**	**Cucumber**	**10**	**10**
13	**Spain**	**Murcia/Alicante**	**Tomato**	**10**	**10**
14	**Italy**	**Sicily**	**Melon**	**10**	**20**
15	**Italy**	**Sicily**	**Melon**	**NA**	**10**

NA: not applicable

The studies were conducted according to OECD Guidance[2] and were GLP compliant for the field, analytical and report phases, including assessment reports. The studies were monitored by ECPA and conducted using internationally recognized contract research organizations.

Briefly, the exposure was determined using standardized passive dosimetry methodology. This entailed the use of inner and outer dosimeters for body exposure, protective gloves and hand washes for hand exposure, face and neck washes for head exposure. Inhalation exposure was monitored using a suitable collection device located in the breathing zone to collect the inhalable fraction of airborne particles.

Analysis of the work practices and exposure data has identified four exposure scenarios:
High crop (>0.5m):

- Standard scenario – insignificant contact with treated foliage
- Intensive scenario – direct contact with treated foliage

Low crop (<0.5m):

- Standard scenario – insignificant contact with treated foliage
- Intensive scenario – direct contact with treated foliage

In the **'Standard'** scenario, operators wore polyester/cotton standard working coveralls.

[2] OECD (1997) Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application OECD Environmental Health and Safety Publications Series on Testing and Assessment No. 9

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In certain cropping scenarios, where contact to treated foliage cannot be avoided rain suit coveralls/trousers are commonly used. Exposure of these operators was determined for an **'Intensive'** scenario.

Algorithms using the 75th percentile of the exposure distributions have been developed based on normalization for the amount of kg a.s. handled or applied. These have been generated for each of the four scenarios' data sets and incorporated into a Microsoft Excel-based model [Greenhouse model v_2.1 (20101223).xls].

The model has passed through a workshop with European experts from Member States and was further developed during several commenting periods according to the requirements of Member States authorities.

More details about the model and the underlying studies are given in:

Report:	**KIIIA 7.3.1/01, Members of the ECPA Occupational and Bystander Expert Group, Oct 2010, (Revision 9)**
Title:	Southern European Greenhouse Model Overview
Document No	**M-400719-01-1**
Guidelines:	OECD (1997) Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application OECD Environmental Health and Safety Publications Series on Testing and Assessment No. 9
GLP	Yes

The high crop scenario applies for the application of Fenhexamid WG 50 in tomato. With regard to the crop the intensive scenario cannot be excluded and, hence, is also estimated. The low crop scenario was used for the application in strawberry. For this application intensive contact with the crop during application can be excluded. Thus, only the standard scenario was considered.

The following assumptions are made:

Treated area: 1 ha/day
Dose rate: 0.75 kg a.s./ha

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Table 7.3.1-7: Calculation of operator exposure during greenhouse application, High crop - Standard (Greenhouse Model v_2.1, without and with PPE)

Operator exposure estimate: Greenhouse model. High crop, standard

Product:	Teldor				
Active substance:	Fenhexamid		a.s. concentration:	500	[g/l or kg]
Formulation:	WG		PPE during mix/loading:	Respiration:	None
Dose [l or kg/ha product] :	1.5			Hands:	Gloves
Work rate [ha/day]:	1		PPE during application:	Respiration:	None
Body weight [kg]:	70			Hands:	Gloves
Inhalation absorption [%]	100			Head:	None
Dermal absorption [%]	0.3	(concentrate)		Body:	Coverall
	8.6	(dilution)			

Calculation of route exposure:

Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]			
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected	
I_M =	0.013344		1.750	0.00014297			I = Inhalation
$D_{M(H)}$ =	2.295118	0.029685	0.750	0.02459065		0.00031810	D = Dermal
I_A =	0.676955		0.750	0.00725309			M = Mix/Loading
$D_{A(C)}$ =	0.806061		0.750	0.00863636			A = Application
$D_{A(H)}$ =	25.190388	0.021652	0.750	0.26998970		0.0002320	C = Head
$D_{A(B)}$ =	17.084126		0.750	0.183044			H = Hands
							B = Body

Absorbed dose:

Route		Absorption [%]	Unprotected		Protected	
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.3	0.024591	0.000738	0.000318	0.000001
	Application	8.6	0.461578	0.039696	0.191913	0.0165045
Inhalation:	Mix/Loading	100	0.00014297	0.00014297	0.00014297	0.00014297
	Application	100	0.007253	0.007253	0.007253	0.007253
		Total =		**0.047165**		**0.023901**

Table 7.3.1-9: Calculation of operator exposure during greenhouse application, High crop - Intensive Contact (Greenhouse Model v_2.1, without and with PPE)

Operator exposure estimate: Greenhouse model. High crop, intensive contact with treated crop

Product:	Teldor				
Active substance:	Fenhexamid		a.s. concentration:	500	[g/l or kg]
Formulation:	WG		PPE during mix/loading:	Respiration:	None
Dose [l or kg/ha product] :	1.5			Hands:	Gloves
Work rate [ha/day]:	1		PPE during application:	Respiration:	None
Body weight [kg]:	70			Hands:	Gloves
Inhalation absorption [%]	100			Head:	None
Dermal absorption [%]	0.3	(concentrate)		Body:	Impervious clothing
	8.6	(dilution)			

Calculation of route exposure:

Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]		
	"Unprotected"	"Protected"		Unprotected	Reduction factor (-)	Protected
I_M =	0.013344		0.750	0.00014297		
$D_{M(H)}$ =	2.295118	0.029589	0.750	0.024589055		0.00031810
I_A =	0.824467		0.750	0.008833358		
$D_{A(C)}$ =	1.066230		0.750	0.011423889		
$D_{A(H)}$ =	not applicable	1.051509	0.750			0.0112662
$D_{A(B)}$ =	not applicable	2.173683615	0.750			0.023289

I = Inhalation
D = Dermal
M = Mix/Loading
A = Application
C = Head
H = Hands
B = Body

Absorbed dose:

Route		Absorption [%]	Unprotected: Estimated route exposure [mg/kg bw/day]	Unprotected: Systemic exposure [mg/kg bw/day]	Protected: Estimated route exposure [mg/kg bw/day]	Protected: Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.3	0.024589	0.000738	0.000318	0.000001
	Application	10			0.045979	0.0039542
Inhalation:	Mix/Loading	100	0.00014297	0.00014297	0.00014297	0.00014297
	Application	100	0.008834	0.008834	0.008834	0.008834
		Total =				**0.012932**

Narrow or no rows in greenhouse high crops result in additional exposure via direct contact with treated foliage that cannot be avoided. Exposure is substantially different to the 'Standard' crop scenario, thus forms a unique 'Intensive' exposure scenario. Protected operators with intensive contact to treated foliage in the high crop scenario would wear an impervious coverall and gloves during mixing/loading and application. A safety phrase must always be incorporated on product labels for this scenario to ensure that exposure due to contact with treated crop is minimised by use of spray tight protective clothing (Cat. III, type 4; High crop: overall or jacket/trousers), or avoided by use of engineering controls.

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Table 7.3.1-10: Calculation of operator exposure during greenhouse application, Low crop – Standard (Greenhouse Model v_2.1, without and with PPE)

Operator exposure estimate: Greenhouse model, Low crop, standard

Product:	Teldor				
Active substance:	Fenhexamid		a.s. concentration:	500	[g/l or kg]
Formulation:	WG		PPE during mix/loading:	Respiration:	None
Dose [l or kg/ha product] :	1.5			Hands:	Gloves
Work rate [ha/day]:	1		PPE during application:	Respiration:	None
Body weight [kg]:	70			Hands:	Gloves
Inhalation absorption [%]	100			Head:	None
Dermal absorption [%]	0.3	(concentrate)		Body:	Impervious clothing
	8.6	(dilution)			

Calculation of route exposure:

Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]		
	"Unprotected"	"Protected"		Unprotected	Reduction factor (-)	Protected
I_M =	0.013344		0.750	0.00014297		
$D_{M(H)}$ =	2.295118	0.029589	0.750	0.024589055		0.00031810
I_A =	0.443296		0.750	0.004749600		
$D_{A(C)}$ =	0.011494		0.750	0.000123145		
$D_{A(H)}$ =	5.710485	0.000333	0.750	0.061193		0.0000025
$D_{A(B)}$ =	0.372960		0.750	0.003996		

I = Inhalation
D = Dermal
M = Mix/Loading
A = Application
C = Head
H = Hands
B = Body

Absorbed dose:

Route		Absorption [%]	Unprotected: Estimated route exposure [mg/kg bw/day]	Unprotected: Systemic exposure [mg/kg bw/day]	Protected: Estimated route exposure [mg/kg bw/day]	Protected: Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.3	0.024501	0.000738	0.000318	0.000001
	Application	8.6	0.065303	0.002616	0.004122	0.0003545
Inhalation:	Mix/Loading	100	0.00014297	0.00014297	0.00014297	0.00014297
	Application	100	0.004750	0.004750	0.004750	0.004750
		Total =		**0.010582**		**0.005248**

IIIA 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 IIIA 7.3.1.

IIIA 7.3.3 Measurement of operator exposure

Since the risk assessment carried out indicated that the acceptable operator exposure level (AOEL) for fenhexamid 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.

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IIIA 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 IIIA 7.4.1.

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

Scenario	Application technique	Person	Systemic exposure* [mg/kg bw/day]	% of AOEL#
Bystander	FCS	Adult Child	0.00042 0.00033	0.14 0.11
Resident	FCS	Adult Child	0.000050 0.000141	0.017 0.047
Bystander	BAA	Adult Child	0.00144 0.00116	0.48 0.39
Resident	BAA	Adult Child	0.00018 0.00050	0.06 0.17

FCS = Field crop sprayer, BAA = Broadcast air assisted sprayer
#: AOEL = 0.3 mg/kg bw/day
*: Considers the 60 kg adult and 16.15 kg child

Based on these results there is no unacceptable risk anticipated for the bystander/resident with the intended professional uses of Fenhexamid WG 50.

IIIA 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.

3 [redacted]. (2008): Guidance for Exposure and Risk Evaluation for Bystanders and
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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 not assumed to occur following applications in the greenhouse.
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.
Corresponding exposure estimates are presented in the following.

A. Bystander exposure
Exposure calculations are performed according to the following equations:

Dermal exposure due to spray drift

SDE_B = (AR x D x BSA x DA) / BW   where:
SDE_B = Systemic Exposure of Bystanders via the Dermal Route (mg/kg bw/day)
AR = max. Application Rate (grapes = 80 mg a.s./m^2, field crops = 100 mg a.s./m^2)
D = Drift (1.23% for use in grapes and 0.29% for use in field crops)

BSA = Exposed Body Surface Area (1 m^2: adult, 0.21 m^2: child)
DA = Dermal Absorption (8.6%)
BW = Body Weight (60 kg: adult, 16.15 kg: child)

Inhalation exposure due to spray drift

SIE_B = (I_A* x AR x A x 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 = 0.8 kg a.s. /ha, field crops = 1 kg a.s. /ha)

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

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A = Area Treated (grapes = 8 ha, field crops = 20 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 fenhexamid when applied via field crop sprayer (use in strawberries, covers also the use in tomato)

Adults			Children		
Bystander of Field Crop, tractor mounted trailed					
Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (100 x 0.29% x 1 x 3.6 %) / 60 Absorbed dose:	0.0004157	mg/kg bw/day	Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (100 x 0.29% x 0.21 x 3.6%) / 16.15 Absorbed dose:	0.0003243	mg/kg bw/day
Inhalation exposure: $SIE_B = (I_A * \times AR \times A \times T \times IA) / BW$ (0.001 x 1 x 20 x 5/360 x 100%) / 60 Absorbed dose:	0.00000463	mg/kg bw/day	Inhalation exposure: $SIE_B = (I_A * \times AR \times A \times T \times IA) / BW$ (0.001/1.74 x 1 x 20 x 5/360 x 100%) / 16.15 Absorbed dose:	0.000009885	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:	**0.00042**	**mg/kg bw/day**	**Total absorbed dose:**	**0.000334**	**mg/kg bw/day**
% of AOEL:	**0.14**		**% of AOEL:**	**0.111**	

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

Adults	Children
Bystander of High Crop, tractor mounted/trailed	
Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (80 x 1.23% x 1 x 8.6 %) / 60 Absorbed dose: 0.00141 mg/kg bw/day	Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (80 x 1.23% x 0.21 x 8.6 %) / 16.15 Absorbed dose: 0.0011 mg/kg bw/day
Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.018 x 0.8 x 8 x 5/360 x 100%) / 60 Absorbed dose: 0.00002667 mg/kg bw/day	Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.018/1.74 x 0.8 x 8 x 5/360 x 100%) / 16.15 Absorbed dose: 0.00005624 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: 0.00144 mg/kg bw/day	**Total absorbed dose: 0.00116 mg/kg bw/day**
% of AOEL: 0.48	**% of AOEL: 0.387**

B. Resident exposure

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 0.008 mg a.s. /cm² = 0.016 mg a.s. /cm²)
(field crops: 2 x 0.01 mg a.s. /cm² = 0.02 mg a.s. /cm²)

D = Drift (1.07% for use in grapes and 0.24% for use in field crops)

TTR = Turf Transferable Residues (5%)

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

H = Exposure Duration (2 hours)

DA = Dermal Absorption (% = 8.6% for fenhexamid)

BW = Body Weight (adult = 60 kg, child = 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/m³): vapour pressure of fenhexamid is very low: 4 x 10^{-9} Pa at 20 °C. Acc. to guideline the compound is a 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/m³).

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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 x AR x D x TTR x SE x SA x Freq x H x OA) / BW
Where:
SOE_H = Systemic Oral Exposure via the Hand to Mouth Route (mg/kg bw/day)
AR = Application Rate (grapes: 2 x 0.008 mg a.s. /cm^2 = 0.016 mg a.s. /cm^2)
(field crops: 2 x 0.01 mg a.s. /cm^2 = 0.02 mg a.s. /cm^2)
D = Drift (1.07% for use in grapes and 0.24% for use in field crops)
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 x AR x D x DFR x IgR x OA) / BW
Where:
SOE_O = Systemic Oral Exposure via the Object to Mouth Route (mg/kg bw/day)
AR = Application Rate (grapes: 2 x 0.008 mg a.s. /cm^2 = 0.016 mg a.s. /cm^2)
(field crops: 2 x 0.01 mg a.s. /cm^2 = 0.02 mg a.s. /cm^2)
D = Drift (1.07% for use in grapes and 0.24% for use in field crops)
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.

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Table 7.4.1-4: Calculations for resident exposure to fenhexamid when applied via field crop sprayer (use in strawberries, covers also the use in tomato)

Adults	Children
Resident: Exposure after application with Field Crop, tractor mounted/trailed	
Dermal exposure: SDE_R = (AR x D x TTR x TC x H x DA) / BW (0.02 x 0.24% x 5% x 7300 x 2 x 8.6%) / 60 Absorbed dose: 0.00005022 mg/kg bw/d	Dermal exposure: SDE_R = (AR x D x TTR x TC x H x DA) / BW (0.02 x 0.24% x 5% x 2600 x 2 x 8.6%) / 16.15 Absorbed dose: 0.0000646 mg/kg bw/d
Inhalation exposure: SIE_R = (AC_V x IR x IA) / 1000 x BW (0 x 16.57 x 100%) / 60 Absorbed dose: 0.0 mg/kg bw/d	Inhalation exposure: SIE_R = (AC_V x IR x IA) / BW (0 x 8.3 x 100%) / 16.15 Absorbed dose: 0.0 mg/kg bw/d
	Oral exposure (hand-to-mouth transfer): SOE_H = (AR x D x TTR x SE x SA x Freq x H x OA) / BW (0.02 x 0.24% x 5% x 50% x 20 x 20 x 2 x 100%) / 16.15 Absorbed dose 0.00005944 mg/kg bw/d
	Oral exposure (object-to-mouth transfer): SOE_O = (AR x D x DFR x IgR x OA) / BW (0.02 x 0.24% x 20% x 25 x 100%) / 16.15 Absorbed dose 0.00001436 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: 0.0000502 mg/kg bw/d	**Total absorbed dose: 0.000141 mg/kg bw/d**
% of AOEL: 0.0167	**% of AOEL: 0.047**

Table 7.4.1-5: Calculations for resident exposure to fenhexamid 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 x D x TTR x TC x H x DA) / BW (0.016 x 1.07% x 5% x 7300 x 2 x 8.6%) / 60 Absorbed dose: 0.0001791 mg/kg bw/d	Dermal exposure: SDE_R = (AR x D x TTR x TC x H x DA) / BW (0.016 x 1.07% x 5% x 2600 x 2 x 8.6%) / 16.15 Absorbed dose: 0.000237 mg/kg bw/d
Inhalation exposure: SIE_R = (AC_V x IR x IA) / 1000 x BW (0 x 16.57 x 100%) / 60 Absorbed dose: 0.0 mg/kg bw/d	Inhalation exposure: SIE_R = (AC_V x IR x 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 x D x TTR x SE x SA x Freq x H x OA) / BW (0.016 x 1.07% x 5% x 50% x 20 x 20 x 2 x 100%) / 16.15 Absorbed dose 0.000212 mg/kg bw/d
	Oral exposure (object-to-mouth transfer): SOE_O = (AR x D x DFR x IgR x OA) / BW (0.016 x 1.07% x 20% x 25 x 100%) / 16.15 Absorbed dose 0.000053 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: 0.000179 mg/kg bw/d	**Total absorbed dose: 0.000502 mg/kg bw/d**
% of AOEL: 0.0597	**% of AOEL: 0.167**

IIIA 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 IIIA 7.4 and IIIA 7.4.1.

IIIA 7.5 Worker exposure

Fenhexamid WG 50 is intended for the spray treatment in tomatoes, strawberries, and grapes. In grapes work activities are tasks like pruning/thinning/harvesting which are done by farmers usually throughout the growing season. In strawberries and tomatoes the relevant task is harvesting.
A comparison of the corresponding exposure estimates with the proposed AOEL (percentage of the AOEL) is presented in table 7.5-1. Detailed calculations are presented in chapter IIIA 7.5.1.

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

Crop	Systemic exposure [mg/kg bw/day]*	% of AOEL [0.3 mg/kg bw/day]
Tomatoes / Strawberries	0.260	87
Grapes	0.224	75

* Assumes a 60 kg worker. Dermal absorption of fenhexamid of 8.6%

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Based on this exposure estimate there is no unacceptable risk anticipated for the worker with the intended uses of Fenhexamid WG 50.

IIIA 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. A calculation for protective equipment is not made, i.e. P always set to 1.

<u>Considerations on Transfer Coefficients (TC)</u>

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 [cm²/hr]
Tomatoes	2500
Grapes	4500
Strawberries	3000

<u>Considerations on DFR:</u>

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.

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

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Calculations consider the maximum number of applications and a conservative dissipation between applications. DFR dissipation is commonly approximated by pseudo-first order decay – that is, a reduction in concentration over time due to a variety of degradation processes e.g. hydrolysis or photolysis. Dissipation may also be influenced by leaf expansion and plant growth, particularly during the early phases of plant development. In a first approach, a conservative assumption using a DT_{50} of 30 days is made for the dissipation between applications. The minimum spray interval is always applied. The DFR after n applications is calculated according to the following formula:

$$DFR_{n\ appl.} = ((DFR_0 \times AR^1) \times 0.5^{d1}) + ((DFR_0 \times AR^2) \times 0.5^{d2}) + \ldots + ((DFR_0 \times AR^n) \times 0.5^{dn})$$

Where
- $DFR_{n\ appl.}$ = *DFR after n applications (µg as/cm²)*
- DFR_o = *Initial DFR, directly after application (µg as/cm²)*
- AR = *Application rate (kg a.s./ha)*
- d^n = *no. of DT_{50} periods after n applications*

Depending on the crop a maximum of two (grape), three (tomato/strawberries) and four (strawberries) consecutive sprays per season are considered in this risk assessment. 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 a 7 day period (i.e. 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.

Further assumptions/considerations to estimate exposure of the worker are summarised below:

Work rate (WR): 8 hour per day
Clothing penetration (P): 1, which means no special clothing request is taken into consideration
Dermal absorption: 8.6%
Body weight of the worker: 60 kg

Detailed calculations of worker exposure during re-entry in strawberry:

Maximum application rate: AR = 0.75 kg a.s./ha
Number of applications: 4
Minimum spray interval: 7 days
PHI: 1 day
No. of DT_{50} periods:
d^1 = (Int 1 + Int 2 + Int 3 + PHI)/ DT_{50}= (7 + 7 + 7 + 1)/30 = 0.73
d^2 = (Int 2 + Int 3 + PHI)/ DT_{50}= (7 + 7 + 1)/30 = 0.50
d^3 = (Int 3 + PHI)/ DT_{50}= (7 + 1)/30 = 0.27
d^4 = PHI/ DT_{50}= 1/30 = 0.03

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$DFR_{n\ appl.} = ((DFR_0 \times AR^1) \times 0.5^{d1}) + ((DFR_0 \times AR^2) \times 0.5^{d2}) + \ldots + ((DFR_0 \times AR^n) \times 0.5^{dn})$
$= ((3 \times 0.75) \times 0.5^{0.73}) + ((3 \times 0.75) \times 0.5^{0.5}) + ((3 \times 0.75) \times 0.5^{0.27}) + ((3 \times 0.75) \times 0.5^{0.03})$
$= 7.01$ µg as/cm²

E = $(DFR_{n\ appl.} \times TC \times WR \times P \times DA)/BW$
$= (7.01 \times 3000 \times 8 \times 1 \times 0.086)/(60)$
$= 0.241$ mg/kg bw/day

Maximum application rate: AR = 1 kg a.s./ha
Number of applications: 3
Minimum spray interval: 7 days
PHI: 1 day
No. of DT_{50} periods: $d^1 = (Int\ 1 + Int\ 2 + PHI)/ DT_{50} = (7 + 7 + 1)/30 = 0.50$
$d^2 = (Int\ 2 + PHI)/ DT_{50} = (7 + 1)/30 = 0.27$
$d^3 = PHI/ DT_{50} = 1/30 = 0.03$

$DFR_{n\ appl.} = ((DFR_0 \times AR^1) \times 0.5^{d1}) + ((DFR_0 \times AR^2) \times 0.5^{d2}) + \ldots + ((DFR_0 \times AR^n) \times 0.5^{dn})$
$= ((3 \times 1.0) \times 0.5^{0.5}) + ((3 \times 1.0) \times 0.5^{0.26}) + ((3 \times 1.0) \times 0.5^{0.03})$
$= 7.55$ µg as/cm²

E = $(DFR_{n\ appl.} \times TC \times WR \times P \times DA)/BW$
$= (7.55 \times 3000 \times 8 \times 1 \times 0.086)/(60)$
$= 0.260$ mg/kg bw/day

Detailed calculations of worker exposure during re-entry in tomato:

Covered by calculations for strawberry

Detailed calculations of worker exposure during re-entry in grapes:

Maximum application rate: AR = 0.8 kg a.s./ha
Number of applications: 2
Minimum spray interval: depends on BBCH, not shorter than 7 days
PHI: 14 days, however re-entry calculated for interval of one day as other activities than harvesting are possible
No. of DT_{50} periods: $d^1 = (Int\ 1 + PHI)/ DT_{50} = (7 + 1)/30 = 0.27$
$d^2 = PHI/ DT_{50} = 1/30 = 0.03$

$DFR_{n\ appl.} = ((DFR_0 \times AR^1) \times 0.5^{d1}) + ((DFR_0 \times AR^2) \times 0.5^{d2}) + \ldots + ((DFR_0 \times AR^n) \times 0.5^{dn})$
$= (3 \times 0.8) \times 0.5^{0.27}) + ((3 \times 0.8) \times 0.5^{0.03})$
$= 4.34$ µg as/cm²

E = $(DFR_{n\ appl.} \times TC \times WR \times P \times DA)/BW$
$= (4.34 \times 4500 \times 8 \times 1 \times 0.086)/(60)$
$= 0.224$ mg/kg bw/day

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IIIA 7.5.2 Estimation of worker exposure using personal protective equipment

Estimations of worker exposure using PPE as an additional layer of clothing and/or gloves are not performed because the exposure of workers without using PPE is acceptable. For details see IIIA 7.5 and IIIA 7.5.1.

IIIA 7.5.3 Estimation of worker exposure using data on dislogeable residues

Dislodgeable foliar residue studies were not performed because the estimation of worker exposure is acceptable for re-entry directly after the application when the spray deposit has dried. For details see IIIA 7.5 and IIIA 7.5.1.

IIIA 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 IIIA 7.5 and IIIA 7.5.1.

IIIA 7.6 Dermal absorption

The extent of dermal absorption of fenhexamid was investigated *in vivo* using the rat and a WP 50 formulation as well as *in vitro* using human and rat skin and a WG 50 formulation. Summaries of the studies are given in the following sections. A conclusion and recommendation regarding the dermal absorption of fenhexamid from a WG formulation is given below.

The *in vivo* rat study indicated that the mean percent absorption of fenhexamid was 2%, following application of the neat formulation, 6% for a representative intermediate dilution of 2 g/L and was 18% following application at a lower representative dilution of 0.2 g/L.

The *in vitro* study indicated that the mean percentage of [^{14}C]-fenhexamid considered to be potentially absorbable over a period of 24 hours for the neat formulation (500 g/kg) was 0.15% and 1.13% for the human and rat skin respectively. The mean percentage of [^{14}C]-fenhexamid considered to be potentially absorbable for the intermediate dose (5 g/L) was 0.62% and 1.03% for the human and rat skin respectively. The mean percentage of [^{14}C]-fenhexamid considered to be potentially absorbable for the low dose (0.375 g/L) was 5.83% and 12.22% for the human and rat skin respectively.

Therefore combining the data from both the *in vivo* and the *in vitro* studies provides the following estimated human *in vivo* absorption values: 500 g/kg = 0.3%, 5 g/L = 3.6%, 0.375 g/L = 8.6%, using the formula below:

$$\text{Estimated Human } \textit{in vivo} \text{ abs \%} = \text{Rat } \textit{in vivo} \text{ abs \%} \times \frac{\text{Human } \textit{in vitro} \text{ abs \%}}{\text{Rat } \textit{in vitro} \text{ abs \%}}$$

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Table 7.6-1 Summary of the percutaneous penetration of fenhexamid as an active ingredient of a WG formulation

	Concentration of fenhexamid (g/kg or L)					
	500[a]		5[b]		0.375[c]	
Species	Human	Rat	Human	Rat	Human	Rat
***In vitro* %absorption**	0.15	1.13	0.62	4.03	5.83	12.22
***In vitro* H/R ratio**	0.13		0.60		0.48	
Estimated Human *in vivo* % bsorption	**0.27**		**3.61**		**8.59**	

[a]: using the rat *in vivo* value of 2% absorption.
[b]: using the rat *in vivo* value of 6% absorption.
[c]: using the rat *in vivo* value of 18% absorption.

IIIA 7.6.1 Dermal absorption, in vivo

Dermal absorption of fenhexamid, *in vivo*

Report:	**KIIIA 7.6.1 /01; [redacted] 1997,**
Title:	Dermal Absorption of [Phenyl-UL-^{14}C]-TM-402 50 WP formulation in male rats (preliminary and definitive phases)
Organisation:	[redacted]
Report No.:	CHW 6775-100, issued on 31st January 1997. **M-006701-01-1**
Dates of experimental work:	Start: 19th September 1996 End: 25th November 1996
Guidelines:	Environmental Protection Agency FIFRA, 40 CFR Part 158, Subdivision F, Series 85-3
Deviations:	None
GLP:	Yes

Material and methods

Rat:

Species, strain: Rat, Charles River Crl:CD®BR strain

Source: [redacted], USA.

Sex: Male.

Body weights: 182 - 219 g.

Age: Approximately 7 weeks old.

Acclimatisation & Housing: The rats were acclimated for at least one week before being placed on test. During acclimation, the animals were examined once daily for abnormalities indicative of health problems. In addition, the animals were observed at least twice daily for morbidity, mortality, and any signs of toxicity. During acclimation, the rats were housed individually in stainless steel wire-mesh, screen-bottom cages suspended on racks, with absorbent paper liners. During the test period, the rats were housed individually in metabolism cages designed for the separation and collection of urine and faeces.

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Animal identification:	Ear tags.	
Environmental conditions:	Temperature:	22 ± 3°C
	Humidity:	50 ± 20%
	Photoperiod:	12 hour light/dark cycles.

Food: Certified Rodent Diet #5002 (PMI® Feeds, Inc.) was provided ad libitum, and the lot numbers were recorded. The diet is routinely analyzed by the manufacturer for nutritional components and environmental contaminants.

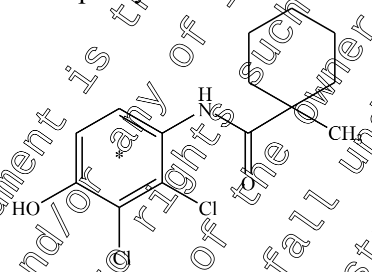
Water: Fresh water was provided ad libitum from an automatic watering system. Samples of the water are routinely analyzed by CHW for total dissolved solids, conductivity, specified microbiological content, selected elements, heavy metals, organophosphates, and chlorinated hydrocarbons. The results are on file at CHW.

Test Material:

Non-radiolabelled: Batch: T950821ELB04.
Purity = 99.2%.

Radiolabelled: [Phenyl-UL-14C]-TM-402 (fenhexamid)
Batch: 1065/1.
Specific activity: 92.7 µCI/mg.
Radiopurity of the formulation: 99.2%.

Structural formula:



^{14}C denotes position of radiolabel

Formulation: Dose suspensions for Groups 2, 5, and 6 were prepared by combining appropriate amounts of the radioactive formulation supplied by the sponsor, the non-radioactive Formulation and water. For Groups 1 and 4, the dose suspensions were prepared by suspending the appropriate amounts of the radioactive formulation in water. The dose suspensions were thoroughly mixed using magnetic stir bar, and vortex-mixing.

Treatment: At least 16 hours before dosing, the back and shoulders of each animal were shaved, and the shaved area was washed with acetone. The site for application of the test material (approximately 12.5 cm2) was defined and protected by a rectangular plastic enclosure, which was affixed to the back of each rat with cyanoacrylate-based glue. A 100% silicone sealant was applied on the outside of the enclosure for sealing purposes, and an Elizabethan collar was placed on each animal's neck to protect the dose application site.

Approximately 100 µL of the dosing suspension was applied within the enclosure. The weight of the dosing syringe was recorded before and after dosing. The test material was spread evenly across the surface of the skin site using a glass rod (spreader). The glass rod was then rinsed with approximately 3.0 mL of methanol and wiped with a gauze pad; the rinse and wipe were collected for analysis. After test material application, rubber cement was applied to the top of the enclosure and was covered with a non-occlusive filter paper cover. An Elizabethan collar was placed on the animal's neck to protect the dose application site.

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Treatment Groups

There were 6 treatment groups with Groups 1 & 2 used in the preliminary phase and Groups 3 to 6 in the definitive phase.
Groups 1 & 4 were treated at the rate of 0.2 g/L.
Groups 2 & 6 were treated at the rate of 20 g/L.
Group 5 was treated at the rate of 2 g/L.
Group 3 was treated with vehicle only.
Fours rats per group were sacrificed at 0.5, 1, 24, 10, 24 and 120 hours after application.

Sampling:

The skin wash occurred immediately before the scheduled sacrifice, with the exception of the 24-hour and 120-hour sample collection intervals, for which the skin wash procedure was performed at the 10-hour time point. Approximately 10 to 15 minutes prior to the scheduled skin wash, the rats were anaesthetized with ketamine via an intramuscular injection to the thigh. The Elizabethan collar was removed. The non-occlusive filter paper cover was removed from the plastic enclosure and placed in a 100-mL container. Twenty-five gauze pads were removed from a prelabelled, pre-tared 1000-mL plastic container and immersed in either a 2% Ivory soap solution or water. The dose application site was alternately washed and rinsed using the gauze pads and dried with four cotton-tipped applicators.

The accumulated post dose faeces and urine from each animal were collected for Groups 3 through 6. Immediately following the skin wash, all animals were anesthetized with halothane, with the exception of the animals that were to be sacrificed at 24 hours and 120 hours post dose. The definitive phase animals were then exsanguinated by cardiac puncture, and the blood was collected into heparinized tubes. Residual urine was collected from the urinary bladder and added to the urine sample. For both phases, the skin from the dose site (enclosure included) was excised and collected, and the residual carcass was retained. Cages were washed with 1% trisodium phosphate solution (TSP) and wiped with gauze pads (cage wipes) for Groups 4, 5, and 6. All samples collected were retained for radioanalysis.

Preliminary Phase (Groups 1 and 2). At sacrifice, the non-occlusive cover, enclosure, skin wash, skin at application site, and carcass were collected from each animal.

Definitive Phase (Group 3 - Control). Urine and faeces were collected from control animals at 24 hours post dose. At sacrifice, the non-occlusive cover, enclosure, skin wash, blood, residual urine from the bladder, skin at application site, and carcass were collected from each animal.

Definitive Phase (Groups 4, 5, and 6). If available, urine and faeces were collected from four animals per group per time point (0.5, 1, 2, 4, 10, 24, and 120 hours post dose sacrifice times). For the animals sacrificed at 120 hours post dose, urine and faeces were collected at 24-hour intervals until 120 hours post dose. Urine samples were collected in plastic containers surrounded by ice for the animals sacrificed after 24 hours post dose. At sacrifice (4 rats/time point), the following were collected from each animal: non-occlusive cover, enclosure, skin wash, blood, cage wash and wipe, residual urine from the bladder, skin at application site, and carcass.

Radioassay:

The amounts of radioactivity in the various samples were determined by liquid scintillation counting (LSC).

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Findings:

There were no treatment related clinical signs observed during the study. After a single topical application of the [^{14}C]-fenhexamid at 20 g/L or 0.2 g/L, the mean recoveries for rats sacrificed at 0.5 hours post dose were 96.3% for Group 1 and 97.7% for Group 2. The percentages of radioactivity detected in the skin wash were 87.7% and 97.0% for Groups 1 and 2, respectively. Amounts of 7.96% and 0.57% were retained in or on the skin at the application site for Groups 1 and 2, respectively
Unsurprisingly, no radioactivity was recovered from the control group (N° 3). The mean recovery of radioactivity was 91.6%, 96.1% and 94.8% for groups 4, 5 and 6 respectively.

The results are presented in Tables 7.6.1-1 to 7.6.1-3.

The highest direct absorption levels, at 120 hours post dose, were 14.9%, 5.52%, and 1.70% of the total dose applied for Groups 4, 5, and 6, respectively.
The indirect or potential absorption was taken as the sum of direct absorption and the amount detected in/on the skin. It ranged from 8.44% to 21.0%, 2.31% to 7.62% and 0.89% to 2.63% for Groups 4, 5, and 6, respectively.

In general, increasing absorption (expressed as % of administered radioactivity) versus exposure time within the group was noted for the lowest dose group. At higher dose levels, the highest absorption level within the groups was observed at 10 hours post dose, and it accounted for 7.62% (14.0 µg) and 2.63% (48.7 µg) for Groups 5 and 6, respectively.

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Table 7.6.1-1.: The mean distribution of radioactivity after a single topical application of [14C]-fenhexamid from a 20 g/L WP 50 formulation

Dose Group 20 g/L (n= 4 rats/group[d])	% of applied dose							
	Hours post application							
	0.5		1		2		4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT								
Cover wash	0.04	0.03	0.12	0.08	0.03	0.02	0.15	0.10
Enclosure rinse	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Skin wash [a]	96.1	1.16	93.3	2.91	93.2	1.96	93.8	0.64
SKIN COMPARTMENT								
Treated skin	0.77	0.41	1.01	0.46	1.35	0.30	1.54	0.25
SYSTEMIC COMPARTMENT								
Blood	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Carcass	0.12	0.25	0.23	0.08	0.35	0.07	0.77	0.42
Cage wash	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Cage wipe	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Urine	n.d.	n.a.	<0.005	n.a.	<0.005	n.a.	0.02	0.01
Faeces	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Total Recovered	97.0	1.02	94.7	2.50	94.9	1.90	96.3	1.05
Absorbed Indirect [b]	0.89	0.42	1.25	0.52	1.71	0.27	2.33	0.67
Absorbed Direct [c]	0.12	0.25	0.23	0.08	0.36	0.07	0.79	0.42

Dose Group 20 g/L (n= 4 rats/group)	% of applied dose					
	Hours post application					
	10		24		120	
	Mean	SD	Mean[d]	SD	Mean	SD
SURFACE COMPARTMENT						
Cover wash	0.07	0.04	0.19	0.19	0.09	0.06
Enclosure rinse	0.01	0.01	n.d.	n.a.	0.01	0.01
Skin wash [a]	88.7	4.66	92.2	2.49	91.7	2.14
SKIN COMPARTMENT						
Treated skin	1.58	0.66	0.87	0.42	0.44	0.23
SYSTEMIC COMPARTMENT						
Blood	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Carcass	0.99	0.21	1.14	1.06	n.d.	n.a.
Cage wash	n.d.	n.a.	n.d.	n.a.	0.06	0.07
Cage wipe	n.d.	n.a.	n.d.	n.a.	0.03	0.02
Urine	0.04	0.01	0.08	0.02	0.28	0.12
Faeces	0.02	0.04	0.48	0.09	1.32	0.22
Total Recovered	91.4	4.37	95.0	3.68	94.0	2.42
Absorbed Indirect [b]	2.63	0.63	2.57	1.30	2.14	0.38
Absorbed Direct [c]	1.02	0.19	1.70	0.97	1.70	0.33

n.d. = not detectable, n.a. = not applicable, SD = standard deviation

[a] Skin wash at 10 hours

[b] Total radioactivity minus radioactivity from non-occlusive cover, enclosure rinse and skin wash.

[c] Total radioactivity from blood, carcass, cage wash, cage wipe, urine and faeces.

[d] Animal N° C-4981 was excluded from all calculations because the skin wash was not performed before sacrifice.

Table 7.6.1-2.: The mean distribution of radioactivity after a single topical application of [14C]-fenhexamid from a 2 g/L WP 50 formulation

Dose Group 2 g/L (n= 4 rats/group)	% of applied dose							
	Hours post application							
	0.5		1		2		4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT								
Cover wash	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Enclosure rinse	0.16	0.05	0.49	0.32	0.10	0.05	0.18	0.16
Skin wash [a]	93.2	1.35	91.8	4.66	92.1	1.76	90.5	3.98
SKIN COMPARTMENT								
Treated skin	1.88	0.21	3.11	1.61	3.97	0.77	4.16	1.90
SYSTEMIC COMPARTMENT								
Blood	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Carcass	0.42	0.11	0.40	0.32	0.87	0.28	1.28	0.48
Cage wash	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Cage wipe	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Urine	<0.005	n.a.	<0.005	n.a.	0.02	0.01	0.03	0.01
Faeces	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Total Recovered	95.6	1.49	95.8	3.80	97.0	2.07	96.2	2.47
Absorbed Indirect [b]	2.31	0.32	3.51	1.62	4.86	1.06	5.47	2.17
Absorbed Direct [c]	0.42	0.11	0.40	0.32	0.89	0.29	1.31	0.48

Dose Group 2 g/L (n= 4 rats/group)	% of applied dose					
	Hours post application					
	10		24		120	
	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT						
Cover wash	0.03	0.00	0.03	0.00	0.07	0.09
Enclosure rinse	0.25	0.25	0.29	0.09	0.34	0.11
Skin wash [a]	87.9	1.72	86.9	2.76	90.3	4.63
SKIN COMPARTMENT						
Treated skin	5.01	1.61	3.49	0.32	1.40	0.25
SYSTEMIC COMPARTMENT						
Blood	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Carcass	2.52	0.69	2.19	0.68	n.d.	n.a.
Cage wash	0.02	0.03	0.06	0.05	0.25	0.11
Cage wipe	n.d.	n.a.	0.02	0.02	0.08	0.03
Urine	0.07	0.03	0.22	0.05	0.93	0.29
Faeces	n.d.	n.a.	1.47	0.34	4.25	1.15
Total Recovered	95.7	1.48	94.7	3.27	97.6	3.21
Absorbed Indirect [b]	7.62	2.02	7.45	0.82	6.92	1.64
Absorbed Direct [c]	2.60	0.71	3.96	0.56	5.52	1.50

n.d. = not detectable, n.a. = not applicable, SD = standard deviation

[a] Skin wash at 10 hours

[b] Total radioactivity minus radioactivity from non-occlusive cover, enclosure rinse and skin wash.

[c] Total radioactivity from blood, carcass, cage wash, cage wipe, urine and faeces.

Table 7.6.1-3.: The mean distribution of radioactivity after a single topical application of [14C]-fenhexamid from a 0.2 g/L WP 50 formulation

Dose Group 0.2 g/L (n= 4 rats/group)	% of applied dose							
	Hours post application							
	0.5		1		2		4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT								
Cover wash	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Enclosure rinse	0.16	0.12	0.13	0.03	0.13	0.09	0.31	0.24
Skin wash [a]	86.5	2.16	77.1	3.23	76.9	1.82	74.8	0.93
SKIN COMPARTMENT								
Treated skin	8.44	1.88	10.2	1.85	8.95	0.59	9.46	0.62
SYSTEMIC COMPARTMENT								
Blood	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Carcass	n.d.	n.a.	2.83	3.22	5.12	1.81	6.85	1.48
Cage wash	n.d.	n.a.	n.d.	n.a.	0.04	0.07	0.05	0.12
Cage wipe	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Urine	<0.005	n.a.	0.02	0.03	0.09	0.10	0.15	0.12
Faeces	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Total Recovered	95.1	2.70	90.3	1.19	91.3	2.06	91.6	2.29
Absorbed Indirect [b]	8.44	1.87	13.0	4.15	14.2	1.30	16.5	1.47
Absorbed Direct [c]	<0.005	n.a.	2.86	3.24	5.25	1.85	7.05	1.39

Dose Group 0.2 g/L (n= 4 rats/group)	% of applied dose					
	Hours post application					
	10		24		120	
	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT						
Cover wash	0.04	0.05	0.02	0.04	0.07	0.00
Enclosure rinse	0.64	0.29	0.15	0.04	0.21	0.15
Skin wash [a]	70.9	4.35	69.9	4.70	70.3	4.27
SKIN COMPARTMENT						
Treated skin	10.1	1.70	8.06	1.55	6.05	2.05
SYSTEMIC COMPARTMENT						
Blood	n.d.	n.a.	0.03	0.04	n.d.	n.a.
Carcass	9.37	2.12	5.72	3.88	n.d.	n.a.
Cage wash	n.d.	n.a.	0.28	0.14	0.54	0.55
Cage wipe	n.d.	n.a.	0.13	0.04	0.22	0.44
Urine	0.30	0.11	1.21	0.66	2.58	2.68
Faeces	0.08	0.16	4.82	1.66	11.6	11.7
Total Recovered	91.4	3.48	90.3	6.33	91.5	2.09
Absorbed Indirect [b]	19.8	1.98	20.3	3.89	21.0	2.76
Absorbed Direct [c]	9.73	2.07	12.2	4.11	14.9	4.77

n.d. = not detectable, n.a. = not applicable, SD = standard deviation
[a] Skin wash at 10 hours
[b] Total radioactivity minus radioactivity from non-occlusive cover, enclosure rinse and skin wash.
[c] Total radioactivity from blood, carcass, cage wash, cage wipe, urine and faeces.

The amount of dermal absorption of fenhexamid was not linear to the dose. Maximum dermal absorption of fenhexamid in male rats was calculated using an exponential saturation model that disregards residues at the skin test sites. The maximum excretion of the test material was estimated by extrapolating the amount of dose recovered in excreta to a time at which the cumulative excretion curve reached a plateau. Maximum dermal absorption values were determined as 18.26%, 5.73%, and 1.82% of the radioactive dose for Groups 4, 5, and 6, respectively.

Conclusion:
The overall recoveries for rats dermally dosed with [Phenyl-UL-^{14}C]-fenhexamid at 0.2 g/L (1.38 µg/cm^2), 2 g/L (14.7 µg/cm^2), and 20 g/L (148 µg/cm^2) were 91.6%, 96.1%, and 94.8% respectively, with the majority of the radioactivity (75.2%, 90.4%, and 92.7%) being found in the skin washes. The dose area was 12.5 cm^2/animal, and 6.05% to 10.2%, 1.40% to 5.01% and 0.44% to 1.58% of the total dose applied was detected in/on the skin of the application site for Groups 4, 5, and 6, respectively.
Not a data requirement according to Regulation 1107/2009/EEC or Directive 91/414/EEC.

The direct absorption, at 120 hours post dose, was up to 14.9%, 5.52%, and 1.70% of total dose applied for Groups 4, 5, and 6, respectively. Indirect absorption of fenhexamid increased with time for the lowest dose group, Group 4, with the highest absorption occurring at 120 hours post dose, and accounting for 21.0% (3.61 (µg) of the total dose applied. At higher dose levels, the highest indirect absorption level within the groups was observed at 10 hours post dose, accounting for 7.62% (14.0 µg) and 2.63% (48.7 µg) of the total dose applied for Groups 5 and 6, respectively.

The extrapolated maximum dermal absorption of fenhexamid in male rats was 18.26%, 5.73%, and 1.82% of the total dose applied for Groups 4, 5, and 6, respectively. The amount of dermal absorption of fenhexamid was not linear to the dose.

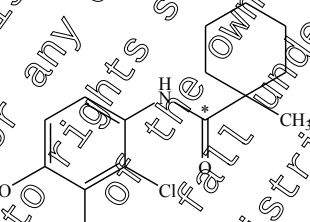
IIIA 7.6.2 Comparative dermal absorption, in vitro using rat and human skin

Report:	**KIIIA 7.6.2/01; [redacted] 2009**
Title:	Fenhexamid WG 50: [^{14}C]-fenhexamid: Comparative *in vitro* dermal absorption study using human and rat skin,
Report N°:	SA 09113, issued on 17th December 2009
Document N°:	Unpublished, **M-360644-01-1**
Dates of experimental work:	Start: 18th August 2009 End: 16th September 2009
Guidelines:	OECD guideline for the testing of chemicals; skin absorption: *in vitro* Method 428 (April 2004), OECD Environmental health and safety publications series on testing and assessment N°28, Guidance document for the conduct of skin absorption studies (March 2004), EC guidance document on dermal absorption Sanco/222/2000 rev.7, (2004).
Deviations:	None
GLP	Yes

Material and methods

Rat skin:	
Species, strain:	Rat, Wistar Rj: WI (IOPS HAN).
Source:	[redacted] (France).
Sex:	Male.
Number:	10
Anatomical site:	Dorsal
Rat Skin Preparation:	Each animal was killed by cervical dislocation. After sacrifice the skin was clipped and removed for use in the study. The dorsal skin was dermatomed by use of a mini-dermatome to obtain samples of ca 430 to 510 µm in thickness.
Human skin:	Source: Biopredic, Rennes, France. Number and sex: 7 donors, female. Anatomical region: Abdomen. Thickness: 415 to 550 µm.

Test Material:

Non-radiolabelled:	Batch: KTS10158-1-1. Purity = 98.7%.
Radiolabelled:	[carboxamide-^{14}C] fenhexamid Batch: KATH 6755. Specific activity: 4.18 MBq/mg. Radiopurity of the formulation: >99%.
Structural formula:	 *denotes position of radiolabel
Formulation:	The formulation used in this experiment was the a fenhexamid WG 50 formulation (specification number 102000007271) used at three nominal concentrations: 500 g a.s./kg, 5 g a.s./L and 0.375 g a.s./L.
Test system:	A flow-through diffusion cell system ([redacted], France) was used to study the absorption of the test substance (exposure area of 1 cm2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid was Eagle's medium supplemented with 5% bovine serum albumin and gentamycin (50 mg/L) at a pH of ca. 7.4. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2°C (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.
Skin integrity:	Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Tewameter TM300 system, Courage & Khazaka) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 15 g/hm² were considered potentially damaged and were not

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used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

Treatment: The dose preparation was applied to the split-thickness skin sample with a pipette at the rate of approximately 5 mg/cm2 or10 µL/cm2 exposed skin. The dose preparations were assayed for radioactivity content (by LSC) by using dose checks (surrogate dose) taken before, during and after the dosing process.

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

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

Findings:

The fenhexamid was demonstrated to be soluble in the receptor fluid up to the maximum amount formulation applied. The solubility in the receptor fluid was deemed to be sufficient to reduce any risk of back diffusion.

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

Good recovery data were obtained, with mean total recoveries of radioactivity in the range of 102.2% to 104.1% of the applied dose.

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For the neat formulation, almost all the radioactivity was removed by swabbing (103.7% and 101.0% of dose for human and rat skin, respectively) and by removal of the surface dose (0.06% and 1.45% of dose for human and rat skin, respectively). For the intermediate representative dilution, almost all the radioactivity was also removed by swabbing (102.5% and 100.7% of dose for human and rat skin, respectively) and by removal of the surface dose (0.12% and 0.84% of dose for human and rat skin, respectively). For the low representative dilution, the vast majority of the radioactivity was also removed by swabbing (95.8% and 85.8% of dose for human and rat skin, respectively) and by removal of the surface dose (0.64% and 5.10% of dose for human and rat skin, respectively).

Since the swabbing procedure was intended to reflect a simple washing regimen at the end of the working day, the amount of radioactivity retrieved in this compartment was considered to be non-absorbed. Since the material recovered in the surface tape-strips (first two tape-strips) could be associated with surface residues following incomplete removal of the dose after an 8-hour exposure period and/or material from the superficial stratum corneum, the amount of radioactivity retrieved in this compartment was considered to be non-absorbed.

Based on these results, the mean total amount of radioactivity considered as non-absorbed for the neat formulation was 104.0% and 102.7% dose in the human and rat skin, respectively, the mean total amount of radioactivity considered as non-absorbed for the intermediate representative dilution was 102.7% and 101.6% dose in the human and rat skin, respectively and the mean total amount of radioactivity considered as non-absorbed for the low representative dilution was 96.4% and 90.9% dose in the human and rat skin, respectively.

The overall amount of [^{14}C]-fenhexamid considered to be directly absorbed was represented by the radioactivity present in the receptor fluid, receptor fluid at termination time and receptor chamber. This accounted for means of 0.04% (human) and 0.12% (rat) of the dose applied for the neat formulation, for means of 0.50% (human) and 0.84% (rat) of the dose applied for the intermediate representative dilution and for means of 4.59% (human) and 5.19% (rat) of the dose applied for the low representative dilution.

The amount of radioactivity recovered in the skin (after tape-stripping and including surrounding skin) in the neat formulation accounted for means of 0.05% (human) and 0.25% (rat) of the applied dose, for means of 0.04% (human) and 0.06% (rat) of the dose applied for the intermediate representative dilution and for means of 0.56% (human) and 2.05% (rat) of the dose applied for the low representative dilution.

The mean quantity of radioactivity recovered in the stratum corneum with the neat formulation accounted for 0.05% (human) and 0.76% (rat) of the applied dose, for 0.08% (human) and 0.14% (rat) of the applied dose for the intermediate representative dilution and for 0.68% (human) and 4.98% (rat) of the applied dose for the low representative dilution.

The radioactivity found in the skin compartment (skin, surrounding skin and stratum corneum) could be considered to be potentially absorbable. Therefore, the mean total amount of radioactivity considered to be potentially absorbable for the neat formulation was 0.15% and 1.13% dose for the

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human and rat skin, respectively. The mean total amount of radioactivity considered to be potentially absorbable for the intermediate representative dilution was 0.62% and 1.03% dose for the human and rat skin respectively. The mean total amount of radioactivity considered to be potentially absorbable for the low representative dilution was 5.83% and 12.22% dose for the human and rat skin respectively.

Table 7.6.2-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]-fenhexamid in an WG formulation at the rates of 500 g/kg, 5 g/L and 0.375 g/L to human and rat skin samples.

(Results expressed in terms of percentage of applied radioactivity).

	Distribution of radioactivity (% dose)											
Dose Levels	Neat formulation: High dose (SYP13458, 500 g/kg)				Dilution: Intermediate dose (SYP13461, 5 g/L)				Dilution: Low dose (SYP13463, 0.375 g/L)			
Species	Human (n=6)		Rat (n=6)		Human (n=6)		Rat (n=6)		Human (n=6)		Rat (n=6)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT												
Skin swabs (8h)	103.68	2.02	100.95	2.86	102.4	2.12	100.6	2.34	92.07	9.27	83.72	6.55
Skin swabs (24h)[a]	0.03	0.03	0.08	0.05	0.07	0.09	0.08	0.06	3.70	4.12	2.05	1.93
Surface Dose (tape-strips 1 & 2)	0.06	0.04	1.45	0.90	0.12	0.18	0.84	0.57	0.64	0.56	5.10	1.93
Donor chamber	0.18	0.13	0.23	0.18	0.03	0.07	0.05	0.03	n.d.	n.a.	0.04	0.10
Total % non-absorbed	*103.95*	*2.02*	*102.71*	*3.00*	*102.67*	*2.13*	*101.58*	*2.41*	*96.41*	*10.16*	*90.91*	*7.10*
SKIN COMPARTMENT												
Skin [b]	0.05	0.03	0.25	0.33	0.04	0.04	0.06	0.08	0.56	0.50	2.05	3.73
Stratum corneum [c]	0.05	0.04	0.76	0.51	0.08	0.07	0.14	0.28	0.68	0.64	4.98	3.10
Total % at dose site	*0.10*	*0.05*	*1.01*	*0.61*	*0.12*	*0.09*	*0.19*	*0.29*	*1.24*	*0.81*	*7.02*	*4.85*
RECEPTOR COMPARTMENT												
Receptor fluid (0-24h)	0.04	0.02	0.12	0.03	0.50	0.35	0.84	0.37	4.59	2.18	5.19	2.13
Receptor chamber	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Total % directly absorbed [d]	*0.04*	*0.02*	*0.12*	*0.03*	*0.50*	*0.35*	*0.84*	*0.37*	*4.59*	*2.18*	*5.19*	*2.13*
Total % Potentially Absorbable	*0.15*	*0.05*	*1.13*	*0.61*	*0.62*	*0.36*	*1.03*	*0.47*	*5.83*	*2.33*	*12.22*	*5.30*
TOTAL % RECOVERY	104.1	2.03	103.8	2.38	103.3	2.17	102.6	1.91	102.2	3.65	103.1	1.81

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

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Conclusion:

The dermal penetration of [14C]-fenhexamid through human and rat dermatomed skin from the WG 50 formulation was investigated at three concentrations corresponding to the neat product (500 g /kg) and to two representative dilutions (5 and 0.375 g/L), respectively.

The mean percentage of [14C]-fenhexamid considered to be potentially absorbable (directly absorbed plus total remaining at dose site) over a period of 24 hours for the neat fenhexamid WG 50 formulation was 0.15% and 1.13% for the human and rat skin, respectively, yielding a factor difference of 7.5 between the two species for the neat product.

The mean percentage of [14C]-fenhexamid considered to be potentially absorbable (directly absorbed plus total remaining at dose site) over a period of 24 hours for the intermediate representative dilution of the fenhexamid WG 50 formulation was 0.62% and 1.03% for the human and rat skin respectively, yielding a factor difference of 1.7 between the two species for the intermediate dose formulation.

The mean percentage of [^{14}C]-fenhexamid considered to be potentially absorbable (directly absorbed plus total remaining at dose site) over a period of 24 hours for the representative low representative dilution of the fenhexamid WG 50 formulation was 5.83% and 12.22% for the human and rat skin respectively, yielding a factor difference of 2.1 between the two species for the low dose formulation.

IIIA 7.7 Dislogeable residues

IIIA 7.7.1 Dislogeable residues - foliar

Not a data requirement according to Regulation 1107/2009/EEC or Directive 91/414/EEC.

IIIA 7.7.2 Dislogeable residues - soil

Not a data requirement according to Regulation 1107/2009/EEC or Directive 91/414/EEC.

IIIA 7.7.3 Dislogeable residues - indoor surface re-volatization

Not a data requirement according to Regulation 1107/2009/EEC or Directive 91/414/EEC.

IIIA 7.8 Epidemiology

Not a data requirement according to Regulation 1107/2009/EEC or Directive 91/414/EEC.

IIIA 7.9 Data on formulants

IIIA 7.9.1 Material safety data sheet for each formulant

Safety data sheet for each formulant is provided in document H of this AIR2 submission.

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IIIA 7.9.2 Available toxicological data for each formulant

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

IIIA 7.10 Domestic animal/livestock safety

Not a data requirement according to Regulation 1107/2009/EEC or Directive 91/414/EEC.

IIIA 7.11 Other/special studies

None necessary.

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