NOA449280

NOA449280 SL (A16003E) - Primary Skin Irritation Study in Rabbits (4 Hour Semi-Occlusive Application)

Final Report

DATA REQUIREMENT(S): OECD [Section 4, number 404]
EPA [OPPTS 870.2500]
Commission Regulation (EC) No 440/2008
Japanese MAFF [12 NohSan No. 8147]

AUTHOR(S): G. Arcelin

STUDY COMPLETION DATE: 17-Sep-2009

PERFORMING LABORATORY: Harlan Laboratories Ltd.
Wölferstrasse 4
4414 Füllinsdorf / Switzerland

LABORATORY PROJECT ID: Report Number: C26666
Study Number: C26666
Task Number: T002528-07

SPONSOR: Syngenta Ltd
Jealott's Hill, International Research Centre
Bracknell, Berkshire, RG42 6EY, United Kingdom

STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

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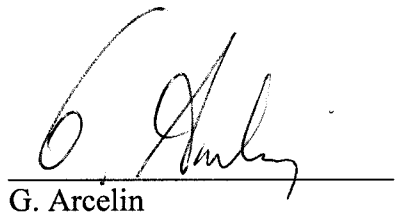
GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

The pH measurement of the test item was performed before the study initiation date. This procedure is, therefore, excluded from this statement.

This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26, 1997 by decision of the OECD Council [C(97)186/Final].

There were no circumstances that may have affected the quality or integrity of the data.



G. Arcelin
Study Director
Acute Toxicology

17. Sep. 2009
Date

Performing Laboratory:

Harlan Laboratories Ltd.,
Wölferstrasse 4
4414 Füllinsdorf / Switzerland

FLAGGING STATEMENT

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QUALITY ASSURANCE GLP STATEMENT

Harlan Laboratories Ltd., Zelgliweg 1, 4452 Itingen / Switzerland

Harlan Laboratories Study:	C26666
Syngenta Task No:	T002528-07
Test Item:	NOA449280 SL
Study Director:	G. Arcelin
Study Title:	NOA449280 SL (A16003E)- Primary Skin Irritation Study in Rabbits (4-Hour Semi-Occlusive Application)

The general facilities and activities are inspected at least once a year and the results are reported to the responsible person and the management.

Study procedures, with the exception of the pH measurement of the test item, were periodically audited. The study plan and this report were audited by the Quality Assurance. The dates are given below.

Dates and Types of QA Inspections		**Dates of Reports to the Study Director and Test Facility Management**
12-Mar-2009	Study Plan	12-Mar-2009
27-Mar-2009	Process Based (Test Item, Test System, Dose Preparation, Treatment, Raw Data)	27-Mar-2009
03-Jul-2009	Report	

This statement also confirms that this final report reflects the raw data.

Quality Assurance: Dr. Z. Bratoljic-Melkay

Z. Bratoljic Melkay

Date: 17-SEP-2009

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Dr. C. Simon	Study Director until 08-Jul-2009
G. Arcelin	Study Director from 09-Jul-2009
G. Arcelin	Deputy Study Director until 08-Jul-2009
E. Rached	Deputy Study Director from 09-Jul-2009
T. Fink	Head of Harlan Laboratories Quality Assurance
R. Doran	Syngenta Study Manager

Study Dates

Experimental Starting Date:	18-Mar-2009
Experimental Completion Date:	30-Mar-2009
Acclimatization:	18-Mar-2009 to 22-Mar-2009 (one female) 18-Mar-2009 to 23-Mar-2009 (one male and one female)
Treatment:	23-Mar-2009 (one female) 24-Mar-2009 (one male and one female)
Observation of Local Findings:	Throughout 1 hour after treatment.
Termination:	30-Mar-2009

Deviations from the guidelines

None

Retention of samples

See other below

Performing laboratory test substance reference number

216594/B

Other

Harlan Laboratories Ltd. (4452 Itingen / Switzerland) will retain the study plan, study plan amendment, raw data, sample of test item(s) and the original final report of the present study for at least ten years. No data will be discarded without the Sponsor's written consent.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

1.1 Study design

The primary skin irritation potential of NOA449280 SL (A16003E) was investigated according to OECD test guideline no. 404. The test item was applied by topical semi-occlusive application of 0.5 mL to the intact left flank of each of three young adult New Zealand White rabbits. The duration of treatment was four hours. The scoring of skin reactions was performed 1, 24, 48, and 72 hours after removal of the dressing.

1.2 Results

The primary irritation index was calculated by totalling the mean cumulative scores at 24, 48 and 72 hours and then dividing by the number of data points. The primary irritation index was 0.00 (max. 8.0).

The application of NOA449280 SL to the skin resulted in mild signs of irritation, including erythema, in all three animals 1-hour post-dosing. These effects were reversible and were no longer evident 24 hours after treatment. The end of the observation period for all animals was at 72 hours post treatment. The test item caused no staining of the treated skin. No corrosive effects were noted on the treated skin of any animal at any of the measuring intervals and no clinical signs were observed. Thus, the test item did not induce significant or irreversible damage to the skin.

1.3 Conclusion

According to Draize classification criteria NOA449280 SL (A16003E) is considered to be “not irritant” to rabbit skin (P.I.I. = 0).

2.0 INTRODUCTION

2.1 Purpose

The purpose of this primary skin irritation study was to assess the possible irritation potential when a single dose of NOA449280 SL (A16003E) was placed on the skin of rabbits for approximately four hours.

This study should provide a rational basis for hazard assessment in man as skin contact is one of the possible routes of human exposure.

The test item was administered at 0.5 mL/animal, the dose specified in the test guidelines for a liquid test item.

2.2 Guidelines

The study was done according to the following guidelines:

OECD Guidelines for Testing of Chemicals, Section 4, number 404 “Acute Dermal Irritation / Corrosion”, adopted April 24, 2002.

United States Environmental Protection Agency, Health Effects Division Test Guidelines, OPPTS 870.2500 Acute Dermal Irritation EPA 712-C-98-196, August 1998.

Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), B.4 ACUTE TOXICITY: DERMAL IRRITATION/CORROSION (Official Journal No L 142, 31/05/2008 p. 0182-0190.

Japanese MAFF Test Data for Registration of Agricultural Chemicals, Test Guidelines, Skin irritation studies, 12 NohSan No. 8147, Agricultural Production Bureau, November 24, 2000 [English translation by IAI:ACIS, revised on June 26, 2001 (13 Seisan No. 1739) and December 10, 2002 (14 Seisan No. 7269)].

2.3 Test facility

This study was performed in an AAALAC-accredited laboratory in accordance with the Swiss Animal Protection Law under license no. 56.

3.0 MATERIALS AND METHODS

3.1 Test substance

The following information was provided by the Sponsor:

Identification:	NOA449280 SL (A16003E)
Product Code:	A16003E
Description:	Liquid; brown
Batch Number:	J8308/145
Density:	1079 kg/m^3
Stability of Test Item:	Stable under specified storage conditions.
Reanalysis Date:	31 May 2011
Storage Conditions:	At a temperature < 30°C (room temperature, range of 20 ± 5 °C, provided by Harlan Laboratories), light protected.
Safety Precautions:	Routine hygienic procedures were used to ensure the health and safety of the personnel.

The Certificate of Analysis is shown in Appendix 1

3.2 Experimental design

0.5 mL (per animal) of NOA449280 SL (A16003E) was measured with a syringe and applied undiluted as it was delivered by the Sponsor.

The pH of the test item was measured before the study initiation date and was found to be 7.

According to Commission Directive 2004/73/EC, B.4. and OECD Guidelines 404, a test item needs not to be tested if the pH-value is less than 2 or greater than 11.5, owing to its predictable corrosive properties.

Four days before treatment, the left flank was clipped with an electric clipper, exposing an area of approximately 100 cm^2 (10 cm x 10 cm). The skin of the animals was examined one day before treatment and re-grown fur of all animals was clipped again.

No animal was noted with overt signs of skin injury or marked irritation that could interfere with the interpretation of the results.

On the day of treatment, 0.5 mL of NOA449280 SL (A16003E) was placed on a surgical gauze patch (ca. 2.5 cm x 2.5 cm). This gauze patch was applied to the intact skin of the clipped area. The patch was covered with a semi-occlusive dressing. The dressing was wrapped around the abdomen and anchored with surgical adhesive tape.

The duration of treatment was 4 hours. Then the dressing was removed and the skin was flushed with lukewarm tap water to clean the application site. Approximately 1 hour following the removal of the patches, and 24, 48 and 72 hours later, the test sites were examined for evidence of dermal irritation and evaluated according to the scoring system by Draize (1959).

As it was suspected that the test item might produce irritancy, a single animal (1 female) was treated first. As neither a corrosive effect nor a severe irritant effect was observed after the 4-hour exposure, the test was completed using the two remaining animals for an exposure period of 4 hours.

The viability/mortality was recorded daily from acclimatization of the animals to the termination of the test.

The clinical signs were recorded daily from acclimatization of the animals to the termination of test.

The body weights were recorded at start of acclimatization, on the day of application and at termination of observation.

3.2.1 Animals

Animal Species and Strain:	Young Adult New Zealand White Rabbit, SPF
Rationale:	Recognized by international guidelines as a recommended test system.
Breeder/Supplier:	Harlan Laboratories B.V. Kreuzelweg 53 NL-5961 NM Horst / The Netherlands Postbus 6174 NL-5960 AD Horst / The Netherlands
Number of Animals per Test:	3 (Animals of both sexes were used)
Age:	21 weeks (male) 15 - 16 weeks (females)

Identification:	By unique cage number and corresponding ear number.
Acclimatization:	Under laboratory conditions after health examination. Only animals without any visual signs of illness were used for the study.
Randomization:	Selected by hand at time of delivery. No computer generated randomization program.
Allocation:	Male No. 43 Female Nos. 44, 45

3.2.2 Husbandry

Room Number:	0501 / Harlan Laboratories Ltd, Füllinsdorf
Conditions:	**Standard Laboratory Conditions** Air-conditioned with ranges for room temperature 17-23 °C, relative humidity 30-70% and approximately 10-15 air changes per hour. Room temperature and humidity were monitored continuously and values outside of these ranges may have occasionally occurred, usually following room cleaning. These transient variations are considered not to have any influence on the study and, therefore, these data are not reported but are retained at Harlan Laboratories. The animals were provided with an automatically controlled light cycle of 12 hours light and 12 hours dark. Music was played during the daytime light period.
Accommodation:	Individually in stainless steel cages equipped with feed hoppers and drinking water bowls. Wood blocks (Harlan Laboratories Ltd, Füllinsdorf) and haysticks 4642 (batch no. 69/08, Provimi Kliba AG, 4303 Kaiseraugst / Switzerland) were provided for gnawing.
Diet:	Pelleted standard Provimi Kliba 3418 rabbit maintenance diet *ad libitum* (batch no. 82/08) provided by Provimi Kliba AG, 4303 Kaiseraugst / Switzerland. Results of analysis for contaminants are archived at Harlan Laboratories Ltd.
Water:	Community tap water from Füllinsdorf, *ad libitum*. Results of bacteriological, chemical and contaminant analyses are archived at Harlan Laboratories Ltd.

3.3 *Post mortem* investigations

All rabbits were killed by an intravenous injection of pentobarbitone into the ear vein at a dose of at least 1 mL/kg body weight (162 mg sodium pentobarbitone/kg body weight) and discarded. No necropsy was performed.

3.4 Data evaluation

The skin reaction was assessed according to the numerical scoring system listed in the Commission Regulation (EC) No 440/2008 of 30 May 2008 which was based on the Draize score system.

The skin reaction was assessed at approximately 1, 24, 48 and 72 hours after exposure (removal of the dressing, gauze patch and test item).

Data were summarized in tabular form, showing for each individual animal the irritation scores for erythema and oedema at all measurement intervals. Any lesions were described, including the degree and nature of irritation, corrosion or any other toxic effects observed, and their reversibility.

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 is positive when the mean score is 2 or greater. The test is positive for irritation when at least 2 animals are positive for the same endpoint (erythema/eschar or oedema).

The Cumulative Scores for the Skin Irritation Scores were calculated too 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 totaling the mean cumulative scores at 24, 48 and 72 hours and then dividing by the number of available figures.

The irritation was classified according to the following criteria:

P.I.I. = 0	Not Irritant
$0 < P.I.I. \leq 2$	Mild Irritant
$2 < P.I.I. \leq 5$	Moderate Irritant
$5 < P.I.I.$	Severe Irritant

Viability/mortality, clinical signs and dermal findings were recorded on data sheets and transcribed for compilation and analysis.

Body weights were recorded on-line.

No statistical analysis was performed.

The RCC Tox Computer System (RCC-Tox-Lims) has been validated with respect to data collection, storage and retrievability.

4.0 RESULTS AND DISCUSSION

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. The mean erythema as well as oedema scores of the three animals were 0.00 each.

Very slight erythema was noted in all three animals at the 1-hour observation. Thereafter, all animals were free of local findings from 24 to 72 hours, the end of observation time.

The test item caused no staining of the treated skin. No corrosive effects were noted on the treated skin of any animal at any of the measuring.

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

The male slightly lost body weight (-1.2%) during the acclimatisation period but recovered by the end of the study. Otherwise, the body weights of all rabbits were considered to be within the normal range of variability.

5.0 CONCLUSION

The application of NOA449280 SL (A16003E) to the intact skin resulted in mild signs of irritation in all three animals at the 1-hour observation. Thereafter, all animals were free of local findings from 24 to 72 hours.

According to Draize classification criteria NOA449280 SL (A16003E) is considered to be “not irritant” to rabbit skin (P.I.I. = 0).

6.0 REFERENCES

Literature references listed are available upon request.

External references

Draize, J.H. (1959): Dermal Toxicity. In Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, pp. 46-49. Austin, Texas: Association of Food and Drug Officials of the United States.

Draize, J.H., Woodward, G. & Calvery, H.O. (1944): Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exper. Therap. 83: 377-390.

TABLES SECTION

GLOSSARY FOR TABLE 1

Grading of Skin Reactions

ERYTHEMA AND ESCHAR FORMATION

No erythema	0
Very slight erythema	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beef redness) or eschar formation (injuries in depth preventing erythema) reading	4

OEDEMA FORMATION

No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well-defined by definite raising)	2
Moderate oedema (edges raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

Primary Irritation Index (P.I.I.)

The irritation was classified according to the following criteria:

P.I.I. = 0	Not Irritant
$0 < P.I.I. \leq 2$	Mild Irritant
$2 < P.I.I. \leq 5$	Moderate Irritant
$5 < P.I.I.$	Severe Irritant

TABLE 1 Skin Irritation Scores - Individual Values

Animal Number	Sex	Evaluation Interval*	Erythema	Oedema	Cumulative Score	Cumulative Mean
43	M		1	0	1.00	
44	F	**1 hour**	1	0	1.00	1.00
45	F		1	0	1.00	
43	M		0	0	0.00	
44	F	**24 hours**	0	0	0.00	0.00
45	F		0	0	0.00	
43	M		0	0	0.00	
44	F	**48 hours**	0	0	0.00	0.00
45	F		0	0	0.00	
43	M		0	0	0.00	
44	F	**72 hours**	0	0	0.00	0.00
45	F		0	0	0.00	

* Examinations were performed at the specified times after removal of the dressing.

TABLE 2 Skin Irritation Scores - Mean Values after 24, 48 and 72 Hours

Animal Number	Sex	Erythema	N	Oedema	N	Primary Skin Irritation Index
43	M	0.00	3	0.00	3	
44	F	0.00	3	0.00	3	**0.00**
45	F	0.00	3	0.00	3	
Mean score		0.00		0.00		

N=number of available data points

TABLE 3 Body Weights

Body weight in grams				
Animal No.	Sex	First Day of Acclimatization	Day of Treatment	Last Day of Observation
43	male	3092	3056	3244
44	female	2782	2897	2974
45	female	2623	2782	2925

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

GLP Testing Facility WMU
Analytical Development &
Product Chemistry GS2131

Syngenta Crop Protection Münchwilen AG
Breitenloh 5
CH-4333 Münchwilen

Certificate of Analysis

A16003E
NOA449280 SL (200)
J8308/145

Batch Identification	**J8308/145**
Product Code	**A16003E**
Other Product Code(s)	---

Chemical Analysis
(Active Ingredient Content)

– **Identity of the Active Ingredient(s)***	**confirmed**
– **Content of NOA449280***	**18.3 % w/w corresponding to 197 g/l**
Methodology used for Characterization	HPLC

The Active Ingredient(s) content is within the FAO limits.

Physical Analysis

– **Appearance**	**brown liquid**
– **Density ***	**1079 kg/m^3**

Stability:

– **Storage Temperature**	**< 30°C**
– **Reanalysis date**	**End of May 2011**

The stability of this test substance will be controlled by reanalysis of material held in the inventory at Syngenta Crop Protection Muenchwilen AG at the appropriate time.

This Certificate of Analysis summarizes data which originates either from a single study or from several individual studies. Tests marked with an asterisk (*) have been conducted in compliance with GLP. Raw data, documentation, study plans, any amendments to study plans and reports pertaining to this/these study/studies are stored under the study number(s) referenced below within the archives of the GLP Testing Facility WMU at Syngenta Crop Protection Muenchwilen AG.

Characterisation: 119332 Reanalysis:

Authorisation: Andrew McIntyre 14th January 2009

Dr. A. McIntyre
Analytical Development & Product Chemistry

APPENDIX 2 Individual Local Findings

Animal No. 43, Male

After 1 hour:	Erythema:	Very slight erythema
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT
After 24 hours:	Erythema:	NO ABNORMAL FINDINGS NOTED
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT
After 48 hours:	Erythema:	NO ABNORMAL FINDINGS NOTED
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT
After 72 hours:	Erythema:	NO ABNORMAL FINDINGS NOTED
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT

APPENDIX 2 Individual Local Findings (continued)

Animal No. 44, Female

After 1 hour:	Erythema:	Very slight erythema
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT
After 24 hours:	Erythema:	NO ABNORMAL FINDINGS NOTED
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT
After 48 hours:	Erythema:	NO ABNORMAL FINDINGS NOTED
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT
After 72 hours:	Erythema:	NO ABNORMAL FINDINGS NOTED
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT

APPENDIX 2 Individual Local Findings (continued)

Animal No. 45, Female

After 1 hour:	Erythema:	Very slight erythema
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT
After 24 hours:	Erythema:	NO ABNORMAL FINDINGS NOTED
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT
After 48 hours:	Erythema:	NO ABNORMAL FINDINGS NOTED
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT
After 72 hours:	Erythema:	NO ABNORMAL FINDINGS NOTED
	Oedema:	NO ABNORMAL FINDINGS NOTED
	Scaling:	NO ABNORMAL FINDINGS NOTED
	Staining:	NO STAINING PRESENT

APPENDIX 3 GLP-Certificate

The Swiss GLP Monitoring Authorities

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Federal Department of Home Affairs DHA
Federal Office of Public Health FOPH

Federal Department of the Environment, Transport, Energy and Communications DETEC
Federal Office for the Environment FOEN

swissmedic
Swiss Agency for Therapeutic Products

Statement of GLP Compliance

According to Article 14 paragraph 3 Ordinance on Good Laboratory Practice [OGLP, SR 813.112.1]

The notification authority for chemicals confirms that the following test facility was inspected with respect to the compliance with the Swiss Ordinance on Good Laboratory Practice, adopted on 18th May 2005 [OGLP, SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted on 26th November 1997 by decision of the OECD Council [C(97)186/Final].

Unequivocal name and address of the test facility:	Areas of expertise according to article 3 paragraph 1 letter d OGLP:
Harlan Laboratories Ltd. Zelgliweg 1 4452 Itingen, Switzerland.	1./ Physical-chemical testing, 2./ Toxicity studies, 4./ Environmental toxicity studies on aquatic and terrestrial organisms, 5./ Studies on behaviour in water, soil and air; bioaccumulation, 6./ Residue studies, 7./ Studies on effects on mesocosms and natural ecosystems, 8./ Analytical and clinical chemistry testing, 9./ Other studies (safety pharmacology and animal metabolism).

Inspection authority: Federal Office for the Environment (FOEN) / Federal Office of Public Health (FOPH) / Swiss Agency for Therapeutic Products (Swissmedic)

Date of inspection: 05th to 09th and 26th to 30th November 2007

Date of decision: 30th April 2008

Based on the above mentioned decision it can be confirmed that the above mentioned test facility is able to conduct studies according to the aforementioned areas of expertise in compliance with the principles of GLP. The above mentioned test facility is listed in the register and GLP list according to the Article 14 OGLP and is inspected on a regular basis according to Article 6 paragraph 2 OGLP.

Swiss Federal Office of Public Health
Consumer protection directorate
Notification authority for chemicals
CH-3003 Bern

FEDERAL OFFICE OF PUBLIC HEALTH

Bern, 12th November 2008, The Head, Dr. Dag Kappes.

The notification authority for chemicals is the coordination and decision authority for the good laboratory practice (GLP) for the FOEN, the FOPH and Swissmedic.

Swiss Federal Office of Public Health, Consumer protection directorate, Notification authority for chemicals, CH-3003 Bern.

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