TECAM
LABORATORIOS

CONFIDENTIAL

Final Report RL3393/2007 – 3.0MN-B
December 13th 2007

Study Number 3393/2007 – 3.0MN
Mammalian Erythrocyte Micronucleus Test for
GLIFOSATO TÉCNICO HELM

Reference Methodology
OECD Guideline for the Testing of Chemicals
Mammalian Erythrocyte Micronucleus Test 474 (1997)

Sponsor
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STUDY COMPLIANCE STATEMENT

The present study was conducted according to the OECD Principles on Good Laboratory Practice (OECD Environment Health and Safety Publications, as revised in 1997) and "Norma NIT-DICLA-028 (INMETRO, Sep/03, Rev.01)" under the supervision of the Study Director.

I declare that this report constitutes a true and faithful record of the procedures undertaken and the results obtained during the performance of the study.

[redacted] (MSc) 12/13/07

Study Director

[redacted]

KEY PERSONNEL

Name	Responsibility
[redacted] (MSc)	Study Director
[redacted] (PhD)	Test Unit Manager
[redacted]	Technical Staff
	Technical Staff
	Animal Care

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QUALITY ASSURANCE STATEMENT

The study plan, final report and original data from this study have been reviewed for adherence to the principles of the Good Laboratory Practice by the Quality Assurance Unit. The final report was considered to be a correct and faithful record of the raw data.

Proceedings of the present study were inspected by process-based inspection and the compliance with the Good Laboratory Practice was confirmed.

Dates of inspections and the dates on which the findings were reported to the Study Director and Test Facility Management are given below.

Phase of Study	Inspection	Reporting to Study Director and to Management
Experimental	Nov/28/2007	Nov/28/2007
Study plan	Oct/29/2007	Oct/29/2007
Raw data	Dec/10/2007	Dec/10/2007
Final report	Dec/10/2007	Dec/10/2007
	Dec/13/2007	Dec/13/2007

[redacted]

Dec/13/2007

Quality Assurance Unit

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RESUMO

O teste do micronúcleo foi realizado com o objetivo de avaliar o possível efeito mutagênico da substância-teste **GLIFOSATO TÉCNICO HELM** em células eucarióticas "in vivo". Três grupos de camundongos machos da linhagem Swiss receberam, por via oral, as doses da substância-teste correspondentes a 8 mg/kg peso corpóreo (pc); 15 mg/kg pc e 30 mg/kg pc. Dois grupos controle, negativo e positivo, receberam o veículo (água deionizada, 5 mL/kg pc) e ciclofosfamida (75 mg/kg pc), respectivamente. Preparações de medula óssea foram avaliadas em teste cego para a presença de micronúcleos, assim como para a relação entre eritrócitos policromáticos e normocromáticos. As lâminas foram decodificadas e o número total de células de cada grupo foi comparado utilizando-se o teste do χ^2. A comparação entre os grupos controle negativo e positivo demonstrou um aumento estatístico significativo do número de micronúcleos (χ^2=315,4; p<0,001). A diferença entre o número de micronúcleos dos grupos tratados e o controle negativo não foi estatisticamente significativa nas doses de 8 mg/kg pc (χ^2=2,14; p=0,144) e 15 mg/kg pc (χ^2=3,12; p=0,077). Na dose de 30 mg/kg pc (χ^2=5,44; p=0,020) foi observada diferença estatística considerada não relevante biologicamente. Nas condições de teste, a substância teste **GLIFOSATO TÉCNICO HELM** representada pela amostra de lote nº 2007091801 não apresentou efeito mutagênico.

ABSTRACT

The micronucleus test was performed to evaluate the mutagenic potential of **GLIFOSATO TÉCNICO HELM** in eucariotic cells "in vivo". Three groups of Swiss mice were treated by oral administration at 8 mg/kg bw; 15 mg/kg bw and 30 mg/kg bw. Two concurrent control groups, negative and positive received the vehicle (deionized water, 5 mL/kg bw) and cyclophosphamide (75 mg/kg bw), respectively. Bone marrow cells of the animals were blindly evaluated for the presence of micronuclei, as well as for the relation between polychromatic and normochromatic erythrocytes. Slides were decoded and the total number of cells of each group was compared using the chi-square test. Comparison between negative and positive controls demonstrated a significant increase in the micronucleus number (χ^2=315.4; p<0.001). The difference between the number of micronucleus in the groups treated with **GLIFOSATO TÉCNICO HELM** and the concurrent negative control was not statistically significant at 8 mg/kg bw (χ^2=2.12; p= 0.144) and 15 mg/kg bw (χ^2=3.12; p=0.077). At 30 mg/kg bw (χ^2=5.44; p=0.020) the statistically significance was not considered to be biologically relevant. Under the conditions of this study, **GLIFOSATO TÉCNICO HELM** (batch nº 2007091801) did not induce an increase of micronucleus number in mouse bone marrow erythrocytes.

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1. INTRODUCTION

The micronucleus assay evaluates the mutagenic effects on eucariotic cells by the ability of a specific test substance to induce structures called micronuclei in the polychromatic erythrocytes (PCE) of bone marrow of treated mice. It provides an indirect measure of the induction of structural or numerical chromosome aberrations after exposure of animals to the test substance.

2. MATERIALS AND METHODS

The present test was conducted according to methodology described by the "OECD Guideline for the Testing of Chemicals" (Mammalian Erythrocyte Micronucleus Test - 474, 1997).

2.1 Test substance information

Identification: GLIFOSATO TÉCNICO HELM.

Protocol: 3393/2007 – 3.0.

Received on: Oct/29/2007.

Manufactured on: Sep/17/2007.

Expiry date: Sep/17/2009.

Batch Nº: 2007091801.

Common name of a.i.: Glyphosate.

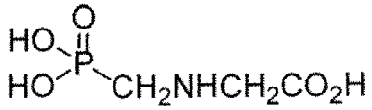
Declared concentration of a.i.: 950 g/kg.

Analysed concentration of a.i.[1]: 980.1 g/kg (Appendix 1).

Class: Herbicide.

IUPAC name: *N*-(phosphonomethyl)glycine.

Chemical and structural formula: $C_3H_8NO_5P$



CAS RN: [107-83-6].

Homogeneity: Homogeneous (visual inspection).

Stability (a.i.): Stable (CIPAC MT 46, 54°C, 14 days).

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Formulation: Technical grade.

Physical state: Solid.

[1]: Analysis performed at Tecam Tecnologia Ambiental.

2.2 Study dates

Initial date:	Oct/29/2007.
Tolerability test:	Nov/08/2007 to Nov/24/2007.
Acclimatization:	Nov/20/2007 to Nov/25/2007.
Experimental phase:	Nov/26/2007 to Nov/28/2007.
Slide analysis:	Dec/04/2007 to Dec/10/2007.

2.3 Test system

Animals:	Swiss mice.
Source:	Paulistec (Mairiporã – SP).
Age:	9-10 weeks.
Sex:	male.
Received:	Nov/14/2007 and Nov/19/2007.
Acclimatization:	Animals were acclimatized for 5 days prior to dosing in a controlled room; all the animals were inspected during this period; animals exhibiting abnormal signs during this period were not used for the study.
Housing:	Animals were housed using conventional polypropilene rodent cages (Beiramar, 30 x 20 x 13 cm) with six animals per cage.
Feeding:	Pelleted commercial diet for the species (Biobase Biotec) was provided *ad libitum* throughout acclimatization and test periods; feed is analysed by TECAM/SP periodically for microbiological contaminants. In view of the

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aim and duration of the study the contaminants occurring in commercial feed should not influence the results.

Drinking water: Filtered water was provided *ad libitum* throughout acclimatization and test periods. The drinking water is analysed by TECAM/SP periodically for chemical and microbiological contaminants. In view of the aim and duration of the study there are no special requirements exceeding the specification of drinking water.

Bedding: Aspen wooden chips previously irradiate and prepared by Biotécnicas were provided for the animals and were changed twice a week.

Identification: Cage cards displaying animal number, sex, born date, sample code, dose and study dates were fixed to each cage; animals were weighed and identified individually with tail marking.

2.4 Study conditions

Temperature and relative humidity were monitored three times a day. Values outside the range may have occasionally occurred, usually following room cleaning. These transient variations were considered not to have influence on the study and therefore were not reported, but retained at Tecam. Temperature ranged from 18 to 21°C and average humidity was 57%. Animals were provided with an automatically controlled light cycle of 12 hours light and 12hours dark. The environmental conditions in the animal room were controlled and recorded five days a week.

2.5 Tolerability test and dose selection

In tolerability test the doses were set considering two treatments (0 h e 24 h). employing a series of fixed dose levels selected on a log basis to define a maximum tolerated dose (MTD) according to Mackay & Elliott (1992).

5 **8** 12.5 20 30 **50** 80 125 200 **320** 500 800 1250 **2000** mg/kg bw

As indicated in Table 1, two male animals were dosed at the core dose levels (in bold and underlined), starting at 2000 mg/kg bw employing deionized water as a vehicle. Two dosed animals showed prostration, ataxia and deaths were observed on day 3. Additionaly 3 animals were dosed at 320 mg/kg bw. Prostration and ataxia were observed in all animals on day 1 and deaths were observed in all animals on day 2. Three animals were dosed at 50 mg/kg bw and one death was observed on day 1. Additionaly 3 groups of 3 male animals were dosed at the 3 intermediate dose levels below that core dose level (30 mg/kg bw, 20 mg/kg bw and 12.5 mg/kg bw). No mortality was observed in this intermediate dose levels. The highest dose level which did not produce severe toxicity or lethality was 30 mg/kg bw. Thefore it was selected as the MTD. Other doses employed at the main test were 15 mg/kg bw and 8 mg/kg bw.

2.6 Route of administration

The route of administration was oral gavage. Individual body weights were measured prior to dosing and test volume was adjusted to ensure a constant volume of administration in all test groups.

2.7 Prepare of test solutions

Deionized water was used as the negative control and as the vehicle for the test substance and the positive control.

2.8 Treatment schedule

Animals were treated twice at 0 and 24 h (two treatments at 24 hours interval) and sampled approximately 24 hours following the final treatment. Only males were

employed since no information showing significative differences between male and female sensitivity and/or toxicity was available for the test substance. Extensive studies of the activity of known clastogens in mouse bone marrow micronucleus test have shown that in general male mice are more sensitive than female mice for micronucleus induction. Where differences were seen they were only quantitative and not qualitative (Collaborative Study Group for the Micronucleus Test, 1986; Muller et al., 1999).

Concurrent vehicle and positive controls were included employing the same treatment schedule of the test substance. Except for the treatment with the test substance, animals in the control groups were handled in an identical manner to animals of the treatment group. According to the recommendations of the "Gene Tox Program of the United States Environmental Protection Agency" (Mavournin et al., 1990) at least 6 animals should be analysed per group. Animals were identified by numbers at random and were divided into the following groups:

Dose group	Dose level (mg/kg bw)[1]	Concentration (mg/mL)	Tested animals	Analysed animals
Vehicle control (deionized water)	-	-	6	6
Positive control (cyclophosphamide[2])	75	15	6	6
GLIFOSATO TÉCNICO HELM	8	1.6	6	6
GLIFOSATO TÉCNICO HELM	15	3	6	6
GLIFOSATO TÉCNICO HELM	30	6	6	6

[1] Dose volume: 5 mL/kg bw for all groups; [2]Genuxal®

2.9 Slide preparation and analysis

Immediately following sacrifice (approximately 24 hours after the final treatment), both femur were dissected from each animal and aspirated with foetal calf serum. Bone marrow smears were prepared after centrifugation and re-suspension. Slides were air

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dried, fixed and stained in Wright-Giemsa and coded with the same numbers used for animal identification. Slides were blind evaluated using an optical microscope. The polychromatic erythrocyte (PCE) and normochromatic erythrocyte (NCE) ratio was established for each animal by scoring a total of 2000 erytrocytes (PCE+NCE). For each animal the number of micronucleated polychromatic erythrocytes (MNPCE) was counted in 3000 PCE.

2.10 Data analysis

A modified chi-square test according to Pereira (1991) was employed for analysis of the results. Positive and negative controls were compared to ensure that the assay was performed according to the prescribed standards. The biological relevance of the results was considered together with the statistical significance to evaluate the effects. A test substance is considered to be active in the test system if there is a clear dose-related increase in the micronuclei frequency and a statistically significant increase (5 %) in micronuclei frequency compared to negative control at any tested dose. Historical negative control data from our laboratory may also be employed for comparison between groups. Equivocal responses are repeated or confirmed in an optimized test condition, always including a three-dose protocol.

2.11 Acceptance criteria

The quality of the slides should allow a clear differentiation between PCE and NCE. The result obtained in the positive control has to be significantly increased when compared to negative control.

2.12 Archives

All documents related to this study (raw data, study plan and copy of the final report) will be properly stored for at least 10 years at the laboratory address: R. Fábia, 59 - 05051-030- S. Paulo – SP, Brazil. A sample of the test substance will be retained for 2 years. All the original raw data and records of this study are the property of the Sponsor and will not be discarded without the Sponsor's consent.

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3. RESULTS

Six animals were analysed in the experimental and control groups. A total of 18000 cells were analysed per group (Tables 2 to 6). The quality of the slides allowed a clear differentiation between PCE and NCE. Analysis of the cells showed an approximate 1:1 PCE/NCE rate indicating that there was not a very highly toxic effect of the test substance in the bone marrow of treated animals.

A modified chi-square test according to Pereira (1991) was employed for comparison between positive and negative controls, as well as the negative control and experimental groups. Comparison between negative and positive controls demonstrated a significant increase in the micronucleus number (χ^2=315.4; p<0.001) as shown in Table 7. The positive control group treated with cyclophosphamide induced a highly significant increase in the frequency of micronuclei indicating sensitivity of the test system. In the vehicle control group the results were consistent to the historical data.

When animals treated with **GLIFOSATO TÉCNICO HELM** were compared to the concurrent negative control group, no statistically significant increase in the number of micronuclei was observed at 8 mg/kg bw (χ^2=2.14; p=0.144); 15 mg/kg bw (χ^2= 3.12; p=0.077) as shown in Table 8. While 11 micronuclei were observed in the 18000 PCE of the negative control group, 19 micronuclei were analysed in the 18000 PCE of the group treated at 8 mg/kg bw and 21 micronuclei were analysed in the 18000 PCE of the group treated at 15 mg/kg bw. At 30 mg/kg bw statistical significant results were obtained (χ^2=5.44; p=0.020) as show in Table 8. Although statistically significant when compared to the concurrent negative control group, this result has no biological relevance when compared to historical control and published data.

Historical data from our laboratory presents a mean frequency for over 5 years of approximately 1 MNPCE/1,000. Published negative control data from 581 papers on micronucleated bone marrow polychromatic erythrocytes (MNPCE) found an overall mean frequency between 1.88 MNPCE/1,000 and 1.95 MNPCE/1,000 PCE (Salamone & Mavorunin, 1994). This 1994 compilation suggests that the historical negative control frequency for a mouse stock should fall between 1 and approximately 3.4 MNPCE/1,000 to accommodate all commonly used strains. Therefore, the frequency of

micronuclei observed at 30 mg/kg bw of 1.39 MNPCE/1000 was considered to be within the historical control and published data. Furthermore the active ingredient of the present test substance (glyphosate) is reported in the literature to be not mutagenic (Tomlin, 2006).

4. CONCLUSION

Under the condition of the test, **GLIFOSATO TÉCNICO HELM** (batch nº 2007091801) did not induce damage to the chromosomes or the mitotic apparatus of mice bone marrow after two oral administration with a 24 hours interval at dose levels of at 8 mg/kg; 15 mg/kg and 30 mg/kg body weight (bw).

5. REFERENCES

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Tomlin, C.D.S (ed.) **The e-Pesticide Manual: a World Compendium**. 14 ed. British Crop Protection Council, 2006.

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Table 1 – Mouse acute toxicity test (tolerability test).

DOSE (mg/kg bw)	NUMBER ANIMALS	NUMBER DEATHS	MORTALITY (%)
2000	2	2	100
320	3	3	100
50	3	1	33.33
30	3	0	0
20	3	0	0
12.5	3	0	0

Table 2 – Negative control group (deionized water, 5 mL/kg bw).

ANIMAL	CODE	PCE	NCE	PCE/NCE	PCE	MNPCE	% MN
1	8964	986	1014	0.97	3000	1	0.03
2	8966	1004	996	1.01	3000	2	0.07
3	9097	994	1006	0.99	3000	3	0.10
4	9168	950	1050	0.90	3000	1	0.03
5	9329	987	1013	0.97	3000	2	0.07
6	9395	1019	981	1.04	3000	2	0.07
TOTAL	-	**5940**	**6060**	**0.98**	**18000**	**11**	**0.06**

PCE : Polychromatic erythrocyte
NCE : Normochromatic erythrocyte
MN : Micronuclei

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Table 3 – Positive control group (cyclophosphamide, 75 mg/kg bw).

ANIMAL	CODE	PCE	NCE	PCE/NCE	PCE	MNPCE	% MN
1	9264	744	1256	0.59	3000	52	1.73
2	9285	745	1255	0.59	3000	56	1.87
3	9296	810	1190	0.68	3000	59	1.97
4	9301	853	1147	0.74	3000	44	1.47
5	9339	862	1138	0.76	3000	68	2.27
6	9343	712	1288	0.55	3000	68	2.27
TOTAL	**-**	**4726**	**7274**	**0.65**	**18000**	**347**	**1.93**

PCE : Polychromatic erythrocyte
NCE : Normochromatic erythrocyte
MN : Micronuclei

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Table 4 - Treated group (**GLIFOSATO TÉCNICO HELM**, 8 mg/kg bw).

ANIMAL	CODE	PCE	NCE	PCE/NCE	PCE	MNPCE	% MN
1	9266	982	1018	0.96	3000	4	0.13
2	9388	988	1012	0.98	3000	3	0.10
3	9393	961	1039	0.92	3000	3	0.10
4	9441	977	1023	0.96	3000	3	0.10
5	9485	953	1047	0.91	3000	3	0.10
6	9527	985	1015	0.97	3000	3	0.10
TOTAL	**-**	**5846**	**6154**	**0.95**	**18000**	**19**	**0.11**

PCE : Polychromatic erythrocyte
NCE : Normochromatic erythrocyte
MN : Micronuclei

Table 5 - Treated group (**GLIFOSATO TÉCNICO HELM**, 15 mg/kg bw).

ANIMAL	CODE	PCE	NCE	PCE/NCE	PCE	MNPCE	% MN
1	9190	878	1122	0.78	3000	5	0.17
2	9454	966	1034	0.93	3000	2	0.07
3	9463	968	1032	0.94	3000	4	0.13
4	9492	945	1055	0.90	3000	3	0.10
5	9508	948	1052	0.90	3000	3	0.10
6	9536	936	1064	0.88	3000	4	0.13
TOTAL	**-**	**5641**	**6359**	**0.89**	**18000**	**21**	**0.12**

PCE : Polychromatic erythrocyte
NCE : Normochromatic erythrocyte
MN : Micronuclei

Table 6 - Treated group (**GLIFOSATO TÉCNICO HELM**, 30 mg/kg bw).

ANIMAL	CODE	PCE	NCE	PCE/NCE	PCE	MNPCE	% MN
1	9258	969	1031	0.94	3000	4	0.13
2	9267	959	1041	0.92	3000	3	0.10
3	9345	978	1022	0.96	3000	3	0.10
4	9379	1038	962	1.08	3000	4	0.13
5	9412	975	1025	0.95	3000	5	0.17
6	9516	982	1018	0.96	3000	6	0.20
TOTAL	**-**	**5901**	**6099**	**0.97**	**18000**	**25**	**0.14**

PCE : Polychromatic erythrocyte
NCE : Normochromatic erythrocyte
MN : Micronuclei

Table 7 – Frequency of micronucleated polychromatic erythrocytes (MNPCE): comparison between negative and positive control groups by means of a chi-square (χ^2) calculation.

GROUPS	N° PCE	N° MNPCE observed	N° MNPCE expected	$\frac{(obs - exp)^2}{exp}$
Negative	18000	11	179.0	157.7
Positive	18000	347	179.0	157.7
TOTAL	**36000**	**358**	**358.0**	**315.4***

* χ^2 ; $p < 0.001$

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Table 8 – Frequency of micronucleated polychromatic erythrocytes (MNPCE): comparison between negative control and treated groups that received **GLIFOSATO TÉCNICO HELM** by means of a chi-square (χ^2) calculation.

GROUPS	Nº PCE	Nº MNPCE observed	Nº MNPCE expected	$\frac{(obs - exp)^2}{exp}$
Negative	18000	11	15.0	1.07
[1]Dose 8 mg/kg bw	18000	19	15.0	1.07
TOTAL	**36000**	**30**	**30.0**	**2.14***
Negative	18000	11	16.0	1.56
[2]Dose 15 mg/kg bw	18000	21	16.0	1.56
TOTAL	**36000**	**32**	**32.0**	**3.12***
Negative	18000	11	18.0	2.72
[3]Dose 30 mg/kg bw	18000	25	18.0	2.72
TOTAL	**36000**	**36**	**36.0**	**5.44***

* χ^2 ; [1]p=0.144; [2]p=0.077; [3]p=0.020

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APPENDIX 1

REPORT OF ANALYSIS PROTOCOL Nº.: 3393/2007 – 1.0

Sponsor: HELM DO BRASIL MERCANTIL LTDA

Adress: Rua Alexandre Dumas, 2220 – 4º Andar – 04717-004, São Paulo - SP.

1. TEST SUBSTANCE INFORMATION

Identification: GLIFOSATO TÉCNICO HELM.

Protocol: 3393/2007 – 1.0.

Batch Nº: 2007091801.

Manufactured on: 09/17/2007.

Expiry date: 09/17/2009.

Common name of a.i.: Glyphosate.

IUPAC name: *N*-(phosphonomethyl)glycine.

2. EXPERIMENTAL

Equipment: High Liquid Performance Chromatograph 1200 Series (HPLC) AGILENT TECHNOLOGIES – TECAM 83 0 EQ.

3. DATES

Initial date: 12/07/2007.

Final date: 12/12/2007.

4. RESULTS

Protocol Nº.	Result
3393/2007 – 1.0	960 1 g/kg

5. METODOLOGY

Analytical method: TECAM: POP Nº022/07 Rev. 01 – Teor de Glifosato

6. SIGNATURES

[redacted] 12/13/07 (mm dd yy)

Study Director

[redacted] 12/13/07 (mm dd yy)

Quality Assurance

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APPENDIX 2

The Swiss GLP Monitoring Authorities

Swiss Federal Office of Public Health | Swiss Agency for the Environment, Forests and Landscape | swissmedic Swissmedic Swiss Agency for Therapeutic Products

Statement of GLP Compliance

It is hereby confirmed that

during the period of August 29 - 31, 2005

the following Test Facility of **TECAM**
Tecnologia Ambiental Ltda
05051-030 São Paulo
Brazil

was inspected by the Federal Office of Public Health with respect to the compliance with the Swiss legislation on Good Laboratory Practice.

Test Facility	Areas of expertise
TECAM - Tecnologia Ambiental São Roque Ltda.	- Toxicity studies - Mutagenicity studies

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

Swiss Federal Office of Public Health
Consumer Protection Directorate
Notification Authority
The Head

Berne, December 2005

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