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Summary of Results

[Not QAU-Checked]

DHDPS

Maternal Toxicity Study in Wistar Rats
(Range-Finding)

Oral Administration (Gavage)

Study Director:

TEST FACILITY

Experimental Toxicology and Ecology
BASF SE
67056 Ludwigshafen, Germany

TEST FACILITY PROJECT IDENTIFICATION

Project No.: 10R0066/05R022

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(attached: Tables)

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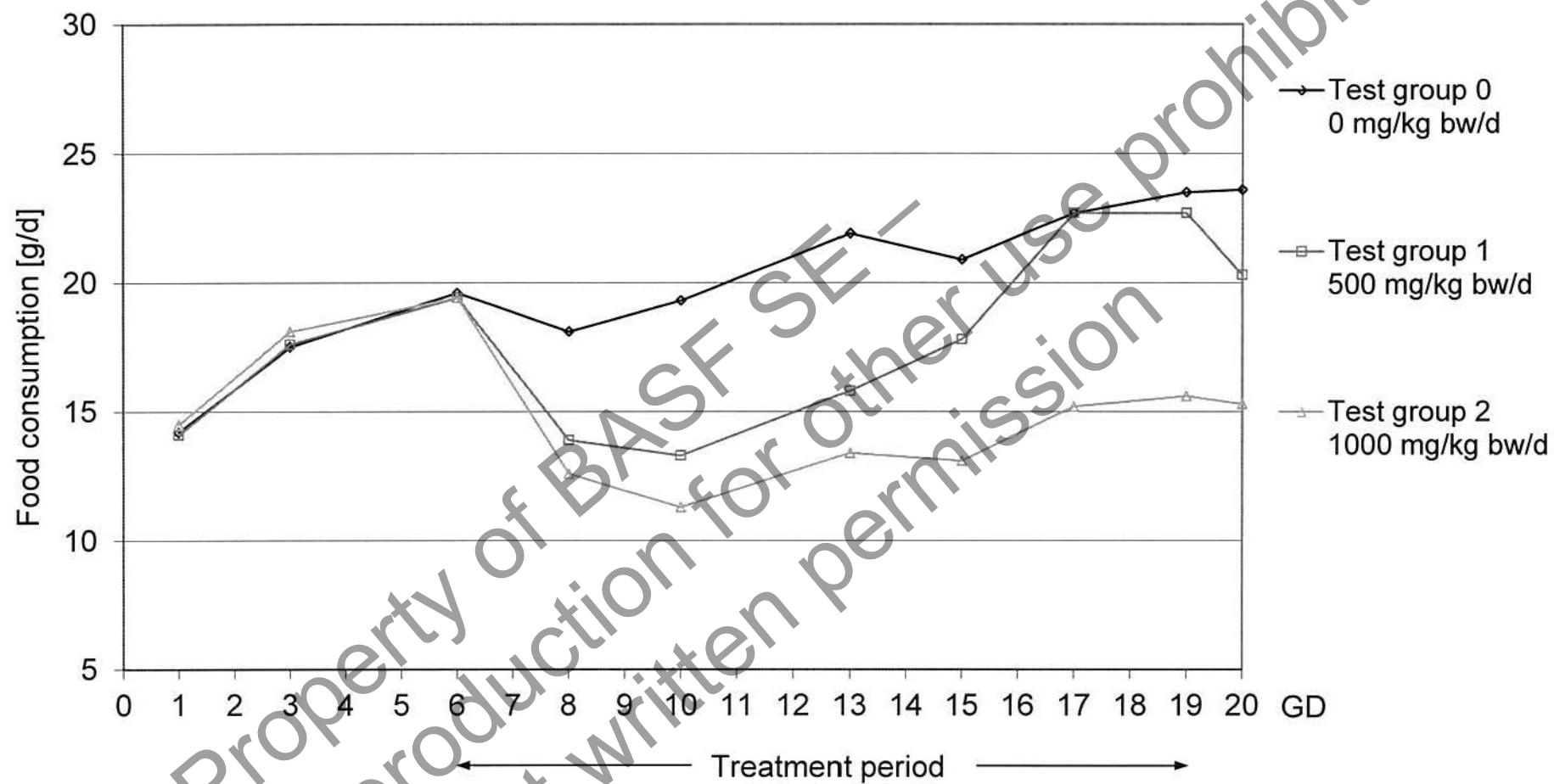
Project No.: 10R0236/09R125 – DHDPs

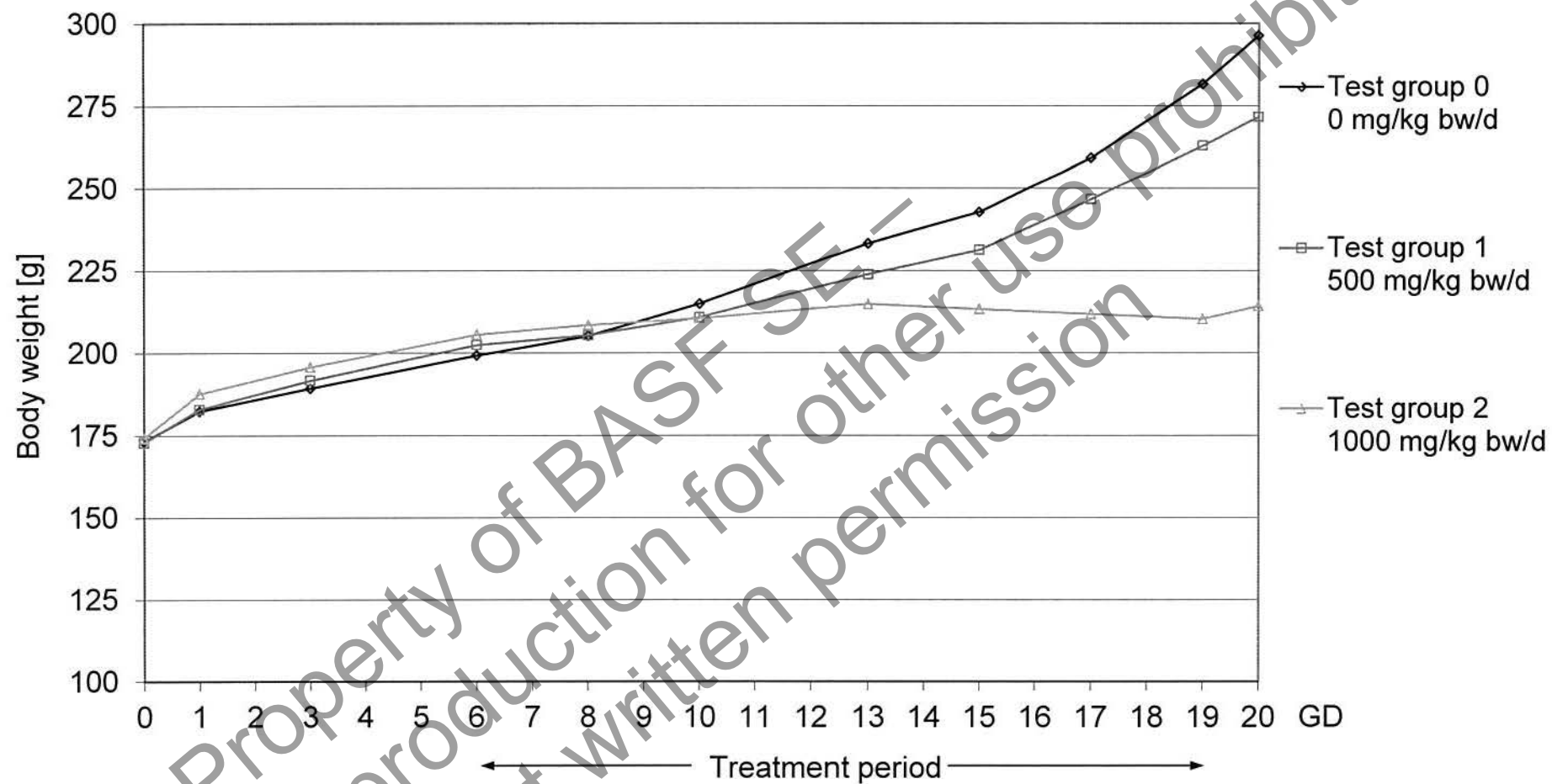
Maternal Toxicity Study in Wistar Rats (Range-Finding); Oral Administration (Gavage)

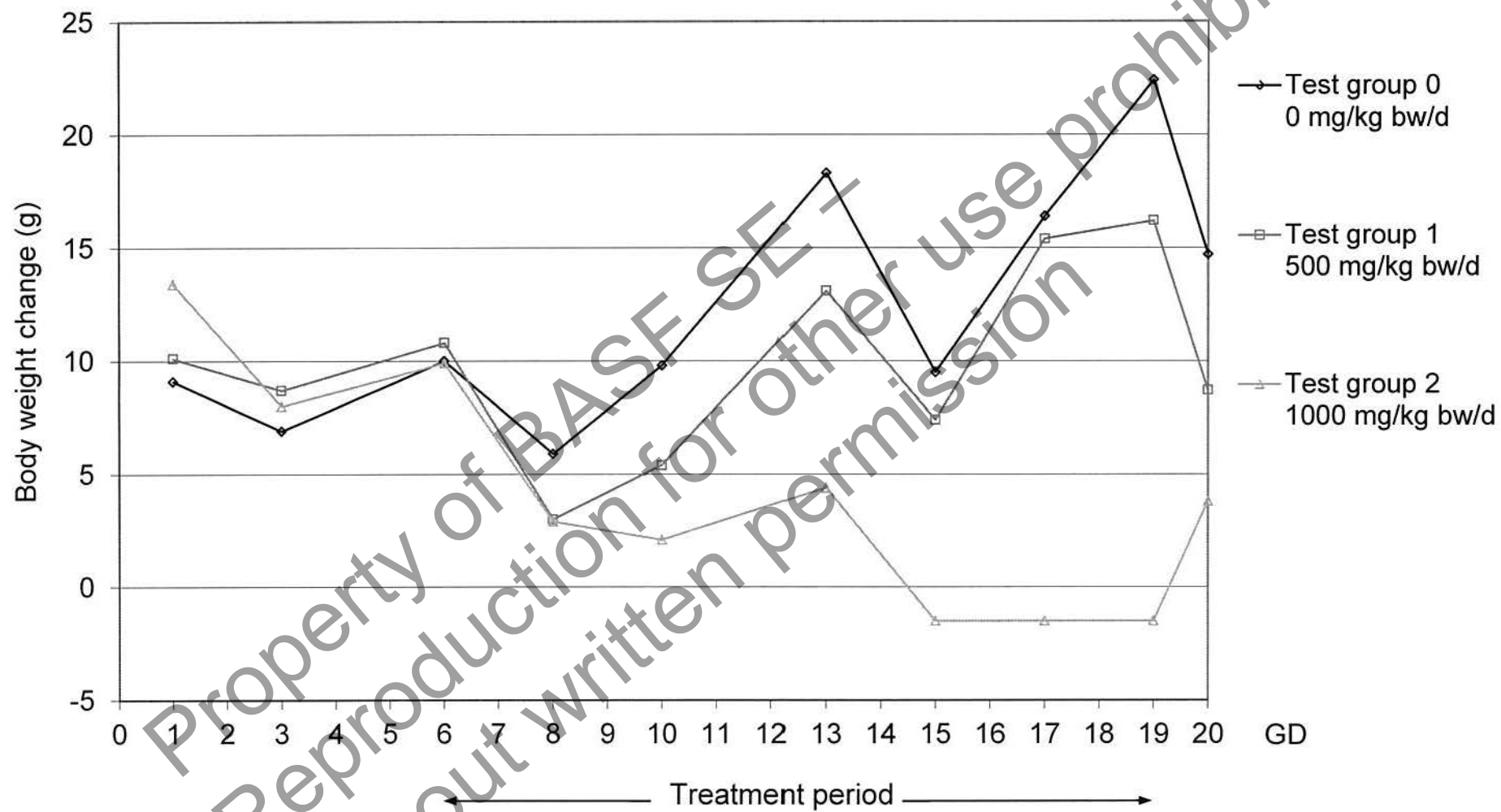
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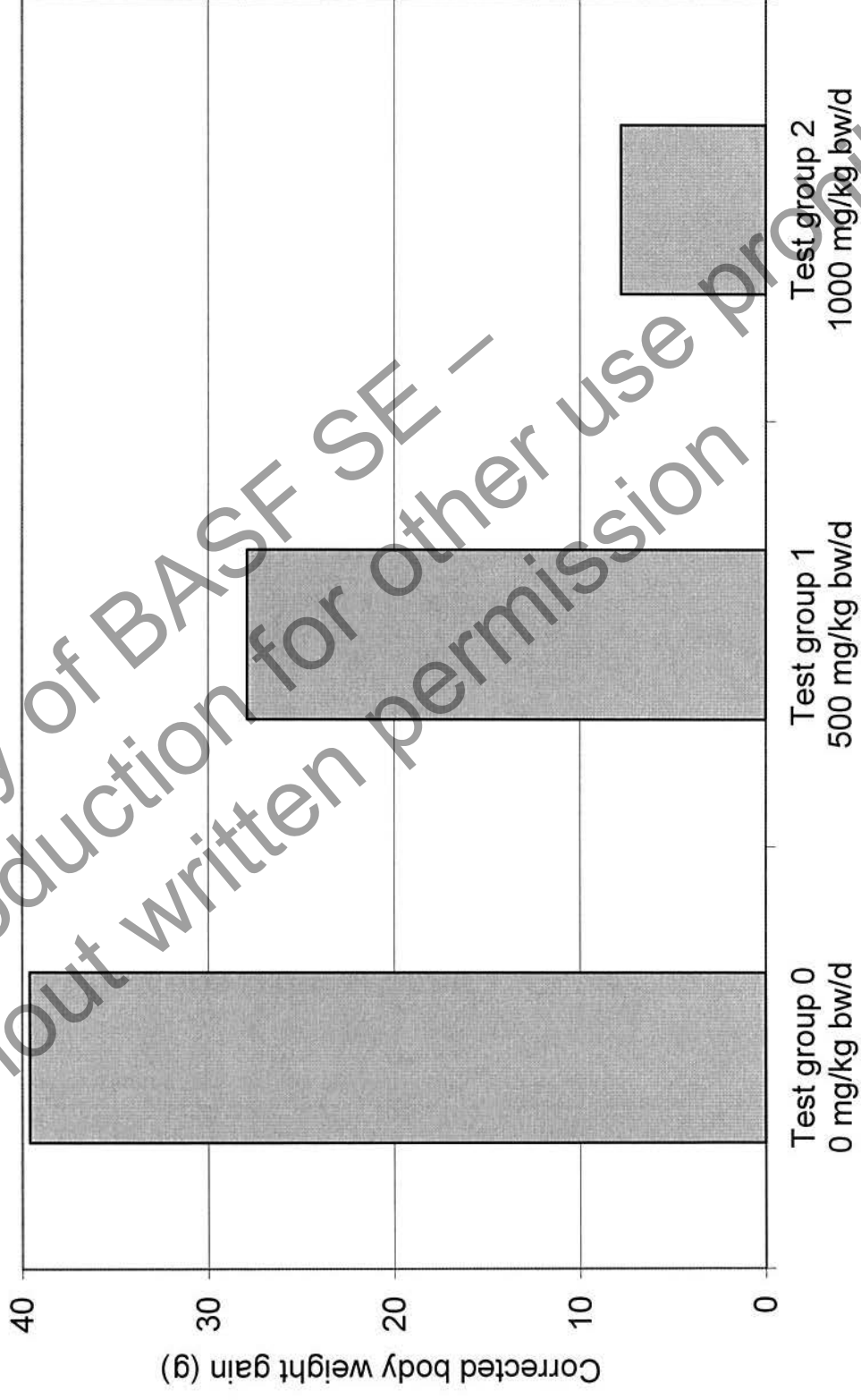
Dosage: 0; 500; 1000 mg/kg bw/d; GD 6-19

Parameter mg/kg body weight/day	Test group 0 0	Test group 1 500	Test group 2 1000
Females mated/pregnant:	10/10	10/10	10/10
Clinical observations:	NAD	Piloerection (3/10) Vaginal discharge (1/10)	Salivation (9/10) Piloerection (8/10) Vaginal discharge (5/10)
FC (0 - 6) FC (6 - 19) FC (0 - 20)	18.0 g 21.1 g 20.3 g	17.9 g (-0.3%) 17.5 g (-16.9%) 17.8 g (-12.3%) FC (6 - 13, 19 - 20) = < Control */**	18.1 g (0.7%) 13.5 g (-36.1%) 15.0 g (-26.2%) FC (6 - 20) = < Control **
BW (0) BW (6) BW (19) BW (20)	173.2 g 199.2 g 281.6 g 296.3 g	172.8 g (-0.2%) 202.4 g (1.6%) 262.9 g (-6.6%) 271.6 g (-8.3%)	174.2 g (0.6%) 205.5 g (3.2%) 210.3 g (-25.3%)** 214.2 g (-27.7%)** BW (13 - 20) = < Control */**
BWC (0 - 6) BWC (6 - 19) BWC (0 - 20) BWC (8 - 10) BWC (19 - 20)	26.0 g 82.4 g 123.1 g 9.8 g 14.7 g	29.6 g (13.6%) 60.5 g (-26.5%)* 98.8 g (-19.8%) 5.4 g (-45.0%)* 8.7 g (-40.9%)*	31.3 g (20.4%) 4.8 g (-94.2%)** 40.0 g (-67.5%)** 2.1 g (-79.0%)** 3.8 g (-74.0%)** BWC (8 - 20) = < Control **
Uterus weight:	57.5 g	41.4 g (-28.1%)	0.8 g (-98.6%)
Carcass weight:	238.8 g	230.2 g (-3.6%)	213.4 g (-10.6%)**
Corrected body weight gain:	39.6 g	27.9 g (-29.6%)*	7.8 g (-80.2%)**









Study

10R0066/05R022

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22-Jul-2013 11:00

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary - Clinical Observation

Sex: Female - Phase: Gestation

		Test Group 0	Test Group 1	Test Group 2
		0 mg/kg bw/d	500 mg/kg bw/d	1000 mg/kg bw/d
day 0 -> 20	Animals examined	N	10	10
	Animals with signs	N	3	9
	dead	N	10	10
	sacrificed scheduled	N	10	10
	head	N	0	9
	salivation	N	0	9
	genitals	N	1	5
	vaginal discharge	N	0	5
	fur	N	3	8
	piloerection	N	10	10
normal		N	10	10
NAD		N	10	10

Study

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22-Jul-2013 11:00

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Food Consumption Per Day

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
d 0 -> 1	Mean [g]	14.2 ⁿ	14.1	14.5
	S.d.	2.6	2.0	2.9
	N	10	10	10
	Deviation Vs Control		-0.5	2.1
d 1 -> 3	Mean [g]	17.5 ⁿ	17.6	18.1
	S.d.	1.6	1.8	1.5
	N	10	10	10
	Deviation Vs Control		0.9	3.7
d 3 -> 6	Mean [g]	19.6 ⁿ	19.4	19.4
	S.d.	1.9	1.4	1.5
	N	10	10	10
	Deviation Vs Control		-0.9	-1.3
d 6 -> 8	Mean [g]	18.1 ⁿ	13.9 ^{**}	12.6 ^{**}
	S.d.	2.0	2.4	1.0
	N	10	10	10
	Deviation Vs Control		-23.4	-30.5
d 8 -> 10	Mean [g]	19.3 ⁿ	13.3 ^{**}	11.3 ^{**}
	S.d.	2.4	2.9	1.4
	N	10	10	10
	Deviation Vs Control		-31.1	-41.3

d = day; n=DUNNETT; ** p <=0.01

Study

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22-Jul-2013 11:01

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Food Consumption Per Day

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
d 10 -> 13	Mean [g]	21.9 ⁿ	15.8 ^{**}	13.4 ^{**}
	S.d.	2.2	3.6	2.5
	N	10	10	10
	Deviation Vs Control		-28.0	-38.9
d 13 -> 15	Mean [g]	20.9 ⁿ	17.8	13.1 ^{**}
	S.d.	3.0	3.8	2.6
	N	10	10	10
	Deviation Vs Control		-14.5	-37.4
d 15 -> 17	Mean [g]	22.7 ⁿ	22.7	15.2 ^{**}
	S.d.	2.7	3.7	2.0
	N	10	10	10
	Deviation Vs Control		0.0	-33.1
d 17 -> 19	Mean [g]	23.5 ⁿ	22.7	15.6 ^{**}
	S.d.	3.3	4.2	1.4
	N	10	10	10
	Deviation Vs Control		-3.4	-33.6
d 19 -> 20	Mean [g]	23.6 ⁿ	20.3 [*]	15.3 ^{**}
	S.d.	2.7	4.2	1.7
	N	10	10	10
	Deviation Vs Control		-13.8	-35.0

n=DUNNETT; ** p <=0.01; d = day; * p <=0.05

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Food Consumption Per Day

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
d 0 -> 6	Mean [g]	18.0	17.9	18.1
	S.d.	1.6	1.4	1.6
	N	10	10	10
	Deviation Vs Control		-0.3	0.7
d 6 -> 19	Mean [g]	21.1	17.5	13.5
	S.d.	2.4	2.8	1.2
	N	10	10	10
	Deviation Vs Control		-16.9	-36.1
d 0 -> 20	Mean [g]	20.3	17.8	15.0
	S.d.	2.1	2.1	1.1
	N	10	10	10
	Deviation Vs Control		-12.3	-26.2

d = day

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
day 0	Mean	173.2 n	172.8	174.2
	S.d.	9.7	11.4	11.6
	N	10	10	10
	Deviation Vs Control		-0.2	0.6
day 1	Mean	182.3 n	182.9	187.6
	S.d.	10.9	11.1	12.5
	N	10	10	10
	Deviation Vs Control		0.3	2.9
day 3	Mean	189.2 n	191.6	195.7
	S.d.	12.8	11.8	12.1
	N	10	10	10
	Deviation Vs Control		1.3	3.4
day 6	Mean	199.2 n	202.4	205.5
	S.d.	13.9	11.9	13.0
	N	10	10	10
	Deviation Vs Control		1.6	3.2
day 8	Mean	205.1 n	205.3	208.4
	S.d.	14.6	12.5	12.1
	N	10	10	10
	Deviation Vs Control		0.1	1.6

n=DUNNETT

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
day 10	Mean	214.9 n	210.8	210.5
	S.d.	16.0	12.5	11.5
	N	10	10	10
	Deviation Vs Control		-2.0	-2.1
day 13	Mean	233.2 n	223.8	214.8 *
	S.d.	18.6	13.3	14.7
	N	10	10	10
	Deviation Vs Control		-4.0	-7.9
day 15	Mean	242.8 n	231.3	213.3 **
	S.d.	21.3	16.6	14.9
	N	10	10	10
	Deviation Vs Control		-4.7	-12.1
day 17	Mean	259.2 n	246.7	211.8 **
	S.d.	22.6	22.1	13.1
	N	10	10	10
	Deviation Vs Control		-4.8	-18.3
day 19	Mean	281.6 n	262.9	210.3 **
	S.d.	25.9	31.1	12.1
	N	10	10	10
	Deviation Vs Control		-6.6	-25.3

n=DUNNETT; * p<=0.05; ** p <=0.01

Study

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22-Jul-2013 11:03

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0	Test Group 1	Test Group 2
		0 mg/kg bw/d	500 mg/kg bw/d	1000 mg/kg bw/d
day 20	Mean	296.3 n	271.6	214.2 **
	S.d.	27.5	36.1	11.9
	N	10	10	10
	Deviation Vs Control		-8.3	-27.7

n=DUNNETT; ** p <=0.01

Study

10R0066/05R022

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
d 0 -> 1	Mean	9.1 ⁿ	10.1	13.4 [*]
	S.d.	3.2	3.7	5.1
	N	10	10	10
	Deviation Vs Control		11.1	48.1
d 1 -> 3	Mean	6.9 ⁿ	8.7	8.0
	S.d.	3.2	2.4	3.1
	N	10	10	10
	Deviation Vs Control		25.7	15.9
d 3 -> 6	Mean	10.0 ⁿ	10.8	9.9
	S.d.	1.9	2.2	2.6
	N	10	10	10
	Deviation Vs Control		7.5	-1.5
d 6 -> 8	Mean	5.9 ⁿ	3.0	2.9
	S.d.	3.3	2.9	2.6
	N	10	10	10
	Deviation Vs Control		-49.4	-51.1
d 8 -> 10	Mean	9.8 ⁿ	5.4 [*]	2.1 ^{**}
	S.d.	3.0	3.3	3.6
	N	10	10	10
	Deviation Vs Control		-45.0	-79.0

d = day; n=DUNNETT; * p<=0.05; ** p<=0.01

Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
d 10 -> 13	Mean	18.3 n	13.1	4.4 **
	S.d.	3.9	8.3	6.3
	N	10	10	10
	Deviation Vs Control		-28.4	-76.2
d 13 -> 15	Mean	9.5 n	7.4	-1.5 **
	S.d.	3.3	5.4	8.7
	N	10	10	10
	Deviation Vs Control		-21.8	-115.7
d 15 -> 17	Mean	16.4 n	15.4	-1.5 **
	S.d.	3.0	8.4	6.2
	N	10	10	10
	Deviation Vs Control		-5.9	-109.4
d 17 -> 19	Mean	22.4 n	16.2	-1.5 **
	S.d.	3.8	10.7	2.5
	N	10	10	10
	Deviation Vs Control		-27.9	-106.5
d 19 -> 20	Mean	14.7 n	8.7 *	3.8 **
	S.d.	3.7	6.4	2.5
	N	10	10	10
	Deviation Vs Control		-40.9	-74.0

n=DUNNETT; ** p <=0.01; d = day; * p <=0.05

Study

10R0066/05R022

22-Jul-2013 11:04

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
d 0 -> 20	Mean	123.1 n	98.8	40.0 **
	S.d.	20.8	35.2	7.3
	N	10	10	10
	Deviation Vs Control		-19.8	-67.5

n=DUNNETT; ** p <=0.01

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
d 0 -> 6	Mean	26.0 n	29.6	31.3
	S.d.	6.0	4.2	6.8
	N	10	10	10
	Deviation Vs Control		13.6	20.4
d 6 -> 19	Mean	82.4 n	60.5 *	4.8 **
	S.d.	13.9	29.7	5.8
	N	10	10	10
	Deviation Vs Control		-26.5	-94.2
d 0 -> 20	Mean	123.1 n	98.8	40.0 **
	S.d.	20.8	35.2	7.3
	N	10	10	10
	Deviation Vs Control		-19.8	-67.5

d = day; n=DUNNETT; * p<=0.05; ** p <=0.01

Study

10R0066/05R022

22-Jul-2013 11:05

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Uterine Weight Report

Sex: Female

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
Uterus weight (g)	Mean	57.5	41.4	0.8
	S.d.	8.3	26.7	0.2
	N	10	10	10
	Deviation Vs Control		-28.1	-98.6
Carcass Weight (g)	Mean	238.8 n	230.2	213.4 **
	S.d.	22.5	14.7	11.9
	N	10	10	10
	Deviation Vs Control		-3.6	-10.6
Net weight change (g) From Gestation day 6	Mean	39.6 n	27.9 *	7.8 **
	S.d.	11.2	12.5	4.6
	N	10	10	10
	Deviation Vs Control		-29.6	-80.2

n=DUNNETT; ** p <=0.01; * p<=0.05

Carcass Weight = Final Body Weight - Uterine Weight; Net weight change = Carcass Weight - Body Weight from Gestation day 6

Study

10R0066/05R022

22-Jul-2013 11:06

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Pregnancy Status Report - Reproduction F0

Sex: Female

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d
No. of females at start	N	10	10	10
No. of females mated	N	0	0	0
Females with defined Day 0 pc	N	10	10	10
Pregnant	N	10	10	10
- sacrificed scheduled	N	10	10	10
Not pregnant	N	0	0	0
Examined at scheduled c-section	N	10	10	10
- Not pregnant	N	0	0	0
- Pregnant	N	10	10	10
-- With total implant loss	N	0 c	0	0
	%	0.0	0.0	0.0
	P-Value	@1.0000		
-- With viable fetuses	N	0 c	0	0
	%	0.0	0.0	0.0
	P-Value	@1.0000		

c=CHI-SQUARE

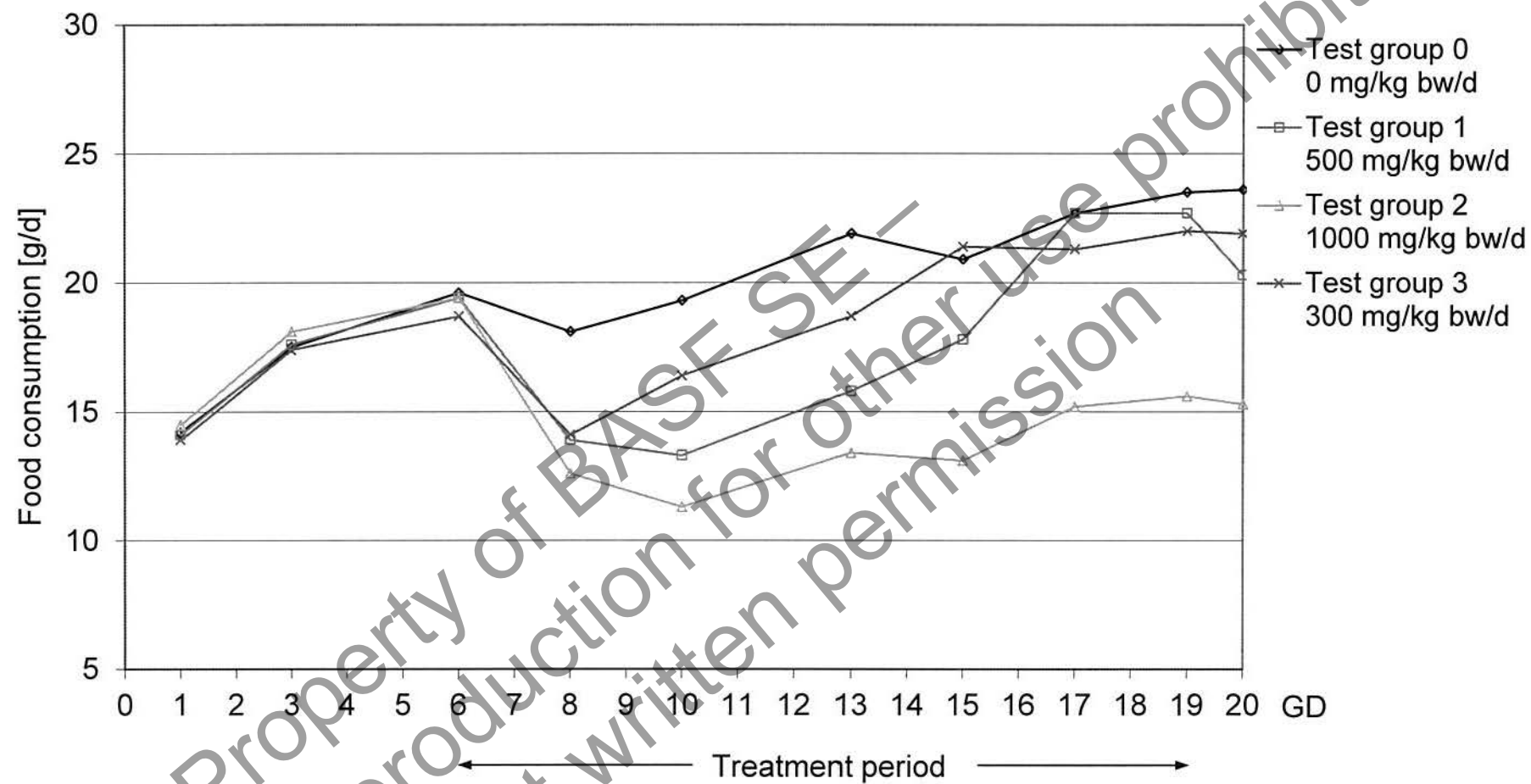
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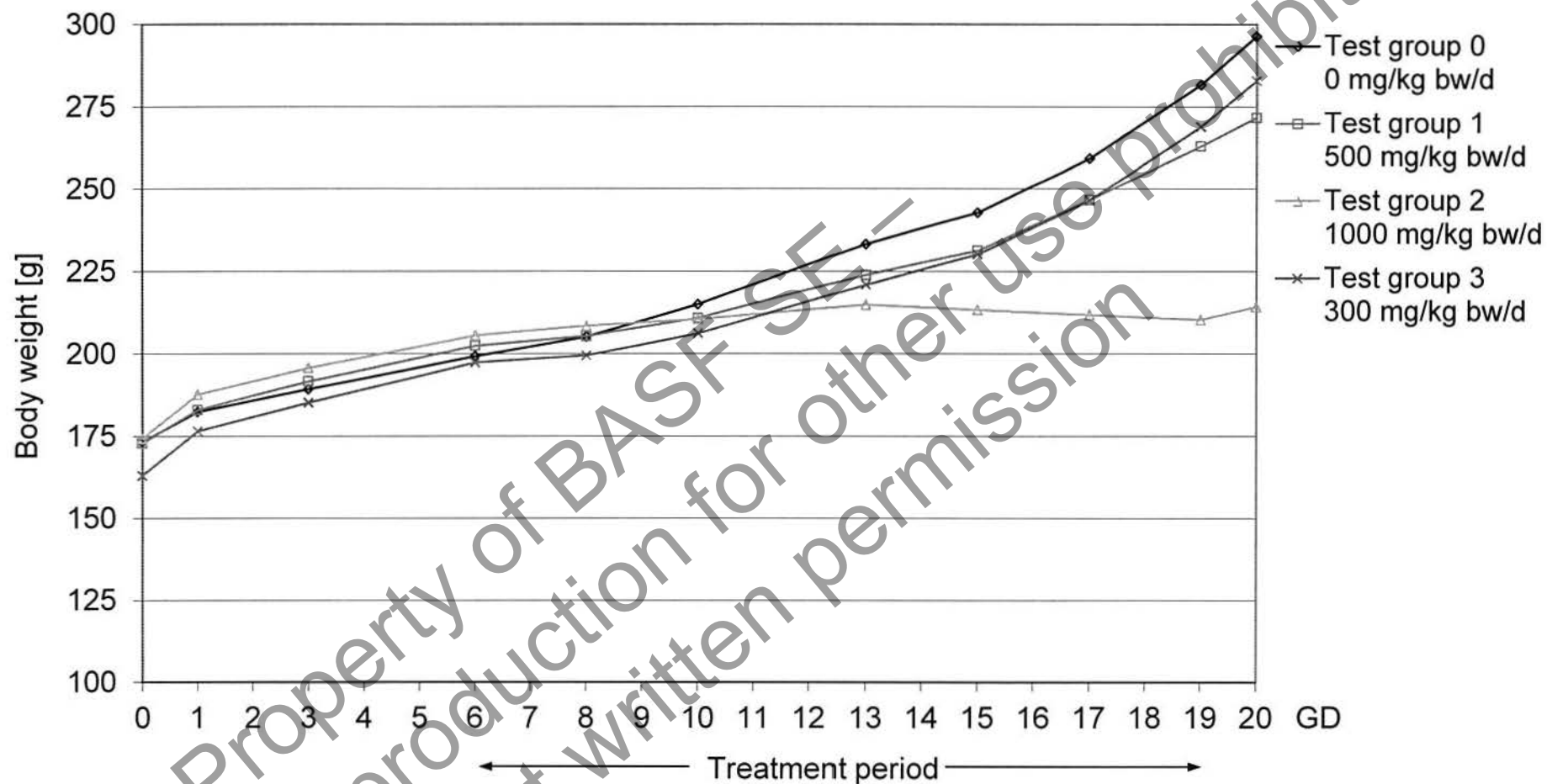
Maternal Toxicity Study in Wistar Rats (Range-Finding); Oral Administration (Gavage)

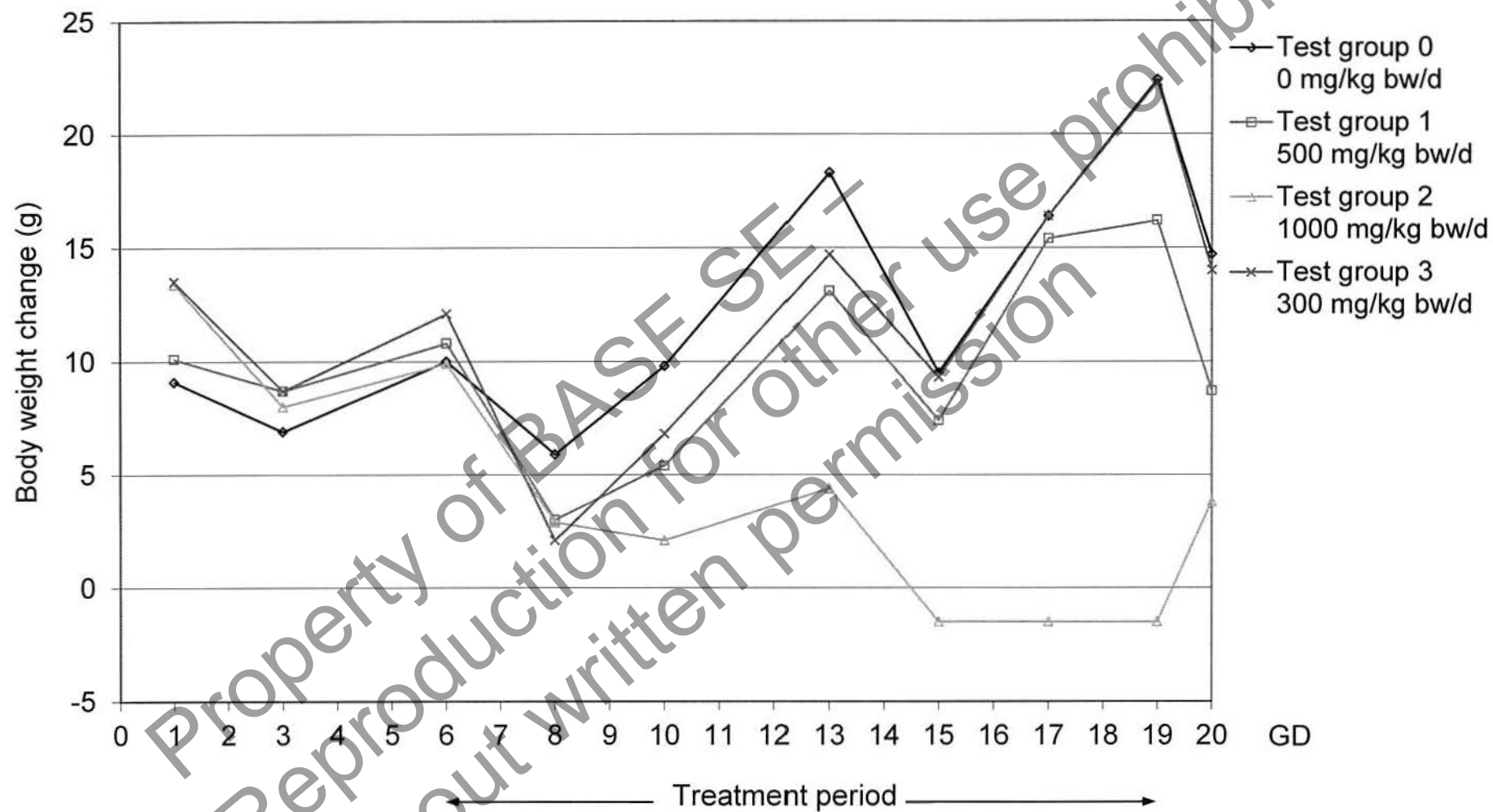
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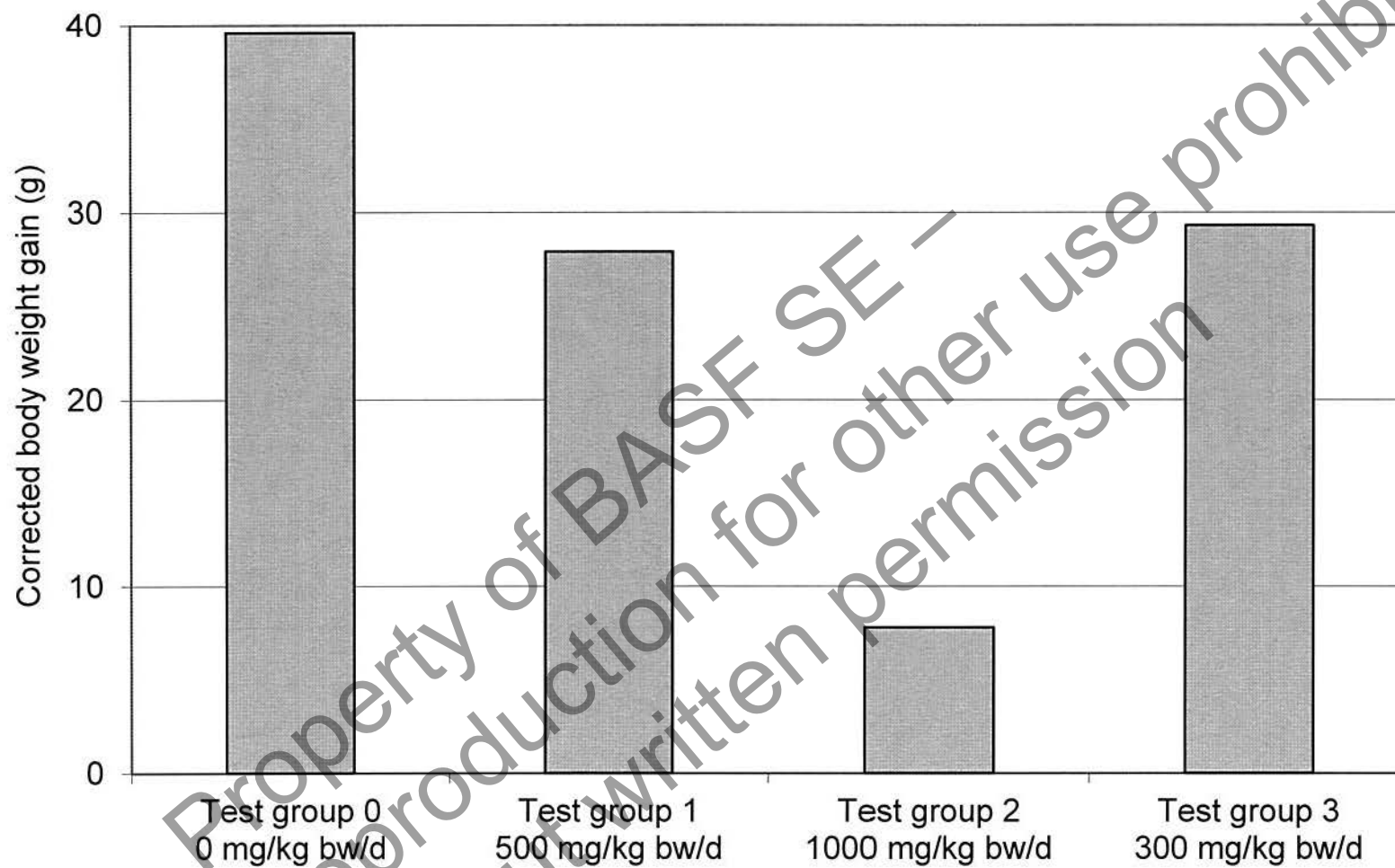
Dosage: 0; 500; 1000; 300 mg/kg bw/d; GD 6-19

Parameter mg/kg body weight/day	Test group 0 0	Test group 1 500	Test group 2 1000	Test group 3 300
Females mated/pregnant:	10/10	10/10	10/10	10/10
Clinical observations:	NAD	Piloerection (3/10) Vaginal discharge (1/10)	Salivation (9/10) Piloerection (8/10) Vaginal discharge (5/10)	NAD
FC (0 - 6) FC (6 - 19) FC (0 - 20)	18.0 g 21.1 g 20.3 g	17.9 g (-0.3%) 17.5 g (-16.9%) 17.8 g (-12.3%) FC (6 - 13, 19 - 20) = < Control */**	18.1 g (0.7%) 13.5 g (-36.1%) 15.0 g (-26.2%) FC (6 - 20) = < Control **	17.5 g 18.9 g 18. G FC (6 - 13) = < Control */**
BW (0) BW (6) BW (19) BW (20)	173.2 g 199.2 g 281.6 g 296.3 g	172.8 g (-0.2%) 202.4 g (1.6%) 262.9 g (-6.6%) 271.6 g (-8.3%)	174.2 g (0.6%) 205.5 g (3.2%) 210.3 g (-25.3%)** 214.2 g (-27.7%)** BW (13 - 20) = < Control */**	162.9 g (-5.9%) 197.3 g (-1.0%) 268.8 g (-4.6%) 282.8 g (-4.6%)
BWC (0 - 6) BWC (6 - 19) BWC (0 - 20) BWC (6 - 8) BWC (8 - 10) BWC (19 - 20)	26.0 g 82.4 g 123.1 g 5.9 g 9.8 g 14.7 g	29.6 g (13.6%) 60.5 g (-26.5%)* 98.8 g (-19.8%) 3.0 g (-49.4%) 5.4 g (-45.0%)* 8.7 g (-40.9%)*	31.3 g (20.4%) 4.8 g (-94.2%)** 40.0 g (-67.5%)** 2.9 g (-51.1%) 2.1 g (-79.0%)** 3.8 g (-74.0%)** BWC (8 - 20) = < Control **	34.4 g (34.4%)** 71.5 g (-13.2%) 119.9 g (-2.6%) 2.1 g (-64.5%)*
Uterus weight:	57.5 g	41.4 g (-28.1%)	0.8 g (-98.6%)	56.2 g (-2.3%)
Carcass weight:	238.8 g	230.2 g (-3.6%)	213.4 g (-10.6%)**	226.6 g (-5.1%)
Corrected body weight gain:	39.6 g	27.9 g (-29.6%)*	7.8 g (-80.2%)**	29.3 g (-25.9%)*









Study

10R0066/05R022

IA- 1

19-Aug-2013 10:11

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary - Clinical Observation

Sex: Female - Phase: Gestation

			Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
day 0 -> 20	Animals examined	N	10	10	10	10
	Animals with signs	N	0	3	9	0
	dead	N	10	10	10	10
	<i>sacrificed scheduled</i>					
	head	N	0	0	9	0
	<i>salivation</i>					
	genitals	N	0	1	5	0
	<i>vaginal discharge</i>					
	fur	N	0	3	8	0
	<i>piloerection</i>					
	normal	N	10	10	10	10
	NAD					

Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Food Consumption Per Day

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
d 0 -> 1	Mean [g]	14.2 n	14.1	14.5	13.9
	S.d.	2.6	2.0	2.9	1.8
	N	10	10	10	10
	Deviation Vs Control		-0.5	2.1	-1.7
d 1 -> 3	Mean [g]	17.5 n	17.6	18.1	17.4
	S.d.	1.6	1.8	1.5	1.8
	N	10	10	10	10
	Deviation Vs Control		0.9	3.7	-0.8
d 3 -> 6	Mean [g]	19.6 n	19.4	19.4	18.7
	S.d.	1.9	1.4	1.5	2.2
	N	10	10	10	10
	Deviation Vs Control		-0.9	-1.3	-4.5
d 6 -> 8	Mean [g]	18.1 n	13.9**	12.6**	14.1**
	S.d.	2.0	2.4	1.0	2.3
	N	10	10	10	10
	Deviation Vs Control		-23.4	-30.5	-22.4
d 8 -> 10	Mean [g]	19.3 n	13.3**	11.3**	16.4*
	S.d.	2.4	2.9	1.4	2.1
	N	10	10	10	10
	Deviation Vs Control		-31.1	-41.3	-15.3

d = day; n=DUNNETT; ** p <=0.01; * p <=0.05

Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Food Consumption Per Day

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
d 10 -> 13	Mean [g]	21.9 ⁿ	15.8 ^{**}	13.4 ^{**}	18.7 [*]
	S.d.	2.2	3.6	2.5	1.5
	N	10	10	10	10
	Deviation Vs Control		-28.0	-38.9	-14.6
d 13 -> 15	Mean [g]	20.9 ⁿ	17.8	13.1 ^{**}	21.4
	S.d.	3.0	3.8	2.6	3.1
	N	10	10	10	10
	Deviation Vs Control		-14.5	-37.4	2.3
d 15 -> 17	Mean [g]	22.7 ⁿ	22.7	15.2 ^{**}	21.3
	S.d.	2.7	3.7	2.0	1.4
	N	10	10	10	10
	Deviation Vs Control		0.0	-33.1	-6.2
d 17 -> 19	Mean [g]	23.5 ⁿ	22.7	15.6 ^{**}	22.0
	S.d.	3.3	4.2	1.4	1.9
	N	10	10	10	10
	Deviation Vs Control		-3.4	-33.6	-6.5
d 19 -> 20	Mean [g]	23.6 ⁿ	20.3 [*]	15.3 ^{**}	21.9
	S.d.	2.7	4.2	1.7	2.8
	N	10	10	10	10
	Deviation Vs Control		-13.8	-35.0	-7.3

n=DUNNETT; ** p <=0.01; * p<=0.05; d = day

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Food Consumption Per Day

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
d 0 -> 6	Mean [g]	18.0	17.9	18.1	17.5
	S.d.	1.6	1.4	1.6	1.9
	N	10	10	10	10
	Deviation Vs Control		-0.3	0.7	-2.9
d 6 -> 19	Mean [g]	21.1	17.5	13.5	18.9
	S.d.	2.4	2.8	1.2	1.7
	N	10	10	10	10
	Deviation Vs Control		-16.9	-36.1	-10.4
d 0 -> 20	Mean [g]	20.3	17.8	15.0	18.6
	S.d.	2.1	2.1	1.1	1.7
	N	10	10	10	10
	Deviation Vs Control		-12.3	-26.2	-8.3

d = day

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
day 0	Mean	173.2 n	172.8	174.2	162.9
	S.d.	9.7	11.4	11.6	11.2
	N	10	10	10	10
	Deviation Vs Control		-0.2	0.6	-5.9
day 1	Mean	182.3 n	182.9	187.6	176.4
	S.d.	10.9	11.1	12.5	12.1
	N	10	10	10	10
	Deviation Vs Control		0.3	2.9	-3.2
day 3	Mean	189.2 n	191.6	195.7	185.1
	S.d.	12.8	11.8	12.1	13.2
	N	10	10	10	10
	Deviation Vs Control		1.3	3.4	-2.2
day 6	Mean	199.2 n	202.4	205.5	197.3
	S.d.	13.9	11.9	13.0	13.5
	N	10	10	10	10
	Deviation Vs Control		1.6	3.2	-1.0
day 8	Mean	205.1 n	205.3	208.4	199.4
	S.d.	14.6	12.5	12.1	14.7
	N	10	10	10	10
	Deviation Vs Control		0.1	1.6	-2.8

n=DUNNETT

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
day 10	Mean	214.9 ⁿ	210.8	210.5	206.1
	S.d.	16.0	12.5	11.5	14.6
	N	10	10	10	10
	Deviation Vs Control		-2.0	-2.1	-4.1
day 13	Mean	233.2 ⁿ	223.8	214.8 [*]	220.8
	S.d.	18.6	13.3	14.7	14.7
	N	10	10	10	10
	Deviation Vs Control		-4.0	-7.9	-5.3
day 15	Mean	242.8 ⁿ	231.3	213.3 ^{**}	230.1
	S.d.	21.3	16.6	14.9	15.6
	N	10	10	10	10
	Deviation Vs Control		-4.7	-12.1	-5.2
day 17	Mean	259.2 ⁿ	246.7	211.8 ^{**}	246.5
	S.d.	22.6	22.1	13.1	15.5
	N	10	10	10	10
	Deviation Vs Control		-4.8	-18.3	-4.9
day 19	Mean	281.6 ⁿ	262.9	210.3 ^{**}	268.8
	S.d.	25.9	31.1	12.1	16.7
	N	10	10	10	10
	Deviation Vs Control		-6.6	-25.3	-4.6

n=DUNNETT; * p<=0.05; ** p<=0.01

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
day 20	Mean	296.3 n	271.6	214.2 **	282.8
	S.d.	27.5	36.1	11.9	17.9
	N	10	10	10	10
	Deviation Vs Control		-8.3	-27.7	-4.6

n=DUNNETT; ** p <=0.01

Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
d 0 -> 1	Mean	9.1 n	10.1	13.4 *	13.5 *
	S.d.	3.2	3.7	5.1	2.5
	N	10	10	10	10
	Deviation Vs Control		11.1	48.1	48.6
d 1 -> 3	Mean	6.9 n	8.7	8.0	8.7
	S.d.	3.2	2.4	3.1	2.2
	N	10	10	10	10
	Deviation Vs Control		25.7	15.9	26.3
d 3 -> 6	Mean	10.0 n	10.8	9.9	12.1
	S.d.	1.9	2.2	2.6	2.1
	N	10	10	10	10
	Deviation Vs Control		7.5	-1.5	20.9
d 6 -> 8	Mean	5.9 n	3.0	2.9	2.1 *
	S.d.	3.3	2.9	2.6	3.3
	N	10	10	10	10
	Deviation Vs Control		-49.4	-51.1	-64.5
d 8 -> 10	Mean	9.8 n	5.4 **	2.1 **	6.8
	S.d.	3.0	3.3	3.6	2.6
	N	10	10	10	10
	Deviation Vs Control		-45.0	-79.0	-31.3

d = day; n=DUNNETT; * p<=0.05; ** p <=0.01

Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
d 10 -> 13	Mean	18.3 ⁿ	13.1	4.4 ^{**}	14.7
	S.d.	3.9	8.3	6.3	1.3
	N	10	10	10	10
	Deviation Vs Control		-28.4	-76.2	-19.6
d 13 -> 15	Mean	9.5 ⁿ	7.4	-1.5 ^{**}	9.3
	S.d.	3.3	5.4	8.7	1.7
	N	10	10	10	10
	Deviation Vs Control		-21.8	-115.7	-2.5
d 15 -> 17	Mean	16.4 ⁿ	15.4	-1.5 ^{**}	16.4
	S.d.	3.0	8.4	6.2	2.2
	N	10	10	10	10
	Deviation Vs Control		-5.9	-109.4	-0.2
d 17 -> 19	Mean	22.4 ⁿ	16.2	-1.5 ^{**}	22.3
	S.d.	3.8	10.7	2.5	2.5
	N	10	10	10	10
	Deviation Vs Control		-27.9	-106.5	-0.5
d 19 -> 20	Mean	14.7 ⁿ	8.7 ^{**}	3.8 ^{**}	14.0
	S.d.	3.7	6.4	2.5	2.0
	N	10	10	10	10
	Deviation Vs Control		-40.9	-74.0	-4.8

n=DUNNETT; ** p <=0.01; d = day

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
d 0 -> 20	Mean	123.1 n	98.8 *	40.0 **	119.9
	S.d.	20.8	35.2	7.3	10.9
	N	10	10	10	10
	Deviation Vs Control		-19.8	-67.5	-2.6

n=DUNNETT; * p<=0.05; ** p <=0.01

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: Gestation

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
d 0 -> 6	Mean	26.0 n	29.6	31.3	34.4 **
	S.d.	6.0	4.2	6.8	4.8
	N	10	10	10	10
	Deviation Vs Control		13.6	20.4	32.0
d 6 -> 19	Mean	82.4 n	60.5 *	4.8 **	71.5
	S.d.	13.9	29.7	5.8	6.7
	N	10	10	10	10
	Deviation Vs Control		26.5	-94.2	-13.2
d 0 -> 20	Mean	123.1 n	98.8 *	40.0 **	119.9
	S.d.	20.8	35.2	7.3	10.9
	N	10	10	10	10
	Deviation Vs Control		-19.8	-67.5	-2.6

d = day; n=DUNNETT; ** p <=0.01; * p<=0.05

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Uterine Weight Report

Sex: Female

		Test Group 0	Test Group 1	Test Group 2	Test Group 3
		0 mg/kg bw/d	500 mg/kg bw/d	1000 mg/kg bw/d	300 mg/kg bw/d
Uterus weight (g)	Mean	57.5	41.4	0.8	56.2
	S.d.	8.3	26.7	0.2	6.5
	N	10	10	10	10
	Deviation Vs Control		-28.1	-98.6	-2.3
Carcass Weight (g)	Mean	238.8 n	230.2	213.4 **	226.6
	S.d.	22.5	14.7	11.9	15.2
	N	10	10	10	10
	Deviation Vs Control		-3.6	-10.6	-5.1
Net weight change (g) From Gestation day 6	Mean	39.6 n	27.9 *	7.8 **	29.3 *
	S.d.	11.2	12.5	4.6	4.7
	N	10	10	10	10
	Deviation Vs Control		-29.6	-80.2	-25.9

n=DUNNETT; ** p <=0.01; * p<=0.05

Carcass Weight = Final Body Weight - Uterine Weight; Net weight change = Carcass Weight - Body Weight from Gestation day 6

Study

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Maternal Toxicity Study in Wistar Rats (Range-Finding)

Oral Administration (Gavage)

Summary Pregnancy Status Report - Reproduction F0

Sex: Female

		Test Group 0 0 mg/kg bw/d	Test Group 1 500 mg/kg bw/d	Test Group 2 1000 mg/kg bw/d	Test Group 3 300 mg/kg bw/d
No. of females at start	N	10	10	10	10
No. of females mated	N	0	0	0	0
Females with defined Day 0 pc	N	10	10	10	10
Pregnant	N	10	10	10	10
- sacrificed scheduled	N	10	10	10	10
Not pregnant	N	0	0	0	0
Examined at scheduled c-section	N	10	10	10	10
- Not pregnant	N	0	0	0	0
- Pregnant	N	10	10	10	10
-- With total implant loss	N	0 c	0	0	0
	%	0.0	0.0	0.0	0.0
	P-Value	@1.0000			
-- With viable fetuses	N	0 c	0	0	0
	%	0.0	0.0	0.0	0.0
	P-Value	@1.0000			

c=CHI-SQUARE

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Maternal Toxicity Study in Wistar Rats (Range-Finding)
Oral Administration (Gavage)

10R0066/05R022
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INCIDENCE OF GROSS LESIONS

psn: 4

COMPARISON OF TEST GROUP 0 (CONTROL) TO TEST GROUP 3

Sacrifice	F1	
Sex	F	
Group	0	3
Animals in selected group	10	10
.....		
No abnormalities	10	8
.....		
Kidneys	.	.
Pelvic dilation	.	2

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Maternal Toxicity Study in Wistar Rats (Range-Finding)
Oral Administration (Gavage)

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ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

psn: 1

COMPARISON OF TEST GROUP 0 (CONTROL) TO TEST GROUP 3

Sacrifice			F1	
Sex			F	
Group			0	3
.....				
Terminal body weight	g	M	238.79	226.59
		% dev	100	95
		SD	22.514	15.213
		n	10	10
.....				
Adrenal glands	mg	M	67.2	63.8
		% dev	100	95
		SD	7.927	7.036
		n	10	10
.....				
Kidneys	g	M	1.655	1.523
		% dev	100	92
		SD	0.232	0.114
		n	10	10
.....				
Liver	g	M	11.799	11.033
		% dev	100	94
		SD	1.577	0.853
		n	10	10
.....				
Spleen	g	M	0.495	0.476
		% dev	100	96
		SD	0.057	0.033
		n	10	10
.....				

*: P ≤ 0.05, **: P ≤ 0.01

Wilcoxon test, two sided

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Maternal Toxicity Study in Wistar Rats (Range-Finding)
Oral Administration (Gavage)

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RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

psn: 3

COMPARISON OF TEST GROUP 0 (CONTROL) TO TEST GROUP 3

				F1	
				F	
Sex					
Group				0	3
.....					
Sacrifice					
Terminal body weight	%	M	100.0	100.0	
		% dev	100	100	
		n	10	10	
.....					
Adrenal glands	%	M	0.028	0.028	
		% dev	100	100	
		SD	0.004	0.002	
		n	10	10	
.....					
Kidneys	%	M	0.691	0.673	
		% dev	100	97	
		SD	0.047	0.042	
		n	10	10	
.....					
Liver	%	M	4.925	4.87	
		% dev	100	99	
		SD	0.261	0.212	
		n	10	10	
.....					
Spleen	%	M	0.208	0.211	
		% dev	100	101	
		SD	0.023	0.019	
		n	10	10	
.....					

*: P <= 0.05, **: P <= 0.01
Wilcoxon test, two sided

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Maternal Toxicity Study in Wistar Rats (Range-Finding)
Oral Administration (Gavage)

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INCIDENCE OF GROSS LESIONS

psn:9201

Sacrifice	F1		
Sex	F		
Group	0	1	2
Animals in selected group	10	10	10
.....			
No abnormalities	10	9	10
Kidneys	.	.	.
Cyst	.	1	.

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Maternal Toxicity Study in Wistar Rats (Range-Finding)
Oral Administration (Gavage)

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ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

psn:9107

			F1		
Sex			F		
Group			0	1	2
.....					
Terminal body weight	g	M	238.79	230.23	213.36 **
		% dev	100	96	89
		SD	22.514	14.731	11.935
		n	10	10	10
.....					
Adrenal glands	mg	M	67.2	68.9	76.9 *
		% dev	100	103	114
		SD	7.927	6.332	8.517
		n	10	10	10
.....					
Kidneys	g	M	1.655	1.633	1.565
		% dev	100	99	95
		SD	0.232	0.099	0.111
		n	10	10	10
.....					
Liver	g	M	11.799	10.702	8.408**
		% dev	100	91	71
		SD	1.577	1.386	0.67
		n	10	10	10
.....					
Spleen	g	M	0.495	0.507	0.476
		% dev	100	102	96
		SD	0.057	0.061	0.053
		n	10	10	10
.....					

*: P ≤ 0.05, **: P ≤ 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

Maternal Toxicity Study in Wistar Rats (Range-Finding)
Oral Administration (Gavage)

10R0066/05R022
22.Jul.2013 RAHE

RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

psn:9109

Sacrifice			F1		
Sex			F		
Group			0	1	2
.....					
Terminal body weight	%	M	100.0	100.0	100.0
	% dev		100	100	100
	n		10	10	10
.....					
Adrenal glands	%	M	0.028	0.03	0.036**
	% dev		100	106	128
	SD		0.004	0.003	0.004
	n		10	10	10
.....					
Kidneys	%	M	0.691	0.71	0.733
	% dev		100	103	106
	SD		0.047	0.03	0.046
	n		10	10	10
.....					
Liver	%	M	4.925	4.634	3.94 **
	% dev		100	94	80
	SD		0.261	0.383	0.212
	n		10	10	10
.....					
Spleen	%	M	0.208	0.22	0.223
	% dev		100	105	107
	SD		0.023	0.021	0.028
	n		10	10	10
.....					

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

Homogeneity and Concentration Control Analysis of DHDPS in 1 % Carboxymethylcellulose in drinking water

1. PROJECT AND TEST SUBSTANCE INFORMATION

Project No.: 10R0066/05R022
Test item (= test substance): DHDPS
Batch No.: 69611767J0

2. SAMPLE DATA

2.1. HOMOGENEITY AND CONCENTRATION CONTROL ANALYSIS

Vehicle: 1 % carboxymethylcellulose in drinking water
Storage conditions of the samples until analysis: Freezer

3. MATERIAL AND METHODS

3.1. SAMPLE PREPARATION AND ANALYSIS

The sample preparation and analysis of the test substance was carried out according to the valid control procedure 05/0066_01-01.

3.2. LIST OF DEVIATIONS

3.2.1. List of deviations from the control procedure

There was no deviation from the described control procedure 05/0066_01-01.

4. RESULTS AND DISCUSSION

4.1. HOMOGENEITY AND CONCENTRATION CONTROL ANALYSIS

The results obtained for the homogeneity and concentration control analyses of DHDPS in 1 % carboxymethylcellulose in drinking water are summarized in the following tables:

All calculated values in the tables are rounded. Calculations were performed with a full set of decimal places.

Date of sample preparation:	04 Aug 2013
Date of sampling:	04 Aug 2013
Date of receipt of sample in analytical laboratory:	05 Aug 2013
Starting date of analytical determination:	08 Aug 2013

Name	Amount	Nominal Conc	Nominal Conc	Mean	RSD
	g/100 mL	g/100 mL	%	%	%
Sample 09	2.812	3.000	93.7%		
Sample 10	2.901	3.000	96.7%		
Sample 11	2.821	3.000	94.0%	94.8%	1.7%

Date of sample preparation:	08 Jul 2013
Date of sampling:	08 Jul 2013
Date of receipt of sample in analytical laboratory:	08 Jul 2013
Starting date of analytical determination:	18 Jul 2013

Name	Amount	Nominal Conc	Nominal Conc	Mean	RSD
	g/100 mL	g/100 mL	%	%	%
Sample 03	4.721	5.0	94.4%		
Sample 04	4.915	5.0	98.3%		
Sample 05	4.950	5.0	99.0%	97.2%	2.5%
Sample 06	10.195	10.0	101.9%		
Sample 07	9.568	10.0	95.7%		
Sample 08	10.166	10.0	101.7%	99.8%	3.5%

Considering the low relative standard deviation in the homogeneity analysis, it can be concluded that DHDPS was distributed homogeneously in 1 % carboxymethylcellulose in drinking water.

The mean values of DHDPS in 1 % carboxymethylcellulose in drinking water were found to be in the range of 90 % – 110 % of the nominal concentrations.

These results demonstrated the correctness of the concentrations of DHDPS in 1 % carboxymethylcellulose in drinking water.

Figures of the calibration curve and examples of chromatograms will follow within this report.

Figure 1: Chromatogram of matrix solution (measured on 18 Jul 2013)

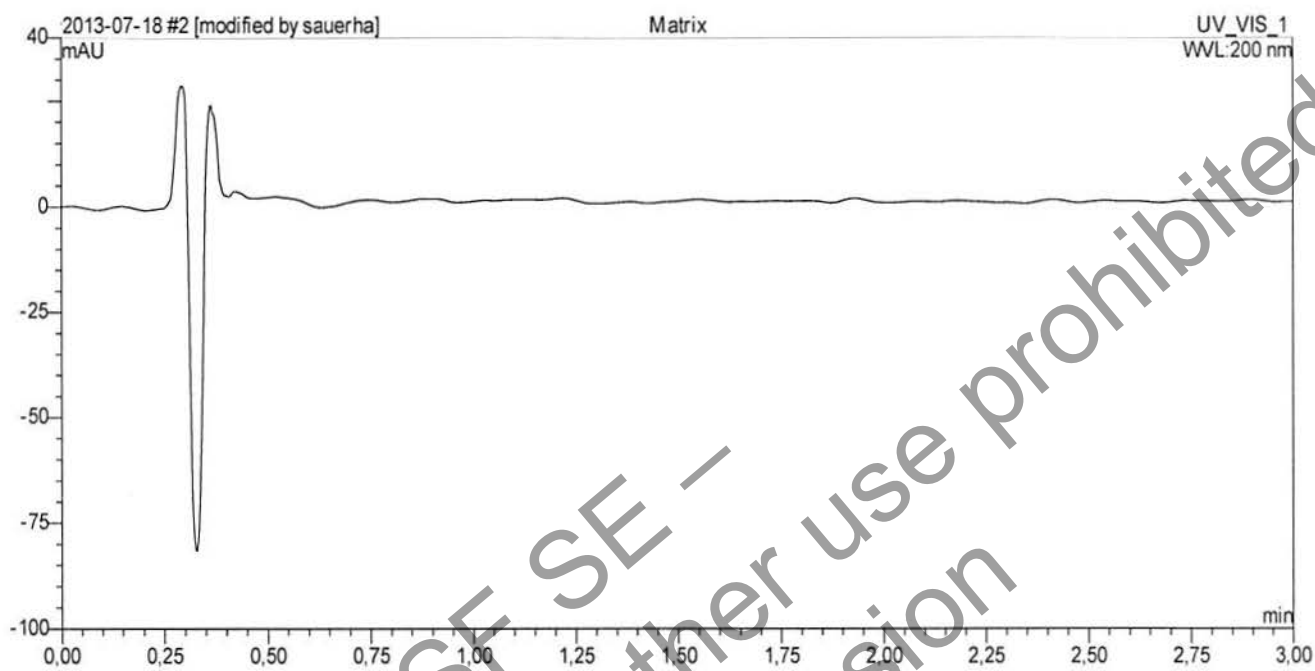


Figure 2: Chromatogram of calibration solution 1 (2.052 mg/100 mL, measured on 18 Jul 2013)

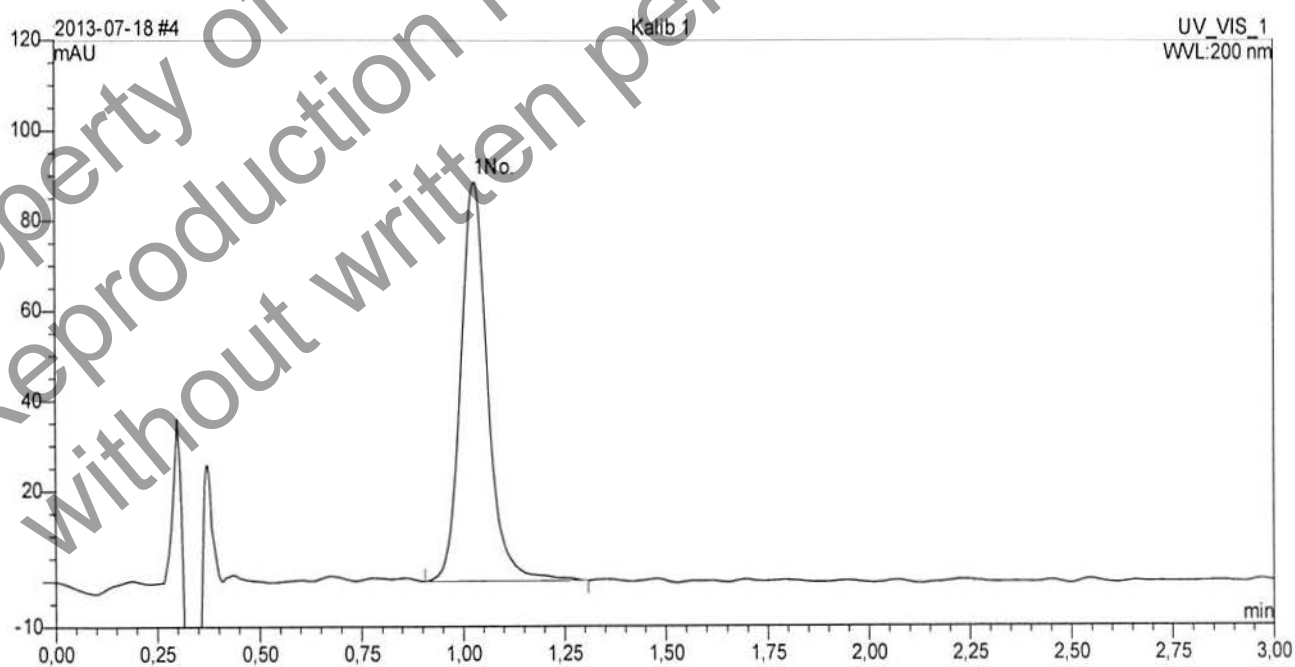


Figure 3: Chromatogram of sample 04 (measured on 18 Jul 2013)

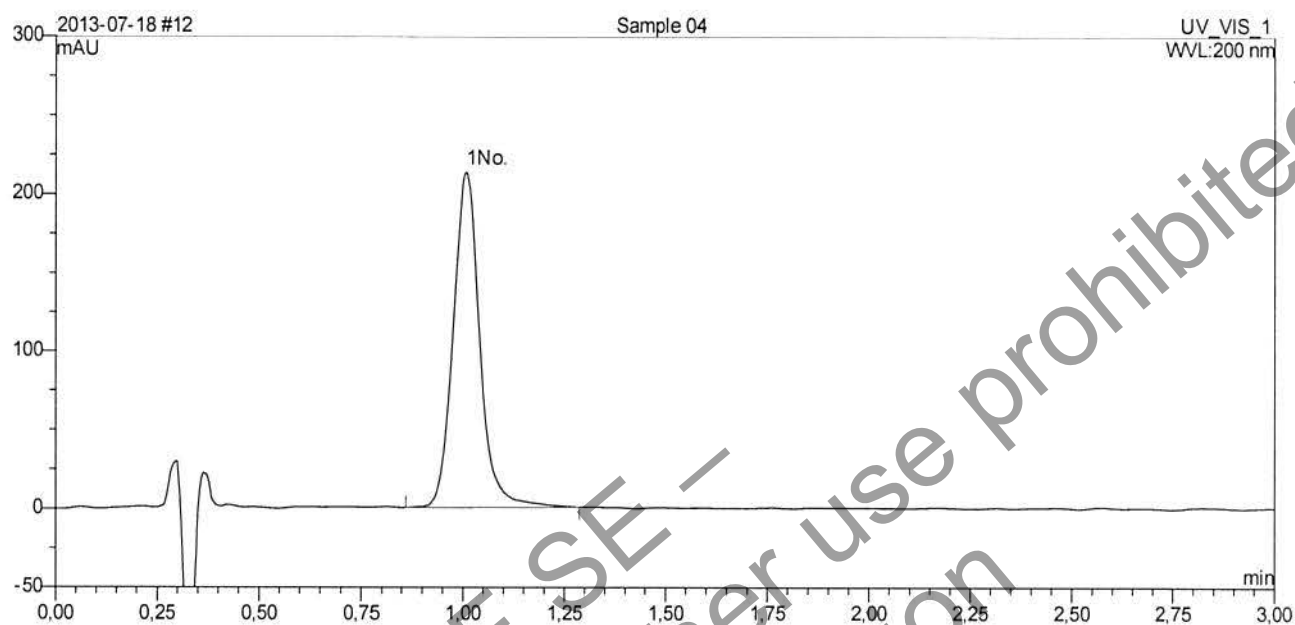
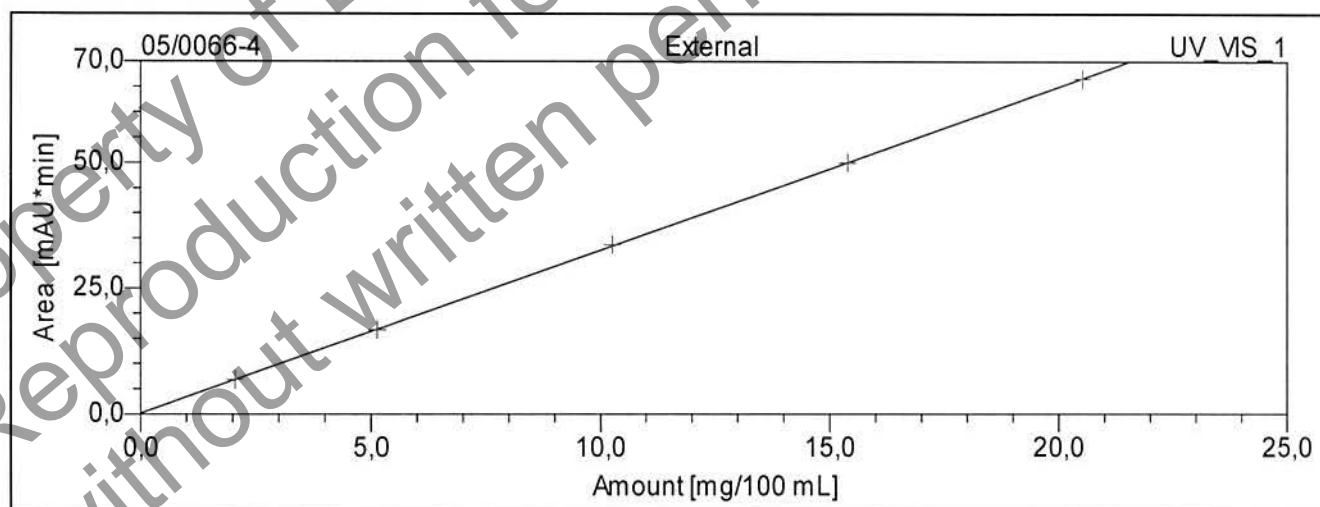


Figure 4: Calibration curve (measured on 18 Jul 2013, Concentration range 2.052 – 20.52 mg/100 mL)



5. APPENDIX

5.1. CONTROL PROCEDURE 05/0066_01-01

BASF SE
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Experimental Toxicology and Ecology / Analytical Chemistry



CONTROL TEST

Test substance number: 05/0066

No.: 05/0066_01-01

Name of test substance: DHDPs

Effective from: 09 Oct 2012

Control procedure: Content (LC) / Carboxymethylcellulose(CMC) in drinking water

Page 1 of 5

Technique	HPLC	
System:	Waters alliance 2487 with auto sampler, Dionex Chromeleon-Software (Dionex), or equivalent system	
Column:	Length: 100 mm Inner diameter: 4.6 mm	
Stationary Phase:	Chromolith Performance RP 18e, Merck or equivalent	
Mobile Phase A:	1000 mL acetonitrile are mixed with 1 mL formic acid (HCOOH)	
Mobile Phase B:	1000 mL water are mixed with 1 mL formic acid (HCOOH)	
Isocratic:		
	Mobile Phase A 20 %	Mobile Phase B 80 %
Injection volume:	10 µL	
Flow rate:	5 mL/min	
Detection:	200 nm	
Column temperature:	Ambient	
Run time:	Approx. 3 min	

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Sample solution: Samples are diluted completely with methanol using appropriate volumetric flasks to obtain sample solutions with test substance concentrations that match the calibration range.
If required, all dilutions are sonicated for 5 minutes to ensure a complete dissolution of the test substance.

The samples are filtered (cellulose filter, 0.2 µm) prior HPLC analysis.

Annotation: If the amount of test substance in the sample solution is outside the calibration range (calibration solutions 1 – 5), an adequate dilution step with matrix solution has to be performed to match the described concentration range.

Matrix solution: The preparation of the matrix solution has to be performed according to the procedure described for sample solution preparation

Stock solution: Approx. 50 mg test substance are dissolved to a final volume of 100 mL with methanol (50 mg/100 mL)

Calibration solution 1: 1.0 mL stock solution are diluted with matrix solution to 25 mL (2 mg/100 mL)

Calibration solution 2: 1.0 mL stock solution are diluted with matrix solution to 10 mL (5 mg/100 mL)

Calibration solution 3: 1.0 mL stock solution are diluted with matrix solution to 5 mL (10 mg/100 mL)

Calibration solution 4: 1.5 mL stock solution are diluted with matrix solution to 5 mL (15 mg/100 mL)

Calibration solution 5: 2.0 mL stock solution are diluted with matrix solution to 5 mL (20 mg/100 mL)

System-suitability solution: System-suitability solution is prepared with a second independent weighing according to calibration solution 3 (10 mg/100 mL)

Procedure After conditioning the HPLC system, sample solutions, matrix solution, calibration solutions and system-suitability solution are injected according to the sequence described in the raw data. All solutions are injected at least once.

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Retention time:

Test substance : 4,4'-Dihydroxydiphenylsulfon:
Approx. 1 min

System suitability:

The calculated content of the system-suitability solution has to be in the range from 95 % to 105 %.

The coefficient of determination (R^2) has to be ≥ 0.990 . If the correlation coefficient (R) is used, this value has to be ≥ 0.995 .

Calculation:

The concentration control measurements are based on external calibration (calibration solutions 1 – 5).

The calculation of the content is performed electronically. (e.g. Dionex Chromeleon – Software, Microsoft Excel). Basic formulas for calculations are described below (e.g. Dionex Chromeleon – Software)

Formulas:**Calibration curve**

$$Y = a \cdot x + b$$

a = slope of calibration curve

b = intercept

Analysed concentration (C_A)

$$C_A = \frac{(Y - b) \cdot V \cdot d}{a \cdot w}$$

or

$$C_A = \frac{(Y - b) \cdot V \cdot d}{a \cdot v}$$

w = weight sample

V = final sample volume

d = dilution factor

v = volume sample

V = final sample volume

d = dilution factor

Analysed concentration (C_A)

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**CONTROL TEST**

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Control procedure: Content (LC) / Carboxymethylcellulose(CMC) in drinking water

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Figure 1.1: Example chromatogram matrix solution (08 Oct 2012, Project no.: 01Y0066/05Y009) for illustration

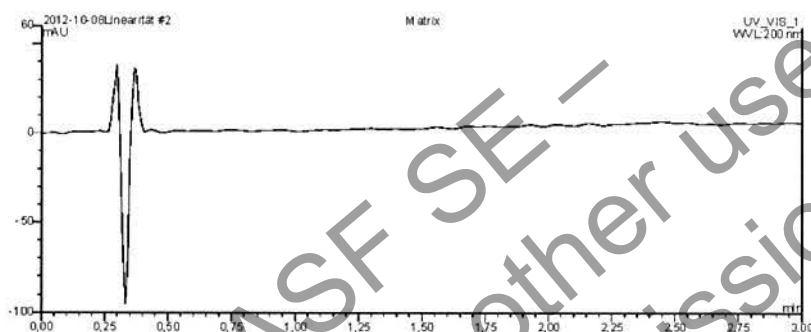
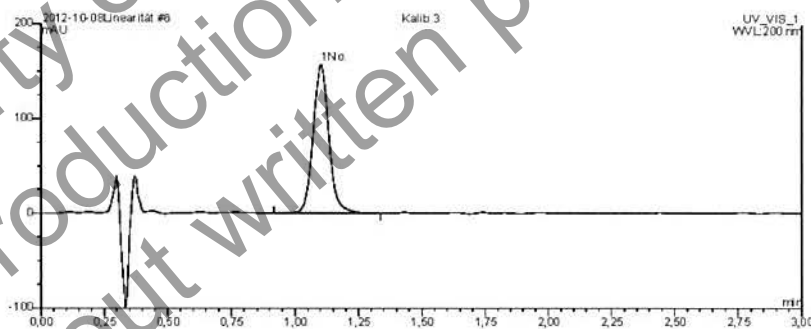


Figure 1.2: Example chromatogram calibration solution (08 Oct 2012, Project no.: 01Y0066/05Y009) for illustration



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Experimental Toxicology and Ecology / Analytical Chemistry



CONTROL TEST

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Figure 1.3 Example calibration curve (08 Oct 2012, Project no.: 01Y0066/05Y009) for illustration

