Aimee Wagstaff, SBN 278480
aimee.wagstaff@andruswagstaff.com
Andrus Wagstaff, PC
7171 West Alaska Drive
Lakewood, CO 80226
Telephone: (303) 376-6360
Facsimile: (303) 376-6361

Attorney for Plaintiffs

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

IN RE ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741
This Document Relates To All Actions	**PLAINTIFFS' NOTICE OF LODGMENT OF *CORRECTED* EXHIBIT NOS. 27 AND 88 TO THE DECLARATION OF AIMEE H. WAGSTAFF, ECF NO. 648**

PLEASE TAKE NOTICE that *Corrected* Exhibit No. 27, ECF No. 648-27, and Exhibit No. 88, ECF No. 654-11, to the Declaration of Aimee H. Wagstaff in Support of Plaintiffs' Memorandum of Law in Opposition to Monsanto Company's *Daubert* and Summary Judgment Motion and in Support of Plaintiffs' *Daubert* Motion, ECF No. 648, are being lodged with the Court on November 1, 2017. These exhibits were missing redactions and were inadvertently filed on October 27, 2017.

DATED: November 1, 2017

Respectfully submitted,

/s/ Aimee H. Wagstaff
ANDRUS WAGSTAFF, PC
Aimee H. Wagstaff, SBN 278480
aimee.wagstaff@andruswagstaff.com
7171 West Alaska Drive
Lakewood, CO 80226
Tel: (303) 376-6360
Counsel for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing document was filed with the Court and electronically served through the CM-ECF system which will send a notification of such filing to all counsel of record. .

DATED: November 1, 2017

/s/ Aimee Wagstaff
ANDRUS WAGSTAFF, PC
Aimee H. Wagstaff, SBN 278480
aimee.wagstaff@andruswagstaff.com
7171 West Alaska Drive
Lakewood, CO 80226
Telephone: (303) 376-6360
Facsimile: (303) 376-6361

EXHIBIT 27

Message

From: FARMER, DONNA R [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=180070]
Sent: 11/24/2003 2:32:41 PM
To: NATARAJAN, SEKHAR [AG/6020] [/O=MONSANTO/OU=AP-6020-01/cn=Recipients/cn=126349]
CC: CARR, KATHERINE H [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=43435]
Subject: RE: Agitation against Roundup

Sekhar,

Your welcome and don't hesitiate to contact us.

Regards,

Donna
-----Original Message-----
From: NATARAJAN, SEKHAR [AG/6020]
Sent: Sunday, November 23, 2003 10:07 AM
To: FARMER, DONNA R [AG/1000]
Cc: DOANE, JULIE R [AG/1000]; CARR, KATHERINE H [AG/1000]; MONTGOMERY, JILL M [AG/5340]; MCDERMOTT, THOMAS J [AG/5040]; FISHER, LORI J [AG/1000]; LAL, DARSHAN; SMETACEK, RANJANA [AG/6020]; KAPOOR, RAJAN D; SMITH, ALLEN T [AG/5340]
Subject: RE: Agitation against Roundup

Thanks Donna for your guidance. Will get back to you if we need any additional support.

RGDS...sekhar

-----Original Message-----
From: FARMER, DONNA R [AG/1000]
Sent: Saturday, November 22, 2003 4:46 AM
To: NATARAJAN, SEKHAR [AG/6020]
Cc: DOANE, JULIE R [AG/1000]; CARR, KATHERINE H [AG/1000]; MONTGOMERY, JILL M [AG/5340]; MCDERMOTT, THOMAS J [AG/5040]; FISHER, LORI J [AG/1000]; LAL, DARSHAN; SMETACEK, RANJANA [AG/6020]; KAPOOR, RAJAN D; SMITH, ALLEN T [AG/5340]
Subject: RE: Agitation against Roundup
Sekhar,

Your Q & A was forward to Kathy Carr and me for review (see attached). I am the toxicologist responsible for glyphosate and glyphosate-based products worldwide and Kathy provides ecotoxicology suppport for glyphosate globally as well as manages the information resources for glyphosate.

As explanation for some of our edits - in many parts of the world there is no such formulation being sold called "Roundup". In addition, in the US we have some lawn and garden products with the Roundup name on them but they contain other active ingredients in addition to glyphosate and they may have different properties from glyphosate. That is why we were using the phrase Roundup herbicides or Roundup agricultural herbicides. When possible it is preferable to use the name of the product that is actually being used and the data that supports that particular formulation.

The terms glyphosate and Roundup cannot be used interchangeably nor can you use "Roundup" for all glyphosate-based herbicides any more. For example you cannot say that Roundup is not a carcinogen...we have not done the necessary

testing on the formulation to make that statement. The testing on the formulations are not anywhere near the level of the active ingredient. We can make that statement about glyphosate and can infer that there is no reason to believe that Roundup would cause cancer.

We cannot support the statement about "no adverse effects whatsoever on flora, or fauna or on the human body". Adverse effects are seen on flora (glyphosate is meant to kill vegetation), adverse effects on fauna - in studies with laboratory animals - even death is seen (LD50 studies for example) and in humans - mild reversible eye and skin irritation are seen with normal use and death can occur in suicide attempts. Therefore we advise using the phrase...."When Roundup herbicides are used according to label directions, no unreasonable adverse effects to people, wildlife, and the environment are expected."

Below is a link to the glyphosate team space where you will find numerous reference materials:

Glyphosate Regulatory & Stewardship TeamSpace: http://w3.monsanto.com/asp/T.asp?id=404.

Also you can send external contacts to the Monsanto site for a number of backgrounders for various items:http://www.monsanto.com/monsanto/layout/sci_tech/crop_chemicals/default.asp

Please don't hesitate to contact me or Kathy or Julie if you have any questions or need any additional information.

Donna
****
Donna R. Farmer, Ph.D.
Manager, Toxicology Programs
Glyphosate-Worldwide
Monsanto Company
800 North Lindbergh Blvd.
Mail Zone A2NE
St. Louis, Missouri 63137

[redacted] - Phone
[redacted] - Cell
[redacted] - Fax

-----Original Message-----
From: DOANE, JULIE R [AG/1000]
Sent: Friday, November 21, 2003 8:34 AM
To: FARMER, DONNA R [AG/1000]; CARR, KATHERINE H [AG/1000]
Subject: FW: Agitation against Roundup
Importance: High
I would appreciate your review of the materials below. I'd like to provide our feedback by COB today. We may also want to remind them of the reference material available via the web, teamspace, etc. Please advise. Thanks inadvance, Julie

-----Original Message-----
From: NATARAJAN, SEKHAR [AG/6020]
Sent: Friday, November 21, 2003 6:39 AM
To: MONTGOMERY, JILL M [AG/5340]
Cc: MCDERMOTT, THOMAS J [AG/5040]; FISHER, LORI J [AG/1000]; LAL, DARSHAN; SMETACEK, RANJANA [AG/6020]; KAPOOR, RAJAN D; SMITH, ALLEN T [AG/5340]; GLOVER, JERRY P [AG/1000]
Subject: Agitation against Roundup
Importance: High

Jill- As I had indicated yesterday in our telecon, we have had a series of adverse reports that have appeared in the southern state of Kerala against Roundup (in local print and TV coverage). Although we have sent rebuttals and explanations, the adverse publicity continues unabated and has started impacting some of our trade and users. The State farmers and NGOs in the past have agitated against "endosulfan" too. We are not sure if any our known Biotech opponents are involved in this activity as the usual " Agent Orange " story is strong.

This story has not hit any mainline press or wire service and we are trying to see if we can quickly get this under control. (understand that some of the local media do not want to even talk to us)

We are attaching herewith the following files:

- A detailed list of allegations/issues. A briefing note to Dr Abraham (Weed Specialist, Dept of Agronomy in the Kerala Ag University) who is willing to talk to the media and explain.
- A quick two pager on Roundup and some Q and A guidelines.

Jerry/Tom/Lori- Do let us know if you have any inputs by Friday evening your time. We plan to get Dr Abraham to meet the press tomorrow. Also forward it to any one else, if required.

RGDS...sekhar

EXHIBIT 88

Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek / Netherlands Organisation for Applied Scientific Research

TNO Nutrition and Food Research

Fax message

Zeist
Utrechtseweg 48
P.O. Box 360
3704 HE
the Netherlands

www.tno.nl

T +31 30-694 41 44
F +31 30-695 72 24

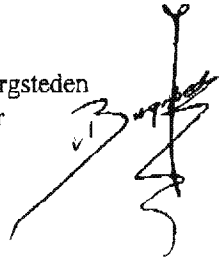
To	Dr. Fabrice Broeckaert Monsanto Europe SA-NV
Fax	[redacted]
From	Johan van Burgsteden TNO Nutrition and Food Research
E-Mail	[redacted]
Direct number	[redacted]
Direct fax	[redacted]
Subject	Study 4478, Unaudited draft report
Date	14 June 2002
Our reference	-
Copy to	-
Number of pages	36

If you have not received all pages, please call us

Dear Fabrice,

Please find herewith the unaudited draft report V4478, entitled "*In vitro* percutaneous absorption study with [14C]glyphosphate using viable rat skin membranes".

Best wishes,
Johan van Burgsteden
Study director



TNO Nutrition and Food Research

Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek / Netherlands Organisation for Applied Scientific Research

Location Zeist
Utrechtseweg 48
P.O. Box 360
3700 AJ Zeist
The Netherlands

www.tno.nl

T +31 30 694 41 44
F +31 30 695 72 24

TNO report

V 4478

In vitro percutaneous absorption study with [^{14}C]glyphosphate using viable rat skin membranes

Date	14 June 2002
Authors	Drs. J.A. van Burgsteden
At request of	Monsanto Europe S.A. Tervuren Avenue 270-272 B-1150 Brussels Belgium
TNO Project number	010.45110
TNO Study number	4478
Sponsor Study code	-
Status report	Unaudited draft report
Previous version	-
Number of pages	35
Number of tables	3
Number of appendices	6

Summary

1. The herbicide glyphosphate in the formulations MON 35012 and MON 0139 70% was examined for *in vitro* percutaneous absorption through viable rat skin membranes Both the concentrated formulation and the field dilution were tested (6.249 and 0.080 mg glyphosphate per cm^2, respectively for MON 35012 and 6.343 and 0.080 mg glyphosphate per cm^2, respectively for MON 0139 70%). After 8 h of exposure, the test substance was removed from the application site, and samples of the receptor fluid were collected for an additional 40 h.

2. Fourty-eight hours after application of concentrated MON 35012, 10.3 ± 4.2 % of the dose glyphosphate had penetrated through rat skin membranes. When MON 35012 was applied as field dilution, the relative penetration of glyphosphate was 2.6 ± 1.4 % after 48 h. For MON 0139 70% these values were 1.3 ± 1.9 % for the concentrate and 1.4 ± 2.2 % for the field dilution. The mean flux constants were 35.6 $\mu g.cm^{-2}.h^{-1}$ (MON 35012 concentrate), 0.127 $\mu g.cm^{-2}.h^{-1}$ (MON 35012 field dilution), 2.01 $\mu g.cm^{-2}.h^{-1}$ (MON 0139 70% concentrate) and 0.100$\mu g.cm^{-2}.h^{-1}$ (MON 0139 70% field dilution). The mean Kp values were 0.089×10^{-3} cm/h (MON 35012 concentrate), 0.025×10^{-3} cm/h (MON 35012 field dilution), 0.005×10^{-3} cm/h (MON 0139 70% concentrate) and 0.019×10^{-3} cm/h (MON 0139 70% field dilution).

3. At the end of the 8-h exposure period, 117.5 % (MON 35012 concentrate), 45.6 % (MON 35012 field dilution), 123.3 % (MON 0139 70% concentrate) and 80.0 % (MON 0139 70% field dilution) of the applied dose glyphosphate could still be removed from the application site with cotton swabs. At the end of the study (48 h after application of the test compound), 4.7 % (MON 35012 concentrate), 23.1 % (MON 35012 field dilution), 2.4 % (MON 0139 70% concentrate) and 2.3 % (MON 0139 70% field dilution) of the applied dose glyphosphate was still present in the skin membranes. At the end of the study (48 hours after application of the test compound), the mass balance was found to be very variable: 132.4 %, 73.4 %, 128.2 % and 82.6 % for MON 35012 concentrate, MON 35012 field dilution, MON 0139 70% concentrate and MON 0139 70% field dilution, respectively.

4. Testosterone was used as a reference compound in this study. The penetration data were in good agreement to the historical data of our laboratory.

5. In conclusion, an 8-hours exposure resulted in a penetration of *ca.* 10 % (MON 35012 concentrate), *ca.* 2.6 % (MON 35012 field dilution), *ca.* 1.3 % (MON 0139 70% concentrate) and *ca.* 1.4 % (MON 0139 70% field dilution) over a period of 48 h in viable rat skin membranes.

Contents

Statement of GLP compliance

We, the undersigned, hereby declare that this report constitutes a true and complete representation of the procedures followed and of the results obtained in this study by TNO Nutrition and Food Research, and that the study was carried out under our supervision. The study was carried out in accordance with the OECD Principles of Good Laboratory Practice.

Drs. J.A. van Burgsteden
(Study director)

Date

Dr. J.P. Groten
(Management)

Date

Quality Assurance Statement

On:	*In vitro* percutaneous absorption study with [14C]glyphosphate using viable rat skin membranes
Report Number:	V4478
Date :	14 June 2002

The protocol was inspected as follows:

Date of inspection:	Date of report:
14 March 2002	14 March 2002

The experimental phase of this study was inspected by the Quality Assurance Unit of TNO Nutrition and Food Research Institute as follows:

Date of inspection:	Date of report:
14 March 2002	14 March 2002

This report was audited as follows:

Dates of audit:	Date of report:

I, the undersigned, hereby declare that this report provides an accurate record of the procedures employed and the results obtained in this study; all inspections were reported to the study director and the management on the dates indicated.

Drs. M.C.T.J. Meeuwsen	Date:
(Quality Assurance Unit)	

GLP compliance monitoring unit statement

Inspectie W&V

ENDORSEMENT OF COMPLIANCE

WITH THE OECD PRINCIPLES OF
GOOD LABORATORY PRACTICE

Pursuant to the Netherlands GLP Compliance Monitoring Programme and according to Directive 88/320/EEC the conformity with the OECD Principles of GLP was assessed on 22-26 November 1999 at

TNO Nutrition and Food Research Institute
Utrechtseweg 48
P.O. Box 360
3700 AJ Zeist

It is herewith confirmed that the afore-mentioned test facility is currently operating in compliance with the OECD Principles of Good Laboratory Practice in the following areas of expertise: Toxicity and Mutagenicity studies, and studies on Metabolism and Kinetics.

The Hague, 23 December 1999

Th. Helder, DVM
GLP Compliance Monitoring Unit

Inspectorate for Health Protection, Commodities and Veterinary Public Health
Ministry of Health, Welfare and Sport

Testing facility

The study was conducted by:

TNO Nutrition and Food Research
Department of Biomolecular Sciences
P.O. Box 360, 3700 AJ ZEIST, the Netherlands
Telephone +31 30 69 44 144
Telefax +31 30 69 57 224
Visitors address: Utrechtseweg 48, Zeist, the Netherlands

This unit is operating in full compliance with the OECD GLP principles.

Contributors

Study director	. Drs. J.A. van Burgsteden[1]
Deputy study director	: Dr. J.J.M. van de Sandt
Management	: Dr. J.P. Groten

[1] Department of Biomolecular Sciences

1 Introduction

At the request of Monsanto Europe S.A. (Louvain-la-Neuve, Belgium), the herbicide glyphosphate was examined in two formulations (MON 35012 and MON 0139 70 %) for *in vitro* percutaneous absorption through viable rat skin membranes. Both the concentrated formulation and the formulation suspended in water (81 times for MON 35012 and 82 times for MON 0139 70 %) in order to obtain the field dilution were tested. Testosterone was used as a reference compound with known *in vitro* absorption characteristics The study outline was based on the draft OECD guideline for the testing of chemicals (skin absorption. *in vitro* method, Draft Guideline 428, December 2000), the ECETOC recommendations (1993) and the report of ECVAM workshop 13 (1996). The study was conducted according to the OECD Principles of Good Laboratory Practice (1997).

2 Experimental

2.1 Test substances

2.1.1 Non-radiolabeled formulations

Name	: MON 35012
Product category	: herbicide
Active ingredient	: glyphosphate; CAS no. 38641-94-0
Molecular formula	: $C_3H_8NO_5P$
Log K_{ow} of active ingredient	: -4.1
MW of active ingredient	: 228.2
Appearance of formulation	: yellow to amber liquid
Composition of formulation	: Isopropylamine salt of glyphosphate (ca. 46 % w/w) Surfactant Cocoamine (ca. 18 % w/w) water and minor formulating ingredients (ca. 35.5 % (w/w)
Density	: 1.1604 g/mL (at 20°C)
Glyphosphate content	: 399.6 g/L (see appendix 1)
Batch number	: A1C1607105
Arrival date	: 16 January 2002
Expiration date	: 22 March 2003
Storage	: ambient temperature
Supplier	: Monsanto Europe S.A.
TNO reference no.	: 020030

Name	: MON 0139 70 %
Product category	: herbicide
Active ingredient	: glyphosphate; CAS no. 38641-94-0
Molecular formula	: $C_3H_8NO_5P$
Log K_{ow} of active ingredient	: -4.1
MW of active ingredient	: 228.2
Appearance of formulation	: Clear liquid
Composition of formulation	: Isopropylamine salt of glyphosphate (ca. 62 % w/w) Inert ingredients (ca. 38 %)
Density	: 1.1782 g/mL (at 20°C)
Glyphosphate content	: 405.5 g/L (see appendix 1)
Batch number	: MVH32/6780138
Arrival date	: 16 January 2002
Expiration date	: 15 January 2004
Storage	: ambient temperature
Supplier	: Monsanto Europe S.A.
TNO reference no.	: 020032

2.1.2 Radiolabeled glyphosphate

Name for the report	: [^{14}C]glyphosphate
Specific activity	: 26.0 mCi/mmole
Batch number	: 2010-05-5
Arrival date	: 24 January 2002
Expiration date	: 2 October 2002
Storage	: <-18°C
Supplier	: Monsanto Company, St. Louis, MO
TNO reference no. (Radioactive materials)	: 595

2.1.3 Reference compounds

Radiolabeled water	: [^{3}H]H_2O
Molecular weight	: 18.0
Specific Activity	: 37 0 MBq/g
Purity	: not determined
Appearance	: clear liquid
Lot no.	: 3249-399
Storage conditions	: 2-10 °C
Arrival date	: 19 February, 2001
Expiration date	: 19 February, 2003
Supplier	: NEN™ Life Science Products
TNO internal reference no. (Radioactive materials)	: 534

Name of the test substance	: Testosterone
Chemical name	: 4-androsten-17β-ol-3-one
Molecular weight	: 288.4
Log Po/w	: 3.31
Batch no.	: H234
Purity	: 98.4 %
CAS. reg. no.	: 58-22-0
Storage conditions	: 2-10 °C
Arrival date	: 7 January 2000
Expiration date	: December 2004
Supplier	: Steraloids Inc. (Newport R.I, USA)
TNO internal reference no.	: 990365

Radiolabeled testosterone	: [4-^{14}C]testosterone
Specific Activity	: 1.983 GBq/mmol
Purity	: > 97 %
Lot no.	: 3379017
Appearance	: clear liquid (ethanol solution)
Storage conditions	: 2-10 °C
Supplier	: NEN™ Life Science Products
Arrival date	: 5 February, 2002
Expiration date	: 5 February, 2007
TNO internal reference no. (Radioactive materials)	: 597

2.1.4 Dose solutions

The dose solution of group RA was prepared by adding radiolabeled glyphosphate to the MON 35012 formulation to yield a radioactive concentration of 2.25 MBq/mL. For group RB, radiolabeled glyphosphate was added to the MON 35012 formulation which was suspended in water 81 times, yielding a radioactive concentration of 1.02 MBq/mL.
The dose solution of group RC was prepared by adding radiolabeled glyphosphate to the MON 0139 70% formulation to yield a radioactive concentration of 2.52 MBq/mL. For group RD, radiolabeled glyphosphate was added to the MON 0139 70% formulation which was suspended in water 82 times, yielding a radioactive concentration of 1.06 MBq/mL.
The dose solution of the reference compound (group RE) was prepared by dissolving non-radiolabeled testosterone and [4-^{14}C]testosterone in ethanol to yield a concentration of 2.45 MBq/ml. Total radioactivity of the dosing solutions was determined in three mock dosings prior to and after the application to the skin membranes.

2.2 Time schedule

The experimental phase of the study was performed between 12 March and 15 March 2002. Radioactive measurements took place until 25 March 2002.

2.3 Source of rat skin

Rat skin was obtained on 12 March 2002 from four male Wistar rats of 7 weeks old (Charles River, Germany). The dorsal and flank skin of the animals was clipped free of fur by means of electric clippers. The culture of rat skin took place immediately after sacrifice of the animals.

2.4 Two-compartment model

Skin membranes of 0.84 ± 0.07mm thickness were cultured in a two-compartment model as described by Van de Sandt *et al.* (1993; 2000). Briefly, sterile glass rings (internal area of ca. 0.64 cm^2) were glued to the skin membranes using cyanoacrylate-based glue. Skin membranes were washed three times for 15 min in medium supplemented with bactericides and fungicides to prevent biological contamination. The skin membranes were then carefully transferred into 6-well plates on a Netwell insert (500 µm mesh), which allows contact of the receptor fluid to the dermal side of the skin, while the stratum corneum remains exposed to the air. The 6-well plates were placed in a humidified incubator gassed with 5% CO_2 and 40% O_2 at 32 °C. To obtain a homogeneous distribution of the receptor fluid the 6-well plates were rocked on a platform ca. 9 times per minute. The receptor fluid (total volume 1.2 ml) consisted of a mixture of DMEM and HAM F12 culture medium (3:1) supplemented with EGF (10 µg/L), hydro-cortisone (400 µg/L), gentamicin (50 mg/L) and Foetal Calf Serum (10 %, v/v).

2.5 Experimental design

The study was conducted according to protocol P4478 entitled "Protocol for an *in vitro* percutaneous absorption study with [^{14}C]glyphosphate using viable human and rat skin membranes", approved by the Study Director on 8 February, 2002 and by the sponsor on 18 February, 2002.

Integrity of the skin membranes was assessed by determining the permeability coefficient (Kp) of tritiated water. Subsequently, MON 35012 and MON 0139 70% were applied topically to the membranes as concentrate and as field dilution. Testosterone was used as reference substance. In all groups, samples of the receptor fluid were collected up to 48 hours.

The overall study design was as follows:

Group	Group size	Test substance	Formulation	Exposure time	Concentration (mg/ml)	Dose a.i [a] (mg/cm²)
RA	6	Glyphosphate	MON 35012 (concentrate)	8 h	400.0	6.250
RB	6	Glyphosphate	MON 35012 (field dilution)	8 h	5.12	0.080
RC	6	Glyphosphate	MON 0139 70% (concentrate)	8 h	405.9	6.343
RD	6	Glyphosphate	MON 0139 70% (field dilution)	8 h	5.12	0.080
RE	6	Testosterone	ethanol[b]	48 h	1.06	0.0165

[a] 10 µl of the test samples was applied on a skin surface of ca. 0.64 cm²
[b] ethanol was carefully evaporated using compressed air

2.6 Assessment of membrane integrity

After an equilibration period of approximately 1 h, the inner side of the glass ring was dried with a sterile gauze swab and 200 µl saline containing tritium water (16.7 kBq/ml) was applied in each glass ring. The rings were covered with a glass cover. Samples of receptor fluid (200 µl) were collected at 1.0, 2.0 and 3.0 h after application. Subsequently, tritium water remaining at the application site was removed with a sterile gauze swab.

2.7 Assessment of percutaneous absorption of glyphosphate

Skin membranes with a permeability coefficient (Kp) of less than 3.5×10^{-3} cm/h for tritiated water were used. In all test groups, 10 µl of the test solution was applied in the glass rings (0.64 cm²). After 8 h of exposure (groups RA, RB, RC and RD) the test compound was removed from the application site with 6 cotton swabs soaked in 3 % aqueous Teepol solution. In all test groups samples of receptor fluid (500 µl) were collected at 1, 2, 4, 6, 8, 10, 20, 24, 28, 44 and 48 h after application of the test compounds. Directly after each sampling the original volume of the receptor fluid was restored by adding 500 µl fresh receptor fluid to each well.

2.8 Determination of mass balance

At the end of the experiment, the recovery of the applied test compounds was determined in four of the six skin membranes per test group. The fifth and sixth skin membrane of each test group were cut in half and fixed in 4% buffered formaldehyde (one half) or embedded in TissueTek and frozen on dry ice (second half) for microscopic evaluation (see section 2.10). In all membranes, the remaining test compound was removed from the application site with 6 cotton swabs soaked in 3 % aqueous Teepol solution. This procedure was performed after 8 h of exposure (groups A, B, C and D) or after 48 h of exposure (group E). After 48 h of exposure, the skin membranes of all three groups were digested in 5 ml 1.5 M KOH in 20% ethanol. The receptor fluid was collected and the wells were washed two times with 1.0 ml ethanol. Total radioactivity was determined in all compartments separately (receptor compartment, skin tissue and dislodged fractions).

2.9 Determination of radioactivity

The radioactivity was determined as DPM, using a LKB/Wallac S1409 scintillation counter. The amount of radioactivity was determined in (aliquots of) the mock dosing samples, the collected receptor fluid samples, the washing fractions and the digested skin. Ultima Gold scintillation liquid (Packard) was added to the samples of the receptor fluid (4 ml per sample), the cotton swabs (4 ml per sample), the washing fractions (15 ml per sample) and samples of the mock dosing samples (4 ml per sample). For the determination of radioactivity in digested skin membranes, 15 ml Hionic-Fluor scintillation liquid (Packard) was added to an aliquot of each digested skin membrane.

2.10 Determination of auroradiography

In two of six membranes per test group, the distribution of the test compound was assessed qualitatively by autoradiography at the end of the study. After removing the remaining test compound from the application site with 6 cotton swabs soaked in 3 % aqueous Teepol solution, the membranes were cut in half and fixed in 4% buffered formaldehyde (one half) or embedded in TissueTek and frozen on dry ice (second half) for microscopic evaluation. The parts of the membranes that were fixed in 4% buffered formalin were processed for embedding in paraffin. Both the fixed and frozen parts of the membranes were sectioned, covered with photographic emulsion for one and two weeks and developed. Hereafter, the sections were stained with haematoxylin and eosin for microscopic evaluation.

2.11 Calculations

- The cumulative penetration of the applied test substances was calculated from the 500 µl receptor fluid samples by the following equation:
  Cumulative $dpm_T = (2.4 \times dpm_T(500\mu l) + \Sigma(dpm_{T-1}(500\mu l)..dpm_1(500\mu l))$
  dpm_T : radioactivity at sampling time T
  dpm_{T-1} : radioactivity at the sampling time preceding T
  dpm_1 : radioactivity at the first sampling time
  The cumulative penetration [DPM] was transformed to the cumulative penetration [µg/cm^2] using the following equation:
  (cumulative penetration [DPM]/applied dose of [ring-U-^{14}C]chlorpropham [DPM]) * applied dose of chlorpropham [µg/cm^2]
- The flux constant [µg.cm^{-2}.h^{-1}] was calculated from the linear portion of the cumulative penetration curve, using the program Microsoft Excell 97 SR.
- Lag time [h] was obtained by extrapolating the linear portion of the cumulative penetration curves to the x-axis, using the program Microsoft Excell 97 SR
- Least-square-method: r^2 was calculated of the linear portion of the cumulative penetration curves, using the program Microsoft Excell 97 SR.
- Kp = flux constant [µg.cm^{-2}.h^{-1}]/applied concentration [µg.cm^{-3}]

2.12 Retention of records, samples and specimens

The remaining test substance will be retained for at least six months after submission of the final report. The raw data, the master copy of the final report and all other information relevant to the quality and integrity of the study, including tissue specimens, paraffin blocks and microscopic slides, were retained in the archives of the TNO Nutrition and Food Research for a period of at least five years (tissue specimens, paraffin blocks) or at least 15 years (slides, raw data) after reporting of the study. At the end of the five year storage period, the sponsor will be asked whether the tissue specimens and paraffin blocks can be discarded, should be stored for an additional period, or transferred to the archives of the sponsor.

2.13 Deviations of the protocol

As of March 15 2002, the name of the Department of Explanatory Toxicology has been changed into Department of Biomolecular Sciences.

Upon request of the sponsor, the experiment has not been performed using viable human skin membranes.

3 Results

3.1 Integrity of skin membranes

Prior to the determination of the percutaneous absorption of glyphosphate and the reference compound (testosterone), the permeability coefficient (Kp) for tritium water was determined in 60 skin membranes. Skin membranes with a Kp value below the cut-off values of 3.5×10^{-3} cm/h were selected for the study. The individual data of the penetration of tritium water through the selected skin membranes are given in appendix 2.

3.2 Percutaneous absorption of glyphophate

The herbicide glyphosphate was examined for *in vitro* percutaneous absorption through viable rat skin membranes in the formulations MON 35012 and MON 0139 70%. MON 35012 and MON 0139 70% were applied topically for 8 h to the skin membranes as concentrate (6.249 and 6.343 mg glyphosphate per cm^2 for MON 35012 and MON 0139 70%, respectively) and as field dilution (0.080 mg glyphosphate per cm^2 for both MON 35012 and MON 0139 70%).

Fourty-eight hours after application of concentrated MON 35012, 10.3 ± 4.2 % of the dose glyphosphate had penetrated through rat skin membranes. When MON 35012 was applied as field dilution, the relative penetration of glyphosphate was 2.6 ± 1.4 % after 48 h. For MON 0139 70% these values were 1.3 ± 1 9 % for the concentrate and 1.4 ± 2.2 % for the field dilution. The mean flux constants were 35.6 $\mu g.cm^{-2}.h^{-1}$ (MON 35012 concentrate), 0.127 $\mu g.cm^{-2}.h^{-1}$ (MON 35012 field dilution), 2.01 $\mu g.cm^{-2}.h^{-1}$ (MON 0139 70% concentrate) and 0.100$\mu g.cm^{-2}.h^{-1}$ (MON 0139 70% field dilution). The mean Kp values were 0.089×10^{-3} cm/h (MON 35012 concentrate), 0.025×10^{-3} cm/h (MON 35012 field dilution), 0.005×10^{-3} cm/h (MON 0139 70% concentrate) and 0.019×10^{-3} cm/h (MON 0139 70% field dilution) (table 1 and 2, appendix 3). At the end of the 8-h exposure period, 117.5 % (MON 35012 concentrate), 45.6 % (MON 35012 field dilution), 123.3 % (MON 0139 70% concentrate) and 80.0 % (MON 0139 70% field dilution) of the applied dose glyphosphate could still be removed from the application site with cotton swabs (appendix 5).

Table 1 **Overview table of the *in vitro* percutaneous penetration of glyphosphate in MON 35012**

Group	A		B	
n	6		6	
Dose glyphosphate	6.249 mg.cm^{-2}		0.080 mg.cm^{-2}	
Penetration within	% of dose	µg.cm^{-2}	% of dose	µg.cm^{-2}
8 h	2.40	150.1	0.84	0.67
24 h	7.59	474.1	1.93	1.55
48 h	10.34	646.3	2.62	2.10
Flux constant [µg.cm^{-2}.h^{-1}]	35.6		0.127	
Kp value [cm.h^{-1}]	0.089 × 10^{-3}		0.025 × 10^{-3}	
Lag time [h]	4.1		3.2	

Table 2 **Overview table of the *in vitro* percutaneous penetration of glyphosphate in MON 0139 70%**

Group	C		D	
n	6		6	
Dose glyphosphate	6.343 mg.cm^{-2}		0.080 mg.cm^{-2}	
Penetration within	% of dose	µg cm^{-2}	% of dose	µg.cm^{-2}
8 h	0.17	10.6	0.35	0.28
24 h	0.94	59.4	1.19	0.95
48 h	1.27	80.8	1.42	1.13
Flux constant [µg.cm^{-2}.h^{-1}]	2.01		0.100	
Kp value [cm.h^{-1}]	0.005 × 10^{-3}		0.019 × 10^{-3}	
Lag time [h]	2.2		4 8	

3.3 Percutaneous absorption of reference compound

Testosterone was used as reference compound and was applied to the skin membranes at a dose of 16.5 µg.cm^{-2} (group E). The cumulative amount that reached the receptor fluid 48 h after application was 3.73 ± 0.74 µg.cm^{-2} (22.61 ± 4.49 %) (table 3, appendix 3). The flux constant was 0.10 µg.cm^{-2}.h^{-1} and the Kp value was 0.093×10^{-3} cm/h. The lag time was 6.5 h.

3.4 Micro autoradiography

Table 3 Overview table of the *in vitro* percutaneous penetration of testosterone

Group	C	
n	6	
Dose [µg . cm^{-2}]	16.5	
Penetration within	% of dose	µg.cm^{-2}
8 h	1.65	0.27
24 h	10.48	1.73
48 h	22.61	3.73
Flux constant [µg.cm^{-2}.h^{-1}]	0.098	
Kp value [cm.h^{-1}]	0.093 × 10^{-3}	
Lag time [h]	6.5	

4 Discussion and conclusions

The herbicide glyphosphate in the formulations MON 35012 and MON 0139 70% was examined for *in vitro* percutaneous absorption through viable rat skin membranes. Both the concentrated formulation and the field dilution were tested (6.249 and 0.080 mg glyphosphate per cm^2 respectively for MON 35012 and 6.343 and 0.080 mg glyphosphate per cm^2 respectively for MON 0139 70%), using an 8-h exposure period.

Fourty-eight hours after application of concentrated MON 35012, 10.3 ± 4.2 % of the dose glyphosphate had penetrated through rat skin membranes. When MON 35012 was applied as field dilution, the relative penetration of glyphosphate was 2.6 ± 1.4 % after 48 h. For MON 0139 70% these values were 1.3 ± 1.9 % for the concentrate and 1.4 ± 2.2 % for the field dilution.

At the end of the 8-h exposure period, 117.5 % (MON 35012 concentrate), 45.6 % (MON 35012 field dilution), 123.3 % (MON 0139 70% concentrate) and 80.0 % (MON 0139 70% field dilution) of the applied dose glyphosphate could still be removed from the application site with cotton swabs. At the end of the study (48 h after application of the test compound), 4.7 % (MON 35012 concentrate), 23.1 % (MON 35012 field dilution), 2.4 % (MON 0139 70% concentrate) and 2.3 % (MON 0139 70% field dilution) of the applied dose glyphosphate was still present in the skin membranes. These results indicate that the amount of glyphosphate that reaches the skin is noticeably higher in the MON 35012 field dilution as opposed to the MON 0139 70% field dilution.

At the end of the study (48 hours after application of the test compound), the mass balance was found to be very variable: 132.4 %, 73.4 %, 128.2 % and 82.6 % for MON 35012 concentrate, MON 35012 field dilution, MON 0139 70% concentrate and MON 0139 70% field dilution, respectively.

Testosterone was used as a reference compound in this study. The penetration data were in good agreement to the historical data of our laboratory.

In conclusion, an 8-hours exposure to MON 35012 resulted in a penetration of ca. 10 % (concentrate) or ca. 2.6 % (field dilution) over a period of 48 h in viable rat skin membranes. An 8 hours exposure to MON 0139 70% resulted in a penetration of ca. 1.3 % (concentrate) or ca. 1.4 % (field dilution) over a period of 48 h in viable rat skin membranes.

5 References

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (1993) Monograph No. 20, Percutaneous Aborption (Ed. D.A. Stringer). Brussels, Belgium.

European Centre for the Validation of Alternative Methods (ECVAM) (1996). Methods for Assessing Percutaneous Absorption. Report of ECVAM Workshop 13. ATLA 24, 81-106.

Organisation for Economic Cooperation and Development (OECD) (2000). OECD guideline for the testing of chemicals. Draft new OECD guideline 428. Skin absorption: *in vitro* method.

Organisation for Economic Co-operation and Development. OECD Principles of Good Laboratory Practice (as revised in 1997), Paris, ENV/MC/CHEM

Sandt J.J.M. van de, Rutten A.A.J.J.L. and van Ommen B. (1993). Species-specific cutaneous biotransformation of the pesticide propoxur during percutaneous absorption *in vitro*. *Toxicology and Applied Pharmacology* 123, 144-150.

Sandt J.J.M. van de, Meuling W.J.A., Elliott G.R., Cnubben N.H.P. and Hakkert B.C. (2000). Comparative *in vitro* - *in vivo* percutaneous absorption of the pesticide propoxur. *Toxicological Sciences* 58, 23-31.

Appendices

Appendix 1 - Certificates of Analyses

Appendix 2 - Individual data of the cumulative penetration of tritium water

Appendix 3 - Individual data of the cumulative penetration of glyphosphate and testosterone through rat skin

Appendix 4 - Figures of the cumulative penetration of glyphosphate through rat skin

Appendix 5 - Individual data of the recovery of glyphosphate and testosterone

Appendix 6 - Microautoradiography of skin membranes

Appendix 1 Certificates of Analyses

IFU Umweltanalytik GmbH · Bleichstr 19 D-75173 Pforzheim

UMWELTANALYTIK GMBH

Chemische und biologische Untersuchungslabors

Bleichstraße 19 · D-75173 Pforzheim

Telefon 07231/9236-0
Telefax 07231/923666
E-Mail: info@ifu-pforzheim.de
Internet: www.ifu-pforzheim.de

CERTIFICATE OF ANALYSIS

Sample:	**MON 0139 70 % solution**
Batch No.:	MVH32/6780138
Density:	1.1782 g/mL (at 20 °C)
Analysis date:	23 January 2002
Expiration date:	January 2004
Assay:	HPLC determination with photodiode array detection according to the method described in the final report of study 20021035/01-RCA. This study has been performed in compliance with the principles of Good Laboratory Practice.
Result:	**Glyphosate acid 405.5 g/L** (Mean from five determinations, RSD: 0.8 %)

Pforzheim, 06 February 2002

A. Witte

Andreas Witte

THIS IS AN EXACT COPY OF THE ORIGINAL DOCUMENT
BY : 13.02.02
DATE :

Appendix 1 Continued

TNO Dispense reference no.:
01 c 2 No

IFU Umweltanalytik GmbH Bleichstr 19 · D-75173 Pforzheim

UMWELTANALYTIK GMBH

Chemische und biologische Untersuchungslabors

Bleichstraße 19 D-75173 Pforzheim

Telefon 07231/9236-0
Telefax 07231/923666
E-Mail: info@ifu-pforzheim.de
Internet www.ifu-pforzheim.de

CERTIFICATE OF ANALYSIS

Sample:	**MON 35012**
Batch No.:	A1C1607105
Density:	1.1604 g/mL (at 20 °C)
Analysis date:	09 May 2001
Expiration date:	May 2003
Assay:	HPLC determination with photodiode array detection according to the method described in the final report of study 20011065/01-RCA. This study has been performed in compliance with the principles of Good Laboratory Practice.
Result:	**Glyphosate acid 399.6 g/L** (Mean from five determinations, RSD: 1.2 %)

Pforzheim, 22 May 2001

Andreas Witte

Appendix 2 Individual data of the cumulative penetration of tritium water

Table I **Cumulative penetration of tritium water through rat skin prior to application of MON 35012 (group A)**

Cumulative radioactivity [dpm]						
Cell number	1	2	3	4	5	6
Time interval 0-1 h	696	174	36	930	942	462
0-2 h	1424	857	702	2183	1741	995
0-3 h	2584	1049	2018	3103	2863	1208
Penetration rate [dpm.cm^{-2}.h^{-1}]	1346	546	1051	1616	1491	629
Kp value [cm h^{-1}.10^{3}]	1 34	0.54	1 05	1.61	1.49	0.63

Table II **Cumulative penetration of tritium water through rat skin prior to application of MON 35012 (group B)**

Cumulative radioactivity [dpm]						
Cell number	1	2	3	4	5	6
Time interval 0-1 h	306	696	222	876	342	456
0-2 h	903	1244	511	1508	951	1936
0-3 h	1285	2938	794	2263	1814	2432
Penetration rate [dpm.cm^{-2}.h^{-1}]	669	1530	414	1179	945	1267
Kp value [cm.h^{-1}.10^{3}]	0.67	1.53	0.41	1.18	0.94	1.26

Appendix 2 Continued

Table III **Cumulative penetration of tritium water through rat skin prior to application of MON 0139 70% (group C)**

Cumulative radioactivity [dpm]						
Cell number	1	2	3	4	5	6
Time interval 0-1 h	126	246	438	780	870	1128
0-2 h	1179	917	1831	1510	1957	1124
0-3 h	2026	1549	2322	2208	3495	2900
Penetration rate [dpm.cm^{-2}.h^{-1}]	1055	807	1209	1150	1820	1510
Kp value [cm.h^{-1}.10^{3}]	1.05	0.80	1.21	1.15	1.82	1.51

Table IV **Cumulative penetration of tritium water through rat skin prior to application of MON 0139 70% (group D)**

Cumulative radioactivity [dpm]						
Cell number	1	2	3	4	5	6
Time interval 0-1 h	156	228	270	468	564	342
0-2 h	614	680	1017	1182	796	843
0-3 h	640	1465	2127	1852	1981	1610
Penetration rate [dpm.cm^{-2}.h^{-1}]	333	763	1108	965	1032	839
Kp value [cm.h^{-1}.10^{3}]	0.33	0.76	1.10	0.96	1.03	0.84

Appendix 2 Continued

Table V **Cumulative penetration of tritium water through rat skin prior to application of testosterone (group E)**

Cumulative radioactivity [dpm]						
Cell number	1	2	3	4	5	6
Time interval 0-1 h	486	468	222	474	672	540
0-2 h	663	864	565	2455	1882	162
0-3 h	1312	1313	665	4639	3407	2208
Penetration rate [$dpm.cm^{-2}.h^{-1}$]	683	684	346	2416	1774	1150
Kp value [$cm.h^{-1}.10^{3}$]	0.68	0.68	0.35	2 41	1.77	1.15

Appendix 3 Individual data of the cumulative penetration of glyphosphate and testosterone through rat skin

Table VI Cumulative penetration of glyphosphate in MON 35012 formulation (concentrate) through rat skin

RA	cumulative absorption (µg/cm²)							
Replicate no	1	2	3	4	5	6	Mean	S D
time (h)								
1	0 16	0 49	0 26	1 69	2 26	0.00	0 81	0 93
2	0 75	3 53	1 37	10 92	21.20	0 53	6 39	8 24
4	107 98	15 00	9,39	55 87	116 73	3.85	51 47	50 68
6	64 80	32 56	28.07	125 50	262 19	11 62	87.46	94 64
8	92 34	56 20	61,22	214.81	452 60	23.44	150 10	162.35
10	116 12	85 66	113,56	317 37	659.57	41,96	222.41	234 30
20	261.09	286 42	329,21	549 25	992 68	143.76	410 27	271 14
24	301 57	367 68	420,17	593 82	975,84	185 58	474 14	280 46
28	335 48	442 41	496 46	625 56	1006 58	221.52	521 17	274 63
44	396,96	646 26	668 53	669,35	1094 78	353,51	642 23	264 68
48	413,77	710 37	658 96	687 44	1084 13	342,96	646 27	261 72
Linear range	6-20	10-24	8-24	6-10	6-10	8-28		
Flux constant (µg/cm²/h)	14,08	20.13	22,15	47 97	99,35	10.02	35 61	33.92
Kp * 10-3 (cm/h)	0 035	0,050	0 055	0,120	0 248	0 025	0,089	0 085
Lag time	1,5	5 7	5 1	3,4	3 4	5,7	4 1	1 7
r²	0 9893	1 0000	0 9996	0 9884	0,9994	0 9997	0,9994	

Table VII Cumulative penetration of glyphosphate in MON 35012 formulation (field dilution) through rat skin

RB	cumulative absorption (µg/cm²)							
Replicate no	1	2	3	4	5	6	Mean	S.D.
time (h)								
1	0 00	0 02	0,00	0 01	0,00	0 01	0,01	0,01
2	0,01	0 10	0,01	0 08	0 01	0 06	0 04	0,04
4	0 06	1 16	0,03	0.34	0,06	0 22	0 31	0,43
6	0 11	1 07	0 07	0 75	0,16	0,42	0 43	0,40
8	0 21	1 46	0,13	1 24	0,29	0 67	0 67	0,57
10	0 37	1 88	0,23	1 73	0 46	0 95	0 94	0,72
20	0 75	2 75	0,55	2 29	0 73	1,45	1 42	0 92
24	0 84	2 93	0,64	2 46	0,81	1 61	1 55	0,96
28	0 94	3 11	0,70	2.58	0 90	1 79	1 67	1,00
44	1 40	3 34	0 95	3 24	1 22	2.62	2 13	1,07
48	1 32	3 46	0,90	3 34	1 17	2,38	2 10	1,13
Linear range	6-10	6-10	6-10	6-10	6-10	6-10		
Flux constant (µg/cm²/h)	0 065	0,204	0 040	0 247	0,073	0 133	0 127	0 083
Kp * 10-3 (cm/h)	0,013	0 040	0,008	0,049	0 014	0,026	0,025	0 016
Lag time	4 5	0 7	4 4	3 0	3 9	2,9	3 2	1 4
r²	0,9825	1 0000	0,9872	1 0000	0,9968	0 9988	0 9942	

Appendix 3 Continued

Table VIII Cumulative penetration of glyphosphate in MON 0139 70% formulation (concentrate) through rat skin

RC	cumulative absorption (µg/cm²)							
Replicate no	1	2	3	4	5	6	Mean	S.D.
time (h)								
1	0.16	0.11	0.19	0.16	0.10	0.29	0.17	0.07
2	0.84	0.24	0.40	0.51	0.28	1.88	0.83	0.54
4	3.73	0.48	1.94	1.39	0.58	8.48	2.81	3.12
6	9.15	1.38	2.05	2.94	0.77	16.84	5.54	6.36
8	17.62	1.16	12.17	4.66	0.84	27.01	10.58	10.40
10	26.80	1.27	81.16	8.14	0.95	38.63	26.13	30.66
20	42.08	2.31	200.03	23.43	1.20	41.64	51.78	74.81
24	46.80	2.56	233.62	29.65	1.30	42.43	59.39	87.51
28	51.55	2.78	262.82	36.21	1.22	42.75	66.22	98.58
44	66.09	3.67	360.74	62.77	1.56	43.36	89.70	135.69
48	58.00	3.26	319.37	58.76	1.51	43.92	80.80	119.65
Linear range	6-10	1-4	2-6	6-44	1-6	6-10		
Flux constant (µg/cm²/h)	4.36	0.12	0.41	1.61	0.13	5.42	2.01	2.32
Kp * 10-3 (cm/h)	0.0107	0.0003	0.0010	0.0040	0.0003	0.0134	0.0050	0.0057
Lag time	3.9	0.1	1.2	5.2	0.0	2.9	2.2	2.1
r²	0.9997	0.9998	0.9834	0.9996	0.9896	0.9983	0.9951	

Table IX Cumulative penetration of glyphosphate in MON 0139 70% formulation (field dilution) through rat skin

RD	cumulative absorption (µg/cm²)							
Replicate no	1	2	3	4	5	6	Mean*	S.D.*
time (h)								
1	0.000	0.000	0.000	0.000	0.000	0.017	0.003	0.007
2	0.000	0.000	0.000	0.000	0.008	0.065	0.015	0.034
4	0.011	0.000	0.008	0.000	0.040	0.317	0.063	0.125
6	0.007	0.004	0.016	0.005	0.172	0.704	0.151	0.279
8	0.008	0.004	0.030	0.010	0.396	1.229	0.280	0.490
10	0.007	0.009	0.045	0.015	0.841	1.773	0.448	0.728
20	0.011	0.018	0.072	0.060	3.020	2.079	0.877	1.330
24	0.017	0.014	0.078	0.078	3.409	2.114	0.952	1.481
28	0.016	0.018	0.081	0.095	3.612	2.129	0.992	1.529
44	0.018	0.024	0.094	0.184	4.257	2.178	1.122	1.752
48	0.020	0.026	0.097	0.184	4.300	2.167	1.133	1.783
Linear range	6-10	8-10	6-10	6-10	8-20	6-10		
Flux constant (µg/cm²/h)	ND	0.003	0.007	0.002	0.218	0.287	0.100	0.132
Kp * 10-3 (cm/h)	ND	0.0005	0.0014	0.0005	0.0426	0.0522	0.0194	0.0257
Lag time	ND	6.4	3.9	4.0	6.2	3.4	4.9	1.4
r²	ND	1.0000	0.9998	0.9963	1.0000	0.9999	0.9996	

* mean of replicates 2,3 4,5 and 6

Appendix 3 Continued

Table X Cumulative penetration of testosterone through rat skin

Group RE	cumulative absorption testosterone (µg/cm²)							
Replicate no	1	2	3	4	5	6	Mean	S.D.
time (h)								
1	0 00	0 00	0 00	0,00	0 00	0 00	0 00	0,00
2	0 00	0 00	0,00	0,00	0.00	0 00	0.00	0 00
4	0 03	0 02	0.02	0 05	0 04	0 04	0.03	0.01
6	0 12	0 08	0,07	0,22	0 14	0 15	0 13	0 05
8	0 26	0 17	0.17	0.46	0 29	0 30	0,27	0.10
10	0 43	0 30	0 30	0 72	0 46	0 46	0.45	0 16
20	1 34	0 97	1,07	2 02	1 35	1 29	1,34	0.37
24	1 74	1.26	1,43	2 53	1 77	1 52	1,73	0 43
28	2 10	1 60	1 82	3 04	2 14	1 99	2 12	0 49
44	3 32	2 64	3,25	4 69	3,32	3 13	3,39	0 69
48	3 70	2.95	3 59	5 15	3 57	3,43	3 73	0 74
Linear range	20-28	20-28	20-28	8-24	20-28	20-28		
Flux constant (µg/cm²/h)	0 095	0 079	0 093	0 130	0 100	0 091	0.098	0 017
Kp * 10-3 (cm/h)	0 090	0 075	0,088	0 123	0 094	0,096	0 093	0 016
Lag time	5 7	7 6	6,6	4 5	5 4	6 1	6 5	1 5
r²	0 9993	1,0000	0 9997	0 9999	0,9991	1 0000	0 9997	

Appendix 4 Figures of the cumulative penetration of glyphosphate through rat skin

Figure I Cumulative penetration of glyphosphate in MON 35012 formulation (concentrate) through rat skin

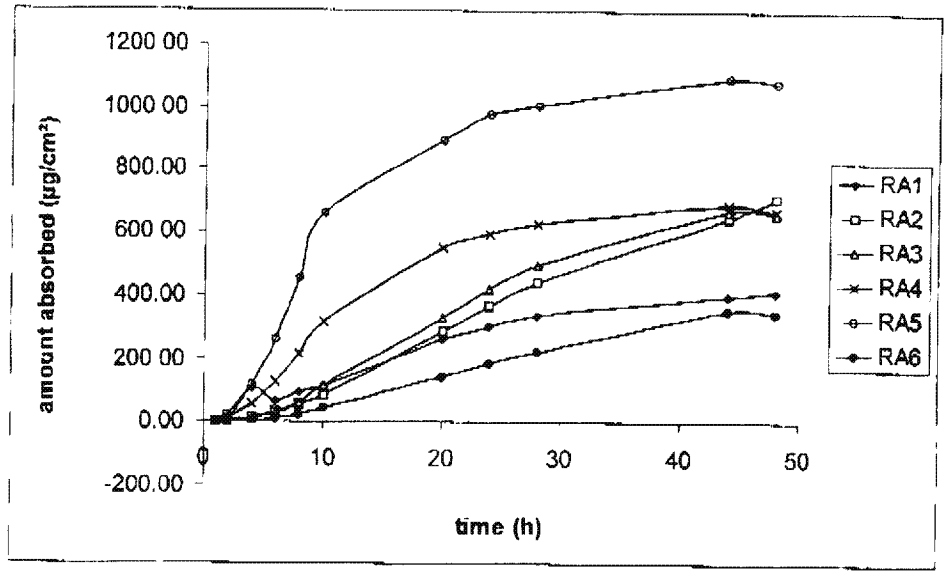
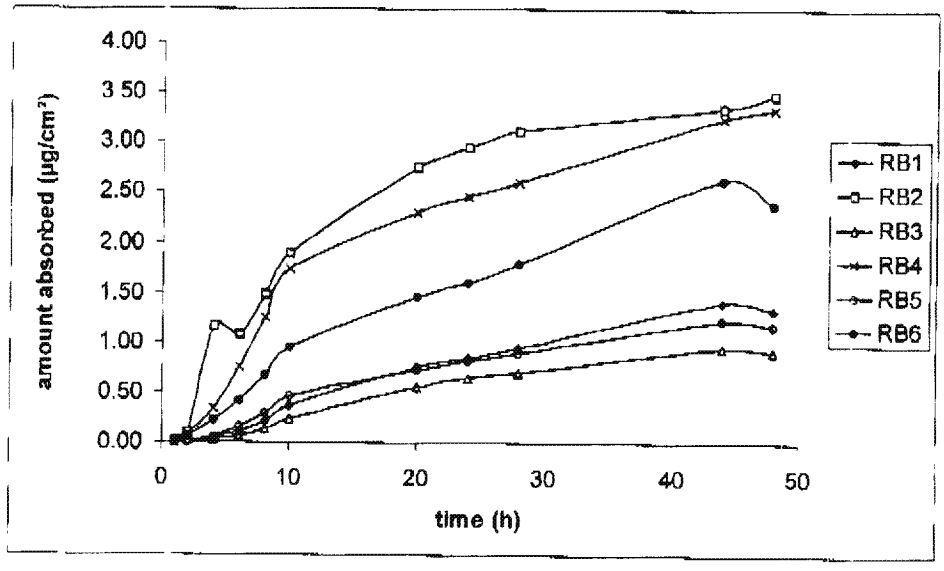


Figure II Cumulative penetration of glyphosphate in MON 35012 formulation (field dilution) through rat skin



Appendix 4 Continued

Figure III Cumulative penetration of glyphosphate in MON 0139 70% formulation (concentrate) through rat skin

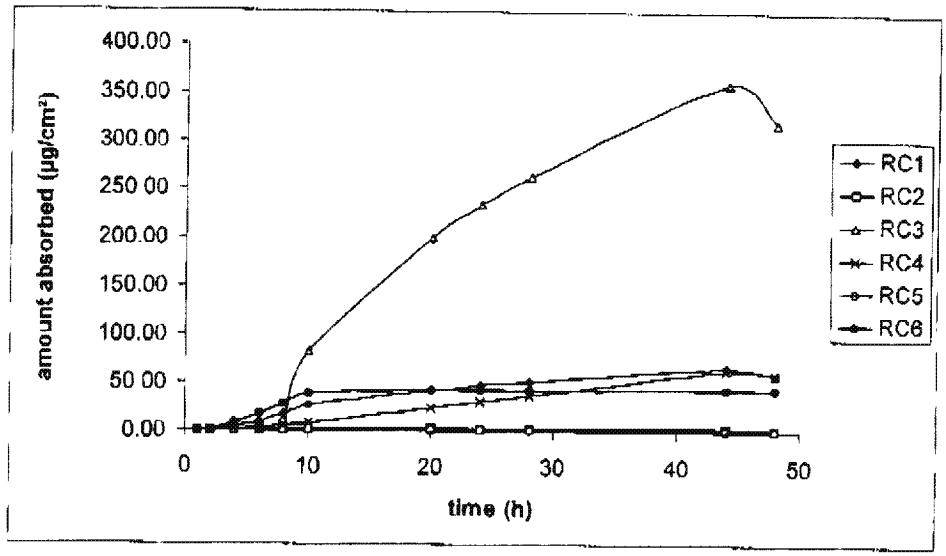
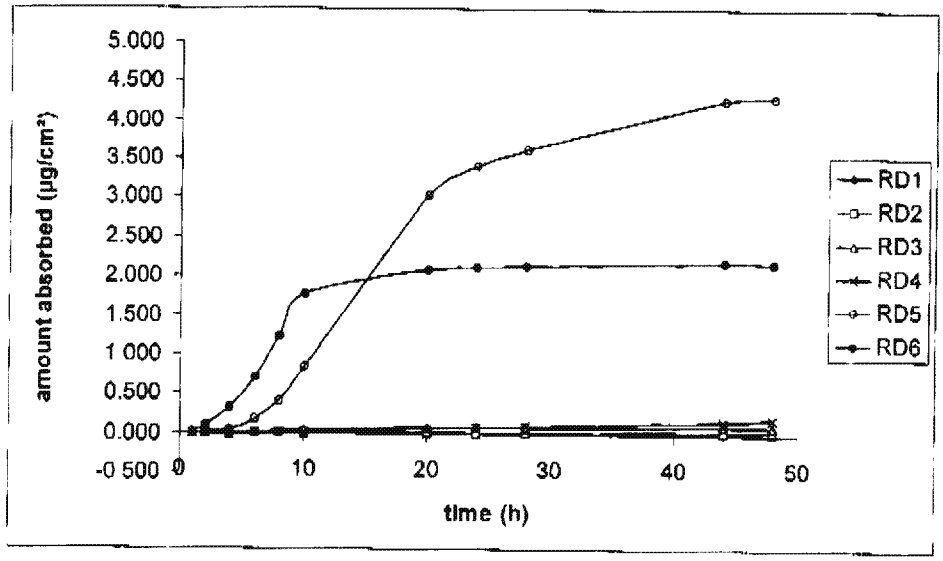


Figure IV Cumulative penetration of glyphosphate in MON 0139 70% formulation (field dilution) through rat skin



Appendix 5 Individual data of the recovery of glyphosphate and testosterone

Table XI Recovery of glyphosphate in MON 35012 formulation (concentrate) in rat skin (group RA)

% of dose								
Dose applied [mg.cm^{-2}]	6 249							
Cell number	1	2	3	4	5	6	Mean	SD
Cell wash + samples	6.0	9 3	9.4	10 2	ND	ND	8.5	1.8
Ring	0.2	0.3	0 4	0.2	ND	ND	0.3	0.1
Skin rinse	133.0	114.1	124.5	98 6	ND	ND	117.5	14.8
Skin membrane	3.9	5.4	8.4	1 2	ND	ND	4.7	3.0
Total recovery	143.4	131.3	144.0	110.7	ND	ND	132.4	15.6

ND: not determined

Table XII Recovery of glyphosphate in MON 35012 formulation (field dilution) in rat skin (group RB)

% of dose								
Dose applied [mg.cm^{-2}]	0.080							
Cell number	1	2	3	4	5	6	Mean	SD
Cell wash + samples	3.1	6 2	2 3	5.7	ND	ND	4 3	1.9
Ring	1.6	2 3	1 3	2.0	ND	ND	1.8	0.4
Skin rinse	41.3	47 6	51.1	42.3	ND	ND	45 6	4.6
Skin membrane	25.0	21.0	21 9	24.7	ND	ND	23.1	2 0
Total recovery	69.7	75.4	75.5	73.2	ND	ND	73.4	2.7

ND: not determined

Appendix 5 Continued

Table XIII Recovery of glyphosphate in MON 0139 70% formulation (concentrate) in rat skin (group RC)

% of dose								
Dose applied [mg cm^{-2}]	6.343							
Cell number	1	2	3	4	5	6	Mean	SD
Cell wash + samples	1.1	0 1	5.1	2.6	ND	ND	2.2	2.2
Ring	0.2	0.0	0.5	1 8	ND	ND	0.6	0.8
Skin rinse	126.4	127.9	106 8	132.2	ND	ND	123.3	11.3
Skin membrane	0.9	0 4	4.5	3 6	ND	ND	2 4	2.0
Total recovery	128.4	128.4	117 4	138.7	ND	ND	128.2	8.7

ND: not determined

Table XIV Recovery of glyphosphate in MON 0139 70% formulation (field dilution) in rat skin (group RD)

% of dose								
Dose applied [mg.cm^{-2}]	0.080							
Cell number	1	2	3	4	5	6	Mean	SD
Cell wash + samples	0.0	0.1	0 1	0.2	ND	ND	0 1	0.1
Ring	0.0	0.0	0 0	0.0	ND	ND	0.0	0.0
Skin rinse	77.5	80.2	84 5	77.8	ND	ND	80.0	3 3
Skin membrane	2.3	2.6	1.3	3.1	ND	ND	2.3	0.7
Total recovery	79.9	82.9	86.0	81.6	ND	ND	82.6	2.6

ND: not determined

Appendix 5 Continued

Table XV Recovery of testosterone in rat skin (group RE)

% of dose								
Dose applied [mg.cm^{-2}]	16.5							
Cell number	1	2	3	4	5	6	Mean	SD
Cell wash + samples	23.3	16.6	16.9	26.2	ND	ND	20.8	4.7
Ring	5.9	2.9	0.4	1.6	ND	ND	2.7	2.4
Skin rinse	5.6	5.7	7.8	5.4	ND	ND	6.1	1.1
Skin membrane	65.0	70.8	69.8	59.3	ND	ND	66.2	5.3
Total recovery	96.7	95.9	98.2	96.6	ND	ND	96.8	0.9

ND. not determined

Appendix 6 Microautoradiography of skin membranes