III A Section 6_16 Annex Point VI.3.5 XI.2	**Additional data on human exposure**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	Please see section A6.12.2.2 in which a Clinical trial phase I study , acute single dose, called Pharmacological effects of medetomidine in humans shows clinical pharmacology.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	4th November 2010	
Evaluation of applicant's justification	Agree with applicant	
Conclusion	Justification acceptable	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

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Dose-ranging study

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1 REFERENCE

1.1	**Reference**	[redacted] Dexmedetomidine Clinical Study Report. Dexmedetomidine Dose-Ranging Study to Evaluate the Effects of Dexmedetomidine on Sedation.
1.2	**Data protection**	Yes
1.2.1	Data owner	I-Tech AB
1.2.2	Criteria for data protection	Data on new a.s. for first approval.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No guideline available.
2.2	**GLP**	Study performed according to GCP (Good Clinical Practice) when applicable and GLP when applicable.
2.3	**Deviations**	Not applicable since no guideline study.

3 MATERIALS AND METHODS

3.1	**Persons exposed**	
3.1.1	Number of persons	Total of 73 whereas 72 completed the study.

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3.1.2 Other information

Table 6.3a: Summary of Subject Demographics

Parameter	Total Number of Subjects Treated		
	Part I	Part IIa	Part IIb
N[a]	40	8	25
	Mean ± SD		
Age (years)	28.3 ± 7.67	23.1 ± 5.33	30.4 ± 8.63
Height (cm)	174.2 ± 9.50	171.3 ± 7.50	173.6 ± 10.59
Weight (kg)	68.3 ± 10.01	65.9 ± 8.72	69.8 ± 9.82
	n (%)[a]		
Gender			
Male	20 (50%)	1 (13%)	12 (48%)
Female	20 (50%)	7 (88%)	13 (52%)
Ethnic origin			
Caucasian	37 (93%)	6 (75%)	23 (92%)
Black	1 (3%)	0	0
Other[b]	2 (5%)	2 (25%)	2 (8%)
Smoking history			
Ex-tobacco user	11 (28%)	0	8 (32%)
Non-tobacco user	12 (30%)	6 (75%)	9 (36%)
Tobacco user	17 (43%)	2 (25%)	8 (32%)
Alcohol use			
No	10 (25%)	3 (38%)	8 (32%)
Yes	30 (75%)	5 (63%)	17 (68%)

a: "N" denotes total number of subjects in each study part; "n" denotes number of subjects within a study part for each parameter.
b: "Other" ethnic origin includes Hindoslani (1 [3%] Part I), Hindustani (1 [3%] Part I; 1 [13%] Part IIa), White/Black (1 [13%] Part IIa; 1 [4%] Part IIb), and Moroccan (1 [4%] Part IIb).
NOTE: Part I used a 1-hour infusion of dexmedetomidine or placebo; Part IIa used a 12-hour infusion of dexmedetomidine or placebo; Part IIb used a 24-hour infusion of dexmedetomidine or placebo.
Data source: Tables 11.2.1, 11.2.2, 11.2.3

3.2 Exposure Intravenous bolous injection, followed by transfusion.

3.2.1 Reason of exposure: Dose-ranging study for medical approval

3.2.2 Frequency of exposure: One bolous injection followed by transfusion.

3.2.3 Overall time period of exposure:
Part I:
1 h 10 min bolous injection followed by 50 min transfusion.
Part II:
12-24 h 10 min bolous injection followed by either 12 h or 24 h transfusion.

3.2.4 Duration of single exposure: See above.

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3.2.5	Exposure concentration/dose	Phase I Dosing in µg/kg/h Target Steady State (ng/mL dexmedetomidine in plasma) Loading Infusion (LI) Maintenance Infusion (MI) 0.1 ng/mL: LI 1,00µg/kg/h MI 0,056 µg/mL/h 0.3 ng/mL: LI 3,00µg/kg/h MI 0,168 µg/mL/h 0.45 ng/mL: LI 4,50µg/kg/h MI 0,252 µg/kg/h 0.6 ng/mL: LI 6,00µg/kg/h MI 0,337 µg/kg/h 1.25 ng/mL*: LI 3,70µg/kg/h MI 1,000 µg/kg/h Phase II. 12 h infusion 0,3ng/mL: LI 3,00 µg/kg/h MI 0,168 µg/kg/h Phase II. 24 h infusion 0,3 ng/mL LI 3,00 µg/kg/h MI 0,168 µg/kg/h 0,6 ng/mL LI 6,00 µg/kg/h MI 0,337 µg/kg/h 1,25 ng/mL* LI 3,70 µg/kg/h MI 0,700 µg/kg/h *During the 1-hour infusion, a 35 minute loading infusion and a 25 minute maintenance infusion were used for the 1,25 ng/mL dosing group; during the 24 hour infusion, a 35 min loading infusion and a ≤24 hour maintenance infusion were used for the 1,25 ng/mL dexmedetomidine dosing group.
3.2.6	Other information	

3.3 Treatment

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Dose-ranging study

Table 5.5.1a: Study Procedures and Schedule of Assessments

Part I: 1-Hour Infusion	Screening (within 4 weeks prior to dosing)	Day -1	Day of Dosing Baseline	During 1-Hour Infusion	Post Infusion >1-3 hours	Post Infusion >3-6 hours	Post Infusion >6 hours to Discharge	Prior to Discharge
Informed consent/medical history	X							
Alcohol/smoking history	X							
Recording of concomitant medications[a]	X	X	X	X	X	X	X	X
Hematology	X	X						X
Blood chemistry	X	X						X
Urinalysis	X	X						X
Drug and alcohol screening		X						
Pregnancy test (if applicable)		X						
Virology (HBsAg, HCV, HIV)	X							
Physical examination	X	X						X
12-lead ECG	X							X
Cardiac monitoring			Continuously monitored from 30 minutes prior to infusion to 4 hours after infusion					
Blood sample of DEX			X	X[b]	X[c]	X[d]	X[e]	
Body temperature	X	X	X					X
BP, HR, RR	X	X	X	q 5 min	q 15 min	q 1 hour	q 4 hours	X
SpO_2[f]			X	q 5 min	q 15 min	q 1 hour	q 4 hours	X
VAS, Ramsay, CFF, BIS			X	q 5 min	q 15 min	q 1 hour	q 4 hours	

DEX = dexmedetomidine; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ECG = electrocardiogram; BP = blood pressure; HR = heart rate; RR = respiratory rate; SpO_2 = oxygen saturation by pulse oximeter; q = every; min = minute; VAS = visual analogue scale; CFF = critical flicker fusion threshold; BIS = bispectral index

a: Includes medications from one week prior to screening
b: At end of loading dose and at end of maintenance dose (60 minutes)
c: 1.25 hours after start of infusion
d: 2.5 hours after start of infusion
e: 5 and 9 hours after start of infusion
f: Monitored continuously and recorded at the indicated time points

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Table 5.5.1a: Study Procedures and Schedule of Assessments (continued)

Part II: Session I: 12-Hour Infusion	Screening (within 4 weeks prior to dosing)	Day -1	Day of Dosing Baseline	During 12-Hour Infusion 1-3 hours	>3-6 hours	>6-12 hours	Post Infusion >12-18 hours	>18-36 hours	Prior to Discharge
Informed consent/medical history	X								
Alcohol/smoking history	X								
Recording of concomitant medications[a]	X	X	X	X	X	X	X	X	X
Hematology	X	X							X
Blood chemistry	X	X							X
Urinalysis	X	X							X
Drug and alcohol screening		X							
Pregnancy test (if applicable)		X							
Virology (HBsAg, HCV, HIV)	X								
Physical examination	X	X							X
12-lead ECG	X								X
Cardiac monitoring			Continuously monitored from 30 minutes prior to infusion to 4 hours after infusion						
Blood sample of DEX			X	X[b]	X[c]	X[d]	X[e]	X[f]	
Body temperature	X	X	X						X
BP, HR, RR	X	X	X	q 5 min	q 15 min	q 1 hour	q 1 hour	q 4 hours	X
SpO_2[g]			X	q 5 min	q 15 min	q 1 hour	q 1 hour	q 4 hours	X
VAS, Ramsay, CFF, BIS			X	q 5 min	q 15 min	q 1 hour	q 1 hour	q 4 hours	

DEX = dexmedetomidine; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ECG = electrocardiogram; BP = blood pressure; HR = heart rate; RR = respiratory rate; SpO_2 = oxygen saturation by pulse oximeter; q = every; min = minute; VAS = visual analogue scale; CFF = critical flicker fusion threshold; BIS = bispectral index

a: Includes medications from one week prior to screening
b: At 5, 10, 20, 25, 30, 60, and 150 minutes
c: At 5 hours
d: At 8.5 and 12 hours
e: At 12.25, 13, 14.5, and 17 hours after the start of the infusion
f: At 21, 28, and 36 hours after the start of the infusion
g: Monitored continuously and recorded at the indicated time points

Dexmedetomidine HCl (Abbott-85499)
Study No. DEX-97-028
Clinical/Statistical Report
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Table 5.5.1a: Study Procedures and Schedule of Assessments (continued)

Part II: Sessions II, III, & IV: 24-Hour Infusion	Screening (within 4 weeks prior to dosing)	Day -1	Day of Dosing Baseline	During 12-Hour Infusion 1-3 hours	>3-6 hours	>6-24 hours	Post Infusion >24-30 hours	>30-48 hours	Prior to Discharge
Informed consent/medical history	X								
Alcohol/smoking history	X								
Recording of concomitant medications[a]	X	X	X	X	X	X	X	X	X
Hematology	X	X							X
Blood chemistry	X	X							X
Urinalysis	X	X							X
Drug and alcohol screening		X							
Pregnancy test (if applicable)		X							
Virology (HBsAg, HCV, HIV)	X								
Physical examination	X	X							X
12-lead ECG	X								X
Cardiac monitoring			Continuously monitored from 30 minutes prior to infusion to 4 hours after infusion						
Blood sample of DEX			X	X[b]	X[c]	X[d]	X[e]	X[f]	
Body temperature	X	X	X						X
BP, HR, RR	X	X	X	q 5 min	q 15 min	q 1 hour	q 1 hour	q 4 hours	X
SpO_2[g]			X	q 5 min	q 15 min	q 1 hour	q 1 hour	q 4 hours	X
VAS, Ramsay, CFF, BIS			X	q 5 min	q 15 min	q 1 hour	q 1 hour	q 4 hours	

DEX = dexmedetomidine; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ECG = electrocardiogram; BP = blood pressure; HR = heart rate; RR = respiratory rate; SpO_2 = oxygen saturation by pulse oximeter; q = every; min = minute; VAS = visual analogue scale; CFF = critical flicker fusion threshold; BIS = bispectral index

a: Includes medications from one week prior to screening
b: At 5, 10, 20, 25, 30, 60, and 150 minutes
c: At 5 hours
d: At 8.5, 12, 18, and 24 hours after the start of the infusion
e: At 24.25, 25, 26.5, and 29 hours after the start of the infusion
f: At 33, 40, and 48 hours after the start of the infusion
g: Monitored continuously and recorded at the indicated time points

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3.4 Remarks

No remarks.

4 RESULTS

Pharmacodynamic endpoints.

Visual Analouge Scale of Sedation(VAS-Sedation), Critical Flicker Fusion (CFF), Ramsey score, Bispectral Index (BIS) as well as measurements of oxygen saturation by pulse oximeter (SpO_2), blood pressure (BP), heart rate (HR), respiratory rate (RR), and body temperature.

Trained, blinded raters were to assess sedation in both parts of the study at baseline, during infusion and postinfusion.

VAS-Sedation is a self-administrated assessment of the level of alertness based upon the subject's response to his/her name, was used as a measurement of sedation. The VAS was a 100 mm line with endpoints of very alert (0) to very sleepy (100).

Ramsey sedation score using the scale below

6=asleep, no response

5=asleep, but sluggish response to light glabellar tap or loud auditory stimulus

4=asleep but with brisk response to light glabellar tap or loud auditory stimulus

3=subject responds to demands

2=subject cooperative, orientated and tranquil

1=subject anxious, agitated, or restless.

Pharmacokinetic endpoints

Primary endpoint was dexmedetomidine plasma levels.

Other endpoints are summerized in tables below.

4.1 Clinical Signs

Main clinical sign is sedation. In the first table below 8.1.1a which summerize the VAS evaluation. The next table 8.4a is the correlation between the dexmedetomidine plasma level and the Ramsey sedation score in order to evaluate level of sedation. The last pharmacodynamic results is the result from the CCF end points, summerized in table 8.2.1a.

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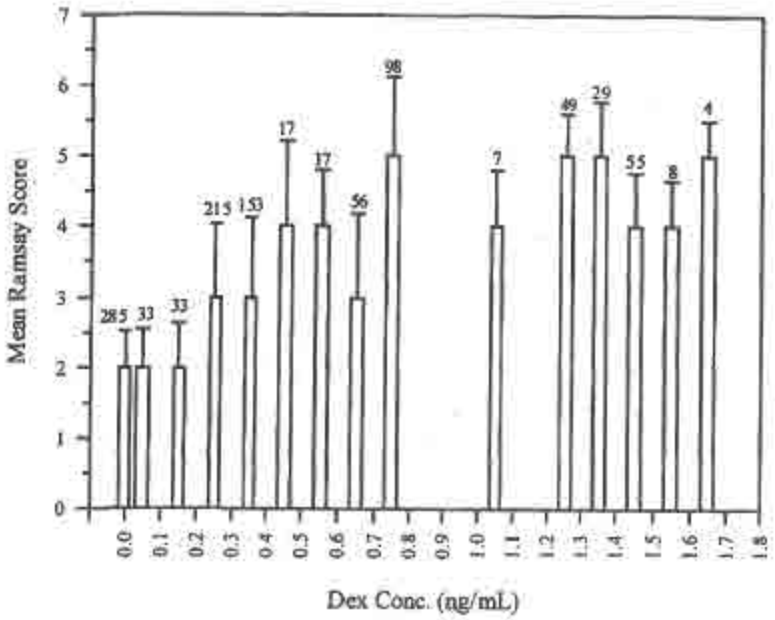
Table 8.1.1a: Summary of Average VAS - Sedation by Time Interval, Pharmacodynamic Evaluable Subjects

Time Interval VAS - Sedation Score (mm)	Placebo	Dexmedetomidine Target Concentrations				
		0.1 ng/mL	0.3 ng/mL	0.45 ng/mL	0.6 ng/mL	1.25 ng/mL
0-1 hour						
N	18	6	18	6	12	12
Mean	14.66	19.89	48.34*†	56.72*†	61.11*†‡	59.22*†
0-12 hours						
N	8	N/A	12	N/A	6	6
Mean	17.60	N/A	48.06*	N/A	76.91*‡	84.63*‡
0-24 hours						
N	6	N/A	6	N/A	6	6
Mean	32.50	N/A	49.80*	N/A	76.38*‡	79.84*‡

N = number of subjects; N/A = not applicable
* Statistically significant ($p \leq 0.05$) versus placebo
† Statistically significant ($p \leq 0.05$) versus dexmedetomidine 0.1 ng/mL
‡ Statistically significant ($p \leq 0.05$) versus dexmedetomidine 0.3 ng/mL

Data source: Tables 11.8.1.1, 11.8.1.2

Figure 8.4a: Mean Ramsay Sedation Scores vs. Dexmedetomidine Concentration



For each Ramsay score, a dexmedetomidine plasma concentration (ng/mL) was linearly interpolated from the surrounding dexmedetomidine values, if not measured. A mean Ramsay score was then calculated for each 0.1 ng/mL increment of dexmedetomidine. Each bar is centered over the mean of the dexmedetomidine increment and represents the mean Ramsay score for that dexmedetomidine concentration range. The number above each bar is the number (N) of Ramsay scores used to compute the mean at that dexmedetomidine concentration range. Bars comprised of less than 4 values were omitted.
Data Source: Figure 5, Drug Metabolism Report (Appendix 13.3)

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Table 8.1.2a: Summary of Average CFF Scores by Time Interval, Pharmacodynamic Evaluable Subjects

Time Interval CFF Score (Hz)	Placebo	Dexmedetomidine Target Concentrations				
		0.1 ng/mL	0.3 ng/mL	0.45 ng/mL	0.6 ng/mL	1.25 ng/mL
0-1 hour						
N	18	6	18	6	12	12
Mean	33.01	29.61	32.93	27.06	33.75	36.35$
0-12 hours						
N	8	N/A	12	N/A	6	6
Mean	34.09	N/A	30.28	N/A	31.37	35.19
0-24 hours						
N	6	N/A	6	N/A	6	6
Mean	35.93	N/A	28.58	N/A	30.48	35.25

N = number of subjects; N/A = not applicable
$ Statistically significant ($p \leq 0.05$) versus dexmedetomidine 0.45 ng/mL.
Data source: Tables 11.9.1.1 and 11.9.1.2

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The pharmacokinetic parameters are summarised in tables below. Table 7.1a summarises the overall pharmacokinetic parameters and the tables 7.1b and 7.1c presents the different parameters for each part of the study.

Table 7.1a: Noncompartmental Pharmacokinetic Parameters, All Regimens, Parts I and II (N=54)

PK Parameter	$t_{1/2}$* h	β l/h	CL L/h	MRT h	V_{ss} L	V_{ss} L/kg
Mean	2.06	0.34	38.75	2.43	91.03	1.32
SD	0.43	0.07	9.87	0.75	25.48	0.35
CV	23.9	20.9	25.5	30.8	28.0	26.2
Minimum	1.46	0.19	16.96	1.34	29.07	0.61
Maximum	3.68	0.48	64.85	5.28	180.99	2.32

N = number of subjects; PK = pharmacokinetic; $t_{1/2}$ = terminal half-life; β = terminal rate constant; CL = total body clearance; MRT = mean residence time; V_{ss} = volume of distribution at the steady state; SD = standard deviation; CV = coefficient of variation

a: Presented as the harmonic mean and pseudo standard deviation

Data source: Drug Metabolism Report, Appendix 13.3

Table 7.1b: Summary of Noncompartmental Pharmacokinetic Parameters by Dose, Part I

		Loading Infusion Duration (Total Infusion = 1 hour)				
		10 minutes				35 minutes
		Dexmedetomidine Target Concentration				
Parameter	Unit	0.1 ng/mL	0.3 ng/mL	0.45 ng/mL	0.6 ng/mL	1.25 ng/mL
C_{max}	ng/mL	0.21 ± 0.11	0.83 ± 0.41	0.91 ± 0.29	1.76 ±0.71	2.40 ± 0.56
t_{max}	h	0.31 ± 0.37	0.45 ± 0.46	0.30 ± 0.37	0.15 ± 0.01	0.57 ± 0.00
AUC	ng•h/mL	0.36 ± 0.09	1.33 ± 0.17	1.56 ± 0.29	2.78 ± 0.66	4.48 ± 0.82
$t_{1/2}$*	h	1.80 ± 0.36	2.08 ± 0.48	2.00 ± 0.09	1.92 ± 0.42	2.20 ± 0.52
MRT	h	2.52 ± 0.53	2.66 ± 1.34	2.10 ±0.37	2.14 ± 0.35	2.40 ± 0.62
CL	L/h	41.5 ± 12.9	30.0 ± 4.6	42.9 ± 7.5	33.7 ± 14.1	39.6 ± 10.5
V_{ss}	L	105.5 ± 42.6	76.2 ± 28.4	88.9 ± 14.5	72.9 ± 31.3	91.5 ± 18.8
C_{ei}	ng/mL	0.08 ± 0.01	0.26 ± 0.04	0.37 ± 0.08	0.62 ± 0.13	1.25 ± 0.33
AUC/mg	ng/mL/mg	25.7 ± 6.5	34.0 ± 5.0	24.0 ± 4.4	34.6 ± 15.1	26.6 ± 6.4

C_{max} = maximum observed plasma concentration; t_{max} = time of C_{max}; AUC = area under the plasma concentration-time curve; $t_{1/2}$ = terminal phase half-life; MRT = mean residence time; CL = total body clearance; V_{SS} = volume of distribution at the steady state; C_{ei} = observed dexmedetomidine plasma concentration at the end of the infusion

a: Presented as the harmonic mean and pseudo standard deviation

Data source: Drug Metabolism Report, Appendix 13.3

Table 7.1c: Summary of Noncompartmental Pharmacokinetic Parameters by Dose, Part II

		Loading Infusion (min) / Total Infusion (h) Duration			
		10 min / 12 h	10 min / 24 h		35 min / 24 h
		Dexmedetomidine Target Concentration			
Parameter	Unit	0.3 ng/mL	0.3 ng/mL	0.6 ng/mL	1.25 ng/mL
C_{max}	ng/mL	0.87 ± 0.25	1.05 ± 0.17	1.59 ± 0.51	2.40 ± 0.59
t_{max}	h	0.12 ± 0.03	0.14 ± 0.01	0.13 ± 0.01	1.88 ± 3.25
AUC	ng•h/mL	3.72 ± 0.71	7.29 ± 1.54	17.68 ± 2.84	37.76 ± 7.03
$t_{1/2}$*	h	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61
MRT	h	1.96 ± 0.55	2.42 ± 0.60	2.75 ± 0.74	2.89 ± 1.01
CL	L/h	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5
V_{ss}	L	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Avg C_{ss}	ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20
AUC/mg	ng/mL/mg	22.4 ± 5.3	23.7 ± 3.6	29.1 ± 4.9	28.3 ± 5.7

min = minutes; h = hours; C_{max} = maximum observed plasma concentration; t_{max} = time of C_{max}; AUC = area under the plasma concentration-time curve; $t_{1/2}$ = terminal phase half-life; MRT = mean residence time; CL = total body clearance; V_{SS} = volume of distribution at the steady state; Avg C_{ss} = average steady-state concentration of dexmedetomidine (samples at 2.5 to 9 hours for the 12-hour infusion and samples at 2.5 to 18 hours for the 24-hour infusions)

a: Presented as the harmonic mean and pseudo standard deviation

Data source: Drug Metabolism Report, Appendix 13.3

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4.2 Results of examinations

Pharmacodynamic results:
Regardless of the length of the infusion, dexmedetomidine-treated subjects consistently exhibited greater average sedation than placebo-treated subjects, as measured by mean VAS-Sedation scores and by the average percentage of time at Ramsay sedation scores of 3, 4, or 5. Analysis of VAS-Sedation scores revealed no statistically significant difference between the 0.6 ng/mL and 1.25 ng/mL dexmedetomidine groups. Analysis of the percent of time at Ramsay sedation scores of 3, 4, or 5 revealed a dose-response among dexmedetomidine-treated subjects, with the 0.6 ng/mL and 1.25 ng/mL groups exhibiting a longer duration of sedation than the 0.3 ng/mL group during the 12- and 24-hour infusions.

Overall, the rate of development of sedation (measured by the median time to a Ramsay score of 4 or higher within the first hour) was rapid during dexmedetomidine administration, ranging from a median of 15 minutes (0.6 ng/mL group) to 33 minutes (0.3 ng/mL group) after the start of the infusion. Further, the rate of development of sedation was statistically significantly faster among dexmedetomidine-treated subjects than among placebo-treated subjects, as measured by mean VAS-Sedation scores and by median Ramsay sedation scores during the first hour of the 24-hour infusion.

Dexmedetomidine-treated subjects and placebo-treated subjects had similar results for the CFF threshold, indicating that, in spite of sedation, dexmedetomidine-treated subjects were easily arousable and able to complete the test.

Safety results:
Dexmedetomidine was safe and well tolerated. The most commonly noted adverse events in both parts of the study among dexmedetomidine-treated subjects were somnolence and dry mouth. There were no obvious differences among dexmedetomidine dosing groups in frequency and types of adverse events. Bradycardia was reported in two subjects. One subject, in the 0.3 ng/mL dexmedetomidine 12-hour infusion group, had mild bradycardia concurrent with an episode of hypotension; the other subject, in the 1.25 ng/mL dexmedetomidine 24-hour infusion group, had mild sinus bradycardia approximately 13 hours after initiation of the infusion.

No subjects died or experienced serious adverse events in this study. One subject in the 0.3 ng/mL 24-hour infusion dexmedetomidine group was discontinued from dosing after approximately eight hours when an infiltration of the intravenous catheter characterized as a painful, swollen right hand occurred. The event was considered to be severe and unrelated to study medication.

4.3 Effectivity of medical treatment Not applicable

4.4 Outcome See safety results

4.5 Other No other significant results

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5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The primary objectives of the study were to identify the dose-response relationship for sedation using single intravenous doses of dexmedetomidine.72 healthy volunteers exposed to different dosing regimens and the main endpoint, sedation, was evaluated. Further, a vast range of pharmacodynamic and pharmacokinetic parameters were investigated.

5.2 Results and discussion

A relationship between dosing, plasma levels and degree of sedation was established. A midrange sedation was reached with plasma levels between 0,3-0,6 ng/mL (corresponding 0,6-1,0 µg/kg dexmedetomidine).

Plasma levels of 0,1ng/ml did not evoke any sedation symptoms, corresponding 0,2 µg/kg dexmedetomidine.

5.3 Conclusion

A NOEC can be established concerning sedation; 0,1 ng/mL dexmedetomidine in plasma, corresponding a dose of 0,2µg/kg dexmedetomidine intravenously.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	13/07/12
Materials and Methods	As stated by the applicant.
Results and discussion	As stated by the applicant.
Conclusion	As stated by the applicant.
Remarks	None.
	COMMENTS FROM ... (specify)
Date	Give date of comments submitted
Materials and Methods	Discuss if deviating from view of rapporteur member state
Results and discussion	Discuss if deviating from view of rapporteur member state
Conclusion	Discuss if deviating from view of rapporteur member state
Remarks	

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Dermal Absorption

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] Absorption through skin of medetomidine from antifouling paint – a clinical study in healthy volunteer subjects. [redacted] (unpublished).
1.2	**Data protection**	Yes
1.2.1	Data owner	I-Tech AB
1.2.2	Criteria for data protection	Data on new a.s. for first approval.

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No guideline available.
2.2	**GLP**	Study performed according to GCP (Good Clinical Practice) when applicable and GLP when applicable.
2.3	**Deviations**	Some deviations from the study protocol occurred. The deviations were considered to not affect the validity of the study or the interpretation of the results.

3 MATERIALS AND METHODS

3.1	**Substance**	Medetomidine (CAS 86347-14-0) in a solvent and rosin based paint ([redacted]).
3.2	**Persons exposed**	Healthy male and female volunteers in one clinical trial.
3.2.1	Sex	Male and female
3.2.2	Age/weight	Age 18-50, weight 50-110 kg, BMI 18.5-30
3.2.3	Known Diseases	Healthy
3.2.4	Number of persons	16; 8 in main study and 8 in three pilot experiments (n=3, 3 and 2).
3.2.5	Other information	None
3.3	**Exposure**	Dermal exposure
3.3.1	Reason of exposure	Acute single dose to determine dermal absorption.
3.3.2	Frequency of exposure	Single
3.3.3	Overall time period of exposure	6 hours

Doc III A section 6.16.2
Annex Point VI.3.5
XI.2

Additional data on human exposure

Dermal Absorption

3.3.4	Duration of single exposure	6 hours followed by removal and a 18 hour observation period.
3.3.5	Exposure concentration/dose	Pilot study 0.001, 0.01 and 0.1 % w/w in 10 g paint. Main study 1% w/w in 10 g paint. Surface area covered 4 dm^2 on the volunteers back.
3.3.6	Other information	None
3.4	**Examinations**	Blood samples to assess dexmedetomidine and levomedetomidine in blood, systolic and diastolic blood pressure, heart rate, ECG, sedation scores (self-assessed tiredness scores and Maddox wing readings), skin irritation and subjective effects.
3.5	**Treatment**	Removal of paint after 6 hours exposure.
3.6	**Remarks**	None
		4 RESULTS
4.1	**Clinical Signs**	Headache, nausea, dizziness and runny nose were observed but these effects were not related to the medetomidine concentration in the paint. Cardiovascular vital signs, sedation scores and subjective symptoms were not influenced by the treatments.
4.2	**Results of examinations**	The highest dose tested was well tolerated with no clinical signs.
4.3	**Effectivity of medical treatment**	Not applicable.
4.4	**Outcome**	Pilot experiment: 0.001 and 0.01 % treatment subjects had no detectable concentrations of levo- or dexmedetomidine. One subject in the 0.1% treatment had 0.063 ng/mL of dexmedetomidine in one plasma sample (24h) but this was most likely due to sampling problems and a contamination of the sample. Main study: Levomedetomidine concentration in plasma (LLOQ 0.025 ng/mL) were not detected in any blood samples. Six of eight subjects in the main study had detectable concentrations of dexmedetomidine in plasma (LLOQ 0.025 ng/mL). The highest concentration observed was 0.048 ng/mL. In three volunteers detectable concentrations of dexmedetomdine was present in the final sample after 18 hours of recovery. A skin permeability coefficient was calculated for dexmedetomidine based on the highest individual plasma concentration profile observed. A K_p value of 1.54×10^{-6} cm/h was generated.
4.5	**Other**	None

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Dermal absorption of a paint product containing medetomidine was determined in 16 healthy volunteers. Blood plasma concentrations of levo- and dexmedetomidine were recorded as well as clinical signs of sedation or cardiovascular effects.

5.2 Results and discussion

The highest dose tested was 1% of medetomidine (w/w) in 10 g of paint covering 4 dm^2 of the study subject's skin. The treatment was well tolerated. Some clinical signs were recorded but they were not related to the medetomidine exposure. A plasma concentration of 0.048 ng/mL dexmedetomidine was the highest absorption recorded and was used for skin permeability coefficient calculations, K_p. The K_p calculated was $1.54x10^{-6}$ cm/h. The levomedetomidine plasma concentrations were below the detection limit in all subjects.

5.3 Conclusion

No clinical signs of sedation or cardiovascular effects were observed after a 6 hour exposure to a paint containing 1% of medetomidine (w/w). Skin absorption of medetomidine from the paint gave a maximum plasma concentration of 0.048 ng/mL dexmedetomidine and no detectable levomedetomidine. The K_p for dexmedetomidine in a solvent based paint is $1.54x10^{-6}$ cm/h.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16/1/11
Materials and Methods	As stated by the applicant
Results and discussion	As stated by the applicant
Conclusion	As stated by the applicant. A human dermal absorption value of 0.06% can be established for medetomidine in an antifouling paint from this study.
Remarks	None.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A7.1.1.1.1
Annex Point IIA7.6.2.1

Hydrolysis as a function of PH and identification of breakdown products

Official use only

1 REFERENCE

1.1	**Reference**	P. Sydney. 2011 Medetomidine. Abiotic degradation: Hydrolysis as a function of pH. Huntingdon Life Sciences, England. Huntingdon Life Sciences Study Number: FGT0007 (Unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	I-Tech AB
1.2.2		
1.2.3	Criteria for data protection	Data on new a.s. for first approval / authorisation

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes OECD Guideline 111
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	Medetomidine
3.1.1	Lot/Batch number	1230850
3.1.2	Specification	As given in section 2
3.1.3	Purity	[redacted] %
3.1.4	Further relevant properties	Molecular weight: 200.28 g/mol Water solubility: 0.19 g/L at 20°C
3.2	**Reference substances**	No reference substance was used.
3.3	**Test solution**	Please refer to table A7.1.1.1.1-1 and A7.1.1.1.1-2 for details of the test solutions.
3.4	**Testing procedure**	
3.4.1	Test system	The test was carried out using reagent grade chemicals, purified sterile water and sterilised glassware. For further details please refer to table A7.1.1.1.1-3.

Section A7.1.1.1.1 Hydrolysis as a function of PH and identification of breakdown products

Annex Point IIA7.6.2.1

3.4.2	Temperature	50± 0.5 °C
3.4.3	pH	4, 7 and 9.
3.4.4	Duration of the test	120 h.
3.4.5	Number of replicates	2
3.4.6	Sampling	t_0 5 min t_1 2.4 h t_2 120 h
3.4.7	Analytical methods	HPLC. Mobile phase acetonitrile: 0.02M aqueous ammonium acetate (1:1 v/v). UV detection at 220 nm, approximately 3 min retention time.
3.5	**Preliminary test**	Yes A preliminary test determines if the half-life is less than 2.4h or if less than 10% hydrolysis occur after 120 h. If so no further testing is deemed necessary.

4 RESULTS

4.1	**Concentration and hydrolysis values**	The preliminary test result showed less than 10% hydrolysis after 120 h in all treatments. A full study was therefore not performed. Please refer to table A7.1.1.1.1-4
4.2	**Hydrolysis rate constant**	Not applicable
4.3	**Dissipation time**	Not applicable
4.4	**Concentration – time data**	Not applicable
4.5	**Specification of the transformation products**	Not applicable

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	OECD Guideline for Testing of Chemicals, No. 111. The study objective was to determine the rate of hydrolysis of medetomidine as a function of pH. There were no deviations from the Guideline.
5.2	**Results and discussion**	The preliminary study showed that at pH 4, 7 and 9, less than 10% hydrolysis occurred after 5 days. This is considered equivalent to a half-life of greater than one year under environmental conditions and no further testing was performed.
5.2.1	K_H	Not applicable
5.2.2	DT_{50}	Not applicable
5.2.3	r^2	Not applicable

Section A7.1.1.1.1 Hydrolysis as a function of PH and identification of breakdown products

Annex Point IIA7.6.2.1

5.3	**Conclusion**	Medetomidine was determined to be hydrolytically stable under acidic, neutral and basic conditions.
5.3.1	Reliability	Based on the assessment of materials and methods, the appropriate reliability indicator is 1.
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	22/04/2013
Materials and Methods	Applicant version is acceptable
Results and discussion	Applicant version is acceptable
Conclusion	Applicant version is acceptable
Reliability	1
Acceptability	Acceptable
Remarks	In accordance with OECD Guideline 111 medetomidine was shown to be hydrolytically stable at pH 4, 7 and 9 (less than 10% hydrolysis occurred within a 5 d period at an elevated temperature of 50°C). A hydrolytic half-life of greater than 1 year under environmentally relevant conditions (defined as 25°C in the OECD 111 guideline) can therefore be assumed.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A7_1_1_1_1-1: Type and composition of buffer solutions (specify kind of water if necessary)

pH	Type of buffer (final molarity)	Composition
4	Not applicable	3 g potassium dihydrogen orthophosphate and 6.4 g disodium hydrogen orthophosphate dodecahydrate were dissolved in 950 ml purified water. pH was adjusted with orthophosphoric acid to 4.0 ± 0.05 and the volume was then adjusted to 1000 ml with purified water.
7	Not applicable	13.6 g potassium dihydrogen orthophosphate were dissolved in 1900 ml purified water and 60 ml 1M sodium hydroxide was added. pH was adjusted with hydrochloric acid to 7.0 ± 0.05 and the volume was the adjusted to 2000 ml with purified water.
9	Not applicable	16.6 g disodium tetraborate decahydrate and 1.8 g potassium dihydrogen orthophosphate were dissolved in 950 ml purified water. pH was adjusted with hydrochloric acid to 9.0 ± 0.05 and the volume was then adjusted to 1000 ml with purified water.

Table A7_1_1_1_1-2: Description of test solution

Criteria	Details
Purity of water	Purified sterile water
Preparation of test medium	100µl of stock solution, medetomidine in acetonitrile (9g/l), were added to 10 ml buffer solution which had been purged with nitrogen. To the pH 4 samples 10µl of 1 M HCl were also added to maintain test pH. The samples were stored at 50 °C in the dark until sampling. At each sampling time 1 ml of test solution was diluted to 20 ml with acetonitrile:water (1:1 v/v).
Test concentrations (mg a.i./L)	pH 4: 90.99 and 92.00 pH 7: 90.86 and 90.81 pH 9: 90.12 and 90.50
Temperature (°C)	50 ± 0.5 °C
Controls	No control substance was used.
Identity and concentration of co-solvent	Acetonitrile, final concentration 1% in medetomidine – buffer solutions.
Replicates	Two replicates per pH.

Table A7_1_1_1_1-3: Description of test system

Glassware	10 ml Wheaton glass vials
Other equipment	Aglient 1050 Series Liquid Chromatograph with a Zorbax XDB-C8 column
Method of sterilization	No information on method.

Table A7_1_1_1_1-4: Hydrolysis of test compound, transformation products and reference substance, expressed as percentage of initial concentrations, at pH 5, pH 7 and pH 9.

Medetomidine	**Sampling times (*h*)**							
	0	t_1	t_2	t_3	t_4	t_5	t_6	t_n
Parent compound pH 4	90.99 92.00	90.93 90.34	90.03 89.35	-	-	-	-	-
Parent compound pH 7	90.86 90.81	90.96 90.28	89.08 87.11	-	-	-	-	-
Parent compound pH 9	90.12 90.50	91.32 88.71	87.06 86.84	-	-	-	-	-

Section A7.1.1.1.2
Annex Point IIA7.6.2.2

Phototransformation in water including identity of transformation products

Official use only

1 REFERENCE

1.1	**Reference**	Wehrhan, A. 2009 Aqueous Photolysis. Harlan Laboratories Ltd. Switzerland. Harlan Laboratories Study Number: C39435
1.2	**Data protection**	Yes
1.2.1	Data owner	I-Tech AB
1.2.2		
1.2.3	Criteria for data protection	Data on new a.s. for first approval / authorisation

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes OECD Guideline 316
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	Medetomidine
3.1.1	Lot/Batch number	1230850
3.1.2	Specification	As given in section 2
3.1.3	Purity	[redacted] %
3.1.4	Radiolabelling	No
3.1.5	UV/VIS absorption spectra and absorbance value	262-264nm in H_2O/CH_3CN, ε = 259-283$M^{-1}cm^{-1}$
3.1.6	Further relevant properties	Molecular weight: 200.28 g/mol Water solubility: 0.20 g/L at pH 7.9 and 25°C
3.2	**Reference substances**	No reference substance was used.
3.3	**Test solution**	Test solutions were prepared in ethanol (p.a) at the concentration 1.09 g/L (pH 8.5) and 0.109 g/L (pH 8.1).

Section A7.1.1.1.2 Phototransformation in water including identity of transformation products

Annex Point IIA7.6.2.2

3.4	**Testing procedure**	
3.4.1	Test system	Tier 1 of the guideline were conducted using a Perkin Elmer UV/VIS Spectrophotometer Lambda 18.
3.4.2	Properties of light source	UV-absorption spectra were obtained from a Perkin Elmer UV/VIS Spectrophotometer Lambda 18. The cuvettes were of quarts glass with an optical path length of 10 mm. The spectrum was measured from 200 to 800 nm in intervals of 0.5 nm. No other light sources were used.
3.4.3	Determination of irradiance	UV-absorption spectra were obtained from a Perkin Elmer UV/VIS Spectrophotometer Lambda 18. The cuvettes were of quarts glass with an optical path length of 10 mm. The spectrum was measured from 200 to 800 nm in intervals of 0.5 nm.
3.4.4	Temperature	24°C
3.4.5	pH	pH 8.5 (1.09 g/L solution) and 8.1 (0.109 g/L solution).
3.4.6	Duration of the test	No information given.
3.4.7	Number of replicates	No information given.
3.4.8	Sampling	Not applicable for Tier 1 of Phototransformation.
3.4.9	Analytical methods	Not applicable for Tier 1 of Phototransformation.
3.5	**Transformation products**	Not applicable for Tier 1 of Phototransformation.
3.5.1	Method of analysis for transformation products	Not applicable

4 RESULTS

4.1	**Screening test**	Performed Tier 1 of the guideline were conducted and the UV-spectrum of the test item was measured in order to estimate the maximum possible direct photolysis rate constant.
4.2	**Actinometer data**	Not applicable for Tier 1 of Phototransformation.
4.3	**Controls**	Not applicable for Tier 1 of Phototransformation.
4.4	**Photolysis data**	
4.4.1	Concentration values	Not applicable for Tier 1 of Phototransformation.
4.4.2	Mass balance	Not applicable for Tier 1 of Phototransformation.
4.4.3	k^e_p	Not applicable for Tier 1 of Phototransformation.
4.4.4	Kinetic order	Not applicable for Tier 1 of Phototransformation.
4.4.5	k^e_p / k^a_p	Not applicable for Tier 1 of Phototransformation.
4.4.6	Reaction quantum	Not applicable for Tier 1 of Phototransformation.

Section A7.1.1.1.2 Phototransformation in water including identity of transformation products

Annex Point IIA7.6.2.2

	yield (ϕ^{c}_{E})	
4.4.7	k_{pE}	Not applicable for Tier 1 of Phototransformation.
4.4.8	Half-life ($t_{1/2E}$)	Not applicable for Tier 1 of Phototransformation.
4.5	**Specification of the transformation products**	Not applicable for Tier 1 of Phototransformation.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The UV-spectrum of the test item was measured in order to estimate the maximum possible direct photolysis rate constant.
5.2	**Results and discussion**	Absorption of UV light between 290 and 800 nm was low for the test item and the molar decadic adsorption coefficients were below 10 L $mol^{-1}cm^{-1}$. The test item is therefore assumed to be photolytically stable and neither theoretical nor experimental photolytic half lives were determined.
5.2.1	k^{c}_{p}	Not applicable for Tier 1 of Phototransformation.
5.2.2	K_{pE}	Not applicable for Tier 1 of Phototransformation.
5.2.3	ϕ^{c}_{E}	Not applicable for Tier 1 of Phototransformation.
5.2.4	$t_{1/2E}$	Not applicable for Tier 1 of Phototransformation.
5.3	**Conclusion**	The test item is assumed to be photolytically stable.
5.3.1	Reliability	Based on the assessment of materials and methods, the appropriate reliability indicator is 1.
5.3.2	Deficiencies	No

Section A7.1.1.1.2
Annex Point IIA7.6.2.2

Phototransformation in water including identity of transformation products

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	25/08/2010
Materials and Methods	Applicant's version is acceptable
Results and discussion	Applicant's version is acceptable
Conclusion	Applicant's version is acceptable
Reliability	1
Acceptability	Acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A7_1_1_2-1: Description of test solution and controls

Criteria	Details
Purity of water	Not applicable for Tier 1 of Phototransformation.

Preparation of test chemical solution	Test solutions were prepared in ethanol (p.a) at the concentration 1.09 g/L (pH 8.5) and 0.109 g/L (pH 8.1).
Test concentrations (mg a.s./L)	1.09 g/L and 0.109 g/L.
Temperature (°C)	24 ° C
Preparation of a.s. solution	Test solutions were prepared in ethanol (p.a) at the concentration 1.09 g/L (pH 8.5) and 0.109 g/L (pH 8.1).
Controls	No controls used.
Identity and concentration of co-solvent	No co-solvents used.

Table A7_1_1_2-2: Description of test system

Criteria	**Details**
Laboratory equipment	Perkin Elmer UV/VIS Spektrophotometer Lambda 18. Cuvettes of quarts glass with, optical path length of 10 mm. The spectrum was measured from 200 to 800 nm in intervals of 0.5 nm
Test apparatus	Not used.
Properties of artificial light source:	Not used.
Nature of light source	-
Emission wavelenght spectrum	-
Light intensity	-
Filters	-
Properties of natural sunlight:	Not used.
Latitude	-
Hours of daylight	-
Time of year	-
Light intensity	-
Solar irradiance (L_λ)	-

Table A7_1_1_2-3: Screening test results

Absorption curve	Please refer to figure 2 in the reference.
A_λ	Se table A7_1_1_2-6.
ε_λ^c	Se table A7_1_1_2-6
k_{pEmax}	Not applicable for Tier 1 of Phototransformation.
$t_{1/2Emin}$	Not applicable for Tier 1 of Phototransformation.
L_λ	Please refer to table A7_1_1_2-6

Table A7_1_1_2-4: Actinometer data

PNAP/ pyridine concentrations	Not applicable for Tier 1 of Phototransformation.
ϕ^a_E	Not applicable for Tier 1 of Phototransformation.
k^a_p	Not applicable for Tier 1 of Phototransformation.

Table A7_1_1_2-5: Specification and amount of transformation products ***(adjust table size as required)***

CAS-Number	***CAS and/or IUPAC* Chemical Name*(s)***	**Amount [%] of parent compound measured at**		
		pH_1	**pH_2**	**pH_3**

Table A7_1_1_2-6: **Wavelength, average daily solar photon irradiance (L_λ) at 30 °, 40 ° and 50 °latitude. UV-VIS absorbance (A_meas) measured between 290 and 800 nm at 5.44 mmol/L (1.09 g/L) and corresponding molar decadic absorption coefficient (ε).**

Wavelength λ [nm]	latitude 30° Δλ [nm]	latitude 40° L_λ(tab) [mmol cm^{-2} d^{-1}]	latitude 50° L_λ(tab) [mmol cm^{-2} d^{-1}]	Absorbance L_λ(tab) [mmol cm^{-2} d^{-1}]	A_meas [1]	Absorption coefficient ε = A/c*l [L mol^{-1} cm^{-1}]
297.5	2.5	1.09E−04	6.17E−05	2.85E−05	0.0084	1.54
300	2.5	4.11E−04	2.70E−04	1.50E−04	0.0077	1.41
302.5	2.5	1.14E−03	8.30E−04	5.33E−04	0.0076	1.40
305	2.5	2.46E−03	1.95E−03	1.39E−03	0.0076	1.40
307.5	2.5	4.45E−03	3.74E−03	2.89E−03	0.007	1.29
310	2.5	7.02E−03	6.17E−03	5.05E−03	0.0068	1.25
312.5	2.5	1.00E−02	9.07E−03	7.75E−03	0.0065	1.19
315	2.5	1.32E−02	1.22E−02	1.08E−02	0.0058	1.07
317.5	2.5	1.64E−02	1.55E−02	1.40E−02	0.0061	1.12
320	2.5	1.95E−02	1.87E−02	1.71E−02	0.0067	1.23
323.1	3.1	3.46E−02	3.35E−02	3.12E−02	0.0061	1.12
330	6.9	1.18E−01	1.16E−01	1.10E−01	0.0059	1.08
340	10	1.48E−01	1.46E−01	1.40E−01	0.0061	1.12
350	10	1.63E−01	1.62E−01	1.57E−01	0.0053	0.97
360	10	1.80E−01	1.79E−01	1.74E−01	0.0049	0.90
370	10	1.63E−01	1.91E−01	1.86E−01	0.0053	0.97
380	10	2.04E−01	2.04E−01	1.99E−01	0.0039	0.72
390	10	1.93E−01	1.93E−01	1.87E−01	0.0041	0.75
400	10	2.77E−01	2.76E−01	2.69E−01	0.0046	0.85
410	10	3.64E−01	3.64E−01	3.55E−01	0.0033	0.61
420	10	3.74E−01	3.74E−01	3.65E−01	0.003	0.55
430	10	3.61E−01	3.61E−01	3.52E−01	0.0036	0.66
440	10	4.26E−01	4.26E−01	4.17E−01	0.0029	0.53
450	10	4.79E−01	4.80E−01	4.69E−01	0.0031	0.57
460	10	4.85E−01	4.85E−01	4.75E−01	0.0036	0.66
470	10	5.01E−01	5.02E−01	4.91E−01	0.0033	0.61
480	10	5.13E−01	5.14E−01	5.03E−01	0.0035	0.64
490	10	4.85E−01	4.86E−01	4.76E−01	0.0039	0.72
500	10	4.95E−01	4.96E−01	4.85E−01	0.0024	0.44
525	25	1.31E+00	1.31E+00	1.28E+00	0.003	0.55
550	25	1.36E+00	1.36E+00	1.33E+00	0.0035	0.64
575	25	1.37E+00	1.37E+00	1.34E+00	0.002	0.37
600	25	1.38E+00	1.38E+00	1.35E+00	0.0027	0.50
625	25	1.39E+00	1.40E+00	1.37E+00	0.0025	0.46
650	25	1.40E+00	1.41E+00	1.38E+00	0.0025	0.46
675	25	1.40E+00	1.41E+00	1.39E+00	0.002	0.37
700	25	1.39E+00	1.40E+00	1.38E+00	0.0022	0.40
750	50	2.67E+00	2.69E+00	2.66E+00	0.0023	0.42
800	50	2.57E+00	2.59E+00	2.57E+00	0.0017	0.31

Doc III A
Section A7.1.1.2.1 (01)
Biodegradability (ready)

Annex Point IIA7.6.1.1

Official use only

		1 REFERENCE
1.1	**Reference**	Bätscher R,. 2008. Medetomidine: Ready biodegradability in a closed bottle test RCC Ltd., CH-4452 Itingen, Switzerland RCC Study Number: A00360 (Unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	I-Tech AB
1.2.2		
1.2.3	Criteria for data protection	Data on new a.s. for first approval / authorisation
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes. OECD Guideline for Testing of Chemicals, No. 301 D.
2.2	**GLP**	Yes.
2.3	**Deviations**	No.
		3 MATERIALS AND METHODS
3.1	**Test material**	Medetomidine hydrochloride.
3.1.1	Lot/Batch number	24431
3.1.2	Specification	Medetomidine hydrochloride, used instead of medetomidine due to higher solubility in water. Final form in water is pH dependent.
3.1.3	Purity	[redacted] %
3.1.4	Further relevant properties	Molecular weight: 236.7 g/mol Solubility: 24 g/l pKa: 7.1
3.1.5	Composition of Product	Crystalline powder
3.1.6	TS inhibitory to microorganisms	Yes. The results of respiration inhibition test are presented in Dossier Document IIIA, Section 7_4_1_4.
3.1.7	Specific chemical analysis	There was no specific analytical technique was applied to analysis of any compound.
3.2	**Reference substance**	Yes. Sodium benzoate.
3.2.1	Initial concentration of reference substance	3.0 mg/l
3.3	**Testing procedure**	

Doc III A **Biodegradability (ready)**

Section A7.1.1.2.1 (01)

Annex Point IIA7.6.1.1

3.3.1	Inoculum / test species	Details of inoculum or test species are presented in Table A7_1_1_2_1(01)-2.
3.3.2	Test system	Test type, laboratory equipment etc. are shown in Table A7_1_1_2_1(01)-3.
3.3.3	Test conditions	See Table A7_1_1_2_1(01)-4.
3.3.4	Method of preparation of test solution	Test item amounts of 12.08 and 12.06 mg were weighted on the analytical balance and transferred to the Erlenmeyer flasks with test water for the test item treatment and the toxicity control, respectively. No emulsifiers or solvents were used. After stirring for 30 minutes on a magnetic stirrer, clear solutions were obtained.
3.3.5	Initial TS concentration	Test item, medetomidine, concentration and theoretical oxygen demand (ThOD without nitrification) were 2.4 and 5.1 mg/l , respectively. Reference item, sodium benzoate, concentration and ThOD (without nitrification) were 3.0 and 5.0 mg/l, respectively.
3.3.6	Duration of test	28 days
3.3.7	Analytical parameter	BOD – biochemical oxygen demand exerted after each time period was calculated by substracting the oxygen depletion (mg O2/l) of the inoculums control from that exhibited by the test item. Then, the corrected oxygen depletion was divided by the concentration of the test and/or reference item.
3.3.8	Sampling	Exposure day 0, 2, 5, 7, 9, 14, 21, and 28 – test item and inoculums control; in two separate flasks each; Exposure day 0, 2, 7, 14, 21, and 28 – procedure control; in two separate test flasks each; Exposure day 0, 2, 14, 21, and 28 – toxicity control; in one/two test flasks each.
3.3.9	Intermediates/ degradation products	Not identified.
3.3.10	Nitrate/nitrite measurement	Not performed.
3.3.11	Controls	Inoculum control, procedure control (with reference item, sodium benzoate) and toxicity control (test item, medetomidine, and reference item, sodium benzoate together).
3.3.12	Statistics	Statistics was done according to OECD Guideline for Testing Chemicals, No. 301
		4 RESULTS
4.1	**Degradation of test substance**	
4.1.1	Graph	See Figure 1 in RCC Study Number: A00360.
4.1.2	Degradation	There was neither plateau nor significant changes on the biodegradation curve of the test item. Percentage of biodegradation of the test item was about 0 throughout the test period. Medetomidine doesn't show any

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Annex Point IIA7.6.1.1

Biodegradability (ready)

		inhibition to activated sludge microorganisms at tested concentration of 2.4 mg/l under the present test conditions.	
4.1.3	Other observations	No other observations.	
4.1.4	Degradation of TS in abiotic control	There was no abiotic degradation of the test item, medetomidine, under the conditions of the test within 28 days.	X
4.1.5	Degradation of reference substance	Degradation of the reference item, sodium benzoate, was 74 % by an average by exposure Day 14. See Figure 1 in RCC Study Number: A00360.	
4.1.6	Intermediates/ degradation products	There was no degradation of test item observed.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	OECD. Guideline 301 D: no deviations from guideline. The oxygen concentration in the test media was measured in an airtight system with an O_2-electrode using a WTW OXI 539 meter, Germany. The percentage biodegradation of the test and reference items was calculated from the biochemical oxygen demand (BOD) divided on the theoretical oxygen demand (ThOD; ThOD test item is 2.10 mg O_2/mg). A possible nitrification was not taken into account.	
5.2	**Results and discussion**	No significant biochemical oxygen demand (BOD) of the test item, Medetomidine, was recorded throughout the test period. Consequently, Medetomidine was found to be not biodegradable under the conditions of the test within 28 days. In the procedure control, the reference item was degraded by in average 74 % until Day 14 of the test, thus confirming suitability of the activated sludge. In the toxicity control, containing both Medetomidine and the reference item, Sodium benzoate, no inhibitory effect of the biodegradation of the reference item was determined. Thus, Medetomidine, had obviously no inhibitory effect on the activity of activated sludge microorganisms at the tested concentration of 2.4 mg/l.	X
5.3	**Conclusion**	The validity criteria can be considered as good fulfilled (see Table A7_1_1_2_1(01)-5) and the pass levels is fulfilled for reference substance (see Table A7_1_1_2-_1(01)-5). Details are in RCC Study Number: A00360. The results of reference item, sodium benzoate, (3.0 mg/l) treatments confirm the suitability of the activated sludge and the method used.	
5.3.1	Reliability	Based on the assessment of materials and methods, the appropriate reliability indicator is 1.	
5.3.2	Deficiencies	No.	

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Biodegradability (ready)

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	22/04/2013
Materials and Methods	Applicant version is acceptable
Results and discussion	Applicant version is acceptable noting the following:- Section 4.1.4: the UK CA could not locate any details of an abiotic control in the original study report. Since no degradation occurred in the main part of the test either (where both biotic and abiotic degradation could have occurred) this is not of any significance to the overall validity of the test.
Conclusion	Applicant version is acceptable noting the following:- Section 5.2: Biodegradation in the toxicity control (containing medetomidine and the reference item sodium benzoate) reached 28% within 14 d. Since this was marginally greater than the 25% figure (based on ThOD) quoted in OECD 301 the test item is not considered inhibitory to the activated sludge microorganisms. Note also that OECD method 301 D (closed bottle test) was selected since this method allows testing at low concentrations relative to the other methods, and thus reduced the likelihood of the test item being inhibitory.
Reliability	1
Acceptability	Acceptable
Remarks	No degradation of medetomidine occurred and therefore the substance cannot be considered to be ready biodegradable.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A7_1_1_2_1(01)-1:Guideline-methods of EC and OECD for tests on ready/inherent biodegradability (according to OECD criteria); simulation test

Test	EC-method	OECD-Guideline	Test on ready/inherent biodegradability
DOC Die-Away-Test	C.4-A	301A	ready
CO_2 Evolution-Test (Modified Sturm Test)	C.4-C	301B	ready
Modified OECD-Screening-Test	C.4-B	301E	ready
Manometric Respirometry	C.4-D	301F	ready
MITI-I-Test	C.4-F	301C	ready
Closed-Bottle-Test	C.4-E	301D	ready
Zahn-Wellens-test	C.9	302B	Inherent
Modified MITI-Test (II)	-	302C	Inherent
Modified SCAS-Test	C.12	302A	Inherent
Simulation Test with activated Sewage (Coupled Units-Test)	C.10	302A	Simulation Test[1)]

[1)] Test for the determination of the ultimate degradation of test material under conditions which simulate the treatment in an activated sludge plant

Table A7_1_1_2_1(01)-2:Inoculum / Test organism

Criteria	Details
Nature	Aerobic activated sludge
Species	No species, aerobic activated sludge used.
Strain	No strain, aerobic activated sludge used.
Source	Sewage treatment plant treating predominantly domestic wastewater
Sampling site	ARA Ergolz II, Füllinsdorf, Switzerland
Laboratory culture	No. Aerobic activated sludge from a wastewater treatment plant treating predominantly domestic sewage.
Method of cultivation	Not applicable, no cultivation since aerobic activated sludge were used.
Preparation of inoculum for exposure	The sludge was washed twice with tap water by centrifugation and the supernatant liquid phase was decanted. A homogenized aliquot of the final sludge suspension was weighted, thereafter dried and the weight ratio of wet/dry was calculated.
Pretreatment	During holding of two days, the sludge was aerated at room temperature in the dark until use.
Initial cell concentration	Wet sludge was prepared in a concentration of 4g/l test water.

Table A7_1_1_2_1(01)-3:Test system

Criteria	Details
Culturing apparatus	Wide-necked reagent bottles (with conical shoulder, 250 ml) and tightly closed.
Number of culture flasks/concentration	Number of flasks: 16 (test item), 16 (inoculums control), 12 (procedure control), 8 (toxicity control). Test- and reference item concentrations were 2.4 and 3.0 mg/l, respectively
Aeration device	No data.
Measuring equipment	The oxygen concentration in the test media was measured in an airtight system with an O_2-electrode using a WTW OXI 539 meter, Germany.
Test performed in closed vessels due to significant volatility of TS	No

Table A7_1_1_2_1(01)-4:Test conditions

Criteria	Details
Composition of medium	According to the OECD guideline, No. 301
Additional substrate	No
Test temperature	20^0C. Temperature controlled room
pH	7.3-7.4
Aeration of dilution water	Yes. Air-flow. Dissolved oxygen concentration in the test water was finally 8.9 mg/l
Suspended solids concentration	2.4 mg/l medetomidine; 3.0 mg/l reference, sodium benzoate. Filtered inoculums 3.5 ml/5l test solution
Other relevant criteria	30 min. stirring of test solutions

Table A7_1_1_2_1(01)-5:Pass levels and validity criteria for tests on ready biodegradability

	fulfilled	not fulfilled
Pass levels		
70% removal of DOC resp. 60% removal of ThOD or $ThCO_2$	+ For reference substance	
Pass values reached within 10-d window (within 28-d test period) - not applicable to MITI-I-Test - 14-d window acceptable for Closed-Bottle-Test	+ For reference substance (Closed-Bottle Test)	
Criteria for validity		
Difference of extremes of replicate values of TS removal at plateau (at the end of test or end of 10-d window) < 20%	+	
Percentage of removal of reference substance reaches pass level by day 14	+	

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Biodegradation in seawater

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1 REFERENCE

1.1	**Reference**	Jørgensen C. 2010 Aerobic transformation of Medetomidine CC-435 in aquatic sediment systems. DHI, Denmark. DHI Study Number: 11800130 (Unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	I-Tech AB
1.2.2	Criteria for data protection	Data on new a.s. for first approval / authorisation

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes. OECD Guideline for Testing of Chemicals, No. 308.
2.2	**GLP**	Yes.
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	Medetomidine hydrochloride
3.1.1	Lot/Batch number	XIV/27
3.1.2	Specification	As given in section 2
3.1.3	Purity	[redacted] %
3.1.4	Radiolabelling	Yes. Specific activity 665 MBq/mmol
3.1.5	Further relevant properties	Molecular weight: 236.7 g/mol (unlabelled) Solubility: 24 g/l pKa: 7.1
3.1.6	TS inhibitory to microorganisms	Yes. The results of respiration inhibition test are presented in Document IIIA, Section 7_4_1_4.
3.2	**Reference substance**	No
3.3	**Test soultion**	Test solution was prepared by evaporating 10 µL of stock ethanol solution. The test substance was left to dissolve in 100 mL of Milli-Q water during 22 h. The aqueous stock solution was measured to 1690 Bq/mL, corresponding to 0.5 µg/mL.
3.4	**Testing procedure**	
3.4.1	Inoculum / test species	Microorganisms occurring in the water/sediment system used. No inoculums used.
3.4.2	Test system	300 mL glass flasks containing a total amount of 50 g sediment (d.w) and a total amount of 150 mL water, closed with rubber stoppers. Two types of sediment used, one coarse coastal marine sediment and one fine coastal marine sediment.

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Annex Point IIA7.6.1

Biodegradation in seawater

3.4.3	Test conditions	The flasks were incubated in darkness at 15°C ± 2°C.
3.4.4	Initial TS concentration	600 µL of aqueous stock solution was added to the water phase corresponding to 330 ng of TS or 2.2 µg/L.
3.4.5	Duration of test	98 days.
3.4.6	Analytical parameter	Microbial biomass Total organic carbon Redox potential pH Oxygen concentration Chemical analyses of TS ^{14}C in water and sediment Mineralisation of test substance measured as $^{14}CO_2$ and ^{4}C-organic volatiles. Transformation of test substance measured as transformation products/metabolites.
3.4.7	Sampling	Microbial biomass: day 0 and 98 Total organic carbon: day 0 and 98 Redox potential: day 0, 14, 28, 42, 56 and 98 pH: day 0, 14, 28, 42, 56 and 98 Oxygen concentration: day 0, 14, 28, 42, 56 and 98 Chemical analyses of TS: day 0, 14, 28, 42, 56 and 98 ^{14}C in water and sediment: day 0 and 98 $^{14}CO_2$ and ^{4}C-organic volatiles: day 7, 14, 20, 28, 42, 56, 71, 84 and 98 Transformation products: day 98
3.4.8	Method of analysis for transformation /degradation products	Analysis for transformation products were performed by direct infusion into the LC-MS/MS.
3.4.9	Controls	Inactivated water/sediment systems were used as controls for mineralisation and transformation.
3.4.10	Statistics	Transformation half-time was determined by linear regression.

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Annex Point IIA7.6.1

Biodegradation in seawater

4 RESULTS

4.1 Degradation of test substance

4.1.1 Mineralisation

3% mineralisation in the coarse coastal marine sediment, 2% in the fine coastal marine sediment.

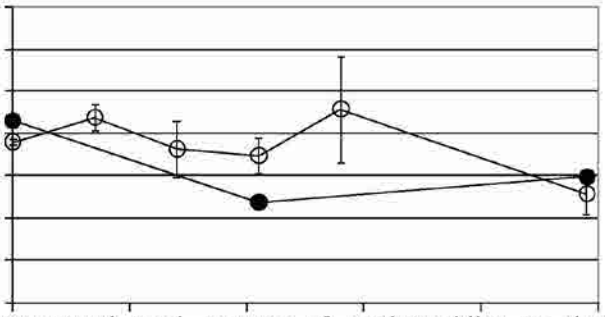
4.1.2 Transformation

A significant decrease in the water concentration and increase in the sediment concentration were observed in both the active and inactive sediment-water systems. When estimating the total amount of test substance in the sediment-water systems for the fine coastal sediment there is a decrease of test substance in the active whereas the inactivated sediment-water systems, did not remained at the initial level. It is therefore difficult to estimate a half life for the test substance in that water/sediment system.
When looking at the total amount of test substance in the coarse costal sediment-water systems there is a decrease of test substance in the active sediment-water systems, whereas the inactivated sediment-water systems remained at the initial level.

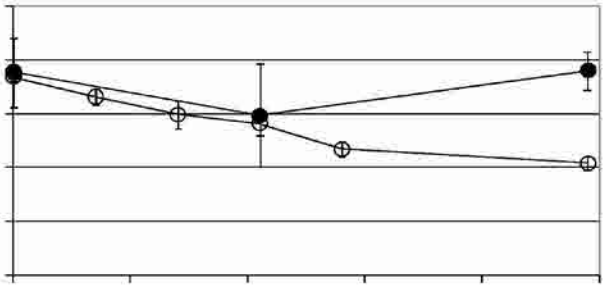
4.1.3 Transformation products

None of the expected transformation products were detected. This may be due to the formation of metabolites different from the anticipated metabolites.

4.1.4 Graph



Measured total amount of medetomidine in three fine coastal sediment sediment-water systems over 98 days. Open marker = active; Filled marker = inactivated control; Vertical bars are equivalent to 1 standard deviation.



Measured total amount of medetomidine in three coarse coastal sediment sediment-water systems over 98 days. Open marker = active; Filled marker = inactivated control; Vertical bars are equivalent to 1 standard deviation.

4.1.5	Other observations	The decrease of test substance may be caused by other processes than transformation such as increased binding to sediment particles, particular to metal oxide ions, which are known to form complexes with the test substance, leading to reduced extraction efficiency.
4.1.6	Degradation of TS in abiotic control	There was no abiotic degradation of the test substance during the conditions of the test.
4.1.7	Intermediates/ degradation products	No degradation products were detected.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The OECD Guideline 308 was performed to evaluate the degradation of medetomidine in a water/sediment system. A concentration of 2.2 µg/L was used to simulate a realistic degradation scenario.

5.2 Results and discussion

The decrease in water concentration and increase in sediment concentration show that medetomidine was adsorbed to the sediment during the first two weeks in both the fine coastal sediment and the coarse costal sediment-water systems. The K_d was higher in the coarsely textured sediment system. The K_{oc} differed significantly between the two sediments indicating that adsorption is governed not only by the organic content but also by other factors. The metal content in the sediment could be such a factor since medetomidine has a strong affinity to complex bind with metal oxides.

The data indicate a decrease over time with a half-life of approximately 110 days in the coarse costal sediment-water systems. Lack of mineralization and detectable metabolites suggest a degradation route different from the anticipated route based on data from elimination studies in humans and mammals or that the decrease was caused by other processes than biodegradation. Due to the low recovery in fine coastal sediment system it is difficult to conclude a half-time for that specific experiment.

5.3 Conclusion

The validity criteria for recovery were fulfilled at the start of the experiment but were only fulfilled for one experiment on day 98.
Mineralisation of medetomidine in the experiment was low, 2-3 %. Transformation occurred in one sediment-water system but no transformation products could be detected. A half-life of 110 days were determined.

5.3.1	Reliability	Based on the assessment of materials and methods, the appropriate reliability indicator is 1.
5.3.2	Deficiencies	Recovery of test substance was below guideline criteria on day 98 in three of four treatments.

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Biodegradation in seawater

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	22/04/2013
Materials and Methods	Not relevant – see remarks below.
Results and discussion	Not relevant – see remarks below.
Conclusion	Not relevant – see remarks below.
Reliability	Not relevant – see remarks below.
Acceptability	Not relevant – see remarks below.
Remarks	This RSS summarised the results from the Jørgensen C. 2010 water sediment study. During the UK CA evaluation of this original study, additional information was supplied by the Applicant in the form of a further supplementary study (Jørgensen C. 2012). In addition further information on the analysis of potential metabolites in water sediment samples from the original 2010 study was provided (Rinne, V. 2012). The original study, and the two further studies from 2012 are all summarised in the RSS at IIIA 7.1.2.2.2. Therefore the UK CA has not evaluated this study in detail as it has been superseded by the later RSS at IIIA 7.1.2.2.2. Please refer to this later RSS for all relevant information on the aerobic aquatic degradation of medetomidine.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A7_1_1_2_3-1: Test conditions

Criteria	Details
Composition of medium	According to the OECD guideline, No. 308
Additional substrate	No
Test temperature	$15^0C \pm 2°C$.
pH	7.2-7.4 (active) and 7.7-8.8 (inactive)
TOC in sediment	4200-4500 mg/kg d.w (fine sediment) 500 mg/kg d.w (coarse sediment)
TOC water (start value)	8.3 mg/L (fine water-sediment system) 4.5 mg/L (coarse water-sediment system)
Biomass in sediment (HPC)	2.3×10^6 (fine active sediment) 6.5×10^6 (coarse active sediment)

Form for justification of the non-submission of data

III A Section 7.1.1.2.3 **Annex Point XII.2.1**	**Biodegradation in seawater**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [x]**	
Detailed justification:	A water/sediment degradation study (IIIA 7.1.2.2.2) in seawater was selected instead of OECD Guideline 306. The water/sediment degradation study is under execution using marine water and will be submitted after completion. Test facility: DHI, Agern Alle 5, DK-2970 HØrsholm, Denmark. Project No. 11800130, GLP Study No. 072-0773. Guidelines: OECD 308 and OECD Principles of GLP.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	24/04/2013	
Evaluation of applicant's justification	Technically the UK CA agrees with the Applicants justification for non-submission because this data requirement can be met by the submission of an acceptable water/sediment degradation study under annex point IIIA 7.1.2.2.2. However the UK CA considered the existing water sediment study under IIIA 7.1.2.2.2 to be unreliable and further information will be required to fulfil this basic data point. However pending submission and evaluation of an acceptable marine water/sediment study the justification for non-submission of data under this data point can be accepted.	
Conclusion	The Applicants justification will be acceptable pending submission and evaluation of an acceptable marine water/sediment study under IIIA 7.1.2.2.2.	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	

III A Section 7.1.1.2.3 Biodegradation in seawater Annex Point XII.2.1
Remarks

Doc III A
Section A7.1.2
Annex Point IIA7.2.1

Rate and route of degradation in aquatic systems including identification of metabolites and degradation products

Official use only

1 REFERENCE

1.1	**Reference**	Jørgensen C. 2010 Aerobic transformation of Medetomidine CC-435 in aquatic sediment systems. DHI, Denmark. DHI Study Number: 11800130 (Unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	I-Tech AB
1.2.2	Criteria for data protection	Data on new a.s. for first approval / authorisation

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes. OECD Guideline for Testing of Chemicals, No. 308.
2.2	**GLP**	Yes.
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	Medetomidine hydrochloride
3.1.1	Lot/Batch number	XIV/27
3.1.2	Specification	As given in section 2
3.1.3	Purity	[redacted] %
3.1.4	Radiolabelling	Yes. Specific activity 665 MBq/mmol
3.1.5	Further relevant properties	Molecular weight: 236.7 g/mol (unlabelled) Solubility: 24 g/l pKa: 7.1
3.1.6	TS inhibitory to microorganisms	Yes. The results of respiration inhibition test are presented in Document IIIA, Section 7_4_1_4.
3.2	**Reference substance**	No
3.3	**Test soultion**	Test solution was prepared by evaporating 10 µL of stock ethanol solution. The test substance was left to dissolve in 100 mL of Milli-Q water during 22 h. The aqueous stock solution was measured to 1690 Bq/mL, corresponding to 0.5 µg/mL.
3.4	**Testing procedure**	
3.4.1	Inoculum / test species	Microorganisms occurring in the water/sediment system used. No inoculums used.
3.4.2	Test system	300 mL glass flasks containing a total amount of 50 g sediment (d.w) and a total amount of 150 mL water, closed with rubber stoppers. Two types of sediment used, one coarse coastal marine sediment and one fine coastal marine sediment.

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Section A7.1.2
Annex Point IIA7.2.1

Rate and route of degradation in aquatic systems including identification of metabolites and degradation products

3.4.3	Test conditions	The flasks were incubated in darkness at 15°C ± 2°C.
3.4.4	Initial TS concentration	600 µL of aqueous stock solution was added to the water phase corresponding to 330 ng of TS or 2.2 µg/L.
3.4.5	Duration of test	98 days.
3.4.6	Analytical parameter	Microbial biomass Total organic carbon Redox potential pH Oxygen concentration Chemical analyses of TS ^{14}C in water and sediment Mineralisation of test substance measured as $^{14}CO_2$ and ^{4}C-organic volatiles. Transformation of test substance measured as transformation products/metabolites.
3.4.7	Sampling	Microbial biomass: day 0 and 98 Total organic carbon: day 0 and 98 Redox potential: day 0, 14, 28, 42, 56 and 98 pH: day 0, 14, 28, 42, 56 and 98 Oxygen concentration: day 0, 14, 28, 42, 56 and 98 Chemical analyses of TS: day 0, 14, 28, 42, 56 and 98 ^{14}C in water and sediment: day 0 and 98 $^{14}CO_2$ and ^{4}C-organic volatiles: day 7, 14, 20, 28, 42, 56, 71, 84 and 98 Transformation products: day 98
3.4.8	Method of analysis for transformation /degradation products	Analysis for transformation products were performed by direct infusion into the LC-MS/MS.
3.4.9	Controls	Inactivated water/sediment systems were used as controls for mineralisation and transformation.
3.4.10	Statistics	Transformation half-time was determined by linear regression.

Doc III A
Section A7.1.2
Annex Point IIA7.2.1

Rate and route of degradation in aquatic systems including identification of metabolites and degradation products

4 RESULTS

4.1 Degradation of test substance

4.1.1 Mineralisation

3% mineralisation in the coarse coastal marine sediment, 2% in the fine coastal marine sediment.

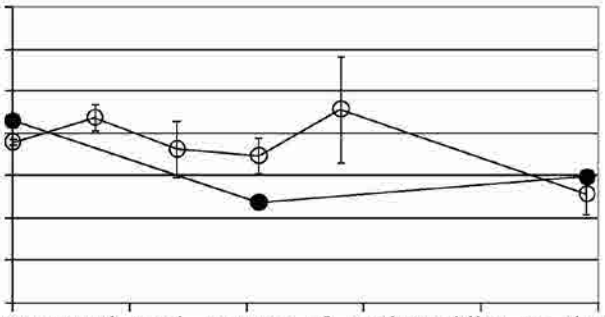
4.1.2 Transformation

A significant decrease in the water concentration and increase in the sediment concentration were observed in both the active and inactive sediment-water systems. When estimating the total amount of test substance in the sediment-water systems for the fine coastal sediment there is a decrease of test substance in the active whereas the inactivated sediment-water systems, did not remained at the initial level. It is therefore difficult to estimate a half life for the test substance in that water/sediment system.
When looking at the total amount of test substance in the coarse costal sediment-water systems there is a decrease of test substance in the active sediment-water systems, whereas the inactivated sediment-water systems remained at the initial level.

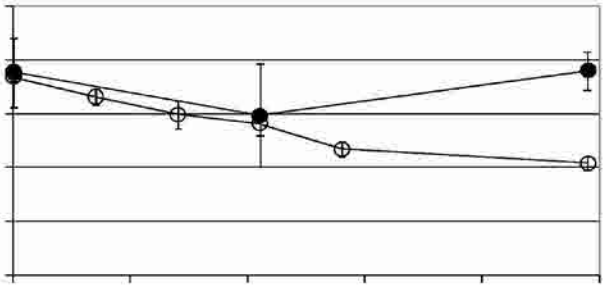
4.1.3 Transformation products

None of the expected transformation products were detected. This may be due to the formation of metabolites different from the anticipated metabolites.

4.1.4 Graph



Measured total amount of medetomidine in three fine coastal sediment sediment-water systems over 98 days. Open marker = active; Filled marker = inactivated control; Vertical bars are equivalent to 1 standard deviation.



Measured total amount of medetomidine in three coarse coastal sediment sediment-water systems over 98 days. Open marker = active; Filled marker = inactivated control; Vertical bars are equivalent to 1 standard deviation.

4.1.5	Other observations	The decrease of test substance may be caused by other processes than transformation such as increased binding to sediment particles, particular to metal oxide ions, which are known to form complexes with the test substance, leading to reduced extraction efficiency.
4.1.6	Degradation of TS in abiotic control	There was no abiotic degradation of the test substance during the conditions of the test.
4.1.7	Intermediates/ degradation products	No degradation products were detected.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The OECD Guideline 308 was performed to evaluate the degradation of medetomidine in a water/sediment system. A concentration of 2.2 µg/L was used to simulate a realistic degradation scenario.

5.2 Results and discussion

The decrease in water concentration and increase in sediment concentration show that medetomidine was adsorbed to the sediment during the first two weeks in both the fine coastal sediment and the coarse costal sediment-water systems. The K_d was higher in the coarsely textured sediment system. The K_{oc} differed significantly between the two sediments indicating that adsorption is governed not only by the organic content but also by other factors. The metal content in the sediment could be such a factor since medetomidine has a strong affinity to complex bind with metal oxides.

The data indicate a decrease over time with a half-life of approximately 110 days in the coarse costal sediment-water systems. Lack of mineralization and detectable metabolites suggest a degradation route different from the anticipated route based on data from elimination studies in humans and mammals or that the decrease was caused by other processes than biodegradation. Due to the low recovery in fine coastal sediment system it is difficult to conclude a half-time for that specific experiment.

5.3 Conclusion

The validity criteria for recovery were fulfilled at the start of the experiment but were only fulfilled for one experiment on day 98.
Mineralisation of medetomidine in the experiment was low, 2-3 %. Transformation occurred in one sediment-water system but no transformation products could be detected. A half-life of 110 days were determined.

5.3.1	Reliability	Based on the assessment of materials and methods, the appropriate reliability indicator is 1.
5.3.2	Deficiencies	Recovery of test substance was below guideline criteria on day 98 in three of four treatments.

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Annex Point IIA7.2.1

Rate and route of degradation in aquatic systems including identification of metabolites and degradation products

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	22/04/2013
Materials and Methods	Not relevant – see remarks below.
Results and discussion	Not relevant – see remarks below.
Conclusion	Not relevant – see remarks below.
Reliability	Not relevant – see remarks below.
Acceptability	Not relevant – see remarks below.
Remarks	This RSS summarised the results from the Jørgensen C. 2010 water sediment study. During the UK CA evaluation of this original study, additional information was supplied by the Applicant in the form of a further supplementary study (Jørgensen C. 2012). In addition further information on the analysis of potential metabolites in water sediment samples from the original 2010 study was provided (Rinne, V. 2012). The original study, and the two further studies from 2012 are all summarised in the RSS at IIIA 7.1.2.2.2. Therefore the UK CA has not evaluated this study in detail as it has been superseded by the later RSS at IIIA 7.1.2.2.2. Please refer to this later RSS for all relevant information on the aerobic aquatic degradation of medetomidine.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A7_1_2 -1: Test conditions

Criteria	Details
Composition of medium	According to the OECD guideline, No. 308
Additional substrate	No
Test temperature	$15^0C \pm 2°C$.
pH	7.2-7.4 (active) and 7.7-8.8 (inactive)
TOC in sediment	4200-4500 mg/kg d.w (fine sediment) 500 mg/kg d.w (coarse sediment)
TOC water (start value)	8.3 mg/L (fine water-sediment system) 4.5 mg/L (coarse water-sediment system)
Biomass in sediment (HPC)	2.3×10^6 (fine active sediment) 6.5×10^6 (coarse active sediment)

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Section A7.1.2.2.1
Annex Point IIA7.2.1

Aerobic aquatic degradation study

Official use only

		1 REFERENCE
1.1	**Reference**	Jørgensen C. 2010 Aerobic transformation of Medetomidine CC-435 in aquatic sediment systems. DHI, Denmark. DHI Study Number: 11800130 (Unpublished)
1.2	**Data protection**	Yes
1.2.1	Data owner	I-Tech AB
1.2.2	Criteria for data protection	Data on new a.s. for first approval / authorisation
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes. OECD Guideline for Testing of Chemicals, No. 308.
2.2	**GLP**	Yes.
2.3	**Deviations**	No
		3 MATERIALS AND METHODS
3.1	**Test material**	Medetomidine hydrochloride
3.1.1	Lot/Batch number	XIV/27
3.1.2	Specification	As given in section 2
3.1.3	Purity	[redacted] %
3.1.4	Radiolabelling	Yes. Specific activity 665 MBq/mmol
3.1.5	Further relevant properties	Molecular weight: 236.7 g/mol (unlabelled) Solubility: 24 g/l pKa: 7.1
3.1.6	TS inhibitory to microorganisms	Yes. The results of respiration inhibition test are presented in Document IIIA, Section 7_4_1_4.
3.2	**Reference substance**	No
3.3	**Test soultion**	Test solution was prepared by evaporating 10 µL of stock ethanol solution. The test substance was left to dissolve in 100 mL of Milli-Q water during 22 h. The aqueous stock solution was measured to 1690 Bq/mL, corresponding to 0.5 µg/mL.
3.4	**Testing procedure**	
3.4.1	Inoculum / test species	Microorganisms occurring in the water/sediment system used. No inoculums used.
3.4.2	Test system	300 mL glass flasks containing a total amount of 50 g sediment (d.w) and a total amount of 150 mL water, closed with rubber stoppers. Two types of sediment used, one coarse coastal marine sediment and one fine coastal marine sediment.

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Aerobic aquatic degradation study

3.4.3	Test conditions	The flasks were incubated in darkness at 15°C ± 2°C.
3.4.4	Initial TS concentration	600 µL of aqueous stock solution was added to the water phase corresponding to 330 ng of TS or 2.2 µg/L.
3.4.5	Duration of test	98 days.
3.4.6	Analytical parameter	Microbial biomass Total organic carbon Redox potential pH Oxygen concentration Chemical analyses of TS ^{14}C in water and sediment Mineralisation of test substance measured as $^{14}CO_2$ and ^{4}C-organic volatiles. Transformation of test substance measured as transformation products/metabolites.
3.4.7	Sampling	Microbial biomass: day 0 and 98 Total organic carbon: day 0 and 98 Redox potential: day 0, 14, 28, 42, 56 and 98 pH: day 0, 14, 28, 42, 56 and 98 Oxygen concentration: day 0, 14, 28, 42, 56 and 98 Chemical analyses of TS: day 0, 14, 28, 42, 56 and 98 ^{14}C in water and sediment: day 0 and 98 $^{14}CO_2$ and ^{4}C-organic volatiles: day 7, 14, 20, 28, 42, 56, 71, 84 and 98 Transformation products: day 98
3.4.8	Method of analysis for transformation /degradation products	Analysis for transformation products were performed by direct infusion into the LC-MS/MS.
3.4.9	Controls	Inactivated water/sediment systems were used as controls for mineralisation and transformation.
3.4.10	Statistics	Transformation half-time was determined by linear regression.

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Annex Point IIA7.2.1

Aerobic aquatic degradation study

4 RESULTS

4.1 Degradation of test substance

4.1.1 Mineralisation

3% mineralisation in the coarse coastal marine sediment, 2% in the fine coastal marine sediment.

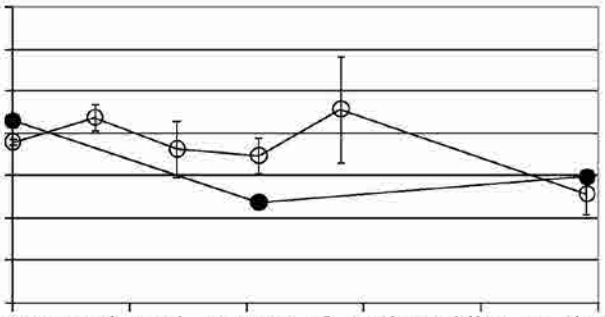
4.1.2 Transformation

A significant decrease in the water concentration and increase in the sediment concentration were observed in both the active and inactive sediment-water systems. When estimating the total amount of test substance in the sediment-water systems for the fine coastal sediment there is a decrease of test substance in the active whereas the inactivated sediment-water systems, did not remained at the initial level. It is therefore difficult to estimate a half life for the test substance in that water/sediment system.
When looking at the total amount of test substance in the coarse costal sediment-water systems there is a decrease of test substance in the active sediment-water systems, whereas the inactivated sediment-water systems remained at the initial level.

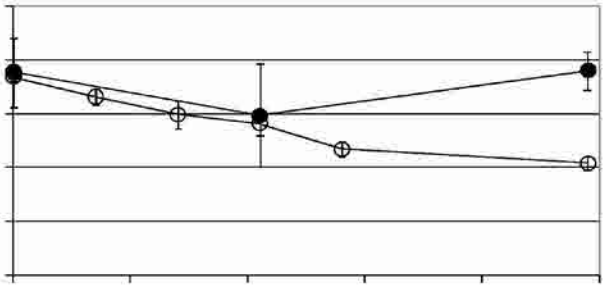
4.1.3 Transformation products

None of the expected transformation products were detected. This may be due to the formation of metabolites different from the anticipated metabolites.

4.1.4 Graph



Measured total amount of medetomidine in three fine coastal sediment sediment-water systems over 98 days. Open marker = active; Filled marker = inactivated control; Vertical bars are equivalent to 1 standard deviation.



Measured total amount of medetomidine in three coarse coastal sediment sediment-water systems over 98 days. Open marker = active; Filled marker = inactivated control; Vertical bars are equivalent to 1 standard deviation.

4.1.5	Other observations	The decrease of test substance may be caused by other processes than transformation such as increased binding to sediment particles, particular to metal oxide ions, which are known to form complexes with the test substance, leading to reduced extraction efficiency.
4.1.6	Degradation of TS in abiotic control	There was no abiotic degradation of the test substance during the conditions of the test.
4.1.7	Intermediates/ degradation products	No degradation products were detected.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

The OECD Guideline 308 was performed to evaluate the degradation of medetomidine in a water/sediment system. A concentration of 2.2 µg/L was used to simulate a realistic degradation scenario.

5.2 Results and discussion

The decrease in water concentration and increase in sediment concentration show that medetomidine was adsorbed to the sediment during the first two weeks in both the fine coastal sediment and the coarse costal sediment-water systems. The K_d was higher in the coarsely textured sediment system. The K_{oc} differed significantly between the two sediments indicating that adsorption is governed not only by the organic content but also by other factors. The metal content in the sediment could be such a factor since medetomidine has a strong affinity to complex bind with metal oxides.

The data indicate a decrease over time with a half-life of approximately 110 days in the coarse costal sediment-water systems. Lack of mineralization and detectable metabolites suggest a degradation route different from the anticipated route based on data from elimination studies in humans and mammals or that the decrease was caused by other processes than biodegradation. Due to the low recovery in fine coastal sediment system it is difficult to conclude a half-time for that specific experiment.

5.3 Conclusion

The validity criteria for recovery were fulfilled at the start of the experiment but were only fulfilled for one experiment on day 98.
Mineralisation of medetomidine in the experiment was low, 2-3 %. Transformation occurred in one sediment-water system but no transformation products could be detected. A half-life of 110 days were determined.

5.3.1	Reliability	Based on the assessment of materials and methods, the appropriate reliability indicator is 1.
5.3.2	Deficiencies	Recovery of test substance was below guideline criteria on day 98 in three of four treatments.

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Section A7.1.2.2.1
Annex Point IIA7.2.1

Aerobic aquatic degradation study

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	22/04/2013
Materials and Methods	Not relevant – see remarks below.
Results and discussion	Not relevant – see remarks below.
Conclusion	Not relevant – see remarks below.
Reliability	Not relevant – see remarks below.
Acceptability	Not relevant – see remarks below.
Remarks	This RSS summarised the results from the Jørgensen C. 2010 water sediment study. During the UK CA evaluation of this original study, additional information was supplied by the Applicant in the form of a further supplementary study (Jørgensen C. 2012). In addition further information on the analysis of potential metabolites in water sediment samples from the original 2010 study was provided (Rinne, V. 2012). The original study, and the two further studies from 2012 are all summarised in the RSS at IIIA 7.1.2.2.2. Therefore the UK CA has not evaluated this study in detail as it has been superseded by the later RSS at IIIA 7.1.2.2.2. Please refer to this later RSS for all relevant information on the aerobic aquatic degradation of medetomidine.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A7_1_2_2_1-1: Test conditions

Criteria	Details
Composition of medium	According to the OECD guideline, No. 308
Additional substrate	No
Test temperature	$15^0C \pm 2°C$.
pH	7.2-7.4 (active) and 7.7-8.8 (inactive)
TOC in sediment	4200-4500 mg/kg d.w (fine sediment) 500 mg/kg d.w (coarse sediment)
TOC water (start value)	8.3 mg/L (fine water-sediment system) 4.5 mg/L (coarse water-sediment system)
Biomass in sediment (HPC)	2.3×10^6 (fine active sediment) 6.5×10^6 (coarse active sediment)

Form for justification of the non-submission of data

III A Section 7.1.2.2.1 **Annex Point XII.2.1**	**Aerobic aquatic degradation study**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [x]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	The active substance will be used in product-type 21: Antifouling products. The products are for use in marine environments only. Degradation in freshwater was therefore not studied. A water/sediment degradation study in seawater will be performed instead.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	24/04/2013	
Evaluation of applicant's justification	The Applicant's justification is considered acceptable. Note that the UK CA considered the existing marine water sediment study under IIIA 7.1.2.2.2 to be unreliable and further information will be required to fulfil this basic data point. However pending submission and evaluation of an acceptable marine water/sediment study the justification for non-submission of data under this data point can be accepted.	
Conclusion	The Applicants justification will be acceptable pending submission and evaluation of an acceptable marine water/sediment study under IIIA 7.1.2.2.2.	
Remarks	None.	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Doc III A
Section A7.1.2.2.2
Aerobic transformation in water

Annex Point IIA7.2.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	Jørgensen C. 2010 Aerobic transformation of Medetomidine CC-435 in aquatic sediment systems. DHI, Denmark. DHI Study Number: 11800130 (Unpublished)	
1.2		Jørgensen C. 2012 Aerobic transformation of Medetomidine CC-435 in aquatic sediment systems. Supplemental study. DHI, Denmark. DHI Study Number: 11809543 (Unpublished)	
1.3		Rinne V. 2012 Analysis of medetomidine and its potential N-methyl-metabolites in sediment and water samples. CRST Bioanalytics, Finland. CRST Study Number: A463 (Unpublished)	
1.4		Nfon E. 2012 Environmental fate of the active substance medetomidine and its metabolites in the aquatic environment. Enviresearch Limited, UK. Enviresearch Study Number E2012-07 (Unpublished)	
1.5	**Data protection**	Yes	
1.5.1	Data owner	I-Tech AB	
1.5.2	Criteria for data protection	Data on new a.s. for first approval / authorisation	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes. OECD Guideline for Testing of Chemicals, No. 308.	
2.2	**GLP**	Yes.	X
2.3	**Deviations**	Yes. Minor deviations in GLP compliance regarding soil composition, counting of radiolabeled ^{14}C test material at DHI and grain size analyses. TOC content below guideline recommendation in one of the test sediments. Mass balance for ^{14}C below guideline criteria in some samples.	X
		3 MATERIALS AND METHODS	
3.1	**Test material**	Medetomidine hydrochloride	
3.1.1	Lot/Batch number	XIV/27	
3.1.2	Specification	As given in section 2	
3.1.3	Purity	[redacted] %	
3.1.4	Radiolabelling	Yes. Specific activity 889 MBq/mmol	X
3.1.5	Further relevant properties	Molecular weight: 200.3g/mol (unlabelled base)	X

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Section A7.1.2.2.2
Annex Point IIA7.2.1

Aerobic transformation in water

3.1.6	TS inhibitory to microorganisms	Yes. The results of respiration inhibition test are presented in Document IIIA, Section 7_4_1_4.	
3.2	**Reference substance**	N-methylmedetomidine used in search for metabolites from OECD 308 study.	
3.3	**Test solution**	Test solution was prepared by evaporating 10 µL of stock ethanol solution. The test substance was left to dissolve in 100 mL of Milli-Q water during 22 h.	
3.4	**Testing procedure**		
3.4.1	Inoculum / test species	Microorganisms occurring in the water/sediment system used. No inoculums used.	
3.4.2	Test system	300 mL glass flasks containing a total amount of 50 g sediment (d.w) and a total amount of 150 mL water, closed with rubber stoppers. Two types of sediment used, one coarse coastal marine sediment and one fine coastal marine sediment.	
3.4.3	Test conditions	The flasks were incubated in darkness at 15°C ± 2°C.	
3.4.4	Initial TS concentration	600 µL of aqueous stock solution was added to the water phase corresponding to 330 ng of TS or 2.2 µg/L.	
3.4.5	Duration of test	98 days.	
3.4.6	Analytical parameter	Microbial biomass Total organic carbon Redox potential pH Oxygen concentration Chemical analyses of TS ^{14}C in water and sediment Mineralisation of test substance measured as $^{14}CO_2$ and ^{4}C-organic volatiles. Transformation of test substance measured as transformation products/metabolites.	
3.4.7	Sampling	Microbial biomass: day 0 and 98 Total organic carbon: day 0 and 98 Redox potential: day 0, 14, 28, 42, 56 and 98 pH: day 0, 14, 28, 42, 56 and 98 Oxygen concentration: day 0, 14, 28, 42, 56 and 98 Chemical analyses of TS: day 0, 14, 28, 42, 56 and 98 ^{14}C in water and sediment: day 0 and 98 $^{14}CO_2$ and ^{4}C-organic volatiles: day 7, 14, 20, 28, 42, 56, 71, 84 and 98 Transformation products: day 98	 X X X
3.4.8	Method of analysis for transformation /degradation products	Analysis for transformation products were performed by direct infusion into the LC-MS/MS.	

3.4.9	Controls	Inactivated water/sediment systems were used as controls for mineralisation and transformation.	
3.4.10	Statistics	Transformation half-time was determined by linear regression.	
		4 RESULTS	
4.1	**Mass balance**	Based on the improved ^{14}C recovery generated in the supplemental study the total mass balance for the fine sediment was 82% in the activated system and 86% in the inactive system. The course sediment had a total mass balance of 89% in the activated system and 95% in the inactivated system (ref 1.2)	X
4.2	**Degradation of test substance**		

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Aerobic transformation in water

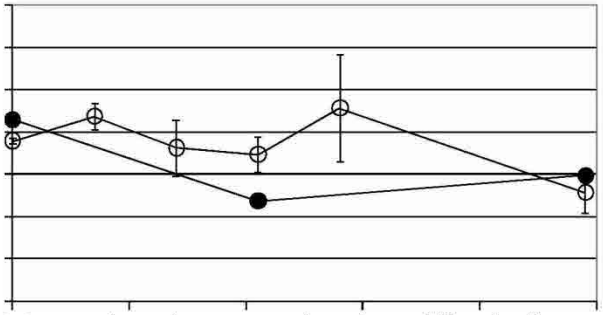
4.2.1 Mineralisation

3% mineralisation in the coarse coastal marine sediment, 2% in the fine coastal marine sediment. Please refer to table A7_1_2_2_2-2 and A7_1_2_2_2-3 for further information.

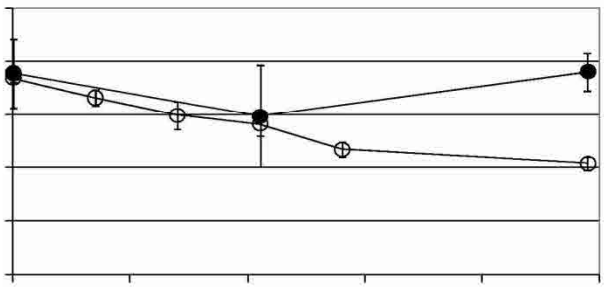
4.2.2 Transformation

A significant decrease in the water concentration and increase in the sediment concentration were observed in both the active and inactive sediment-water systems with both mass balance calculations and chemical analyses.
When estimating the total amount of test substance in the sediment-water systems for the fine coastal sediment there is a decrease of test substance in the active sediment to 57% of the initial concentration whereas the inactivated sediment-water systems did not remained at the initial level as expected but showed a similar decrease (ref 1.1). It is therefore difficult to estimate a half life for the test substance in that water/sediment system.
Based on chemical analyses the amount of test substance in the coarse costal sediment-water systems decrease in the active sediment-water system to 67% of the initial concentration (ref 1.3), whereas the inactivated sediment-water systems remained at the initial level. Since most of the added ^{14}C were recovered the loss of test substance was predicted to have biodegraded.
Please refer to table A7_1_2_2_2-2 and A7_1_2_2_2-3 for further information.

4.2.3 Graph



Measured total amount of medetomidine in fine sediment over 98 days.
Open marker = active Filled marker = inactivated control



Measured total amount of medetomidine in coarse sediment over 98 days. Open marker = active Filled marker = inactivated control

4.2.4	Transformation products	None of the expected transformation products were detected in the original study (ref 1.1). This may be due to the formation of metabolites different from the anticipated metabolites. A QSAR evaluation of the possible transformation products were performed (ref 1.4, IIIA7.1.2.2.3) and the transformation product predicted to be of highest concern was targeted for additional metabolite detection (ref 1.3). No transformation products could be detected. If N-methylmedetomidine would have been present above 1% of the initial test substance concentration if should have been detected with the analytical methods used.	X
4.2.5	Other observations	No other observations.	
4.2.6	Degradation of TS in abiotic control	There was no abiotic degradation of the test substance during the conditions of the test.	
4.2.7	Intermediates/ degradation products	No degradation products were detected.	

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The OECD Guideline 308 was performed to evaluate the degradation of medetomidine in a water/sediment system. A concentration of 2.2 µg/L was used to simulate a realistic degradation scenario. A supplemental study was performed to increase the ^{14}C mass balance which did not meet quality criteria in the initial study. A QSAR evaluation for transformation products was performed and following that the sediment samples from the initial study was re-analysed in attempts to detect the most potent transformation product predicted.	X
5.2	**Results and discussion**	The decrease in water concentration and increase in sediment concentration show that medetomidine was adsorbed to the sediment during the first two weeks in both the fine coastal sediment and the coarse coastal sediment-water systems. The K_d was higher in the coarsely textured sediment system. The K_{oc} differed significantly between the two sediments indicating that adsorption is governed not only by the organic content but also by other factors. The metal content in the sediment could be such a factor since medetomidine has a strong affinity to complex bind with metal oxides.	X X
		The data indicate a decrease over time with a half-life of approximately 168 days in the coarse sediment-water systems. Lack of mineralization suggests a degradation route based on biodegradation. No degradation products was detected and is therefore expected to either occur below LLOQ or degrade to molecules too small for detection. Due to the low recovery in fine coastal sediment system it is difficult to conclude a half-time for that specific experiment.	X X
5.3	**Conclusion**	The validity criteria for recovery were fulfilled at the start of the experiment but were only fulfilled for one experiment on day 98. Mineralisation of medetomidine in the experiment was low, 2-3 %. Transformation occurred in one sediment-water system but no transformation products could be detected. A half-life of 168 days were determined.	X X

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Annex Point IIA7.2.1

Aerobic transformation in water

5.3.1	Reliability	Based on the assessment of materials and methods, the appropriate reliability indicator is 1.	X
5.3.2	Deficiencies	Recovery of ^{14}C was below guideline criteria on day 98 in two of four treatments.	
		TOC content below guideline recommendation in one of the test sediments.	
		Minor deviations in GLP compliance regarding soil composition, counting of radiolabeled ^{14}C test material at DHI and grain size analyses.	X