Product MON 52276
(360 g/L glyphosate acid)

Herbicide for emerged annual, perennial and biennial weeds

Application for Renewal of Approval (AIR 2) according to Commission Regulation (EC) N° 1141/2010

ANNEX III
Summary documentation, TIER II

Document M:

Point 7: Toxicological studies and exposure data and information

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IIIA 7 Toxicological studies and exposure data and information

MON 52276, the lead formulation of the GTF submission, was one of the representative formulations supporting the 2001 Annex 1 inclusion of glyphosate. This formulation is still registered in Europe and its composition has not changed.

IIIA 7.1 Acute toxicity

The conclusions of the 2001 EU evaluation of MON 52276 (acute toxicity profile) are summarized in Table IIIA 7.1-1. All data are still relevant to this submission. However a new dermal sensitization study was subsequently conducted under GLP conditions, following the revised OECD 406 test guideline (modified Buehler; 9 applications). The new dermal sensitization study confirms both the results of the previously submitted non-GLP study and the 2001 EU evaluation for this endpoint.

Table IIIA 7.1-1: Summary of acute toxicity of glyphosate

Annex point (2001 EU Monograph Annex Point)	Title	Guideline	Conclusions	Reference
7.1.1/01 (B.5.11.1.1)	Acute Oral Toxicity Study In Rats	US EPA FIFRA guideline 81-1 (1984), OECD 401 (1987), EEC directive 84/449/EEC method B.1 (1984)	LD_{50}, oral, rat > 5000 mg/kg bw	[redacted]
7.1.2/01 (B.5.11.1.2)	Acute Dermal Toxicity in Rats	US EPA FIFRA guideline 81-2 (1984), OECD 402 (1987), EEC directive 84/449/EEC method B.3 (1984), JMAFF	LD_{50}, dermal, rat > 5000 mg/kg bw	[redacted]
7.1.3 (B.5.11.1.3)	Acute Inhalation	OECD 403	Not Required	---
7.1.4/01 (B.5.11.1.4)	Primary Dermal Irritation in Rabbits	OECD 404 (1992); Commission Directive 92/69/EEC method B.4 (1992), US EPA FIFRA guideline 81-5 (1984)	Not classified for skin irritation	[redacted]
7.1.5/01 (B.5.11.1.5)	Primary Eye Irritation in Rabbits	OECD 405 (1987); EC Directive 92/69/EEC method B.5 (1992), US EPA FIFRA guideline 81-4 (1984)	Not classified for eye irritation	[redacted]
7.1.6 (B.5.11.1.6)	Skin sensitization test in guinea pigs (Buehler patch test)	US EPA FIFRA guideline 81-6; OECD 406 (1987)	Not classified as a dermal sensitizer	[redacted]
7.1.6/01	Skin sensitization test in guinea pigs (modified Buehler; 9 application)	OECD 406 (1992); Commission Directive 96/54/EC B.6 (1996)	Not classified as a dermal sensitizer	[redacted]

Tier II summaries of previously reviewed studies (Sections 7.1.1 – 7.1.5) and new dermal sensitization study (Section 7.1.6) are presented below.

IIIA 7.1.1 Acute oral toxicity

Annex point	Author(s)	Year	Study title
IIIA, 7.1.1/01	[redacted]	1991a	Acute Oral Toxicity Study In Rats. [redacted] Report No.: [redacted]-91-261 Date: 1991-10-18 GLP: yes not published

Guideline:	US EPA FIFRA guideline 81-1 (1984), OECD 401 (1987), EEC directive 84/449/EEC method B.1 (1984).
Deviations:	None
Dates of experimental work:	1991-07-29 to 1991-08-12

Executive Summary

The acute oral toxicity of the test substance, MON 52276, was evaluated in Sprague-Dawley albino rats (5 per sex) by administration of 5000 mg/kg bw by gavage at a dose volume of 4.2 mL/kg bw. No mortality occurred during the study. Clinical signs noted 24 hours after dosing were faecal staining and / or soft stool, as well as oral and / or nasal discharge and hypo activity. There was no effect on body weight gain. The gross necropsy conducted at termination of the study revealed no observable abnormalities. The acute oral LD_{50} was

LD_{50}, oral, rat > 5000 mg/kg bw

According to EU and OECD Globally Harmonized System (GHS) classification criteria the test substance MON 52276 is not to be classified for acute oral toxicity.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	MON 52276
Description:	Amber liquid
Lot/Batch #:	LLN-9105-3135-F
Purity:	30.57% glyphosate acid equivalent
Stability of test compound:	Expiry data: May 1992.

2. Vehicle and/ or positive control: None

3. Test animals:

Species:	Rat albino
Strain:	Sprague-Dawley [CD-Crl:CD (SD)BR]
Source:	[redacted] US
Age:	Approx. 9-12 weeks
Sex:	Males and females
Weight at dosing:	Males: 330 - 354 g; females: 253 – 270 g

Acclimation period:	20 days
Diet/Food:	[redacted], *ad libitum* except for approx. 18 h before dosing and 4 hours after dosing
Water:	Tap water, *ad libitum*
Housing:	Individual housing in suspended, wire bottom, stainless steel cages.
Environmental conditions:	Temperature: 19 - 24°C Humidity: 40 - 70% Air changes: not reported 12-hour light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 1991-07-29 to 1991-08-12

Animal assignment and treatment:
Five fasted rats per sex received the test material at a dose level of 5000 mg/kg bw by oral gavage (limit test). Observations for mortality were made twice daily. A check for clinical signs of toxicity were made at least three times on the day of dosing and once daily thereafter for 14 days. Individual body weights were recorded just prior to fasting, prior to dosing and on Days 7 and 14. On Day 14 all surviving animals were sacrificed, subjected to gross necropsy and all abnormalities were recorded.

II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
Faecal staining and / or soft stool was noted in all animals after dosing on Day 1. A few animals also showed oral and / or nasal discharge, as well as hypo activity.

Table IIIA 7.1-2: Clinical signs observed after acute oral exposure

Clinical sign	Males*	Duration	Females*	Duration
Dry nasal discharge	2/5	Day 1	1/5	Day 1
Oral discharge	2/5	Day 1	0/5	--
Hypoactivity	1/5	Day 1	0/5	Day 1
Faecal staining	4/5	Day 1	1/5	Day 1
Soft stool	4/5	Day 1	5/5	Day 1

* number affected / total number

C. BODY WEIGHT
Body weight gain was unaffected by the administration of the test substance.

D. NECROPSY
The gross necropsy conducted at termination of the study revealed no observable abnormalities.

III. CONCLUSION

The oral LD_{50} of the test material (MON 52276) in rats was greater than 5000 mg/kg bw. Based on the EU and the OECD Globally Harmonized System (GHS) classification criteria, MON 52276 is not to be classified for acute oral toxicity.

IIIA 7.1.2 Acute percutaneous toxicity

Annex point	Author(s)	Year	Study title
IIIA, 7.1.2/01	[redacted]	1991b	Acute Dermal Toxicity Study In Rats. [redacted] Report No.: [redacted]-91-262 Date: 1991-10-18 GLP: yes not published

Guideline: US EPA FIFRA guideline 81-2 (1984)
OECD 402 (1987), EEC directive 84/449/EEC method B.3 (1984), JMAFF.

Deviations: None

Dates of experimental work: 1991-07-30 to 1991-08-13

Executive Summary

The acute dermal toxicity of the test substance, MON 52276, was evaluated in Sprague-Dawley albino rats (5 per sex) by dermal application of 5000 mg/kg bw for 24 hours. No mortality occurred during the study. There were no dermal effects or clinical signs of systemic toxicity. Body weight gain was not affected. The gross necropsy conducted at termination of the study revealed no observable abnormalities. The acute dermal LD_{50} was

LD_{50}, dermal, rat > 5000 mg/kg bw

According to EU and OECD Globally Harmonized System (GHS) classification criteria the test substance MON 52276 is not to be classified for acute dermal toxicity.

I. MATERIALS AND METHODS

1. **Test material:**

Identification:	MON 52276
Description:	Amber liquid
Lot/Batch #:	LLN-9105-3135-F
Purity:	30.8% glyphosate acid equivalent
Stability of test compound:	Expiry data: May 1992 (estimated)

2. **Vehicle and/ or positive control:** None

3. **Test animals:**

Species:	Rat albino
Strain:	Sprague-Dawley [CD-Crl:CD (SD)BR]

Source:	[redacted] US
Age:	Approx. 9-12 weeks
Sex:	Males and females
Weight at dosing:	Males: 312 - 360 g; females: 250 – 262 g
Acclimation period:	21 days
Diet/Food:	[redacted] *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Individual housing in suspended, wire bottom, stainless steel cages.
Environmental conditions:	Temperature: 19 - 24°C Humidity: 40 - 70% Air changes: not reported 12-hour light/dark cycle

B: STUDY DESIGN AND METHODS
In life dates: 1991-07-30 to 1991-08-13

Animal assignment and treatment:
A group of five Sprague-Dawley albino rats per sex received the undiluted test material at a dose level of 5000 mg/kg bw by dermal application to the clipped dorsal skin under an occlusive dressing for 24 hours. The dosing volume was 4.2 mL/kg bw. After 24 hours the dressing was removed and the application area was wiped free of residual test substance. Observations for mortality were made twice daily. A check for clinical signs of toxicity were made at least three times on the day of dosing and once daily thereafter for 14 days. Individual body weights were recorded just prior to clipping (one day before dosing), prior to dosing and on Days 7 and 14. On Day 14 all surviving animals were sacrificed, subjected to gross necropsy and all abnormalities were recorded.

II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
There were no dermal effects observed in any animal throughout the study period. There were no treatment-related clinical signs of toxicity.

C. BODY WEIGHT
Body weight gain was unaffected by the administration of the test substance.

D. NECROPSY
The gross necropsy conducted at termination of the study revealed no observable abnormalities.

III. CONCLUSION

The dermal LD_{50} of the test material (MON 52276) in rats was greater than 5000 mg/kg bw. Based on the EU and the OECD Globally Harmonized System (GHS) classification criteria, MON 52276 is not to be classified for acute dermal toxicity.

IIIA 7.1.3 Acute inhalation toxicity

An acute inhalation toxicity study has not been performed with MON 52276, because the criteria listed in Annex II (7.3.1) of Commission Regulation (EU) 545/2011, as well as draft SANCO/11803/2010 rev 00, are not met (see below):

MON 52276 is not / does not

a) a gas or liquified gas,
The pure active substance, glyphosate acid, is in the form of colorless crystals at ambient temperature, with a melting point of 189.5 °C. The preparation MON 52276 is a soluble liquid (SL) formulation

b) a smoke generating formulation or fumigant,

c) used with fogging/misting equipment,

d) a vapour releasing preparation,
The preparation is not a vapour releasing preparation. It is a soluble liquid (water based), which is mixed with water for application by hydraulic sprayers.

e) an aerosol,

f) a powder or a granule containing a significant proportion of particles of diameter <50 µm (> 1% on a weight basis),
MON 52276 is a soluble liquid, not a powder.

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

h) contain an active substance with a vapour pressure > $1x10^{-2}$ Pa and is not to be used in enclosed spaces such as warehouses or glasshouses,
The active ingredient, glyphosate acid, is essentially non-volatile. Its vapour pressure well below 1×10^{-2} Pa., the threshold for consideration as a volatile substance:

Vapour pressure: 1.31×10^{-5} Pa (25 °C)
Henry's Law Constant: 2.1×10^{-7} Pa × m^3 × mol^{-1}

Based on volatility, the calculated vapour density of glyphosate is less than 1 mg × m^{-3} at 25°C (equivalent to less than 6×10^{-9} moles × m^3).

In MON 52276, the active ingredient is formulated as the isopropylamine salt of glyphosate. The salt is less volatile than the acid:
Vapour pressure: 2.1×10^{-6} Pa (25 °C)
Henry's Law Constant: 4.0×10^{-10} Pa × m^3 × mol^{-1}

The calculated vapour density of the isopropylamine salt of glyphosate is less than 0.2 mg × m^{-3} at 25°C (equivalent to less than 1×10^{-9} moles × m^3).

Conclusion: there is an extremely low risk of exposure by inhalation of vapour from glyphosate acid or its isopropylamine salt during usage or from surfaces to which it has been applied.

Conclusion: there is an extremely low risk of exposure by inhalation of vapour from the surfactant during usage or from surfaces to which it has been applied.

i) to be applied in a manner which generates a significant proportion (greater than 1% on a weight basis) of particles or droplets of diameter <50 µm unless the applicant can justify an alternative approach under Directive 1999/45/EC or Regulation (EC) No 1272/2008, where applicable.
The product is recommended for use by spraying through hydraulic nozzles. Label recommendations propose that the nozzles used to atomise the spray mixture should produce a "medium" to "medium/coarse" spray quality as defined by the International (BCPC) spray classification system. Such nozzles produce a size range droplets suitable to optimise deposition on target weeds while reducing the proportion of droplets susceptible to drift.

Droplet spectra have been measured for MON 52276 using a standard nozzle typical of the type used on field sprayers ([redacted] 1999). The Spraying Systems 11003 nozzle used in the study is classified as producing a "fine/medium" spray and, therefore, represents a worst case in

terms of the proportion of small droplets produced. The results for MON 52276 are comparable to those from studies on other formulations of glyphosate. The droplet size data are measured and reported as % volume, however the specific gravity of a spray solution is close to 1.00.

Volume median diameter	246 µm	
Number median diameter	55 µm	
% total spray volume	< 50 µm	0.71 %
	< 10 µm	0.00 %

Less than 1% of the droplets are smaller than 50 µm, the parameter specified in Commission Regulation 545/2011 as a threshold for consideration of inhalation risk. In addition, droplets less than 10 µm are considered to be respirable. The volume of the spray present containing respirable droplets at the nozzle output was too small to be measured (less than 0.00 %, equivalent to <20 ml of the total volume of approximately 200 litres sprayed per treated hectare). Larger nozzles, such as Spraying Systems 11004, and "low drift nozzles", commonly used by farmers to reduce the risk of drift, produce fewer small droplets and represent an even lower risk than spray from standard nozzles.

Conclusion: there is an extremely low risk of exposure via the inhalation route during the application of MON 52276 as recommended on the product label. This rationale was accepted in the 2001 EU evaluation (Section B.5.11.1.3 of the 2001 EU monograph).

IIIA 7.1.4 Skin irritation

Annex point	Author(s)	Year	Study title
IIIA, 7.1.4/01	[redacted]	1991c	Primary dermal irritation study in rabbits. [redacted] Report No.: [redacted]-91-263 Date: 1991-10-18 GLP: yes not published

Guideline:	OECD 404 (1992); Commission Directive 92/69/EEC method B.4 (1992), US EPA FIFRA guideline 81-5 (1984)
Deviations:	None
Dates of experimental work:	1991-07-22 to 1991-07-25

Executive Summary

In a primary dermal irritation study, young adult New Zealand albino rabbits (4 male, 2 females) were dermally exposed to MON 52276. Two sites of clipped, intact skin of the back was exposed to 0.5 mL of the undiluted test substance, for 4 hours under semi-occlusive conditions. The rabbits were observed for 72 hours. Skin irritation was scored using the Draize scheme 1, 24, 48 and 72 hours after removal of the test substance.

Very slight to slight erythema were observed in two animals. No oedemas were observed at the application site of any animal at any observation time point. The overall mean for the 24, 48 and 72-hour readings were 0.11 for erythema and 0.0 for oedema.

Based on the scores for erythema and oedema and according to the EU and GHS classification criteria, MON 52276 is not to be classified for skin irritation.

I. MATERIALS AND METHODS

1. **Test material:**

Identification:	MON 52276
Description:	Amber liquid
Lot/Batch #:	LLN-9105-3135-F
Purity:	30.57% glyphosate acid equivalent
Stability of test compound:	Expiry data: May 1992 (estimated)

2. **Vehicle and/ or positive control:** None

3. **Test animals:**

Species:	Rabbit
Strain:	New Zealand White
Source:	[redacted] US
Age:	At least 8 weeks
Sex:	Males (4) and females (2)
Weight at dosing:	Males: 312 - 360 g; females: 250 – 262 g
Acclimation period:	49 days
Diet/Food:	Lab Rabbit Chow [redacted]
Water:	Tap water, *ad libitum*
Housing:	Individual housing in suspended, wire bottom, stainless steel cages.
Environmental conditions:	Temperature: 15 - 21°C Humidity: 40 - 60% Air changes: not reported 12-hour light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 1991-07-22 to 1991-07-25

Animal assignment and treatment:

The test was conducted using young adult New Zealand albino rabbits (4 male, 2 females). An amount of 0.5 mL of the undiluted test substance was applied to the intact skin on two sites of the clipped back of the rabbits on an approx. 6.25 cm^2 gauze patch. The patch was covered with a semi-occlusive dressing. After 4 hours of exposure the dressing was removed and the skin was cleaned with water.

Skin reactions were assessed approximately 0.5, 24, 48 and 72 hours after removal of the patch. The animals were observed for mortality and clinical signs twice daily.

II. RESULTS AND DISCUSSION

A. MORTALITY

No mortality occurred.

B. CLINICAL OBSERVATIONS

No clinical signs of systemic toxicity were observed during the study.

D. NECROPSY

No necropsy was performed.

E. SKIN OBSERVATIONS

All six animals exhibited very slight to slight erythema with no oedema. Five of the six animals were free of dermal irritation by 24-hours with the remaining animal free of irritation by 72-hours.

Table IIIA 7.1-3: Mean skin irritation scores

Effect	Mean score for each rabbit (24, 48, 72 hours)						Mean score	Mean score (right & left side)
Animal No. / sex	1♂	2♂	3♀	4♂	5♂	6♀		
Erythema (right side)	0.0	0.0	0.66	0.0	0.0	0.0	0.11	0.11
Erythema (left side)	0.0	0.0	0.66	0.0	0.0	0.0	0.11	
Oedema (right side)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.00
Oedema (left side)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	

III. CONCLUSION

Based on the EU classification criteria, MON 52276 is not to be classified for skin irritation. According to the OECD Globally Harmonized System (GHS) classification criteria MON 52276 is also not classified for skin irritation.

IIIA 7.1.5 Eye irritation

Annex point	Author(s)	Year	Study title
IIIA, 7.1.5/01	[redacted]	1992	Primary eye irritation study in rabbits. [redacted] Report No.: [redacted]-91-60 Date: 1991-09-24 (amended: 1992-02-05) GLP: yes not published

Guideline:	OECD 405 (1987); EC Directive 92/69/EEC method B.5 (1992), US EPA FIFRA guideline 81-4 (1984)
Deviations:	None
Dates of experimental work:	1991-01-14 to 1991-03-11

Executive Summary

In an eye irritation study, 0.1 ml of the undiluted test substance was instilled into the right conjunctival sac of six young adult New Zealand albino rabbits. Animals were observed for 7 days. Eye irritation was scored 1, 24, 48 and 72 hours and 7 days after test item instillation.

Application of MON 52276 into the rabbit eye resulted in slight to moderate conjunctival irritation in all animals. Iridial changes were noted in one animal 1 hour after instillation. There were no corneal effects noted. All eye effects were reversible within 7 days after instillation. The overall mean irritation scores (24 to 72 hours) of the six rabbits were as follows:

- for corneal opacity: 0.0;
- for iris lesions: 0.0
- for conjunctival redness: 1.1
- for chemosis of the conjunctiva: 0.0

Based on the study results, the test substance MON 52276 produced slight and very transient ocular effects. According to EU and GHS classification criteria the test substance MON 52276 is not to be classified for eye irritation

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	MON 52276
Description:	Clear, amber liquid
Lot/Batch #:	LLN-9102-2794-F
Purity:	30.39% glyphosate acid equivalent
Stability of test compound:	Expiry data: May 1992 (estimated)

2. Vehicle and/ or positive control: None

3. Test animals:

Species:	Rabbit
Strain:	New Zealand White
Source:	[redacted] US
Age:	At least 8 weeks
Sex:	Males (4) and females (2)
Weight at dosing:	2.6 – 2.8 kg
Acclimation period:	49 days
Diet/Food:	Lab Rabbit Chow [redacted]
Water:	Tap water, *ad libitum*
Housing:	Individual housing in suspended, wire bottom, stainless steel cages
Environmental conditions:	Temperature: 15 - 21°C
	Humidity: 40 - 60%
	Air changes: not reported
	12-hour light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 1991-01-14 to 1991-03-11

Animal assignment and treatment:
The test was conducted using six (3 per sex) young adult New Zealand white rabbits. An amount of 0.1 mL of the undiluted test substance was applied into the conjunctival sac of the right eye of the rabbits. The treated eyes were not rinsed after instillation. The right left remained untreated and served as the reference control. Eye reactions were assessed according to the EPA scoring system approximately 1, 24, 48 and 72 hours, and 7 days after instillation. Eye examinations using fluorescein were done one day prior to instillation, and at each examination time-point starting with the 24-hour observation until there was no stain retention for two observations. The animals were observed for mortality and clinical signs daily.

II. RESULTS AND DISCUSSION

A. MORTALITY

No mortality occurred.

B. CLINICAL OBSERVATIONS

No clinical signs of systemic toxicity were observed during the study.

C. EYE OBSERVATIONS

Slight to moderate conjunctival irritation (redness, chemosis, discharge) was noted in all rabbits. Slight iridial changes were observed in one animal at the 1-hour reading only. There were no corneal effects noted. Three rabbits were free of ocular changes at the 72-hour reading. The effects in the remaining three rabbits were resolved by Day 7 after instillation.

The group mean irritation scores (24 to 72 hours) were calculated to be 0.0 for corneal opacity, 0.0 for iris lesions, and 1.1 for conjunctival redness, and 0.0 for chemosis of the conjunctiva.

The individual scores for each time point, individual mean and group mean scores (24 to 72 hours) are presented in Table IIIA 7.1-4.

Table IIIA 7.1-4: Eye irritation scores

Rabbit No. (sex)	Scoring [h]	Cornea	Iris	Conjunctivae	
				Redness	Chemosis
1 (♀)	1	0	0	1	1
	24	0	0	1	0
	48	0	0	1	0
	72	0	0	0	0
	Mean (24, 48, 72 h)	**0.0**	**0.0**	**0.7**	**0.0**
2 (♂)	1	0	0	1	1
	24	0	0	1	0
	48	0	0	1	0
	72	0	0	0	0
	Mean (24, 48, 72 h)	**0.0**	**0.0**	**0.7**	**0.0**
3 (♀)	1	0	0	2	1
	24	0	0	0	0
	48	0	0	0	0
	72	0	0	0	0
	Mean (24, 48, 72 h)	**0.0**	**0.0**	**0.0**	**0.0**
4 (♂)	1	0	0*	2	1
	24	0	0	2	0
	48	0	0	2	0
	72	0	0	1	0
	Mean (24, 48, 72 h)	**0.0**	**0.0**	**1.7**	**0.0**
5 (♀)	1	0	0	1	1
	24	0	0	2	0
	48	0	0	2	0
	72	0	0	1	0
	Mean (24, 48, 72 h)	**0.0**	**0.0**	**1.7**	**0.0**
6 (♂)	1	0	0	1	1
	24	0	0	2	0
	48	0	0	2	0
	72	0	0	2	0
	Mean (24, 48, 72 h)	**0.0**	**0.0**	**2.0**	**0.0**
Group mean (24, 48, 72 h)		**0.0**	**0.0**	**1.1**	**0.0**

*Slight iridial effect

III. CONCLUSION

Based on the study results and based on the EU and the OECD Globally Harmonized System (GHS) classification criteria the test substance MON 52276 is not to be classified for eye irritation.

IIIA 7.1.6 Skin sensitization

Annex point	Author(s)	Year	Study title
IIIA, 7.1.6/01	[redacted]	2001	Skin sensitization test in guinea pigs (Modified Buehler test: 9 applications) [redacted] [redacted] Study No.: 2200[redacted]; Report No.: [redacted]-2001-153 Date: 2001-10-25 GLP: yes unpublished

Guideline: OECD 406 (1992), Commission Directive 96/54/EC B.6 (1996)

Deviations: None

Dates of experimental work: 2001-06-19 - 2001-08-01

Executive Summary

MON 52276 was tested for its sensitizing effect on the skin of the guinea pig in the modified Buehler test with nine induction treatments. The test-substance concentrations for the main test were selected based on the results of the pre-test. Both induction and challenge applications were performed with undiluted test substance. The study was performed using one control group consisting of 10 animals, and one test group consisting of 20 animals. None of the animals exhibited a positive skin reaction (defined as scores of ≥ 1) after the challenge treatment. The results of this GLP study confirm the results of the non-GLP study evaluated by the rapporteur in 2001, which followed the previous OECD 406 (1987) test guideline.

Based on the study results, MON 52276 is not to be classified according to EU classification criteria and OECD Globally Harmonized System (GHS) classification criteria for skin sensitisation.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	Mon 52276
Description:	Yellowish liquid
Lot/Batch #:	A1C1204104
Purity:	30.88%
Stability of test compound:	Expiry date: May 2003

2. Vehicle and/ or positive control: Purified water / mercaptobenzothiazole

3. Test animals:

Species:	Guinea pig
Strain:	Hartley, CRL:(HA)BR, (COBS-VAF)
Source:	[redacted] France

Age:	1 – 3 months
Sex:	Males and females
Weight at dosing:	males: 366± 18 g; females: 348 ± 17 g
Acclimation period:	at least 5 days
Diet/Food:	Pelleted diet ([redacted]), *ad libitum*
Water:	Filtered drinking water, *ad libitum*
Housing:	Individually in polycarbonate cages with autoclaved sawdust bedding
Environmental conditions:	Temperature: 21 ± 2°C
	Humidity: 30 - 70%
	Air changes: 12/hour
	12 hours light/dark cycle

B: STUDY DESIGN AND METHODS
In life dates: 2001-06-19 to 2001-08-01

Animal assignment and treatment:
MON 52276 was tested for its sensitising effect on the skin of the guinea pig using the modified Buehler method with nine induction treatments. Male and female Hartley guinea pigs, young adults were used. The test substance concentrations for the main study were selected based on the results preliminary test using test substance concentrations of 100 % and 75 % for both inductions and challenge treatments. The main study was performed in 20 test animals and 10 control animals.
In the main study the nine inductions were done on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 on the same intact flanks of the animals. 24 hours before the applications the treatment area was clipped. All inductions were performed under occlusive conditions with 4×4 cm test patches soaked with the undiluted test substance for 6 hours each. On Day 29 the challenge applications with undiluted test substance and vehicle were done to the clipped posterior right and left flanks of the animals under the same conditions as for the inductions. The control animals were treated with purified water for the induction treatments.
Skin reactions were assessed 24 and 48 hours after each induction and challenge treatment.
Body weights were determined at the first day of treatment of the main study and at termination. Mortality and clinical signs were recorded daily during the study period.
A positive control (reliability check) with a known sensitizer was performed in June 2001 in the laboratory according to the modified Buehler method. The positive control with mercaptobenzothiazole (20%) showed that the chosen guinea pig strain was able to detect sensitizing compounds under the laboratory conditions chosen.
Evaluation criteria for classification as a potential skin sensitizer:
At the 24-hour and/or 48-hour reading, 15% or more of the test animals exhibit a positive response (scores ≥ 1) in the absence of similar results in the vehicle control group.

II. RESULTS AND DISCUSSION

A. MORTALITY
No deaths occurred.

B. CLINICAL OBSERVATIONS
No signs of systemic toxicity were observed.

C. BODY WEIGHT
The body weight was not affected.

D. NECROPSY

No necropsy was performed.

E. SKIN REACTIONS

After the induction treatments discrete erythema (grade 1) were observed in a few animals. After challenge application, except for dryness of the skin at the 24-hour reading in one animal, no skin reactions were observed (see Table IIIA 7.1-5).

Table IIIA 7.1-5: Summary of positive skin responses after challenge exposure

Group	Test substance concentration	Reading time (h)	Number of animals with positive skin responses*
Test substance	100 % MON 52276	24	0/20
		48	0/20
Negative control	0 % MON 52276	24	0/10
	(i.e. 100% purified water)	48	0/10
Positive control**	20 % MBT***	48	7/10

* Number of animals with skin reactions / total number of animals
** Study performed in June 2001
*** MBT = mercaptobenzothiazole

III. CONCLUSION

Based on the EU classification criteria, MON 52276 is not to be classified for skin sensitisation. According to the OECD Globally Harmonized System (GHS) classification criteria MON 52276 is also not classified for skin sensitization.

IIIA 7.1.7 Supplementary studies for combinations of plant protection products

None.

IIIA 7.2 Short-term toxicity studies

No EC data requirement.

IIIA 7.3 Operator exposure

MON 52276 is formulated as a soluble liquid (SL) containing nominal 360 g glyphosate acid/L as the active substance. The product is used as herbicide for the control of annual, perennial and biennial weeds. Applications are made pre- and post-planting, and pre-emergence or pre-harvest of the crops, as well as post-emergence of weeds. Spray treatments are performed using tractor-mounted ground-boom sprayers and knapsack sprayers. A summary of the representative uses for MON 52276 is presented in Table IIIA 7.3-1 below.

Table IIIA 7.3-1: Summary of supported uses of MON 52276

Crop(s)	F	Application rate per treatment		Spray volume	Maximum in-use concentration	Number of treatments	Application technique
		[L product/ha]	[kg a.s./ha]	[L/ha]	[kg a.s./hL]	min - max	
All crops (pre-planting)	F	1 – 6*	0.36 – 2.16	100 - 400	2.16	1 – 2*	Tractor-mounted ground boom sprayer with hydraulic nozzles
All crops (post-planting/pre-emergence of crops)	F	1 - 3	0.36 – 1.08	100 - 400	1.08	1	
Cereals, oil seeds (both pre-harvest)	F	2 - 6	0.72 – 2.16	100 - 400	2.16	1	
Orchard crops, vines, incl. citrus & tree nuts (post emergence of weeds)	F	2 – 8*	0.72 – 2.88	100 - 400	2.88	1 – 3*	Knapsack sprayer
Orchard crops, vines, incl. citrus & tree nuts (post emergence of weeds; spot treatment)	F	2 – 8*	0.72 – 2.88	100 - 400	2.88	1 – 3*	

F = field use
* Maximum dose per season not to exceed 4.32 kg a.s./ha

Packaging profile

Container sizes of the product range from 1 – 20 L. All containers have a 63 mm anti-goggling wide-neck opening.

The review report for glyphosate 6511/VI/99-final – 21 January 2002 is considered to provide the relevant review information. The following table provides the EU endpoints that were in the previous evaluation. Since the last evaluation for glyphosate new studies on the active substance have been performed (see IIA 5 of the dossier for the active substance and chapter IIIA 7.6.2). Based on the new data, more appropriate values for the AOEL and dermal absorption were derived. The assessment below was based on recent product specific dermal absorption data. The exposure estimates were compared to the revised AOEL.

Table IIIA 7.3-2: Endpoints relevant for the MON 52276 operator exposure assessment

End-Point	Glyphosate
	Endpoints used in risk assessment[a]
Dermal penetration (MON 52276)	Concentrate: 0.09 % Spray dilutions: 0.34 %
AOEL	1.2 mg/kg bw/day

[a] Since Annex I inclusion new studies on the active substance have been performed (see AII 5 of the dossier of the active substance, and IIIA 7.6.2) and as a result there are new endpoints, which are used in the risk assessment.

The results of the exposure estimations using different levels of personal protective equipment (PPE) are summarised in the following table. Details of the exposure situations, the assumptions and parameters used for exposure estimations are described in IIIA 7.3.1 and IIIA 7.3.2. Detailed estimations are provided in Appendix 7-1 to Appendix 7-4.

Table IIIA 7.3-3: Estimated operator exposure to glyphosate from the use of MON 52276

	PPE Scenario*	Total systemic exposure** (mg/kg bw/day)	Total systemic exposure as % of AOEL*** (%)
Tractor-mounted spray application to low crops			
German model: Tractor-mounted ground boom sprayer • 20 ha/day • 6 L product/ha (≅ 2.16 kg a.s./ha) • 70 kg operator	None	0.0066	0.55
	None / with standard work wear	0.0034	0.28
UK-POEM: Tractor-mounted ground boom sprayer • 50 ha/day • 6 L product/ha (≅ 2.16 kg a.s./ha) • 100 L/ha • 60 kg operator	None	0.081	6.75
Knapsack applications to low-level targets – outdoors			
UK-POEM: knapsack sprayer • 1 ha/day • 8 L product/ha (≅ 2.88 kg a.s./ha) • 100 L/ha • 60 kg operator	None	0.226	18.8

* No PPE German Model: Operator wearing T-shirt and shorts.
No PPE / standard work wear German model: Operator wearing long work wear (coverall) but no PPE
No PPE UK POEM: Operator wearing long sleeved shirt, long trousers ("permeable") but no gloves
** Taking into account a dermal absorption of 0.09 % for the concentrated product and 0.34% for the spray solution
*** Compared to the proposed AOEL of 1.2 mg/kg bw/day

Assessment

Operator exposure was estimated according to the German model and UK-POEM for tractor-mounted ground boom applications in low crops, and according to the UK-POEM for hand-held spray applications in the field to low-level targets.

During tractor-mounted applications to low crops, the total systemic exposure to glyphosate according to the German model and UK-POEM is 0.0066 mg/kg bw/day and 0.081 mg/kg bw/day, respectively, if no PPE, and in addition for the German model no work wear is considered, is taken into account. These values correspond to 0.55% and 6.75% of the proposed AOEL of 1.2 mg/kg bw/day. With the use of standard work wear but no PPE the German model exposure estimate amounts to 0.0034 mg/kg bw/day, corresponding to 0.28% of the AOEL.

For hand-held applications to low level targets in the field the UK-POEM estimates account for 18.8% of the AOEL without using PPE.

In conclusion, based on worst-case exposure calculations, MON 52276 can be applied safely operators using tractor-mounted and hand-held application techniques without the use of PPE. These exposure data are conservative and higher than actual bio monitoring data, as discussed in section 7.3.3.

IIIA 7.3.1 Estimation of operator exposure assuming personal protective equipment is not used

For the intended use of MON 52276 the following exposure situations have to be considered:

1.) Tractor-mounted spray application to low-level targets - outdoors
2.) Hand-held spray application to low-level targets - outdoors

All exposure situations are addressed in the following.

1.) Tractor-mounted spray application to low-level targets - outdoors

The crops regarding this scenario are all crops pre-emergence, as well as cereals and oilseeds at crop maturity. Spray applications will be performed with tractor-mounted ground boom sprayers.
Exposure evaluations are done with the EU-wide accepted German model[1] and the UK-POEM[2]. According to the German model, the worst-case resulted from the highest application rate, whereas according to the UK-POEM the worst-case results from the highest in-use concentration. The input parameters for the model estimations are summarised in the following table.

Table IIIA 7.3-4: Input parameters for German model and UK-POEM estimations - tractor-mounted application to low crops – no PPE

Task	Mixing/loading and application	
Model	German model	UK-POEM
Model scenario	Tractor-mounted ground boom sprayer	
Clothing	No PPE* coverall and sturdy footwear*	No PPE (= standard work clothing)
Maximum application rate (L product/ha)	6	6
Maximum application rate (kg a.s./ha)	2.16	2.16
Container size	n.a.	10 L, 63 mm closure**
Minimum spray volume (L/ha)	n.a.	100
Treatment area (ha/day)	20	50
Operator bodyweight (kg)	70	60
Dermal absorption - product & spray dilution (%)	0.09 / 0.34	
Inhalation absorption (%)	100***	

* 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 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)

** Considering the application rate of 6 L product/ha and 50 ha treated per day the total amount of product used per day is 300 L. Thus, it is reasonable to use the 10 L-container scenario for estimations. The product is sold in wide neck (63 mm closure) containers, only.

*** Inhalation absorption conservatively assumed as 100%. Only 1% of the partials are considered respirable, while the remaining 99% ingested.

n.a. not applicable

[1] Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protections); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirschaft, Berlin-Dahlem, n° 277, 1992

[2] Estimation of Exposure and Absorption of Pesticides by Spray Operators, Scientific subcommittee on Pesticides and British Agrochemical association Joint Medical Panel Report (UK MAFF), 1986 and the Predictive Operator Exposure Model (POEM) V 1.0, (UK MAFF), 1992, 2007 version. ("UK POEM").

Details of the estimations are presented in Appendix 7-1 to Appendix 7-3. The results are summarised in Table IIIA 7.3-3 in chapter IIIA 7.3.

2.) Hand-held spray application to low-level targets - outdoors

Applications in orchard crops (round the base of the trunk) are performed with hand-held equipment (knapsack sprayer with hydraulic nozzles).

Exposure estimations are done according to the UK-POEM, since only this model covers a scenario for hand-held applications to low-level targets.

The input parameters for the model estimations are summarised in the following table.

Table IIIA 7.3-5: Input parameters for UK-POEM estimations - hand-held application to low-level targets

Task	Mixing/loading and application
Model	UK-POEM
Model scenario	Hand held sprayer: hydraulic nozzles, outdoor low-level target
Clothing	Standard work clothing - no PPE*
Maximum application rate (L product./ha)	8
Maximum application rate (kg a.i./ha)	2.88
Minimum spray volume (L/ha)	100
Container size (L)	10
Treatment area (ha/day)	1
Operator bodyweight (kg)	60
Dermal absorption - product / spray dilution (%)	0.09 / 0.34
Inhalation absorption (%)	100**

* No PPE = Operator wearing long sleeved shirt, long trousers ("permeable") but no gloves

** Inhalation absorption conservatively assumed as 100%. Only 1% of the partials are considered respirable, while the remaining 99% ingested.

Details of the estimations are presented in Appendix 7-4. The results are summarised in Table IIIA 7.3-3 in chapter IIIA 7.3.

IIIA 7.3.2 Estimation of operator exposure assuming personal protective equipment is used

Since the exposure estimations taking no PPE into account predict the systemic operator exposure to be below the AOEL, estimations taking PPE into account are not necessary.

IIIA 7.3.3 Measurement of operator exposure (mixer/loader/applicator)

Not necessary, since the estimations presented in IIIA 7.3.1 predict the operator exposure to be below the AOEL.

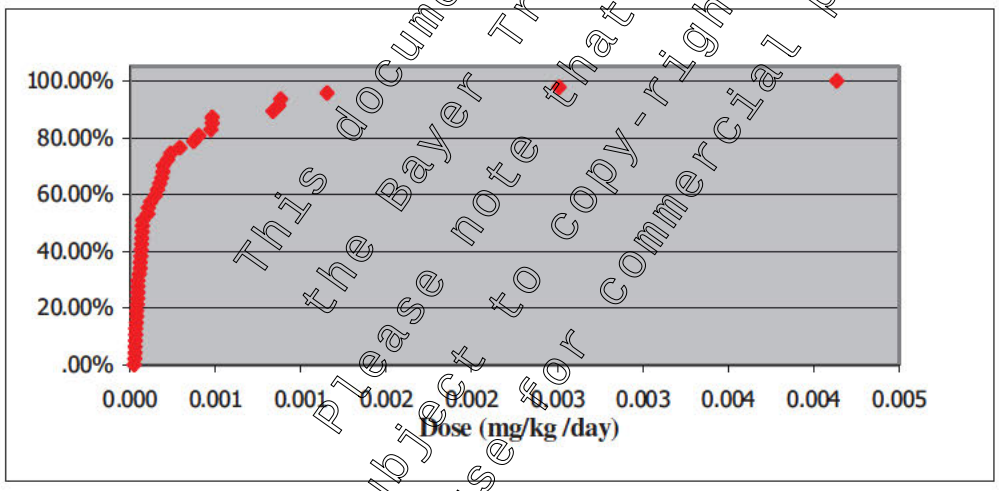
Furthermore, it has to be considered that exposure estimates from both the German BBA model and the UK-POEM are extremely conservative. Both models are based on passive dosimetry data, which tends to result in an over-estimation of real systemic exposure by nearly 10-fold. The complication of converting external potential exposure to external actual exposure based on default clothing permeation factors, and then further translating into a systemic dose based on dermal penetration, is indeed a difficult task. Furthermore, the 3% dermal uptake factor for glyphosate, as defined in the previous EU glyphosate evaluation, is very conservative.

A bio monitoring study of farmers, their spouses and children, the Farm Family Exposure Study (Acquavella et al., 2004[3]), provides for a more realistic assessment of the systemic exposure associated with the application of glyphosate formulations. This study was conducted in a southern (South Carolina) and northern (Minnesota) agricultural production area of the U.S. The purpose of the study was to quantify real-world pesticide exposure immediately before, during and after a pesticide application, and to identify significant exposure determinants. Forty-eight farm families, which included 79 children, provided urine specimens 24 hours before application, and for four consecutive 24-hour periods after. From these urine samples, 24-hour composite samples were created with amounts proportional to the volume of each individual sample, and analyzed for glyphosate residue levels.

Farmers were not instructed or coached by the study investigators on how to apply the products. All farmers used tractor-mounted boom-sprayers and applied Roundup® Ultra (Monsanto Company) over glyphosate tolerant crops early in the growing season. About one-third of the farmers made applications on between 4 and 18 hectares, another third on 18–50 ha, and another third on 50–178 ha. Application rates were according to label recommendations. Sixty percent of the applications were made using a closed-cab tractor. Although the use of gloves is not required by the U.S. Environmental Protection Agency when handling glyphosate products, 71% of the farmers wore rubber gloves during the application. Twenty-seven percent of the farmers repaired their equipment at some time during the application.

Glyphosate concentrations in the farmers' urine ranged from less than the limit of detection (LOD = 1 ppb) to a maximum of 233 ppb. Overall, only 60% of the farmer-applicators had detectable levels on the day of application, declining to only 27% on day 3 after application. Some farmers did not have detectable concentrations of glyphosate in their urine despite applications in excess of 40 hectares. Figure 7.2.3-1 shows the highly skewed cumulative frequency distribution of the systemic doses obtained for the farmer-applicators.

Figure 7.3.3-1: Systemic dose distribution for farmers applying glyphosate (Acquavella, 2004)



The maximum systemic dose was estimated to be 0.004 mg/kg/day. Field notes for this farmer indicated long periods (around 2 hours) of in-field repair of the spray boom, and evidence of spills during mixing and loading. This applicator treated 47 hectares in an open-cab tractor at an average application rate of 1.7 litres of Roundup Ultra/ha (612 g a.e./ha) at a spray volume of about 100 L/ha without wearing gloves.

In this study, the geometric mean systemic dose for farmers was 0.0001 mg/kg bw/day.

[3] Aquavella et al., 2004, Glyphosate Biomonitoring for Farmers and Their Families: Results from the Farm Family Exposure Study; *Env. Health Persp.*, Vol. 112, No. 3, March 2004

IIIA 7.4 Bystander exposure

The exposure estimations for bystanders and residents presented in this dossier are based on the German guidance paper for evaluation of bystander and resident exposure of Martin et al. (2008)[4].

Estimations are presented for both, adults and children. The results are presented in the following.

Bystander exposure

Table IIIA 7.4-1: Estimated bystander exposure to glyphosate and % of the AOEL

	Adult	Child
Dermal exposure (mg/kg bw/day)	0.000036	0.000028
Inhalation exposure (mg/kg bw/day)	0.00001	0.000021
Total systemic exposure (mg/kg bw/day)	0.000046	0.000049
Total systemic exposure as % of AOEL* (%)	< 0.01	< 0.01

* Compared to the AOEL of 1.2 mg/kg bw/day

Assessment
Exposure estimations according to the German guidance paper demonstrate that bystanders are not at risk, if they are exposed to spray drift during the application of MON 52276.
For adults and children, walking alongside a field at distance of 10 m from the spraying device, bystander exposure amounts to 0.000046 mg/kg bw/day and 0.000049 mg/kg bw/day. These exposure estimates corresponds to < 0.01% of the proposed AOEL of glyphosate (1.2 mg/kg bw/day).

Thus, it is concluded that bystanders are not at risk during accidental short-term exposure to spray drift of MON 52276.

Resident exposure

Table IIIA 7.4-2: Estimated resident exposure to glyphosate and % of the AOEL

	Adult	Child
Dermal exposure (mg/kg bw/day)	0.000004	0.000006
Inhalation exposure (mg/kg bw/day)	0.000276	0.000515
Oral exposure (mg/kg bw/day) – due to hand-to-mouth transfer	n.a.	0.000039
Oral exposure (mg/kg bw/day) – due to mouthing	n.a.	0.000010
Total systemic exposure (mg/kg bw/day)	0.00028	0.000568
Total systemic exposure as % of AOEL* (%)	0.02	0.05

* Compared to the AOEL of 1.2 mg/kg bw/day

Assessment
Exposure estimations reveal that residents are not exposed to critical levels of glyphosate. For adults and children staying in a garden adjacent to a field where MON 52276 was applied the predicted exposures amount to 0.00028 mg/kg bw/day and 0.000568 mg/kg bw/day, respectively. These values correspond to 0.02% and 0.05% of the AOEL of glyphosate, for adults and children, respectively.

Thus exposures to MON 52276 from applications in residential areas are considered acceptable.

Conclusion
It is concluded that neither bystanders, nor residents are at risk due to the intended use of MON 52276.

[4] Martin et al., Guidance for exposure and Risk Evaluation for Bystanders and Residents exposed to Plant Protection Products during and after application, J. Verbr. Lebensm., Vol 3, No. 3, p. 272-281, August 2008.

IIIA 7.4.1 Estimation of bystander exposure assuming personal protective equipment is not used

Bystanders are persons whose presence is incidental and unrelated to the application of pesticides. Therefore, bystander exposure is considered to be of short duration. It further can be assumed that any bystander, as soon as becoming aware of the exposure will leave the spraying area.

In addition, residents living or working adjacent to areas that are treated with pesticides may be exposed to pesticide residues during or after application. As for the bystander the presence of residents is incidental and unrelated to the application. However, exposure frequency and duration for residents is different as compared to bystanders.

Possible routes for bystander and residential exposure are via dermal and inhalation contact to the spray drift deposits. In addition, for residents exposure can occur due to volatilized residues after application.

The exposure assessment presented in the following based on the German guidance paper for evaluation of bystander and resident exposure (Martin et al. 2008)[4].

1). Bystander exposure

Bystander exposure results from spray drift that deposits on the body surface or passes the breathing zone. For bystander exposure estimation it is assumed that a bystander is walking along the boundary of a field at a distance of 10 meters from the spraying source. Considering that the drift deposition decreases with an increasing distance from the spraying device, exposure of the bystander is less than the applied dose. Drift data are available form a publication of Rautmann et al. (2001)[5]. For the corresponding exposure scenario in low growing field crops at 10 m distance a drift value of 0.29% of the applied dose is used for estimation of dermal exposure. This value corresponds to the 90th percentile (of individual values) in 10 m distance to the spraying device during applications to low-level targets. It is also assumed, that the person wears some clothing (T-shirt and shorts). Thus, the exposed uncovered body surface of an adult (head, face, neck front and back, forearms, half upper arms, hands, lower half of thighs, lower legs and feet) amounting to about 1 m^2 (US-EPA 1996)[6] is taken into account for estimations. For children the exposed body surface with the same level of clothing amounts to 0.21 m^2 (US EPA 2002)[7], and is applied for estimations.

Since the drift deposition data published by Rautmann et al. (2001) cannot easily be transposed into airborne concentrations and consequent inhalation exposure values, as a conservative evaluation, measured inhalation exposure data for the unprotected operator during spray applications according to the German model (Lundehn et al., 1992)[1], are used for estimation of bystander inhalation exposure.

In the following exposure evaluations are made for adults and children. For exposure estimations the maximum recommended use rate of 6 L MON 52276, as applied to field crops will be taken into account.

A summary of the parameters used for estimation of bystander exposure is given in Table IIIA 7.4-3 below.

[5] Workshop on Risk Assessment and Risk Mitigation Measures in the Context of the Authorization of Plant Protection Products (WORMM) 27.-29. September 1999; Organized by the Federal Biological Research Centre for Agriculture and Forestry,Biology Division, Braunschweig, Germany; edited by R. Forster & M. Streloke; Book 383; Berlin 2001

[6] US-EPA: OPPTS Occupational and Residential Exposure Test Guidelines; Series 875, 1996

[7] Child-Specific Exposure Factors Handbook. National Center for Environmental Assessment - Washington Office, Office of Research and Development, U.S. Environmental Protection Agency. Washington, D. C. 20460, September 2002

Table IIIA 7.4-3: Parameters used for bystander exposure estimation

Parameter		Glyphosate
AR	Maximum application rate (kg a.s./ha)	2.16
ar	Maximum application rate (mg a.s./m^2)	216
DA	Dermal absorption (%)	0.34
IA	Inhalation absorption (%)	100**
D	Spray drift (%)	0.29
T	Duration (minutes)	5
A	Area treated (ha/day)	20
BSA	Exposed body surface (m^2) – adult / child	1 / 0.21
I*	Specific inhalation exposure (mg a.s./ kg a.s. handled) – adult / child#	0.001 / 0.0005747
BW	Bystander body weight (kg) – adult / child	60 / 16.15

Based on geometric mean values proposed by the German BBA Model (Luhndehn at al, 1992) and inhalation rates of 1.74 m^3/h and 1.0 m^3/h for adults and children. Since the German model values based on an application period of 6 hours/day, adjustment to 5 minutes is required for exposure calculations.

** Inhalation absorption conservatively assumed as 100%. Only 1% of the partials are considered respirable, while the remaining 99% ingested.

Bystander exposure for adults and children is estimated according the following equations:

Systemic dermal exposure

$$SDE_B = \frac{ar \times D \times BSA \times DA}{BW}$$

Systemic inhalation exposure

$$SIE_B = \frac{I^* \times AR \times A \times T \times IA}{BW}$$

Total systemic exposure

$$SE_B = SDE_B + SIE_B$$

Detailed estimations are provided in Appendix 7-5 and Appendix 7-6. The results of the estimations are summarised in Table IIIA 7.4-1 in chapter IIIA 7.4.

2) Resident exposure

Residents are persons who live, work or are present in any other institution adjacent to an area where a pesticide has been applied. Their presence is incidental and unrelated to pesticide application activities.

Possible scenarios for residential exposure are persons who are standing, working, or sitting in a garden adjacent to the application area. They could be exposed to the plant protection products mainly via the dermal route from spray drift deposits and by inhalation of vapour drift (depending on the vapour pressure of the active substances). In addition, for small children oral exposure via hand-to-mouth transfer or mouthing behaviour has to be considered.

As for the bystander it is assumed that residents are unlikely to take actions to avoid or control exposure, and they wear only light clothing and no protective equipment. In addition, as conservative approach it is assumed that residents are located directly downwind of the centre of the treatment area at a distance of 10 m from the point of spray emission.

Considering that residents are dermally exposed to residue deposits it can be assumed that residues from more than one application are present. Thus, as proposed by Martin et al. (2008)[4] the 82nd percentile drift value is used. The corresponding drift value for field crops is 0.24% at a distance of 10 m to the treated area. For this scenario it is recommended that the accumulated application rate for two applications should

be used. However, since the maximum dose per season is lower than twice the maximum application rate the maximum dose per season (i.e. 4.32 kg a.s./ha; 12 L product/ha) will be taken into account for estimations.
Furthermore, it is reasonable to assume that residents stay longer in gardens than bystanders being present near an application site. Therefore, a default value of 2 hours (US-EPA, 2001)[8] is used for resident risk evaluations.
According to Martin et al (2008)[4] inhalation exposure has only to be considered for semi-volatile (vapour pressures (VP) of 1 x 10^{-5} – 5 x 10^{-3} Pa) and volatile (VP of ≥ 5 x 10^{-3} Pa) active substances. The active substance contained in MON 52276, glyphosate is considered semi-volatile according to the above given definition (VP (glyphosate) 1.31 x 10^{-5} Pa). Therefore, inhalation exposure for residential exposure is taken into account for estimations.
A summary of the parameters used for resident exposure of adults and children are given in the following table.

Table IIIA 7.4-4: Parameters used for resident exposure estimations

Parameter		Glyphosate
	Maximum application rate (kg a.s/ha) – maximum dose per season	4.32
AR	Maximum application rate (mg a.s./cm^2) - maximum dose per season*	0.0432
DA	Dermal absorption (%)	0.34
IA	Inhalation absorption (%)	100
OA	Oral absorption (%)	30
AC_V	Airborne concentration of vapour (mg/m^3)**	0.001
D	Spray drift (%) – 82nd percentile value***	0.24
T	Duration (hours)	2
TTR	Turf transferable residues (%) – adult / child	5
TC	Transfer coefficient (cm^2/hour) – adult / child	7300 / 2600
IR	Inhalation rate (m^3/day) – adult / child	16.57 / 8.31
SE	Salivation extraction factor (%) – children only	50
SA	Surface area of hands (cm^2) – children only	20
F	Frequency of hand-to-mouth events (events/hour) – children only	20
DFR	Dislodgeable foliar residues (%) – children only	20
IgR	Ingestion rate for mouthing of grass (cm^2)	25
BSA	Exposed body surface (m^2) – adult / child	1 / 0.21
BW	Resident body weight (kg) – adult / child	60 / 16.15

* According to Martin et al. 2008 the two-time rate is recommended for more than one application. Since the maximum dose/season is lower than twice the maximum application rate, the maximum dose/season is used.
** Since glyphosate is semi-volatile, i.e. the vapour pressure is between 1 x 10^{-5} Pa and 5 x 10^{-3} Pa (VP (glyphosate) of 1.31 x 10^{-5} Pa), the AC_V value is 0.001 mg/m^3.
*** According to Rautmann et al. (2001)

Resident exposure for adults and children is estimated according the following equations:

Systemic dermal exposure

$$SDE_R = \frac{AR \times D \times TTR \times TC \times T \times DA}{BW}$$

Systemic inhalation exposure

$$SIE_R = \frac{AC_V \times IR \times IA}{BW}$$

[8] US EPA (U. S. Environmental Protection Agency) (2001) Recommended revisions to the standard operating procedures (SOPs) for residential exposure assessment. Science Advisory Council for Exposure, Policy Number 12 (Original: December 18, 1997, Revised: February 22, 2001).

Systemic exposure due to hand-to-mouth transfer (children only)

$$SOE_H = \frac{AR \times D \times TTR \times SE \times SA \times F \times T \times OA}{BW}$$

Systemic exposure due to mouthing (children only)

$$SOE_O = \frac{AR \times D \times DFR \times IgR \times OA}{BW}$$

Total systemic exposure

Adults

$$SE_R = SDE_R + SIE_R$$

Children

$$SE_R = SDE_R + SIE_R + SOE_H + SOE_O$$

Detailed estimations are provided in Appendix 7-7. The results of the exposure estimations are summarised in Table IIIA 7.4-2 in chapter IIIA 7.4.

IIIA 7.4.2 Measurement of bystander exposure

Measurement of bystander exposure is not required since model estimations predict the systemic exposure to be within the AOEL.

IIIA 7.5 Worker exposure

For the intended uses of MON 52276 there are no foreseen re-entry activities.. The only reasonable re-entry scenario is inspection of the crops. However, for spray treatments pre- and post-planting, and pre-emergence of the crops, as well as post-emergence of weeds in orchards, crop inspection activities normally require no dermal contact to the foliage, but rather consist of a visual inspection.

As worst-case re-entry exposure during 2 hours of crop inspection activities following pre-harvest treatment of cereals and oilseeds were assessed. Exposure evaluations were done according to the German worker re-entry model (Krebs et al., 2000)[9]. The results are presented below.

Table IIIA 7.5-1: Estimated worker exposure to glyphosate and % of the AOEL

Scenario	Unprotected professional worker during crop inspection after pre-harvest treatments in cereals or oilseeds*
Dermal exposure (mg/person/day)	21.6
Absorbed dose (mg/kg bw/day)	0.0012
Total systemic exposure as % of AOEL** (%)	0.1

* Worker wearing shoes, socks, long-sleeved shirt, and long trousers

** Compared to the AOEL of 1.2 mg/kg bw/day

[9] Krebs. et al.; 2000; Uniform Principles for Safeguarding the Health of Workers Re-entering Crop Growing Areas after Application of plant protection products (Nachrichtenbl. Deut. Pflanzenschutzdienstes, 52(1), p. 5-9, 2000

Assessment
Worker exposure was estimated taking into account conservative worst-case assumptions, regarding dislodgeability, deposition and transfer of the residues.
For a professional worker wearing adequate work clothing but no PPE when performing re-entry activities like crops inspection, the estimated systemic exposure to glyphosate amounts to 0.0012 mg/kg bw/day. This value corresponds to only 0.1 % of the proposed AOEL of 1.2 mg/kg bw/day for glyphosate.

IIIA 7.5.1 Estimation of worker exposure assuming personal protective equipment is not used

Worker exposure is estimated based on the German worker re-entry model[9].

The following assumptions are considered for exposure assessment:
- Due to the low vapour pressure of glyphosate respiratory exposure is considered not relevant.
- Re-entry exposure is predominantly via the dermal route (skin contact with the treated surfaces)

For the dermal exposure the transfer of residues to the skin or clothes depends on:
- The intensity of contact with surfaces which can be described by a generic transfer coefficient (in cm^2/hour)
- The amount of dislodgeable foliar residues (or transferable residues on surfaces) (µg a.s./cm^2)
- The exposure duration (hours/day)

The amount of residues on the treatment area depends on:
- Application rate
- Extent of remaining residues from previous applications

Since pre-harvest treatments performed only once per season only the residues remaining from one application nedd to be considered.

As an estimate, it is presumed that workers re-enter the treated crop after the spray has dried.

Dislodgeable foliar residues
As first tier a Dislodgeable Foliar Residue (DFR) default value of 1 µg a.s./cm² for an application rate of 1 kg a.s./ha, can be assumed. This value is derived according to the following consideration:
An application rate of 1 kg a.s./ha is equivalent to 10 µg/cm^2.
With two-sided leaves this value corresponds to 5 µg/cm^2.
Assuming a leaf area index (LAI) of ca. 3 - 5 the value is reduced to 1-1.66 µg/cm^2, resulting in a DFR-value of about 1 µg/cm^2.

Transfer coefficient
For the transfer of residues from foliage to the clothes or skin of a worker, the German re-entry model proposes a transfer coefficient of 30,000 cm²/person/h be used in initial estimates of exposure. This value is considered to represent a worst case for potential dermal worker exposure, being derived from tasks requiring intensive contact with foliage. However, where it is considered less intensive contact with the foliage will occur the risk assessment may be refined by the use of alternative transfer coefficients. For scouting activities after pre-harvest applications it is reasonable to assume a much lower intensity of contact with the plant surface than for tasks like hand harvesting. Therefore, a transfer coefficient of 5,000 cm^2/person/h as proposed by the German re-entry model will be taken into account, which still is considered a conservative approach. This TC value represents a worker wearing adequate work clothing (long sleeved shirt, trousers, socks, shoes), but no personal protective clothing (PPE), like gloves.

Pre-harvest treatments of MON 52276 are done only once per season. Thus, only the one-time application rate is considered for estimations. This is in contrast to the resident re-entry evaluation (see IIIA 7.4), which considered the two-time application rate for MON 52276. Additionally a work duration of 2 hours per day for scouting activities are taken into account.

Thus, an overall conservative approach is chosen to assess exposure of the professional worker. The parameters used for the calculation of worker exposure are summarised in the following table.

Table IIIA 7.5-2: Parameters used for worker exposure estimation

Parameter		Value for glyphosate
DFR	Dislodgeable foliar residues (default) (µg/cm^2 x kg a.s./ha)	1
TC	Transfer coefficient (cm^2/hour)*	5000
T	Working time (hours/day)	2
AR	Maximum application rate (kg a.s./ha) – pre-harvest application	2.16
DA	Dermal absorption (%)	0.34
BW	Worker body weight (kg)	60

* TC for re-entry activities with less contact to treated foliage (according to Krebs et al., 2000[9]); considered clothing: Worker wearing shoes, socks, long-sleeved shirt, and long trousers

Worker exposure for adults and children is estimated according the following equations:

Dermal exposure

$$D\,(\text{mg/person/day}) = \frac{DFR \times AR \times TC \times T}{1000}$$

Total absorbed dose

$$\text{Total absorbed dose}\,(\text{mg/kg bw/d}) = \frac{D \times DA}{BW}$$

The results of the estimation are summarised in Table IIIA 7.5-1 in chapter IIIA 7.5.

IIIA 7.5.2 Estimation of worker exposure assuming personal protective equipment is used

Not necessary, since estimations without personal protective equipment predict the worker exposure to be below the AOEL.

IIIA 7.5.3 Estimation of worker exposure assuming personal protective equipment is used and using data generated on dislogeable residues under the proposed conditions of use

Not necessary, since estimations without personal protective equipment predict the worker exposure to be below the AOEL.

IIIA 7.5.4 Measurement of worker exposure

Not necessary, since estimations without personal protective equipment predict the worker exposure to be below the AOEL.

IIIA 7.6 Dermal absorption

The dermal absorption of glyphosate was assessed *in vitro* through human skin with MON 52276. The results are summarised below. A detailed summary is provided in IIIA 7.6.2.

Table IIIA 7.6-1: Summary of glyphosate dermal absorption from MON 52276

Study	% of applied dose*			Reference
	concentrate	Spray dilutions		
SL formulation	**360 g/L**	**29.6 g/L**	**2.51 g/L**	
In vitro (human skin)	0.086	0.169	0.342	IIIA 7.6.2 [redacted], 2010

* The absorption values correspond to total amounts potentially absorbable through human skin (i.e. amounts of radioactivity recovered in the receptor fluid and remaining skin after tape stripping with two strips).

The results of the *in vitro* study predict the dermal absorption of glyphosate from potential exposure to a 360 g/L glyphosate formulation would be less than 1%.

IIIA 7.6.1 Dermal absorption in vivo in the rat

No *in vivo* dermal absorption study has been performed.

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

A dermal absorption study in human skin was performed. A summary of this study is presented below.

Annex point	Author(s)	Year	Study title
IIA, 7.6.2/01	[redacted]	2010	360 g/L Glyphosate SL Formulation (MON 522276) – In vitro absorption of Glyphosate through human epidermis [redacted] Study No.: [redacted]2084, Report No.: [redacted]2084-[redacted] Date: 2010-02-19 GLP: yes Unpublished

Guideline: OECD 428

Deviations: None

Dates of experimental work: 2009-06-09 - 2009-08-26

Executive Summary

The objective of this study was to evaluate the potential dermal absorption of glyphosate from a 360 g/L SL formulation concentrate, as well as from two representative in-use dilutions prepared as 1:12.5 (v/v) and 1:150 (v/v) aqueous dilutions.

^{14}C-glyphosate was incorporated into the concentrate formulation and dilutions prior to application. The doses were applied to human epidermal membranes at a rate of 10 µL/cm^2 and left unoccluded for an exposure period of 24 hours. The absorption process was followed by taking samples of the receptor fluid (physiological saline) at recorded intervals throughout the exposure period. The distribution of glyphosate within the test system and a 24-hour absorption profile were determined. All samples were analysed by liquid scintillation counting (LSC).

Conclusion

The results of this *in vitro* study indicate the dermal absorption of glyphosate through human skin is very slow, and that the vast majority of glyphosate will be washed off during normal washing procedures.

The total amounts absorbed after 24 hours were 0.009 %, 0.029% and 0.092 % for the concentrate, 1:12.5 (v/v) and 1:150 (v/v) dilution, respectively. The reported total potentially absorbable amounts, represented by the mean absorbed dose together with the amounts in the remaining skin were 0.064 %, 0.134 % and 0.277 %, respectively. However, these were based on 5 tape strips to remove test material remaining in the *stratum corneum*. Individual tape strip values were reported so as to permit recalculations based on the removal of only 2 tape strips, as follows; 0.086%, 0.169% and 0.342% biologically available for the concentrate, 1:12.5 (v/v) and 1:150 (v/v) dilution, respectively.

Thus, the results predict that the dermal absorption of glyphosate from potential exposure to this 360 g/L glyphosate / L SL formulation would be less than 1%, irrespective of whether two or five tape strips were considered to contain non-biologically available glyphosate.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test materials:

a) Non radio-labelled test substance:

Identification:	Isopropyamine salt of glyphosate techn. material (glyphosate-IPA)
Description:	Clear, water white to amber viscous liquid (solution in water)
Lot/Batch #:	A8B60170S0
Chemical purity:	Glyphosate-IPA: 63.81 % Glyphosate acid: 47.28%
Stability of test compound:	Expiry date: 2012-01-25

b) Analytical reference standard:

Identification:	Glyphosate acid
Description:	White solid
Lot/Batch #:	GLP-0810-19515
Chemical purity:	99.8 %
Stability of test compound:	Expiry date: 2011-01-31

c) Radio-labelled test substance

Identification:	^{14}C-glyphosate (as glyphosate acid)
Lot/Batch #:	53463-3-23
Chemical purity:	99.8 %
Radiochemical purity:	97.8 % (confirmed by analysis)
Specific activity:	47 mCi/mmol; 1739 MBq/mmol; 277.9 µCi/mg; 10.28 MBq/mg
Stability of test compound:	Not reported

c) Blank formulation

Identification:	Proprietary surfactant blend (MON 8153)
Concentration of a.s.:	0 %
Description:	Not reported
Lot/Batch #:	Not reported
Stability of test compound:	Not reported

d) Formulated test substance

Identification:	MON 52276
	The formulation concentrate used was not supplied as complete formulation, but had to be prepared from the ingredients a) and c) described above, to allow the incorporation of the radiolabel.
	The test substance concentration in the prepared formulation was confirmed by analysis.

2. Test skin source:

Species:	Human
Source:	Tissue bank (not further specified)

B: STUDY DESIGN AND METHODS

Preparation of skin samples:
Human skin samples were immersed in water at 60 °C for 40-45 seconds and the epidermis was teased away from the dermis. Each membrane was given an identifying number and stored frozen, at approximately -20 ºC, on aluminium foil until required for use.

Test substance preparation
Three test substance concentrations representing the formulation concentrate and two field dilutions were prepared at target concentrations of 360 g/L, 29.6 g/L and 2.51 g/L. The nominal radioactivity contained in the dose preparations was 3.3 MBq.

Radioactive stock solution of ^{14}C-glyphosate
Dry ^{14}C-glyphosate was solubilised in 2 mL of water and mixed thoroughly.

High dose (formulation concentrate, 360 g/L)
A pre-mix was prepared by mixing 3900 mg glyphosate-IPA technical material with an appropriate amount of proprietary surfactant blend. 78 µL (≡ 78 mg) of the radioactive stock solution was mixed with 482 mg of the pre-mix. Water was added to give a total weight of 585 mg. The solution was mixed well. Assuming a density of 1.17 g/mL, the total weight was equivalent of 0.5 mL at a nominal concentration of 369 g glyphosate/L.

Intermediate dose, (1:12.5 (v/v) aqueous dilution, 29.6 g/L)
A pre-mix was prepared by mixing 305.92 mg glyphosate-IPA technical material with an appropriate amount of proprietary surfactant blend. 78 µL (≡ 78 mg) of the radioactive stock solution was mixed with 38.01 mg of the pre-mix. Water was added to give a total weight of 500 mg. The solution was mixed well. Assuming a density of 1 g/mL, the total weight was equivalent of 0.5 mL at a nominal concentration of 29.6 g glyphosate/L.

Low dose (1:150 (v/v) aqueous dilution, 2.51 g/L)
A pre-mix was prepared by mixing 76.90 mg glyphosate-IPA technical material with an appropriate amount of proprietary surfactant blend. 78 µL (≡ 78 mg) of the radioactive stock solution was mixed with 2.64 mg of the pre-mix. Water was added to give a total weight of 500 mg. The solution was mixed well. Assuming a density of 1 g/mL, the total weight was equivalent of 0.5 mL at a nominal concentration of 2.51 g glyphosate/L.

Analyses of dose preparations
The radioactivity content of the stock solution was determined by liquid scintillation counting (LSC) analyses of sub-samples of solvent dilutions. The radiochemical purity of the radiolabelled test substance was determined by high performance liquid chromatography (HPLC).
The radioactivity content and homogeneity of the dose preparations were checked by LSC analyses. The radiochemical purity and stability was measured by HPLC analyses.

Preparation of diffusion cells
The skin membranes were placed in static glass diffusion cells providing an exposure area of 2.54 cm^2 of skin. The cells had a receptor volume of approximately 4.5 mL.
An integrity test was performed by measuring the electrical resistance across the skin membranes. Membranes with a resistance of ≥ 10 kΩ were considered having a normal integrity and used for the absorption study.
Physiological saline was chosen as receptor fluid. The skin surface temperature was maintained at 32 ± 1 °C using a water bath.

Test substance application and sampling
Prior to dosing a pre-treatment sample of 500 µL was taken from each diffusion cell, and replaced by an equal amount of fresh receptor fluid.
Each dose formulation was applied to the skin membrane at the rate of 10 µL/cm^2 exposed skin area (25.4 µL dose), corresponding to target concentration of 3693 mg/cm^2, 296 µg/cm^2 and 25.1 µg/cm^2 for the high, intermediate and low dose level, respectively. The applications were left un-occluded for 24 hours.
Receptor fluid samples (500 µL) were taken by an auto-sampler at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours after application. After each sampling the removed amount of receptor fluid was replaced by an equal amount of fresh receptor fluid.

Terminal procedures
After the last sampling, 24 hours after application the remaining receptor fluid was discarded. The receptor chamber was rinsed with receptor fluid that was also discarded.
The donor chamber was carefully removed and the undersides wiped with a single natural sponge, pre-wetted with 3%Teepol L® in water, which was added to the wash sponges. The donor chamber was washed with deionised water and a sample was taken for LSC analysis.
The epidermal surface of the skin was decontaminated by gently swabbing the application site with natural sponges pre-wetted with 3% Teepol L® in water. Decontamination was shown to be complete following assessment of residual radioactivity levels on the skin surface with a Geiger counter. The skin surface was washed with further sponges pre-wetted with water. All the sponges were combined and digested in Soluene 350® and made up to a recorded volume. A sample was taken for analysis.
The surface of the skin was allowed to dry naturally
Each skin membrane was tape stripped using 3M Scotch 'Magic' tape to a maximum of five strips. The tape strips were soaked individually in 30% v/v methanol in water to extract any test material. The extracts were sequentially numbered and analysed by LSC. In some cases, it was not possible to take the full five tape strips as the epidermis began to tear, therefore tape stripping was discontinued. The last tape strip for these diffusion cells was digested with the remaining epidermis, so as not to underestimate residues in the remaining epidermis compartment. The remaining epidermis was carefully removed from the receptor chamber and digested in Soluene 350® and the whole digest analysed by LSC.

Analysis of samples
Liquid samples of the receptor fluid, washing solutions, digested wash sponges, tape strip extracts and digested epidermis by LSC using a Packard 3100 TR LSC counter and Goldstar as scintillation fluid.
Results of the analysis of the samples of receptor fluid collected in the study were expressed as amounts of glyphosate in the receptor solution in terms of (µg/cm^2. The amounts absorbed, rates of absorption (µg/cm^2/h) and 'percentage of dose absorbed' were calculated. Membranes with absorption profiles that indicate membrane damage during the course of the experiment have been excluded from calculations. The results of the mass balance and distribution determinations are expressed in terms of amount absorbed and 'percentage of applied dose
The absorbed dose is considered the glyphosate detected in the receptor fluid, while the potentially biologically available proportion of the dose is regarded as the sum of absorbed dose and the amount recovered from the epidermis after tape stripping. The test material removed from the surface of the epidermis by the washing procedure, as well as the glyphosate recovered from the epidermis at the end of the exposure is considered unabsorbed.

II. RESULTS AND DISCUSSION

A. ANALYSES OF UNFORMULATED ^{14}C-GLYPHOSATE
HPLC analysis of the unformulated sample of ^{14}C-glyphosate confirmed a radiochemical purity of 97.8%.

B. ANALYSES OF DOSE PREPARATIONS
The achieved concentration of glyphosate in the dose preparations was calculated to be 369.3, 29.6 and 2.52 g glyphosate /L in the formulation concentrate, 1/12.5 v/v dilution and 1/150 v/v dilution, respectively.

LCS analyses confirmed the dose solutions to be homogeneous.

C. DERMAL ABSORPTION OF GLYPHOSATE

The determnined distribution of radioactivity for the different dose groups are summarised in Table IIIA 7.6-2 below.

Table IIIA 7.6-2: Summary of results for dermal absorption of ^{14}C-glyphosate - SL formulation

Dose preparation	**High (concentrate)**		**Intermediate (1:12.5 v/v dilution)**		**Low (1:150 v/v dilution)**	
Nominal concentration [g/L]	360		29.6		2.51	
Actual concentration [g/L]	369.3		29.6		2.52	
Applied dose [µL/cm^2]	10		10		10	
Applied dose [µg/cm^2]	3693		296		25.2	
Number of cells accessed	4*		6		4*	
	Distribution of radioactivity (mean values)					
	µg/cm^2	% of applied dose	µg/cm^2	% of applied dose	µg/cm^2	% of applied dose
Surface compartment						
Stratum corneum (5 tape strips)	2.39	0.065	0.386	0.130	0.081	0.320
Stratum corneum (first 2 tape strips)	1.57	0.043	0.283	0.096	0.065	0.256
Skin wash	3656	99.0	288	97.4	24.8	98.4
Donor chamber	83.4	2.26	6.67	2.26	<LOQ	0.008
Receptor compartment						
Receptor fluid (0-24 h)	0.322	0.009	0.086	0.029	0.023	0.092
Total absorbed	**0.322**	**0.009**	**0.086**	**0.029**	**0.023**	**0.092**
Remaining epidermis (after 5 tape strips)	2.02	0.055	0.310	0.105	0.047	0.185
Remaining epidermis (after 2 tape strips)	2.84	0.077	0.413	0.140	0.063	0.250
Total potentially absorbable** (after 5 tape strips)	2.343	0.063	0.396	0.134	0.070	0.276
Total potentially absorbable (after 2 tape strips)**	**3.162**	**0.086*** **	**0.499**	**0.169**	**0.086**	**0.342*** **
Total recovery	**3744**	**101**	**296**	**100**	**25.0**	**99.0**
Absorption rates [µg/cm^2/h] (0-24h)	0.014		0.003		0.001	

* Some cells for these applications were excluded from calculations as the analytical data indicated that the epidermal membrane may have been damaged during application.
** Total potentially absorbable = total absorbed + remaining epidermis
*** Dermal absorption values used for exposure assessment

The overall total recovery for the three dose levels was good, with mean values of 99.0 – 101 % of the applied dose.

Glyphosate absorption from the 360 g/L concentrate formulation was essentially constant over the entire 24 hour exposure period (mean rate = 0.014 µg/cm^2/h). By the end of the exposure period, the mean total amount of absorbed glyphosate was 0.322 µg/cm^2 (0.009% of applied dose).

From the intermediate and low-dose aqueous dilutions of the formulation, absorption was fastest during the early period of absorption, with 0.010 µg/cm^2/h, (0-1h) and 0.004 µg/cm^2/h, (0-2h), respectively. The rates after this early period until the end of the exposure at 24h were 0.003 µg/cm^2/h and 0.001 µg/cm^2/h for the intermediate and low dose dilutions, respectively. At the end of the exposure period, the mean total amounts of absorbed glyphosate were 0.086 and 0.023 µg/cm^2 (0.029% and 0.092% of applied dose), respectively.

For the formulation concentrate and both aqueous dilutions, the vast majority of the applied glyphosate was removed from the surface of the epidermis during the washing procedure at the end of the 24-hour exposure period (mean 97.4-99.0%). The mean total amount of glyphosate recovered from the epidermis was 0.120%, 0.235% and 0.505% of the applied dose for the concentrate, intermediate and low dose dilution, respectively.
The amount of potentially biologically available glyphosate (absorbed + epidermis after tape striping) for the concentrate, intermediate and low dose dilutions were 0.064%, 0.134% and 0.277% respectively for 5 tape strips and more conservatively 0.086%, 0.169% and 0.342% respectively for only 2 tape strips.

III. CONCLUSION

The results of this *in vitro* dermal absorption study indicate that the absorption of glyphosate through human skin is very limited and very slow. The vast majority of glyphosate was removed from the skin by the washing procedures.
The total absorbed amounts after 24 hour exposure were 0.009 %, 0.029 % and 0.092 % of the applied dose for the formulation concentrate, the 1:12,5 (v/v) and 1:250 (v/v) dilution, respectively.
The corresponding total potentially absorbable amounts, represented by the mean absorbed dose together with the amounts in the remaining skin were 0.063 %, 0.134 % and 0.276 %, respectively for 5 tape strips and more conservatively 0.086%, 0.169% and 0.342% respectively for only 2 tape strips.

IIIA 7.7 Dislogeable residues

No EC data requirement

IIIA 7.7.1 Dislogeable residues – foliar

No EC data requirement

IIIA 7.7.2 Dislogeable residues – soil

No EC data requirement

IIIA 7.7.3 Dislogeable residues – indoor surface re-volatilisation

No EC data requirement

IIIA 7.8 Epidemiology

No EC data requirement

IIIA 7.9 Data on formulants

IIIA 7.9.1 Material safety data sheet for each formulant

Copies of the safety data sheets of the formulants are provided in Document J of this dossier.

IIIA 7.9.2 Available toxicological data for each formulant

Please refer to the material safety data sheets provided in Document J of this dossier.

IIIA 7.10 Domestic animal/livestock safety

No EC data requirement

IIIA 7.11 Other/special studies

None.

Appendix 7-1: German model – tractor-mounted ground boom application (hydraulic nozzles) at low-level targets – 6 L MON 52276/ha; corresponding to 2.16 kg glyphosate / ha – no PPE (without standard work clothing)

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Product	MON 52276		Active substance	glyphosate	
Formulation type	Liquid		a.s. concentration	360	g/l
Dermal absorption from product	0.09	%	Dermal absorption from spray	0.34	%
RPE during mix/loading	None		RPE during application	None	
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	None
Dose	6	l product/ha	Work rate/day	20	ha

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2.4	mg/kg a.s.
Hand contamination/day	103.68	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	103.68	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0.0006	mg/kg a.s.
Inhalation exposure/day	0.02592	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.02592	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed boom sprayer: hydraulic nozzles

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	0.06	0.38	1.6	
Dermal contamination/day	2.592	16.416	69.12	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	88.128	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0.001	mg/kg a.s.
Inhalation exposure/day	0.0432	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.0432	mg/day

ABSORBED DOSE

	Mix/load		Application		
Dermal exposure to a.s.	103.68	mg/day	88.128	mg/day	
Percent absorbed	0.09	%	0.34	%	
Absorbed dose (dermal route)	0.093312	mg/day	0.2996352	mg/day	
Inhalation exposure to a.s.	0.02592	mg/day	0.0432	mg/day	
Total systemic exposure	0.119232	mg/day	0.3428352	mg/day	

PREDICTED EXPOSURE

Total systemic exposure	0.4620672	mg/day
Operator body weight	70	kg
Operator exposure	**0.0066**	mg/kg bw/day

AOEL of glyphosate	1.2	mg/kg bw/day
Percentage of the AOEL	0.55	%

Appendix 7-2: German model – tractor-mounted ground boom application (hydraulic nozzles) at low-level targets – 6 L MON 52276/ha; corresponding to 2.16 kg glyphosate / ha – no PPE (with standard work clothing)

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Product	MON 52276		Active substance	glyphosate	
Formulation type	Liquid		a.s. concentration	360	g/l
Dermal absorption from product	0.09	%	Dermal absorption from spray	0.34	%
RPE during mix/loading	None		RPE during application	None	
PPE during mix/loading	None				
PPE during application: Head	None	Hands	None	Body	Coverall and sturdy footwear
Dose	6	l product/ha	Work rate/day	20	ha

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2.4	mg/kg a.s.
Hand contamination/day	103.68	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	103.68	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0.0006	mg/kg a.s.
Inhalation exposure/day	0.02592	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.02592	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Tractor-mounted/trailed boom sprayer: hydraulic nozzles

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	0.06	0.38	1.6	
Dermal contamination/day	2.592	16.416	69.12	
Protective clothing	none	none	Coverall and sturdy footwear	
Transmission to skin	100	100	5	%
Total dermal exposure to a.s.	22.464	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0.001	mg/kg a.s.
Inhalation exposure/day	0.0432	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.0432	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	103.68	mg/day	22.464	mg/day
Percent absorbed	0.09	%	0.34	%
Absorbed dose (dermal route)	0.0933 12	mg/day	0.0763776	mg/day
Inhalation exposure to a.s.	0.02592	mg/day	0.0432	mg/day
Total systemic exposure	0.119232	mg/day	0.1195776	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0.2388096	mg/day
Operator body weight	70	kg
Operator exposure	**0.0034**	mg/kg bw/day

AOEL of glyphosate	1.2	mg/kg bw/day
Percentage of the AOEL	0.28	%

Appendix 7-3: UK-POEM – tractor-mounted ground boom application (hydraulic nozzles) at low-level targets – 6 L MON 52276/ha; corresponding to 2.16 kg glyphosate / ha; 100 L/ha – no PPE

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Product	MON 52276		Active substance	glyphosate	
Formulation type	water-based		a.s. concentration	360	mg/ml
Dermal absorption from product	0.09	%	Dermal absorption from spray	0.34	%
Container	10 litres 63 mm closure				
PPE during mix/loading	None		PPE during application	None	
Dose	6	l/ha	Work rate/day	50	ha
Application volume	100	l/ha	Duration of spraying	6	h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	6	litres product/ha
Work rate	50	ha/day
Number of operations	30	/day
Hand contamination	1.5	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	1.5	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

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

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	1.5	ml/day	41.55	ml/day
Concen. of a.s. product or spray	360	mg/ml	21.6	mg/ml
Dermal exposure to a.s.	540	mg/day	897.48	mg/day
Percent absorbed	0.09	%	0.34	%
Absorbed dose	0.486	mg/day	3.051432	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	21.6	mg/ml
Inhalation exposure to a.s.	1.296	mg/day
Percent absorbed	100	%
Absorbed dose	1.296	mg/day

PREDICTED EXPOSURE

Total absorbed dose	4.833432	mg/day
Operator body weight	60	kg
Operator exposure	**0.081**	mg/kg bw/day
AOEL	1.2	mg/kg bw/day
Percentage of the AOEL	6.75	%

Appendix 7-4: UK-POEM – hand-held sprayer application (hydraulic nozzles) at low-level targets – 8 L MON 52276/ha; corresponding to 2.188 kg glyphosate / ha, 100 L/ha – no PPE

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Hand-held sprayer (15 l tank): hydraulic nozzles. Outdoor, low level target				
Product	MON 52276		Active substance	glyphosate	
Formulation type	water-based		a.s. concentration	360	mg/ml
Dermal absorption from product	0.09	%	Dermal absorption from spray	0.34	%
Container	10 litres 63 mm closure				
PPE during mix/loading	None		PPE during application	None	
Dose	8	l/ha	Work rate/day	1	ha
Application volume	100	l/ha	Duration of spraying	6	h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	8	litres product/ha
Work rate	1	ha/day
Number of operations	7	/day
Hand contamination	0.35	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	0.35	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Hand-held sprayer (15 l tank): hydraulic nozzles. Outdoor, low level target				
Application volume	100	spray/ha			
Volume of surface contamination	50	ml/h			
Distribution	Hands		Trunk	Legs	
	25%		25%	50%	
Clothing	None		Permeable	Permeable	
Penetration	100%		10%	18%	
Dermal exposure	10		2.5	4.5	ml/h
Duration of exposure	6	h			
Total dermal exposure to spray	102	ml/day			

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0.35	ml/day	102	ml/day
Concen. of a.s. product or spray	360	mg/ml	28.8	mg/ml
Dermal exposure to a.s.	126	mg/day	2937.6	mg/day
Percent absorbed	0.09	%	0.34	%
Absorbed dose	0.1134	mg/day	9.98784	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.02	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	28.8	mg/ml
Inhalation exposure to a.s.	3.456	mg/day
Percent absorbed	100	%
Absorbed dose	3.456	mg/day

PREDICTED EXPOSURE

Total absorbed dose	13.55724	mg/day
Operator body weight	60	kg
Operator exposure	**0.226**	mg/kg bw/day
AOEL	1.2	mg/kg bw/day
Percentage of the AOEL	18.83	%

Appendix 7-5: Bystander exposure of adults

Product		**MON 52276**	Formulation type	liquid
Application rate of product	[L / ha]	6		
Active substance		**glyphosate**		
Content of a.s.	g/L	360		
Application rate of a.s. (AR)	[kg a.s./ha]	2.1600		
(ar)	[mg a.s./m^2]	216		
Dermal absorption (DA)	[%]	0.34%		
Inhalation absorption (IA)	[%]	100%		
Application equipment		Tractor-mounted ground boom sprayer		
Drift (D)	[%]	0.29%	(90th percentile)	
Duration (T)	[min]	5		
Area treated (A)	[ha/day]	20		
Exposed body surface area (BSA)	[m^2]	1		
Bodyweight (BW)	[kg]	60		
Specific inhalation exposure (I*)	[mg/kg a.s]	0.001		
Adults		**glyphosate**		
Systemic dermal exposure SDE_B	[mg/kg bw/day]	3.57048E-05		
(SDE_B = (ar x D x BSA x DA)/BW				
Systemic inhalation exposure SIE_B	[mg/kg bw/day]	0.00001		
(SIE_B = (I* x AR x A x T x IA)/BW				
Total systemic exposure (SE_B)	**[mg/kg bw/day]**	**0.000046**		
(SE_B = SDE_B + SIE_B)				
AOEL	[mg/kg bw/day]	1.2		
Percent of AOEL	**[%]**	**0.0038**		

Appendix 7-6: Bystander exposure of children

Product		**MON 52276**	Formulation type	liquid
Application rate of product	[L / ha]	6		
Active substance		**glyphosate**		
Content of a.s.	g/L	360		
Application rate of a.s. (AR)	[kg a.s./ha]	2.1600		
(ar)	[mg a.s./m^2]	216		
Dermal absorption (DA)	[%]	0.34%		
Inhalation absorption (IA)	[%]	100%		
Application equipment		Tractor-mounted ground boom sprayer		
Drift (D)	[%]	0.29%	(90th percentile)	
Duration (T)	[min]	5		
Area treated (A)	[ha/day]	20		
Exposed body surface area (BSA)	[m^2]	0.21		
Bodyweight (BW)	[kg]	16.15		
Specific inhalation exposure (I*)	[mg/kg a.s]	0.000574713		
Children		**glyphosate**		
Systemic dermal exposure SDE_B	[mg/kg bw/day]	2.78564E-05		
(SDE_B = (ar x D x BSA x DA)/BW				
Systemic inhalation exposure SIE_B	[mg/kg bw/day]	2.13516E-05		
(SIE_B = (I* x AR x A x T x IA)/BW				
Total systemic exposure (SE_B)	**[mg/kg bw/day]**	**0.000049**		
(SE_B = SDE_B + SIE_B)				
AOEL	[mg/kg bw/day]	1.2		
Percent of AOEL	**[%]**	**0.0041**		

Appendix 7-7: Resident exposure of adults and children

Product		**MON 52276**	Formulation type	liquid
Application rate of product	[L / ha]	12	(max. dose/season)	
Active substance		**glyphosate**		
Content of a.s.	g/L	360		
Application rate of a.s.	[kg a.s./ha]	4.320		
(AR)	[mg a.s./cm^2]	0.0432		
Dermal absorption (DA)	[%]	0.34%		
Inhalation absorption (IA)	[%]	100%		
Oral absorption (OA)	[%]	30%		
Airborne concentration of vapour (AC_V)	[mg/m^3]	0.001		

		Adults	**Children**	
Drift (D)	[%]	0.24%	0.24%	(82nd percentile)
Duration (T)	[hours]	2.0	2.0	
Turf Transferable Residues (TTR)	[%]	5.00%	5.00%	
Transfer coefficient (TC)	[cm^2/hour]	7300	2600	
Inhalation rate (IR)	[m^3/day]	16.57	8.31	
Saliva extraction factor (SE)	[%]		50.00%	
Surface area of hands (SA)	[cm^2]		20	
Frequency of hand-to mouth events (FR)	[events/hour]		20	
Dislodgeable foliar residues (DFR)	[%]		20.00%	
Ingestion rate for mouthing of grass (IgR)	[cm^2]		25	
Bodyweight (BW)	[kg]	60	16.15	

Adults

		glyphosate
Systemic dermal exposure SDE_R (SDE_R = (AR x D x TTR x TC x T x DA)/BW	[mg/kg bw/day]	4.31412E-06
Systemic inhalation exposure SIE_R (SIE_R = (AC_V x IR x IA)/BW	[mg/kg bw/day]	0.000276167
Total systemic exposure (SE_R) (SE_R = SDE_R + SIE_R)	**[mg/kg bw/day]**	**0.00028**
AOEL	[mg/kg bw/day]	1.2
Percent of AOEL	**[%]**	**0.02**

Children

		glyphosate
Systemic dermal exposure SDE_R (SDE_R = (AR x D x TTR x TC x T x DA)/BW	[mg/kg bw/day]	5.7085E-06
Systemic inhalation exposure SIE_R (SIE_R = (AC_V x IR x IA)/BW	[mg/kg bw/day]	0.000514551
Systemic oral exposure (SOE_H) (SOE_H = (AR x D x TTR x SE x SA x FR x T x OA)/BW	[mg/kg bw/day]	3.85189E-05
Systemic oral exposure (SOE_O) (SOE_O = AR x D x DFR x IgR x OA)/BW	[mg/kg bw/day]	9.62972E-06
Total systemic exposure (SE_B) (SE_R = SDE_R + SIE_{R+} SOE_H + SOE_O)	**[mg/kg bw/day]**	**0.000568**
AOEL	[mg/kg bw/day]	1.2
Percent of AOEL	**[%]**	**0.05**