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- Flutolanil -

B.6 Toxicology and metabolism data and assessment of risks for humans

Rapporteur Member State: The Netherlands

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Draft Assessment Report and Proposed decision of the Netherlands prepared in the context of the possible approval of flutolanil under Regulation (EC) 1107/2009

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B.6 Toxicology and metabolism data and assessment of risks for humans

There are two versions of 'MONCUT 40 SC'; with or without a coloured dye depending upon the target market and field of use. The version without a dye is known by the development code names "40SC (EU)", "40SC (NPE-free)" or "EXP10066A". The version with a dye is known by the development code name "40SC (EU-D)".

Comment RMS: the formulation composition of the representative formulation MONCUT 40SC changed over time. Although the composition of the representative product since the inclusion of flutolanil in Annex I of Dir 91/414/EEC is provided in Volume 4, it has to be made clear by the notifier which formulation is the representative formulation used for the acute toxicity studies as this remains unclear.

B.6.1 Acute toxicity

The table below summarises the results of acute toxicity testing with Moncut 40SC.

Table B.6.1-1: Summary of acute toxicity of Moncut 40 SC

Endpoint	Value	Classification	Reference
Acute oral toxicity	LD_{50} >2000 mg/kg	None	[redacted] (2007a)
Acute dermal toxicity	LD_{50} >4000 mg/kg	None	[redacted] (1989)
Acute Inhalation toxicity	LD_{50}> 5 mg/L air	None	Theoretical consideration
Skin irritation	Not irritating	None	[redacted] (2007b)
Eye Irritation	Not irritating	None	[redacted] (2007c)
Skin sensitisation	Not sensitising	None	[redacted] (2007)

B.6.1.1 Oral

Previous evaluation	Newly submitted for the purpose of the renewal.
Evaluation of the RMS	Study is considered acceptable and in accordance to OECD guideline 423. A GLP certificate is not included in the study report but the performing lab is known to be GLP certified. Classification for acute oral toxicity according to Regulation (EC) No 1272/2008 is not required.

reference	:	[redacted] (2007a)	exposure	:	By gavage
Report number	:	T-3117	doses	:	2000 mg/kg
test substance	:	Flutolanil 40SC	GLP	:	Yes
species	:	Fischer (F344/DuCrlCrlj) rats	guideline	:	OECD 423 (2001)
group size	:	3/ step	acceptability	:	Acceptable

Executive Summary

An acute oral toxicity study was conducted on rats using the Acute Toxic Class Method. All dose levels in this study refer to mg formulation/kg bw.

Step I: Three female rats received an oral dose, by gavage, of Flutolanil 40SC at a level of 2000mg/kg on Day 0. No animal died during the 14-day observation period.

Step II: A further three female rats were dosed, by oral gavage, with Flutolanil 40SC at a level of 2000mg/kg on Day 0. No animal died during the 14-day observation period.

At gross necropsy, diaphragmatic nodules in the liver and spleen were observed in one animal. These finding are considered to be inherent or spontaneous changes that are sometimes observed in this strain of rat, therefore this observation is not judged to be dose related.
Based on the above results, the median lethal dose (LD_{50}) to female rats of Flutolanil 40SC after a single oral dose is >2000mg/kg.
Flutolanil 40SC is therefore not classified for oral toxicity according Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1.	**Test materials:**	Flutolonil 40SC
	Description:	Milky-white opaque liquid
	Lot/Batch:	7AE8802F
	Purity:	41.0%
	Stability:	Stable
2.	**Vehicle:**	Distilled water
3.	**Test animals**	
	Species:	Rat
	Strain:	Fischer (F344/DuCrlCrlj)
	Age:	8 - 9 weeks
	Weight at dosing:	111.3g to 123.2g
	Source:	[redacted]
	Acclimatisation period:	8 - 13 days
	Diet:	Pellet diet Labo-MR stock
	Water:	Local tap water, *ad libitum*
	Housing:	Housed individually or in groups of up to 3 in FRP resin cages (approx. 380mm×260mm×180mm height) with wire mesh floors.
4.	**Environmental conditions**	
	Temperature:	19°C – 25°C
	Humidity:	30% - 70% relative humidity
	Air changes:	12-15 per hour
	Photoperiod:	12 hours of artificial light in each 24-hour period.

B. STUDY DESIGN AND METHODS

1. In life dates:

02 - 27 February 2007

2. Animal assignment and treatment

Step I: Three female rats received a single oral dose of the test item by gavage at 2000mg/kg body weight.

Step II: A further three females were treated by oral gavage at a dose of 2000mg/kg body weight.

All animals were observed for clinical signs of toxicity 0.25, 0.5, 1, 3 and 6 hours after dosing (Day 0) and then once daily until Day 14.
All surviving animals were sacrificed on Day 14 and subjected to gross/macroscopic necropsy.

3. Statistics

Group means and standard deviations of bodyweights were calculated by Microsoft© Excel 2000.

II. RESULTS AND DISCUSSION

A. MORTALITY

There were no deaths prior to gross necropsy.

B. CLINICAL OBSERVATIONS

No overt signs of clinical toxicity were observed.

C. BODYWEIGHT

The mean bodyweight of animals in Step I increased from 114.4g (Day 0) to 154.3g (Day 14)

The mean bodyweight of animals in Step II increased from 119.5g (Day 0) to 157.0g (Day 14)

D. NECROPSY

Diaphragmatic nodules in the liver and spleen were observed in one animal. These finding are considered to be inherent or spontaneous changes that are sometimes observed in this strain of rat, therefore this observation is not judged to be dose related.

E. DEFICIENCIES

None

III CONCLUSIONS

The acute oral LD50 of Flutolanil 40SC was determined to be >2000mg/kg. Flutolanil 40SC is therefore not classified as harmful by ingestion according to Regulation (EC) 1272/2008.

B.6.1.2 Dermal

Previous evaluation	DAR 2005
Evaluation of the RMS	No comments on previous study evaluation. The formulation composition of the representative formulation MONCUT 40SC changed over time. It should be noted that the formulation used in this study is different to the current specification, i.e. this formulation contained NPE and some other co-formulants. Therefore, it remains questionable if the results are can be considered a valid and acceptable assessment for the classification of the dermal toxicity of Moncut 40 SC. However, considering that flutolanil and the coformulants have not been classified for acute dermal toxicity, classification for this acute toxicity endpoint is not required according to the calculation rules.

reference : [redacted] (1989) exposure : dermal

Report number	:	T-3072	doses	:	4000 mg/kg kg/bw
test substance	:	Flutolanil 40 SC	GLP	:	yes
species	:	Rats	guideline	:	OECD guideline 402 (1987)
group size	:	5/ sex	acceptability	:	acceptable

Executive Summary

The dorsal fur of ten rats (five males and five females) was clipped and the test material equal to 4000 mg/kg bw was applied using a semi-occlusive dressing. After twenty-four hours the dressing was removed and the skin washed with tissue moistened with tap water. The animals were observed daily for 14 days after which time gross necropsy was performed.

No mortalities were noted. On Days 1 and 2, two rats were observed to display lethargic behaviour but by Day 3 all animals behaved normally. On Days 2–5 slight erythema and swelling was noted in two female rats and crust formation was also noted in one female rat. By Day 8, all effects had fully reversed.

At gross necropsy, white particles were found in the bladders of two rats (both males). No other findings were noted.

Based on the above results, the median lethal dose (LD_{50}) of Flutolanil 40 SC after a single twenty-four dermal application is >4000 mg/kg bw.

Flutolanil 40 SC is therefore not classified for dermal toxicity under Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1.	**Test materials:**	Flutolonil 40SC
	Description:	White opaque liquid
	Lot/Batch:	F-001
	Purity:	Not indicated
	Stability:	Stable
2.	**Vehicle:**	None
3.	**Test animals**	
	Species:	Rat
	Strain:	Wistar SPF
	Age:	Approx. 7 weeks
	Weight at dosing:	Males: 212–247 g Females: 186–209g
	Source:	[redacted]
	Acclimatisation period:	5 days
	Diet:	Pellet diet (Kliba 343)
	Water:	Local tap water, *ad libitum*
	Housing:	Housed individually in polycarbonate cages containing sawdust.
4.	**Environmental conditions**	
	Temperature:	21°C ±3ºC
	Humidity:	30% - 70% relative humidity
	Air changes:	15 per hour
	Photoperiod:	12 hours of artificial light in each 24-hour period.

B. STUDY DESIGN AND METHODS

1. In life dates:

25 October – 8 November 1989

2. Animal assignment and treatment

The dorsal fur of ten rats (five males & five females) was clipped equal to an area of approximately 5cm×7cm the day before dosing.

Test material at a dose of 4000 mg/kg bw was applied to the skin with an area of approximately 25cm² (5×5 cm) for males and 18cm² (3.5×5 cm) for females. The application area was covered by a gauze patch fixed to aluminium foil which was secured by an elasticated bandage.

After twenty-four hours, the bandage and gauze were removed and the treated skin was wiped with a tissue moistened with tap-water.

The animals were observed twice daily for mortality and behaviour and weighed on Days 8 and 15. On Days 5, 8 and 15 records of skin reactions were taken.

3. Statistics

As there were no mortalities, no statistical analysis was conducted.

II. RESULTS AND DISCUSSION

A. MORTALITY

There were no deaths prior to gross necropsy.

B. CLINICAL OBSERVATIONS

The table below shows the number of rats with clinical findings on day following application of Flutolanil 40 SC.

Table B.6.1.2-1: clinical observations in rats treated with Moncut 40SC

Sex	Observation	Day														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Male	lethargy	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0
	Slight erythema	0	0	-	-	0	-	-	0	-	-	-	-	-	-	0
	Slight swelling	0	0	-	-	0	-	-	0	-	-	-	-	-	-	0
	Crust formation	0	0	-	-	0	-	-	0	-	-	-	-	-	-	0
Female	Lethargy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Slight erythema	0	1	-	-	1	-	-	0	-	-	-	-	-	-	0
	Slight swelling	0	1	-	-	0	-	-	0	-	-	-	-	-	-	0
	Crust formation	0	0	-	-	1	-	-	0	-	-	-	-	-	-	0

'-' No observation recorded

C. BODYWEIGHT

The mean bodyweight of males increased from 235 g (SD 14.3 g) to 308 (SD 13.8 g) from Day 0 to Day 15. The mean bodyweight of females increased from 197 g (SD 8.3 g) to 223 (SD 6.9 g) from Day 0 to Day 15

D. NECROPSY

White particles were observed in the bladders of two male rats. No other abnormalities were noted.

E. DEFICIENCIES

None

III CONCLUSIONS

The acute dermal LD_{50} of Flutolanil 40SC was determined to be >4000mg/kg bw.

Flutolanil 40SC is therefore not classified for dermal toxicity under Regulation (EC) 1272/2008.

B.6.1.3 Inhalation

Previous evaluation	Newly submitted in support of renewal
Evaluation of the RMS	Calculation rules are considered acceptable. Classification according to Regulation (EC) No. 1272/2008 is not required.

A study to determine acute inhalation toxicity shall be carried out where the plant protection product:

(a) is a gas or liquified gas;

(b) is a smoke generating plant protection product or fumigant;

(c) is used with fogging/misting equipment;

(d) is a vapour releasing plant protection product;

(e) is supplied in an aerosol dispenser;

(f) is in a form of a powder or granules containing a significant proportion of particles of diameter <50 µm (> 1% on a weight basis),

(g) is to be applied from aircraft in cases where inhalation exposure is relevant;

(h) contains an active substance with a vapour pressure > 1 × 10-2 Pa and is to be used in enclosed spaces such as warehouses or glasshouses;

(i) is to be applied by spraying.

The acute inhalation LC_{50} of flutolanil is >5.98 g/L air and the vapour pressure of flutolanil is low, 4.1×10^{-7} Pa at 20ºC. Moncut SC is a soluble concentrate that is applied by in planter treatment before catching up by planting chains and by broadcast application with boom sprayer, followed by soil incorporation. Moncut 40SC thus does not meet any of the above requirements except that it is

applied by spraying. When applying Moncut 40SC by spraying, it is diluted with water, making it unlikely to generate a significant proportion of particles in the respirable range (< 50µm). Considering this and taking into account animal welfare, the RMS did not considered it justified to perform a study and therefore the calculation rules were applied by the RMS. None of the coformulants are classified for inhalation toxicity (see Doc J). Classification according to Regulaction (EC) No. 1272/2008 is not required.

B.6.1.4 Skin irritation

Previous evaluation	Study newly submitted in support of the evaluation.
Evaluation of the RMS	The study is considered acceptable and performed according to OECD 404. Classification according to regulation (EC) No. 1272/2008 is not required. **RMS:** According to Commission Regulation (EU) No. 284/2013 a weight-of-evidence analysis shall be performed on the existing relevant data, before undertaking in vivo studies for corrosion/irritation of the plant protection product. Where insufficient data are available, they can be developed through application of sequential testing. However, such a tiered approach was not followed as an in vivo study was performed without any in vitro data being available. However, considering that the study was carried out in 2007 prior to the adoption of the new data requirements the study is considered to be acceptable.

reference	:	[redacted] (2007b)	exposure	:	Topical application
Report number	:	T-3118	doses	:	0.5 ml undiluted material
test substance	:	Flutolanil 40SC	GLP	:	yes
species	:	rabbits	guideline	:	in accordance with OECD 404 (2002)
group size	:	3	acceptability	:	acceptable

Executive Summary

Three female rabbits had the fur clipped from the dorsal area. The test item (0.5mL) was applied by topical application to the exposed skin and covered by a semi-occlusive dressing for 4 hours. After this time the dressing was removed and the site gently washed with warm water.

The scoring of skin reactions was performed at approximately 1, 24, 48 and 72 hours after patch removal. No erythema or oedema was recorded on any animal.

There were no mortalities and no overt clinical signs of toxicity were observed throughout the study.

The body weights gains of all rabbits were considered to be within the normal range of variability.

Flutolanil 40SC is not classified as a skin irritant under Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Flutolanil 40SC
Description: Milky-white opaque liquid
Lot/Batch: 7AE8802F

	Purity:	41.0%
	Stability of test compound:	Stable
2.	**Vehicle:**	Test material dosed as supplied
3.	**Test animals**	
	Species:	Rabbit
	Strain:	Japanese white (Kbl: JW)
	Age:	9-10 weeks
	Weight at dosing:	2.05– 2.13kg
	Source:	[redacted]
	Acclimatisation period:	13 days
	Diet:	Pellet diet Labo-R stock, *ad libitum*
	Water:	Filtered tap water, *ad libitum*
	Housing:	Housed individually wire mesh bottomed FRP cages (380mm×545mm×455mm high)
4.	**Environmental conditions**	
	Temperature:	17 – 23°C
	Humidity:	30 – 70% relative humidity
	Air changes:	12 to 15 per hour
	Photoperiod:	12 hours light in each 24 hour period

B. STUDY DESIGN AND METHODS

1. In life dates:

14 – 19 February 2007

2. Animal assignment and treatment

The day before treatment, the fur on the dorsal part of the test animal was removed by electric clippers. Initially only one rabbit was treated and, since no severe skin reactions were observed in this rabbit, either immediately or after the 4-hour exposure or for a period of 48 hours thereafter, the test was completed using two further rabbits.

Test material (0.5mL), as supplied, was uniformly mounted on surgical lint (2.5cm×2.5cm). The lint was placed on the exposed skin and covered with a semi-occlusive dressing.
After approximately 4 hours exposure, the dressing was removed and the skin was gently cleaned with warm water. The skin was observed and scored for erythema and oedema according to the Draize score at approximately 1, 24, 48 and 72 hours after removal of the dressing.

II. RESULTS AND DISCUSSION

A. FINDINGS

Irritation indices following a topical treatment of Flutolanil 40SC to the skin of Rabbits are shown in the tables below.

Table B.6.1.4-1: Erythema indices following topical treatment with MONCUT 40SC

	Erythema	Positive responder

Animal No.	1h	24h	48h	72h	Mean score >2.3
001F	0	0	0	0	No
		Mean score = 0			
002F	0	0	0	0	No
		Mean score = 0			
003F	0	0	0	0	No
		Mean score = 0			

Table B.6.1.4-2: Oedema indices following topical treatment with MONCUT 40SC

	Oedema				Positive responder
Animal No.	1h	24h	48h	72h	Mean score >2.3
001F	0	0	0	0	No
		Mean score = 0			
002F	0	0	0	0	No
		Mean score = 0			
003F	0	0	0	0	No
		Mean score = 0			

Clinical signs

No overt signs of systemic toxicity were observed.

III. CONCLUSIONS

Flutolanil 40SC is not classified as a dermal irritant under Regulation (EC) 1272/2008.

B.6.1.5 Eye irritation

Previous evaluation	Study newly submitted in support of the evaluation.
Evaluation of the RMS	The study is considered acceptable and is performed according to OECD 405. Minor irritation to the eyes of the testes animals were observed which was completely reversible. Based on the study classification for eye irritation is not required according to regulation (EC) No. 1272/2008. **RMS:** According to Commission Regulation (EU) No. 284/2013 a weight-of- evidence analysis shall be performed on the existing relevant data before undertaking in vivo studies for eye corrosion/irritation of the plant protection product. Where available data are considered insufficient, further data may be developed through application of sequential testing. However, such a tiered approach was not followed as an in vivo study was performed without any in vitro data being available. However, considering that the study was carried out in 2007 prior to the adoption of the new data requirements the study is considered to be acceptable.

Report number	:	T-3119	doses	:	0.1 mL
test substance	:	Flutolanil 40SC	GLP	:	Yes
species	:	rabbits	guideline	:	In accordance to OECD 405 (2002)
group size	:	3	acceptability	:	acceptable

Executive Summary

Three Japanese white rabbits were administered a single ocular dose of 0.1mL of Flutolanil 40SC into the conjunctival sac of the left eye.

The eyes were assessed for ocular reactions 1, 24, 48 and 72 hours after test item administration. Slight redness was observed in the conjunctivae from 1 to 48 hours after instillation. This reaction disappeared by the 72 hours appraisal. Slight chemosis and discharge was observed at 1 hour after instillation, but these reactions disappeared by 24 hours post instillation.

Flutolanil 40SC is not classified as an eye irritant under Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Flutolanil 40SC
Description: Milky-white opaque liquid
Lot/Batch: 7AE8802F
Purity: 41.0%
Stability of test compound: Stable.
2. Vehicle: Test material dosed as supplied.
3. Test animals
Species: Rabbit.
Strain: Japanese white (Kbl: JW).
Age: 9 weeks
Weight at dosing: 2.02 – 2.15kg
Source: [redacted]
Acclimatisation period: 12 days
Diet: Pellet diet Labo-R stock, *ad libitum*
Water: Filtered tap water, *ad libitum*.
Housing: Housed individually wire mesh bottomed FRP cages (380mm×545mm×455mm high)
4. Environmental conditions
Temperature: 17 – 23°C.
Humidity: 30 - 70% relative humidity
Air changes: 12 - 15 per hour.
Photoperiod: 12 hours light in each 24 hour period.

B. STUDY DESIGN AND METHODS

1. In life dates:

20 - 23 February 2007

2. Animal assignment and treatment

The eyes of the animals were examined one day prior to the test item administration. Only those animals without any signs of ocular injury or irritation were used.

On the day of treatment, approx. 0.1mL of the test item was placed in the conjunctival sac of the left eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for about one second to prevent loss of test item. The right eye was left untreated and served as the control.
Initially a single female rabbit was treated and since no severe eye reactions were observed, up to 24 hours post exposure, the study was completed using the remaining two female rabbits.

The eyes of each animal were examined at approximately 1, 24, 48 and 72 hours after treatment and were scored according to the Draize system. Clinical observations were made once daily from the day of treatment.

II. RESULTS AND DISCUSSION

A. FINDINGS

The individual and mean scores for the observed ocular lesions are shown in the Tables below.

Table 6.1.5-1: Corneal opacity

Animal	1h	24h	48h	72h	Positive responder Mean score:	
					≥3	≥1
008F	0	0	0	0	No	No
		Mean score = 0				
009F	0	0	0	0	No	No
		Mean score = 0				
010F	0	0	0	0	No	No
		Mean score = 0				

Table 6.1.5-2: Iritis

Animal	1h	24h	48h	72h	Positive responder Mean score:	
					≥1.5	≥1
008F	0	0	0	0	No	No
		Mean score = 0				
009F	0	0	0	0	No	No
		Mean score = 0				
010F	0	0	0	0	No	No
		Mean score = 0				

Table 6.1.5-3: Conjunctival erythema

Animal	1h	24h	48h	72h	Positive responder Mean score ≥2

008F	1	1	1	0	No
		Mean score = 0.6			
009F	1	1	0	0	No
		Mean score = 0.3			
010F	1	1	0	0	No
		Mean score = 0.3			

Effects fully reversible

Table 6.1.5-4: Conjunctival chemosis

Animal	1h	24h	48h	72h	Positive responder Mean score ≥2
008F	1	0	0	0	No
		Mean score = 0			
009F	1	0	0	0	No
		Mean score = 0			
010F	1	0	0	0	No
		Mean score = 0			

Effects fully reversible

III. CONCLUSIONS

Flutolanil 40SC is not classified as an eye irritant under Regulation (EC) 1272/2008.

B.6.1.6 Skin sensitisation

Previous evaluation	Study newly submitted in support of the evaluation.
Evaluation of the RMS	The study was performed according to OECD 429 and is considered acceptable. Classification according to Regulation (EC) No. 1272/2008 is not required. The main experiment was repeated because the incorporation of ^{3}HTdR in vehicle control group in the first experiment was significantly low statistically when compared to the historical control data.

reference	:	[redacted] (2007)	exposure	:	Topical application
Report number	:	T-3148	doses	:	25, 50 and 100% (v/v)
test substance	:	Flutolanil 40SC	GLP	:	yes
species	:	mice	guideline	:	In accordance with OECD 429 (2002)
group size	:	3 groups of 5 animals	acceptability	:	acceptable

Executive summary

Three groups, each of five animals, were treated by daily application of 50µL (25µL per ear) of the test substance at doses of 25%, 50% and 100% v/v for three consecutive days. A vehicle control group of five animals was treated with distilled water alone. A positive control group of five animals was treated with α-hexylcinnamaldehyde in acetone/olive oil (4:1 , v/v). Five days after the first topical application of the test and control substances, the animals were treated intravenously with ^{3}H-methyl thymidine (^{3}HTdR). The animals were sacrificed 5 hours later. The draining auricular lymph nodes were excised and pooled for each group. A single cell suspension of lymph node cells was prepared and ^{3}HTdR incorporation was measured.

Stimulation index observed in Flutolanil 40SC treated groups were all less than 3.0. The ^{3}HTdR incorporation of positive control group was clearly increased compared with the vehicle control group and the stimulation index was greater than 3.0.

It was concluded that Futolanil 40SC is not classified as a potential dermal sensitiser under the conditions of this study.

I. MATERIALS AND METHODS

A. MATERIALS

1.	**Test material 1:**	Flutolonil 40SC
	Description:	White opaque liquid
	Lot/Batch:	7AE8802F
	Purity:	41% w/w
	Stability:	Stable
	Test material 2:	α-hexylcinnamaldehyde (HCA)
	CASRN	101-86-0
	Description:	Yellow clear solution
	Lot/Batch:	CEH5329
	Purity:	97.8%
	Stability:	Stable
2.	**Vehicle**	Distilled water
3.	**Test animals**	
	Species:	Mouse, females only
	Strain:	CBA/JN crlj
	Age:	Approx. 8 weeks
	Weight at dosing:	20.18–24.04 g
	Source:	[redacted]
	Acclimatisation period:	1 week
	Diet:	Pellet diet (Labo-MR)
	Water:	Local tap water, *ad libitum*
	Housing:	Individually in stainless steel cages (150mm×210mm×170mm)
4.	**Environmental conditions**	
	Temperature:	19–25ºC
	Humidity:	30–70% relative humidity
	Air changes:	15 per hour
	Photoperiod:	12 hours of artificial light in each 24-hour period.

B. STUDY DESIGN AND METHODS

1. In-life dates:

21 March–17 April 2007

2. Animal assignment and treatment

Three groups of five animals were treated with the test material at doses of 25, 50 or 100% v/v by topical application to the dorsum of each ear for three consecutive days (Days 1–3). Two separate groups of five animals were similarly treated with either the vehicle or with the positive control (HCA) at 25% v/v.

Five days after the first topical application (Day 6) all animals were injected via the tail vein with 250 µL of ^{3}H-methyl thymidine (^{3}HTdR). Five hours after the administration of ^{3}HTdR the animals were

scrificed (by diethylether exposure) and the auricular nodes from each ear of each group were excised and pooled in 1 mL of PBS

A single cell suspension of the pooled lymph node cells was prepared by gentle mechanical disaggregation through a Cell Strainer (70µm Nylon, BD Falcon™). The lymph node cells were rinsed through the Cell Strainer with about 5 mL of PBS into a centrifuge tube. The pooled lymph node cells were centrifuged at 190 g for ten minutes. The pellet was re-suspended in 10 mL of PBS and re-pelleted by centrifugation. The pellet was re-suspended in 3 mL of 5 % trichloroacetic acid (TCA) for precipitation of macromolecules.

After 18 hours incubation at 4°C, the precipitates were recovered by centrifugation at 450 g for ten minutes, and then re-suspended in 1 mL of TCA. The suspension was transferred to scintillation vials containing 10 mL of scintillation fluid (Ultima Gold XR) and counted on the liquid scintillation counter (Tri-Carb 2900TR). Scintillation counting data (cpm) were automatically converted to amounts of radioactivity (dpm) with instrument installed external standard and quenching library.

Prior to the measurement, a background value was counted from 10 blank vials containing 1 mL TCA and 10 mL scintillation fluid. Mean value of the background was calculated and four times the standard deviation from the mean was considered as the range for the detection limit.

The level of ^{3}HTdR incorporated in to the lymph node cells of each experimental group was expressed as dpm per animal. Final results were expressed as the stimulation index (SI), which was obtained by dividing the dpm for each treatment group by the dpm of the vehicle control group.

All animals were observed daily for any clinical signs, either of local irritation at the application site or of systemic toxicity.

3. Statistics

The stimulation index was calculated using Microsoft® Excel 2002 (1 0.6501.6735 SP-3).

II. RESULTS AND DISCUSSION

A. MORTALITY

There were no deaths prior to gross necropsy.

B. CLINICAL OBSERVATIONS

No abnormal clinical signs or local irritation at the application site were noted after application of the test substance and vehicle. In the animals treated with the positive control substance, slight irritation was observed after day 2 or day 3.

Bodyweight was not affected by treatment of the test or the control substances.

The table below summarises the ^{3}HTdR incorporation and stimulation index.

Table B.6.1.6-1: ^{3}HTdR incorporation and stimulation index

Test or control subst.	Dose	^{3}HTdR incorporation	Stimulation index

	(% v/v)	dpm/group	dpm/animal	
Vehicle (distilled water)	-	789	158	-
Flutolanil 40 SC	25	485	97	0.6
	50	600	120	0.8
	100	622	125	0.8
Positive control (HCA)	25	7830	1566	9.9

III CONCLUSIONS

The Stimulation Indices were all less than 3.0 and no dose-response was observed. Therefore it is concluded that Flutolanil 40 SC is not classified as a dermal sensitiser under Regulation (EC) 1272/2008.

B.6.1.7 Supplementary studies on the plant protection product

None.

B.6.1.8 Supplementary studies for the combination of plant protection products

Not relevant.

B.6.2 Dermal absorption

A study to determine the dermal absorption of flutolanil from Moncut 40SC has not been conducted because the estimation of the exposure to operators, workers and bystanders is acceptable when the default values according to the EFSA guidance on dermal absorption (2012) are used. However, since the oral absorption of flutolanil is lower than 75%, the oral absorption value of 70% can be considered representative for dermal absorption of in use dilutions containing ≤ 5% active substance. For the risk assessment a dermal absorption value of 25% was used for the concentrate and a value of 70% for the in use dilution.

B.6.3 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document J)

B.6.4 Exposure data

Product information

Product: Moncut 40SC

Purpose: fungicide in agricultural situations as a potato tuber treatment and in horticultural situations as a soil treatment for the growing of tulip and iris bulbs

Active substance (a.s.): Flutolanil

Product type: Suspension Concentrate

Table 6.4-1 describes the critical use patterns that has been defined following of the individual GAPs for each crop.

Table 6.4-1 Summary of critical use (i.e. worst case)

Application equipment	Representative Crop	Max Application rate (kg product/ha)	Max Application rate (kg a.s./ha)	Minimum Spray dilution (L/ha)	Number applications
Tractor mounted, low crop	Tulip, iris	6	2.76	150-400	1
In store treatment Canopied hydraulic or spinning disc equipment	Potato Seed tuber treatment (ware, seed and starch potatoes)	0.8	0.368* 0.2 L product/tonne potatoes (in 2 L water/tonne)	-	1

* Based on planting rate of 4 t tubers/ha.

B.6.4.1 Operator exposure

Estimations of potential operator exposure for the formulation MONCUT 40SC applied by means of broadcast application are made for the intended critical uses described in table 6.4-1 and the following predictive models:

- EFSA AOEM

The exposure estimations were compared to the Acceptable Operator Exposure Level of 0.26 mg/kg bw/day (see Volume 1, level 2, point 2.6.13). For the dermal absorption a value of 25% is used for the concentrate and 70% for the spray dilution (see B.6.2).

B.6.4.1.1 Estimation of operator exposure without personal protective equipment

The input parameters that were applied in the models for the operator exposure estimation are described in Table B.6.4.1.1-1 to B.6.4.1.1-3.

Table B.6.4.1.1-1 Input parameter in the EFSA AOEM model

Application method	Input parameter
Tractor-mounted sprayer, field crops	Treated area: 50 ha/day Max. dose rate: 2.76 kg active substance/ha Operator body weight: 60 kg

The operator exposure estimates assuming that no protective clothing is worn are summarized in Table B.6.4.1.1-2. The detailed calculator spreadsheet are included in Appendix 1.

Table B.6.4.1.1-2 Exposure prediction and risk assessment

Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)[1]	% of AOEL[2]
tractor mounted boom sprayer application outdoors to low crops – tulip, iris			
6 kg MONCUT 40SC/ha corresponding to 2.76 kg flutolanil per ha			

AOEM, longer term - 50 ha/day - 60 kg operator	No PPE (work wear)	1.185	**456**
	PPE (work wear and gloves during mixing, loading and application)	0.059	23

[1] Systemic exposure based on dermal absorption of 25% for mixing and loading and 70% for application of MONUCUT 40SC for application in tulip and iris.

There is no satisfactory model to estimate the application of flutolanil to potato tubers using conventional canopied hydraulic or spinning disc equipment. A study has been conducted to measure the exposure to operators using this equipment. This study was also included in the DAR of flutolanil (addendum 4) and was evaluated by the UK. The study was therefore not re-evaluated in detail.

Report:	**Ridgeway, J (2006)**
Title	Determination of dermal and inhalation exposure of commercial seed-potato application equipment operators during mixing/loading and application using RhiNo, a soluble concentrate containing 460 g/L flutolanil
Report No.	H-3003
Guidelines:	OECD Series on testing and assessment No. 9: Guidance document on the conduct of studies of occupational exposure to pesticides during agricultural application, 1997 (OECD/GD(97)148)
GLP:	Yes
Deviations:	None

Executive Summary

This study was conducted to determine the dermal and inhalation exposure of operators of commercial seed potato application equipment during the normal work practices associated with mixing/loading and application using RHINO, a soluble concentrate containing 460g/l flutolanil.

All normal work practices associated with mixing/loading and application to seed potatoes were considered including monitoring of application equipment, packing of treated seed and forklift driving when moving both untreated and treated seed. A total of 3 operators were monitored at each of 5 sites; all were experienced in the work activities they carried out. The conditions and practices monitored at the site were considered typical of the region and also representative of conditions in other seed treatment. Whilst performing their work operators were subject to recorded observation.

Five applications were monitored at separate sites during February, March and April 2005 in areas of the UK which were representative of commercial seed potato treatment practice. The test item was applied to seed potatoes at a target recommended use rate of 92.0g flutolanil/tonne of potatoes, equivalent to 0.2 litres product/tonne, in a water volume of 2.0 litres/tonne. This application covers the current GAP applied for.

Dermal exposure to the test item was measured by operators wearing standardised whole-body outer and inner dosimeters. The outer dosimeter consisted of a polyester/cotton fibre blend coverall and separate hood to determine head exposure which was considered to be representative of what operators would normally wear when treating seed potatoes. The inner dosimeter consisted of a two-piece set of cotton undergarments covering arms, legs and torso.

Hand exposure was measured by operators wearing protective gloves. Actual dermal exposure of the hands was measured by operators wearing white cotton gloves beneath the protective gloves.

Inhalation exposure was measured by means of personal air sampling pumps and an IOM head/filter located in the operator's breathing zone.

On the day of treatment, fortification specimens of each of the matrices were taken to establish the stability of specimens taken from operators under on site, storage and transit conditions. Fortifications were run concurrently with the operator specimens and were exposed to the same environmental conditions for a similar period. They were conducted at two fortification levels, one high and one low, each with three replicates, together with two replicates of a control (included to assess any flutolanil contamination). In addition three travel fortification specimens for each matrix were fortified and frozen immediately to confirm stability of the residue during storage and transit conditions, however following analysis of field fortification specimens analysis was not required.

Specimens were analysed for residues of flutolanil using soxhlet extraction with acetone (outer dosimeters, inner dosimeters, hoods, protective gloves and inner cotton gloves), and ultrasonication/vortex mixing with acetone for air filters. Quantification of residues was by coupled gas chromatography-mass spectrometry using chemical ionization in the negative mode. No specimens recorded residues below the limit of quantification therefore no correction of data was required.

A summary of the results is shown in the table below.

Table B.6.4.1.1-3: Summary of operator exposure during mixing/loading and application using RhiNo, a soluble concentrate containing 460 g/L flutolanil

Unit of Exposure	Type of exposure	Min.	Max.	Mean	SD
mg/operator	Potential dermal exposure excluding hands	26.094	105.983	56.280	30.923
	Potential hand exposure	25.223	150.875	74.434	49.118
	Actual dermal exposure excluding hands	0.955	10.093	4.229	3.835
	Actual hand exposure	0.149	4.240	1.491	1.597
	Inhalation exposure [1)]	0.038	0.696	0.298	0.259
mg/kg bw	Potential dermal exposure excluding hands	0.326	1.178	0.687	0.313
	Potential hand exposure	0.280	2.155	0.973	0.718
	Actual dermal exposure excluding hands	0.012	0.112	0.050	0.041
	Actual hand exposure	0.002	0.047	0.018	0.017
	Inhalation exposure [1)]	0.001	0.010	0.004	0.004
mg/kg ai handled	Potential dermal exposure excluding hands	11.535	53.635	33.374	20.204
	Potential hand exposure	12.765	77.487	40.825	25.068
	Actual dermal exposure excluding hands	0.538	8.524	2.737	3.375
	Actual hand exposure	0.126	2.146	0.767	0.804
	Inhalation exposure [1)]	0.034	0.256	0.139	0.092

[1)] Based on an average breathing rate of 16.7 L/min.

I. MATERIALS AND METHODS

Test Material

The test item was a formulated product called RHINO (flutolanil 460 g/L SC) with batch number 420314.

Test system

The test system comprised the test subjects (operators) and the passive dosimetry equipment they were wearing whilst treating seed potatoes with RHINO in commercial seed treatment situations in the UK.

The test item RHINO was contained in sealed 1L containers which were emptied into the spray tanks at mixing/loading.

While performing their tasks, each operator wore dosimeters consisting of a coverall for the outer dosimeter with separate hood, a long-sleeved T-shirt and long johns for the inner dosimeter and personal air sampler. Protective gloves were worn as per the operators standard work practices over white cotton gloves.

Monitoring typical operators under typical conditions provided the best estimate of exposure. The proposed method allowed estimation of the amount of test item which was potentially available for dermal and inhalation exposure.

A total of 3 operators were used at each of 5 sites, all of whom were experienced in the specific work activity carried out. Written assurances that operators knew of no handicaps that would affect their work, and written consent to co-operate in the study was obtained from each operator prior to trial commencement. Personal details from each of the operators, (including name, age, sex, bodyweight, height, previous experience in the work activity and a general health statement) were maintained in the study raw data. In order to maintain confidentiality, each operator was identified only by their unique identity number.

None of the operators had handled or applied RHINO just prior to the study.

The application equipment used in the study was assumed to have been cleaned, maintained and calibrated in accordance with normal commercial practice.

Application parameters

Each trial consisted of a typical days work in a commercial seed potato treatment environment, both in terms of volume of seed treated and duration of the application process. The sites were selected to be representative of conditions under which the product is used commercially in the UK. The planned application rate was as specified on the RHINO product label. The various application parameters are outlined below.

Table B.6.4.1.1-4: Application parameters applied in the operator exposure study

Concentration:	460 g/L
Application volume:	0.2 L per tonne of seed
Application equipment:	Conventional canopied hydraulic or spinning disc potato spraying equipment mounted on a rolling conveyor
Timing of Application:	February-April 2005
Weight of seed treated:	Min 11.6 tonnes, max 47 tonnes
Duration of application:	Min 2 hours 37 minutes, max 3 hours 43 minutes

Description of monitored tasks

Before each monitoring day, the purpose of the study and the sampling procedures associated with each matrix were explained to operators. Operators received training regarding glove and dosimeter removal. The importance of adopting hygienic methods to minimise cross contamination was emphasised.
Just before treatment began the air sampling pump was started, thereafter, they were checked periodically to ensure correct operation. Observation of the entire application process was conducted and any events which may have increased exposure were recorded. The time when treatment ceased and the air sampling pumps turned off was noted.
Study team members conducted fortification of field recovery specimens (dermal and respiratory exposure dosimeters, i.e. outer and inner dosimeters, protective and cotton gloves, and air sampler) at two rates. These were exposed to similar environmental conditions for a similar time period as the equivalent operator matrices and run in parallel with operator mixing/loading or application. At one site, three fortifications of each matrix were made and immediately frozen to confirm the stability of flutolanil residues during storage and transit, however analysis of these specimens was not required following analysis of the site's field fortification specimens.
The study team collected the following environmental data; air temperature and relative humidity within the building throughout the treatment period.
The study team members removed the air sampling pump and processed the air filter specimens. The operator removed their protective gloves which were collected and processed by the study team, followed by the cotton gloves. The operator's footwear was removed before they walked into a clean room where the outer and inner dosimeters were removed and hung up, the inner dosimeter was dissected and processed by the study team, followed by the outer dosimeter. Specimens of the various matrices from the operators and the field fortification specimens were collected, packaged and labelled by the study team and were either returned within a short period for deep frozen storage or placed into temporary frozen storage before return.

Exposure monitoring techniques

In order to intercept contamination the operators were dressed as follows;

- Normal clothing and exterior footwear.
- Inner dosimeter consisting of full length cotton underwear garments comprising white long sleeved cotton T-shirt and white cotton long johns covering the arms, legs and torso.
- An outer dosimeter consisting of a white polyester/cotton fibre blend overall, worn outside any parts of footwear which extend along the leg and separate hood.
- Gauntlet nitrile gloves which protect the hands and lower arms, and extend outside the lower sleeves of the coverall, to be worn as per operators normal working practices, worn over white cotton gloves.
- A calibrated CASELLA VORTEX TIMER 2 Pump sited on a belt around the operators waist, drawing air from the region of the face at a nominal rate of 2.0 litres/minute, through a fibreglass IOM air filter attached via a clip to the white cotton overalls.

Inner dosimeters were worn over the regular clothing of the operator and directly under the outer dosimeter and fitted well so that they were not exposed beneath the outer dosimeter and avoided any exposure of the operators skin. As these dosimeters acted as collection media for the test item, they were worn throughout the periods of monitoring and were removed at the end, with the assistance of members of the study team.

Protective nitrile gloves were taken for determination of potential dermal exposure. Actual dermal exposure of the hands was determined by taking the white cotton gloves worn beneath the protective nitrile gloves.

Exposure of the head was assessed by taking the separate hood of the outer dosimeter. In the DAR it was noted that as the hoods were of snooded "pork pie" type, the brim is presumed to have provided some protection from contamination to the face/neck area. Consequently, this was considered to negate the need to correct exposure estimates for the fact that no face/neck wipe samples were taken.

The CASELLA VORTEX TIMER 2 pumps were attached to a fibreglass filter and IOM head using Tygon® tubing. The complete apparatus was calibrated prior to use by attaching the IOM head to a calibrated rotameter and measuring the flow rate through the head, with adjustments made to achieve a flow rate of 2.0 L/min. Immediately following calibration, a pump was positioned on a belt around the spray operators' waist, with the IOM filter and head drawing air from the region of the face at a nominal flow rate of 2.0 litres/minute, attached via a clip to the white cotton overalls. The Tygon® tubing connecting the sampling head to the pump was positioned where it would not impede the operator, and was secured in place with a clip.

Periodically throughout the monitoring periods, the pumps were checked to ensure that they were still running, and the tubing checked to ensure that there were no kinks in it. Operators were instructed to inform a study team member if the pump failed to operate or the tubing became kinked and the airflow obstructed.

All donning of spray operator garments was carried out on clean plastic sheeting in areas remote from the work activities.

Analytical method

The method involved soxhlet extraction with acetone (outer dosimeters, inner dosimeters, hoods, protective gloves and inner cotton gloves), and ultrasonication/vortex mixing with acetone for air filters. Quantitation of residues was by coupled gas chromatography-mass spectrometry using chemical ionization in the negative mode.

The limit of detection (LOD) for flutolanil under the conditions used in the study was ca. 0.25 ρg. No specimens recorded residues below the limit of quantification therefore no correction of data was required.

Statistical analysis

Results were not subject to transformations, however, for procedural recoveries and field fortifications means and standard deviations were calculated. In addition the overall Coefficient of Variance (CV%) for procedural recovery was calculated.

II. RESULTS AND DISCUSSION

Correction for analytical recovery

Mean procedural and field fortification recoveries were all within specified limits of 70-110% therefore no corrections were required to the Operator specimens. As already noted in the DAR (addendum 4), the level of replication for procedural recovery was variable. At some fortification levels for various matrices, only one sample was taken, even when recovery was as low as 64%. This low level of replication is a recurrent theme throughout the trial.

Determination of exposure

Potential dermal exposure (excluding hands) is the sum of residues detected on the coverall (arms, legs and torso), the inner dosimeter (arms, legs and torso) and hood.

Actual dermal exposure (excluding hands) is the sum of residues detected on the inner dosimeter (arms, legs and torso) and hood.

Potential hand exposure is the sum of residues on protective glove and in cotton glove specimens.

Actual hand exposure is the sum of residues on cotton glove specimens.

The time used to calculate exposure per unit time is the number of minutes recorded on the air sampling pumps as this corresponds to the actual duration of the work activities.

Calculation of inhalation exposure is based on a breathing rate of 20.83 L/min, equal to 1.25 m^3/ hour, based on the EFSA guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. Inhalation exposure for each operator is calculated according to the following formula:

$$\text{Inhalation exposure} = \frac{\text{Residues per filter (mg)} \times \text{Pump running time (min)} \times \text{Breathing rate (L/h)}}{\text{Air volume sampled (L)}}$$

The table below summarises the results. The dosimeters and clothing of one operator from each site was selected for analysis on the basis of the worst-case exposure.

Table B.6.4.1.1-5: Results obtained in the operator exposure study

Unit of Exposure	Type of exposure	Operator					Min	Max	Mean	SD
		Site 01-01	Site 02-01	Site 03-02	Site 04-01	Site 05-01				
mg/operator	Potential dermal exposure excluding hands	38.1260	105.9825	48.0879	26.0940	63.1109	26.0940	105.9825	56.2803	30.9228
	Potential hand exposure	59.0038	25.2230	150.8753	45.3217	91.7446	25.2230	150.8753	74.4337	49.1179
	Actual dermal exposure excluding hands	1.0162	5.8067	3.2760	0.9545	10.0926	0.9545	10.0926	4.2292	3.8348
	Actual hand exposure	0.6704	4.2398	1.1712	1.2270	0.1490	0.1490	4.2398	1.4915	1.5970
	Inhalation exposure [1)]	0.048	0.441	0.868	0.126	0.378	0.0480	0.8680	0.3722	0.3226

mg/kg bw	Potential dermal exposure excluding hands	0.5447	1.1776	0.6870	0.3262	0.7012	0.3262	1.1776	0.6873	0.3128
	Potential hand exposure	0.8429	0.2803	2.1554	0.5665	1.0194	0.2803	2.1554	0.9729	0.7180
	Actual dermal exposure excluding hands	0.0145	0.0645	0.0468	0.0119	0.1121	0.0119	0.1121	0.0500	0.0412
	Actual hand exposure	0.0096	0.0471	0.0167	0.0153	0.0017	0.0017	0.0471	0.0181	0.0173
	Inhalation exposure [1)]	0.0007	0.0049	0.0124	0.0016	0.0042	0.0007	0.0124	0.0048	0.0046
mg/kg ai handled	Potential dermal exposure excluding hands	33.6802	53.6349	11.5346	14.7174	53.3031	11.5346	53.6349	33.3740	20.2039
	Potential hand exposure	52.1235	12.7647	36.1898	25.5622	77.4870	12.7647	77.4870	40.8254	25.0678
	Actual dermal exposure excluding hands	0.8977	2.9386	0.7858	0.5384	8.5242	0.5384	8.5242	2.7369	3.3748
	Actual hand exposure	0.5922	2.1456	0.2809	0.6920	0.1258	0.1258	2.1456	0.7673	0.8038
	Inhalation exposure [1)]	0.042	0.223	0.208	0.071	0.319	0.0.042	0.319	0.1728	0.1147

1) Based on an average breathing rate of 20.83 L/min

III. CONCLUSIONS

Results for individual body parts indicate that most of the contamination occurred where operators came into contact with the treated seed, either directly or by touching equipment involved in the treating and movement of the seed. However, a comparison between residues found on protective gloves and cotton gloves indicate that the protective gloves worn by monitored workers were very effective in preventing exposure to the hands.

The following observations can be made of exposure received on various matrices during application:

The protective gloves received the highest levels of exposure, primarily due to direct contact with treated seed. Residue levels found in the cotton gloves were relatively low. This indicates that the protective gloves worn by monitored workers were effective in preventing exposure to the hands. Protective gloves reduced exposure of the hands by a mean of 98%.

The protected body parts represented by the inner dosimeter received low levels of exposure. Generally, the outer dosimeter was very effective in reducing exposure. The inner dosimeters received approximately 7.5% of the total contamination of the outer dosimeters. Exposure to Operator 1 at Site 5 was higher than Operators at the other sites due to repeated touching of the hood with protective gloves during treating as he found the hood uncomfortable during the monitoring process.

(Ridgway, 2006)

Taking into account the results from the operator exposure study, the operator exposure to flutolanil can be calculated as follows:

Normal workwear worn, gloves not worn:
((Actual dermal exposure excluding hands + potential hand exposure) x dermal absorption) + inhalation exposure/bodyweight)
((10.0926 + 150.8753) x 0.70) + 0.868 / 60 = 1.89 mg/kg

This is equivalent to 727% of the AOEL. Therefore the risks to operators not wearing gloves is considered to be unacceptable.

Normal workwear and gloves are worn:
((Actual dermal exposure excluding hands + actual hand exposure) x dermal absorption) + inhalation exposure/bodyweight)
((10.0926 + 4.2398) x 0.70) + 0.868 / 60 = 0.18 mg/kg
This is equivalent to 69% of the AOEL. Therefore the risks to operators wearing gloves is considered to be acceptable.

Please note that a dermal absorption value of 70% was used as a worst case assumption since a clear distinction in the exposure levels between the different activities such as mixing/loading and application is not made. In addition, it should be noted that there was a difference in throughput ranging from 11.6 tonnes to 47 tonnes per day. Moreover, since the variability between study subjects is considerably. The number of replicates in this study is relatively low since the exposure of only 5 subjects were monitored instead of a minimum of 10 subjects as indicated in the OECD guideline on occupational exposure. Taking this into account calculations were made using the maximum exposure levels observed instead of the 75th percentiles given for the 15 operators in the study as originally done in the DAR.

Conclusion
The EFSA AOEM estimates show that for the intended use of the formulation Moncut 40SC the predicted systemic exposure for the unprotected operator is 456% and 23% for the protected operator wearing gloves during mixing, loading and application.

Since there are no acceptable models to estimate the exposure to operators during application to potato tubers, the study to monitor exposures to personnel applying Moncut 40SC by conventional canopied hydraulic or spinning disc equipment is presented as a worst-case. Based on an operator study, the exposure to MONCUT 40SC is considered acceptable provided that the operator wears PPE.

Since the exposure to operators using in-planter equipment would be lower than for those operating conventional canopied hydraulic or spinning disc equipment, the above study is adequately protective for all application methods used to treat tubers supported by the GAP.

B.6.4.1.2 Estimation of operator exposure with personal protective equipment

The estimated operator exposure with personal protective equipment is included in B.6.4.1.1.

B.6.4.2 Bystander and resident exposure

Estimations of potential bystander and resident exposure for the formulation MONCUT 40SC are made for the intended critical uses described in table 6.4-1 and the following predictive models:

- EFSA AOEM

Table B.6.4.2-1 Resident exposure prediction and risk assessment

Exposure group	Exposure route	Total absorbed dose (mg/kg bw/day)[1]	% of AOEL
tractor mounted boom sprayer application outdoors to low crops – tulip and iris			
6 kg MONCUT 40SC/ha corresponding to 2.76 kg flutolanil per ha			
Resident, child	Spray drift	0.3458	**132.99**
	Vapour	0.0011	0.41
	Surface deposits	0.0297	11.42
	Entry into treated crops	0.3260	**125.39**
	All pathways (mean)	0.4732	**181.99**
Resident, adult	Spray drift	0.0828	31.83
	Vapour	0.0002	0.09
	Surface deposits	0.0132	5.06
	Entry into treated crops	0.1811	69.66
	All pathways (mean)	0.1936	74.46

A bystander risk assessment is required for PPPs that have significant acute toxicity or the potential to exert toxic effects after a single exposure. Since for flutolanil an AAOEL was determined (0.28 mg/kg bw/day) a risk assessment was made for the bystander using this value.

Table B.6.4.2-4 Bystander exposure prediction and risk assessment

Exposure group	Exposure route	Total absorbed dose (mg/kg bw/day)[1]	% of AOEL
tractor mounted boom sprayer application outdoors to low crops – tulip and iris			
6 kg MONCUT 40SC/ha corresponding to 2.76 kg flutolanil per ha			
Resident, child	Spray drift	0.7836	**279.86**
	Vapour	0.0011	0.38
	Surface deposits	0.0895	31.96
	Entry into treated crops	0.3260	**116.44**

Resident, adult	Spray drift	0.0002	76.12
	Vapour	0.0397	0.08
	Surface deposits	0.1811	14.17
	Entry into treated crops	0.7836	64.69

The resident and bystander exposure estimates show that the exposure exceeds the AOEL or AAOEL for children. However, for the use on flower bulbs, MONCUT 40SC is applied to bare soil with broadcast spray equipment and incorporated into the soil pre planting (BBCH00). Therefore, the scenario 'entry into treated crops' is not considered relevant for the intended application of MONCUT 40SC and the EFSA AOEM thus represents an overestimation.

For adults it is concluded that there is no undue risk to any bystander or residents after accidental exposure to MONCUT 50 SC.

For children a refined risk assessment is made considering the use of vehicle mounted drift reduction.

Table B.6.4.2-3 Resident exposure prediction and risk assessment – drift reduction

Exposure group	Exposure route	Total absorbed dose (mg/kg bw/day)[1]	% of AOEL
tractor mounted boom sprayer application outdoors to low crops – tulip and iris			
6 kg MONCUT 40SC/ha corresponding to 2.76 kg flutolanil per ha			
Resident, child	Spray drift	0.1729	66.49
	Vapour	0.0011	0.41
	Surface deposits	0.0148	5.71
	Entry into treated crops	0.3260	**125.39**
	All pathways (mean)	0.3671	**141.19**

Table B.6.4.2-4 Bystander exposure prediction and risk assessment – drift reduction

Exposure group	Exposure route	Total absorbed dose (mg/kg bw/day)[1]	% of AOEL
tractor mounted boom sprayer application outdoors to low crops – tulip and iris			
6 kg MONCUT 40SC/ha corresponding to 2.76 kg flutolanil per ha			
Resident, child	Spray drift	0.3918	**139.93**
	Vapour	0.0011	0.38
	Surface deposits	0.0447	15.98
	Entry into treated crops	0.3260	**116.44**

The resident and bystander exposure estimates for children using drift reduction show that the exposure still exceeds the (A)AOEL (141% and 116% of the (A)AOEL). However, as indicated above for the use on flower bulbs, MONCUT 40SC is applied to bare soil with broadcast spray equipment

and incorporated into the soil pre planting (BBCH00). Children are thus not expected to be exposed to deposits present on treated crops and the scenario 'entry into treated crops' can thus be considered not representative. The sum of the scenarios spray drift, vapour pressure and surface deposits results in 73% of the AOEL based on the 75th percentile values and 41% of the AOEL when mean values are considered. For residential children it can thus be concluded that there is no undue risk after accidental exposure to MONCUT 40SC following exposure via spray drift, vapour and surface deposits provided that drift reduction is applied. However, for bystanders the exposure to children resulting from drift still exceeds the AAOEL when using drift reduction (140% of the AAOEL). The exposure to flutolanil as a result of spray drift is thus not acceptable and the applicant is requested to provide a refined risk assessment.

B.6.4.3 Worker exposure

The application of Moncut 40SC to flower bulbs is as an overall spray to bare soil followed by incorporation to a depth of at least 10 cm. There is no requirement for workers to re-enter the treated area after application, therefore an assessment of the risks to workers is not considered necessary.

Moncut 40SC that is applied to potato tubers during the planting process are covered by soil immediately they fall to the ground. The soil is formed into ridges 15–20 cm high, therefore workers re-entering the treated field are not at risk of exposure to Moncut 40SC. Please see section B3 for a description of the equipment used. Additionally, worker re-entry exposure was discussed during the PRAPeR 24 meeting for the first approval of flutolanil (see DAR Addendum 4, dated October 2007). This meeting concluded that the German re-entry model does not contain reliable default values (TC and DFR) appropriate for the intended use and that there is no need for unreliable model calculations.

Application to potatoes by conventional canopied hydraulic or spinning disc equipment involves tubers being treated under a canopy and then moved by conveyor belt into containers, please see Doc M-CP3 for a description of the equipment used. Workers engaged in packing and re-positioning containers of treated tubers may be exposed to flutolanil. There is no acceptable model available to estimate the exposure of workers to this type of activity but see section B3.

In the study summarised in Section B.6.4.1, three 'operators' were monitored for their exposure to flutolanil whilst applying a 460 g/L SC formulation to potato tubers by conventional canopied hydraulic or spinning disc equipment. Monitoring took place at 5 different sites which meant that 15 different 'operators' were monitored. The weight of tubers treated across the five sites was between 11.6 and 47 tonnes taking between 2h 37m and 3h 43m to complete the application of between 2.5 and 8.9 L of product.

The typical activities carried out by the three operators at each site are summarised below.

Operator 1. Mixing & loading of product, checking the coverage of the treated tubers, checking the function of the spinning disc and nozzles. Occasionally levelling full trays.

Operator 2. Levelling full trays of tubers, moving them to a pallet, picking debris from treated tubers.

Operator 3. Stacking full trays on a pallet, moving full pallets to storage area with a forklift truck and occasionally levelling full trays.

Operator 1 performed typical 'operator' activities whilst Operators 2 and 3 performed what could be described as typical 'worker' activities. However, Operator 1 occasionally performed some worker activities as well.

The dosimeters and clothing of one operator from each site was selected for analysis on the basis of the worst-case exposure. Operator 1 from sites 1, 2, 4 and 5 was selected and Operator 2 from site 2 was selected. Since Operator 2 from site 3 (Operator 03-02) is representative of a worker, a summary of the findings for this individual is shown below.

Table 6.3.4-1: The measured exposure for Operator 03-02 (70 kg male).

Unit of Exposure	Type of exposure	Operator 03-02
mg/operator	Potential dermal exposure excluding hands	48.088
	Potential hand exposure	150.875
	Actual dermal exposure excluding hands	3.376
	Actual hand exposure	1.171
	Inhalation exposure [1)]	0.868
mg/kg bw	Potential dermal exposure excluding hands	0.687
	Potential hand exposure	2.155
	Actual dermal exposure excluding hands	0.74
	Actual hand exposure	0.017
	Inhalation exposure [1)]	0.01

[1)] Based on an average breathing rate of 20.83 L/min (1.25 m^3/ h)

Assuming a 70% dermal absorption factor and a 100% inhalation absorption factor, the total systemic exposure for operator 03-02 is given by the following equations:

Normal workwear worn, gloves not worn:

((3.376 + 150.875) x 0.70) + 0.868 / 60 = 1.81 mg/kg

This is equivalent to 696% of the AOEL. Therefore the risks to workers not wearing gloves is considered to be unacceptable.

Normal workwear and gloves are worn:

((3.376 + 1.171) x 0.70) + 0.868 / 60 = 0.07 mg/kg

This is equivalent to 27% of the AOEL. Therefore the risks to workers wearing gloves is considered to be acceptable. As already noted in the DAR, the study did not account for the possibility that treated seed potatoes might be bagged rather than left in bulk storage boxes. This could represent another

possible exposure component during the seed treatment operation. Nevertheless, considering the worst-case exposure assessment and the relatively low %AOEL calculated for the worker, no adverse health effects are to be expected for bagging activities. However, bear in mind that the majority of subjects included in this stud performed tasks including handling the product and the treatment equipment, and handling the treated potatoes post treatment were performed. It is considered that the exposure assessment for operators therefore also covers the range of tasks involved in the treatment process including levelling/moving trays and sorting out stones/damaged potatoes post treatment. Since planting of potatoes is generally done using mechanical planters, the manual handling of potatoes during planting is not a relevant exposure scenario and was therefore not considered for risk assessment. Thus, the 'Operator' will encounter the highest exposure so the measurement of exposure to operators will be protective of those engaged in worker activities and the assertion that worker exposures is less than for operators will, in the main, be true.

B.6.5 Exposure and risk assessment

Operator exposure:
The EFSA AOEM estimates show that for the intended use of the formulation MONCUT 40SC is considered acceptable provided that PPE is worn.

Bystander and resident exposure:
The bystander and resident exposure estimates made for adults show that the exposure is below the AOEL. Therefore, It is concluded that there is no undue risk to any adult bystander or adult residents after accidental exposure to MONCUT 40SC. However, for children no safe use can be indicated and therefore the applicant is requested to provide a refined risk assessment or drift reduction needs to be applied.

Worker exposure:
It is concluded that there is no unacceptable risk anticipated for the protected worker wearing gloves when re-entering crops treated with MONCUT 40SC on the day of application.

B.6.6 References relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner
CP 7.1.1/01	[redacted]	2007a	Acute oral toxicity study of flutolanil 40SC in rats. [redacted] T-3117 Y N	Y	Y	Article 59(1) & (2) of Regulation (EC) 1107/2009 applies	Nihon-Nohyaku Co. Ltd
CP 7.1.2/01	[redacted]	1989	Assessment of acute dermal toxicity with Flutolanil 40 SC [redacted] T-3072 Y N	Y	N	-	Nihon-Nohyaku Co. Ltd
CP 7.1.4/01	[redacted]	2007b	Skin irritation study of Flutolanil 40SC in rabbits [redacted] T-3118 Y N	Y	Y	Article 59(1) & (2) of Regulation (EC) 1107/2009 applies	Nihon-Nohyaku Co. Ltd
CP 7.1.5/01	[redacted]	2007c	Eye irritation study of Flutolanil 40SC in rabbits [redacted] T-3119 Y N	Y	Y	Article 59(1) & (2) of Regulation (EC) 1107/2009 applies	Nihon-Nohyaku Co. Ltd
CP 7.1.6/01	[redacted]	2007	Flutolanil 40SC: Local Lymph Node Assay in Mice [redacted] T-3148 Y N	Y	Y	Article 59(1) & (2) of Regulation (EC) 1107/2009 applies	Nihon-Nohyaku Co. Ltd
CP 7.2.1/01	Ridgeway, J	2006	Determination of dermal and inhalation exposure of commercial seed-potato application equipment	N	Y	Article 59(1) & (2) of Regulation (EC) 1107/2009 applies	Nihon-Nohyaku Co. Ltd

			operators during mixing/loading and application using Rhino, a soluble concentrate containing 460 g/L flutolanil Agriserach UK Ltd H-3003 Y N				

Appendix 1-1: Detailed exposure models

Substance	Flutolanil	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-2,76 kg a.s. /ha	Spray dilution = 18,4 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Bare soil / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 25	Dermal for in use diluation = 70	Oral = 70	Inhalation = 100	
RVNAS	0,26 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Appendix 1-1.1 Operator exposure for MONCUT 40SC outdoor spray applications – no PPE

Operator exposure for Moncut 40SC outdoor spray applications

Application rate of active substance	2,76	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	138	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	25,00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	70,00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downward sprayingVehicle-mounted

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	215627	825210	AOEM	
	Body	113898	301415	AOEM	
	Head	7160	39269	AOEM	
	Protected hands (gloves)	851	27333	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	1874	20183	AOEM	
	Protected head (hood and face shield)	115	2223	AOEM	
	Inhalation	16	32	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	20469	84613	AOEM	
	Body	11445	58997	AOEM	
	Head	541	1631	AOEM	
	Protected hands (gloves)	615	5921	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	314	770	AOEM	
	Inhalation	12	50	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	106,9174147	71,1198812	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	1,7819569	1,1853314	
% of RVNAS	685,37%	455,90%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	393,2242107	282,1571642	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	6,5537368	4,7026194	
% of RVAAS	#DEEL/0!	#DEEL/0!	

Appendix 1-1.2 Operator exposure for MONCUT 40SC outdoor spray applications –PPE

Application rate of active substance	2,76	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	138	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	25,00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	70,00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downward sprayingVehicle-mounted

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	215627	825210	AOEM	
	Body	113898	301415	AOEM	
	Head	7160	39269	AOEM	
	Protected hands (gloves)	851	27333	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	1874	20183	AOEM	
	Protected head (hood and face shield)	115	2223	AOEM	
	Inhalation	16	32	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	20469	84613	AOEM	
	Body	11445	58997	AOEM	
	Head	541	1631	AOEM	
	Protected hands (gloves)	615	5921	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	314	770	AOEM	
	Inhalation	12	50	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	106,9174147	3,5285456	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	1,7819569	0,0588091	
% of RVNAS	685,37%	22,62%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	393,2242107	27,6032979	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	6,5537368	0,4600550	
% of RVAAS	#DEEL/0!	#DEEL/0!	

Appendix 1-1.3 Resident exposure for MONCUT 40SC outdoor spray applications

Croptype	Bare soil		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		*i_AppEquip*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		*i_FormVal*
Buffer strip	2-3	m	*i_Buffer*
Application rate of the product	2,76	kg a.s./ha	*i_AppRate*
Concentration of active substance (in-use dilution for liquid applications)	18,4	g a.s./l	*d_ConcAS*
Dermal absorption of product	25,00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	70,00%		*i_AbsorpInuse*
Oral absorption	70,00%		*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	8,28	µg a.s./cm^2	*d_DFR*
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa	Pa	*i_Volat*
Concentration in air	0,001	mg/m^3	*d_AirCon*
Resident dermal spray drift exposure 75th percentile - adult	0,47	ml spray dilution/person	
Resident dermal spray drift exposure 75th percentile - child	0,327	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - adult	0,00010	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - child	0,00022	ml spray dilution/person	
Resident dermal spray drift exposure mean - adult	0,22318	ml spray dilution/person	
Resident dermal spray drift exposure mean - child	0,18	ml spray dilution/person	
Resident inhal. spray drift exposure mean - adult	0,00009	ml spray dilution/person	
Resident inhal. spray drift exposure mean - child	0,00017	ml spray dilution/person	
Exposure duration dermal	2	hours	*d_ReExpDur*
Exposure duration inhalation	24	hours	*d_ReExpDurInhal*
Exposure duration entry into treated crops	0,25	hours	*d_ExpDurTreatCrop*
Light clothing adjustment factor	18,0%		*d_ClothAF*
Breathing rate adult	0,23	m^3/day/kg	*d_BreathRAd*
Breathing rate child (1-3 year old)	1,07	m^3/day/kg	*d_BreathRCh*
Drift percentage on surface (75th percentile)	5,60%		
Drift percentage on surface (mean)	4,10%		
Turf transferable residues percentage	5,00%		*d_Turf*
Transfer coeff. of surface deposits-adult	7300	cm^2/hour	*d_ReTCAd*
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm^2/hour	*d_ReTCCh*
Saliva extraction percentage	50,00%		*d_SalExt*
Surface area of hands mouthed	20	cm^2	*d_AreaHM*
Frequency of hand to mouth activity	9,5	events/hour	*d_ReFreqHM*
Ingestion rate for mouthing of grass per day	25	cm^2	*d_MouthGrass*
Dislodgeable residues percentage transferability for object to mouth	20,00%		*d_DRP*
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500	cm^2/h	*d_TcEntryAd*
Transfer coefficient for entry into treated crops (75th percentile) - chi	2250	cm^2/h	*d_TcEntryCh*
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm^2/h	*d_TcEntryAd*
Transfer coefficient for entry into treated crops (mean) - child	1794	cm^2/h	*d_TcEntryCh*

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	3,4576912	0,0107000	0,2969870	3,2602500	4,7318589
Total systemic exposure per kg body weight	0,3457691	0,0010700	0,0296987	0,3260250	0,4731859
% of RVNAS	132,99%	0,41%	11,42%	125,39%	181,99%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	4,9657920	0,0138000	0,7898016	10,8675000	11,6158615
Total systemic exposure per kg body weight	0,0827632	0,0002300	0,0131634	0,1811250	0,1935977
% of RVNAS	31,83%	0,09%	5,06%	69,66%	74,46%