Animal assignment and treatment: In a primary dermal irritation study, three male, young adult, New Zealand White rabbits were each given a dermal application of 0.5 g of undiluted Glyphosate Technical (96.3% w/w Glyphosate technical).

Approximately 24 hours prior to the test the hair was clipped from the back and flanks of the animals with an electric clipper, exposing an area approximately 10 cm x 10cm. Animals with overt signs of skin injury or marked irritation which may have interfered with the interpretation of the results were not used in the test.

On the day of treatment, 0.5g of glyphosate technical was placed on a surgical gauze pad (approximately 2.5 cm x 2.5 cm). This gauze pad was applied to the intact skin of the clipped area and was kept in contact with the skin by a patch with a surrounding adhesive hypoallergenic plaster. The entire trunk of the animals was then wrapped with plastic wrap held in place with an elastic stocking.

The dressing was left in place for 4 hours after which it was removed and the skin was flushed with lukewarm tap water to clean the application site so that any reactions (erythema) were clearly visible.

As it was suspected that the test item might produce irritancy a single animal was treated first. As no corrosive effect was observed after the 4-hour exposure, the test was completed using the two remaining animals.

The animals were checked daily for signs of systemic toxicity and mortality. Body weights were recorded on the day of application and at termination of observations.

The skin reaction was assessed according to the numerical scoring system listed in the Commission Directive 2004/73/EC, April 29, 2004 which was based on the Draize scoring system (***Draize, 1959; Draize et al 1944)*** approximately 1, 24, 48 and 72 hours after the removal of the dressing, gauze patch and test item. The mean score was calculated across 3 scoring times (24, 48 and 72 hours after patch removal) for each animal for erythema/eschar grades and for oedema grades, separately. An animal was positive when the mean score was 2 or greater. The test was positive for irritation when at least 2 animals were positive for the same endpoint (erythema/eschar or oedema).

The Cumulative Scores for the Skin Irritation Scores were calculated and represent the sum of all numerical scores for each animal at each time point. The resulting Mean Cumulative Skin Irritation Score was calculated for all animals at each time point.

The Primary Irritation Index (P.I.I.) was calculated by totalling the mean cumulative scores at 24, 48 and 72 hours and then dividing by the number of available figures.

II. RESULTS AND DISCUSSION

No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred. The bodyweights of all rabbits were considered to be within the normal range of variability. There was no staining of the skin, alterations or corrosive effects.

At the observations 1 and 24 hours after patch removal, very slight erythema (score 1) was observed in one animal. No signs of irritation were observed in the other treated animals throughout the study.

As no signs of irritation were observed 72 hours after patch removal, the study was terminated after the 72 hour observation.

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Table 5.2-23: Individual and mean skin irritation scores of Glyphosate technical

Time	Erythema			Oedema		
Animal number	606	622	620	606	622	620
after 1 hour	0	1	0	0	0	0
after 24 hours	0	1	0	0	0	0
after 48 hours	0	0	0	0	0	0
after 72 hours	0	0	0	0	0	0
mean score 24-72 h	0	0.3	0	0	0	0

III. CONCLUSION:

According to the Draize classification criteria, glyphosate technical is considered to be a "mild-irritant" to rabbit skin (P.I.I. = 0.11).

IIA 5.2.5 Eye irritation

In the 2001 EU glyphosate evaluation undiluted glyphosate acid was found to be strongly irritating to rabbit eyes, requiring classification as severely irritating and labelling as **R41 – 'Risk of serious damage to eyes'** according to EU classification criteria. The corresponding GHS classification is **'Irreversible effects on the eye/serious damage to eyes (Category 1)'**. Recently performed studies on the eye irritating potential of glyphosate acid supported the previous findings ([redacted] 2007, [redacted] 2009b). There was markedly less eye irritation observed with the salts used in glyphosate based formulations. Glyphosate salts in formulations are of a more neutral pH than glyphosate acid which is not the form used in commercial products. Thus, the glyphosate salts need not to be classified for eye irritation.

Table 5.2-24: Summary of eye irritation studies with glyphosate acid

	Reference (Data owner)	Species Strain	Number and /or sex of animals	Purity [%]	Amount applied Exposure conditions	Effects / Result
Studies from the 2001 evaluation	Annex B-5.2.6.1, Glyphosate Monograph [redacted] 1994c (Herbex)	Rabbit NZW	1 ♀	95	0.1 mL (ca. 76 mg)	Due to strong ocular effects the test was stopped for humane reasons after 1 hour irritant
	Annex B-5.2.6.1, Glyphosate Monograph [redacted] 1994f (Alkaloida)	Rabbit NZW	4 ♀	97.2	100 mg (pure)	Significant ocular lesions, especially chemosis irritant
	Annex B-5.2.6.1, Glyphosate Monograph [redacted] 1991e (FSG)	Rabbit NZW	2 ♂, 1 ♀	96.8	100 mg	Mortality (1♀: severe enteritis and opacity); significant ocular lesions that were not reversible within 3 weeks moderately irritating
	Annex B-5.2.6.1, Glyphosate Monograph [redacted] 1991b (I. Pi. Ci.)	Rabbit NZW	3 ♂	98	100 mg (pure)	Several ocular effects (score 1 & 2) that were reversible within 3 days slightly irritant

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	Reference (Data owner)	Species Strain	Number and /or sex of animals	Purity [%]	Amount applied Exposure conditions	Effects / Result
Studies from the 2001 evaluation	Annex B-5.2.6.1, Glyphosate Monograph [redacted] 1990d (AGC)	Rabbit NZW	3 ♀	98.1	100 mg	Corneal opacity not reversible within 7 days (2♀), iris lesions not reversible within 6 days (1♀), conjunctivcal redness not reversible within 6 days (3 ♀) slightly irritant
	Annex B-5.2.6.1, Glyphosate Monograph [redacted] 1989d (CHE)	Rabbit NZW	1 ♂	98.6	100 mg (pure)	Due to strong ocular effects the test was stopped for humane reasons after treatment of the first of six animals moderately to severely irritating
	IIA 5.2.5 [redacted] 1996 (CHE)	Rabbit NZW	6 ♂, 3 ♀	98.2	65 mg one group (3♂, 3 ♀) eyes were not washed; one group (3♂, 3♀) eyes were washed 30 sec after treatment	Severely irritating (washed eyes) moderately irritating (non-washed eyes)
Studies not reviewed in the 2001 evaluation	IIA 5.2.5/01 [redacted] 2007b (NUF)	Rabbit NZW	1 ♂ 2 ♀	95.1	100 mg	Marked, early-onset and transient ocular changes, like very slight to slight corneal opacity, slight to marked conjunctival redness, conjunctival chemosis, reddening of the sclera and discharge. All eye effects were reversible within 10 days after instillation. No signs of corrosion or staining were observed in any eye. irritating
	IIA 5.2.5/02 [redacted] 2009b (HAG)	Rabbit Himalayan	3 ♂	96.4	100 mg (eyes were rinsed 1 h post-application)	slight and fully reversible ocular changes (≤ grade 1); all eye effects were reversible within 8 days after instillation. No signs of corrosion or staining were observed in any eye Non irritant
	IIA 5.2.5/03 [redacted] 1995b (ALS)	Rabbit NZW	12 ♀	97.56	100 mg (pure) (one group without irrigation of eyes, two groups with irrigation of eyes at different time intervals after application)	Severely irritating; animals in the irrigation groups showed reduced eye irritation and faster recovery
	IIA 5.2.5/04 [redacted] 2009c (EXC) (Expert statement)	Rabbit	Not applicable	96.66	Test solution: 1% in purified water	Not performed since pH of test item solution was < 2 (corrosive)

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	Reference (Data owner)	Species Strain	Number and /or sex of animals	Purity [%]	Amount applied Exposure conditions	Effects / Result
Studies not reviewed in the 2001 evaluation	IIA 5.2.5/05 [redacted] 2009d (HAG)	Rabbit Himalayan	3 ♂	98.8	100 mg (eyes were rinsed 1 h post-application)	Non irritant
	IIA 5.2.5/06 [redacted] 2010b (HAG)	Rabbit Himalayan	3 ♂	97.3	100 mg (eyes were rinsed 1 h post-application)	Non irritant
	IIA 5.2.5/07 [redacted] 2009d (HAG)	Rabbit NZW	2♂, 1 ♀	96.4	0.1 mL (93.2 mg)	Irritant
	IIA 5.2.5/08 [redacted] 2005e (HAG)	Rabbit NZW	3 ♂	97.23	0.1 mL (96.0 mg)	Irritant
	IIA 5.2.5/09 [redacted] 2008b (HAG)	Rabbit NZW	1 ♂ 2 ♀	98.05	100 mg	Severely irritating
	IIA 5.2.5/10 [redacted] 1988c (MON)	Rabbit NZW		92.76		Produced corneal opacity and conjunctival irritation with blistering, irritation persisted in 4/5 rabbits on day 21
	IIA 5.2.5/11 [redacted] 1997 (SYN)	Rabbit NZW	6 ♀	95.6	100 mg	Moderately irritant (according to Kay & Chalandra)
	IIA 5.2.5/12 [redacted] 2007d (SYN)	Rabbit NZW	1 ♂ 2 ♀	98.1	100 mg	Slight conjunctival redness, conjunctival chemosis, reddening of the sclera and discharge were observed. These effects were reversible and were no longer evident 7 days after treatment.
	IIA 5.2.5/13 [redacted] 2011b (SYN)	Rabbit NZW	3 ♂	96.3	100 mg	Corrosive. Due to strong ocular effects the test was stopped for humane reasons after 24 hours.

NZW = New Zealand White

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Table 5.2-25: Summary of eye irritation studies with glyphosate salts

	Reference (Data owner)	Species Strain	Number and /or sex of animals /	Purity [%]	Amount applied / Exposure conditions	Results
Studies from the 2001 evaluation	Annex B-5.2.6.2, Glyphosate Monograph [redacted] 1994c (MON / CHE)	Rabbit NZW	1 ♂, 5 ♀	IPA 62%	0.1 mL (pure) (pre-treatement with local anaesthetic)	Iris, conjunctivae: redness & chemosis within 1 h; discharge after 1 h Slightly irritating
	Annex B-5.2.6.2, Glyphosate Monograph [redacted] 1989d (I.Pi.Ci.)	Rabbit NZW	3 ♂, 3 ♀	IPA 62	0.1 mL; ♂: eyes unrinsed; ♀: eyes rinsed	Conjunctival redness (24 h) Slightly irritating
	Annex B-5.2.6.2, Glyphosate Monograph [redacted] 1987e (MON/CHE)	Rabbit NZW	6	NH_4-salt 90.8	0.1g	conjunctivae: redness & chemosis (48h), discharge in all animals within 48 h mucous membrane appearing blistered in all animals after 1 h Slightly irritating

NZW = New Zealand White

Tier II summaries are only presented for studies not previously evaluated in the 2001 EU glyphosate evaluation.
For details regarding studies reviewed during the 2001 EU evaluation we refer to the Monograph and the former dossier.

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Annex point	Author(s)	Year	Study title
IIA, 5.2.5/01	[redacted]	2007b	Glyphosate Technical (NUP 05068): Primary Eye Irritation Study In Rabbits [redacted] [redacted] Study No.: B02305 Data owner: Nufarm Date: 2007-03-06 GLP: yes unpublished

Guideline:	OECD 405 (2002); Commission Directive 2004/73/EC B.5 (2004), JMAFF guideline 2-1-5 (2005)
Deviations:	None
Dates of experimental work:	2007-01-17 - 2007-02-26

Executive Summary

In an eye irritation study, 0.1 g of the undiluted test substance was instilled into the left conjunctival sac of three young adult New Zealand albino rabbits. Animals were observed for 14 days. Eye irritation was scored using the Draize scheme 1, 24, 48 and 72 hours and 7, 10 and 14 days after test item instillation.
Application of glyphosate technical (NUP 05068) into the rabbit eye resulted in the earlyand transient onset of the ocular changes of very slight to slight corneal opacity, slight to marked conjunctival redness, conjunctival chemosis, reddening of the sclera and discharge. All eye effects were reversible within 10

days after instillation. No signs of corrosion or staining were observed in any eye. The individual mean irritation scores (24 to 72 hours) of the three rabbits were as follows:

- for corneal opacity: 1.67, 2.0 and 0.67;
- for iris lesions: 0.0, 0.0, 0.0
- for conjunctival redness: 2.67, 2.22, 2.0
- for chemosis of the conjunctiva: 2.0, 2.0, 1.0.

Based on the study results, the test substance glyphosate technical (NUP 05068) is irritating to the rabbit eye. According to EU classification criteria the test substance glyphosate technical (NUP 05068) is to be classified as irritating to the eyes (Xi, R36). This corresponds to Category 2A according to the OECD Globally Harmonized System (GHS) classification criteria.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate technical

Identification:	NUP 05068
Description:	Solid
Lot/Batch #:	200609062
Purity:	95.1%
Stability of test compound:	Stable under storage conditions (20 ± 5°C), light protected; Expiry date: 2008-09-14

2. Vehicle and/ or positive control: None

3. Test animals:

Species:	Rabbit
Strain:	New Zealand White, SPF
Source:	[redacted] The Netherlands
Age:	15 weeks (male), 12 and 15 weeks (females)
Sex:	One male and 2 females
Weight at dosing:	2.969 kg (male), 2.605 kg and 3.416 kg (females)
Acclimation period:	At least five days
Diet/Food:	Pelleted standard [redacted] rabbit maintenance diet ([redacted]), *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Individually in stainless steel cages with feed hoppers and drinking water bowls. Wood blooks and haysticks were provided for gnawing.
Environmental conditions:	Temperature: 17 - 23°C Humidity: 30 - 70% Air changes: 10 - 15/hour 12 hours light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 2007-01-17 to 2007-02-26

Animal assignment and treatment:
The test was conducted using young adult New Zealand albino rabbits (1 male, 2 females). The test was performed in a sequential manner, first using one animal. Since no corrosive or severe eye effects were observed in the first animal the test was completed using the remaining two rabbits. An amount of 0.1 g of the solid test substance was applied into the conjunctival sac of the left eye of the rabbits. The lids were then gently held together for about one second. The treated eyes were not rinsed after instillation. The right eye remained untreated and served as the reference control. Eye reactions were assessed according to the scoring system listed in Commission Directive 2004/73/EC approximately 1, 24, 48 and 72 hours, as well as 7, 10 and 14 days after instillation. Scleral reddening and ocular discharge was also assessed. The animals were observed for mortality and clinical signs daily. Body weights were determined at beginning of acclimatisation, on the day of application and at termination.

II. RESULTS AND DISCUSSION

A. MORTALITY
No mortality occurred.

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

C. BODY WEIGHT
All rabbits showed the expected body weight gain.

D. NECROPSY
No necropsy was performed.

E. EYE OBSERVATIONS
Very slight to slight corneal opacity were observed in all rabbits from 1 hour after instillation up to 72 hours. No signs of iritis, corrosion or staining were observed in any animal throughout the study period. One hour after instillation slight to moderate conjunctival redness was observed in the treated eyes of all rabbits. By 24 hours the redness increased to marked in two animals and to moderate in one rabbit. After 48 hours the conjunctival redness decreased in all rabbits. Only slight redness was observed in the rabbits after 7 days. Moderate to marked chemosis of the conjunctivae was observed from 1 hour after instillation up to 24 hours. The swelling decreased with time. 72 hours after treatment slight swelling was still present in two animals. One hour after instillation two rabbits exhibited moderate ocular discharge. Moderate or marked discharge was observed in all animals at the 24-hour reading time point. This persisted at the 48-hour reading as slight or moderate in all rabbits. After 72 hour slight discharge was still present in one rabbit.
Reddening of the sclera was observed in all animals. However, one hour after instillation sclera of one animal was not assessable due to conjunctival swelling. In two animals moderate or marked reddening of the sclera was observed at this time point. After 24 hours all rabbits showed marked reddening of the sclera. This sign persisted in the rabbits as moderate or marked at the 48- and 72-hour readings. In one animal slight reddening was still present after 7 days. All rabbits were free of ocular signs by day 10 after instillation.

The group mean irritation scores (24 to 72 hours) were calculated to be 1.5 for corneal opacity, 0.0 for iris lesions, and 2.2 conjunctival redness, and 1.7 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 5.2-26.

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Table 5.2-26: Results of the eye irritation test

Animal	Scoring [h]	Cornea		Iris	Conjunctiva		Sclera
		Opacity	Area		Redness	Chemosis	
Rabbit 1 (male)	1	1	1	0	2	3	3
	24	2	2	0	3	3	3
	48	2	2	0	3	2	3
	72	1	1	0	2	1	2
	Day 7	0	0	0	1	0	1
	Day 10	0	0	0	0	0	0
	Day 14	0	0	0	0	0	0
Mean (24, 48, 72 h)		**1.67**	**---**	**0.0**	**2.67**	**2.0**	**---**
Rabbit 2 (female)	1	1	1	0	1	2	2
	24	2	4	0	2	2	3
	48	2	4	0	2	2	3
	72	2	4	0	2	1	2
	Day 7	0	0	0	1	0	0
	Day 10	0	0	0	0	0	0
	Day 14	0	0	0	0	0	0
Mean (24, 48, 72 h)		**2.0**	**---**	**0.0**	**2.0**	**2.0**	**---**
Rabbit 3 (female)	1	1	4	0	2	3	n.a.
	24	1	4	0	3	2	3
	48	1	4	0	2	1	2
	72	0	0	0	1	0	2
	Day 7	0	0	0	1	0	0
	Day 10	0	0	0	0	0	0
	Day 14	0	0	0	0	0	0
Mean (24, 48, 72 h)		**0.67**	**---**	**0.0**	**2.0**	**1.0**	**---**
Group means		**1.5**	**---**	**0.0**	**2.2**	**1.7**	**---**

n.a. = not assessable due to swelling of the conjunctivae.

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III. CONCLUSION

Based on the study results and on the and according to EU classification criteria the test substance glyphosate technical (NUP 05068) is to be classified as irritating to the eyes (Xi, R36). This corresponds to Category 2A according to the OECD Globally Harmonized System (GHS) classification criteria.

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/02	[redacted]	2009b	Acute Eye Irritation/Corrosion Test Of Glyphosate TC In Rabbits [redacted] Data owner: Helm AG Report No.: 24878 Date: 2009-11-27 GLP: yes unpublished

Guideline: OECD 405 (2002); Commission Directive 2004/73/EC B.5 (2004), OPPTS 870.2400 (1998)

Deviations: None

Dates of experimental work: 2009-10-15 - 2009-10-29

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Executive Summary

In an eye irritation study, 0.1 g of the undiluted test substance was instilled into the right conjunctival sac of three young male adult Himalayan albino rabbits. Animals were observed for 8 days. Eye irritation was scored using the Draize scheme 1, 24, 48 and 72 hours and 4, 5, 6, 7 and 8 days after test item instillation. Application of glyphosate TC into the rabbit eye resulted slight and fully reversible ocular changes, never exceeding Grade 1. All eye effects were reversible within 8 days after instillation. No signs of corrosion or staining were observed in any eye. The individual mean irritation scores (24 to 72 hours) of the three rabbits were as follows:

- for corneal opacity: 1.0, 1.0 and 1.0
- for iris lesions: 1.0, 0.7, 0.3
- for conjunctival redness: 1.0, 1.0, 1.0
- for chemosis of the conjunctiva: 0.7, 0.3, 0.0

Based on the scores for cornea, iris and conjunctiva and according to the EU and OECD Globally Harmonized System (GHS) classification criteria, glyphosate TC is not to be classified for eye irritation.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	Glyphosate TC
Description:	White powder
Lot/Batch #:	2009051501
Purity:	96.4%
Stability of test compound:	At room temperature in the dark stable until May 15, 2011.

2. Vehicle and/ or positive control: None

3. Test animals:

Species:	Rabbit
Strain:	Himalayan
Source:	[redacted] Germany

Age:	Approx. 6.5 - 7.5 months
Sex:	Males
Weight at dosing:	2.5 - 2.8 kg
Acclimation period:	At least 20 days.
Diet/Food:	[redacted] ([redacted] Germany), *ad libitum* before and after the exposure period
Water:	Tap water, *ad libitum* before and after the exposure period
Housing:	Individual housing
Environmental conditions:	Temperature: 20 ± 3°C Humidity: 30 - 70% Air changes: no data 12 hours light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 2009-10-15 to 2009-10-29

Animal assignment and treatment:
The test was conducted using three young male adult Himalayan albino rabbits. The test was performed in a sequential manner, first using one animal. Since no corrosive or severe eye effects were observed in the first animal the test was completed using the remaining two rabbits. An amount of 0.1 g of the solid test substance was applied into the conjunctival sac of the right eye of the rabbits. The lids were then gently held together for about one second. 1 hour after instillation the eyes were rinsed with 20 mL NaCl solution. The left eye remained untreated and served as the reference control. Eye reactions were assessed according to the scoring system listed in Commission Directive 2004/73/EC approximately 1, 24, 48 and 72 hours, as well as 4, 5, 6, 7 and 8 days after instillation. The animals were observed for mortality and clinical signs daily. Body weights were determined at beginning of the study and at termination.

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II. RESULTS AND DISCUSSION

A. MORTALITY
No mortality occurred.

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

C. BODY WEIGHT
There were no effects on body weight noted.

D. NECROPSY
No necropsy was performed.

E. EYE OBSERVATIONS
Corneal opacity (grade 1) was observed in all animals 24 to 72 hours, in animal no. 2 until 4 days and in animal no. 1 until 7 days after instillation. The fluorescein test performed 24 hours after instillation demonstrated corneal staining in all animals. The fluorescein test performed 7 days after instillation demonstrated corneal staining only in animal no. 1.
Irritation of the **iris** (grade 1) was observed in all animals 24 hours, in animal no. 2 until 48 hours and in animal no. 1 until 72 hours after instillation.

Conjunctival redness (grade 1) was observed in all animals 60 minutes to 72 hours, in animal no. 1 until 4 days and in animal no. 2 until 5 days after instillation.
Chemosis (grade 1) was observed in all animals 60 minutes, in animal no. 2 until 24 hours and in animal no. 1 until 48 hours after instillation.

In addition, secretion was observed in all animals 60 minutes after instillation. There were no systemic intolerance reactions. All rabbits were free of ocular signs by Day 8 after instillation.

The group mean irritation scores (24 to 72 hours) were calculated to be 1.0 for corneal opacity, 0.7 for iris lesions, and 1.0 conjunctival redness and 0.3 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 5.2-27.

Table 5.2-27: Results of the eye irritation test

Animal	Scoring [h]	Cornea	Iris	Conjunctiva	
				Redness	Chemosis
Rabbit 1	1	0	0	1	1
	24	1	1	1	1
	48	1	1	1	1
	72	1	1	1	0
	Day 4	1	0	1	0
	Day 5	1	0	0	0
	Day 6	1	0	0	0
	Day 7	0	0	0	0
Mean (24, 48, 72 h)		**1.0**	**1.0**	**1.0**	**0.7**
Rabbit 2	1	0	0	1	1
	24	1	1	1	1
	48	1	1	1	0
	72	1	0	1	0
	Day 4	0	0	1	0
	Day 5	0	0	1	0
	Day 6	0	0	0	0
	Day 7	—	—	—	—
Mean (24, 48, 72 h)		**1.0**	**0.7**	**1.0**	**0.3**
Rabbit 3	1	0	0	1	1
	24	1	1	1	0
	48	1	0	1	0
	72	1	0	1	0
	Day 4	0	0	0	0
	Day 5	—	—	—	—
	Day 6	—	—	—	—
	Day 7	—	—	—	—
Mean (24, 48, 72 h)		**1.0**	**0.3**	**1.0**	**0.0**
Group means		**1.0**	**0.7**	**1.0**	**0.3**

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III. CONCLUSION

Based on the scores for cornea, iris and conjunctiva and according to the EU and OECD Globally Harmonized System (GHS) classification criteria, glyphosate TC is not to be classified for eye irritation.

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/03	[redacted]	1995b	HR-001: Primary Eye irritation study in rabbits. [redacted] Report No.: [redacted]95-0034 Data owner: Arysta LifeScience Date: 1995-06-29 GLP: yes unpublished

Guideline: U.S. EPA FIFRA Guideline Subdivision F
MAFF 59 Nohoin No. 4200 (1985)

Deviations: None

Dates of experimental work: 1995-05-09 – 1995-05-30

Executive Summary

HR-001 was applied to the eye of 12 female specific pathogen free New Zealand white rabbits to evaluateits primary eye irritating potential. This study was performed according to the method of Draize. Firstly 6 animals were assigned to Group A (the group without eye irrigation after application). Secondly, 3 animals each were assigned to Group B (the group with eye irrigation at 30 seconds after application) and Group C (the group with eye irrigation at 4 minutes after application), since the eye irritation was observed in Group A.

- Irritation of cornea: at 1 hour after application, all animals of Group A showed score 2, the easily discernible translucent area, details of iris slightly obscured. At 24 hours after application, one animal of Group A showed score 3, opacreous area, no details of iris visible, size of pupil barely discernible. At 1 or 24 hours after application, all animals of Group B and one animal of Group C showed score 1, the scattered or diffuse areas of opacity, details of iris clearly visible. As for the area of cornea involved, Group A showed score 4, greater than the three quarters, up to whole area of the cornea. Group B showed score 2, greater than one quarter, but less than half, or score 3, greater than half, but less than three quarters. Group C showed score 2. These opacities disappeared by Day 16 in 3 of 6 animals of Group A, and the opacity (opacity score 1) remained until Day 21 in other 3 animals of Group A. In Group B, the opacity disappeared by Day 4 and in Group C by 48 hours after application.

- Irritation of iris: at 1 hour after application, al animals of Group A and C showed score 1, the congestion and/or markedly deepened rugae of iris. In Group B, one animal showed score at 1 hour and 2 animals showed score 2 at 24 hours after application. The irritation of iris disappeared by Day 10 in Group A, by 48 hours in Group B and by 24 hours in Group C after application.

- Irritation of conjunctivae: at 1 hour after application, all groups showed redness score 1, the definite hyperaemia of some blood vessels, and chemosis score 2, the obvious swelling with partial eversion of lids. In addition, Groups A and B showed chemosis score 3, i.e. the swelling with lids about half closed. Groups B and C showed discharge score 2, i.e. the discharge with moistening of the lids and hairs just adjacent to lids, and Groups A and C showed discharge score 3, i.e. the discharge with moistening of the lids and hairs and considerable area around the eye. By

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24 or 48 hours after application, score 1 redness of conjunctivae in all animals of Group A and in one animal each of Groups B and C had changed to score 2, i.e. the diffuse and crimson colored redness. And score 3 by 24 hours after application. These conjunctival irritations gradually began to decrease thereafter, and disappeared by Day 16 in Group A and by Day 17 in Groups B and C.

- Corneal vascularisation: on Day 10, the corneal vascularisation was observed in 3 animals of Group A. This sign remained until Day 21 after application.

Based on the study results, the test substance glyphosate technical (HR-001) is irritating to the rabbit eye. According to EU classification criteria the test substance glyphosate technical (HR-001) is to be classified as irritating to the eyes (Xi, R36). This corresponds to Category 2 according to the OECD Globally Harmonized System (GHS) classification criteria.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate technical

Identification:	HR-001
Description:	White crystal
Lot/Batch #:	T-941209
Purity:	97.56%
Stability of test compound:	Not mentioned in the report

2. Vehicle and/or positive control: None

3. Test animals:

Species:	Rabbit
Strain:	New Zealand White, Kbl:NZW
Source:	[redacted]
Age:	11 weeks
Sex:	females
Weight at dosing:	2.378 kg (Group A), 2.357 kg (Group B) and 2.426 kg (Group C)
Acclimation period:	Eleven days
Diet/Food:	Pellet Diet [redacted]
Water:	Water filtrated and sterilized, *ad libitum*
Housing:	Individually in stainless steel cages.
Environmental conditions:	Temperature: 24°C Humidity: 52.8 – 57.9% Air changes: 15/hour 12 hours light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 1995-04-28 – 1995-05-30

Animal assignment and treatment:

12 female specific pathogen free New Zealand rabbits were given a single ocular instillation of 0.1 g of technical glyphosate. The dose was instilled in the conjunctival sac of left eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for about one second in order to prevent loss of test substance. The left eyes of animals in the eye treated groups were irrigating with water at 30 seconds (3 animals) or 2 minutes (3 animals) after application. The right eye remained untreated. All animals were observed for primary eye irritation 1, 24, 48 and 72 hours, 4, 7, 10, 13, 16, 19 and 21 days after instillation. The cornea, iris and conjunctive were examined with a hand slit-lamp during a subsequent 21-day observation period. Body weights were measured prior to application, and after the final observation.

II. RESULTS AND DISCUSSION

A. MORTALITY
No mortality occurred.

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

C. BODY WEIGHT
All rabbits showed the expected body weight gain.

D. NECROPSY
No necropsy was performed.

E. EYE OBSERVATIONS
Results of the no eye irrigating group are summarised in the Table 5.2-28.

Without eye irrigation

- *Irritation of cornea*
  At 1 hour after application, all animals showed score 2, the easily discernible translucent aera, details of iris slightly obscured. At 24 hours after application, one animal showed score 3, nacreous area, no details of iris visible, size of pupil barely discernible. These opacities remained until Day 21 in three animals.

- *Irritation of iris*
  At 1 hour after application, all animals showed score 1, the congestion and/or markedly deepened rugae of iris. The irritation disappeared by Day 10.

- *Irritation of conjunctivae*
  At 1 hour after application, all groups showed redness score 1, the definite hyperemia of some blood vessels. At 24 or 48 hours after application, score 2 redness of conjunctivae in all animals. These conjunctival irritations gradually began to decrease thereafter, and disappeared by Day 16.
  At 1 hour after application, 4 animals showed chemosis score 2, the obvious swelling with partial eversion of lids. In addition, 2 animals showed score 3, the swelling with lids about half closed. The chemosis disappeared by Day 7.

With eye irrigation (30 seconds or 2 minutes after application)
The irridial and conjunctival irritations observed in irrigation group were almost the same as those in non-irrigating group, while the corneal irritation was slighter.

Animals in the irrigating groups showed reduced eye irritations and faster recovery as compared with animals of the non-irrigating group. Each of irrigation at 30 seconds or 2 minutes after application was effective for reduction of irritation and for recovery.

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Table 5.2-28: Results of the eye irritation without eye irrigation after application*:

Animal	Scoring [h]	Cornea		Iris	Conjunctiva		
		Opacity	Area		Redness	Chemosis	Discharge
Rabbit 1 (female)	1	2	4	1	1	2	3
	24	2	4	1	2	2	3
	48	2	4	1	2	2	3
	72	2	4	1	2	2	1
	Day 4	1	3	1	2	1	0
	Day 7	1	2	0	1	0	0
	Day 10	1	1	0	1	0	0
	Day 13	1	1	0	1	0	0
	Day 16	1	1	0	0	0	0
	Day 19	1	1	0	0	0	0
	Day 21	1	1	0	0	0	0
Mean (24, 48, 72 h)		**2.0**	**---**	**1.0**	**2.0**	**2.0**	**---**
Rabbit 2 (female)	1	2	4	1	1	2	3
	24	3	4	1	2	2	3
	48	3	4	1	2	2	3
	72	2	3	1	2	1	1
	Day 4	2	2	1	2	1	0
	Day 7	1	2	0	1	0	0
	Day 10	1	2	0	1	0	0
	Day 13	1	2	0	1	0	0
	Day 16	1	2	0	0	0	0
	Day 19	1	2	0	0	0	0
	Day 21	1	2	0	0	0	0
Mean (24, 48, 72 h)		**2.67**	**---**	**1.0**	**2.0**	**1.67**	**---**
Rabbit 3 (female)	1	2	4	1	1	3	3
	24	2	4	1	2	3	3
	48	2	4	1	2	2	3
	72	2	4	1	2	2	3
	Day 4	2	3	1	2	1	0
	Day 7	1	2	1	1	0	0
	Day 10	1	2	0	1	0	0
	Day 13	1	2	0	1	0	0
	Day 16	1	2	0	0	0	0
	Day 19	1	2	0	0	0	0
	Day 21	1	2	0	0	0	0
Mean (24, 48, 72 h)		**2.0**	**---**	**1.0**	**2.0**	**2.33**	**---**
Rabbit 4 (female)	1	2	4	1	1	3	3
	24	2	4	1	2	3	3
	48	2	4	1	2	2	3
	72	2	3	1	2	2	1
	Day 4	2	2	1	2	1	1
	Day 7	1	2	0	1	0	0
	Day 10	1	2	0	1	0	0
	Day 13	1	2	0	1	0	0
	Day 16	0	0	0	0	0	0
	Day 19	0	0	0	0	0	0
	Day 21	0	0	0	0	0	0
Mean (24, 48, 72 h)		**2.0**	**---**	**1.0**	**2.0**	**2.33**	**---**

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Animal	Scoring [h]	Cornea		Iris	Conjunctiva		
		Opacity	Area		Redness	Chemosis	Discharge
Rabbit 5 (female)	1	2	4	1	1	2	3
	24	2	4	1	2	2	3
	48	2	4	1	2	2	3
	72	2	4	1	2	2	1
	Day 4	1	2	1	2	1	0
	Day 7	1	2	0	1	0	0
	Day 10	1	1	0	1	0	0
	Day 13	0	0	0	0	0	0
	Day 16	0	0	0	0	0	0
	Day 19	0	0	0	0	0	0
	Day 21	0	0	0	0	0	0
Mean (24, 48, 72 h)		**2.0**	**---**	**1.0**	**2.0**	**2.0**	**---**
Rabbit 6 (female)	1	2	4	1	1	2	3
	24	2	4	1			
	48	2	2	1	2	2	2
	72	1	2	0	2	1	0
	Day 4	1	1	0	1	0	0
	Day 7	0	0	0			0
	Day 10	0	0	0			0
	Day 13	0	0	0	0	0	0
	Day 16	0	0	0	0	0	0
	Day 19	0	0	0	0	0	0
	Day 21	0	0	0	0	0	0
Mean (24, 48, 72 h)		**1.67**	**--**	**0.67**	**2.0**	**1.67**	**---**
Group means		**2.1**	**--**	**1.0**	**2.0**	**2.0**	**---**

* - according to the report

Table 5.2-29: **Results of the eye irritation with eye irrigation (30 seconds after application)*:**

Animal	Scoring [h]	Cornea		Iris	Conjunctiva		
		Opacity	Area		Redness	Chemosis	Discharge
Rabbit 7 (female)	1	1	2	1	1	3	2
	24	1	2	1	1	2	3
	48	1	1	0	2	2	1
	72	1	1	0	1	1	1
	Day 4	0	0	0	1	0	0
	Day 7	0	0	0	0	0	0
Mean (24, 48, 72 h)		**1.0**	**---**	**0.33**	**1.33**	**1.67**	**---**
Rabbit 8 (female)	1	0	0	0	1	2	2
	24	1	0	0	1	2	2
	48	1	1	0	1	1	1
	72	0	0	0	1	0	0
	Day 4	0	0	0	1	0	0
	Day 7	0	0	0	0	0	0
Mean (24, 48, 72 h)		**0.67**	**---**	**0.0**	**1.0**	**1.0**	**---**
Rabbit 9 (female)	1	1	2	1	1	2	2
	24	1	3	1	2	2	3
	48	1	3	0	2	1	1
	72	1	2	0	1	1	1
	Day 4	0	0	0	1	0	0
	Day 7	0	0	0	0	0	0
Mean (24, 48, 72 h)		**1.0**	**---**	**0.33**	**1.67**	**1.33**	**---**
Group means		**0.9**	**---**	**0.2**	**1.3**	**1.3**	**---**

* - according to the report

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III. CONCLUSION

Based on the study results and on the and according to EU classification criteria the test substance glyphosate technical (HR-001) is to be classified as irritating to the eyes (Xi, R36). This corresponds to Category 2 according to the OECD Globally Harmonized System (GHS) classification criteria.

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/04	[redacted].	2009c	Expert Statement Glyphosate technical: Primary eye irritation study in rat [redacted] Data owner: Excel Report No.: C22847 Date: 2009-01-23 GLP: yes not published

Guideline: OECD 405 (2002)
Council Regulation (EC) No 440/2008 (2008)

Deviations: None

Dates of experimental work: 2009-01-22

Executive Summary

A pH measurement was performed with the test item in a 1% (w/w) solution in purified water before the study initiation. The pH of the test item was found to be 1.93.

According to the OECD Guidelines 405 and Council Regulation (EC) No 440/2008 B.5:
Physicochemical properties and chemical reactivity: Substances exhibiting pH extremes such as ≤ 2,0 may have strong local effects. If extreme pH is the basis for identifying a substance as corrosive or irritant to the eye, then its acid reserve (buffering capacity) may also be taken into consideration.

It is assumed that the test substance item has corrosive properties; therefore, no eye irritation study in rabbits with Glyphosate Technical was performed.

According to EU and OECD Globally Harmonized System (GHS) classification criteria the test substance glyphosate technical is classified for eye irritation:

- *Xi R41 (Risk of serious damage to eyes);*
- *Category 1, H318 (Causes serious eye damage).*

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III. CONCLUSION

The eye irritation of the test material (glyphosate technical) was concluded to be positive. Based on the EU and the OECD Globally Harmonized System (GHS) classification criteria, glyphosate technical is classified for eye irritation: Category 1, H318 (Causes serious eye damage).

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/05	[redacted]	2009d	Acute Eye Irritation/Corrosion Test of Glyphosate TC in Rabbits [redacted] Data owner: Helm AG Report No.: [redacted]23914 Date: 2009-04-30 GLP: yes unpublished

Guideline: OECD 405 (2002)
US EPA OPPTS 870.2400.

Deviations: Personnel change of the head of the Quality Assurance Unit:
until January 31, 2009: [redacted]
as of February 01, 2009: [redacted]
[redacted] The minor deviation did not have any effect on the validity and integrity of the scientific results obtained in this study.

Dates of experimental work: 2009-02-02 - 2009-02-25

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Executive Summary
Under the present test conditions, a single instillation of 100 mg Glyphosate TC per animal into the conjunctival sac of the right eye of three rabbits caused the following changes:
Corneal opacity (grade 1) was observed in animal no. one 24 to 72 hours and in animal no. three 24 and 48 hours after instillation.
The fluorescein test performed 24 hours after instillation revealed corneal staining in animal no. 1 and 3 (up to 1/4 of the surface).
Conjunctival redness (grade 1) was observed in all animals 60 minutes t o 48 hours, in animal no. 1 until 72 hours after instillation.
Chemosis (grade 1) was observed in animal no. one 24 and 48 hours after instillation. In addition, secretion was observed in all animals 60 minutes after instillation. The irises were not affected by instillation of the test item.
There were no systemic intolerance reactions.
According to the EC-Commission directive 67/548/EEC and its subsequent amendments on the approximation of the laws, regulations and administrative provision relating to the classification, packaging and labelling of dangerous substances and the results obtained under the present test conditions Glyphosate TC was

non - irritating

to eyes, hence, no labelling is required.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate

Identification:	Glyphosate TC
Description:	White powder
Lot/Batch #:	20080801
Purity:	98.8%
Stability of test compound:	No data given in the report.

2. Vehicle and/ or positive control: No vehicle used

3. Test animals:

Species:	Rabbit
Strain:	Himalayan
Source:	[redacted] Germany
Age:	Approx. 4 - 32.5 months
Sex:	Male
Weight at dosing:	Animal no. 1 : 4.0 kg Animal no. 2: 3.9 kg Animal no. 3: 4.1 kg
Acclimation period:	At least 20 adaptation days
Diet/Food:	Commercial diet, [redacted] served as food. The food was available ad libitum before and after the exposure period.
Water:	Tap water, *ad libitum*
Housing:	The animals were kept singly in cages measuring 380 mm x 425 mm x 600 mm (manufactured [redacted] Germany).
Environmental conditions:	Temperature: 20 ± 3 °C Humidity: 30 - 70% 12-hour light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 2009-02-02 to 2009-02-15

Animal assignment and treatment:
100 mg of the test item was administered into one eye each of three animals. The test item was placed into the conjunctival sac of the right eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for about one second in order to prevent loss of the material. The left eye, which remained untreated, served as a control.The test was performed initially using one animal. As no corrosive or severe irritant effects were observed in this animal, 2 further animals were employed 24 hours after start of the initial test.
1 hour after instillation the eyes were rinsed with 20 mL NaCl solution. The eyes were examined ophthalmoscopically with a slit lamp prior to the administration and 1 , 24, 48, 72 hours and 4 days after the administration. The eye reactions were observed and registered. 24 hours after administration, fluorescein was applied to the eyes before being examined to aid evaluation of the cornea for possible lesions.

II. RESULTS AND DISCUSSION

A. MORTALITY

There were no mortalities during the study.

B. CLINICAL OBSERVATIONS

A single instillation of 100 mg Glyphosate TC per animal into the conjunctival sac of the right eye of three rabbits caused the following changes:

Corneal opacity (grade 1) was observed in animal no. one 24 t o 72 hours and in animal no. three 24 and 48 hours after instillation.

The fluorescein test performed 24 hours after instillation revealed cornea1 staining in animal no. 1 and 3 (up to 1/4 of the surface).

Conjunctival redness (grade 1) was observed in all animals 60 minutes to 48 hours, in animal no. 1 until 72 hours after instillation.

Chemosis (grade 1) was observed in animal no. one 24 and 48 hours after instillation.

In addition, secretion was observed in all animals 60 minutes after instillation.

The irises were not affected by instillation of the test item.

There were no systemic intolerance reactions.

III. CONCLUSION

According to the EC-Commission directive 67/548/EEC and its subsequent amendments on the approximation of the laws, regulations and administrative provision relating to the classification, packaging and labelling of dangerous substances and the results obtained under the present test conditions Glyphosate TC was non – irritating to eyes, hence, no labelling is required.

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/06	[redacted]	2010b	Acute Eye Irritation/Corrosion Test of Glyphosate TC in Rabbits [redacted] Data owner: Helm AG Report No.: [redacted]24606 Date: 2010-01-06 GLP: yes unpublished
Guideline:			OECD 405 (2002) US EPA OPPTS 870.2400.
Deviations:			No deviations from the Study Plan.
Dates of experimental work:			2009-10-26 - 2009-11-12

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Executive Summary

Under the present test conditions, a single instillation of 100 mg Glyphosate TC per animal into the conjunctival sac of the right eye of three rabbits caused the following
changes:

Corneal opacity (grade 1) was observed in all animals 24 to 72 hours, in animal no. 1 until 4 days and in animal no. 3 until 5 days after instillation. The fluorescein test performed 24 hours after instillation revealed cornea1 staining in all animals (1/2 to 3/4 of the surface). Irritation of the iris (grade 1) was observed in all animals 24 and 48 hours, in animal no. 3 until 72 hours after instillation. Conjunctival redness (grade 1 or 2) was observed in all animals 60 minutes to 4 days, in animal no. 3 until 6 days after

instillation. Chemosis (grade 1) was observed in all animals 60 minutes and 24 hours after instillation. In addition, secretion was observed in all animals 60 minutes and 24 hours after instillation.
There were no systemic intolerance reactions.
According to the EC-Commission directive 67/548/EEC and its subsequent amendments on the approximation of the laws, regulations and administrative provision relating to the classification, packaging and labelling of dangerous substances and the results obtained under the present test conditions Glyphosate TC was

non - irritating

to eyes, hence, no labelling is required.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate

Identification:	Glyphosate TC
Description:	White powder
Lot/Batch #:	20090506
Purity:	97.3%
Stability of test compound:	No data given in the report

2. Vehicle and/ or positive control: No vehicle was used

3. Test animals:

Species:	Rabbit
Strain:	Himalayan
Source:	[redacted] Germany
Age:	Approx. 6 - 8 months
Sex:	Male
Weight at dosing:	At dosing Animal no. 1 : 2.5 kg Animal no. 2: 2.5 kg Animal no. 3: 2.7 kg
Acclimation period:	At least 20 adaptation days
Diet/Food:	Commercial diet, [redacted] as food. The food was available *ad libitum* before and after the exposure period.
Water:	Tap water, *ad libitum*
Housing:	The animals were kept singly in cages measuring 380 mm x 425 mm x 600 mm (manufacturer: [redacted] Germany).

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Environmental conditions: Temperature: 20 ± 3°C
Humidity: 30 - 70%
12-hour light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 2009-10-26 to 2009-11-12

Animal assignment and treatment:
100 mg of the test item were administered into one eye each of three animals. The test item was placed into the conjunctival sac of the right eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for about one second in order to prevent loss of the material. The left eye, which remained untreated, served as a control. The test was performed initially using one animal. As no corrosive or severe irritant effects were observed in this animal, 2 further animals were employed 24 hours after start of the initial test.
1 hour after instillation the eyes were rinsed with 20 mL NaCl solution. The eyes were examined ophthalmoscopically with a slit lamp prior to the administration and 1, 24, 48, 72 hours and 4 to 7 days after the administration. The eye reactions were observed and registered.
24 hours and 7 days after administration, fluorescein was applied to the eyes before being examined to aid evaluation of the cornea for possible lesions.

II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
Corneal opacity (grade 1) was observed in all animals 24 to 72 hours, in animal no. 1 until 4 days and in animal no. 3 until 5 days after instillation. The fluorescein test performed 24 hours after instillation revealed corneal staining in all animals (1/2 to 3/4 of the surface). Irritation of the iris (grade 1) was observed in all animals 24 and 48 hours, in animal no. 3 until 72 hours after instillation. Conjunctival redness (grade 1 or 2) was observed in all animals 60 minutes to 4 days, in animal no. 3 until 6 days after instillation. Chemosis (grade 1) was observed in all animals 60 minutes and 24 hours after instillation. In addition, secretion was observed in all animals 60 minutes and 24 hours after instillation.There were no systemic intolerance reactions.

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III. CONCLUSION

According to the EC-Commission directive 67/548/EEC and its subsequent amendments on the approximation of the laws, regulations and administrative provision relating to the classification, packaging and labelling of dangerous substances and the results obtained under the present test conditions Glyphosate TC was non - irritating to eyes, hence, no labelling is required.

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/07	[redacted].	2009d	Glyphosate – Acute Eye Irritation Study in Rabbits [redacted] Data owner: Helm AG Report No.: 12172-08 Date: 2009-03-11 GLP: yes unpublished

Guideline: US EPA OPPTS 870.2400
Equivalent to OECD 405 (2002).

Deviations: Humidity was in the range of 33-92% instead of 30-70%. This deviation did not affect the study outcome.

Dates of experimental work: 2008-11-10 - 2008-11-27

Executive Summary
An acute eye irritation study was conducted on three albino rabbits using test substance Glyphosate. The test substance, 0.1 mL by volume (93.2 mg), was placed into the conjunctival sac of the right eye of each animal selected for testing. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24-hour observation. There were no positive effects exhibited in any eyes on Day 10 after treatment. The test substance is rated

moderately irritating

and assigned to Toxicity Category II.

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** Glyphosate
   Identification: Glyphosate Tech Grade Mixed 5-Batch
   Description: White powder
   Lot/Batch #: 080704-1 thru 5
   Purity: 96.4%
   Stability of test compound: No data given in the report.
2. **Vehicle and/ or positive control:** No vehicle was used
3. **Test animals:**
   Species: Albino rabbit
   Strain: New Zealand White
   Source: [redacted]
   Age: Approx. 3 months
   Sex: 2 males and 1 female (nulliparous and non-pregnant)
   Weight at dosing: Males: 2.200-2.400 kg; Female: 2.300 kg
   Acclimation period: 5 days
   Diet/Food: [redacted] Lab Rabbit Diet [redacted] 8 oz. daily

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Water:	Tap water, *ad libitum*
Housing:	Individual housing in suspended, wire bottom, stainless steel cages.
Environmental conditions:	Temperature: 22 ± 3°C
	Humidity: 30 - 70%
	Air changes: 10 - 12/hour
	12-hour light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 2008-11-10 to 2008-11-27

Animal assignment and treatment:
Healthy albino rabbits were released from quarantine. Both eyes of each animal were carefully examined within 24 hours prior to treatment with a fluorescein sodium ophthalmic solution and cobalt-filtered light. Both eyes of each animal were again carefully examined just prior to treatment, but without the fluorescein sodium ophthalmic solution. Only those animals without eye defects or irritation were selected for testing. On Day 0, a dose of 0.1 mL by volume (93.2 mg) of the undiluted test substance was placed into the conjunctival sac of the right eye of each animal by gently pulling the lower lid away from the eyeball to form a cup into which the test substance was dropped. The lids were gently held together for one second to prevent loss of material. The untreated left eyes served as comparative controls. The grades of ocular reaction were recorded at 1, 24, 48 and 72 hours, and at 4, 7, 10, 14 and 17 days after treatment. The corneas of all treated eyes were examined immediately after the 24 hour observation with a fluorescein sodium ophthalmic solution. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24-hour observation.

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II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
The maximum average irritation score of 3 1.7, obtained at 24 hours after treatment, was used to rate Glyphosate moderately irritating. Fluorescein staining was observed in two of three eyes at 24 hours after treatment and was not observed in any eyes on Day 10 after treatment.Toxicity categories are determined by the presence and duration of corneal involvement, iridic irritation, and positive conjunctival irritation. Any corneal involvement or iridic irritation with a score of 1 or more is considered positive. Any conjunctival irritation (redness or chemosis) with a score of 2 or more is considered positive.

III. CONCLUSION

Based on the maximum average irritation score of 3 1.7, the test substance Glyphosate is rated moderately irritating. Since all positive effects had cleared on Day 10 after dosing, the test substance is assigned to Toxicity Category 11. No irritation was observed in any eyes on Day 17.

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/08	[redacted]	2005e	Eye Irritation/Corrosion Effects in rabbits (Oryctolagus cuniculus) of Glyphosate 95 TC [redacted] Data owner: Helm AG Report No.: [redacted]15277 Date: 2005-04-04 GLP: yes unpublished

Guideline: US EPA OPPTS 870.2400
OECD 405 (2002).

Deviations: No deviations from Study Plan.

Dates of experimental work: 2004-05-26 - 2004-06-05

Executive Summary
A primary eye irritation test was conducted with rabbits to determine the potential for Glyphosate Acid Technical to produce irritation from a single instillation via the ocular route. Under the conditions of this study, the test substance is classified as

severely irritating

to the eye.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate

Identification: Glyphosate Acid Technical
Description: White crystalline powder
Lot/Batch #: 040205
Purity: 97.3%
Stability of test compound: No data given in the report.

2. Vehicle and/ or positive control: No vehicle was used.

3. Test animals:

Species: Rabbit
Strain: New Zealand albino
Source: [redacted]
Age: Young adult
Sex: Male
Weight at dosing: No data given in the report
Acclimation period: 7 days
Diet/Food: Pelleted [redacted] Rabbit Chow [redacted]
Water: Tap water, *ad libitum*

Housing:	The animals were singly housed in suspended stainless steel caging with mesh floors which conform to the size recommendations in the most recent *Guide for the Care and Use of Laboratory Animals DHEW (NIH).* Litter paper was placed beneath the cage and was changed at least three times per week
Environmental conditions:	Temperature: 18-22°C 12-hour light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 2004-05-26 to 2004-06-05

Animal assignment and treatment:
A primary eye irritation test was conducted with rabbits to determine the potential for Glyphosate Acid Technical to produce irritation from a single instillation via the ocular route. Under the conditions of this study, the test substance is classified as severely irritating to the eye. Prior to use, the test substance was ground to a powder. One-tenth of a milliliter (0.06 grams) of the ground test substance was instilled into the right eye of three healthy rabbits. The left eye remained untreated and served as a control. Ocular irritation was evaluated by the method of Draize *et al.* One hour after test substance instillation, all three treated eyes exhibited cornea1 opacity, iritis, and conjunctivitis. The overall incidence and severity of irritation decreased gradually over time. All animals were free of ocular irritation by Day 10 (study termination).

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II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
All animals appeared active and healthy. Apart from the eye irritation noted below, there were no other signs of gross toxicity, adverse pharmacologic effects or abnormal behavior. One hour after test substance instillation, all three treated eyes exhibited corneal opacity, iritis, and conjunctivitis. The overall incidence and severity of irritation decreased gradually over time. All animals were free of ocular irritation by Day 10 (study termination).

III. CONCLUSION

Under the conditions of this study, Glyphosate Acid Technical is classified as severely irritating to the eye.

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/09	[redacted]	2008b	Acute Eye Irritation/Corrosion Study in Rabbits with Glyphosate Technical [redacted] Data owner: Helm AG Report No.: [redacted]3996.312.599.07 Date: 2008-09-12 GLP: yes unpublished

Guideline: OECD 405 (2002).

Deviations: The experimental phase initiation and experimental phase conclusion dates were updated.

Dates of experimental work: 2008-05-26 - 2008-06-17

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Executive Summary

The acute eye irritation/corrosion potential of GLYPHOSATE TECHNICAL was evaluated in three New Zealand White rabbits. The test was initially conducted using one rabbit. Because some severe ocular reactions were observed in the initial test, only one additional animal was tested to confirm the response. Each animal received a 0.1 g dose of the test item undiluted in the conjunctival sac of the left eye. After application, 1/2 of the animals was examined at approximately 1,24,48,72 hours, and 7 and 14 days, and 1/2 of the animals was examined at approximately 1, 24,48,72 hours, and 7, 14 and 21 days to verify the presence of lesions in the cornea, iris, eyelid and eyeball conjunctivae, and for behavioral and clinical alterations. The untreated right eye was used as a negative control. The test item applied in the eye of the rabbits produced corneal opacity, iritis (circumcorneal injection), conjunctival hyperemia, edema and secretion in 2/2 test eyes. Corneal opacity and conjunctival hyperemia were still noted at the final of the observation period in 1/2 test eyes. All irritation signs had returned to normal by the 14-day time point following treatment to 1/2 test eyes. Fluorescein sodium dye detected treatment-related changes to the surface of the cornea in 2/2 test eyes. Additional ocular changes observed included: blepharitis and a small raised off area on the corneal surface. Based on the "UN GHS / EU CLP Criteria for Classification (UN, 2009; EC, 2008)" the ocular classification is "Category 1 **Irreversible effects on the eye".**

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate

Identification:	Glyphosate Technical
Description:	White powder
Lot/Batch #:	20070606
Purity:	98.05%
Stability of test compound:	No data given in the report.

2. Vehicle and/ or positive control: No vehicle was used

3. Test animals:

Species:	Rabbit
Strain:	New Zealand White
Source:	[redacted] - Brazil

Age:	18 weeks old
Sex:	One male and one female
Weight at dosing:	between 3.346 and 3.624 kg
Acclimation period:	5 to 6 days
Diet/Food:	Pelleted and autoclaved commercial diet for rabbits ([redacted] - *Brazil*)
Water:	Tap water, *ad libitum*
Housing:	The animals were housed individually in galvanized steel cages. Autoclaved wood shavings were placed in a tray below the cages to collect excrements.
Environmental conditions:	Temperature: 17 - 22°C Humidity: 30 - 70% Air changes: 10 - 15/hour 12-hour light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 2008-05-26 to 2008-06-17

Animal assignment and treatment:
0.1 g of the test item was applied to the eye of each animal. The test item was applied into the conjunctival sac of the left eye of each animal after gently pulling the lower lid away from the eyeball. Following application, the eyelids were gently held together for about one second in order to prevent test item loss. The right eye that remained untreated was used as a negative control.
The test was performed initially using one animal for evaluation of any irritant/corrosive effect of the test item to the eye. Because some severe ocular reactions were observed in the initial test, only one additional animal was tested to confirm the response.

II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
The following additional ocular changes were noted to the animals during the observation period:

Rabbit #04: Blepharitis at the 48- and 72-hr time points.

Rabbit #05: Blepharitis at the 24-, 48- 72-hr, and 7- and 14-day time points; and a small raised off area on the corned surface in the right inferior quadrant at the 21-day time point.

III. CONCLUSION

Based on the "UN GHS / EU CLP Criteria for Classification (UN, 2009; EC, 2008)" the ocular Classification for Glyphosate Technical is "Category l Irreversible effects on the eye".

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/10	[redacted]	1988c	Primary Eye Irritation Study of Glyphosate Batch/Lot/NBR No. XLI-55 in New Zealand White Rabbits [redacted] Data owner: Monsanto [redacted] Report No.: [redacted]-88-29 Date: 1988-06-08 GLP: yes unpublished

Guideline:	US EPA 81-4
Deviations:	None
Dates of experimental work:	1988-04-11 to 1988-05-02

Executive Summary

In an eye irritation study, 0.1 g of the undiluted test substance was instilled into the conjunctival sac of one eye of six young adult New Zealand rabbits. Animals were observed for 21 days. Eye irritation was scored using the Draize scheme 1, 24, 48 and 72 hours and 7, 14, and 21 days after test substance instillation.

Under the conditions of this study, Glyphosate produced corneal opacity and conjunctival irritation with blistering in all rabbits after test article instillation. Three rabbits exhibited pannnus on the cornea; one rabbit had prominent vascularization of the conjunctiva and another animal had a blood-like discharge. One rabbit was found dead 20 days after dose administration. This death was not considered treatment related. Corneal opacity persisted through study day 21 (termination) in three of five (3/5) animals. Of the remaining two rabbits, one exhibited slight conjunctival discharge at study termination and the other rabbit's treated eye appeared normal 14 days after dose administration. The group mean irritation scores (24 to 72 hours) of the six rabbits were as follows:

- for corneal opacity: 2.1;
- for iris lesions: 0.2;
- for conjunctival redness: 2.0;
- for conjunctival chemosis: 1.6.

Based on the study results, the test substance glyphosate is severely irritating to the rabbit eye. According to EU classification criteria the test substance glyphosate is to be classified as risk of serious damage to eyes (Xi, R41). This corresponds to Category 1 according to the OECD Globally Harmonized System (GHS) classification criteria.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	Glyphosate
Description:	White powder
Lot/Batch #:	XLI-55
Purity:	97.76%
Stability of test compound:	Stored at room temperature

2. Vehicle and/ or positive control: None

3. Test animals:

Species:	Rabbit
Strain:	New Zealand White
Source:	[redacted] US
Age:	Young adult
Sex:	Not specified
Weight at dosing:	Between 2-3 kg
Acclimation period:	At least five days
Diet/Food:	[redacted] Rabbit Ration certified feed ([redacted] US), *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Individually in wire mesh cages
Environmental conditions:	Temperature: 20 – 23.9°C Humidity: 40 – 60% Air changes: Not specified Light cycle: 12 hours light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 1988-04-11 to 1988-05-02

Animal assignment and treatment:
The test was conducted using six young adult New Zealand albino rabbits. The test substance (0.1 g) was instilled into one eye of each rabbit. The lower eyelid was pulled gently away from the eyeball to form a cup (conjunctival sac) and the test substance inserted therein. The lids were then held together for one second and released. Following scoring at 24 hours after dose administration, any residual material was rinsed from the eye with physiological saline. Treated and untreated eyes were examined at 1, 24, 48, and 72 hours, and 7, 14, and 21 days after test substance instillation. The cornea, iris, and conjunctiva were scored separately according to the Draize system. The animals were observed twice daily for mortality at least five hours apart. Body weights were obtained on study day 1 prior to dose administration and at death. At study termination, surviving animals were euthanized by intracardiac injection of sodium pentobarbital and discarded.

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II. RESULTS AND DISCUSSION

A. MORTALITY
One rabbit was found dead 20 days after dose administration. Prior to death, this animal exhibited anorexia, and gross necropsy revealed a clear gel-like substance in the large intestine. These findings are consistent with mucoid enteropathy, a condition occasionally noted in stock laboratory rabbits. Therefore, the death was considered spontaneous and unrelated to treatment.

B. CLINICAL OBSERVATIONS
Not reported.

C. BODY WEIGHT
Not reported.

D. NECROPSY

Not reported.

E. EYE OBSERVATIONS

At one hour after test substance instillation, all animals exhibited conjunctival irritation (redness, swelling, blistering and discharge). Corneal opacity was noted one hour after test substance instillation in four of six (4/6) animals. Corneal opacity and conjunctival irritation were noted in all rabbits at the 24, 48 and 72 hour ad 7 day examinations. Three rabbits exhibited pannus on the cornea; two eyes (iris) had sluggish reactions to light; one rabbit had prominent vascularization of the conjunctival and another animal had a blood-like discharge. Corneal opacity persisted through study termination (day 21) in three of five (3/5) rabbits. Of the remaining two rabbits, one exhibited slight conjunctival discharge at study termination and the other rabbit's treated eye appeared normal 14 days after dose administration.

The group mean irritation scores (24 to 72 hours) were calculated to be 2.1 for corneal opacity, 1.2 for iris lesions, 2.0 for conjunctival redness, and 2.6 for conjunctival chemosis. The individual scores for each time point, individual mean and group mean scores (24 to 72 hours) are presented in Table 5.2-30.

Table 5.2-30: Results of the Eye Irritation Test [a]

Animal No.	Scoring [h]	Cornea		Iris	Conjunctivae		
		Opacity	Area		Redness	Chemosis	Discharge
Rabbit 1	1	2	1	0	2	2 [b]	2
	24	2	3	0	2	2 [b]	2
	48	3	1	2	2	2 [b]	2 [c]
	72	3 [d]	1	0	2	2 [b]	2
	7 days	3 [d]	1	0	2	1	0
	14 days	2	1	0	1	0	0
	21 days	2	1	0	0	0	0
Mean	**24-72 h**	**2.7**		**0.0**	**2.0**	**2.0**	
Rabbit 2	1	2	1	0	2	2 [b]	3
	24	2	2	0	2	4 [b]	3
	48	2	2	0	2	4 [b]	2
	72	1	1	0	2	2 [b]	1
	7 days	2	1	0	1	1	0
	14 days	2	1	0	0	0	1
	21 days	0	0	0	0	0	1
Mean	**24-72 h**	**1.7**		**0.0**	**2.0**	**3.3**	
Rabbit 3	1	2	1	0	2	2 [b,e]	2
	24	2	2	1	2	4 [b,e]	2
	48	2	1	1	2	3 [b,e]	2
	72	2	1	1	2	3 [b,e]	2
	7 days	3 [d]	2	1	3	2 [b]	2
	14 days	2	1	1	1	0	0
	21 days	2	1	0	0	0	0
Mean	**24-72 h**	**2.0**		**1.0**	**2.0**	**3.3**	
Rabbit 4	1	0	0	0	2	3 [b]	3
	24	1	4	0	2	4 [b]	3
	48	1	3	0	2	2 [b]	2
	72	1	3	0	2	2 [b]	2
	7 days	3	1	0	2	2	1
	14 days	0	0	0	0	0	0
	21 days	0	0	0	0	0	0
Mean	**24-72 h**	**1.0**		**0.0**	**2.0**	**2.7**	

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Animal No.	Scoring [h]	Cornea		Iris	Conjunctivae		
		Opacity	Area		Redness	Chemosis	Discharge
Rabbit 5	1	0	0	0	2	2 [b]	2
	24	2	2	0	2	2 [b]	2
	48	2	2	0	2	2 [b]	2
	72	3	1	0	2	2 [b]	1
	7 days	4 [d]	1	1	2	2	1
	14 days	3 [d]	1	1	2	1	0
	21 days	3 [d]	1	0	1	0	0
Mean	**24-72 h**	**2.3**		**0.0**	**2.0**	**2.0**	
Rabbit 6	1	2	1	0	2	2 [b]	3
	24	2	2	0	2	2 [b]	2
	48	3	1	0	2	2 [b]	2
	72	3	1	0	2	2 [b]	0
	7 days	2	1	0	1	1	0
	14 days	2	1	0	1	0	0
	21 days	- [f]	-	-	-	-	-
Mean	**24-72 h**	**2.7**		**0.0**	**2.0**	**1.0**	
Group mean	**24-72 h**	**2.1**		**0.2**	**2.0**	**2.6**	

[a] Scores for treated eyes; untreated eyes appeared normal at all times.
[b] Mucus membrane of the eyelid appeared blistered.
[c] Blood-like discharge noted.
[d] Pannus on the cornea.
[e] Prominent vascularisation of the conjunctiva.
[f] Animal found dead 20 days after dose administration.

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III. CONCLUSION

Based on the study results and on the and according to EU classification criteria the test substance glyphosate is to be classified as risk of serious damage to the eyes (Xi, R41). This corresponds to Category 1 according to the OECD Globally Harmonized System (GHS) classification criteria.

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/11	[redacted]	1997	Glyphosate Acid: Eye Irritation to the Rabbit [redacted] Data owner: Syngenta Report No.: [redacted]/5138 Date: 1997-03-18 GLP: yes not published

Guideline: OECD 405 (2002): OPPTS 870.2400 (1998): 2004/73/EC B.5 (2004)

Deviations: None.

Dates of experimental work: 1996-04-04 to 1997-03-18

Excecutive summary

In a primary eye irritation study, 100 mg of Glyphosate acid (95.6 % w/w was instilled into the conjunctival sac of the left eye of one of six young adult, New Zealand White albino female rabbits. When the eye irritation potential had been fully assessed in the first animal, the test substance was applied

into the test eye of the remaining five animals, as described previously. Immediately after the application of the test substance, an assessment of the initial pain reaction of the rabbit was made using a six-point scale.

As the initial pain reaction of the first rabbit was moderate and the irritation was less than severe, the eyes of the remaining rabbits were pre-treated with five drops of local anaesthetic (OPHTHAINE, 0.5% proparacaine hydrochloride solution) at three minute intervals between each drop.

The eyes were examined and the Draize scale (***Draize 1959***) was used to assess the grade of ocular reaction approximately one hour and 1, 2, 3, 4, 7 and 8 days after application where necessary. In addition, as an aid in the assessment of corneal damage, fluorescein staining was used at all readings from 1 day after application. A modified form of the Kay and Calandra system (***Kay and Calandra 1962***) was used to interpret and classify the numerical scores.

Corneal, iridial and conjunctival effects were seen in all animals for up to 4 days. All signs of irritation had completely regressed in five animals 7 days after application. Slight conjunctival redness was seen in the remaining animal on day 7; the animal had completely recovered by day 8.

Glyphosate acid is a moderate irritant (class 5 on a 1-8 scale) to the rabbit eye.

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I. MATERIALS AND METHODS

A. MATERIALS

Test Material:	Glyphosate acid
Description:	Technical, white solid
Lot/Batch number:	P24
Purity:	95.6 % w/w
CAS#:	Not reported
Stability of test compound:	The test substance was used within the expiry date

Vehicle and/or positive control: None

Test Animals:

Species	Rabbit
Strain	New Zealand White albino
Age/weight at dosing	Young adult / 2951-3702 g
Source	[redacted] UK.
Housing	Individually in aluminium sheet cages in racks suitable for animals of this strain and the weight range expected during the course of the study.
Acclimatisation period	At least 6 days
Diet	[redacted] UK) *ad libitum*
Water	Mains water *ad libitum*
Environmental conditions	Temperature: 17±2°C Humidity: 40-70% Air changes: Approximately 25/hour Photoperiod: 12 hours light / 12 hours dark

B: STUDY DESIGN AND METHODS:

In-life dates: Start: 22 May 1996 End: 6 July 1996

Animal assignment and treatment: Initially, the test substance (approximately 100mg) was applied into the conjunctival sac of the left eye of one rabbit by gently pulling the lower lid away from the eyeball to form a cup into which the test substance was dropped. The lids were then gently held together for 1-2 seconds after which the animal was released. The other eye was untreated (control eye).

When the eye irritation potential had been fully assessed in the first animal, the test substance was applied into the test eye of the remaining five animals, as described previously.

As the initial pain reaction of the first rabbit was moderate and the irritation was less than severe, the eyes of the remaining rabbits were pre-treated with five drops of local anaesthetic (OPHTHAINE, 0.5% proparacaine hydrochloride solution) at three minute intervals between each drop.

Both eyes of each rabbit were examined within the twenty-four hours prior to dosing. The examination consisted of a visual assessment with the aid of fluorescein and only rabbits without any apparent eye defects or ocular irritation were used.

Immediately after the application of the test substance, an assessment of the initial pain reaction of the rabbit was made using a six-point scale.

The eyes were examined and the Draize scale (***Draize 1959***) was used to assess the grade of ocular reaction approximately one hour and 1, 2, 3, 4, 7 and 8 days after application where necessary. In addition, as an aid in the assessment of corneal damage, fluorescein staining was used at all readings from 1 day after application. A modified form of the Kay and Calandra system (***Kay and Calandra 1962***) was used to interpret and classify the numerical scores.

II. RESULTS AND DISCUSSION

No deaths occurred. No systemic signs of toxicity were noted during the study.

Application into the eye caused moderate initial pain in the first animal dosed, therefore the subsequent five animals were pre-treated with the local anaesthetic OPHTHAINE prior to dosing. The group initial pain reaction was none to moderate (class 0-3 on a 0-5 scale).

Corneal effects, consisting of slight to mild opacity affecting up to the entire cornea, were seen in all animals during the first two days, persisting to day 4 in five rabbits. Slight iritis was seen in all animals during the first two days, persisting to day 3 in two rabbits. Conjunctival, effects consisting of slight to moderate redness, slight to mild chemosis and slight to severe discharge, were seen in all animals up to day 4.

Additional observations included mucoid discharge, eye closed, irregular corneal surface, convoluted eyelids, erythema of the upper and/or lower eyelids, raised corneal opacity, Harderian gland discharge and nictitating membrane partially haemorrhagic.

All signs of irritation had completely regressed in five animals 7 days after application. Slight conjunctival redness was seen in the remaining animal on day 7; the animal had completely recovered by day 8.

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Table 5.2-31: Eye irritation scores of Glyphosate acid (95.6 % w/w) according to the Draize scheme

Time	Cornea						Iris						Conjunctiva											
													Redness						Chemosis					
Animal number	17	18	19	7	8	9	17	18	19	7	8	9	17	18	19	7	8	9	17	18	19	7	8	9
after 1 hour	0	0	0	1	1	1	0	0	0	0	0	0	1	2	2	1	2	2	2	2	1	1	1	2
after 24 hours	1	1	2	2	1	2	0	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2
after 48 hours	1	1	1	2	1	2	1	1	1	1	1	1	2	2	2	2	2	2	1	1	2	2	2	2
after 72 hours	0	1	1	2	1	2	0	0	0	0	1	1	1	2	2	2	2	2	1	1	1	2	2	2
mean scores 24-72h	1.3						0.7						1.9						1.4					
after 4 days	0	1	1	1	1	1	0	0	0	0	0	0	1	1	1	2	2	2	0	1	1	1	1	2
after 7 days	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	-0	0
after 8 days	-	-	-	-	0	-	-	-	-	-	0	-	-	-	-	-	0	-	-	-	-	-	0	-

III. CONCLUSION

Glyphosate acid is a moderate irritant (class 5 on 1-8 scale) to the rabbit eye.

Annex point	Author(s)	Year	Study title
IIA, 5.2.5/12	[redacted]	2007d	Glyphosate Technical Material: Primary Eye Irritation Study in Rabbits [redacted] Data owner: Syngenta Report No.: RR2788 Date: 2007-03-26 GLP: yes not published

Guideline: OECD 405 (2002): OPPTS 870.2400 (1998): 2004/73/EC B.5 (2004)

Deviations: None.

Dates of experimental work: 2006-12-22 to 2007-03-26

Excecutive summary

In a primary eye irritation study, 0.1 g of Glyphosate Technical Material was instilled into the conjunctival sac of the left eye of each of three young adult New Zealand albino rabbits (1 male and 2 females). The animals were then observed for 7 days. The ocular reaction was assessed according to the numerical scoring system listed in the Commission Directive 2004/73/EC, 29 April 2004, at approximately 1, 24, 48 and 72 hours as well as 7 days after instillation.

The instillation of Glyphosate Technical Material into the eye resulted in mild, early-onset and transient ocular changes, such as reddening of the conjunctivae and sclerae, discharge and chemosis. These effects were reversible and were no longer evident 7 days after treatment, the end of the observation period. No abnormal findings were observed in the cornea or iris of any animal at any of the examinations. No corrosion was observed at any of the measuring intervals. No staining of the treated eyes by the test item was observed and no clinical signs were observed.

Thus, Glyphosate Technical Material did not induce significant or irreversible damage to the rabbit eye.

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I. MATERIALS AND METHODS

A: MATERIALS:

Test Material:	Glyphosate Technical Material
Description:	Technical, white powder
Lot/Batch number:	0507
Purity:	96.1% w/w Glyphosate acid
CAS#:	
Stability of test compound:	Stable under storage conditions of room temperature (range of 20°C ± 5°C), protected from light and humidity.

Vehicle and/or positive control: The test substance was undiluted.

Test Animals:

Species	Rabbit
Strain	New Zealand White (SPF)
Age/weight at dosing	Male: 11-12 weeks / 2640 g; Females: 14-16 weeks / 2990 and 3001 g
Source	[redacted] The Netherlands
Housing	Individually in stainless steel cages equipped with feed hoppers and drinking water bowls.
Acclimatisation period	5/6 days
Diet	Pelleted standard [redacted] rabbit maintenance diet *ad libitum*.
Water	Community tap water *ad libitum*
Environmental conditions	Temperature: 17-23°C Humidity: 30-70% Air changes: 10-15 per hour Photoperiod: 12 hours light, 12 hours dark.

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B: STUDY DESIGN AND METHODS:

In-life dates: Start: 27 December 2006 End: 4 January 2007

Animal assignment and treatment: On the day of treatment, 0.1 g of Glyphosate Technical Material was placed into the conjunctival sac of the left eye of each animal after gently pulling the lid away from the eyeball. The lids were then gently held together for about one second to prevent loss of the test substance. The right eye remained untreated and acted as the reference control. The treated eyes were not rinsed after instillation of the test substance.

As it was suspected that the test substance might produce irritancy, a single female was treated first. As neither a corrosive effect nor a severe irritant effect was observed after 1- and 24- hour examinations, the test was completed using the two remaining animals.

The ocular reaction (ie. corneal opacity, iridic effects, conjunctivae and chemosis) was assessed according to the numerical scoring system listed in the Commission Directive 2004/73/EC, 29 April 2004, at approximately 1, 24, 48 and 72 hours, as well as 7 days after instillation. Additionally, ocular discharge, reddening of the sclerae and staining of conjunctivae, sclerae and cornea by the test substance was assessed according to the scheme presented in the guideline.

The animals were observed daily throughout the study for viability, mortality and clinical signs. Bodyweights were measured at the start of acclimatisation, on the day of treatment and at termination of the observation period.

II. RESULTS AND DISCUSSION

No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred. No abnormal findings were observed in the cornea or iris of any animal at any of the measurement intervals.

Moderate reddening of the conjunctivae was noted in all animals at the 1-hour reading and persisted in one animal as slight until the 48-hour reading and in two animals as moderate to slight until 72 hours after treatment. Slight to obvious swelling (chemosis) was observed in all three animals at the 1-hour reading and persisted as slight in one animal until the 48-hour reading and in one animal as moderate until 24 hours after instillation. Slight to moderate reddening of the sclerae was noted in all animals at the 1- and 24 hour reading and persisted as slight reddening until the 48-hour reading. Slight to moderate ocular discharge was seen in all animals at the 1-hour reading and persisted as slight to moderate discharge in two animals at the 24-hour reading. No abnormal findings were observed in the treated eye of any animal 7 days after treatment, the end of the observation period for all animals. No staining of the treated eyes produced by the test substance was observed and no corrosion of the cornea was observed at any of the reading times.

Table 5.2-32: Eye irritation scores of Glyphosate Technical according to the numerical scoring system listed in the Commission Directive 2004/73/EC, 29 April 2004

Time	Cornea			Iris			Conjunctiva					
							Redness			Chemosis		
Animal number	31M	32F	33F	31M	32F	33F	31M	32F	33F	31M	32F	33F
after 1 hour	0rd	0rd	0rd	0	0	0	2	2	2	1	2	2
after 24 hours	0	0rd	0rd	0	0	0	1	2	2	0	1	2
after 48 hours	0[r]	0	0[r]	0	0	0	1	2	2	0	0	1
after 72 hours	0	0	0	0	0	0	0	1	1	0	0	0
mean scores 24-72h	0	0	0	0	0	0	0.67	1.67	1.67	0	0.33	1
After 7 days	0	0	0	0	0	0	0	0	0	0	0	0

M = male, F = female, d = discharge, r = reddening of the sclerae.

III. CONCLUSION

The instillation of Glyphosate Technical Material into the eye resulted in mild, early-onset and transient ocular changes. These effects were reversible and were no longer evident 7 days after treatment. Thus, the test item did not induce significant or irreversible damage to the rabbit eye.

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Annex point	Author(s)	Year	Study title
IIA, 5.2.5/13	[redacted]	2011b	Glyphosate technical: Acute eye irritation study in rabbits [redacted] Data owner: Syngenta Report No.: 10/218-005N Date: 2011-05-13 GLP: yes not published

Guideline: OECD 405 (2002): OPPTS 870.2400 (1998): 2004/73/EC B.5 (2008)

Deviations: None.

Dates of experimental work: 2010-12-10 to 2011-05-13

Excecutive summary

In a primary eye irritation study, 0.1 g of Glyphosate Technical (96.3% w/w Glyphosate technical) was instilled into the conjunctival sac of the left eye of one adult male New Zealand White rabbit. The untreated right eye served as the control. Immediately following instillation, an assessment of initial pain was made. Scoring of irritation effects was performed approximately 1 and 24 hours after test material instillation. Irritation was scored according to the Draize numerical evaluation (***Draize JH, 1977***).

Based on the symptoms, no further animals were dosed and the study was terminated after the 24 hour observation (Regulation (EC) No 440/2008).

Initial Pain Reaction (IPR) scores were taken after instillation into the eye and a score of 3 (on a 0-5 scale) was observed. Conjunctival redness, chemosis and conjunctival discharge, as well as corneal opacity, were observed in the rabbit at 1 and 24 hours after application. Additionally, corneal erosion, redness of the conjunctiva with pale areas, pink, clear ocular discharge, oedema of the eyelids, a few black points on the conjunctiva and dry surface of the eye were noted at one hour after the treatment. Fluorescein staining was positive at the 24 hour observation.

No clinical signs of systemic toxicity were observed in the animal during the study and no mortality occurred.

Under the conditions of this study, Glyphosate Technical is classified as corrosive to the eye.

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I. MATERIALS AND METHODS

A: MATERIALS:

Test Material: Glyphosate technical

Description:	Technical, dry white powder
Lot/Batch number:	569753(BX20070911)
Purity:	96.3% w/w Glyphosate technical
CAS#:	Not reported
Stability of test compound:	Stable under storage conditions (room temperature range <30°C), recertification date end August 2011

Vehicle and/or positive control: None

Test Animals:

Species	Rabbit
Strain	New Zealand White
Age/weight at dosing	Approximately 12 weeks / 3035 g
Source	[redacted] Hungary
Housing	Individually in metal cage
Acclimatisation period	13 days
Diet	[redacted] Base – [redacted] diet ([redacted] Hungary) *ad libitum*
Water	Municipal tap water *ad libitum*
Environmental conditions	Temperature: 20±3°C Humidity: 24-64% Air changes: 15-20/hour Photoperiod: 12 hours light/12 hours dark

B: STUDY DESIGN AND METHODS:

In-life dates: Start: 21 December 2011 End: 22 December 2011

Animal assignment and treatment: The primary eye irritation potential of Glyphosate Technical (96.3% w/w Glyphosate technical) was investigated according to OECD test guideline no. 405. Approximately 1 hour before the start of the test, the eyes of the provisionally selected test rabbits were examined for evidence of ocular irritation or defect using a hand-held slit-lamp. The animal used in the study was free of ocular damage. Initially, a single rabbit was treated.

An amount of 0.1 g of the test material was placed into the conjunctival sac of the left eye, formed by gently pulling the lower lid away from the eyeball. The upper and lower eyelids were held together for about 1 second immediately after treatment, to prevent loss of the test material, and then released. The right eye remained untreated and was used for control purposes.

Immediately after administration of the test material, an assessment of the initial pain reaction was made according to 0-5 scale. Following review of the ocular responses produced in the first treated animal, no further animals were treated. The treated eyes were not rinsed after instillation.

The ocular reaction (i.e. corneal opacity, iridic effects, conjunctivae and chemosis) was assessed approximately 1 and 24 hours following treatment, according to the numerical evaluation described by Draize (***Draize, 1977***).

The treated eye was further examined using 2% fluorescein solution before treatment and then 24 hours after treatment.

Additionally, any other signs of eye irritation were recorded.

II. RESULTS AND DISCUSSION

No clinical signs of systemic toxicity were observed in the animal during the study and no mortality occurred. The body weight was considered to be within the normal range of variability.

An initial pain reaction score of 3 (on a 0-5 scale) was recorded.

Conjunctival redness, chemosis and conjunctival discharge, as well as corneal opacity, were observed in the rabbit 1 and 24 hours after application. Additionally, corneal erosion, redness of the conjunctiva with pale areas, pink, clean ocular discharge, oedema of the eyelids, a few black points on the conjunctiva and

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dry surface of the eye were noted one hour after the treatment. Fluorescein staining was positive at the 24 hours observation.

Based on the symptoms, no further animals were dosed and the study was terminated after the 24 hour observation (Regulation (EC) No 440/2008).

Table 5.2-33: Eye irritation scores of Glyphosate Technical according to the Draize scheme

Time	Cornea	Iris	Conjunctiva		
			Redness	Chemosis	Discharge
after 1 hour	2	0	2	3	3
after 24 hours	3	1	3	4	3

III. CONCLUSION

Under the conditions of this study, Glyphosate Technical is classified as corrosive to the eye.

IIA 5.2.6 Skin sensitisation

In the 2001 EU glyphosate evaluation neither glyphosate acid nor the salts have shown sensitizing effects in guinea pigs. However, only the acid and the IPA were tested under the more stringent conditions of the Magnusson-Kligman test. Since the previous evaluation several new studies for skin sensitizing effects have been conducted according to recent guidelines. The data all confirmed that glyphosate and glyphosate salts (as illustrated by the IPA salt) do not possess a skin sensitising potential, and need not to be classified.

Table 5.2-34: Summary of skin sensitisation studies with glyphosate acid

	Reference (Data owner)	Species Strain	Number and/or sex of animals	Purity [%]	Exposure conditions	Test Method	Results
Studies from the 2001 evaluation	Annex B-5.2.7.1, Glyphosate Monograph [redacted]1994d (Herbex)	Guinea pig Dunkin Hartley	15 ♀	95	Induction: 1% w/v in arachis oil; challenge: 25% w/w or 50% w/w in arachis oil	MKT	Not sensitising
	Annex B-5.2.7.1, Glyphosate Monograph [redacted]1993 (Luxan)	Guinea pig English	48 (both sexes)	≥ 95	Intradermal induction: 5% in propylene glycol; topical: 50% in petrolatum	MKT	Not sensitising
	Annex B-5.2.7.1, Glyphosate Monograph [redacted] 1991 (AGC)	Guinea pig Dunkin Hartley	38 ♀	Not stated	Intradermal induction: 0.1% (w/v) in water; topical: 50% (w/v) in water; challenge: 25% (w/w) in water	MKT	Not sensitising
	Annex B-5.2.7.1, Glyphosate Monograph [redacted] & 1989e (CHE)	Guinea pig Dunkin Hartley	46 ♀	98.6	induction: 10% in water; challenge: 25% in water	MKT	Not sensitising

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	Reference (Data owner)	Species Strain	Number and /or sex of animals	Purity [%]	Exposure conditions	Test Method	Results
Studies not reviewed in the 2001 evaluation	IIA 5.2.6/01 [redacted] 2007c (NUF)	Guinea pig	20 ♀/test 10 ♀/control	95.1	Intradermal induction: 3% (w/v) in PEG-300; topical induction: 50% (w/v) in PEG-300; challenge: 25% (w/v) in PEG-300	MKT	Not sensitising
	IIA 5.2.6/02 [redacted] 2010b (HAG)	Guinea pig, Dunkin Hartley	15 ♀ (+ 20 for positive control)	96.4	Intradermal induction: 0.01% in water; topical induction: 50%; challenge: 25%	MKT	Not sensitising
	IIA 5.2.6/03 [redacted] 1995c (ALS)	Guinea pig Hartley	60 ♀	97.56	Intradermal induction: 5% (w/w) in paraffin oil, topical induction: 25% (w/v) in white petrolatum; challenge: 25% (w/w) in white petrolatum	MKT	Not sensitising
	IIA 5.2.6/04 [redacted] 2009d (EXC)	Guinea pig	15 ♂	96.66	Intradermal induction: 10% (w/w) in purified water; topical induction: 50% (w/w) in purified water; challenge: 15% (w/w) in purified water	MKT	Not sensitising
	IIA 5.2.6/05 [redacted] 2009d (HAG)	Guinea pig	15 ♂ (+ 20 for positive control)	98.8	Intradermal induction: 0.01% in water, topical induction: 50%; challenge: 50%	MKT	Not sensitising
Studies not reviewed in the 2001 evaluation	IIA 5.2.6/06 [redacted] 2010h (HAG)	Guinea pig	15 ♂ (+ 20 for positive control)	97.3	Intradermal induction: 0.5% in water; topical induction: 50%; challenge: 25%	MKT	Not sensitising
	IIA 5.2.6/07 [redacted] 2009e (HAG)	Guinea pig	15 ♂ 15 ♀	96.4	400 mg moistened induction and challange	Buehler Test	Not sensitising
	IIA 5.2.6/08 [redacted] 2005f (HAG)	Guinea pig	30 ♂♀	97.23	70 % in water induction and challange	Buehler Test	Not sensitising
	IIA 5.2.6/09 [redacted] 2008 (HAG)	Guinea pig	30 ♂	98.05	50 % inductions and challange	Buehler Test	Not sensitising

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	Reference (Data owner)	Species Strain	Number and /or sex of animals	Purity [%]	Exposure conditions	Test Method	Results
Studies not reviewed in the 2001 evaluation	IIA 5.2,6/10 [redacted] 2006 (NUF)	Guinea pig	20 ♀/test 10 ♀/control	95.7	Intradermal induction: 0.195% (w/v) in isotonic saline; topical induction: 60% (w/v) in water; challenge: 60% (w/v) & 30% (w/v) in water	MKT	Not sensitising
	IIA 5.2.6/11 [redacted] 1996d (SYN)	Guinea pig	20 ♀/test 10 ♀/control	95.6	Intradermal induction: 0.1% (w/v) in water; topical induction: 75% (w/v) in water; challenge: 75% (w/v) & 30% (w/v) in water	MKT	Not sensitising
	IIA 5.2.6/12 [redacted] 2007 (SYN)	Mouse CBA	4 ♀/group	96.1	Glyphosate acid dose levels: 0, 10, 25, 45 (% w/v) Hexylcinnamaldehyde positive control demonstrated sensitivity of study	LLNA	Not sensitising
	IIA 5.2.6/13 [redacted] 2011 (SYN)	Mouse CBA	4 ♀/group	96.3	Glyphosate acid dose levels: 0, 10, 25, 50 (% w/v) Hexylcinnamaldehyde positive control demonstrated sensitivity of study	LLNA	Not sensitising

MKT = Magnusson Kligman Maximisation Test
LLNA = Local Lymph Node Assay

Table 5.2-35: Summary of skin sensitisation studies with glyphosate salts

	Reference (Data owner)	Species Strain	Number and /or sex of animals	Purity [%]	Exposure conditions	Test Method	Result
Studies from the 2001 evaluation	Annex B.5.2.7.2, Glyphosate Monograph [redacted] 1994d (MON / CHE)	Guinea pig, Dunkin Hartley	38 ♀	IPA 62.2%	Induction: 25% w/v (injection) and 100% (topical); challenge: 100%	MKT	Not sensitizing
	Annex B.5.2.7.2, Glyphosate Monograph [redacted] 1984* (MON)	Guinea pig	16	IPA 53.8%	Induction and challange: 100%	Modified Buehler Test	Not sensitising

* Study was considered supplementary data in the 2001 EU glyphosate evaluation
MKT = Magnusson Kligman Maximisation Test

Tier II summaries are only presented for confirmatory studies not previously evaluated in the 2001 EU glyphosate evaluation.
For details regarding studies reviewed during the 2001 EU evaluation we refer to the Monograph and the former dossier.

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Annex point	Author(s)	Year	Study title
IIA, 5.2.6/01	[redacted]	2007c	Glyphosate Technical (NUP 05068): Contact Hypersensitivity in Albino Guinea Pigs, Maximisation Test [redacted] [redacted] Study No.: B02316 Data owner: Nufarm Date: 2007-03-06 GLP: yes unpublished

Guideline: OECD 406 (1992), Commission Directive 96/54/EC B.6 (1996), JMAFF guideline 12-1-6 (2005)

Deviations: No

Dates of experimental work: 2007-01-10 - 2007-02-15

Executive Summary

Glyphosate technical (NUP 05068) was tested for its sensitizing effect on the skin of the guinea pig in the Maximisation Test. The test-substance concentrations for the main test were selected based on the results of the pre-test. The intradermal induction was performed with a 5% dilution of the test item in PEG 300 and an emulsion of Freund's Complete Adjuvant (FCA)/physiological saline. The epidermal induction was conducted for 48 h under occlusion with the test item at 50% one week after the intradermal induction.

Two weeks after induction the animals were challenged by epidermal application of the test item at 25% under occlusive dressing.

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.

Based on the study results, glyphosate technical (NUP 05068) is not to be classified according to EU classification criteria and OECD Globally Harmonized System (GHS) criteria for skin sensitisation.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate technical

Identification:	NUP 05068
Description:	Solid
Lot/Batch #:	200609062
Purity:	95.1%
Stability of test compound:	Stable under storage conditions (20 ± 5°C), light protected; Expiry date: 2008-09-14

2. Vehicle and/ or positive control: Polyethylene glycol 300 (PEG 300)

3. Test animals:

Species:	Guinea pig
Strain:	Albino Dunkin Hartley, CRL:(HA)BR, SPF

Source:	[redacted] Germany
Age:	5 - 6 weeks
Sex:	female
Weight at dosing:	Pre-tests: 362 – 372 g; main test: 337 – 381 g
Acclimation period:	Main test: at least 10 days
Diet/Food:	Pelleted standard [redacted] guinea pig breeding / maintenance diet ([redacted]), *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Individually in Makrolon type 4 cages with standard softwood bedding
Environmental conditions:	Temperature: 22 ± 3°C Humidity: 30 - 70% Air changes: 10 - 15/hour 12 hours light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 2007-01-10 to 2007-02-15

Animal assignment and treatment:
Glyphosate technical (NUP 05068) was tested for its sensitising effect on the skin of the guinea pig using the Maximisation test according to Magnusson and Kligman. Female Dunkin Hartley guinea pigs, young adults with body weights ranging from 337 to 381 g were used. The test substance concentrations for the main study were selected based on the results of the pre-testing performed with three animals. The main study was performed in 20 test animals and 10 control animals.
The induction phase consisted of an intradermal injection at day 1 and an epidermal application on day 8. On day 1 the test substance was injected (0.1 mL/site) into the clipped dorsal skin from the scapular region at a concentration of 3% either in PEG 300 or in a 1:1 (v/v) mixture of Freund´s Complete Adjuvant and physiological saline. On day 8 the test substance was topically applied at a concentration of 50% to the clipped and shaved skin of the scapular area and covered with an occlusive dressing, which was left in place for 48 hours. The reaction sites were assessed 24 and 48 hours after removal of the bandage.
The challenge was conducted on day 22 by an occlusive patch containing 0.2 mL of the test material at a concentration of 25% in PEG 300 that was applied to the clipped and shaved left flank of each animal for 24 h. The clipped and shaved right flank of each animal was treated in the same way with the vehicle only (PEG 300). 24 and 48 hours after removal of the dressing skin reactions were scored according the Magnusson and Kligman grading scale.
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 not included in this study. However, a separate study was performed from June to August 2006 in the laboratory. The positive controls with alpha-hexylcinnamaldehyde (3% in PEG 300) 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, 30% 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
All animals showed the expected gain in body weight with the exception of one of the pre-test animals that did not gain body weight between the day of epidermal application and day of sacrifice one week later.

D. NECROPSY
No necropsy was performed.

E. SKIN REACTIONS
No skin reactions were observed 24 or 48 h after the challenge treatment with glyphosate technical (NUP 05068) in the control or test group.

III. CONCLUSION

Based on the EU classification criteria, glyphosate technical (NUP 05068) is not to be classified for skin sensitization. According to the OECD Globally Harmonized System (GHS) classification criteria glyphosate technical (NUP 05068) is also not classified for skin sensitization.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/02	[redacted]	2010b	Examination Of Glyphosate TC In The Skin Sensitisation Test In Guinea Pigs According To Magnusson And Kligman (Maximisation Test) [redacted] Data owner: Helm AG Report No.: 24879 Date: 2010-01-22 GLP: yes unpublished

Guideline:	OECD 406 (1992); Commission Directive 96/54/EC B.6 (1996), OPPTS 870.2600 (1998)
Deviations:	None
Dates of experimental work:	2009-10-15 - 2009-11-28

Executive Summary

Glyphosate TC was tested for its sensitizing effect on the skin of the guinea pig in the Maximisation Test. The test-substance concentrations for the main test were selected based on the results of the pre-test. The intradermal induction was performed with a 0.01% dilution of the test item in physiological saline and an emulsion of Freund's Complete Adjuvant (FCA)/physiological saline. The epidermal induction was conducted for 48 h under occlusion with the test item at 50% one week after the intradermal induction.
Two weeks after induction the animals were challenged by epidermal application of the test item at 25% under occlusive dressing. The study was performed using a control group consisting of five animals, one test group consisting of ten animals and a positive control group consisting of 20 animals.
None of the vehicle control or test animals exhibited a positive skin reaction (defined as scores of ≥ 1) after the challenge treatment. Animals treated with the positive control benzocaine in 40% ethanolic 0.9%

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NaCl solution exhibited a sensitising reaction in all animals in form of a discrete or patchy erythema (grade 1).
Based on the study results and according to the EU and OECD Globally Harmonized System (GHS) classification criteria, glyphosate TC is not to be classified for skin sensitization.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	Glyphosate TC
Description:	White powder
Lot/Batch #:	2009051501
Purity:	96.4%
Stability of test compound:	At room temperature in the dark stable until May 15, 2011.

2. Vehicle and/ or positive control: Purified water

3. Test animals:

Species:	Guinea pig
Strain:	Dunkin Hartley
Source:	[redacted] Germany
Age:	32 days
Sex:	Female
Weight at dosing:	312 - 355 g; positive control group: 249 - 317 g
Acclimation period:	At least 5 days.
Diet/Food:	[redacted] Germany), *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	In pairs in Makrolon cages ([redacted]) with granulated textured wood bedding
Environmental conditions:	Temperature: 22 ± 3°C Humidity: 55 ± 15% Air changes: no data 12 hours light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 2009-10-15 to 2009-11-28

Animal assignment and treatment:
Glyphosate TC was tested for its sensitising effect on the skin of the guinea pig using the Maximisation test according to Magnusson and Kligman. Female Dunkin Hartley guinea pigs, young adults with body weights ranging from 312 to 355 g were used. The test substance concentrations for the main study were selected based on the results of the pre-testing performed with eight animals. The main study was performed in 10 test animals, 5 control animals and 20 positive control animals.
The induction phase consisted of an intradermal injection at Day 0 and an epidermal application on Day 7. On Day 0 the test substance was injected (0.1 mL/site) into the clipped dorsal skin of the shoulder region at a concentration of 0.01% in *aqua ad iniectabilia*, together with injections of Freund´s Complete

Adjuvant in physiological saline, or test item in a 1:1 (v/v) mixture of Freund´s Complete Adjuvant and physiological saline.
On Day 6 the skin was shaved and coated with 0.5 mL sodium laurylsulfate 10% in vaseline in order to induce a local irritation. On Day 7 the test substance was topically applied at a concentration of 50% to the clipped and shaved skin of the shoulder region using the patch technique. The patch was left occluded in place for 48 hours.
The challenge was conducted on Day 21 by an occlusive patch at a concentration of 25% in *aqua ad iniectabilia* which was applied to the clipped and shaved left flank of each animal for 24 h. The clipped and shaved right flank of each animal was treated in the same way with the vehicle alone. 24 and 48 hours after removal of the dressing skin reactions were scored according the Magnusson and Kligman grading scale.

The animals of the positive control group were treated with a 2% benzocaine solution intracutaneously in the induction phase and with a 5% solution topically in the induction phase and at challenge.

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.

Evaluation criteria for classification as a potential skin sensitizer:
At the 24-hour and/or 48-hour readings, 30% 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
All animals showed the expected gain in body weight.

D. NECROPSY
No necropsy was performed.

E. SKIN REACTIONS
No skin reactions were observed 24 or 48 h after the challenge treatment with glyphosate TC in the control or test group.
Animals treated with the positive control benzocaine in 40% ethanolic 0.9% NaCl solution exhibited a sensitising reaction in all animals in form of a discrete or patchy erythema (grade 1).

III. CONCLUSION

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

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Annex point	Author(s)	Year	Study title
IIA, 5.2.6/03	[redacted]	1995	HR-001: Dermal sensitisation study in Guinea pigs. [redacted] Study No.: [redacted]95-0036 Data owner: Arysta LifeScience Date: 1995-06-28 GLP: yes Unpublished

Guideline: U.S. EPA FIFRA Guideline Subdivision F

Deviations: None

Dates of experimental work: 1995-04-19 – 1995-05-13

Executive Summary

HR-001 was applied to the skin of female Hartley strain guinea pigs to evaluate its dermal sensitizing potenital. This study was performed according to the guinea pig maximization test. DNCB (2,4-dinitrochlorobenzene) was used as the positive control substance. Animals were assigned to the following 4 groups:

- 20 animals to the test substance treatment group, treated with the test substance both at the induction and challenge,
- 20 animals to the negative control group for the test substance, treated with the test substance at the challenge but not at the induction,
- 10 animals to the DNCB treatment group treated with DNCB both at induction and challenge, and
- 10 animals to the negative control group for DNCB, treated with DNCB at the challenge but not at the induction.

Concentrations of 5%, 25% and 25% of the test substance, and concentrations of 0.1%, 1% and 0.5% of DNCB were selected as the dose for intradermal induction, topical induction, and challenge, respectively. Skin reaction to the challenge was observed 24 and 48 hours after removal of the patch and dermal sensitization rates were calculated.

All 20 animals in the test substance treatment group exhibited the reaction of 0 (no reaction).

All 20 animals in the negative control group for the test substance also exhibited score 0. Thus the sensitizing rate, i.e. the percentage of animals positively sensitized, was 0% in the test substance treatment group.

The DNCB treatment group was evaluated on 9 animals group because one animal died at Day 12 after intradermal induction. All 9 animals exhibited a reaction of score 3 (intense redness and swelling). On the other hand, all 10 animals in the negative control group for DNCB exhibited a score of 0. Thus the sensitizing rate of DNCB was greater than 100%. This was sufficient to assure the reliability of this study.

Based on the study results, glyphosate technical (HR-001) is not to be classified according to EU classification criteria and OECD Globally Harmonized System (GHS) criteria for skin sensitisation.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate technical

Identification: HR-001

Description: White crystal

Lot/Batch #: T-941209

Purity: 97.56%

Stability of test compound: Not mentioned in the report

2. Vehicle and/ or positive control: Polyethylene glycol 300 (PEG 300)

3. Test animals:

Species: Guinea pig

Strain: Hartley, Crj:Hartley

Source: [redacted] Japan

Age: 6 weeks

Sex: female

Weight at dosing: 332 – 423 g at the time of intradermal injection

Acclimation period: 1 week

Diet/Food: Pellet diet [redacted], *ad libitum*

Water: Filtered and sterilized water, *ad libitum*

Housing: Aluminium cage with wire-mesh floor

Environmental conditions: Temperature: 23.9°C
Humidity: 51.8 – 56.2%
Air changes: 15/hour
12 hours light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 2007-01-10 to 2007-02-15

Animal assignment and treatment:
The test was carried out according to the maximization method of Magnusson and Kligman.
20 female specific pathogen free Hartley guinea pigs (Crj:Hartley) were exposed to concentrations of 5%, 25% and 25% glyphosate technical for intradermal induction (3 pairs of injection), topical induction (applied with an occlusive dressing) and challenge (applied with an occlusive dressing) respectively. These doses selected for both induction and challenge application in the main study were based on the results of range-finding studies. DCNB (2,4-dichlorobenzene) was used (in a 10 female group) as the positive control substance at concentrations of 0.1 %, 1% and 0.5% for intradermal induction, topical induction and challenge, respectively. Groups of 10 and 20 animals were used for the negative control group for DCNB (treated with DCNB at the challenge but not at the induction) and negative control group for technical glyphosate (treated with test substance at the challenge but not at the induction), respectively. Skin reaction to the challenge was observed 24 and 48 hours after temoval of the patch and dermal sensitisation rates were calculated. Body weights were measured at the first induction and 48 hours after the removal of the patch.

II. RESULTS AND DISCUSSION

A. MORTALITY

One animal died in the DNCB treatment group. At necroscpy of the dead animal, consolidation of lung and hydrothorax were noted. These findings were associated with the hindrance of circulation and the respiratory abnormality, which led to the death. The remaining animals in this groupdid not show any abnormality in the health condition and the skin reactions were clearly observed.

B. CLINICAL OBSERVATIONS

No signs of systemic toxicity were observed.

C. BODY WEIGHT

No abnormal body weight changes were noted in any animal of the four groups.

D. NECROPSY

No necropsy was performed.

E. SKIN REACTIONS

No oedema or erythema were observed in test animals following challenge with 25 % technical glyphosate. The rate of sensitization in the test substance treatment group was therefore 0%.
On the other hand, the rate of sensitization in the DCNB treatment group was 100%, which was considered to sufficiently assure the reliability of this study.

III. CONCLUSION

Based on the EU classification criteria, glyphosate technical (HR-001) is not to be classified for skin sensitization. According to the OECD Globally Harmonized System (GHS) classification criteria glyphosate technical (HR-001) is also not classified for skin sensitization.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/04	[redacted]	2009d	Glyphosate Technical: Contact Hypersensitivity in albino guinea pigs – Maximization-Test [redacted] Data owner: Excel Report No.: C 22908 Date: 2009-05-15 GLP: yes not published
Guideline:			OECD 406 (1992) Commission Regulation (EC) No 440/2008 (2008); method B.6
Deviations:			None
Dates of experimental work:			2009-01-14 to 2009-02-27

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Executive Summary

Glyphosate Technical was tested for its sensitizing effect on the skin of guinea pig in the Maximization-Test. No mortality occurred during the study, hence no necropsies were performed. No clinical signs of systemic toxicity were observed in the animals. No positive/skin reactions were observed in the animals in the challenge procedure. There was no effect on body weight gain. The Glyphosate Technical in the Maximization-Test was concluded to be

Not sensitising to the skin

According to EU and OECD Globally Harmonized System (GHS) classification criteria the test substance glyphosate technical is not to be classified for skin sensitisation.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	Glyphosate Technical
Description:	Solid
Lot/Batch #:	GI-1045
Purity:	96.66 %
Stability of test compound:	Expiry date: July 2010 Test item dilution: Stable in purified water for 2 days.

2. Vehicle and/ or positive control:

Purified water

3. Test animals:

Species:	Guinea pig
Strain:	Albino Dunkin Hartley, CRL:(AH)BR, SPF
Source:	[redacted] Germany
Age:	4 – 6 weeks (at pre-test / at beginning of acclimatization period)
Sex:	Male
Weight at dosing:	348 – 358 g (at pre-test) 335 – 365 g (at beginning of acclimatization period)
Acclimation period:	Approx. 2 weeks (for main study)
Diet/Food:	Pellet standard [redacted] guinea pig breeding / maintenance diet batch nos. 55/08 and 72/08, containing Vitamin C [redacted] Switzerland), *ad libitum*.
Water:	Tap water, *ad libitum*
Housing:	Individually in Makrolon type-4 cages with standard softwood bedding [redacted] / Switzerland)
Environmental conditions:	Temperature: 22 ± 3°C Humidity: 30 – 70 % Air changes: 10 - 15/hour 12-hour light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 2009-01-14 to 2009-02-27

Animal assignment and treatment:
Glyphosate Technical was tested for its sensitizing effect on the skin of guinea pig in the Maximization-Test according to Magnusson-Kligman. Fifteen (10 test and 5 control) male Albino Dunkin Hartley CRL:(AH)BR, SPF guinea pigs, 4-6 weeks of age, and 335-365 g of weight were employed for this study.
The concentrations of test substance for the main test were selected based on the results of a pre-test (during the acclimatization period of the main animals).
The intradermal induction of sensitization in the test group was performed in the nuchal region with a 10 % dilution of the test item in purified water and in an emulsion of Freund's Complete Adjuvant (FCA)/physiological saline. The epidermal induction of sensitization was conducted for 48 hours under occlusion with the test item at 50 % in purified water one week after the intradermal induction. The

animals of the control group were intradermally induced with purified water and FCA/physiological saline and epidermally induced with purified water under occlusion.
Two weeks after epidermal induction the control and test animals were challenged by epidermal application of the test item at 15 % in purified water and purified water alone under occlusive dressing.
Cutaneous reactions were evaluated at 24 and 48 hours after removal of the dressing (according to the criteria laid down in test guidelines).
A positive control (reliability check) with a known sensitizer was not included in this study. However, a separate study was performed in the laboratory. The positive controls with α-hexylcinnamaldehyde at 3% in PEG 300 showed that the chosen guinea pig strain was able to detect sensitizing compounds under the laboratory conditions chosen.
Body weights were determined at delivery/acclimatization start, at the end of the pretest, at test day 1 (day of treatment), and at the termination of the study. Mortality was checked daily.

II. RESULTS AND DISCUSSION

A. MORTALITY

There were no treatment related deaths during the course of the study, hence no necropsies were performed.
One pre-test animal was found in bad conditions before the start of pre-test and during the acclimatization period of the main test animals. This animal was sacrificed for ethical reasons and replaced by a new animal.

B. CLINICAL OBSERVATIONS

No signs of systemic toxicity were observed in the animals.

C. BODY WEIGHT

The body weight of the animals was within the range commonly recorded for animals of this strain and age.
One animal lost visible amount of body weight (31 g) before the start of the intradermal pre-test. It was killed for ethical reasons and replaced by another animal.

D. NECROPSY

No necropsies were performed.

E. SKIN REACTIONS

Skin Effects in the Intradermal Induction (Test Day 1)

The expected and common findings were observed in the control and test group after the different applications using FCA intradermally. These findings consisted of erythema, oedema, necrotizing dermatitis, encrustation and exfoliation of encrustation.

Skin Effects in the Epidermal Induction (Test Day 8)

Control group – No erythematous or oedematous reaction was observed in the animals treated with purified water only.
Test group – Discrete/patchy erythema was observed in eight out of ten test animals at the 24-hour observation and persisted in seven animals up to the 48-hour reading after treatment with the test item at 50 % in purified water.

Skin Effects in the Challenge Procedure

Control group and Test group – No positive/skin reactions were observed in the animals when treated with either purified water only or when treated with the test item at 15 % in purified water.

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III. CONCLUSION

Based on the above mentioned findings in the Magnusson & Kligman Test in guinea pigs and in accordance to Commission Directive 2001/59/EC, Glyphosate Technical does not have to be classified and labelled as a skin sensitizer.
Based on the EU and the OECD Globally Harmonized System (GHS) classification criteria, glyphosate technical is not to be classified for skin sensitization.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/05	[redacted]	2009d	Examination of Glyphosate TC in Skin Sensitisation Test in Guinea Pigs according to Magnusson and Kligman (Maximisation Test) [redacted] Data owner: Helm AG Report No.: [redacted]23915 Date: 2009-05-19 GLP: yes unpublished

Guideline: OECD 406
US EPA OPPTS 870.2600

Deviations: Personnel change of the head of the Quality Assurance Unit:
until January 31, 2009: [redacted]
as of February 1, 2009: [redacted]
This minor deviation did not have any effect on the validity and integrity of the scientific results obtained in this.

Dates of experimental work: 2009-02-04 - 2009-03-28

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Executive Summary

The purpose of this study was to determine the potential of Glyphosate TC to produce skin sensitisation reactions in guinea pigs in a test model according to MAGNUSSON and KLIGMAN. A 0.5% suspension of Glyphosate TC in aqua ad iniectabilia chosen for the 1st (intracutaneous) induction stage revealed a discrete or patchy erythema 24 and 48 hours after administration. 2 mL of a 50% suspension of Glyphosate TC in aqua ad iniectabilia/animal chosen for the 2nd (topical) induction stage was not irritating to the shaved skin in the preliminary experiment. Hence, in the main study the skin was coated with sodium laurylsulfate on the day before the 2nd induction in order to induce a local irritation. The challenge with 2 mL of a 50% suspension of Glyphosate TC in aqua ad iniectabilia/animal revealed no skin irritation in any animal and, thus, the test item had no sensitising properties. The vehicle control revealed no skin reactions. Animals of the same strain treated with benzocaine in 40% ethanolic 0.9% NaCl solution exhibited a sensitising reaction in all animals in form of a discrete or patchy erythema (grade 1). The body weight gain of the animals treated with Glyphosate TC was within the range of the vehicle control at study termination. The significant difference in body weight between test item-treated and control animals at start of the study is regarded to be without any biological relevance. Behaviour of the animals remained unchanged. Under the present test conditions, Glyphosate TC was found to be

not sensitising

to guinea pigs in a test model according to MAGNUSSON and KLIGMAN.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate

Identification: Glyphosate TC
Description: White powder
Lot/Batch #: 20080801
Purity: 98.8%
Stability of test compound: No data given in the report.

2. Vehicle and/ or positive control: *Aqua ad iniectabilia*/ Benzocaine

3. Test animals:

Species: Guinea pig
Strain: Dunkin-Hartley
Source: [redacted]
Germany
Age: 32 days
Sex: Male
Weight at dosing: 313 – 358 g
(excluding positive control group)
Positive control group: 271 – 331 g
Acclimation period: At least 5 days
Diet/Food: Commercial diet, [redacted] served as food. The food was offered *ad libitum.*
Water: Tap water, *ad libitum*
Housing: The animals were kept in pairs in MAKROLON cages ([redacted]). Granulated textured wood [redacted] Germany) was used as bedding material in the cages. The cages were changed and cleaned twice a week.
Environmental conditions: Temperature: 22 ± 3°C
Humidity: 55 ± 15%
12-hour light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 2009-02-04 to 2009-03-28

Animal assignment and treatment:
The purpose of this study was to determine the potential of Glyphosate TC to provoke skin sensitisation reactions in guinea pigs. Possible sensitising properties of the test item were evaluated by administration of the test item to the shoulder region, first by intracutaneous application (stage 1) and 7 days later by topical administration (stage 2, exposure time: 48 hours). In a challenge test (stage 3) the test item was

again applied topically but to the flank region (exposure time: 24 hours). This area was then examined for reactions which might indicate sensitising properties of the test item.
Induction: The skin reaction results of the first induction exposure were evaluated at 24 and 48 hours, of the second induction at 48 and 72 hours after beginning of exposure.
Challenge:
Days 23 and 24:
21 hours after removing the filter paper the challenge area was cleaned and cleared of hair if necessary three hours later (at 48 hours from the start of challenge application) the skin reaction was observed and recorded. 24 hours after this observation a second observation (72 hours) was made and recorded.

II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
Behaviour of the animals remained unchanged. Given the negative response in all treated animals further testing was not considered necessary in order to reduce animal experiments for animal welfare reasons.

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

III. CONCLUSION
Under the present test conditions Glyphosate TC revealed no sensitising properties in guinea pigs in a test model according to MAGNUSSON and KLIGMAN.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/06	[redacted]	2010b	Examination of Glyphosate TC in Skin Sensitisation Test in Guinea Pigs according to Magnusson and Kligman (Maximisation Test) [redacted] Data owner: Helm AG Report No.: [redacted]24607 Date: 2010-04-19 GLP: yes unpublished

Guideline: OECD 406
US EPA OPPTS 870.2600.

Deviations: The following minor deviations were noted:
The batch no. of the sodium lauryl sulfate was 081 K0078 and not 121 H0370 as stated in the Study Plan.
Freund's complete adjuvant was manufactured by [redacted] Germany, and not by [redacted] USA, as stated in the Study Plan.
These minor deviations from the Study Plan did not affect the validity and scientific results of the study.

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Dates of experimental work: 2009-10-26 - 2010-01-30

Executive Summary

The purpose of this study was to determine the potential of Glyphosate TC to produce skin sensitisation reactions in guinea pigs in a test model according to MAGNUSSON and KLIGMAN. A 0.5% concentration of Glyphosate TC in aqua ad iniectabilia chosen for the 1st (intracutaneous) induction stage revealed a discrete or patchy erythema in all 10 animals 24 and 48 hours after adminstration. 2 mL of a 50% concentration of Glyphosate TC in aqua ad iniectabilia/animal chosen for the 2nd (topical) induction stage was non-irritating to the shaved skin in the preliminary experiment. Hence, in the main study the skin was coated with sodium laurylsulfate on the day before stage 2 induction in order to induce a local irritation. The challenge with 2 mL of a 25% concentration of Glyphosate TC in aqua ad iniectabilia/animal revealed no skin irritation in any animal and, thus, the test item had no sensitising properties.The vehicle control revealed no skin reactions. Animals of the same strain treated with benzocaine in 40% ethanolic 0.9% NaCl solution exhibited a sensitising reaction in all animals in form of a discrete or patchy erythema (grade 1). The animals gained the expected weight within the test period. Behaviour of the animals remained unchanged. Under the presen t test conditions, Glyphosate TC was found to be

not sensitising

to guinea pigs in a test model according to MAGNUSSON and KLIGMAN.

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I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** Glyphosate
   - Identification: Glyphosate TC
   - Description: White powder
   - Lot/Batch #: 20090506
   - Purity: 97.3%

   Stability of test compounds: No data given in the report.
2. **Vehicle and/ or positive control:** *Aqua ad iniectabilia*
   Benzocaine
3. **Test animals:**
   - Species: Guinea pig
   - Strain: Dunkin-Hartley
   - Source: [redacted]
     Germany
   - Age: 32 days
   - Sex: Male
   - Weight at dosing: 299 - 364 g
     (excluding positive control group)
     Positive control group: 319 - 346 g
   - Acclimation period: At least 5 days
   - Diet/Food: Commercial diet, [redacted] served as food. The food was offered ad libitum

Water:	Tap water, *ad libitum*
Housing:	The animals were kept in pairs in MAKROLON cages ([redacted]). Granulated textured wood ([redacted] Germany) was used as bedding material in the cages. The cages were changed and cleaned twice a week.
Environmental conditions:	Temperature: 22 ± 3°C Humidity: 55 ± 15% 12-hour light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 2009-10-26 to 2010-01-30

Animal assignment and treatment:
The purpose of this study was to determine the potential of Glyphosate TC to provoke skin sensitisation reactions in guinea pigs. Possible sensitising properties of the test item were evaluated by administration of the test item to the shoulder region, first by intracutaneous application (stage 1) and 7 days later by topical administration (stage 2, exposure time: 48 hours). In a challenge test (stage 3) the test item was again applied topically but to the flank region (exposure time: 24 hours). This area was then examined for reactions which might indicate sensitising properties of the test item.
Induction: The skin reaction results of the first induction exposure were evaluated at 24 and 48 hours, of the second induction at 48 and 72 hours after beginning of exposure.
Challenge: Days 23 and 24: 21 hours after removing the filter paper the challenge area was cleaned and cleared of hair if necessary three hours later (at 48 hours from the start of challenge application) the skin reaction was observed and recorded. 24 hours after this observation a second observation (72 hours) was made and recorded.

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II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
Behaviour of the animals remained unchanged. Given the negative response in all treated animals further testing was not considered necessary in order to reduce animal experiments for animal welfare reasons.

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

III. CONCLUSION

Under the present test conditions Glyphosate TC revealed no sensitising properties in guinea pigs in a test model according to MAGNUSSON and KLIGMAN.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/07	[redacted]	2009e	Glyphosate – Skin Sensitization Study in Guinea Pigs. Buehler Test. [redacted] Data owner: Helm AG Report No.: 12174-08 Date: 2009-03-11 GLP: yes unpublished

Guideline: US EPA OPPTS 870.2600
Equivalent to OECD 406.

Deviations: Humidity was in the range of 25-98% instead of 30-70%. This deviation did not affect the study outcome.

Dates of experimental work: 2008-11-30 - 2009-01-02

Executive Summary

A skin sensitization study was conducted on 15 male and 15 female short-haired albino guinea pigs to determine if test substance Glyphosate produced a sensitizing reaction. Males and females were assigned to each of two groups, designated Groups I (5/sex) and II (10/sex). Group I animals remained untreated during the induction phase of the study and served as a naive control group. Group II animals, the test group, were treated with 400 mg of test substance moistened with 2 mL of deionized water. The animals were treated once weekly for three weeks, for a total of three treatments. After a two week rest period, all animals (Groups I and II) were challenged at a virgin test site with an application of 400 mg of test substance moistened with 2 mL of deionized water. The test substance produced neither irritation in the test animals (Group II) nor the naive control animals (Group I) after the challenge treatment, and therefore did not elicit a sensitizing reaction in guinea pigs. The test substance, Glyphosate, produced neither irritation in the test animals (Group II) nor the naive control animals (Group I) after the challenge treatment, and therefore did not elicit a sensitizing reaction in guinea pigs and is therefore

not sensitizing.

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I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** Glyphosate
   - Identification: Glyphosate Tech Grade Mixed 5-Batch
   - Description: White powder
   - Lot/Batch #: 080704-1 thru 5
   - Purity: 96.4%
   - Stability of test compound: No data given in the report.
2. **Vehicle and/ or positive control:** Deionised water/ alpha-Hexylcinnamaldehyde
3. **Test animals:**
   - Species: Guinea Pig
   - Strain: Hartley-Albino
   - Source: [redacted]
   - Age: Approx. 4 weeks

Sex:	Males and Females
Weight at dosing:	Males: 359-414 g; Females: 341-387 g
Acclimation period:	5 days
Diet/Food:	[redacted] Guinea Pig Diet [redacted]; available *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Individual housing in suspended, wire bottom, stainless steel cages.
Environmental conditions:	Temperature: 22 ± 3°C Humidity: 30 - 70% Air changes: 10 - 12/hour 12-hour light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 2008-11-30 to 2009-01-02

Animal assignment and treatment:
Observations for skin reactions at each test site were made approximately 24 hours after each treatment. In addition, observations for skin reactions were made approximately 48 hours after the first induction treatment and 48 hours after the challenge treatment. An average score for each time period was obtained by adding all of the scores for each time period and dividing by the number of test sites scored for that time period. The test substance is considered a sensitizer if the mean irritation scores, the total number of animals with scores, and/or the total number of scores for the virgin test site in the test group after the challenge treatment are appreciably greater than those for the naive challenge group. The average skin reaction score of this study was 0.0.

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II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
The test substance, Glyphosate, produced neither irritation in the test animals (Group II) nor the naive control animals (Group I) after the challenge treatment, and therefore did not elicit a sensitizing reaction in guinea pigs.

III. CONCLUSION
The test substance, Glyphosate, produced neither irritation in the test animals (Group II) nor the naive control animals (Group I) after the challenge treatment, and therefore did not elicit a sensitizing reaction in guinea pigs and is therefore not sensitizing.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/08	[redacted]	2005f	Glyphosate acid technical – Dermal Sensitization in Guinea Pigs (Buehler Method) [redacted] Data owner: Helm AG Report No.: [redacted]15279 Date: 2005-04-04 GLP: yes unpublished

Guideline: US EPA OPPTS 870.2600
OECD 406.

Deviations: No deviations from the Study Plan

Dates of experimental work: 2004-05-03 - 2004-06-03

Executive Summary

A dermal sensitization test was conducted with guinea pigs to determine the potential for Glyphosate Acid Technical to produce sensitization after repeated topical applications. A 70% w/w mixture of the test substance in distilled water was topically applied to twenty healthy test guinea pigs, once each week for a three-week induction period. Twenty-seven days after the first induction dose, a challenge dose of the test substance at its highest non-irritating concentration (HNIC, determined in the preliminary irritation screen to be a 70% w/w mixture in distilled water) was applied to a naive site on each guinea pig. A naive control group (ten animals) was maintained under the same environmental conditions and treated with the test substance at challenge only. Approximately 24 and 48 hours after each induction and challenge dose, the animals were scored for erythema. Based on the results of this study, the test substance is

not considered to be a contact sensitizer.

The positive response observed in the historical positive control validation study with alpha-Hexylcinnamaldehyde Technical (HCA) validates the test system used in this study.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate

Identification:	Glyphosate Acid Technical
Description:	White crystalline powder
Lot/Batch #:	040205
Purity:	97.23%
Stability of test compound:	No data given in the report.

2. Vehicle and/ or positive control: Distilled water/
alpha-Hexylcinnamaldehyde Technical

3. Test animals:

Species:	Guinea pig
Strain:	Hartley albino
Source:	[redacted]
Age:	Young adult
Sex:	Male and Female
Weight at dosing:	327-391 g

Acclimation period:	5 or 38 days
Diet/Food:	Pelleted [redacted] Guinea Pig Chow [redacted]
Water:	Tap water, *ad libitum*
Housing:	The animals were group housed in suspended stainless steel caging with mesh floors or plastic perforated bottom caging.
Environmental conditions:	Temperature: 18-22°C 12-hour light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 2004-05-03 to 2004-06-03

Animal assignment and treatment:
In order to evaluate the sensitization response at challenge, two indices were used, one for incidence and one for severity (Ritz, H. and Buehler, E., 1980) in the test and vehicle control animals. The incidence index was the ratio of animals with erythema scores greater than 0.5 per number of animals evaluated, and is presented for both the 24 and 48 hour intervals after challenge evaluation intervals as follows: Incidence Index =Number of erythema scores greater than 0.5 / Number of animals evaluated The severity index is the mean erythema score, and is calculated for both the 24 and 48 hour after challenge evaluation intervals according to the following formula: Severity Index = Sum of erythema scores/Number of animals evaluated. The following criteria were used to classify the test substance as a potential contact sensitizer (Robinson, et al., 1990): At the 24-hour and/or 48-hour scoring interval, 15% or more of the test animals exhibit a positive response (scores > 0.5) in the absence of similar results in the vehicle control group. The positive reaction at the 24-hour interval must persist to 48 hours in at least one test animal.

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II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS
Induction Phase:

Test Animals (70% w/w mixture of the test substance in distilled water): Very faint erythema (0.5) was observed for most test sites during the induction phase.

Test Animals (70% w/w mixture of the test substance in distilled water): Very faint erythema (0.5) was observed at six of twenty test sites 24 hours following the challenge application. Similar irritation persisted at one affected site through 48 hours.

III. CONCLUSION

Based on these findings and on the evaluation system used, Glyphosate Acid Technical is not considered to be a contact sensitizer.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/09	[redacted]	2008	Skin Sensitisation Test for Glyphosate Technical in Guinea Pigs. Buehler Test. [redacted] Data owner: Helm AG Report No.: [redacted]3996.318.431.07 Date: 2008-09-30 GLP: yes unpublished

Guideline: OECD 406.

Deviations: 1. The experimental phase initiation and experimental phase conclusion dates were updated,
2. The test item was applied using DMSO as vehicle.
The deviations listed above had no negative impact on the outcome of the study.

Dates of experimental work: 2008-06-12 - 2008-07-12

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Executive Summary

The skin sensitisation test with GLYPHOSATE TECHNICAL in guinea pigs (Cavia porcellus) was carried out according to the Buehler Test Method and the Guideline 406 of the Organisation for Economic Co-operation and Development (OECD, 1992), in order to evaluate its skin sensitisation potential. A pilot study was conducted in order to determine the suitable doses of test substance for induction and challenge applications. The induction and challenge doses chosen were 0.5 g of test item (equivalent to 1 ml, of a 50% w/v test solution). One test solution for each application was made using DMSO as vehicle to increase the contact area and to allow transdermal absorption. A sample of each solution was sent for quantitative analysis using High Performance Liquid Chromatography (HPLC) equipment. After each application cotton lint patches were held in contact with the skin for an approximated 6-hour exposure period. Twenty treatment animals were exposed to the test item in inductions and challenge applications. Ten control animals were exposed to the vehicle on inductions and to the test item on challenge application. Skin reactions were evaluated approximately 30 and 54 hours after each application by clinical examination (inductions) and according to the Magnusson & Kligman's grading scale (pilot study and challenge). Neither compound-related clinical signs nor behavioral alterations were observed during inductions. No animal from control group was positive for the test item after challenge application. One animal from treatment group was positive for the test item after challenge application. Therefore, the epidermal application of GLYPHOSATE TECHNICAL using DMSO as vehicle did

not cause skin sensitisation

in guinea pigs, according to the Buehler Test Method.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glyphosate

Identification:	Glyphosate Techical
Description:	White powder
Lot/Batch #:	20070606
Purity:	98.05%

Stability of test compound: No data given in the report.

2. **Vehicle and/ or positive control:** DMSO

3. **Test animals:**

Species:	Guinea Pig
Strain:	Hartley
Source:	[redacted], Brazil
Age:	Eight to nine weeks old
Sex:	Male
Weight at dosing:	444 - 556 g
Acclimation period:	7 days
Diet/Food:	Pelleted commercial diet - [redacted]
Water:	Tap water, *ad libitum*
Housing:	88 x55 x 28 cm polypropylene cages with autoclaved wood shavings containing five animals per cage during the experimental phase were used.
Environmental conditions:	Temperature: 18 - 23°C Humidity: 30 - 70% Air changes: 10 - 15/hour 12-hour light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 2008-06-12 to 2008-07-17

Animal assignment and treatment:
The contact sites to the skin (left flank for inductions and right flank for challenge) at each application day were mechanically and closely clipped free of hair using an electrical razor. Skin was observed for lesions after clipping the fur. According to the Buehler's application method, animals were exposed to cotton lint patches with an approximated 6 cm² surface area. Treatment animals were exposed to patches loaded with 1 mL of 50% (w/v) test solutions in DMSO (equivalent 0.5 g of the test item) for the induction and challenge applications. Control animals were exposed to patches loaded with 1 mL of vehicle on inductions and loaded with 1 mL of test solution on challenge, therefore being submitted to the same procedures as treatment animals, except on inductions. Since control animals were not exposed to the test item on inductions, a hypersensitive state could not be induced in these animals, which then constituted a negative control in order to allow the differentiation between skin irritation and skin sensitisation at challenge. Patches were held in contact with the skin by an occlusive dressing during an approximated 6-hour exposure period in each application, after which patches were carefully removed from the skin and any residue cleaned up using DMSO. Four applications were carried out, with a seven-day interval between inductions and a fourteen-day interval between third induction and challenge. Animals were clinically examined approximately 30 and 54 hours after each application. Skin reactions were evaluated in agreement with Magnusson & Kligman's grading scale after challenge application.

II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities during the study.

B. CLINICAL OBSERVATIONS

Neither compound-related clinical signs nor behavioral alterations were observed during inductions. No animal from control group was positive for the test item after challenge application. One animal from treatment group was positive for the test item after challenge application.

III. CONCLUSION

The epidermal application of GLYPHOSATE TECBNICAL using DMSO as vehicle did not cause skin sensitisation in guinea pigs, according to the Buehler Test Method.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/10	[redacted]	2006	Glyphosate Technical: Skin Sensitisation in the Guinea Pig - Magnusson and Kligman Maximisation method Data owner: Nufarm Study No.: [redacted]05/2015 Report No.: 2060/009 Date: 2006-01-13 GLP: yes unpublished

Guideline: § OECD Guidelines for the Testing of Chemicals No. 406 "Skin Sensitisation" adopted 17 Jun 1992
§ Method B6 Acute Toxicity (Skin Sensitisation) of Commission Directive 96/54/EC
§ Japanese Ministry of Agriculture, Forestry and Fisheries (JMAFF), Testing Guidelines for Toxicology Studies 12 Nohsan No. 8147, Guideline No. 2-1-6, revised on 24 November 2004 and 13 Seisan No. 3986 of October 10, 2001

Deviations: None

Dates of experimental work: 05 September 2005 to 13 October 2005

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Executive Summary

Twenty test and ten control animals were used for the main study. Two phases were involved in the main test; an induction of a response by intradermal injection and topical application and a topical challenge of that response. Based on the results of sighting tests, the concentrations of test material for the topical induction and topical challenge phases were selected as follows: Intradermal Induction : 0.195% (v/v) in isotonic sodium chloride solution; Topical Induction : 60% (w/w) in distilled water; Topical Challenge : 60% (w/w) and 30% (v/v) in distilled water. Under the conditions of the test, the test material produced a 0% (0/18) sensitisation rate and was classified as a non-sensitiser to guinea pig skin.
Glyphosate Technical did not meet the criteria for classification as a sensitiser according to EU labelling regulations Commission Directive 2001/59/EC. No symbol and risk phrase are required.

According to EU and OECD Globally Harmonized System (GHS) classification criteria the test substance glyphosate does not require classification for this endpoint.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	Glyphosate Technical
Description:	white powder
Lot/Batch #:	H05H016A
Purity:	95.7%
Stability of test compound:	No data available

2. Vehicle and/ or positive control:

Distilled water

3. Test animals:

Species:	Guinea Pigs
Strain:	albino Dunkin Hartley
Source:	[redacted]
Age:	Not specified.
Sex:	Female
Weight at dosing:	295 to 370 gg
Acclimation period:	5 days
Diet/Food:	Not specified. The diet, drinking water and bedding were routinely analysed and were considered not to contain any contaminant that could reasonably be expected to affect the purpose or integrity of the study.
Water:	Tap water, ad libitum
Housing:	in groups of two or three in makrolon cages furnished with woodflakes
Environmental conditions:	Temperature: 19 to 25°C Humidity: 30 to 70% Air changes: not specified 12-hour light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 05 September 2005 to 13 October 2005

Animal assignment and treatment:
The method used for assessing the sensitising properties of the test material was based on the Guinea Pig Maximisation Test of Magnusson B & Kligman A M, (1969) J. Invest. Dermatol. 52: 268 - 276. A group of thirty guinea pigs was used for the main study, twenty test and ten control. Two phases were involved in the main study; (a) an induction of a response and (b) a challenge of that response. Induction of the Test Animals: A row of three injections (0.1 ml each) was made on each side of the spine, consisting of a) Freund's Complete Adjuvant plus isotonic sodium chloride in the ratio 1:1 b) a 0.195% (v/v) formulation of the test material in isotonic sodium chloride c) a 0.195% (v/v) formulation of the test material in a 1:1 preparation of Freund's Complete Adjuvant plus isotonic sodium chloride. On Day 6, the scapular region of all test and control animals was shaved and sodium lauryl sulphate (10% in petroleum jelly) was spread evenly over the area to create local irritation. On Day 7 the same area on the shoulder region used previously for intradermal injections was treated with a topical application of the test material formulation

(60% (w/w) in distilled water) under occlusive dressing for 48 hours. The intradermal induction on the control animals was performed using an identical procedure without the test material. Injection b) was therefore the vehicle alone, injection c) was a 50% formulation of the vehicle in a 1:1 preparation of Freund's Complete Adjuvant plus isotonic sodium chloride. Similarly, the topical induction procedure was identical to that used for the test animals except that the test material was omitted. For the challenge phase, test material formulation at the maximum non- irritant concentration (60% (w/w) in distilled water) was applied to one side of the shorn flank of each animal under an occlusive dressing. To ensure that the maximum non- irritant concentration was used at challenge, the test material at a concentration of 30% (v/v) in distilled water was similarly applied under an occlusive dressing to the opposite skin site on the shorn flank. After 24 hours, the dressing was carefully removed and discarded. The topical challenge sites were cleaned if required. Prior to the 24-hour observation the flanks were clipped to remove regrown hair. Approximately 24 and 48 hours after challenge dressing removal, the degree of erythema and oedema was quantified. Any other reactions were also recorded.
None of the animals exposed to test material showed any signs of sensitisation after the challenge phase.

II. RESULTS AND DISCUSSION

A. MORTALITY

One test group animal was found dead on Day 3 and one other test group animal was found dead on Day 5. The cause of death was not determined but was considered not to be treatment related. The absence of these animals was considered not to affect the purpose or integrity of the study.

B. CLINICAL OBSERVATIONS

The concentration chosen for use in the Intradermal Induction phase of the main test was 0.195% (v/v) in isotonic sodium chloride solution (maximal non necrotising concentration (MNNC)). The concentration chosen for use in the Topical Induction phase of the main test was 60% (w/w) in distilled water (maximal non irritant concentration (MNIC)). The concentrations chosen for use in the Topical Challenge phase of the main test were 60% (w/w) (maximal non irritant concentration (MNIC)) and 30% (v/v) in distilled water (1/2 MNIC).

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 demonstrated no observable abnormalities.

III. CONCLUSION

The test material produced a 0% (0/18) sensitisation rate and was classified as a NON-SENSITISER to guinea pig skin under the conditions of the test. The test material did not meet the criteria for classification as a sensitiser according to EU labelling regulations Commission Directive 2001/59/EC. No symbol and risk phrase are required.

Based on the EU and the OECD Globally Harmonized System (GHS) classification criteria, glyphosate is not to be classified for this endpoint.

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Annex point	Author(s)	Year	Study title
IIA, 5.2.6/11	[redacted]	1996d	Glyphosate Acid: Skin Sensitisation To The Guinea Pig [redacted] Data owner: Syngenta Report No.: [redacted]4699 Date: 1996-08-23 GLP: yes not published

Guideline: OECD 406 (1992): OPPTS 870.2600 (2003): 96/54/EC B.6 (1996)

Deviations: None

Dates of experimental work: 1996-07-11 to 1996-08-23

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Excecutive summary

In a dermal sensitization study with glyphosate acid (95.6% w/w a.i.) young adult female, Albino Cr1 (HA) BR guinea pigs were tested using the method of ***Magnusson and Kligman (1970)***. The study involved the treatment of guinea pigs using two procedures: the potential induction of an immune response and a challenge of that response. In the main study a 0.1% w/v preparation in deionised water was used for the intradermal injections and a 75% w/v preparation in deionised water was used for the topical application. For challenge concentrations of 75 and 30% (w/v) in deionised water were used.

Challenge of previously-induced guinea pigs with a 75% w/v preparation of glyphosate acid in deionised water elicited a response characteristic of an irritant.

Challenge of previously-induced guinea pigs with a 30% w/v preparation of glyphosate acid in deionised water did not elicit a skin sensitisation response.

A positive control study using hexylcinnamaldehyde demonstrated the sensitivity of the test system.

Glyphosate acid is not a skin sensitiser under the conditions of the test.

I. MATERIALS AND METHODS

A: MATERIALS:

Test Material: Glyphosate acid

Description:	Technical, white solid
Lot/Batch number:	P24
Purity:	As given in report 95.6% a.i
CAS#:	Not reported
Stability of test compound:	Not reported

Vehicle and/or positive control: Deionised water

Test Animals:

Species	Guinea pig
Strain	Albino Cr1 (HA) BR
Age/weight at dosing	Young adult females / 250-317 g
Source	[redacted] UK
Housing	Individually in suspended cages in racks suitable for animals of this strain and the weight range expected during the course of the study.
Acclimatisation period	At least 6 days
Diet	[redacted] supplied by [redacted] UK *ad libitum*
Water	Mains water *ad libitum*
Environmental conditions	Temperature: 17 ± 2°C Humidity: 40-70% Air changes: Approximately 15 changes/hour Photoperiod: 12 hours light, 12 hours dark

B: STUDY DESIGN AND METHODS:

In-life dates: Start: 25 April 1995 End: 19 May 1995

Animal assignment and treatment: In a dermal sensitization study with glyphosate acid (95.6% w/w a.i.) young adult, female, Albino Cr1 (HA) BR guinea pigs were tested using the method of ***Magnusson and Kligman (1970)***. The study involved the treatment of guinea pigs using two procedures: the potential induction of an immune response and a challenge of that response.

Induction: An area approximately 5 x 5 cm on the scapular region of each animal was clipped free of hair and a row of three injections (0.05-0.1 mL each) was made on each side of the mid-line. The injections were:

i) Top: Freund's Complete Adjuvant plus deionised water in the ratio 1:1;

ii) Middle: a 0.1% w/v preparation of the test substance in deionised water;

iii) Bottom: a 0.1 % w/v preparation of the test substance in a 1: 1 preparation of Freund's Complete Adjuvant plus deionised water.

Control animals were treated the same as the test animals, except that they were treated with deionised water in place of the test substance.

One day prior to topical induction, the application site was clipped and 0.5 mL of a 10% w/v preparation of sodium lauryl sulphate in paraffin wax was applied in order to provoke a mild inflammatory response.

One week after intradermal injection, the scapular area was treated with a topical application of the test substance as a 75% w/v preparation in deionised water. This preparation (0.2-0.3 mL) was applied on filter paper (approximate size 4 cm x 2 cm) which was held in place by a piece of surgical tape. The tape was covered by a strip of adhesive bandage (approximate size 20-30 cm x 5 cm) and secured by a piece of self-adhesive PVC tape. This occlusive dressing was kept in place for approximately 2 days.

Deionised water only was applied to the filter paper for control animals.

The application sites were checked approximately 1 day after removal of the dressings.

Challenge: Two weeks after the topical inductions, an area, approximately 15 cm x 5 cm, on both flanks of all the test and control animals, was clipped free of hair. An occlusive dressing was prepared

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which consisted of two pieces of filter paper (approximate size 1 cm x 1.5-2.0 cm) stitched to a piece of rubber sheeting (approximate size 12 cm x 5 cm).

A 75% w/v preparation of the test substance in deionised water (0.05-0.1 mL) was applied to one of the pieces of filter paper and a 30% w/v preparation in deionised water (0.05-0.1 mL) was applied to the second piece of filter paper. The dressing was placed on the shorn flank of the guinea pig so that the 75% w/v preparation was on the left and the 30% w/v preparation was on the right. It was then covered with a strip of adhesive bandage (approximate size 25-40 cm x 7.5 cm) which was secured by a self-adhesive PVC tape.

After approximately 1 day, the dressings were carefully removed. Skin sites were examined approximately 1 and 2 days after removal of the dressings and any erythematous reactions were quantified and recorded, using a four-point scale.

Positive Controls: The sensitising potential of hexylcinnamaldehyde (HCA) was assessed essentially as described above to demonstrate the sensitivity of the strain of animals used and the reliability of the experimental technique. A concentration of 0.3% w/v HCA in corn oil was used for the intradermal injections and HCA was used undiluted for the topical induction and challenge applications.

II. RESULTS AND DISCUSSION

Bodyweights: There were no treatment-related effects on bodyweight during the study.

Induction reactions and duration: Not reported.

Challenge reactions and duration: Following challenge of previously induced guinea pigs with a 75% w/v preparation of the glyphosate acid in deionised water, scattered mild redness was seen in three of the twenty test animals and one of the ten control animals. This response is considered to be due to skin irritation following topical challenge. The basis for this conclusion is that an equivalent reaction was seen in one of the ten control animals and the reaction was restricted to the 24 hour clinical observation only, which is characteristic of a mild skin irritation reaction rather than skin sensitisation.

Following challenge of previously induced guinea pigs with a 30% w/v preparation of the glyphosate acid in deionised water, no reaction was seen in any of the test or control animals. The net percentage response was calculated to be 0%.

Positive control: Following challenge of previously induced guinea pigs, scattered mild redness or moderate diffuse redness was observed in 14/20 test animals. Scattered mild redness was seen in two of the ten control animals. The net % response was 50% and, therefore, HCA was classified as a moderate skin sensitiser which demonstrated the sensitivity of the strain of animals used and the reliability of the experimental technique.

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Table 5.2-36: Number of animals with positive signs following challenge

	Test flank			
	Challenge at 75%		Challenge at 30%	
Scored after:	24 hours	48 hours	24 hours	48 hours
Main test – test group	3/20	0/20	0/20	0/20
Main test – negative vehicle control	1/10	0/10	0/10	0/10
	Challenge at 100%			
	24 hours		48 hours	
Positive control – test group	14/20		13/20	
Positive control – vehicle control	2/10		0/10	

III. CONCLUSION

Glyphosate acid is not a skin sensitiser under the conditions of the test.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/12	[redacted]	2007	Glyphosate Technical Material: Skin Sensitisation (Local Lymph Nodes Assay In The Mouse). [redacted] Data owner: Syngenta Report No.: R61837/0004 Date: 2007-02-09 GLP: yes not published

Guideline: OECD 429 (2002): OPPTS 870.2600 (2003): 2004/73/EC B.42 (2004)

Deviations: None

Dates of experimental work: 2007-01-05 to 2007-02-09

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Excecutive summary

A sample of glyphosate technical material was assessed for its skin sensitisation potential using the mouse Local Lymph Node Assay ***(Kimber and Basketter 1992, Kimber et al, 1994)***. The assay determines the level of T lymphocyte proliferation in the lymph nodes draining the site of chemical application by measuring the amount of radiolabelled thymidine incorporated into the dividing cells. The test substance was applied as 10, 25 or 45% w/v preparations in dimethyl sulphoxide.

Groups of four female CBA/Ca/Ola/Hsd mice were used for this study. Approximately 25µl of a 10, 25 or 45% w/v preparation of the test substance in dimethyl sulphoxide was applied to the dorsal surface of each ear. A vehicle control group was similarly treated using dimethyl sulphoxide alone. The procedure was repeated daily for 3 consecutive days. Three days after the third application, all the animals were injected, via the tail vein, with approximately 250µl of phosphate buffered saline (PBS) containing 20µCi of a 2.0Ci/mmol specific activity ^{3}H-methyl thymidine. Approximately 5 hours later, the animals were humanely killed by inhalation of halothane vapour followed by cervical dislocation. The draining auricular lymph nodes were removed from each animal and, together with the nodes from the other animals in the group, were placed in a container of PBS.

A single cell suspension was prepared by mechanical disaggregation of lymph nodes through a 200-mesh stainless steel gauze. The cell suspensions were then washed three times by centrifugation with

approximately 10 ml of PBS. Approximately 3ml of 5% w/v trichloroacetic acid (TCA) was added and, after overnight precipitation at 4°C, the samples were pelleted by centrifugation and the supernatant was discarded. The cells were then resuspended in approximately 1ml of TCA.

The lymph node suspensions were transferred to scintillation vials and 10ml of scintillant (Optiphase) was added prior to β-scintillation counting using a Packard Tri-Carb 3100TR Liquid Scintillation Counter.
The reliability of the test system was assessed in a positive control study using a known sensitiser (hexylcinnamaldehyde) ***(Dearman et al, 2001).***

The application of the test substance at concentrations of 10, 25 and 45 %w/v in dimethyl sulphoxide resulted in an isotope incorporation which was less than 3-fold at all concentrations. Consequently, the test substance is considered not to be a skin sensitiser under the conditions of the test.

In the positive control study, the application of hexylcinnamaldehyde at concentrations of 5%, 10% and 25% w/v in acetone in olive oil (4:1) resulted in a greater than 3-fold increase in isotope incorporation at the 25 %w/v concentration. Therefore, hexylcinnamaldehyde was shown to be a skin sensitiser, confirming the validity of the protocol used for the study.

In conclusion, glyphosate technical material is considered not to be a skin sensitiser under the conditions of the test.

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I. MATERIALS AND METHODS

A: MATERIALS:

Test Material:	Glyphosate Technical Material
Description:	Technical, white solid.
Lot/Batch number:	0507
Purity:	96.1%
Stability of test compound:	Stable under storage conditions; ambient temperature in the dark.

Vehicle and/or positive control: The vehicle for the test substance was dimethyl sulphoxide. The vehicle for the positive control substance (hexylcinnamaldehyde) was acetone in olive oil.

Test Animals:	
Species	Mouse
Strain	CBA/Ca/Ola/Hsd
Age/weight at dosing	8-12 weeks ; 16.5-20.8 g
Source	[redacted] UK.
Housing	Maximum 4 per cage, in cages suitable for animals of this strain and weight range.
Acclimatisation period	At least 5 days
Diet	Diet ([redacted]), supplied by [redacted] UK. *ad libitum*
Water	Mains water supplied by an automatic system *ad libitum*
Environmental conditions	Temperature: 22 ± 3°C Humidity: 30-70% Air changes: A minimum of 15 changes/hour Photoperiod: Artificial, 12 hours light / 12 hours dark.

B: STUDY DESIGN AND METHODS:

In-life dates: Start: 10th January 2007 End: 16th January 2007

Animal assignment and treatment: A sample of glyphosate technical material was assessed for its skin sensitisation potential using the mouse Local Lymph Node Assay. The assay determines the level of T lymphocyte proliferation in the lymph nodes draining the site of chemical application by measuring the amount of radiolabelled thymidine incorporated into the dividing cells. The test substance was applied as 10, 25 or 45% w/v preparations in dimethyl sulphoxide. Groups of four female CBA/Ca/Ola/Hsd mice were used for this study.

Dose selection rationale: Approximately 25µl of a 10, 25 or 45% w/v preparation of the test substance was used in this study as 45% w/v was the limit of solubility.

Treatment preparation and administration: Approximately 25µl of a 10, 25 or 45% w/v preparation of the test substance in dimethyl sulphoxide was applied, using a variable volume micro-pipette, to the dorsal surface of each ear. A vehicle control group was similarly treated using dimethyl sulphoxide alone. The procedure was repeated daily for 3 consecutive days. Three days after the third application, all the animals were injected, via the tail vein, with approximately 250µl of phosphate buffered saline (PBS) containing 20µCi of a 2.0Ci/mmol specific activity ^{3}H-methyl thymidine. Approximately 5 hours later, the animals were humanely killed by inhalation of halothane vapour followed by cervical dislocation. The draining auricular lymph nodes were removed from each animal and, together with the nodes from the other animals in the group, were placed in a container of PBS.

A single cell suspension was prepared by mechanical disaggregation of lymph nodes through a 200-mesh stainless steel gauze. The cell suspensions were then washed three times by centrifugation with approximately 10 ml of PBS. Approximately 3ml of 5% w/v trichloroacetic acid (TCA) was added and, after overnight precipitation at 4°C, the samples were pelleted by centrifugation and the supernatant was discarded. The cells were then resuspended in approximately 1ml of TCA.

The lymph node suspensions were transferred to scintillation vials and 10ml of scintillant (Optiphase) was added prior to β-scintillation counting using a Packard Tri-Carb 3100TR Liquid Scintillation Counter.

The reliability of the test system was assessed in a positive control study using the same method with a known sensitiser (hexylcinnamaldehyde) applied as 5%, 10% or 25% w/v preparations in acetone in olive oil.

Statistics / Data Evaluation: The results are expressed as a disintegrations per minute (dpm) value per lymph node for each group. The activity of each test group is then divided by the activity of the vehicle control group to give a test:control ratio known as the stimulation index (SI), for each concentration.

The criterion for a positive response is that one or more concentrations of the test substance should elicit a 3-fold or greater increase in isotope incorporation relative to the vehicle control group. The assay is able to identify those materials that elicit responses in standard guinea pig tests for skin sensitisation ***(Kimber et al, 1994)***. Consequently, a test substance which does not fulfil the above criterion is designated as unlikely to be a skin sensitiser.

II. RESULTS AND DISCUSSION

Group Mean Counts per Minute: The application of the test substance at concentrations of 10, 25 and 45 % w/v in dimethyl sulphoxide resulted in an isotope incorporation which was less than 3-fold at all concentrations. Consequently, the test substance is considered not to be a skin sensitiser under the conditions of the test.

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Table 5.2-37: Radiolabel incorporation into lymph-nodes of mice treated with glyphosate technical material

Concentration of NOA446510 (%w/v)	Number of lymph nodes assayed	Disintegrations per minute (dpm)	dpm per lymph node	Test control ratio (SI)
0 (vehicle only)	8	3912	489	N/A
10	8	2394	299	0.6
25	8	3292	412	0.8
45	8	4067	508	1.0

N/A = not applicable

In the positive control study, the application of hexylcinnamaldehyde at concentrations of 5%, 10% and 25% w/v in acetone in olive oil (4:1) resulted in a greater than 3-fold increase in isotope incorporation at the 25 % w/v concentration. Therefore, hexylcinnamaldehyde was shown to be a skin sensitiser, confirming the validity of the protocol used for the study.

Table 5.2-38: Radiolabel incorporation into lymph-nodes of mice treated with the positive control substance (hexylcinnamaldehyde)

Concentration of hexylcinnamaldehyde (%w/v)	Number of lynph nodes assayed	Disintegrations per minute (dpm)	dpm per lymph node	Test control ratio (SI)
0 (vehicle only)	8	5939	742	N/A
5	8	10141	1264	1.7
10	8	13947	1718	2.3
25	8	38015	4752	6.4

III. CONCLUSION

Glyphosate technical material is considered not to be a skin sensitiser under the conditions of the test.

Annex point	Author(s)	Year	Study title
IIA, 5.2.6/13	[redacted]	2011	Glyphosate technical: Local lymph node assay in the mouse [redacted] Data owner: Syngenta Report No.: 10/218-037E Date: 2011-04-21 GLP: yes not published

Guideline: OECD 429 (2010)

Deviations: None

Dates of experimental work: 2010-10-20 to 2011-04-21

Excecutive summary

A sample of Glyphosate Technical (96.3% w/w Glyphosate technical) was assessed for its skin sensitisation potential using the mouse Local Lymph Node Assay, following dermal exposure when administered topically to young adult, female CBA/J Rj mice.

The test item solutions were applied on the dorsal surface of ears of experimental animals (25 µL/ear) for 3 consecutive days (Days 1, 2 and 3). There was no treatment on Days 4, 5 and 6. On Day 6. Five hours

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prior to termination animals were intravenously injected via the tail vein with tritiated methyl thymidine (^{3}HTdR). Cell proliferation in the local lymph nodes was measured by incorporation of ^{3}HTdR and the values obtained were used to calculate stimulation indices (SI).

Groups of 4 mice received 50, 25 or 10% w/v glyphosate technical in propylene glycol (PG), PG alone (negative controls) or 25% α-Hexylcinnamaldehyde in PG (positive controls).

No mortality, systemic toxicity or local irritation was observed during the study. No treatment related effects were observed on animal body weights in any treated groups.

Stimulation index values of the test item were 1.0, 1.0 and 1.2 at treatment concentrations of 50, 25 and 10% (w/v), respectively. A significant lymphoproliferative response (stimulation index value of 12.2) was noted for α-Hexylcinnamaldehyde in this experiment, confirming the validity of the protocol used for this study.

In conclusion, under the conditions of the present assay, Glyphosate Technical tested in a suitable vehicle, was shown to have no skin sensitisation potential (non-sensitiser) in the Local Lymph Node Assay.

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I. MATERIALS AND METHODS

A: MATERIALS:

Test Material:	Glyphosate technical
Description:	Technical, dry white powder
Lot/Batch number:	5697539 (BX2007091-1)
Purity:	96.3% w/w Glyphosate technical
CAS#:	Not reported
Stability of test compound:	Stable under storage conditions (room temperature range 2-8°C), recertification date end August 2011

Vehicle and/or positive control: The vehicle for the test substance was propylene glycol

Test Animals:	
Species	Mice
Strain	CBA/J Rj
Age/weight at dosing	9-10 weeks / 20.1-21.6 g
Source	[redacted] France
Housing	Group housed in Type II. polypropylene/polycarbonate cages
Acclimatisation period	13 days
Diet	[redacted] "Autoclavable complete feed for rats and rats – breeding and maintenance" produced by [redacted] Germany *ad libitum*
Water	Tap water *ad libitum*
Environmental conditions	Temperature: 22±3°C Humidity: 30-70% Air changes: 15-20 air changes per hour Photoperiod: 12 hours light / 12 hours dark

B: STUDY DESIGN AND METHODS:

In-life dates: Start: 20 October 2010 End: 26 October 2010

A sample of Glyphosate Technical (96.3% w/w Glyphosate technical) was assessed for its skin sensitisation potential using the mouse Local Lymph Node Assay, following dermal exposure when administered topically to young adult, female CBA/J Rj mice.

Animal assignment and treatment:
Dose selection rationale: A Preliminary Irritation/Toxicity Test was performed on CBA/J Rj mice using two doses, at test item concentrations of 50 and 25 (w/v)%, respectively. This preliminary experiment was conducted in a similar experimental manner to the main study, but it was terminated on Day 6 without radioactive proliferation assay.

During the Preliminary Irritation/Toxicity Test no mortality, systemic toxicity or local irritation were observed. No treatment related effect on body weights was observed. The observations recorded in this preliminary test suggest that the formulations, the application of the material and the local effects on the animal are acceptable for a valid LLNA.

Based on the results of the preliminary experiments the following dose levels were selected for the main assay: 0 (negative control), 10, 25 and 50 w/v% Glyphosate Technical, and positive control (25% HCA in PG). Each group comprised four mice.

Treatment and observations: Each animal was topically dosed once a day for 3 consecutive days (Days 1, 2 and 3) on the dorsal surface of each ear with 25 µl of the appropriate formulation, applied using a pipette. There was no treatment on Days 4, 5 and 6.

All animals were observed at least once daily (Days 1-6) for any clinical signs, including local irritation and systemic toxicity. Individual body weights were recorded on Day 1 (beginning of the assay) and at Day 6 (prior to ^{3}HTdR injection).

Proliferation assay: On Day 6 each mouse was intravenously injected via the tail vein with 250 µL of sterile PBS (phosphate buffered saline) containing approximately 20 µCi of ^{3}HTdR using a gauge 25G1" hypodermic needle with 1 mL sterile syringe. Once injected, the mice were left for 5 hours.

Five hours after intravenous injection, the mice were killed by CO_2 asphyxiation. The draining auricular lymph nodes were excised by making a small incision on the skin between the jaw and sternum, pulling the skin gently back towards the ears and exposing the lymph nodes. The nodes were then removed using forceps and the carcasses discarded. The nodes of mice from each test group was pooled and collected in separate Petri dishes containing a small amount (1-2 mL) of PBS to keep the nodes wet before processing.

A single cell suspension (SCS) of pooled lymph node cells (LNCs) were prepared and collected in disposable tubes by gentle mechanical disaggregating of the lymph nodes through a cell strainer using the plunger of a disposable syringe. The cell strainer was washed with PBS (up to 10 mL). Pooled LNCs were pelleted with a relative centrifugal force (RCF) of 190 x g (approximately) for 10 minutes at 4°C. After centrifugation supernatants were discarded. Pellets were gently resuspended and 10 mL of PBS was added to the tubes. The washing step was repeated twice. This procedure was repeated for each group of pooled lymph nodes.

After the final washing step, the suspensions were centrifuged and the supernatants were removed leaving a small volume (<0.5 mL) of supernatant above each pellet. Each pellet was gently agitated before suspending the LCNs in 3 mL of 5% TCA (trichloroacetic acid) for precipitation of macromolecules. After incubation with 5% TCA at 2-8°C overnight (approximately 18 hours) precipitate was recovered by centrifugation at 190 x g for 10 minutes at 4°C), and supernatants were removed and pellets were resuspended in 1 mL of 5% TCA solution and dispersed using an ultrasonic water bath. Each precipitate was transferred to a suitable sized scintillation vial with 10 mL of scintillation liquid and thoroughly mixed. The vials were loaded into a β-scintillation counter and ^{3}HTdR incorporation was measured for up to 10 minutes per sample. The β-counter expressed the ^{3}HTdR incorporation as the number of radioactive

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disintegrations per minute (DPM). Similarly, background radiation levels were also measured in two 1 mL aliquots of 5% TCA.

Statistics / Data evaluation: In the absence of any positive results, the statistical analysis of the data was not performed.

DPM was measured for each pooled group of nodes. The measured DPM values were corrected with the background DPM value ("DPM"). The results were expressed as "DPN" (DPM divided by the number of lymph nodes) following the industry standard for data presentation.

A stimulation index of 3 or greater is the criteria for defining a positive result.

The test item is regarded as a sensitiser if both of the following criteria are fulfilled:

- That exposure to at least one concentration resulted in an incorporation of ^{3}HTdR at least 3-fold or greater than recorded in control mice, as indicated by the stimulation index.
- The data are compatible with a conventional dose response, although allowance must be made (especially at high topical concentrations) for either local toxicity or immunological suppression.

II. RESULTS AND DISCUSSION

Clinical observation: No mortality or signs of systemic toxicity were observed during the Main Study. No cutaneous reactions were observed at the site of the treatment in any treatment groups.

Body weight: No treatment related effects were observed on body weight.

Proliferation assay: Appearance of the lymph nodes was normal in the negative control group and in the test item treated groups. Larger than normal lymph nodes was observed in the positive control group.

No mortality, cutaneous reactions or signs of toxicity were observed in the positive control group. A significant lymphoproliferative response (stimulation index value of 12.2) was noted for α-Hexylcinnamaldehyde in this experiment. The results of the positive control group demonstrated the appropriate performance of the assay.

III. CONCLUSION

In conclusion, under the conditions of the present assay, Glyphosate Technical tested in a suitable vehicle, was shown to have no skin sensitisation potential (non-sensitiser) in the Local Lymph Node Assay.

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IIA 5.3 Short term toxicity

The 2001 EU evaluation concluded low oral subacute and subchronic toxicity of glyphosate acid.
The lowest NOEL observed was 50 mg/kg bw/day in a subacute rangefinding study. However the subsequent definitive 90-day study did not demonstrated these effects when dosed up to 1000 mg/kg/day and therefore the rangefinder observations were considered spurious. NOAEL values ranged from about 168 to over 1200 mg/kg bw/day in 90-day feeding studies in rats, which reflect differences in dose selection. Some lower values found in dogs were obtained in studies of limited scientific value but these rather equivocal findings were not confirmed in more recent experiments using much higher doses. Changes in clinical chemistry parameters and liver weight changes might indicate liver effects at high doses in rats. Soft stools and diarrhea, together with occasionally reduced body weight gain and food consumption, suggest irritation of the gastrointestinal tract. In some oral rat studies and in one experiment with mice, effects on salivary glands are considered adaptive responses to local oral irritation due to chewing an organic acid mixed into the diet (See IIA 5.10). Repeated dermal exposure of rabbits and rats to glyphosate did not result in any systemic effects. Dermal irritation was observed only at doses as high as 5000 mg/kg bw/day in rabbits or 1000 mg/kg bw/day in rats. Subacute inhalation toxicity of glyphosate

active ingredient in rats is low. Up to the highest tested concentration of 3.8 mg/L air, neither local nor systemic toxicity was noted upon repeated exposure.

IIA 5.3.1 Oral 28-day toxicity

No new sub-acute oral toxicity studies have been performed. Table 5.3-1 summaries the studies performed in rats and dogs previously evaluated in the 2001 EU glyphosate evaluation. Despite some slight changes in haematological, clinical chemistry parameters and soft faeces, there were no adverse effects in rats after exposure to glyphosate. In dogs there were no treatment-related findings observed up to 1000 mg/kg bw/day. In rats, a NOAEL was found to be 50 mg/kg bw day when administered for four weeks in a range finding study, but these effects were not identified in the subsequent 90-day definitive study and thus were considered spurious. The 2004 JMPR review also concluded "In contrast to a 4-week study in rats conducted at the same testing facility [redacted] 1989), the incidence of nephrocalcinosis in the 13-week study ([redacted] 1991) was evenly distributed among dose groups and sexes and did not follow a dose–response relationship, and is therefore clearly not treatment-related. Thus, the previous finding was not confirmed". The glyphosate taskforce proposes that the NOAEL for this study is 250 mg/kg bw/day and the LOAEL is 1000 mg/kg bw/day based on the increased incidence in soft faeces in males.

Table 5.3-1: Summary of sub-acute toxicity studies with glyphosate acid

	Reference (Data owner)	Type of study Species	Dose levels	NOEL / NOAEL	Targets / Main effects
Studies from the 2001 evaluation	Annex B-5.3.1, Glyphosate Monograph [redacted] 1991f (FSG)	28-day, oral diet Rat, Wistar	0, 200, 2000, 20000 ppm	NOEL: 2000 ppm (≅ 100 mg/kg bw/day)	20000 ppm ((≅ 1959 mg/kg bw/day (calculated value)) ALAT and BUN ↑, Hb ↓ (effects were reversible)
	Annex B-5.3.1, Glyphosate Monograph [redacted] 1989 (CHE)	4-week, oral diet Rat, Sprague-Dawley	0, 50, 250, 1000, 2500 mg/kg bw/day	NOEL: 50 mg/kg bw/day NOAEL: 250 mg/kg bw/day	≥ 250 mg/kg bw/day: Increased incidence of (very mild to slight) nephrocalcinosis in ♀; equivocal increases in serum ALAT and AP (without corollary histopatholgy) 1000 mg/kg bw/day: soft faeces in ♂; increased plasma phosphate ♂
	Annex B-5.3.1, Glyphosate Monograph Goburdhun & [redacted] 1989 (CHE)	21 / 14-day, oral capsule Dog, Beagle	21-day: 100, 300, 1000 mg/kg bw/day (1st, 2nd, 3rd week) 14-day: 1000 mg/kg bw/day	1000 mg/kg bw/day	No remarkable findings

↓ = decreased; ↑ = increased;

IIA 5.3.2 Oral 90-day toxicity (rodents)

The 2001 EU glyphosate evaluation concluded that the lowest NOEL was about 100 mg/kg bw/day in 90-day feeding studies in rats with the first effects occurring in the range 250-300 mg/kg bw/day, however in most studies higher NOAELs were established. Liver effects were observed indicated by clinical chemistry and organ weight changes in rats. Soft stools and diarrhoea, together with occasionally reduced bodyweight gain and food consumption, suggest irritation of the gastrointestinal tract at high dose levels. Decreased urinary pH was noted in some studies at high doses, with blood in the urine reported in one study. In some oral rat studies and in one mouse study, cellular alterations in salivary glands were observed upon histopathological examination. The glyphosate taskforce believes these salivary gland

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findings are a non-adverse adaptive response to treatment with a low pH diet (See IIA 5.10). Overall the mouse is less sensitive than the rat with only effects observed on body weight at very high dose levels.
Additional studies included in this submission also demonstrate that glyphosate is of low oral toxicity. The NOAELs ranged between 79-765 mg/kg bw/day and the lowest LOAEL observed in rats was 569 mg/kg bw/day ([redacted] 1995). Consistent with the previously reviewed studies effects were observed on clinical chemistry parameters (often non-specific markes of mild toxicity), bodyweight gain and food consumption at high dose levels. Additionally caecum distension and an increase in caecum weight were observed in both a 13 week rat study ([redacted] 1995) and a 13 week mouse study ([redacted] 1995) . This effect appeared to be dose related at very high dose levels in both species but was not assocated with any corollary histopathological changes and is therefore of uncertain toxicological relevance. In contrast, in another 13 week dietary rat study ([redacted] 1996) mucosal atrophy of the caecum was observed where there was no associated weight change. Another finding in male mice that had been previously reported was cystitis of the urinary bladder in animals dosed at 6295 mg/kg bw/d.
Overall the NOEL/NOAEL levels established in the 90-day dietary studies in rats varied between approximately 80 and 1600 mg/kg bw/d, the wide range of values being an artifact of dose selection. The lowest effect dose was in the range of 550 mg/kg bw day ([redacted] 1995). Mice appeared to be less sensitive, with substantially higher NOAEL values, the lowest of which was 600 mg/kg bw/d.

Table 5.3-2: Summary of short-term toxicity studies with glyphosate acid

	Reference (data owner)*	Type of study Species	Dose levels	NOEL / NOAEL	Targets / Main effects
Studies from the 2001 evaluation	Annex B-5.3.2.1, Glyphosate Monograph [redacted] 1989 (CHE 1)	90-day, oral diet Rat, Sprague-Dawley	0, 30, 300, 1000 mg/kg bw/day	NOAEL: 300 mg/kg bw/day	1000 mg/kg bw/day: Clinical chemistry, cellular alterations in paratoid salivary glands, decreased urinary pH (♂ only)
	Annex B-5.3.2.1.2, Glyphosate Monograph IIA 5.3.2/02 [redacted] 1993 (Alkaloida, ALK)	13-week, oral diet Rat, Sprague-Dawley	0, 2000, 6000, 20000 ppm (≅ 0, 125.2/156.3, 371.9/481.2, 1262/1686.5 mg/kg bw/day ♂/♀)	NOAEL = 6000 ppm (≅ 379.1/481.2 mg/kg bw/day ♂/♀)	1262.1/1686.5 mg/kg bw/day ♂/♀ (calculated values): Diarrhea, blood in urine, organ weight changes
	Annex B-5.3.2.1, Glyphosate Monograph [redacted] 1992 (FSG)	90-day, oral diet (+ 2-week recovery) Rat, Wistar	0, 200, 2000, 20000 ppm	2000 ppm (147/196 mg/kg bw/day (♂/♀))	1000 mg/kg bw/day: Clinical chemistry, reduced body weight gain

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	Reference (data owner)*	Type of study Species	Dose levels	NOEL / NOAEL	Targets / Main effects
Studies from the 2001 evaluation	Annex B-5.3.2.1, Glyphosate Monograph [redacted] 1989 (Barclay, BCL)	13-week, oral diet (+ 5-week recovery) Rat, CD	0, 2000, 3000, 5000, 7500 ppm	NOEL: 7500 ppm (ca. 375 mg/kg bw/day)	No treatment-related effects
	Annex B-5.3.2.1, Glyphosate Monograph [redacted] 1987 (MON)	90-day, oral diet Rat, Sprague-Dawley	0, 1000, 5000, 20000 ppm	NOEL: 20000 ppm (1267/1623 mg/kg bw/day (♂/♀))	No treatment-related effects
Studies not reviewed in the 2001 evaluation	IIA 5.3.2/01 [redacted] 1996 (1st revision of study) (SYN)	90-day, oral, diet Rat, Alpk:APfSD	0. 1000, 5000, 20000 ppm	NOEL: 5000 ppm (414/447 mg/kg bw/day ♂/♀	1612/1821 mg/kg bw/day (♂/♀): Reduced body weight, food consumption and utilisation reduced in ♂ only, clinical chemistry changes (changes (↑ALP, ALT)
	IIA 5.3.2/03 [redacted] 1996 (NUF)	90-day, oral, diet Rat, Sprague-dawley	0, 1000, 10000, 50000 ppm (≅ 0, 730/844, 7300/8414, 37006/4188 mg/kg bw/day (♂/♀)	1000 ppm (70/80 mg/kg bw/day ♂/♀)	730/844 mg/kg bw/day (♂/♀): Clinical chemistry changes, mucosal atrophy of the caecum
	IIA 5.3.2/04 [redacted], 1995 (ALS 1)	13-week, oral, diet Rat, Sprague-Dawley	0, 3000, 10000, 30000 ppm (≅ 168/195, 569/637, 1735 / 1892 mg/kg bw/day (♂/♀))	NOAEL: 3000 ppm (168/195 mg/kg bw/day ♂/♀)	10000 ppm (≅ 569/637 mg/kg bw/day (♂/♀)): caecum distention; caecum weight increased without histopathological findings 30000 ppm (≅ 1735 / 1892 mg/kg bw/day (♂/♀)): caecum distention; caecum weight increased without histopathological findings, reduced body weight and lower food efficiency; increased AP activity in ♀

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Reference (data owner)*		Type of study Species	Dose levels	NOEL / NOAEL	Targets / Main effects
Studies not reviewed in the 2001 evaluation	IIA 5.3.2/05 [redacted] 1995 (ALS 2)	13-week, oral, diet Mouse, ICR	0, 5000, 10000, 50000 ppm (≡ 0, 600/765, 1221/1486, 6295/7435 mg/kg bw/day (♂/♀)	NOAEL: 5000 ppm (600/765 mg/kg bw/day ♂/♀)	10000 ppm (1221 / 1486 mg/kg bw/day ♂/♀): caecum distention ♀, increased absolute and relative caecum weight 50000 ppm 6295 / 7435 mg/kg bw/day ♂/♀):: reduced bodyweight and food consumption, decreased fodd efficiency ♀, haematological changes in ♀, blood chemistry changes, caecum distention and increased absolute and relative caecum weight in both sexes without histopathological changes in the caecum; cystitis of the urinary bladder in ♂
Studies from the 2001 evaluation	Annex B-5.3.2.2, Glyphosate Monograph [redacted] 1991 (CHE 2)	13-week, oral, diet, Mouse, CD-1	0, 200, 1000, 4500 mg/kg bw/day	NOEL: 4500 mg/kg bw/d	No treatment-related effects

*: Number refers to data presented in Figure 5.11-2 in chapter IIA 5.11
↓ = decreased; ↑ = increased;

Tier II summaries are only presented for studies not previously evaluated in the 2001 EU glyphosate evaluation.
For details regarding studies reviewed during the 2001 EU evaluation we refer to the Monograph and the former dossier.

Annex point	Author(s)	Year	Study title
IIA, 5.3.2/01	[redacted]	1996	First Revision To Glyphosate Acid: 90 Day Feeding Study In Rats [redacted] Laboratory Report No.: [redacted] 1599 Data owner: Syngenta Date: 1996-11-07 GLP: yes not published

Guideline: No guideline statement, but in accordance with OECD 408 (1998), OPPTS 870.3100 (1998), 2001/59/EC B.26 (2001)

Deviations: None

Dates of experimental work: 1996-02-25 to 1996-05

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Executive Summary
In a subchronic toxicity study, groups of twelve male and twelve female Alpk:AP (now known as Alpk:APfSD) Wistar-derived rats were fed diets containing 0 (control), 1000, 5000 or 20000 ppm glyphosate acid for 90 consecutive days.

Clinical observations, bodyweights, food consumption and blood biochemistry parameters were measured and at the end of the scheduled period, the animals were killed and subjected to a full examination post mortem. Cardiac blood samples were taken for clinical pathology, selected organs were weighed and specified tissues were taken for subsequent histopathology examination

Males fed 20000 ppm glyphosate acid showed small reductions in bodyweight gain, food consumption and food utilisation efficiency compared to controls. There were associated minor reductions in plasma urea, total protein and triglycerides. Increased levels of plasma ALT and ALP were seen in both male and female rats at the top dose and are considered to indicate an altered liver metabolism but there was no evidence of histological change in this organ.

Effects in rats fed 5000 ppm glyphosate acid were confined to marginal increases in plasma ALT levels in females and in both plasma ALT and ALP levels in males. The magnitude and isolated nature of these effects leads them to be considered of no biological significance.

5000 ppm glyphosate acid is considered to represent the no-effect level for glyphosate acid in this study.

Conclusion
Glyphosate acid when fed to rats at a level of 20000 ppm resulted in reduced growth (males only) and associated changes in clinical chemistry. The latter also provided limited evidence for an altered liver metabolism which was not associated with any histopathological change.

Toxicologically significant changes were confined to the 20000 ppm glyphosate acid dose level and occurred mainly in male rats. The minor changes in clinical chemistry seen at 5000 ppm glyphosate acid were considered biologically insignificant and this was, therefore, judged to be the no-effect level for glyphosate acid in this study.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	Glyphosate acid
Description:	White solid
Lot/Batch #:	P15
Purity:	97.4%
Stability of test compound:	Not reported

2. Vehicle and/ or positive control: Plain diet / none

3. Test animals:

Species:	Rat
Strain:	Alpk:APfSD
Source:	[redacted] UK
Age:	36-38 days
Sex:	Male and female

Weight at dosing:	♂ 98-170 g; ♀ 96-140 g
Acclimation period:	Approximately 1 week
Diet/Food:	CTI diet, *ad libitum,* (except during collection of urine samples)
Water:	Mains water, *ad libitum,* (except during collection of urine samples)
Housing:	4/cage, sexes separately in stainless steel cages 34.0 x 37.5 x 20.3 cm giving a floor area of 1275cm^2
Environmental conditions:	Temperature: 21 ± 2°C
	Humidity: 36 - 60%
	Air changes: ≥ 15/hour
	12 hours light/dark cycle

B: STUDY DESIGN AND METHODS

In life dates: 1986-02-25 to 1986-05

Animal assignment and treatment:
The study was divided into six single-sex replicates (randomised blocks). Each replicate consisted of four cages, one per treatment group. The animals were randomly allocated to cages.
The study consisted of one control and three treatment groups each containing twelve male and twelve female rats.

Table 5.3-3: Study design

Test group	Dietary concentration (ppm)	Males	Females
Control	0	12	12
Low	1060	12	12
Mid	5000	12	12
High	20000	12	12

The experimental diets were made in 60 kg batches by adding the appropriate amount of glyphosate acid to the diet using dry premixes.

Samples from all dietary levels (including controls) were taken from both batches prepared for the study and analysed quantitatively for glyphosate acid. The homogeneity of glyphosate acid in CT1 diet was determined by analysing samples from the low and high dose levels from the first batch of diet. The chemical stability of glyphosate acid in diet was determined at the highest and lowest dose levels at 1, 4, 6 and 10 weeks after preparation. Analysis was by high performance liquid chromatography (HPLC).

Mortality
Each animal was checked for mortality or signs of morbidity at least once daily during the treatment period.

Clinical observations
A check for clinical signs of toxicity was made once daily on all animals. In addition, a detailed clinical examination was performed at least once before of the beginning of the treatment period and then once a week until the end of the study.

Body weight
The bodyweight of each animal was recorded immediately before feeding of the experimental diets commenced and then on the same day, where practicable, of each subsequent week until termination. The

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body weight determination was done on the same day on which the detailed clinical examination was performed.

Food consumption and untilisation
Food consumption was recorded continuously throughout the study for each cage of rats and calculated as a weekly mean (g food/rat/day) for each cage. The food utilisation value per cage was calculated as the bodyweight gained by the rats in the cage per 100 g of food eaten.

Ophthalmoscopic examination
The eyes of all animals from the control group and the 20000 ppm glyphosate acid dose level group were examined in the week prior to termination, using an indirect ophthalmoscope and a mydriate to dilate the pupil.

Haematology and clinical chemistry
At termination, all surviving rats were bled by cardiac puncture and the blood samples were collected both in tubes containing EDTA as anticoagulant and also in tubes containing 0.11M trisodium citrate. These samples were submitted for haematological examination and the following parameters measured: haemoglobin, haematocrit, red blood cell count, MVC, MCHC, MCH, kaolin cephalin times, thrombocytes, leucocytes, differential white cell count, red blood cell morphology, prothrombin time.

For clinical chemistry analysis blood samples were collected by tail vein bleeding at week 4 of the study and by cardiac puncture at termination (week 13). The blood was collected in lithium heparinised tubes and the following parameters measured: glucose, urea, total protein, albumin, total cholesterol, triglycerides, alkaline phosphatase (ALP), aspartate aminotransferase (ASAT), and alanine aminotransferase (ALAT).

Urinalysis
Urine samples were collected over an 18 hour (approximately) period from all rats during week 13 (the week prior to termination). During urine collection, the rats were individually housed in metabolism cages and denied access to food and water. The following parameters were measured:volume, pH, specific gravity, proteins, glucose, ketones, and urobilinogen.

Sacrifice and pathology
On completion of the treatment period, all surviving animals were sacrificed and subjected to a gross pathological examination. Any macroscopic findings were recorded.
The following organ weights were determined: adrenals, brain, epididymides, heart, kidneys, liver, and testes. Paired organs were weight together.

Tissue samples were taken from the following organs and preserved in buffered formalin: all gross lesions, adrenals, aorta, bone marrow (femur), brain, caecum, colon, duodenum, epididymides, eyes (stored), Harderian gland (stored), heart, ileum, jejunum, kidneys, larynx (stored), liver, lungs, lymph nodes (cervical and mesenteric), mammary gland, ovaries, oviducts, pancreas, pituitary gland, prostrate, rectum, salivary glands, seminal vesicles, spinal cord, sciatic nerve, skin, spleen, stomach, testes, thymus, thyroid gland, trachea, urinary bladder, uterus (with cervix), voluntary muscle and nasal cavity.
Following fixation, all tissues from the control and 20000 ppm glyphosate acid groups (except those stored) were processed by standard methods, embedded in paraffin wax, sectioned at 5µm, stained with haematoxylin and eosin and examined by light microscopy. Liver, kidney, adrenals, lungs and abnormal tissues from animals fed 1000 ppm or 5000 ppm glyphosate acid were also processed to blocks and were examined histologically.

Statistics
All data were evaluated using analysis of variance (bodyweight gain from start of study, final bodyweight, haematology, clinical chemisty – blood and urine, total food consumption and utilisation, organ weights) and covariance (organ weights on terminal bodyweights) for each specified parameter using the GLM procedure in SAS (1982).

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II. RESULTS AND DISCUSSION

A. MORTALITY

There were no mortalities.

B. CLINICAL OBSERVATIONS

The incidence of clinical findings was low and none was unequivocally related to treatment. There was a low incidence of diarrhoea (during the second week of the study) in the group receiving 20000 ppm glyphosate acid. The faeces of both sexes at this dose level were observed to be paler than those of control or other test groups.

C. BODY WEIGHT

No relevant differences in the mean body weight gain were noted between controls and animals given 1000 or 5000 ppm.

Bodyweight gain was reduced in male rats fed 20000 ppm glyphosate acid from the first week of the study. The bodyweights continued to diverge from control values as the study progressed, and final bodyweights were approximately 8% lower than those of controls (see Table 5.3-4).

Table 5.3-4: Intergroup comparison of bodyweight gain – selected timepoints from start of study

Timepoint	Mean cummulative bodyweight gain (g)							
	Initial	Week 1	Week 2	Week 4	Week 7	Week 10	Week 13	Final weight
Dose (ppm)	Males							
0	135	51.8	104.0	185.5	254.6	305.1	333.3	468.3
1000	140.3	54.3	106.3	187.5	253.4	304.1	327.0	467.3
5000	136.3	51.8	103.4	186.1	255.1	306.3	331.9	468.3
20000	134.5	45.1**	94.0*	166.3**	226.0**	272.00**	295.8**	430.3**
	Females							
0	121.3	36.6	47.4	81.6	112.8	130.8	143.3	264.6
1000	122.2	27.7	51.4	82.7	113.1	132.1	146.0	268.2
5000	121.3	25.0	50.2	82.9	110.0	129.5	138.4	259.8
20000	118.6	24.3	53.5**	83.5	115.1	132.7	142.5	261.1

* Statistically significant from controls, $p<0.05$ (Student´s t-test, 2-sided)

** . Statistically significant from controls, $p<0.01$ (Student´s t-test, 2-sided)

D. FOOD CONSUMPTION AND TEST SUBSTANCE INTAKE

The food consumption of males fed 20000 ppm glyphosate acid was reduced from the fifth week of the study compared to control values but the reduction was small and did not attain statistical significance in any week. The food utilisation efficiency of males at this dose level was reduced throughout the study. The food consumption and food utilisation efficiency of males fed 1000 or 5000 ppm glyphosate acid and of females at all dose levels were similar to those of controls.

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Table 5.3-5: Intergroup comparison of food utilisation (g growth/100 g food)– selected timepoints from start of study

	Dietary concentration of glyphosate acid (ppm)							
	Males				Females			
Weeks	0	1000	5000	20000	0	1000	5000	20000
1-4	25.15	24.85	24.99	22.89	15.73	15.42	15.78	15.91
5-8	11.25	11.09	11.36	10.31	7.49	6.74	6.71	7.29
9-13	6.45	5.76	6.05	5.88	3.08	3.95	3.10	2.96
Overall (1-13)	13.59	13.30	13.44	12.54	8.28	8.34	8.14	8.25

* Statistically significant from controls, $p<0.05$ (Student´s t-test, 2-sided)

Calculated mean test compound intakes are presented in the following table.

Table 5.3-6: Overall mean test compound intake

	Dietary concentration of glyphosate acid (ppm)							
	Males				Females			
Weeks	0	1000	5000	20000	0	1000	5000	20000
1-13	0	81.33	413.5	1612	0	90.42	446.9	1821

* Statistically significant from controls, $p<0.05$ (Student´s t-test, 2-sided)

E. OPHTHALMOSCOPIC EXAMINATION

There were no test substance-related ophthalmological findings at the end of the treatment period. The small incidence of findings recorded was within the normal background incidence for rats of this age and strain.

F. HAEMATOLOGY AND CLINICAL CHEMISTRY

Haematology

There were no treatment-related effects noted in any dose group.

Blood clinical chemistry

The plasma activities of alanine transaminase (ALAT) and alkaline phosphatase (ALP) were increased in both sexes fed 20000 ppm glyphosate acid throughout the study. Plasma aspartate transaminase activity was increased in females fed 20000 ppm glyphosate acid at week 4 only.

Plasma ALT activity was also increased in males receiving 5000 ppm glyphosate acid at weeks 4 and 13 and in females at week 4 only.

The plasma ALP activities of males receiving 5000 or 1000 ppm glyphosate acid were marginally increased. These increases were not dose-related and for the 1000 ppm glyphosate acid group were attributed to the high values in 3 out of 12 males. These marginal differences from the control group are considered to be of doubtful significance and not to be treatment-related.

Plasma urea levels were marginally decreased in both sexes at week 13 and in males at week 4 in the 20000 ppm glyphosate acid group.

Males receiving glyphosate acid showed marginal reductions in plasma glucose levels at week 4 but not at week 13. Females at 20000ppm glyphosate acid showed a slight increase in this parameter at week 13 only.

Plasma cholesterol levels were unaffected by treatment with glyphosate acid. Plasma triglyceride levels were slightly reduced in males receiving 20000 ppm glyphosate acid at both weeks 4 and 13, the effect being greater at week 13.

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Both males and females receiving glyphosate acid showed marginal reductions in plasma albumin and total protein. The changes were not consistent, showed no dose-response relationship and are therefore considered to be of dubious significance.

Table 5.3-7: Intergroup comparison of selected clinical chemistry parameters

		Dietary concentration of glyphosate acid (ppm)							
		Males				Females			
Parameter	Week	0	1000	5000	20000	0	1000	5000	20000
ALAT	4	61.0	66.8	76.0**	83.8**	47.3	50.8	57.7*	73.8**
	13	51.9	52.3	62.3*	65.2**	45.0	45.2	46.2	55.0**
ALP	4	273	326**	320*	411**	188	199	212	309**
	13	148	159	176*	215**	91	94	99	140**
ASAT	4	62.8	67.0	69.1	68.5	56.0	57.0	57.5	64.8**
Urea	4	47.0	45.8	44.6	43.6*	45.8	45.3	46.8*	44.2
	13	41.9	39.9	40.0	37.7*	40.6	40.1	42.1	35.9*
Glucose	4	143	133*	132*	128**	141	146	142	136
	13	191	186	208	197	182	183	183	208**
Triglycerides	4	151	145	147	136	80	75	88	84
	13	153	157	144	120**	72	74	77	77

* Statistically significant from controls, $p<0.05$ (Student's t-test, 2-sided)
** . Statistically significant from controls, $p<0.01$ (Student's t-test, 2-sided)

G. URINALYSIS

There were no treatment-related findings.

H. NECROPSY

Organ weights

Absolute heart weight of top dose males was reduced compared to controls but the reduction reflected the reduced bodyweight. There were no other differences in organ weights which were considered to be related to treatment

Gross pathology

A small number of lesions were observed, none of which was related to treatment.

Histopathology

There were no histopathological findings related to treatment. The incidence of findings was low and, with one exception, of a type commonly found in rats of this strain and age. A uterine leiomyosarcoma was seen in a female fed 5000 ppm glyphosate acid. Whilst the occurrence of a malignant tumour of smooth muscle in the uterus of a young rat is unusual, this isolated finding in an intermediate dose group is considered not to be related to treatment.

III. CONCLUSION

Under the experimental conditions of the study and taking into account the reduced growth (males only) and biologically insignificant changes in clinical chemistry parameters at the high dose-level, the No Observed Adverse Effect Level (NOAEL) is considered to be 5000 ppm (equivalent to 414 and 447 mg/kg bw/day for amles and females, respectively).

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Annex point	Author(s)	Year	Study title
IIA, 5.3.2/02	[redacted]	1993	90 Day Range Feeding Study of Glyphosate in Rats [redacted] Laboratory Report No.: 011-0001 Data owner: Alkaloida - Monsanto Date: 1993 GLP: yes not published

Guideline: No guideline statement, but in accordance with OECD 408 (1981)

Deviations: None

Dates of experimental work: 1993-02-17 to 1993-05-21

Executive Summary

In a subchronic toxicity study, groups of ten male and ten female Sprague-Dawley rats were fed diets containing 0 (control), 2000, 6000 or 20000 ppm glyphosate acid for 13 consecutive weeks.

Clinical observations were done daily. Bodyweights and food consumption was assessed in weekly intervals. Haematological, blood biochemistry parameters, as well as urine analysis were conducted prior to start of treatment and at termination. At the end of the scheduled period the animals were killed and subjected to a full examination post mortem and selected organs were weighed and specified tissues were taken for subsequent histopathology examination.

There were no mortalities in any of the dose groups. The only treatment-related clinicalfinding was diarrhoea in all high-dose males and in 9 high-dose females. Mean body weights were comparable between all groups. The mean body weight gains were significantly different between groups at several time points, but the total mean body weight gain was similar in all dose groups. There were no differences in food consumption. There were no treatment-related findings in the haematological and clinical chemistry parameters. Urinalysis showed marginal increases in the mean scores for ketones, blood, protein and RBCs in mid- and high-dose males which were of no biological relevance. In mid- and high-dose females the number of rats with 1 RBC/hpf was also increased. Together with the appearance of blood in these groups this change seems to be treatment-related. There were no indications for microscopic hematuria found during the histopathologic examinations.

Conclusion

Glyphosate acid when fed to rats at a level of 20000 ppm resulted in clinical signs of toxicity and slight increases in blood urine and RBC counts in urine. The minor changes in urinalysis seen at 6000 ppm glyphosate acid were considered biologically insignificant and this was, therefore, judged to be the NOAEL for glyphosate acid in this study.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Identification:	Glyphosate acid
Description:	Greyish-white or yellowish-white crystalline powder
Lot/Batch #:	46540992
Purity:	97.5%
Stability of test compound:	1994-10-01

2. Vehicle and/ or positive control: Plain diet / none

3. Test animals:

Species:	Rat
Strain:	Sprague-Dawley (Crl:CD®BR VAF/Plus®)
Source:	[redacted] USA
Age:	approx. 5 weeks
Sex:	Male and female
Weight at dosing:	♂ 208.2-249.9 g; ♀ 159.8-202 g
Acclimation period:	14 days
Diet/Food:	[redacted] certified Laboratory Rodent Chow [redacted] *ad libitum* (except during collection of urine samples)
Water:	Tap water, *ad libitum*
Housing:	Individually in stainless steel cages
Environmental conditions:	Temperature: 18 - 26°C Humidity: 30 – 55 ± 15% Air changes: ≥ 10/hour 12 hours light/dark cycle

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B: STUDY DESIGN AND METHODS

In life dates: 1993-02-17 to 1993-05-21

Animal assignment and treatment:
In a 90-day oral toxicity study groups of 10 Sprague-Dawley per sex received daily doses of 0, 2000, 6000 and 20000 ppm in the diet. The test diets were prepared weekly and stored at room temperature. Samples of the control and test substance diets were analysed for stability and homogeneity. Dietary preparations were analysed for achieved concentrations weekly during the first 4 weeks, and then every fourth week thereafter.

Table 5.3-8: Group mean weekly bodyweights and standard deviations (sd)

Test group	Dietary concentration (ppm)	Males	Females
Control	0	10	10
Low	2000	10	10
Mid	6000	10	10
High	20000	10	10

The experimental diets were prepared weekly by adding the appropriate amount of glyphosate acid to the diet.
The homogeneity of glyphosate in the diet was determined by replicate samples from each dose level. Achieved concentrations were determined by analysing samples from each dose level during weeks 1 to 4, and every fourth week thereafter The chemical stability of glyphosate acid in diet at room temperature was determined for all dose levels after preparation. Analysis was done by high performance liquid chromatography (HPLC).

Mortality
Each animal was checked for mortality or signs of morbidity twice daily during the treatment period.

Clinical observations
A check for clinical signs of toxicity was made once daily on all animals.

Body weight
The bodyweight of each animal was recorded on Day 1 before start of treatment and weekly thereafter.

Food consumption and untilisation
Individual food consumption was recorded weekly.

Ophthalmoscopic examination
The eyes of all animals from all dose groups were examined prior to initiation and just prior to termination. The examoination included macroscopic and opthalmoscopic examinations of the anterior portion of the eye, the optic media, and the ocular fundus.

Haematology and clinical chemistry
Prior to initiation and at termination, blood samples from all rats were taken by puncture of the retroorbital sinus after anesthetization. These samples were submitted for haematological and clinical chemistry examination. The following haematological parameters measured were measured: haemoglobin, haematocrit, red blood cell count, MCV, MCHC, MCH, thrombocytes, leucocytes, and a blood smear examination (including differential white cell count).

For clinical chemistry analysis the following parameters measured: glucose, urea, total protein, albumin, globulin, albumin/globulin ratio, total cholesterol, creatinine, calcium, phosphorous, sodium, potassium, chloride, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase.

Urinalysis
Urine samples were collected overnight from all rats prior to start of treatment and at termination. During urine collection, the rats were individually housed in metabolism cages and denied access to food. The following parameters were measured: volume, pH, specific gravity, nitrites, blood, leukocytes proteins, glucose, ketones, bilirubin and urobilinogen.

Sacrifice and pathology
After 13 weeks of consecutive treatment, all surviving animals were sacrificed and subjected to a gross pathological examination. Any macroscopic findings were recorded.
The following organ weights were determined: adrenals, brain, epididymides, heart, kidneys, liver, seminal vesicles, and testes or ovaries. Organ-to-bodyweight and organ-to-brain weights were determined.

Tissue samples were taken from the following organs and preserved in buffered formalin: all gross lesions, adrenals, aorta, bone marrow (sternum), brain, caecum, colon, duodenum, epididymides, eyes, femur (incl. articular surface), heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (mandibular and mesenteric), mammary gland, nasal turbinate, nasal cavity, oesophagus, ovaries, pancreas, pituitary gland, prostrate, rectum, salivary glands (sublingual), spinal cord, sciatic nerve, skeletal muscle, skin, spleen, stomach, testes, thymus, thyroid/parathyroids, trachea, urinary bladder All tissue sampled freom the control and high dose group were examined histopathologically. From the mid- and low- dose only tissues from lungs, liver, kidneys and gross lesions were subjected to histopathological evaluation.

Statistics
Mean and standard deviation were calculated for all quantitative data. Comparisons with controls were done using ANOVA with a post hoc Dunnett´s t Test or Duncan´s multiple range test. A 95% confidence level ($p<0.05$) was used to determine statistically significant differences between control and treated groups.

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II. RESULTS AND DISCUSSION

A. MORTALITY

There were no mortalities.

B. CLINICAL OBSERVATIONS

The only obvious treatment-related finding was diarrhoea observed in 10/10 males and 9/10 females in the high-dose group. Diarrhoea was also observed in one male of the low dose group.

Table 5.3-9: Intergroup comparison of clinical findings

	Dietary concentration of glyphosate acid (ppm)							
	Males				Females			
Finding	0	2000	6000	20000	0	2000	6000	20000
Diarrhoea	0/10	1/10	0/10	10/10	0/10	0/10	0/10	9/10

* Statistically significant from controls, p<0.05)
** Statistically significant from controls, p<0.01

C. BODY WEIGHT

Mean body weights were not significantly different between test substance and control animals. The mean body weight gains were however significantly different from controls at several intervals (see Table 5.3-10). The total mean body weights over the entire study period were not different.

Table 5.3-10: Intergroup comparison of body weights and bodyweight gain - selected timepoints from start of study

Timepoint	Mean body weight or body weight gain (g)					
	Initial body weight	Final body weight	Weigh gain Day 43	Weight gain Day 50	Weight gain Day 85	Total weight gain
Dose (ppm)	Males					
0	224.6	510.3	3.4	39.4	12.6	285.7
2000	231.0	530.8	9.1	29.3	9.2	299.7
6000	229.0	526.0	17.1*	28.6	11.1	297.0
20000	224.6	502.9	21.1**	19.3**	1.9*	288.4
	Females					
0	178.3	321.9	6.9	16.6	6.1	143.7
2000	179.7	331.3	7.5	14.7	6.2	151.6
6000	176.0	316.1	7.8	15.7	2.4	140.1
20000	176.9	309.0	7.8	4.8*	2.8	132.0

* Statistically significant from controls, p<0.05 (Student´s t-test, 2-sided)
** . Statistically significant from controls, p<0.01 (Student´s t-test, 2-sided)

D. FOOD CONSUMPTION AND TEST SUBSTANCE INTAKE

There were no treatment-related effects. The mean food consumption in treatment groups was not significantly different from controls..

Calculated mean test compound intakes are presented in the following table.

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