CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Substance Name: methyl N-(isopropoxycarbonyl)-L-valyl-(3RS)-3-(4-chlorophenyl)-β-alaninate; Valifenalate

EC Number: -

CAS Number: 283159-90-0

Index Number: -

Contact details for dossier submitter:

National Public Health Center, Directorate of Chemical Safety and Competent Authorities (on behalf of the Hungarian MSCA)

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H-1097

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Version number: 1 **Date: January 2018**

Annex III Historical control data *See Annex conf. 52.*

Carcinogenicity study: OECD 451

Mouse (Crl: CD-1™ (ICR) BR)

50/sex/group

See Annex conf. 52.

Hepatocellular tumours are relatively common in male CD-1 mice, however the incidence of these tumours in males and females given 850 or 5000 ppm exceeded the background range seen in studies of this duration performed recently at this laboratory (see text tables 3 and 4). For males, at 850 ppm the incidence of adenoma and carcinoma was 28 and 8% respectively, and at 5000 ppm the incidences were 32 and 20%, respectively. For females, the incidence of adenoma was 4 and 10% at 850 and 5000 ppm, respectively.

Text-table 3
Historical control data for hepatocellular tumours in recent studies performed at the Eve Research Centre (Males)

Code number Start date Study duration (weeks)	cdm094 Jan-94 78	cdm097 Jul-94 79	cdm105 Sep-96 78	cdm107 Sep-97 78	cdm108 May-98 78	cdm110 Nov-98 78	Total	Range of percentages*
Liver								
Hepatocellular adenoma								
Incidence	6	10	11	4	6	10	47	
Percentage*	11.5%	19.2%	21.2%	7.8%	12.0%	20.0%	15.31%	7.8 - 21.2
Hepatocellular carcinoma								
Incidence	2	3	1	1	1	4	12	
Percentage*	3.8%	5.8%	1.9%	2.0%	2.0%	8.0%	3.91%	1.9 - 8.0
Number of animals examined	52	52	52	51	50	50	307	

Text-table 4
Historical control data for hepatocellular tumours in recent studies performed at the Eve Research Centre (Females)

Code number Start date Study duration (weeks)	cdm094 Jan-94 78	cdm097 Jul-94 80	cdm105 Sep-96 78	cdm107 Sep-97 78	cdm108 May-98 78	cdm110 Nov-98 78	Total	Range of Percentages*
Liver								
Hepatocellular adenoma								
Incidence	1	0	0	0	0	0	1	
Percentage*	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.33%	0.0 - 1.9
Hepatocellular carcinoma								
Incidence	0	0	0	0	0	0	0	
Percentage*	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.00%	0.0 - 0.0
Number of animals examined	52	52	52	51	50	50	307	

Annex III Historical control data *See Annex conf. 27.*

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HISTO - 1
01-APR-10

OECD 416 - P GENERATION / F1 LITTERS
HISTORICAL DATA - BREEDING

STRAIN: RAT / HanRcc:WIST

PARAMETER	STUDY 1 MAY-02	STUDY 2 NOV-02	STUDY 3 FEB-04	STUDY 4 OCT-04	STUDY 5 JUN-04
Number of females	23	24	23	24	24
Duration of gestation					
Mean per female	21.8	21.6	21.5	21.8	21.5
St.dev.	0.4	0.6	0.5	0.4	0.6
N	23	23	23	24	24
Implantations					
Mean per female	12.2	12.8	14.1	13.3	14.1
St.dev.	2.0	1.8	2.6	1.7	1.8
N	23	24	23	24	24
Post Implantation loss					
Mean per female	0.5	0.2	1.3	1.1	1.3
St.dev.	0.7	0.4	1.6	1.4	1.3
Number of females	23	24	23	24	24
Number of females affected	10	5	15	13	15
Dead pups at first litter check					
Females affected	0	0	1	1	0
Total	0	0	1	1	0
Mean per female	0.0	0.0	0.0	0.0	0.0
St.dev.	0.0	0.0	0.2	0.2	0.0
Number of females	23	24	23	24	24
Living pups at first litter check					
Total	269	302	295	293	309
Mean per female	11.7	12.6	12.8	12.2	12.9
St.dev.	2.0	2.0	2.1	2.2	1.9
Number of females	23	24	23	24	24
Percent of male pups	52.0	49.0	53.0	48.0	52.0
Postnatal loss until culling					
Percent of living pups	1.1	1.0	1.4	4.8	1.6
Females affected	3	3	3	2	4
Total	3	3	4	14	5
Mean per female	0.1	0.1	0.2	0.6	0.2
St.dev.	0.3	0.3	0.5	2.7	0.5
Number of females	23	24	23	24	24
Living pups after culling					
Total	184	191	184	184	193
Mean per female	8.0	8.0	8.0	7.7	8.0
St.dev.	0.0	0.2	0.0	1.4	0.2
Number of females	23	24	23	24	24
Postnatal loss after culling					
Percent of living pups	0.0	0.0	1.1	1.1	1.0
Females affected	0	0	2	2	2
Total	0	0	2	2	2
Mean per female	0.0	0.0	0.1	0.1	0.1
St.dev.	0.0	0.0	0.3	0.3	0.3
Number of females	23	24	23	24	24
Living pups at day 21					
Total	184	191	182	182	191
Mean per female	8.0	8.0	7.9	7.6	8.0
St.dev.	0.0	0.2	0.3	1.6	0.2
Number of females	23	24	23	24	24
Percent of male pups	51.0	49.0	52.0	49.0	51.0

Annex III Historical control data *See Annex conf. 27.*

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HISTO -
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OECD 416 - P GENERATION / F1 LITTERS
HISTORICAL DATA - BREEDING

STRAIN: RAT / HanRcc:WIST

PARAMETER	STUDY 6 JUN-05	STUDY 7 JAN-06	STUDY 8 NOV-06	STUDY 9 DEC-06	STUDY 10 DEC-07
Number of females	24	24	22	22	23
Duration of gestation					
Mean per female	21.5	21.4	21.8	21.6	21.5
St.dev.	0.6	0.5	0.53	0.58	0.51
N	24	24	22	22	22
Implantations					
Mean per female	13.8	13.7	13.1	12.6	13.4
St.dev.	1.7	1.6	2.20	2.65	1.20
N	24	24	22	22	23
Post Implantation loss					
Mean per female	1.7	1.6	1.6	1.2	1.2
St.dev.	2.0	1.5	1.62	1.97	1.19
Number of females	24	24	22	22	23
Number of females affected	17	18	15	13	14
Dead pups at first litter check					
Females affected	3	2	1	2	1
Total	4	3	5	2	1
Mean per female	0.2	0.1	0.2	0.1	0.0
St.dev.	0.5	0.5	1.07	0.29	0.21
Number of females	24	24	22	22	23
Living pups at first litter check					
Total	291	290	253	250	281
Mean per female	12.1	12.1	11.5	11.4	12.2
St.dev.	2.9	1.7	2.74	3.36	1.41
Number of females	24	24	22	22	23
Percent of male pups	53.0	50.0	45.0	52	53
Postnatal loss until culling					
Percent of living pups	0.7	0.7	1.6	0.4	0.7
Females affected	2	2	4	1	2
Total	2	2	4	1	2
Mean per female	0.1	0.1	0.2	0.0	0.1
St.dev.	0.3	0.3	0.39	0.21	0.29
Number of females	24	24	22	22	23
Living pups after culling					
Total	185	192	170	166	184
Mean per female	7.7	8.0	7.7	7.5	8.0
St.dev.	1.4	0.0	0.94	1.18	0.00
Number of females	24	24	22	22	23
Postnatal loss after culling					
Percent of living pups	0.5	0.0	0.0	0.6	0.0
Females affected	1	0	0	1	0
Total	1	0	0	1	0
Mean per female	0.0	0.0	0.0	0.0	0.0
St.dev.	0.2	0.0	0.00	0.21	0.00
Number of females	24	24	22	22	23
Living pups at day 21					
Total	184	192	170	165	184
Mean per female	7.7	8.0	7.7	7.5	8.0
St.dev.	1.4	0.0	0.94	1.19	0.00
Number of females	24	24	22	22	23
Percent of male pups	51.0	50.0	47	51	53

Annex III Historical control data *See Annex conf. 27.*

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HISTO - 3
01-APR-10

OECD 416 - P GENERATION / F1 LITTERS
HISTORICAL DATA - BREEDING

STRAIN: RAT / HanRcc:WIST

PARAMETER	STUDY 1 MAY-02	STUDY 2 NOV-02	STUDY 3 FEB-04	STUDY 4 OCT-04	STUDY 5 JUN-04
Birth index	95.7	98.4	91.0	91.8	91.2
Viability index	98.9	99.0	98.6	95.2	98.4
Weaning index	100.0	100.0	98.9	98.9	99.0

HARLAN LABORATORIES LTD.
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HISTO - 4
01-APR-10

OECD 416 - P GENERATION / F1 LITTERS
HISTORICAL DATA - BREEDING

STRAIN: RAT / HanRcc:WIST

PARAMETER	STUDY 6 JUN-05	STUDY 7 JAN-06	STUDY 8 NOV-06	STUDY 9 DEC-06	STUDY 10 DEC-07
Birth index	87.9	88.4	87.8	90.3	91.2
Viability index	99.3	99.3	98.4	99.6	99.3
Weaning index	99.5	100.0	100.0	99.4	100.0

Annex III Historical control data *See Annex conf. 27.*

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HISTO - 1
01-APR-1(

OECD 416 - F1 GENERATION / F2 LITTERS
HISTORICAL DATA - BREEDING

STRAIN: RAT / HanRcc:WIST

PARAMETER	STUDY 1 MAY-02	STUDY 2 NOV-02	STUDY 3 FEB-04	STUDY 4 OCT-04	STUDY 5 JUN-04
Number of females	22	21	22	23	24
Duration of gestation					
Mean per female	21.8	21.8	21.5	21.7	21.8
St.dev.	0.4	0.4	0.5	0.6	0.5
N	21	21	22	22	24
Implantations					
Mean per female	12.7	12.7	12.9	12.9	13.5
St.dev.	1.5	2.1	1.6	1.7	2.0
N	21	21	22	23	24
Post Implantation loss					
Mean per female	0.6	1.1	1.1	1.1	1.3
St.dev.	0.7	1.3	1.2	1.3	1.6
Number of females	21	21	22	23	24
Number of females affected	10	12	15	13	15
Dead pups at first litter check					
Females affected	1	0	1	0	0
Total	2	0	2	0	0
Mean per female	0.1	0.0	0.1	0.0	0.0
St.dev.	0.4	0.0	0.4	0.0	0.0
Number of females	21	21	22	23	24
Living pups at first litter check					
Total	254	244	258	272	291
Mean per female	12.1	11.6	11.7	11.8	12.1
St.dev.	1.9	2.3	1.6	2.0	2.6
Number of females	21	21	22	23	24
Percent of male pups	50.0	50.0	52.0	50.0	45.0
Postnatal loss until culling					
Percent of living pups	0.4	7.4	0.0	8.5	3.1
Females affected	1	4	0	3	5
Total	1	18	0	23	9
Mean per female	0.0	0.9	0.0	1.0	0.4
St.dev.	0.2	2.6	0.0	3.1	0.9
Number of females	21	21	22	23	24
Living pups after culling					
Total	168	161	176	173	190
Mean per female	8.0	7.7	8.0	7.5	7.9
St.dev.	0.0	1.1	0.0	1.8	0.4
Number of females	21	21	22	23	24
Postnatal loss after culling					
Percent of living pups	15.5	2.5	0.6	0.6	1.6
Females affected	10	1	1	1	2
Total	26	4	1	1	3
Mean per female	1.2	0.2	0.0	0.0	0.1
St.dev.	1.7	0.9	0.2	0.2	0.5
Number of females	21	21	22	23	24
Living pups at day 21					
Total	142	157	175	172	187
Mean per female	6.8	7.5	8.0	7.5	7.8
St.dev.	1.7	1.4	0.2	1.8	0.6
Number of females	21	21	22	23	24
Percent of male pups	50.0	51.0	51.0	49.0	46.0

Annex III Historical control data *See Annex conf. 27.*

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HISTO - 2
01-APR-10

OECD 416 - F1 GENERATION / F2 LITTERS
HISTORICAL DATA - BREEDING

STRAIN: RAT / HanRcc:WIST

PARAMETER	STUDY 6 JUN-05	STUDY 7 JAN-06	STUDY 8 NOV-06	STUDY 9 DEC-06	STUDY 10 DEC-07
Number of females	24	23	24	23	22
Duration of gestation					
Mean per female	21.8	21.8	21.7	21.6	21.6
St.dev.	0.4	0.7	0.56	0.50	0.50
N	24	23	23	23	22
Implantations					
Mean per female	12.3	12.2	12.6	13.3	13.8
St.dev.	1.8	2.7	2.32	2.36	1.27
N	24	23	24	23	22
Post Implantation loss					
Mean per female	1.3	1.7	1.3	1.1	1.1
St.dev.	1.9	2.8	2.09	2.09	1.04
Number of females	24	23	24	23	22
Number of females affected	14	14	11	10	14
Dead pups at first litter check					
Females affected	0	2	3	0	1
Total	0	11	4	0	1
Mean per female	0.0	0.5	0.2	0.0	0.0
St.dev.	0.0	1.8	0.48	0.00	0.21
Number of females	24	23	24	23	22
Living pups at first litter check					
Total	263	241	273	281	278
Mean per female	11.0	10.5	11.4	12.2	12.6
St.dev.	2.4	3.8	2.75	2.73	1.84
Number of females	24	23	24	23	22
Percent of male pups	50.0	47.0	55.0	49.0	51.0
Postnatal loss until culling					
Percent of living pups	0.4	4.6	0.0	1.1	0.4
Females affected	1	5	0	3	1
Total	1	11	0	3	1
Mean per female	0.0	0.5	0.0	0.1	0.0
St.dev.	0.2	1.2	0.00	0.34	0.21
Number of females	24	23	24	23	22
Living pups after culling					
Total	188	163	186	179	176
Mean per female	7.8	7.1	7.8	7.8	8.0
St.dev.	0.8	2.0	1.22	0.74	0.00
Number of females	24	23	24	23	22
Postnatal loss after culling					
Percent of living pups	0.0	2.5	0.0	0.6	0.0
Females affected	0	3	0	1	0
Total	0	4	0	1	0
Mean per female	0.0	0.2	0.0	0.0	0.0
St.dev.	0.0	0.5	0.00	0.21	0.00
Number of females	24	23	24	23	22
Living pups at day 21					
Total	188	159	186	178	176
Mean per female	7.8	6.9	7.8	7.7	8.0
St.dev.	0.8	1.9	1.22	0.75	0.00
Number of females	24	23	24	23	22
Percent of male pups	49.0	51.0	51.0	49.0	48.0

Annex III Historical control data *See Annex conf. 27.*

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HISTO - 3
01-APR-10

OECD 416 - F1 GENERATION / F2 LITTERS
HISTORICAL DATA - BREEDING

STRAIN: RAT / HanRcc:WIST

PARAMETER	STUDY 1 MAY-02	STUDY 2 NOV-02	STUDY 3 FEB-04	STUDY 4 OCT-04	STUDY 5 JUN-04
Birth index	95.5	91.4	91.2	91.6	90.1
Viability index	99.6	92.6	100.0	91.5	96.9
Weaning index	84.5	97.5	99.4	99.4	98.4

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HISTO - 4
01-APR-10

OECD 416 - F1 GENERATION / F2 LITTERS
HISTORICAL DATA - BREEDING

STRAIN: RAT / HanRcc:WIST

PARAMETER	STUDY 6 JUN-05	STUDY 7 JAN-06	STUDY 8 NOV-06	STUDY 9 DEC-06	STUDY 10 DEC-07
Birth index	89.2	85.8	90.1	91.8	91.7
Viability index	99.6	95.4	100.0	98.9	99.6
Weaning index	100.0	97.5	100.0	99.4	100.0

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

BODY WEIGHT AND FOOD CONSUMPTION - Years: 1996 – 2000
Males – Pre-mating period

	BODY WEIGHT(g)			FOOD CONSUMPTION(g)		
Day	No.	Mean ±	S.D.	No.	Mean ±	S.D.
0	192	279.250	47.522			
1	33	258.360	51.538			
7	192	330.334	39.354	91	26.077	2.927
8	28	294.007	17.539	38	25.572	2.602
14	192	371.651	37.401	101	25.920	3.311
15	28	334.803	18.506	28	27.423	4.775
21	152	399.751	31.997	76	27.508	3.441
22	28	362.678	22.790	27	23.832	3.277
28	152	433.046	36.499	76	28.050	3.800
29	28	383.989	25.958	28	26.170	3.439
35	104	464.862	43.631	52	28.472	4.092
36	28	402.509	25.388	28	29.195	4.939
42	104	488.696	48.259	52	28.018	3.508
43	28	424.478	28.566	28	26.338	4.113
49	103	508.885	50.892	52	27.700	3.341
50	28	447.999	30.801	28	24.905	2.718
56	103	526.729	52.404	52	26.545	5.435
57	28	460.150	35.649	28	23.823	4.063
63	103	542.922	54.004	52	26.590	4.018
64	28	473.226	36.203	28	25.400	4.452
70	103	558.035	56.994	52	26.658	4.466
71	28	490.616	39.377	28	25.333	3.991

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

BODY WEIGHT AND FOOD CONSUMPTION - Years: 1996 - 2000
Females – Pre-mating period

	BODY WEIGHT(g)			FOOD CONSUMPTION(g)		
N Day	No.	Mean ±	S.D.	No.	Mean ±	S.D.
0	232	252.338	20.924			
1	43	208.358	27.310			
7	232	261.959	21.572	115	18.488	3.585
8	38	221.877	21.802	48	23.668	6.182
14	231	271.236	24.485	125	19.086	4.597
15	38	233.735	23.057	38	21.263	6.409
21	10	273.307	16.705	10	24.205	6.033
22	28	230.860	15.530	28	21.515	4.613
29	28	237.610	15.900	28	23.104	5.455
36	28	243.078	15.267	28	24.370	5.923
43	28	256.753	17.483	28	23.438	6.433
50	28	258.432	17.442	28	20.338	4.097
57	28	262.131	18.503	28	19.138	4.801
64	28	268.802	18.836	28	18.085	3.929
71	28	274.099	18.160	28	18.354	3.017

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

BODY WEIGHT AND FOOD CONSUMPTION - Years: 1996 - 2000
Females - Pregnancy period - Mean A

	BODY WEIGHT(g)			FOOD CONSUMPTION(g)		
Pregnancy day	No.	Mean ±	S.D.	No.	Mean ±	S.D.
0	575	264.137	24.133			
2	6	245.667	12.785			
3	70	282.329	28.441	64	22.698	5.278
4	10	274.800	17.580			
5	10	274.500	18.020			
6	366	289.546	23.447	345	22.590	3.729
7	285	303.579	25.886	269	23.613	13.294
8	381	296.462	24.133	336	22.277	5.301
9	18	314.389	27.536	18	25.278	6.124
10	384	306.406	25.116	345	23.061	5.129
11	18	324.056	27.873	18	25.194	3.904
12	321	314.953	26.188	276	23.636	4.731
13	18	337.833	32.749	18	25.639	3.403
14	562	331.991	27.817	523	23.705	4.722
15	261	333.540	25.952	259	24.755	5.763
16	371	344.162	28.929	328	25.613	5.501
17	117	361.701	28.350	117	24.536	4.918
18	320	372.325	30.593	311	26.972	5.089
20	484	412.403	36.264	473	26.519	4.722
21	28	416.250	42.936	32	24.202	6.452
EGU 16	29	311.397	21.468			
EGU 20	332	319.727	26.288			

Mean A = Calculated on all the surviving females having evident signs of pregnancy, including those that presented 100% post-implantation losses
EGU = Final body weight excluding gravid uterus

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

BODY WEIGHT AND FOOD CONSUMPTION - Years: 1996 - 2000
Females - Lactation period - Mean A

	BODY WEIGHT(g)			FOOD CONSUMPTION(g)		
Lactation day	No.	Mean ±	S.D.	No.	Mean ±	S.D.
0	192	322.380	32.352			
4	28	345.107	28.940	28	33.607	8.188
5	9	327.444	21.559	9	36.600	6.369
7	164	335.677	35.455	155	40.058	11.238
14	155	336.806	44.586	146	55.146	13.777
21	155	312.916	43.146			

Mean A = Calculated on all the surviving females having evident signs of pregnancy, including those that presented 100% post-implantation losses. After parturition Mean A includes surviving females that have later lost their litter both at the time of parturition and during lactation.

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

REPRODUCTIVE PARAMETERS - Years: 1996 - 2000

		Caesarean sectioned females Mean A			
	No. of dams	Mean ±	S.D.	Range Min.	Max
Corpora Lutea No.	393	18.247	3.346	6.000	30.000
Res. Visible at Salewki No.	393	0.000	0.000	0.000	0.000
Early resorptions No.	393	0.959	2.509	0.000	20.000
Late resorptions No.	393	0.020	0.158	0.000	2.000
Total resorptions No.	393	0.980	2.524	0.000	20.000
Viable fetuses No.	393	14.198	4.309	0.000	23.000
Dead fetuses No.	393	0.005	0.071	0.000	1.000
Implantations No.	393	15.173	3.791	0.000	23.000
Pre-implantation losses %	392	16.505	18.085	0.000	100.000
Post-implantation losses %	389	6.483	15.817	0.000	100.000
Live male fetuses No.	349	7.132	2.906	0.000	13.000
Live female fetuses No.	349	7.307	2.957	0.000	17.000
Mean fetal weight g (Mean B)	338	3.723	0.535	1.000	5.901
Male fetal weight g (Mean B)	331	3.857	0.424	1.000	6.110
Female fetal weight g (Mean B)	338	3.631	0.528	1.000	5.770
Placental weight g (Mean B)	338	0.552	0.089	0.389	1.140
Litter weight g (Mean B)	338	55.366	14.154	2.720	94.640
Gravid uterus weight g	382	79.928	28.208	2.567	134.870

Mean A = Calculated on all the surviving females having evident signs of pregnancy, including those that presented 100% post-implantation losses

Mean B = Calculated only on those females with viable fetuses at term

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

OBSERVATION ON FETUSES - Years: 1996 - 2000

	No. of dams	Mean ±	S.D.	Range Min.	Range Max
With ext. malformations	382	0.018	0.134	0.000	1.000
With ext. anomalies	382	0.031	0.189	0.000	2.000
Skeletally exam. fetuses	215	7.600	1.674	1.000	12.000
With skeletal malformations	215	0.060	0.627	0.000	7.000
With skeletal anomalies	215	2.526	2.210	0.000	9.000
With skeletal variants	215	6.744	1.994	0.000	12.000
Wilson's exam. fetuses	223	7.758	2.072	1.000	17.000
With visc. malf. (Wilson's)	223	0.018	0.133	0.000	1.000
With visc. anom. (Wilson's)	223	0.121	0.423	0.000	3.000
With visc. var. (Wilson's)	223	1.309	1.576	0.000	8.000
Normal fetuses	379	9.908	4.668	1.000	22.000

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

OBSERVATION ON FETUSES - Years: 1996 - 2000

No. OF FETUSES WITH MALFORMATIONS		
Visceral malformation		
No. of examined fetuses		1730
Hydrocephaly	1	0.06%
Hydroureter, unilateral	1	0.06%
Hydroureter, bilateral	1	0.06%
Hydronephrosis, bilateral	2	0.12%
External malformation		
No. of examined fetuses		5580
Anasarca	2	0.04%
Craniorachischisis	1	0.02%
Macroglossia	1	0.02%
Cleft palate	2	0.04%
Tail, absence	1	0.02%
Skeletal malformation		
No. of examined fetuses		1634
Interparietal, unossified	5	0.31%
Supraoccipital, unossified	6	0.37%
Parietals and frontals, fused	7	0.43%
Ileum, unossified	1	0.06%
Pubis, unossified	1	0.06%

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

REPRODUCTIVE PARAMETERS - Years: 1996 - 2000

Dams allowed to litter

	Mean ± (n.)	S.D.	Range Min.	Range Max
Implantations No.	15.601(173)	3.061	3.000	21.000
Live born No.	14.188(192)	3.167	2.000	21.000
Stillborn No.	0.042(192)	0.267	0.000	3.000
Post-implantation losses %	8.440(173)	10.465	0.000	69.230
Pregnancy length	21.984 (184)	0.673	17.000	23.000
Birth index %	91.454(183)	10.373	30.770	100.000
Viability index %	94.238(192)	13.979	0.000	100.000
Weaning index %	95.577(154)	15.614	0.000	100.000

Mean A = Calculated on all the surviving females having evident signs of pregnancy, including those that presented 100% post-implantation losses. After parturition Mean A includes surviving females that have later lost their litter both at the time of parturition and during lactation.

	Years 1996-2000			
		Range		No. of
	Median	Min.	Max.	Dams
Pre-coital interval (days)	2.300	1.217	3.750	261

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

F1 PUPS BODY WEIGHT (g) - LACTATION PERIOD - Years: 1996 - 2000

	MALES		FEMALES		MALES + FEMALES	
	Mean ± (n)	S.D.	Mean ± (n)	S.D.	Mean ± (n)	S.D.
Day 0	6.811 (190)	0.737	6.450 (192)	0.720	6.627 (192)	0.712
Day 4	10.272 (172)	1.666	9.852 (173)	1.555	10.062 (173)	1.570
Day 5	11.678 (9)	1.765	11.214 (9)	1.752	11.457 (9)	1.752
Day 7	17.517 (59)	2.624	16.743 (59)	2.636	17.121 (59)	2.588
Day 8	16.321 (101)	3.005	15.820 (102)	3.043	16.082 (102)	2.923
Day 12	23.792 (100)	3.922	23.140 (101)	4.085	23.472 (101)	3.808
Day 14	37.031 (50)	4.134	35.859 (50)	4.026	36.419 (50)	3.969
Day 21	48.46 (150)	12.424	47.155 (151)	11.907	47.839 (151)	12.081

(n) = No. of litters

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

F1 PUPS TIME APPEARANCE OF REFLEXES (days) - Years: 1996 - 2000

	Median	Range		No. of Litters
		Min.	Max.	
Pinna detachment (daily from day 4 on)	4.000	4.000	4.429	105
Appearence of fur (daily from day 4 on)	6.000	4.000	6.143	103
Pinna Reflex (daily from day 11 on)	11.000	11.000	11.800	103
Surface righting (daily from day 4 on)	4.000	4.000	4.429	105
Eruption of incisors (daily from day 7 on)	8.400	7.000	10.722	103
Eye opening (daily from day 12 on)	14.172	12.667	16.200	102
Corneal reflex (daily from day 12 on)	14.172	12.667	16.200	102
Pupillary reflex (daily from day 12 on)	14.172	12.667	16.200	102
Traction reflex (daily from day 4 on)	5.250	4.000	7.625	105
Grip reflex (daily from day 4 on)	4.538	4.000	6.143	105
Testes descent (daily from day 25 on)	25.000	25.000	28.000	66
Vaginal opening (daily from day 30 on)	32.000	29.000	44.000	132
Balanopreputial gland cleavage (daily from day 25 on)	27.000	25.000	31.000	131
Nipples development (%)	0.000	0.000	0.000	8
Ano-genital distance males (mm)	3.350	3.071	4.067	8
Ano-genital distance females (mm)	2.050	1.320	2.511	9

			Range		No. of Litters
	$ Mean ±	S.D.	Min.	Max.	
Chimney test (on day 14)	93.437	13.738	22.222	100.000	102

$ = mean of % of success

Annex III Historical control data *See Annex conf. 9.*

RBM COLONY DATA : RATS
STRAIN : Sprague Dawley Crl: CD (SD) BR
SOURCE OF SUPPLY : Charles River Italia S.p.A.

F0 ORGAN WEIGHT (g) - Years: 1996 – 2000

	MALES		FEMALES	
	Mean ± (n)	S.D.	Mean ± (n)	S.D.
Final fasting body weight (g)	518.481 (52)	55.712	303.333 (24)	18.389
Liver (g)	18.102 (28)	3.37	11.009 (24)	1.455
Kidneys (g)	3.607 (28)	0.406	2.045 (24)	0.189
Brain (g)	2.210 (28)	0.132	1.928 (24)	0.403
Spleen (g)	0.849 (28)	0.128	0.572 (24)	0.070
Testes (g)	3.462 (169)	0.309		
Prostate (g)	1.157 (28)	0.263		
Adrenals (mg)	60.250 (28)	19.757	70.375 (24)	9.934
Pituitary (mg)	12.786 (28)	3.370	16.061 (33)	4.213
Seminal vesicles (g)	1.609 (28)	0.338		
Epididymides (mg)	1497.292 (48)	119.818		
Ovaries (Ft) (mg)			169.119 (59)	57.456
Uterus (Ft) (g)			4.059 (52)	1.359
Ovaries (Ff) (mg)			103.407 (123)	24.185
Uterus (Ff) (g)			0.628 (67)	0.232

(n) = No. of animal
Ff=females allowed to litter

Ft=caesaren sectioned females

Annex III Historical control data *See Annex conf. 10.*

BODY WEIGHT AND FOOD CONSUMPTION - Years: 1995 - 2000
Females - Pregnancy period - Mean A

	BODY WEIGHT(kg)			FOOD CONSUMPTION(g)		
Pregnancy day	No.	Mean ±	S.D.	No.	Mean ±	S.D.
0	210	3.710	0.344			
2				210	181.393	39.463
4				210	196.310	40.521
6	210	3.883	0.345	209	190.675	39.563
8	6	3.747	0.177	209	183.218	42.556
10	210	3.933	0.343	209	188.251	41.703
12	6	3.808	0.230	210	179.849	39.809
14	210	4.001	0.342	210	174.756	42.895
16	6	3.920	0.179	208	177.325	48.056
18	193	4.059	0.353	209	179.612	50.973
19	210	4.078	0.348			
20				209	179.505	49.002
22				210	179.810	49.577
23	210	4.163	0.352			
24				209	160.510	49.939
26				210	139.152	48.446
28				210	143.965	57.691
29	210	4.264	0.334	210	151.157	59.432
EGU 29	210	3.767	0.316			

Mean A = Calculated on all the surviving females having evident signs of pregnancy, including those that presented 100% post-implantation losses

EGU = Final body weight excluding gravid uterus

Annex III Historical control data *See Annex conf. 10.*

RBM COLONY DATA : RABBITS
STRAIN : New Zealand White
SOURCE OF SUPPLY : Charles River Italia S.p.A.

REPRODUCTIVE PARAMETERS - Years: 1995 - 2000

		Caesarean sectioned females Mean A			
	No. of does	Mean ±	S.D.	Range Min.	Max
Corpora Lutea No.	210	10.005	2.391	4.000	17.000
Early resorptions No.	210	0.319	0.901	0.000	8.000
Late resorptions No.	210	0.295	0.757	0.000	4.000
Total resorptions No.	210	0.629	1.204	0.000	8.000
Viable fetuses No.	210	7.690	2.640	0.000	13.000
Dead fetuses No.	210	0.048	0.290	0.000	3.000
Implantations No.	210	8.471	2.354	3.000	14.000
Pre-implantation losses %	210	15.191	13.492	0.000	70.000
Post-implantation losses %	210	9.573	19.374	0.000	100.000
Live male fetuses No.	210	3.781	1.801	0.000	9.000
Live female fetuses No.	210	3.910	1.992	0.000	9.000
Mean fetal weight g (Mean B)	205	44.621	6.039	24.380	58.647
Male fetal weight g (Mean B)	203	44.686	6.218	24.380	58.595
Female fetal weight g (Mean B)	196	44.167	6.192	26.942	58.750
Placental weight g (Mean B)	205	6.408	1.145	3.690	11.597
Litter weight g (Mean B)	205	349.346	102.008	88.130	564.210
Gravid uterus weight g	210	496.444	147.094	26.030	767.510

Mean A = Calculated on all the surviving females having evident signs of pregnancy, including those that presented 100% post-implantation losses

Mean B = Calculated only on those females with viable fetuses at term

Annex III Historical control data *See Annex conf. 10.*

RBM COLONY DATA : RABBITS
STRAIN : New Zealand White
SOURCE OF SUPPLY : Charles River Italia S.p.A.

OBSERVATION ON FETUSES - Years: 1995 - 2000

	No. of does	Mean ±	S.D.	Range Min.	Range Max
With ext. malformations	205	0.015	0.120	0.000	1.000
With ext. anomalies	205	0.000	0.000	0.000	0.000
With autoptic malformations	205	0.000	0.000	0.000	0.000
With autoptic anomalies	205	0.005	0.070	0.000	1.000
With autoptic variants	205	0.000	0.000	0.000	0.000
Skeletally exam. fetuses	125	7.712	2.510	2.000	13.000
With skeletal malformations	125	0.096	0.296	0.000	1.000
With skeletal anomalies	125	1.624	1.640	0.000	7.000
With skeletal variants	125	3.200	1.963	0.000	9.000
Wilson's exam. fetuses	123	2.569	0.869	1.000	4.000
With visc. malf. (Wilson's)	123	0.008	0.090	0.000	1.000
With visc. anom. (Wilson's)	123	0.049	0.335	0.000	3.000
With visc. var. (Wilson's)	123	0.000	0.000	0.000	0.000
Normal fetuses	199	5.503	2.932	1.000	13.000

Annex III Historical control data *See Annex conf. 10.*

RBM COLONY DATA : RABBITS
STRAIN : New Zealand White
SOURCE OF SUPPLY : Charles River Italia S.p.A.

OBSERVATION ON FETUSES - Years: 1995 - 2000

No. OF FETUSES WITH MALFORMATIONS		
External malformation		
No. of examined fetuses		1615
Thin tail	1	0.06%
Cleft palate	1	0.06%
Spina bifida	1	0.06%
Hepatomphalocele	1	0.06%
Skeletal malformation		
No. of examined fetuses		964
Interparietal, unossified	6	0.62%
Interparietal, misshapen	2	0.21%
Frontals, fused	1	0.10%
Sesamoid bone(s) in the bregmatic fontanella	1	0.10%
Scoliosis	1	0.10%
Ribs, 4th and 5th fused, unilateral	1	0.10%
Ribs, 7th and 8th fused, unilateral	1	0.10%
Ribs, 10th and 11th fused, unilateral	1	0.10%
Vertebrae, 8th thoracic centrum, asymmetric	1	0.10%
Vertebrae, 7th thoracic centrum, hemivertebra	1	0.10%