Study 6

Acute Oral Toxicity Study in Rats, March 26, 1998

"ACUTE ORAL TOXICITY STUDY IN RATS"

EXP. No

Issued on March 26, 1998

SPONSOR

PERFORMING LABORATORY

177

TITLE OF THE STUDY

"Acute oral toxicity study in rats treated with the test article [redacted]

PURPOSE OF THE STUDY

The purpose of the study was to evaluate the oral acute toxicity of the test article [redacted]

178

[redacted]

[redacted] Exp. No. [redacted]

INDEX

FOREWORD 4

QUALITY ASSURANCE STATEMENT 5

RBM MANAGEMENT DECLARATION OF GLP COMPLIANCE 6

SCIENTISTS INVOLVED IN THE STUDY 7

MATERIALS AND METHODS 8

RESULTS 14

SUMMARY AND CONCLUSIONS 17

GROUP DATA 19

- TABLE 1. - Mortality and LD50 calculation 20
- TABLE 2. - Clinical signs (maximum daily frequency) 21
- TABLE 3. - Gross pathology examination 23

APPENDICES 26

- APPENDIX 1. - Clinical signs incidence 27
- APPENDIX 2. - Body weight 30
- APPENDIX 3. - Gross pathology examination 33

This report consists of 36 pages.

Ivrea, March 26, 1998

[redacted]

[redacted] Study Director

179

FOREWORD

On behalf of [redacted], authorized by the [redacted] Health Authorities (1-2) to conduct safety studies, has performed an acute toxicity study by oral route in Sprague Dawley Crl: CD(SD) BR rat ([redacted] - Experiment No. [redacted]), with the test article:

[redacted]

A sample of the substance used, along with pertinent documentation, is held in sufficient quantity in the [redacted] archives and is at the disposal of the Ministero della Sanità.

The undersigned declare that the experiment was conducted using the same batch of substance as that of the sample held on file.

For verification by the Ministero della Sanità, the undersigned moreover guarantee the identification and classification of all those materials, documents and recordings used in conducting the experiment, held on file for a period of at least 10 years from the date of this report. Following this time, they will be placed at the disposal of the Sponsor.

Dr. [redacted]

Scientific Director Recognized by the [redacted] Health Authorities as Responsible for General Toxicology Experimentation

Dr. [redacted]

General Manager of the [redacted]

Ivrea, March 26, 1998

(1): **Pharmaceuticals:**
Authorization dated March 12, 1976 in accordance with "Circolare 73", May 16, 1974

(2): **Chemicals:**
Authorization in accordance with DPR 927/81 (D.M. dated January 7, 1988 published in G.U. No. 12, dated January 16, 1988).

180

[redacted]

[redacted] Exp. No. [redacted]

QUALITY ASSURANCE STATEMENT

[redacted] Experiment number: [redacted]

Study title:

"Acute oral toxicity study in rats treated with the test article [redacted].

Studies of the type described in this report are conducted in a manner which involves frequent repetition of identical or similar procedures.

In compliance with the Principles of Good Laboratory Practice, at the time of this study, procedure-based inspections were made by the Q.A.U. of critical phases and procedures relevant to this type of study. For the inspection of any given procedure, studies were selected at random. All such inspections were reported promptly to the study director and to facility management.

This study was inspected on:

Dates of inspection/audit	Dates of report to Study Director and Management
January 12, 1998 March 26, 1998	January 13, 1998 March 26, 1998

This report has been audited by the Q.A.U. and was found to be an accurate description of such methods and procedures as were used during the conduct of the study and an accurate reflection of the raw data.

Date of final report audit: March 31, 1998

Date : March 31, 1998

[redacted]

Head of Quality Assurance Unit

181

[redacted]

[redacted] Exp. No. [redacted]

[redacted] MANAGEMENT DECLARATION OF GLP COMPLIANCE

Study No. [redacted] entitled :

"Acute oral toxicity study in rats treated with the test article [redacted]

was performed in compliance with the OECD-GLP in the testing of chemicals, [C(81) 30 (final)], regulations also enforced by the [redacted] Health Authority [D.M. dated June 26, 1986 as published in G.U. No. 198, dated August 27, 1986 and D.L. January 27, 1992, No. 120 as published in G.U. (Supplement) No. 40, February 18, 1992].

[redacted]

[redacted] Study Director

Dr. [redacted]

General Manager of the [redacted]

Ivrea, March 31, 98

182

SCIENTISTS INVOLVED IN THE STUDY

STUDY No. [redacted]

"Acute oral toxicity study in rats treated with the test article [redacted]

[redacted] Study Director	Dr. [redacted]
Scientific Director Toxicology	Dr. [redacted]
Head of General Toxicology I Unit	Dr. [redacted]
Centralized Pharmacy Head	Dr. [redacted]
Pharmacy Service Head	Dr. [redacted]

183

MATERIALS AND METHODS

EXPERIMENTAL DESIGN

[redacted] Experiment No.: [redacted]

Test article: [redacted]

Administration route: oral (by gavage)

Duration of treatment period: single administration

Duration of post-treatment observation period: 14 days

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.1) and with Organization for Economic Cooperation and Development Guidelines (section 4, subpart 401, Paris 1981 and subsequent revisions).

TEST SYSTEM

Species, strain and substrain: Sprague Dawley Crl: CD (SD) BR rat

Justification for selection of the test system : the Sprague Dawley rat was chosen as rodent species since it is an appropriate experimental model widely accepted by Health Authorities, with documented susceptibility to a wide range of toxic substances

Number and sex of animals: 5 males /dose at the doses of 82,102 and 128 mg/kg
5 females at the dose of 82 mg/kg

185

Supplier:	[redacted] Shipping slips No.s 0014 (January 2, 1998), 597 (January 23, 1998) and 793 (January 30, 1998).
Body weight (at randomization)	Males: 230 - 348 g Females: 197 - 214 g The weight variation of the animals used for the study did not exceed ± 20% of the mean body weight for each sex.
Age (at randomization)	males and females <3 months
Acclimatization:	at least 5 days before the start of the test. Animals were observed daily to ascertain their fitness for the study.
Housing:	5 animals/sex/cage in air-conditioned room. - Temperature: 22°C ± 2 - Relative humidity: 55% ± 10 - Air changes: about 20 / hour filtered on HEPA 99.97% - Light: 12 hour cycle (7 a.m. - 7 p.m.) - Cage size: grill cages 40.5x38.5x18h cm with stainless steel feeder. The waste that dropped through the grill bottom onto removable paper was periodically disposed of.
Animal identification:	by appropriately coloring different areas of the limbs. Cage card gave experiment number, dosage group, sex and date of administration.
Diet:	GLP 4RF21 top certificate pelleted diet produced by [redacted] feed licencee [redacted] The declared contents, on the label, on dry matter basis (moisture 12%), were:

crude protein	18.50%
crude fat	3.00%
crude fiber	6.00%
crude ash	7.00%

186

The diet was supplemented by the Producer with vitamins and trace elements. The Producer supplies a certificate of analysis for nutrients and contaminants, the levels of which are within the limits proposed by EPA-TSCA (44FR:44053-44093, July 26, 1979).
[redacted] has the animal feed re-analyzed at least twice a year for bacterial contamination.
The diet was available "ad libitum" to the animals.

Water: from the municipal water main system.
Water is filtered and distributed "ad libitum" to the animals by an automatic valve system.
Periodically drinking water is analyzed for microbial count, heavy metals, other contaminants (e.g. solvents, pesticides) and other chemical and physicals characteristics. The accepted limits of quality of the drinking water were those defined in EEC directive 80/778

Contaminants that might interfere with the objectives of the study were not expected to be present in diet or drinking water.

TEST ARTICLE CHARACTERIZATION

Identification:	[redacted]
Batch:	[redacted]
Characteristics:	white solid
Manufacturing date:	October 14, 1997
Expiry date:	December, 2000
Storage conditions:	at room temperature

VEHICLE CHARACTERIZATION

Deionized water

TEST ARTICLE FORMULATE PREPARATION

When necessary, an exact amount of test article was weighed in a suitable graduated container and was made up to final volume with vehicle to obtain the concentration required.

Formulates were given to rats within two hours of the preparation.

TEST DESCRIPTION

Administration route: oral (by gavage)

Reason for selection of administration route: possible ingestion by humans

Experimental design:

Dose* mg/kg	Treated animals	Treatment date	Final killing
128	5 males	February 3, 1998	Found dead
102	5 males	February 27, 1998	March 13, 1998
82	5 males	February 17, 1998	March 3, 1998
82	5 females	March 4, 1998	March 18, 1998

* The dose levels were defined on the basis of a preliminary study.

Administration method: The volumes to be administered were 10 ml/kg on the basis of body weight taken just before treatment. The administration was done by gavage to rats which had been fasted about 16 hours. Feed was returned to the rats about three hours after the test article administration.

Observation period: 14 days after administration

Observation of clinical signs and mortality: at 30 minutes, 2, 4 and 6 hours on the first day after the administration (day 1) and then twice a day up to termination of the observation period

Body weight: twice pre-trial (at randomization and on day 1 just before administration) and on days 3, 8 and 14. On day 1 the animals were weighed after a 16-hour fasting period.

Gross pathology:	on all animals which died during the observation period and on animals killed (fasted overnight) by excision of the femoral arteries, after i.p. overdosage anesthesia with 5% sodium pentobarbital, at the end of the observation period
Histology:	portions of any abnormal entities found in any of the necropsied animals were collected. The tissue samples were fixed and preserved in 10% buffered formalin. Histologic examination was not performed.
LD_{50} and its statistical limits:	LD_{50} was calculated by the method of the Probit (Bliss - Finney) - A.P. Rosiello et al., J. Tox. and Env. Health, 3: 797-809, 1977.

RECORD FILING

The protocol, a reserve sample of the batch of the test article used, the raw data bound in a register numbered [redacted], the specimens, the final report and all other documents pertinent to the conduct of this study, including records and reports of maintenance, cleaning, calibration and inspection of equipment, analysis of diet and water are filed at [redacted] premises for ten years from the issue date of this report and then sent to the Sponsor.

PROCEDURAL DETAILS

The study was conducted in accordance with the procedures described in the [redacted] Standard Operating Procedures (SOP's) collection.

Protection of animals used in the experiment is in accordance with Directive 86/609/EEC, enforced by the [redacted]. L. No. 116 of January 27, 1992.

Physical facilities and equipment for accommodation and care of animals are in accordance with the provisions of EEC Council Directive 86/609.

The Institute is fully authorized by Competent Veterinary Health Authorities.

RESULTS

190

CLINICAL OBSERVATIONS

MORTALITY *(TABLE 1)*

The mortality which occurred at the various doses is given below:

Dose (mg/kg)	82	102	128
Treated animals	5M+5F	5M	5M
Mortality Total (%)	0 0%	2M 40%	5M 100%

The deaths occurred within 13 days of dosing, with the first case observed on day 6 after administration in the 128 mg/kg group.

The LD_{50} was calculated to be 99.5 mg/kg with 95% confidence limits of 92.1 - 108 mg/kg.

CLINICAL SIGNS *(TABLE 2 AND APPENDIX 1)*

The main clinical changes induced by administration of the test article were piloerection and hunched posture, starting days 6-9 after dosing in males of all dose groups. In the highest dose dose group (128 mg/kg), these changes were accompanied by sedation or hypoavtivity.

Recovery was achieved at the end of the observation period in the surviving animals.

No changes of note were seen in females given the lowest dose (82 mg/kg).

BODY WEIGHT *(APPENDIX 2)*

Decrease in body weight or retarted growth was found in animals of the various dose groups mainly during the first week of the observation period.

POST-MORTEM EXAMINATION

GROSS PATHOLOGY *(TABLE 3 AND APPENDIX 3)*

At the necropsy of animals which died before the end of the observation period, the main macroscopic findings were marked or moderate liver paleness and decreased size of spleen. Moreover, kidney medulla congestion was seen in one rat.

No appreciable findings were detected at the gross examination in animals which were sacrificed at the end of the observation period.

SUMMARY AND CONCLUSIONS

Experimental data from a toxicity study in which Sprague Dawley Crl:CD(SD) BR rats were treated by oral route with the test article [redacted] are given in this report.

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.1) and with Organization for Economic Cooperation and Development Guideline (section 4, subpart 401, Paris 1981 and subsequent revisions).

The test article was administered as a solution in deionized water at the doses of 82, 102 and 128 mg/kg to groups of 5 males/dose and at the dose of 82 mg/kg also to 5 females for confirmation in the other sex . The volume of administration was 10 ml/kg.

All rats were treated after a 16-hour fasting period. The day of treatment was considered day 1 of the study. The animals were weighed twice before treatment (at randomization and on day 1 just before treatment) and on days 3, 8 and 14. They were clinically observed for 14 days following the treatment. Macroscopic examination was performed on all animals which died before the end of the study. On day 15 the surviving rats were killed (fasted overnight) by excision of the femoral arteries after i.p. overdosage anesthesia with 5% sodium pentobarbital and were subjected to a thorough autopsy.

The mortality which occurred at the various doses is given below:

Dose (mg/kg)	82	102	128
Treated animals	5M+5F	5M	5M
Mortality Total (%)	0 0%	2M 40%	5M 100%

The deaths occurred within 13 days of dosing, with the first case observed on day 6 after administration in the 128 mg/kg group.

The LD_{50} was calculated to be 99.5 mg/kg with 95% confidence limits of 92.1 - 108 mg/kg.

The main clinical changes induced by administration of the test article were piloerection and hunched posture, starting days 6-9 after dosing in males of all dose groups. In the highest dose dose group (128 mg/kg), these changes were accompanied by sedation or hypoavtivity.

Recovery was achieved at the end of the observation period in the surviving animals.

No changes of note were seen in females given the lowest dose (82 mg/kg).

Depression in body weight growth was found in animals of the various dose groups mainly during the first week of the observation period.

At the necropsy of animals which died before the end of the observation period, the main macroscopic findings were marked or moderate liver paleness and decreased size of spleen.

No appreciable findings were detected at the gross examination in animals which were sacrificed at the end of the observation period.

In conclusion, the **LD_{50}** of the test article [redacted] when administered to rats as a single dose by oral route, was **99.5 mg/kg (95% confidence limits: 92.1-108 mg/kg)**. The compound induced delayed toxicity (liver was mainly involved) in animals given the higher doses.

Dr. [redacted]
[redacted] Study Director

March 26, 1998

Dr. [redacted]
Scientific Director Recognized by the [redacted] Health Authorities as Responsible for General Toxicology Experimentation

194

GROUP DATA

195

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

TABLE 1. - Mortality and LD50 calculation (p. 1)

Males - Females

Dose (mg/kg)		82	102	128
Treated animals		10	5	5
Day	6	0	0	1
	7	0	0	2
	8	0	0	2
	11	0	1	0
	13	0	1	0
Total no.	(day 14)	0	2	5
Total (%)		.0%	40.0%	100.0%

Median lethal dose (LD50)	=	99.54		
95% confidence limits	=	92.08	-	107.59
Slope (SE)	=	7.67		1.68
Heterogeneity	p =	.348 NS		
Linear regression	y =-30.2867+7.6702x			

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

TABLE 2. - Clinical signs (maximum daily frequency) (p. 1)
(no. of animals affected, from-to)

	Males		
Dose (mg/kg)	82	102	128
no. of treated animals	5	5	5
Death	-	2 11d-13d	5 6d- 8d
Sedation	-	-	1 7d- 7d
Hypoactivity	-	-	1 7d- 7d
Piloerection	3 9d-12d	3 9d-12d	4 6d- 7d
Hunched posture	3 9d- 9d	3 8d-12d	3 6d- 7d
Recovery	5 13d	3 13d	-

- (not observed) from-to (first-last observation in one or more animals)
Time : d (days)

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

TABLE 2. - Clinical signs (maximum daily frequency) (p. 2)
(no. of animals affected, from-to)

	Females
Dose (mg/kg)	82
no. of treated animals	5
No clinical signs	5 30m-14d

from-to (first-last observation in one or more animals)
Time : m (minutes) d (days)

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

TABLE 3. - Gross pathology examination (p. 1)
(no. of cases, mean severity, %)

Dead or agonal sacrificed an.	Males		
Dose (mg/kg)	82	102	128
no. of animals	0	2	5
no. of animals without appreciable lesions	0	0	0
General observation			
cannibalized	-	1 50.00%	0
Kidneys			
medulla, congestion	-	0	1(2.0) 20.00%
Liver			
pale	-	1(2.0) 50.00%	5(3.0) 100.00%
Spleen			
decreased size	-	1(2.0) 50.00%	4(2.0) 80.00%

- (not examined)
Severity : 0(very slight) 1(slight) 2(moderate) 3(severe)

199

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

TABLE 3. - Gross pathology examination (p. 2)
(no. of cases, mean severity, %)

Final killing

	Males		
Dose (mg/kg)	82	102	128
no. of animals	5	3	0
no. of animals without appreciable lesions	5	3	0

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

TABLE 3. - Gross pathology examination (p. 3)
(no. of cases, mean severity, %)

Final killing	Females
Dose (mg/kg)	82
no. of animals	5
no. of animals without appreciable lesions	5

100

[redacted]

APPENDICES

202

[redacted] Exp. No. [redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 1. - Clinical signs incidence (p. 1)
(no. of animals affected)

Dose (mg/kg) 82

Cage # 7M	Day 1				2		3		4		5		6		7		8		9		10		11		12		13		14	
Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
No clinical signs	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	2	2	2	2	2	2	4	4	5	5	5	5
Piloerection																			2	2	3	3	3	3	1	1				
Hunched posture																			3	3										

Cage # 8F	Day 1				2		3		4		5		6		7		8		9		10		11		12		13		14	
Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
No clinical signs	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Time: m (minutes) h (hours) M (morning) A (afternoon)

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 1. - Clinical signs incidence (p. 2)
(no. of animals affected)

Dose (mg/kg) 102

Cage # 9M	Day	1				2		3		4		5		6		7		8		9		10		11		12		13		14	
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
Death																								1				1			
No clinical signs		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	2	2	2	2	2	2	3	3	3	3	3	3	3	3
Piloerection																				3	3	3	3	1	1	1	1				
Hunched posture																		3	3	3	3	3	3	1	1	1	1				

Time: m (minutes) h (hours) M (morning) A (afternoon)

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 1. - Clinical signs incidence (p. 3)
(no. of animals affected)

Dose (mg/kg) 128

Cage # 5M	Day	1				2		3		4		5		6		7		8
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M
Death														1		2		2
No clinical signs		5	5	5	5	5	5	5	5	5	5	5	5					
Sedation																1	1	
Hypoactivity																1	1	
Piloerection														4	4	2	2	
Hunched posture														3	3	2	2	

Time: m (minutes) h (hours) M (morning) A (afternoon)

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 2. - Body weight (g) (p. 1)
(individual)

Dose (mg/kg) 82

Week	day	31M	32M	33M	34M	35M	36F	37F	38F	39F	40F
	0	329	330	335	348	345	204	197	214	210	206
1	1	306	311	315	329	327	187	185	186	188	189
1	3	310	316	313	337	325	209	200	221	223	216
2	8	287	256	300	323	320	218	209	230	231	222
2	14	368	375	354	388	388	229	220	244	246	248

206

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 2. - Body weight (g) (p. 2)
(individual)

Dose (mg/kg) 102

Week	day	41M	42M	43M	44M	45M
	0	245	247	230	230	257
1	1	218	228	193	192	234
1	3	226	229	193	183	229
2	8	224	241	150	190	171
2	14	288	289		246	

207

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 2. - Body weight (g) (p. 3)
(individual)

Dose (mg/kg)		128				
Animal #		21M	22M	23M	24M	25M
Week	day					
	0	296	287	275	281	295
1	1	266	260	257	261	264
1	3	275	255	246	253	266

208

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 3. - Gross pathology examination (p. 1)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 102

An#	Death day/code#		TISSUE	Gross observations
43M	13	M2	Liver	pale, diffuse, moderate
			Spleen	decreased size, diffuse, moderate
45M	11	M2	General observation	cannibalized

209

Death code : M2 (Natural death)

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 3. - Gross pathology examination (p. 2)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 128

An#	Death day/code#		TISSUE	Gross observations
21M	8	M2	Liver	pale, diffuse, severe
			Spleen	decreased size, diffuse, moderate
22M	7	M2	Liver	pale, diffuse, severe
23M	6	M2	Liver	pale, diffuse, severe
			Spleen	decreased size, diffuse, moderate
24M	7	M2	Liver	pale, diffuse, severe
			Spleen	decreased size, diffuse, moderate
25M	8	M2	Kidneys	medulla, congestion, diffuse, moderate
			Liver	pale, diffuse, severe
			Spleen	decreased size, diffuse, moderate

Death code : M2 (Natural death)

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 3. - Gross pathology examination (p. 3)
(individual)

Final killing

Dose (mg/kg) 82

An#	Death day	T I S S U E	Gross observations
31M	15	General observation	no macroscopically appreciable lesions
32M	15	General observation	no macroscopically appreciable lesions
33M	15	General observation	no macroscopically appreciable lesions
34M	15	General observation	no macroscopically appreciable lesions
35M	15	General observation	no macroscopically appreciable lesions
36F	15	General observation	no macroscopically appreciable lesions
37F	15	General observation	no macroscopically appreciable lesions
38F	15	General observation	no macroscopically appreciable lesions
39F	15	General observation	no macroscopically appreciable lesions
40F	15	General observation	no macroscopically appreciable lesions

118

[redacted]

Test article: [redacted]
Title : Acute oral toxicity study in rats
[redacted] exp. : [redacted]

APPENDIX 3. - Gross pathology examination (p. 4)
(individual)

Final killing

Dose (mg/kg) 102

An#	Death day	TISSUE	Gross observations
41M	15	General observation	no macroscopically appreciable lesions
42M	15	General observation	no macroscopically appreciable lesions
44M	15	General observation	no macroscopically appreciable lesions

214

[redacted]