

Disclaimer

This document has been submitted in response to a solicitation by the California Office of Environmental Health and Hazard Assessment (OEHHA) to BASF Corporation (BASF). The submission of this document to a public docket maintained by OEHHA is not a waiver of BASF's ownership rights. No consent is granted for third party use of this document for any purpose, in any jurisdiction. Specifically, no consent is granted for the use of this document in any regulatory activity or registration, whether international, national, or local, including, but not limited to the Regulation Evaluation Authorization and Restriction of Chemicals ("REACH") regulation in the European Union.

STUDY TITLE

Summary Report

[not QAU-checked]

DHDPS

Repeated-dose 28-day toxicity study in Wistar rats

Administration by gavage

Range-finding study

TEST FACILITY PROJECT IDENTIFICATION

Project No. 30C0066/05S020

TEST FACILITY

BASF SE

Experimental Toxicology and Ecology

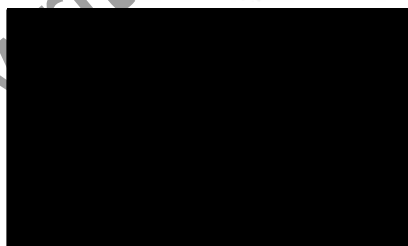
67056 Ludwigshafen, Germany

SPONSOR

BASF SE

67056 Ludwigshafen, Germany

Study director:



13 Sep 2013

This document contains manufacturing and trade secrets of the sponsor(s). It is the property of the sponsor(s) and may be used only for that purpose for which it was intended by the sponsor(s). Every other or additional use, exploitation, reproduction, publication or submission to other parties require the written permission of the sponsor(s), with the exception of regulatory agencies acting within the limits of their administrative authority.

1. Summary

1.1. Methods

The objective of the study was to determine the toxicological profile of the test substance including the target organs and the "no observed adverse effect level" (NOAEL) after 4 weeks oral administration by gavage, before the beginning of a subsequent repeated-dose 90-day oral toxicity study in Wistar rats.

The test substance was administered by gavage to groups of 5 male and 5 female Wistar rats for 28 days. The dose levels were set to 0 (test group 0), 50 (test group 1), 150 (test group 2) and 500 mg/kg body weight/day (test group 3). Drinking water containing 1% carboxymethylcellulose served as vehicle. At the end of the administration period, the animals were sacrificed and necropsied. The weights of adrenal glands, kidneys and livers were determined. In addition, these organs plus the cecum were fixed and assessed by histopathology.

After completion of the first study phase, the test substance was administered by gavage to additional groups of 5 male and 5 female Wistar rats for 28 days at dose levels of 0 and 1000 mg/kg body weight/day (test groups 10 and 11). At the end of the administration period, the animals were sacrificed and necropsied, the same organ weights were determined. Again, these organs plus the cecum were fixed and assessed by histopathology.

1.2. Results

The following is a summary of the most relevant results:

Test group 11: 1000 mg/kg body weight/day

Clinical Examinations:

- Lower mean body weights in male animals, i.e. -8.1% on study day 28
- Lower body weight change values in male animals, i.e. on study days 21 (-13%) and 28 (-18%)

Pathology

- Decreased terminal body weight of male animals (-8%)
- Increased weight of the adrenal glands of male animals (absolute +45%, relative +59%)
- Increased weight of the liver in female animals (absolute +17%, relative +20%)

- Increased relative weight of the kidney of male (+18%) and female animals (+12%)
- Dilation of the cecum in all male and female animals
- Minimal hypertrophy / hyperplasia of the cecal mucosa in all male and 4 female animals
- Minimally increased apoptosis of cecal mucosal cells in all male and 3 female animals
- Nuclear crowding in proximal tubules of the kidney in 3 male animals
- Mineralization of the medulla in 2 male animals
- Minimal centrilobular hypertrophy in the liver of all female animals

Test group 3: 500 mg/kg body weight/day**Clinical Examinations:**

- No treatment-related, adverse effects were observed.

Pathology

- Increased relative weight of the liver in female animals (+13%)
- Minimal centrilobular hypertrophy in the liver of all male and 2 female animals
- Dilation of the cecum in all male and female animals characterized by shortening of crypts and epithelial thinning
- Nuclear crowding in proximal tubules of the kidney in 4 male animals
- Mineralization of the medulla in 2 male animals
- Increased incidence of basophilic tubules (grading was minimal in all animals): all male and 3 female animals while the incidence in controls was 1/5 in both male and females

Test group 2: 150 mg/kg body weight/day**Clinical Examinations:**

- No treatment-related, adverse effects were observed.

Pathology

- Increased relative weight of the liver in female animals (+8%).
- No histopathology was performed.

Test group 1: 50 mg/kg body weight/day

Clinical Examinations:

- No treatment-related, adverse effects were observed.

Pathology

- No test substance-related findings were observed.
- No histopathology was performed.

Property of BASF SE –
Reproduction for other use prohibited
without written permission

2. Tables Section

CLINICAL EXAMINATIONS (MEAN VALUES AND SUMMARY TABLES)

Observations Report	IA- 1 - IA-16
Food consumption	IA-17 - IA-20
Body weight	IA-21 - IA-24
Body weight change	IA-25 - IA-28

PATHOLOGY (MEAN VALUES AND SUMMARY TABLES)

Absolute weights - mean values (male)	IC - 1
Absolute weights - mean values (female)	IC - 2
Relative weights - mean values (male)	IC- 3
Relative weights - mean values (female)	IC- 4
Incidence of gross lesions	IC- 5
Incidence and grading of microscopic findings	IC- 6
Absolute weights - mean values (male) (Test groups 10, 11)	IC - 7
Absolute weights - mean values (female) (Test groups 10, 11)	IC - 8
Relative weights - mean values (male) (Test groups 10, 11)	IC- 9
Relative weights - mean values (female) (Test groups 10, 11)	IC-10
Incidence of gross lesions (Test groups 10, 11)	IC-11
Incidence and grading of findings in target organs (Test groups 10, 11)	IC-12

3. Supplement

Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002

ANALYTICAL REPORT

DHDPS

Stability Analysis in 1% Carboxymethylcellulose in Drinking Water

Project No. 01Y0066/05Y009

Homogeneity and Concentration Control Analysis of DHDPS in 1%
carboxymethylcellulose in Drinking Water

Property of BASF SE –
Reproduction for other use prohibited
without written permission

IA-1
22-Apr-2013 08:10
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Male** - Phase: **In-life**

		0 / M	1 / M	2 / M	3 / M
day 0 -> 30 [-01:00-00:00]	Animals examined	N	5	5	5
	normal	N	5	5	5
	NAD	%	100.0	100.0	100.0

IA- 2
22-Apr-2013 08:10
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Male** - Phase: **In-life**

	0 / M	1 / M	2 / M	3 / M
Animals examined	N	5	5	5
normal	N	5	5	5
NAD	%	100.0	100.0	100.0

day 0 -> 30
[00:00-02:00]

IA- 3
22-Apr-2013 08:10
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Male** - Phase: **In-life**

	0 / M	1 / M	2 / M	3 / M
Animals examined	N	5	5	5
normal	N	5	5	5
NAD	%	100.0	100.0	100.0

day 0 -> 30
[02:00-05:00]

IA- 4
22-Apr-2013 08:14
ToxData© System 3.0

Study 30C0066/05S020

Summary - Clinical Observation

Sex: **Male** - Phase: **In-life**

	0 / M	1 / M	2 / M	3 / M
Animals examined	N 5	5	5	5
dead	N 5	5	5	5
sacrificed scheduled	% 100.0	100.0	100.0	100.0
normal	N 5	5	5	5
NAD	% 100.0	100.0	100.0	100.0

day 31 [00:00 - 24:00] -> [00:00 - 24:00]

IA- 5
22-Apr-2013 08:16
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Male** - Phase: **In-life**

		10 / M	11 / M
	N	5	5
Animals examined	N	0	0
Animals with signs	%	0.0	0.0
head	N	0	0
salivation	%	0.0	0.0
normal	N	5	5
NAD	%	100.0	100.0

day 0 -> 30
[-01:00-00:00]

IA- 6
22-Apr-2013 08:16
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Male** - Phase: **In-life**

		10 / M	11 / M
	N	5	5
Animals examined	N	0	3
Animals with signs	%	0.0	60.0
head	N	0	3
salivation	%	0.0	60.0
normal	N	5	5
NAD	%	100.0	100.0

day 0 -> 30
[00:00-02:00]

IA-7
22-Apr-2013 08:16
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Male** - Phase: **In-life**

		10 / M	11 / M
day 0 -> 30 [02:00-05:00]	Animals examined	5	5
	Animals with signs	0	0
		0.0	0.0
	head	0	0
	salivation	0.0	0.0
	normal	0	0
	NAD	5	5
	%	100.0	100.0

IA- 8
22-Apr-2013 14:06
ToxData© System 3.0

Study 30C0066/05S020

Summary - Clinical Observation

Sex: **Male** - Phase: **In-life**

		10 / M	11 / M
Animals examined	N	5	5
Animals with signs	N	0	3
	%	0.0	60.0
dead	N	5	5
sacrificed scheduled	%	100.0	100.0
head	N	0	3
salivation	%	0.0	60.0
normal	N	5	5
NAD	%	100.0	100.0

day 0 [DCO] -> day 31 [00:00 - 24:00]

IA- 9
22-Apr-2013 08:48
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Female** - Phase: **In-life**

		0 / F	1 / F	2 / F	3 / F
day 0 -> 30 [-01:00-00:00]	Animals examined	N	5	5	5
	normal	N	5	5	5
	NAD	%	100.0	100.0	100.0

IA- 10
22-Apr-2013 08:48
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Female** - Phase: **In-life**

	0 / F	1 / F	2 / F	3 / F
Animals examined	N	5	5	5
normal	N	5	5	5
NAD	%	100.0	100.0	100.0

day 0 -> 30
[00:00-02:00]

IA- 11
22-Apr-2013 08:48
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Female** - Phase: **In-life**

	0 / F	1 / F	2 / F	3 / F
Animals examined	N	5	5	5
normal	N	5	5	5
NAD	%	100.0	100.0	100.0

day 0 -> 30
[02:00-05:00]

IA- 12
22-Apr-2013 08:51
ToxData© System 3.0

Study 30C0066/05S020

Summary - Clinical Observation

Sex: **Female** - Phase: **In-life**

	0 / F	1 / F	2 / F	3 / F
Animals examined	N 5	5	5	5
dead	N 5	5	5	5
sacrificed scheduled	% 100.0	100.0	100.0	100.0
normal	N 5	5	5	5
NAD	% 100.0	100.0	100.0	100.0

day 31 [00:00 - 24:00] -> [00:00 - 24:00]

IA- 13
22-Apr-2013 08:53
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Female** - Phase: **In-life**

		10 / F	11 / F
	N	5	5
Animals examined	N	0	0
Animals with signs	%	0.0	0.0
head	N	0	0
salivation	%	0.0	0.0
normal	N	5	5
NAD	%	100.0	100.0

day 0 -> 30
[-01:00-00:00]

IA- 14
22-Apr-2013 08:53
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Female** - Phase: **In-life**

		10 / F	11 / F
	N	5	5
Animals examined	N	0	5
Animals with signs	%	0.0	100.0
head	N	0	5
salivation	%	0.0	100.0
normal	N	5	5
NAD	%	100.0	100.0

day 0 -> 30
[00:00-02:00]

IA- 15
22-Apr-2013 08:53
ToxData© System 3.0

Study 30C0066/05S020

Summary Signs Dosing Related - Clinical Observation

Sex: **Female** - Phase: **In-life**

		10 / F	11 / F
	N	5	5
Animals examined	N	0	0
Animals with signs	%	0.0	0.0
head	N	0	0
salivation	%	0.0	0.0
normal	N	5	5
NAD	%	100.0	100.0

day 0 -> 30
[02:00-05:00]

IA- 16
22-Apr-2013 14:07
ToxData© System 3.0

Study 30C0066/05S020

Summary - Clinical Observation

Sex: **Female** - Phase: **In-life**

		10 / F	11 / F
Animals examined	N	5	5
Animals with signs	N	0	5
	%	0.0	100.0
dead	N	5	5
sacrificed scheduled	%	100.0	100.0
head	N	0	5
salivation	%	0.0	100.0
normal	N	5	5
NAD	%	100.0	100.0

day 0 [DCO] -> day 31 [00:00 - 24:00]

IA- 17
22-Apr-2013 14:02
ToxData© System 3.0

Study 30C0066/05S020

Summary Food Consumption Per Day

Sex: **Male** - Phase: **In-life**

	0 / M	1 / M	2 / M	3 / M
d 6 -> 7				
Mean [g]	22.2	19.1	19.2	18.8
N	1	1	1	1
Deviation Vs Control		-14.0	-13.5	-15.3
d 13 -> 14				
Mean [g]	19.9	18.2	18.3	19.4
N	1	1	1	1
Deviation Vs Control		-8.5	-8.0	-2.5
d 20 -> 21				
Mean [g]	19.4	19.8	20.3	19.3
N	1	1	1	1
Deviation Vs Control		2.1	4.6	-0.5
d 27 -> 28				
Mean [g]	20.5	20.4	19.5	18.0
N	1	1	1	1
Deviation Vs Control		-0.5	-4.9	-12.2

d = day

IA- 18
22-Apr-2013 09:47
ToxData© System 3.0

Study 30C0066/05S020

Summary Food Consumption Per Day

Sex: **Male** - Phase: **In-life**

		10 / M	11 / M
d 6 -> 7	Mean [g]	20.1	18.5
	N	1	1
	Deviation Vs Control		-8.0
d 13 -> 14	Mean [g]	21.3	21.2
	N	1	1
	Deviation Vs Control		-0.5
d 20 -> 21	Mean [g]	20.6	20.3
	N	1	1
	Deviation Vs Control		-1.5
d 27 -> 28	Mean [g]	23.6	20.8
	N	1	1
	Deviation Vs Control		-11.9

d = day

IA- 19
22-Apr-2013 09:49
ToxData© System 3.0

Study 30C0066/05S020

Summary Food Consumption Per Day

Sex: **Female** - Phase: **In-life**

	0 / F	1 / F	2 / F	3 / F
d 6 -> 7				
Mean [g]	12.6	14.1	10.4	12.3
N	1	1	1	1
Deviation Vs Control		11.9	-17.5	-2.4
d 13 -> 14				
Mean [g]	10.8	12.6	11.3	13.2
N	1	1	1	1
Deviation Vs Control		16.7	4.6	22.2
d 20 -> 21				
Mean [g]	14.0	11.5	14.6	13.8
N	1	1	1	1
Deviation Vs Control		-17.9	4.3	-1.4
d 27 -> 28				
Mean [g]	13.2	13.4	14.6	19.3
N	1	1	1	1
Deviation Vs Control		1.5	10.6	46.2

d = day

IA- 20
22-Apr-2013 09:50
ToxData© System 3.0

Study 30C0066/05S020

Summary Food Consumption Per Day

Sex: **Female** - Phase: **In-life**

		10 / F	11 / F
d 6 -> 7	Mean [g]	12.2	12.5
	N	1	1
	Deviation Vs Control		2.5
d 13 -> 14	Mean [g]	13.6	16.0
	N	1	1
	Deviation Vs Control		17.6
d 20 -> 21	Mean [g]	14.3	16.0
	N	1	1
	Deviation Vs Control		11.9
d 27 -> 28	Mean [g]	16.2	16.0
	N	1	1
	Deviation Vs Control		-1.2

d = day

IA- 21
22-Apr-2013 10:21
ToxData© System 3.0

Study 30C0066/05S020

Summary Body Weights BW / Body Weights [g]

Sex: **Male** - Phase: **In-life**

		0 / M	1 / M	2 / M	3 / M
day 0	Mean	168.8 n	168.0	165.0	166.6
	S.d.	8.4	7.2	8.4	8.4
	N	5	5	5	5
	Deviation Vs Control		-0.5	-2.3	-1.3
day 7	Mean	209.6 n	213.7	210.8	207.1
	S.d.	11.0	13.1	11.5	13.3
	N	5	5	5	5
	Deviation Vs Control		1.9	0.6	-1.2
day 14	Mean	243.4 n	250.1	246.4	240.9
	S.d.	13.2	17.2	14.1	16.3
	N	5	5	5	5
	Deviation Vs Control		2.8	1.2	-1.0
day 21	Mean	266.2 n	276.3	269.9	261.4
	S.d.	17.1	23.0	17.6	15.3
	N	5	5	5	5
	Deviation Vs Control		3.8	1.4	-1.8
day 28	Mean	286.3 n	298.2	289.6	275.4
	S.d.	22.3	29.4	22.6	17.6
	N	5	5	5	5
	Deviation Vs Control		4.2	1.2	-3.8

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

IA- 22
22-Apr-2013 10:19
ToxData© System 3.0

Study 30C0066/05S020

Summary Body Weights - BW / Body Weights [g]

Sex: **Male** - Phase: **In-life**

		10 / M	11 / M
day 0	Mean	169.9 n	169.4
	S.d.	5.3	6.7
	N	5	5
	Deviation Vs Control		-0.3
day 7	Mean	209.5 n	205.8
	S.d.	3.8	7.5
	N	5	5
	Deviation Vs Control		-1.8
day 14	Mean	250.5 n	242.9
	S.d.	6.2	15.1
	N	5	5
	Deviation Vs Control		-3.0
day 21	Mean	281.4 n	266.6
	S.d.	7.0	15.5
	N	5	5
	Deviation Vs Control		-5.3
day 28	Mean	304.8 n	280.2 *
	S.d.	10.8	17.5
	N	5	5
	Deviation Vs Control		-8.1

Statistic Profile = Student's t-test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=STUDENT

IA- 23
22-Apr-2013 10:22
ToxData© System 3.0

Study 30C0066/05S020

Summary Body Weights BW / Body Weights [g]

Sex: Female - Phase: In-life

		0 / F	1 / F	2 / F	3 / F
day 0	Mean	127.8 n	124.7	127.7	125.1
	S.d.	2.2	4.4	5.9	4.1
	N	5	5	5	5
	Deviation Vs Control		-2.4	-0.1	-2.1
day 7	Mean	142.1 n	141.2	138.1	139.3
	S.d.	7.2	5.0	7.4	6.5
	N	5	5	5	5
	Deviation Vs Control		-0.6	-2.8	-2.0
day 14	Mean	153.8 n	155.4	154.6	153.5
	S.d.	12.5	6.6	10.9	3.8
	N	5	5	5	5
	Deviation Vs Control		1.0	0.5	-0.2
day 21	Mean	169.4 n	162.7	167.8	165.5
	S.d.	11.5	7.8	10.7	8.3
	N	5	5	5	5
	Deviation Vs Control		-3.9	-0.9	-2.3
day 28	Mean	178.3 n	175.2	176.2	177.6
	S.d.	11.9	7.1	11.8	7.8
	N	5	5	5	5
	Deviation Vs Control		-1.7	-1.2	-0.4

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
n=DUNNETT

IA- 24
22-Apr-2013 10:24
ToxData© System 3.0

Study 30C0066/05S020

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		10 / F	11 / F
day 0	Mean	134.7 n	132.9
	S.d.	4.0	8.8
	N	5	5
	Deviation Vs Control		-1.3
day 7	Mean	146.6 n	144.2
	S.d.	5.2	7.9
	N	5	5
	Deviation Vs Control		-1.6
day 14	Mean	166.3 n	166.4
	S.d.	5.4	6.5
	N	5	5
	Deviation Vs Control		0.1
day 21	Mean	177.0 n	180.3
	S.d.	5.2	10.3
	N	5	5
	Deviation Vs Control		1.9
day 28	Mean	188.5 n	187.5
	S.d.	2.6	14.0
	N	5	5
	Deviation Vs Control		-0.5

Statistic Profile = Student's t-test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=STUDENT

IA- 25
22-Apr-2013 10:31
ToxData© System 3.0

Study 30C0066/05S020

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

Sex: **Male** - Phase: **In-life**

		0 / M	1 / M	2 / M	3 / M
d 0 -> 7	Mean	40.8 n	45.7	45.8	40.5
	S.d.	5.2	6.4	4.5	5.8
	N	5	5	5	5
	Deviation Vs Control		12.0	12.4	-0.6
d 0 -> 14	Mean	74.6 n	82.1	81.4	74.3
	S.d.	9.1	11.3	6.3	9.0
	N	5	5	5	5
	Deviation Vs Control		10.2	9.2	-0.3
d 0 -> 21	Mean	97.4 n	108.3	104.9	94.8
	S.d.	13.1	17.3	9.6	8.4
	N	5	5	5	5
	Deviation Vs Control		11.2	7.7	-2.7
d 0 -> 28	Mean	117.4 n	130.3	124.6	108.9
	S.d.	18.7	24.4	15.0	12.7
	N	5	5	5	5
	Deviation Vs Control		10.9	6.1	-7.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day, n=DUNNETT

IA- 26
22-Apr-2013 10:34
ToxData© System 3.0

Study 30C0066/05S020

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

Sex: **Male** - Phase: **In-life**

		10 / M	11 / M
d 0 -> 7	Mean S.d. N	39.6 n 3.3 5	36.3 3.2 5
	Deviation Vs Control		-8.3
d 0 -> 14	Mean S.d. N	80.6 n 3.9 5	73.5 10.6 5
	Deviation Vs Control		-8.8
d 0 -> 21	Mean S.d. N	111.5 n 4.1 5	97.2* 11.9 5
	Deviation Vs Control		-12.8
d 0 -> 28	Mean S.d. N	134.8 n 7.9 5	110.8** 13.3 5
	Deviation Vs Control		-17.8

Statistic Profile = Student's t-test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day, n=STUDENT

IA- 27
22-Apr-2013 10:32
ToxData© System 3.0

Study 30C0066/05S020

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

Sex: Female - Phase: In-life

		0 / F	1 / F	2 / F	3 / F
d 0 -> 7	Mean	14.3 n	16.5	10.4	14.2
	S.d.	5.2	1.8	6.9	4.5
	N	5	5	5	5
	Deviation Vs Control		15.5	-27.2	-0.6
d 0 -> 14	Mean	26.0 n	30.7	26.9	28.4
	S.d.	10.5	4.6	8.1	2.0
	N	5	5	5	5
	Deviation Vs Control		17.9	3.4	9.3
d 0 -> 21	Mean	41.5 n	38.0	40.0	40.4
	S.d.	9.7	5.5	8.1	4.3
	N	5	5	5	5
	Deviation Vs Control		-8.6	-3.6	-2.8
d 0 -> 28	Mean	50.4 n	50.4	48.5	52.5
	S.d.	10.5	3.9	8.3	6.3
	N	5	5	5	5
	Deviation Vs Control		0.0	-3.9	4.1

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day, n=DUNNETT

IA- 28
22-Apr-2013 10:36
ToxData© System 3.0

Study 30C0066/05S020

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

Sex: Female - Phase: In-life

		10 / F	11 / F
d 0 -> 7	Mean S.d. N	11.9 n 3.5 5	11.3 9.2 5
	Deviation Vs Control		-5.2
d 0 -> 14	Mean S.d. N	31.6 n 5.4 5	33.5 6.5 5
	Deviation Vs Control		5.8
d 0 -> 21	Mean S.d. N	42.4 n 6.3 5	47.4 7.0 5
	Deviation Vs Control		11.9
d 0 -> 28	Mean S.d. N	53.9 n 3.6 5	54.6 6.5 5
	Deviation Vs Control		1.3

Statistic Profile = Student's t-test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day, n=STUDENT

BASF

PATHOLOGY REPORT

IC 1/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats

19.Jun.2013 HAMA

Administration by gavage, Range-finding study

ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

Sacrifice			F1			
Sex			M			
Group			0	1	2	3
.....						
Terminal body weight	g	M	274.78	283.5	279.4	257.5
	% dev		100	103	102	94
	SD		21.328	25.811	19.466	17.919
	n		5	5	5	5
.....						
Adrenal glands	g	M	0.061	0.072	0.061	0.068
	% dev		100	119	101	113
	SD		0.007	0.009	0.008	0.008
	n		5	5	5	5
.....						
Kidneys	g	M	2.114	2.182	2.206	2.22
	% dev		100	103	104	105
	SD		0.215	0.227	0.258	0.273
	n		5	5	5	5
.....						
Liver	g	M	7.258	7.894	7.396	7.31
	% dev		100	109	102	101
	SD		0.835	1.038	0.691	0.879
	n		5	5	5	5
.....						

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

Kruskal-Wallis H and Wilcoxon test, two sided

BASF

PATHOLOGY REPORT

IC 2/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats

19.Jun.2013 HAMA

Administration by gavage, Range-finding study

ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

Sacrifice			F1			
Sex			F			
Group			0	1	2	3
.....						
Terminal body weight	g	M	170.16	164.88	167.08	163.48
		% dev	100	97	98	96
		SD	11.26	7.856	10.465	10.132
		n	5	5	5	5
.....						
Adrenal glands	g	M	0.076	0.07	0.079	0.076
		% dev	100	91	104	100
		SD	0.008	0.007	0.006	0.005
		n	5	5	5	5
.....						
Kidneys	g	M	1.378	1.252	1.372	1.346
		% dev	100	91	100	98
		SD	0.091	0.09	0.047	0.039
		n	5	5	5	5
.....						
Liver	g	M	4.584	4.61	4.842	4.972
		% dev	100	101	106	108
		SD	0.323	0.346	0.189	0.227
		n	5	5	5	5
.....						

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

Kruskal-Wallis H and Wilcoxon test, two sided

BASF

PATHOLOGY REPORT

IC 3/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats

19.Jun.2013 HAMA

Administration by gavage, Range-finding study

RELATIVE WEIGHTS - MEAN VALUES (MALE)

Sacrifice			F1			
Sex			M			
Group			0	1	2	3
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		5	5	5	5
.....						
Adrenal glands	%	M	0.022	0.026	0.022	0.027
	% dev		100	115	99	120
	SD		0.003	0.003	0.002	0.004
	n		5	5	5	5
.....						
Kidneys	%	M	0.77	0.77	0.788	0.86
	% dev		100	100	102	112
	SD		0.052	0.046	0.049	0.064
	n		5	5	5	5
.....						
Liver	%	M	2.639	2.781	2.645	2.838
	% dev		100	105	100	108
	SD		0.185	0.229	0.123	0.277
	n		5	5	5	5
.....						

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

Kruskal-Wallis H and Wilcoxon test, two sided

BASF

PATHOLOGY REPORT

IC 4/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats

19.Jun.2013 HAMA

Administration by gavage, Range-finding study

RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

Sacrifice			F1			
Sex			F			
Group			0	1	2	3
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		5	5	5	5
.....						
Adrenal glands	%	M	0.045	0.042	0.047	0.047
	% dev		100	94	105	104
	SD		0.006	0.004	0.005	0.003
	n		5	5	5	5
.....						
Kidneys	%	M	0.811	0.759	0.824	0.826
	% dev		100	94	102	102
	SD		0.047	0.021	0.069	0.054
	n		5	5	5	5
.....						
Liver	%	M	2.696	2.795	2.904*	3.052*
	% dev		100	104	108	113
	SD		0.137	0.152	0.158	0.258
	n		5	5	5	5
.....						

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

Kruskal-Wallis H and Wilcoxon test, two sided

BASF

PATHOLOGY REPORT

IC 5/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats
Administration by gavage, Range-finding study

19.Jun.2013 HAMA

INCIDENCE OF GROSS LESIONS

Sacrifice	-----							
Sex	F1							
Group	M				F			
Animals in selected group	0	1	2	3	0	1	2	3
.....	5	5	5	5	5	5	5	5
No abnormalities	5	5	5	5	5	5	5	5

Property of BASF SE –
Reproduction for other use prohibited
without written permission

BASF

PATHOLOGY REPORT

IC 6/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats
Administration by gavage, Range-finding study

19.Jun.2013 HAMA

INCIDENCE AND GRADING OF MICROSCOPIC FINDINGS

Sacrifice		F1							
Sex		M				F			
Group		0	1	2	3	0	1	2	3
Animals in selected group		5	5	5	5	5	5	5	5
.....									
Adrenal cortex	exam.	5	.	.	5	5	.	.	5
Adrenal medulla	exam.	5	.	.	5	5	.	.	5
Cecum	exam.	5	.	.	5	5	.	.	5
Dilation	5	.	.	.	5
	P.	.	.	.	5	.	.	.	5
Kidneys	exam.	5	.	.	5	5	.	.	5
Tubules, basophilic, (m)f	.	1	.	.	5	1	.	.	3
	1.	1	.	.	5	1	.	.	3
Nuclear crowding	4
	1.	.	.	.	4
Mineralization, medulla, (m)f	2	4	.	.	4
	1.	.	.	.	2	4	.	.	3
	2.	1
Cyst(s)	1
	P.	.	.	.	1
Liver	exam.	5	.	.	5	5	.	.	5
Hypertrophy, centrilobular	5	.	.	.	2
	1.	.	.	.	5	.	.	.	2
Infiltration, lymphoid, (m)f	5	.	.	.	5	5	.	.	5
	1.	5	.	.	5	5	.	.	5

BASF

PATHOLOGY REPORT

IC 7/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats

19.Jun.2013 HAMA

Administration by gavage, Range-finding study

ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

(TEST GROUPS 10, 11)

Sacrifice			F1	
Sex			M	
Group			10	11
.....				
Terminal body weight	g	M	288.14	263.82 *
	% dev		100	92
	SD		11.499	15.19
	n		5	5
.....				
Adrenal glands	g	M	0.052	0.076**
	% dev		100	145
	SD		0.007	0.005
	n		5	5
.....				
Kidneys	g	M	2.06	2.218
	% dev		100	108
	SD		0.152	0.222
	n		5	5
.....				
Liver	g	M	7.074	7.064
	% dev		100	100
	SD		0.695	0.322
	n		5	5
.....				

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

Wilcoxon test, two sided

BASF

PATHOLOGY REPORT

IC 8/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats

19.Jun.2013 HAMA

Administration by gavage, Range-finding study

ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

(TEST GROUPS 10, 11)

				F1	
				F	
				10	11
Sacrifice					
Sex					
Group					
.....					
Terminal body weight	g	M	177.16	171.34	
		% dev	100	97	
		SD	3.741	9.513	
		n	5	5	
.....					
Adrenal glands	g	M	0.079	0.069	
		% dev	100	88	
		SD	0.014	0.011	
		n	5	5	
.....					
Kidneys	g	M	1.396	1.51	
		% dev	100	108	
		SD	0.095	0.042	
		n	5	5	
.....					
Liver	g	M	4.644	5.42 *	
		% dev	100	117	
		SD	0.219	0.604	
		n	5	5	
.....					

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

Wilcoxon test, two sided

BASF

PATHOLOGY REPORT

IC 9/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats

19.Jun.2013 HAMA

Administration by gavage, Range-finding study

RELATIVE WEIGHTS - MEAN VALUES (MALE)

(TEST GROUPS 10 ,11)

Sacrifice		F1	
Sex		M	
Group		10	11
.....			
Terminal body weight	%	M	100.0
		% dev	100
		n	5
			100.0
.....			
Adrenal glands	%	M	0.018
		% dev	100
		SD	0.003
		n	5
.....			
Kidneys	%	M	0.714
		% dev	100
		SD	0.03
		n	5
.....			
Liver	%	M	2.454
		% dev	100
		SD	0.21
		n	5
.....			

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

Wilcoxon test, two sided

BASF

PATHOLOGY REPORT

IC 10/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats

19.Jun.2013 HAMA

Administration by gavage, Range-finding study

RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

(TEST GROUPS 10, 11)

Sacrifice			F1	
Sex			F	
Group			10	11
.....				
Terminal body weight	%	M	100.0	100.0
		% dev	100	100
		n	5	5
.....				
Adrenal glands	%	M	0.045	0.041
		% dev	100	91
		SD	0.008	0.006
		n	5	5
.....				
Kidneys	%	M	0.788	0.884*
		% dev	100	112
		SD	0.047	0.058
		n	5	5
.....				
Liver	%	M	2.621	3.158**
		% dev	100	120
		SD	0.1	0.223
		n	5	5

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

BASF

PATHOLOGY REPORT

IC 11/12

30C0066/05S020

19.Jun.2013 HAMA

Repeated-dose 28-day toxicity study in Wistar rats
Administration by gavage, Range-finding study

INCIDENCE OF GROSS LESIONS
(TEST GROUPS 10, 11)

Sacrifice	F1			
Sex	M		F	
Group	10	11	10	11
Animals in selected group	5	5	5	5
.....			
No abnormalities	4	.	4	.
Cecum
Dilation	.	5	.	5
Glandular stomach
Erosion/ulcer	1	.	.	.
Liver
Focal constriction	.	.	1	.

Property of BASF SE –
Reproduction for other use prohibited
without written permission

BASF

PATHOLOGY REPORT

IC 12/12

30C0066/05S020

Repeated-dose 28-day toxicity study in Wistar rats
Administration by gavage, Range-finding study

19.Jun.2013 HAMA

INCIDENCE AND GRADING OF FINDINGS IN TARGET ORGANS
(TEST GROUPS 10, 11)

Sacrifice		F1			
Sex		M		F	
Group		10	11	10	11
Animals in selected group		5	5	5	5
.....					
Cecum	exam.	5	5	5	5
Dilation		.	5	.	5
	. P.	.	5	.	5
Hypertrophy/hyperplasia, dif		.	5	.	4
	. 1.	.	5	.	4
Apoptosis, enteric cells		.	5	.	3
	. 1.	.	5	.	3
Kidneys	exam.	5	5	5	5
Tubules, basophilic, (m)f		4	5	3	3
	. 1.	4	4	3	3
	. 2.	.	1	.	.
Nuclear crowding		.	3	.	.
	. 1.	.	2	.	.
	. 2.	.	1	.	.
Mineralization, medulla, (m)f		.	2	2	3
	. 1.	.	2	2	3
Liver	exam.	5	5	5	5
Hypertrophy, centrilobular		.	.	.	5
	. 1.	.	.	.	5
Infiltration, lymphoid, (m)f		5	5	5	5
	. 1.	5	5	5	5
Constriction, focal		.	.	1	.
	. P.	.	.	1	.

Competence Center Analytics

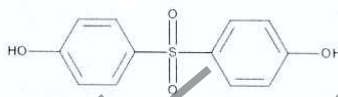
Final Report

Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)



The Chemical Company

Page 1 of 11

Test item	4,4'-Dihydroxydiphenylsulfon
Chemical identity	4,4'-Sulfonyldiphenol (DHDPS)
Chemical structure	
Batch identification	69611767J0
Date of production (test item)	Nov 28, 2011
Origin of test item	[REDACTED]
PSN	05/0066-4
CAS no.	80-09-1
Sponsor	[REDACTED]
Date of receipt of order	Dec 07, 2011
Date of receipt of test item	Dec 15, 2011
Testing facility	Competence Center Analytics, BASF SE, D-67056 Ludwigshafen
Study director	[REDACTED]
Storage cond. test item	Room temperature, moisture protection
Test period	Jan 13, 2012 – Feb 28, 2012
Storage of records	GLP archives, Competence Center Analytics
Storage of sample of test item	Archives, Competence Center Analytics

Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 2 of 11

Summary of results

The test item was characterized by spectroscopic and chromatographic methods.

¹H-NMR spectroscopy confirmed the structure of the test item. Furthermore, the test item was imaged by its HPLC fingerprint by reversed-phase chromatography. Two peaks with area fractions >0.1% were present. The main component with 99.3% and 99.5% and a by-product with 0.30% and 0.34% at a wavelength of 230 and 250 nm, respectively.

Quantitative ¹H-NMR spectroscopy using the internal standard method yielded a mean purity of the test item of 99.4 g/100 g.

1 Appearance and Homogeneity

Method	Visual Inspection
Result	The test item was a fine white powder. It was obviously homogeneous.
Date of test	Jan 13, 2012
Head of laboratory	[REDACTED]

2 Identity via ¹H-NMR-Spectroscopy

Method	¹ H-NMR spectroscopy
Apparatus	Bruker DPX 401
Reagents	Solvent: DMSO-d ₆ (Euriso-top) Reference standard: Tetramethylsilane TMS (Cambridge Isotope)
Sample preparation	An adequate mass of the test item was filled into a sample tube and dissolved in DMSO-d ₆ containing TMS.
Test parameters	Measuring frequency = 400 MHz, measuring temperature = 30 °C; further parameters see ¹ H-NMR spectrum page 6
Result	The ¹ H-NMR spectrum shows the expected signals for the given structure (see page 6).
Date of test	Feb 23, 2012
Head of laboratory	[REDACTED]

Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 3 of 11

3 Content of Main Component and By-Products

Method ¹H-NMR spectroscopy with internal standard

Apparatus Bruker DPX 401

Reagents Solvent: DMSO-d₆ (Euriso-top)
Reference standard: Tetramethylsilane TMS (Cambridge Isotope)
Internal standard: 1,3,5-Trimethoxybenzene (Sigma Aldrich)
Purity: 100 % (for calc.)
Mol. weight: 168.19 g/mol

Sample preparation About 11-15 mg test item and about 10-15 mg of internal standard were weighed to the nearest 0.01 mg into sample tubes and dissolved in DMSO-d₆ containing TMS as reference standard.

Test parameters Measuring frequency = 400 MHz, measuring temperature = 30 °C; further parameters see at ¹H-NMR spectrum page 7

Result For quantitation, triplicate measurements were carried out. Evaluation was performed by using three protons/molecule of the internal standard (at ~ 6.1 ppm) and 4 protons/molecule of 4,4'-dihydroxydiphenylsulfone (at ~ 7.7 ppm). Exemplary spectrum see page 7.

Content of 4,4'-dihydroxydiphenylsulfone

Det.	test item		internal standard		Resulting mass fraction [g/100g]
	weight [mg]	peak intensity [area units]	weight [mg]	peak intensity [area units]	
1	11.12	400.00	10.40	420.14	99.4
2	11.70	400.00	15.09	578.85	99.5
3	14.40	400.00	10.29	320.86	99.4
mean					99.4

By-products were not detected.

Date of test Feb 28, 2012

Head of laboratory

Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 4 of 11

4 HPLC Fingerprint

Method Reversed-phase high pressure liquid chromatography with UV detection at two wavelengths and area percent evaluation

Apparatus Automated HPLC system, equipped with an autosampler and a UV/Vis detector, connected to an electronical data processing system

Reagents Acetonitrile (Fluka)
Demineralized water obtained from a Milli-Q system

Sample preparation Approximately 30 mg of test item were weighed into a 25 mL volumetric flask and filled up to the mark with acetonitrile. Afterwards, a 2/25 dilution was carried out with a mixture of acetonitrile/water (1/1 v/v).

Test parameters

Column: LiChrospher 100, RP-18 ec, 5 µm, 125 x 3 mm (Macherey Nagel)
Mobile phase A: Acetonitrile/water = 10/90 (V/V)
Mobile phase B: Acetonitrile/water = 90/10 (V/V)
Injection volume: 20 µL
Flow rate: 0.7 mL/min
Oven temperature: 25 °C
UV detection: λ = 230 nm, λ = 250 nm

Gradient elution:

time [min]	0	25	30	31	46
A [%]	85	30	30	85	new
B [%]	15	70	70	15	injection

Result

The HPLC fingerprint shows two peaks with area fractions >0.1%. The peak area of the main component corresponds to 99.3 % at 230 nm and 99.5 % at 250 nm. A by-product with 0.30% and 0.34% was detected at 230 and 250 nm, respectively. These values are the means of two determinations. For details see pages 9-10.

For representative chromatograms of blank run and test item at both wavelengths see pages 8-10.

Date of test Jan 18, 2012 – Jan 19, 2012

Head of laboratory

May 21, 2012
Date

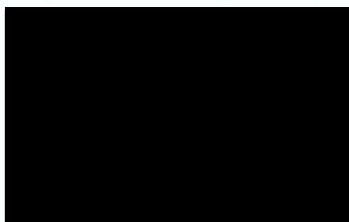
Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 5 of 11

GLP Compliance Statement

This study was conducted in accordance with the OECD Principles of Good Laboratory Practice and the GLP Principles of the German "Chemikaliengesetz" (Chemicals Act).



May 21, 2012
Date

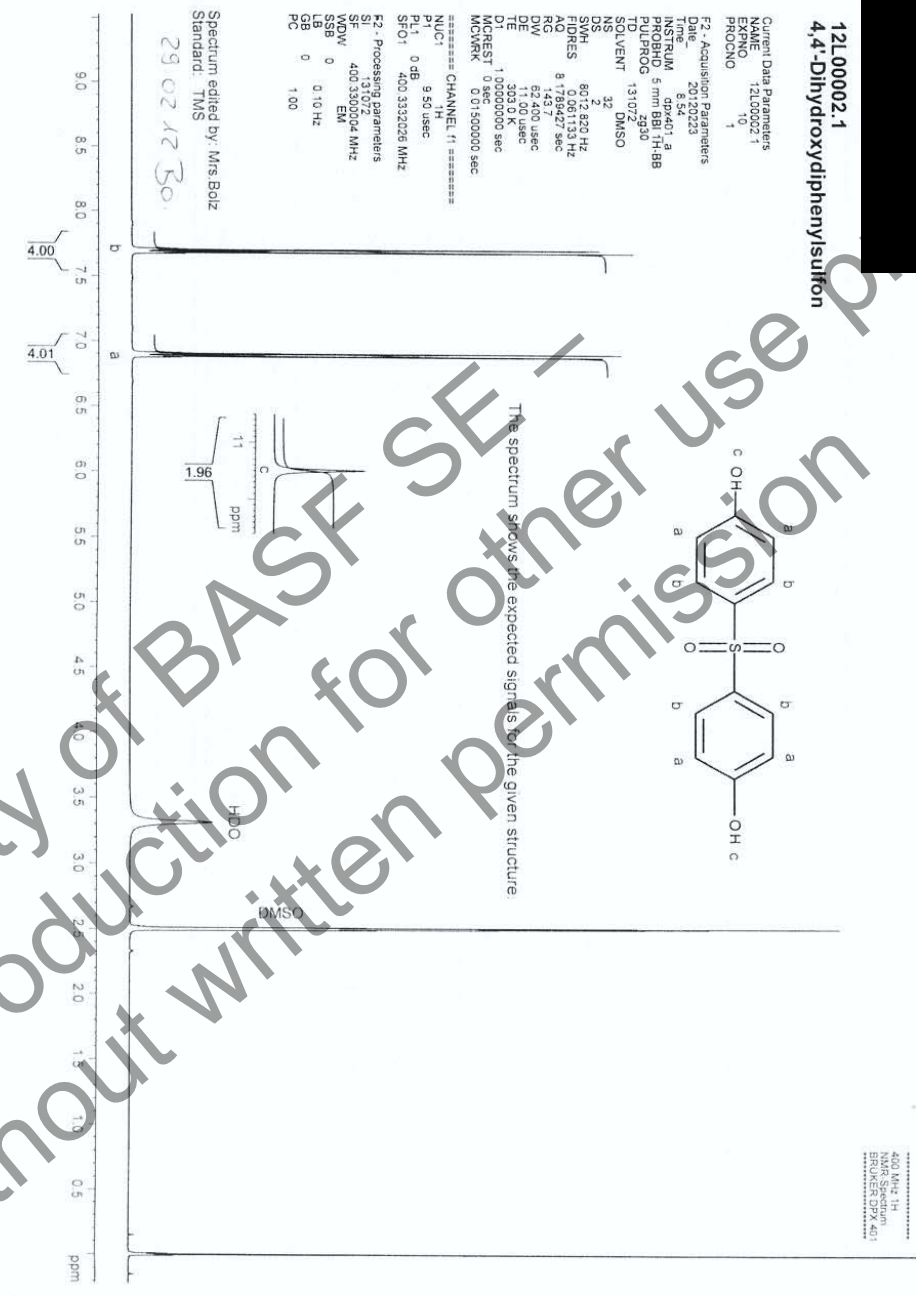
Property of BASF SE –
Reproduction for other use prohibited
without written permission

Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 6 of 11

Identity of test item by ¹H-NMR spectroscopy

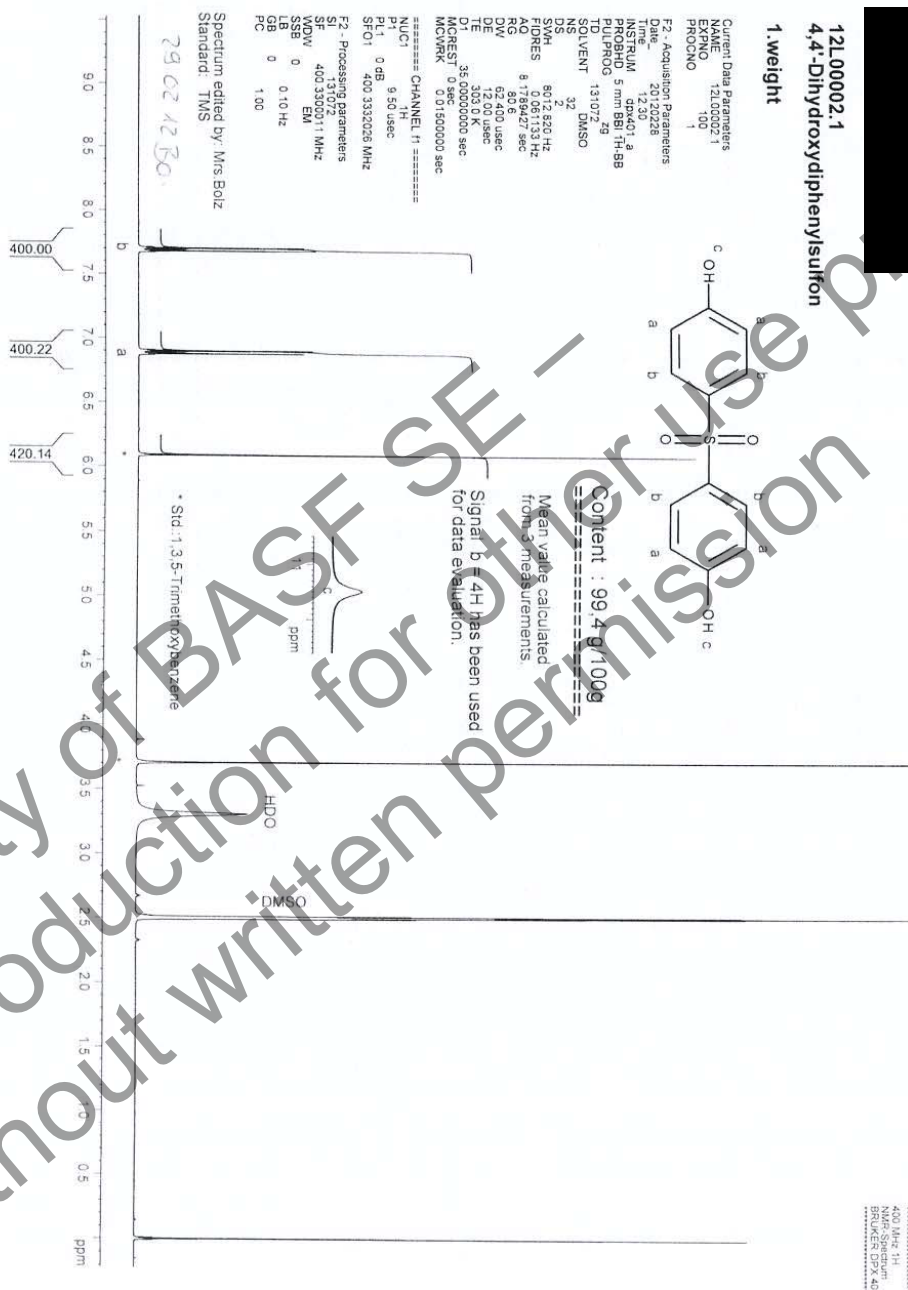


Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 7 of 11

Quantitative ¹H-NMR spectrum of the test item



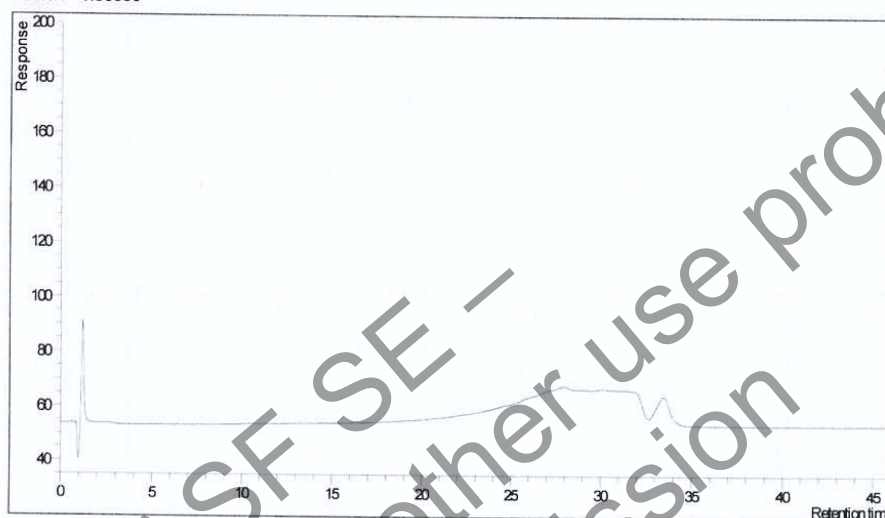
Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 8 of 11

Blank run of HPLC-fingerprint at $\lambda = 230$ nm

Sample : Blindlauf (Acetonitril - 230 nm)
 Conc : 1.00000



Blank run of HPLC-fingerprint at 250 nm

Sample : Blindlauf (Acetonitril - 250 nm)
 Conc : 1.00000



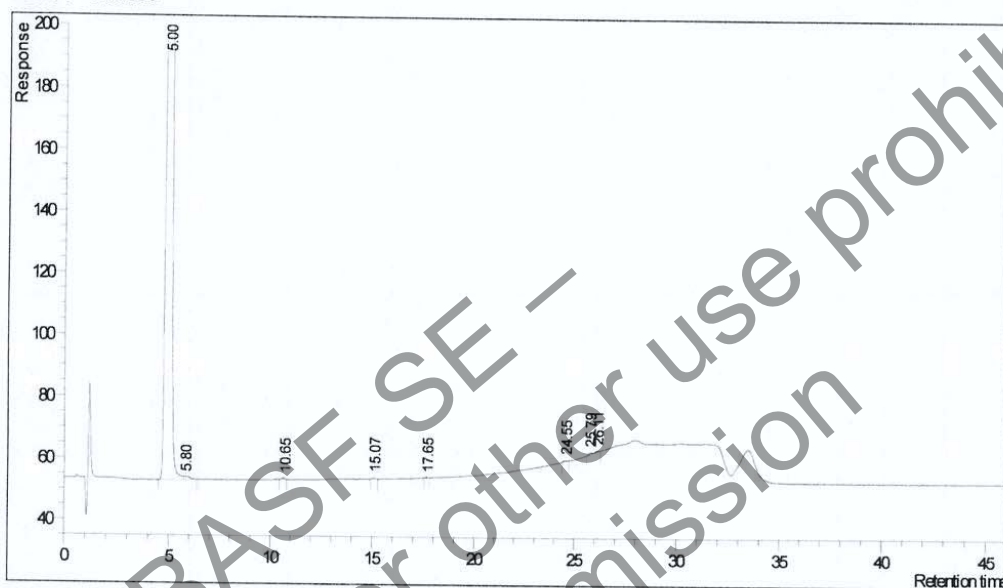
Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 9 of 11

HPLC-fingerprint of test item at 230 nm

Sample : 12L00002 (230 nm) - A
 Conc : 1.00000



Named Peaks					
RT [min]	Height [mV]	Area [mVs]	Area%	Peak Name	
5.000	416.364	6773.860	99.363		BL
5.800	0.953	18.976	0.278		BVU
10.653	0.521	5.218	0.077		VBV
15.073	0.367	3.285	0.048		BBU
17.653	0.235	1.862	0.027		BBU
24.547	0.366	3.884	0.057		BBU
25.793	0.557	6.629	0.097		BBU
26.113	0.332	3.556	0.052		BVU
Sum	419.695	6817.270	99.999		VBV

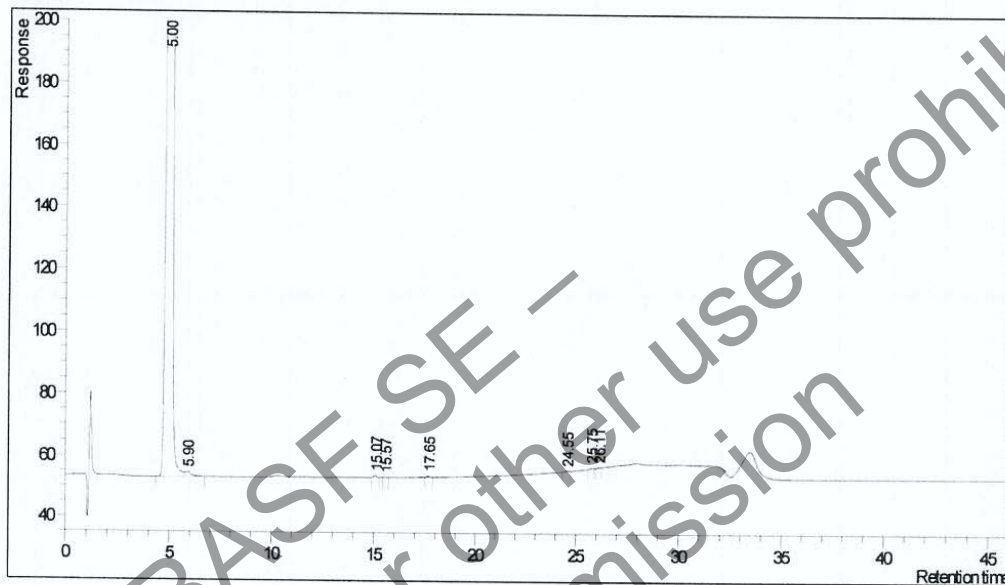
Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 10 of 11

HPLC-fingerprint of test item at 250 nm

Sample : 12L00002 (250 nm) - A
 Conc : 1.00000



Named Peaks

RT [min]	Height [mV]	Area [mVs]	Area%	Peak Name	BL
5.000	572.847	9341.446	99.478		BL
5.900	1.531	34.598	0.368		VBV
15.067	0.593	5.153	0.055		BBU
15.573	0.084	0.676	0.007		BBU
17.653	0.348	3.203	0.034		BBU
24.553	0.230	2.925	0.031		BBU
25.747	0.150	1.594	0.017		BBU
26.107	0.106	0.841	0.009		BBU
Sum	575.889	9390.436	99.999		

Competence Center Analytics

Final Report
Characterization of "4,4'-Dihydroxydiphenylsulfon"
Study No. 12L00002 (confidential)

Page 11 of 11

Statement of the Quality Assurance Unit

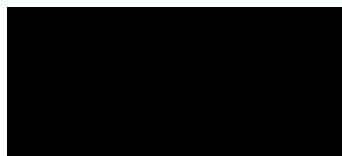
The Quality Assurance Unit inspects the laboratories of the department Competence Center Analytics in regular intervals. Besides these general inspections we inspected the following items of this study in accordance with the OECD Principles of Good Laboratory Practice and the GLP Principles of the German "Chemikaliengesetz" (Chemicals Act). Findings are reported to study director and to management.

Verification of study plan: Jan 10, 2012

Inspection of	Date of inspection	Reported to study director and to management
Conduct of study: HPLC fingerprint	Jan 18, 2012	Jan 18, 2012
Raw data:	May 16, 2012	May 21, 2012
Final report:	May 16, 2012	May 21, 2012

The final report reflects the raw data.

Ludwigshafen



May 21, 2012
Date

STUDY TITLE

ANALYTICAL REPORT

DHDPS

Stability Analysis in

1% Carboxymethylcellulose in Drinking Water

AUTHOR(S)**STUDY COMPLETION DATE**

29 August 2013

TEST FACILITYBASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen, Germany**TEST FACILITY PROJECT IDENTIFICATION**

Project No.: 01Y0066/05Y009

SPONSORBASF SE
67056 Ludwigshafen, Germany

This document contains manufacturing and trade secrets of the sponsor(s). It is the property of the sponsor(s) and may be used only for that purpose for which it was intended by the sponsor(s). Every other or additional use, exploitation, reproduction, publication or submission to other parties require the written permission of the sponsor(s), with the exception of regulatory agencies acting within the limits of their administrative authority.

THIS PAGE IS INTENTIONALLY LEFT BLANK

Property of BASF SE –
Reproduction for other use prohibited
without written permission

GLP COMPLIANCE STATEMENT

This study was conducted in accordance with the OECD Principles of Good Laboratory Practice and the GLP Principles of the German "Chemikaliengesetz" (Chemicals Act) which meet the United States Environmental Protection Agency Good Laboratory Practice Standards [40 CFR Part 160 (FIFRA) and Part 792 (TSCA)], with the exception that recognized differences exist between the GLP Principles/Standards of OECD and the Principles/Standards of FIFRA and TSCA.

Study Director

Typed name of Study Director:

Typed name of Laboratory:



Date: 29 Aug. 2013

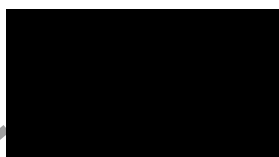
BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen
Germany

THIS PAGE IS INTENTIONALLY LEFT BLANK

Property of BASF SE –
Reproduction for other use prohibited
without written permission


SIGNATURE PAGE

Study Director:



29 Aug. 2013

Management:



27 Aug. 2013

STATEMENT OF THE QUALITY ASSURANCE UNIT

The Quality Assurance Unit (QAU) inspected the study and reported any inspection results to the Study Director and to Management.

The final report reflects the raw data.

Phase of study	Date of inspection (mm-dd-yyyy)	Reported to Study Director and to Management (mm-dd-yyyy)
Study Plan:	10-09-2012	10-09-2012
Conduct of study:	10-12-2012	10-12-2012
Report:	08-08-2013	08-08-2013

Ludwigshafen, 29 August 2013



GLP CERTIFICATE (FROM THE COMPETENT AUTHORITY)



Gute Laborpraxis / Good Laboratory Practice

GLP-Bescheinigung / Statement of GLP Compliance
(gem. / according to § 19 Abs. 1 Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung und der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 2004/9/EG wurde durchgeführt in:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 2004/9/EC at::

Prüfeinrichtung / Test facility

BASF SE
Experimentelle Toxikologie und Ökologie
67056 Ludwigshafen

BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen, Germany

Prüfung nach Kategorien / Areas of Expertise
(gem. / according ChemVwV-GLP Nr. 53/OECD guidance)
1,2,3,4,5,8,9

Kat. 9 – Biochemische und pathologische Untersuchungen zu Wirkmechanismen /
Biochemical and pathological examinations concerning mode of action

Datum der Inspektion / Date of Inspection
(Tag/Monat/Jahr / day.month.year)
19.05.2009 & 06. bis 08.07.2009

Die genannte Prüfeinrichtung befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

The above mentioned test facility is included in the national GLP Compliance Programme and is inspected on a regular basis.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können. Eine erneute behördliche Überprüfung der Einhaltung der GLP-Grundsätze durch die Prüfeinrichtung ist so rechtzeitig zu beantragen, dass die Folgeinspektion spätestens vier Jahre nach dem Beginn der o.g. Inspektion stattfinden kann. Ohne diesen Antrag wird die Prüfeinrichtung nach Ablauf der Frist aus dem deutschen GLP-Überwachungsprogramm genommen und diese GLP-Bescheinigung verliert ihre Gültigkeit.

Based on the inspection report it can be confirmed, that the test facility is able to conduct the aforementioned studies in compliance with the Principles of GLP.

Verification of the compliance of the test facility with the Principles of the GLP has to be applied for in time to allow for a follow-up inspection to take place within four years after commencing the above mentioned inspection. Elapsing this term, the test facility will be taken out of the German GLP-Monitoring Programme and this GLP Certificate becomes invalid.

Unterschrift, Datum / Signature, Date



Dr. Pia Hirsch - stellv. Präsidentin -
(Name und Funktion der verantwortlichen Person / name and function of responsible person)



Siegel

Landesamt für Umwelt, Wasserwirtschaft und Gewerbeaufsicht
Kaiser-Friedrich-Straße 7
55116 Mainz

(Name und Adresse der GLP-Überwachungsbehörde /
Name and address of the GLP Monitoring Authority)

Landesamt für
Umwelt, Wasserwirtschaft
und Gewerbeaufsicht

This document is the property of the sponsors (specified on page 1), use by other parties requires written permission by the sponsors

CONTENTS

TITLE PAGE

BLANK PAGE

GLP COMPLIANCE STATEMENT

BLANK PAGE

SIGNATURE PAGE

STATEMENT OF THE QUALITY ASSURANCE UNIT

GLP CERTIFICATE (FROM THE COMPETENT AUTHORITY)

CONTENTS

1. INTRODUCTION
2. RETENTION OF RECORDS
3. TIME SCHEDULE
4. MATERIAL AND METHODS
 - 4.1. TEST ITEM
 - 4.2. SAMPLE DATA
 - 4.3. TEST SUBSTANCE PREPARATION
 - 4.4. SAMPLE PREPARATION AND ANALYSIS
 - 4.5. LIST OF DEVIATIONS
 - 4.5.1. LIST OF DEVIATIONS FROM THE CONTROL PROCEDURE
5. RESULTS AND DISCUSSION
 - 5.1. ANALYSIS OF STABILITY
 - 5.2. DISCUSSION
- FIGURES
6. APPENDIX
 - 6.1. CONTROL PROCEDURE 05/0066_01-01

1. INTRODUCTION

In the context of toxicological studies the stability of the test substance DHDPS in the vehicle 1% carboxymethylcellulose in drinking water has to be verified. The results of these analyses are reported and discussed.

2. RETENTION OF RECORDS

GLP-relevant records and materials are stored at BASF SE for at least the period of time specified in the GLP principles. Details concerning responsibilities or locations of archiving can be seen from the respective SOPs and from the raw data.

3. TIME SCHEDULE

Study initiation date:	09 October 2012
Experimental starting date:	12 October 2012
Experimental completion date:	19 October 2012

4. MATERIAL AND METHODS

4.1. TEST ITEM

The analyses of the test item (= test substance) were carried out at the Competence Center Analytics of BASF SE, Ludwigshafen, Germany.

Name of test substance: DHDPS

Test substance No.: 05/0066-4

Batch identification: 69611767J0

CAS No.: 80-09-1

Purity: (1) 99.3 and 99.5 %, (HPLC)
(2) 99.4 g/100 g, (1H-NMR)
(according to the project number 12L00002)

Homogeneity: Given

Storage stability: stable until: 28 May 2013
The stability of the test substance under storage conditions over the test period was guaranteed by the sponsor, and the sponsor holds this responsibility.

Additional Test Substance Information

Date of production: 28 Nov 2011

Physical state/ Appearance: Solid / white

Storage conditions: Room temperature

4.2. SAMPLE DATA

Sponsor:	Dr. Buesen; Ms. Pabst
Vehicle:	1% carboxymethylcellulose in drinking water
Target concentration:	0.05 g/100 mL
Duration of the stability test period:	7 days
Storage conditions of the samples during the stability period:	Refrigerator

4.3. TEST SUBSTANCE PREPARATION

51.2 mg of the test substance were dissolved in 5 mL acetone. 0.5 mL of this solution were transferred into 100 mL volumetric flasks. After acetone evaporation at room temperature, 10 mL 1% carboxymethylcellulose in drinking water were added. For each time point a sample was prepared. The final nominal concentration was 0.0512 g / 100 mL.

4.4. 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.

A detailed description of the control procedure is given in the appendix of this report.

4.5. LIST OF DEVIATIONS

4.5.1. LIST OF DEVIATIONS FROM THE CONTROL PROCEDURE

There were no deviations from the described control procedure 05/0066_01-01.

5. RESULTS AND DISCUSSION

5.1. ANALYSIS OF STABILITY

The results obtained for the stability of the test substance in 1% carboxymethylcellulose in drinking water are summarized in the following table.

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

Nominal concentration [g/100 mL]	Time after starting	Concentration found [g/100 mL]	Nominal concentration (%)
0.0512	0h	0.055	107.3
0.0512	4h	0.053	104.9
0.0512	4d	0.055	108.5

The stability samples from 0 hours until 4 days were stored at room temperature

Nominal concentration [g/100 mL]	Time after starting	Concentration found [g/100 mL]	Nominal concentration (%)
0.0512	7d	0.054	106.6

The stability sample for the duration of 7 days was stored in the refrigerator.

5.2. DISCUSSION

Based on the analytical results it is concluded, that DHDPS is stable in 1% carboxymethylcellulose in drinking water over a period of 4 days at room temperature and 7 days in the refrigerator.

All determined concentrations were in the range of 90 % - 110 % of the nominal concentration.

FIGURES

Figure 1: Chromatogram of matrix solution (measured on 19 Oct 2012)

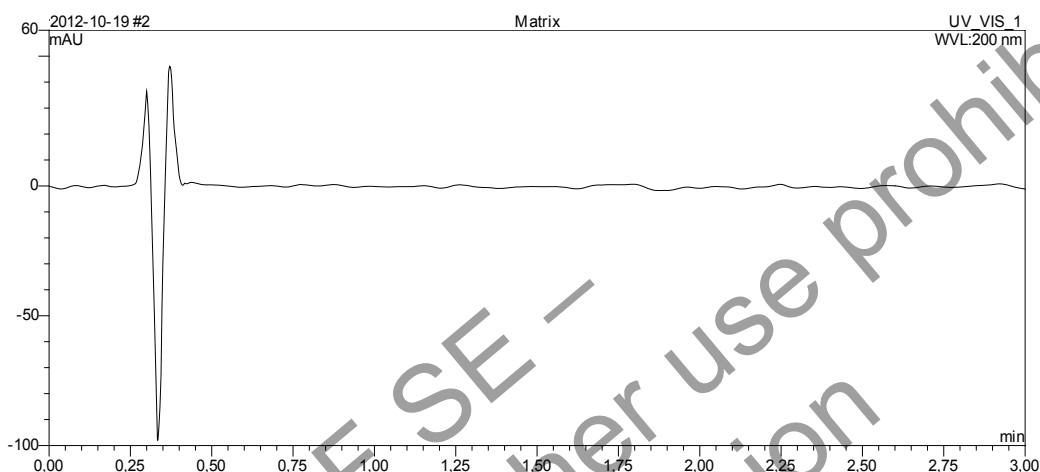


Figure 2: Chromatogram of calibration solution 1 (2.044 mg/100 mL, measured on 19 Oct 2012)

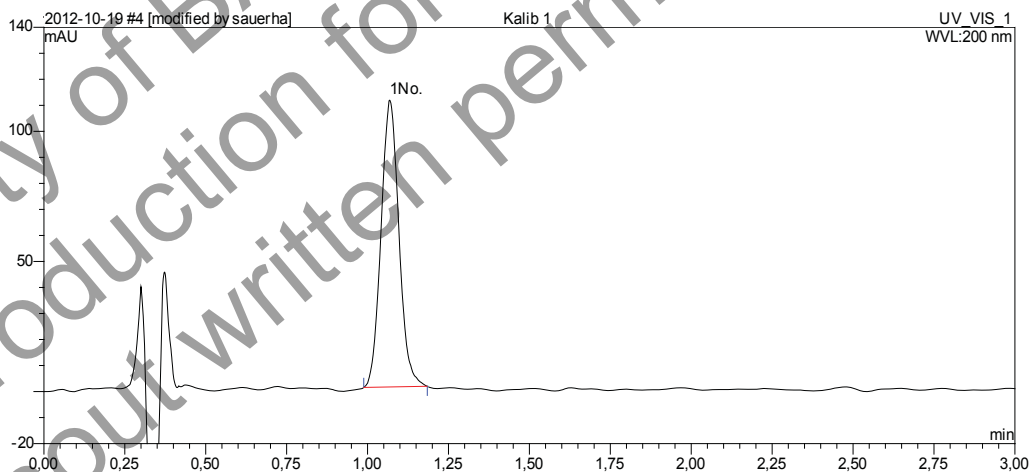


Figure 3: Chromatogram sample solution day 7 (measured on 19 Oct 2012)

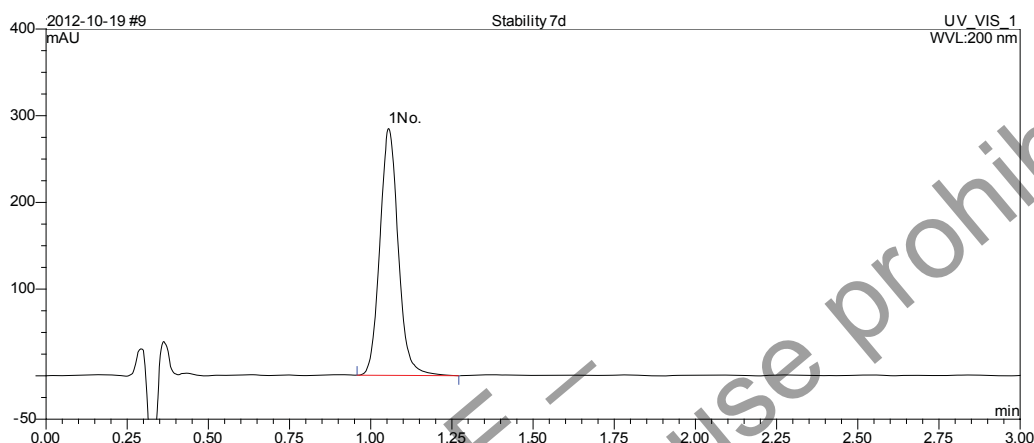
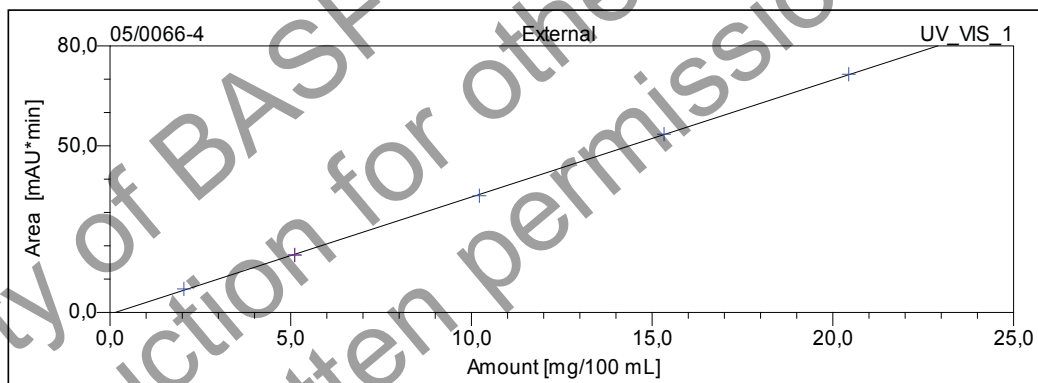


Figure 4: Calibration curve (19 Oct 2012, Concentration range 2.044 – 20.44 mg/100 mL)



6. APPENDIX

6.1. CONTROL PROCEDURE 05/0066_01-01

BASF SE
Test Facility
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

BASF SE
Test Facility
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 2 of 5

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.

BASF SE
Test Facility
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 3 of 5

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

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

w = weight sample
V = final sample volume
d = dilution factor

v = volume sample
V = final sample volume
d = dilution factor

Analysed concentration (C_A)

BASF SE
Test Facility
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 4 of 5

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

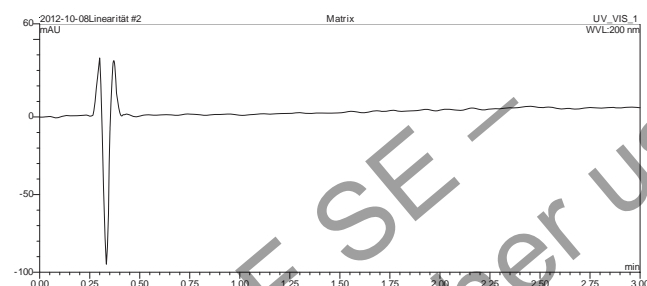
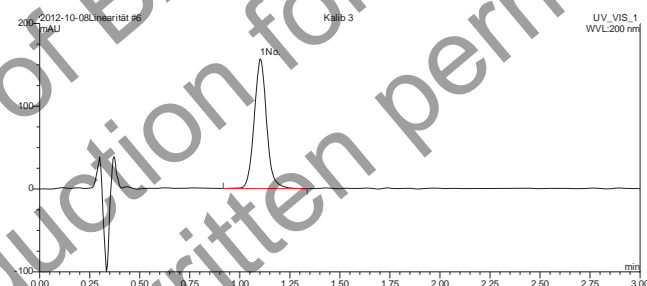


Figure 1.2: Example chromatogram calibration solution (08 Oct 2012, Project no.: 01Y0066/05Y009) for illustration



BASF SE
Test Facility
Experimental Toxicology and Ecology / Analytical Chemistry



CONTROL TEST

Test substance number: 05/0066

No.: 05/0066_01-01

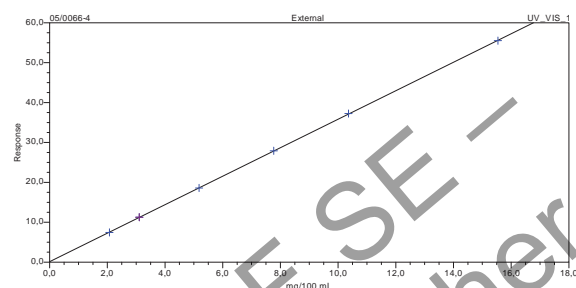
Name of test substance: DHDPs

Effective from: 09 Oct 2012

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

Page 5 of 5

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



Homogeneity and Concentration Control Analysis of DHDPS in 1% carboxymethylcellulose in Drinking Water

1. PROJECT AND TEST SUBSTANCE INFORMATION

Project No.: 30C0066/05S020

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 were carried out according to the valid control procedure 05/0066_01-01.

A detailed description of the control procedure is given in the appendix of this report.

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 analysis of DHDPS in 1% carboxymethylcellulose in drinking water are summarized in the following table:

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

Date of sample preparation: **08 Nov 2012**
Date of sampling: **08 Nov 2012**
Date of receipt of sample in analytical laboratory: **08 Nov 2012**
Starting date of analytical determination: **19 Dec 2012**

Name	Amount	Nominal Conc	Nominal Conc	Mean	RSD
	g/100 mL	g/100 mL	%	%	%
Sample 03	0.494	0.5	98.8%		
Sample 04	0.500	0.5	100.0%		
Sample 05	0.492	0.5	98.4%	99.1%	0.9%
Sample 06	1.485	1.5	99.0%		
Sample 07	5.021	5.0	100.4%		
Sample 08	5.032	5.0	100.6%		
Sample 09	4.982	5.0	99.6%	100.2%	0.5%

Date of sample preparation: **20 Mar 2013**
Date of sampling: **20 Mar 2013**
Date of receipt of sample in analytical laboratory: **20 Mar 2013**
Starting date of analytical determination: **09 Apr 2013**

Name	Amount	Nominal Conc	Nominal Conc	Mean	RSD
	g/100 mL	g/100 mL	%	%	%
Sample 21	9.712	10.0	97.1%		
Sample 22	9.622	10.0	96.2%		
Sample 23	9.622	10.0	96.2%	96.5%	0.5%

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

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 19 Dec 2012)

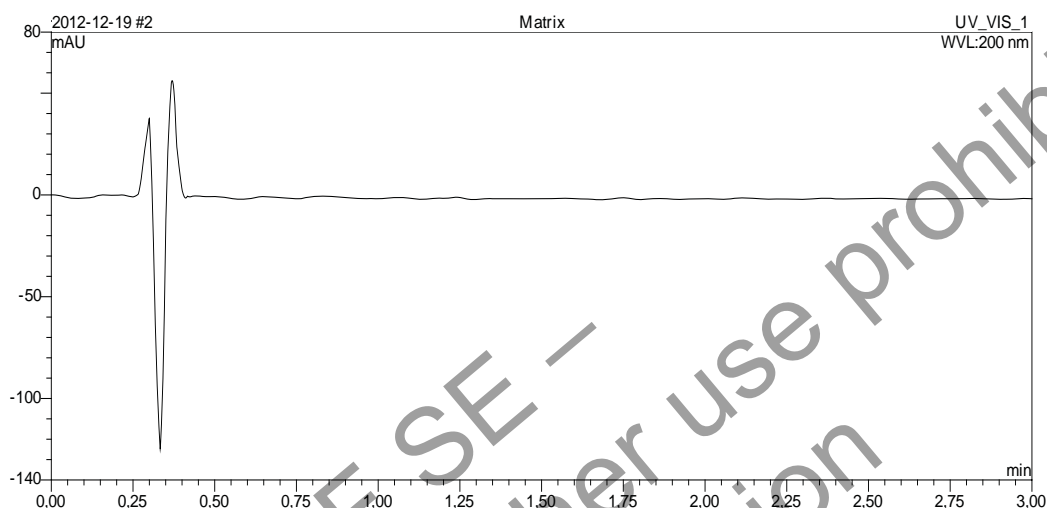


Figure 2: Chromatogram of calibration solution 1 (2.04 mg/100 mL, measured on 19 Dec 2012)

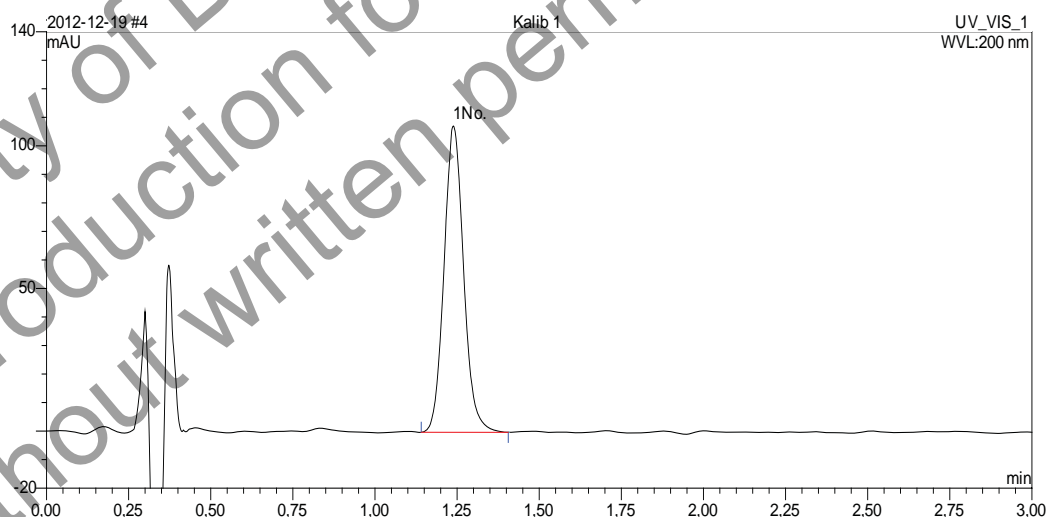


Figure 3: Chromatogram of sample 04 (measured on 19 Dec 2012)

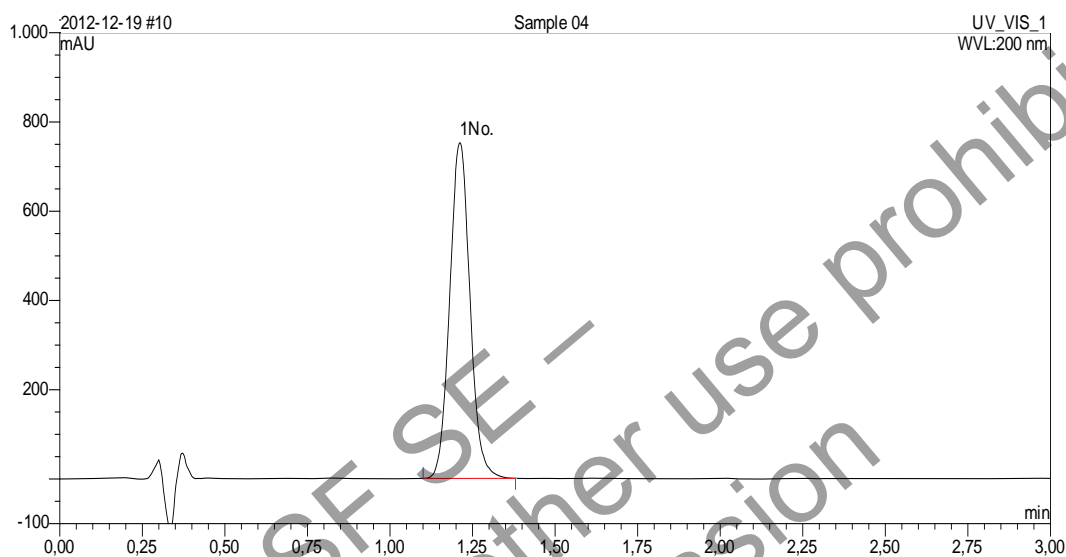
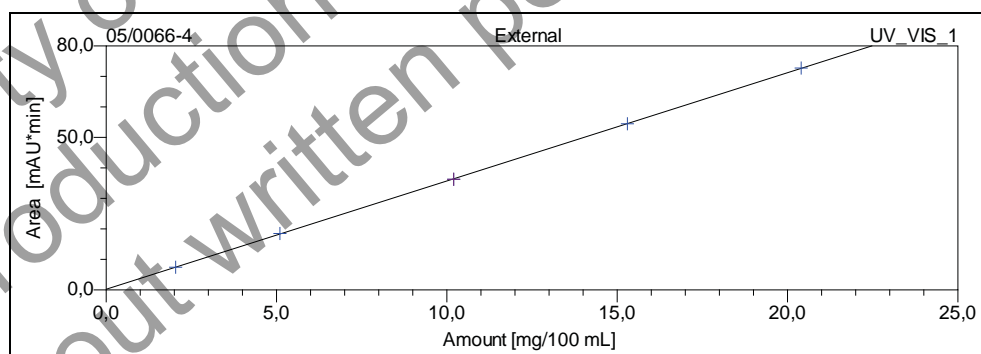


Figure 4: Calibration curve (measured on 19 Dec 2012, Concentration range 2.04 – 20.4 mg/100 mL)



5. APPENDIX

5.1. CONTROL PROCEDURE 05/0066_01-01

BASF SE
Test Facility
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

BASF SE
Test Facility
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 2 of 5

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.

BASF SE
Test Facility
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 3 of 5

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)

BASF SE
Test Facility
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 4 of 5

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

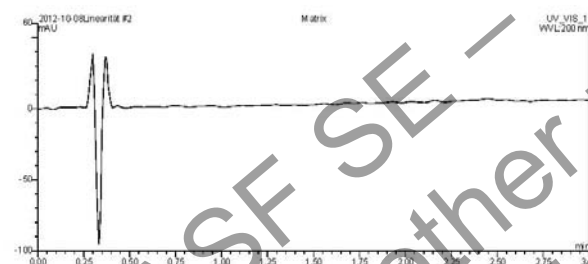
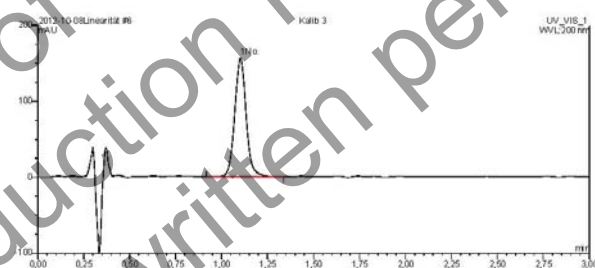


Figure 1.2: Example chromatogram calibration solution (08 Oct 2012, Project no.: 01Y0066/05Y009) for illustration



BASF SE
Test Facility
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 5 of 5

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

