

Investigation of the toxicity of
Citalopram on the embryo-larval
development of Japanese oyster
(*Crassostrea gigas*)



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01/11/2022

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Investigation of the toxicity of Citalopram on the embryo-larval development of Japanese oyster (*Crassostrea gigas*)

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1 Introduction

DHI has conducted a toxicity test assessing the effects of Citalopram on the embryo-larval development of the marine Japanese oyster (*Crassostrea gigas*) under static conditions. It allows the determination of the concentration levels that result in an abnormality in embryo-larval development. The test was performed according to DS/ISO 17244 "Water quality - Determination of the toxicity of water samples on the embryo-larval development of Japanese oyster (*Crassostrea gigas*) and mussel (*Mytilus edulis* or *Mytilus galloprovincialis*) [1].

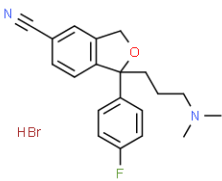
The exposure was performed from fertilized eggs to D larvae. This test aims at determining the No Effect Concentration (NOEC) level and the EC50 concentration, which results in abnormalities for 50 % of exposed larvae in 24 h for the Japanese oyster.

2 Test item

The test item, Citalopram, is a psychopharmacological drug which acts as selective-serotonin-re-uptake-inhibitor (SSRI), and which is used in treatment of depressions by inhibition of the re-uptake of synaptic serotonin (5-HT) in the brain.

The test item was kindly provided by H. Lundbeck A/S as Citalopram HBr. The test item was received at DHI on March 3rd, 2022. The certificate of analysis and the safety data sheet are attached in Annex C and information about the test item is summarized in the table below.

Table 2.1 Information regarding the test item

Product Name:	Citalopram, HBr
Purity	99.9%
Synonyms	Citalopram hydrobromide
Structural formula	
Product Number:	Lu 10-171-B
Batch Number:	2001976
CAS Number:	59729-32-7
Formula:	C ₂₀ H ₂₂ BrFN ₂ O
Average mass	405.35 g/mol
Water solubility	30 g/L

Storage	Store at room temperature, protected from light
Expiry date	01-Mar-2025

3 Test method

3.1 Test solution

A stock solution of Citalopram HBr was prepared by dissolving 12.5 mg in 1000 mL of filtered natural seawater with a salinity of 31.4 PSU. This stock solution corresponds to 10 mg Citalopram/L. The stock solution was used to prepare the dilution series of 0.01; 0.03; 0.1; 0.3 and 1 mg Citalopram/L. The pH in both the stock solution and the dilutions were 7.8 and therefore no adjustment was necessary.

3.2 Test organism

Crassostrea gigas was purchased from Guernsey Sea Farms Ltd., Guernsey. The oysters were ready for spawning as soon as they arrived in the laboratory. The oysters were used directly after arrival and were therefore stored at 20°C until use.

Gametes from the oysters can be obtained by use of different methods according to the ISO standard. In this study the gametes from the males were stripped from the gonads directly by opening the Oysters and inserting a clean, Pasteur pipette into the gonad to a depth of 1 mm to 2 mm and the sperm were collected. The gametes were transferred to separate volumes of seawater and held at 24 °C ± 2 °C (preferably 25 °C).

The gametes from the females were obtained by using thermal stimulation (alternating baths of 15 °C and 28 °C) which induces the females to spawn. After the females has started spawning the females are washed and the water quickly exchanged 2-3 times before letting them spawn into approx.. 200 mL of fresh sea water. The egg solution was filtered through 100 µm to remove faeces etc.

A part of the initial egg suspension was diluted in seawater. The egg density was evaluated by counting the solution several times in a stereo microscope. The initial solution was then adjusted to obtain a final density in the test replicates between 20 000 and 50 000 eggs/L. Fertilization was carried out by adding approx. 10 mL of a very dense suspension of sperm in the beaker containing the eggs (oocytes).

The content of the beaker was homogenized by gently shaking the beaker to avoid polyspermy. A sample was taken from the beaker to check the fertilization rate (each egg shall be surrounded by six to 10 spermatozoa which can be observed on an equatorial plan). The fertilization rate should have reached 90 % to perform the inoculation. When the fertilisation was satisfactory, and before the 4-cell stage was reached, the fertilized eggs were quickly inoculated in the test solutions resulting in 20 000 to 50 000 eggs/L. The test vials were incubated under the conditions described in Table 3.1 for 24 h ± 2h.

After the incubation period of 24h +/- 2, glutaraldehyde, was added to each test vessel to fix and preserve the larvae. The observations of the larvae can then be carried out immediately or up to several weeks later if the test vials are kept hermetically sealed at the ambient temperature of the laboratory. The observations were carried out by taking the appropriate volumes (e.g., 5 x 1 mL) out of a homogeneous test suspension and

using a stereoscopic inverted light microscope fitted with a magnification of at least 200x, but preferably 400x.

100 individuals per replicate were counted. The number of abnormal or dead larvae and the "D-Shaped" (see Figure 3.1) normal larvae were registered. Larvae are considered abnormal if they present at least one of the following anomalies (photos available in ISO 17244):

- shell abnormality: concave or convex hinge, irregular edge (a hinge is considered abnormal if it can be considered that it is not functional)
- mantle abnormality: mantle retracted between the shell's valves or hypertrophied which can go as far as expulsion (the larvae are then categorized as dead)
- segmentation abnormalities: blockage of the embryogenesis
- empty shell: dead larva



Figure 3.1 Oyster normal D larvae

Table 3.1 Summary of test conditions in the ISO 17244 test with Pacific oyster (*Crassostrea gigas*).

Test guideline	ISO 17244 /1/
Test organism	Japanese oyster (also named Pacific oyster) (<i>Crassostrea gigas</i>)
Test organism source	Guernsey Sea Farms Ltd., Guernsey
Test organism life stage	Fertilized eggs
Test concentrations	0; 0.01; 0.03; 0.1; 0.3 and 1 mg Citalopram/L
Test duration	24 ± 2 hours
Test container	20-mL glass vials with 10 mL test solution
Replicates	• 5-10 × laboratory control • 3 × test concentration
Test organisms per replicate	100 organisms per replicate is counted
Endpoint	The number of D larvae and abnormal larvae are counted. Toxicity is expressed as the percentage of abnormal larvae versus the D-shaped normal larvae at the end of the experiment (raw percentage, RPA) and transformed into a net percentage of abnormal larvae (NPA) (see section 5).
Laboratory control medium	Natural seawater (salinity 31.4 PSU) collected at an unpolluted site in the North Sea and then filtered through Millipore filters (10; 5.0; 0.5 and 0.22 µm). The sea water is checked for toxicity towards acartia eggs and N+P are measured before the sea water is used at DHI.

Food regime	No food during testing.
Photoperiod	Total darkness
Temperature	24 ± 2°C
Initial pH	In the laboratory control medium: 8.0 ± 0.3
Validity criteria	The average rate of D larvae in the laboratory controls must be ≥80%
Reference test	Verification of organism sensitivity with copper sulphate pentahydrate (CuSO₄·5H₂O). The test concentrations are included in the range 0 µg/L to 100 µg/L of CuSO₄·5H₂O, or 0 µg/L to 25 µg/L expressed as copper. The value of EC₅₀ should be between 4 µg/L and 16 µg/L expressed as total copper. Dilution series for reference test: 1.5; 3.0; 6.0; 12 and 24 µg Cu/L

4 Chemical analysis

Duplicate samples for chemical analysis were collected from each test concentration and the control at the initiation of the test, and at the termination of the test. Two times 5 mL sample were collected (polyethylene vials (HDPE) and stored frozen at -20 ± 2.0°C. Although samples were collected in duplicate, only one replicate was analysed. The other replicates serve as spare samples and will be discarded after the approval of the report. The samples were shipped on dry ice to the chemical laboratory at Molab, Kristiansand.

5 Statistical analysis

Toxicity was expressed as the percentage of abnormal larvae versus the D-shaped normal larvae at the end of the experiment (raw percentage, RPA) and transformed into a net percentage of abnormal larvae (NPA):

$$\text{RPA} = [(\text{number of abnormal larvae})/(\text{total number of larvae})] \times 100$$

$$\text{NPA} [(\text{test RPA} - \text{control RPA})/(100 - \text{control RPA})] \times 100$$

The statistical analyses were performed using the free software R /1/. The corresponding packages used for the different analysis are described in Section 8, References.

The LOEC/NOEC values were determined by use of the Dunnett's test /3/. The NOEC value ($p > 0.05$) was determined as the highest tested concentration, at which no significant negative effect was observed compared with the control. The LOEC ($p < 0.05$) is the concentration just above the NOEC.

To comply with the conditions of the Dunnett's test, the normality of the data was assessed but only by a visual description using a boxplot /4/. The variance was analysed with a Levene's test /5/.

A Probit analysis was conducted to estimate the EC values. The EC values were calculated to attain the closest possible curve fit.

6 Results

6.1 Results from chemical analysis

Duplicate samples for chemical analysis were collected from each test concentration and the control at the initiation and at the termination of the test.

Two times 5 mL sample were collected (polyethylene vials (HDPE) and stored frozen at $-20 \pm 2.0^{\circ}\text{C}$. Although samples were collected in duplicate, only one replicate was analysed. The other replicates serve as spare samples and will be discarded after the approval of the report.

The test item stability in the test system was verified by analysing the lowest and the highest test concentrations (Table 6.1 and Appendix C). The stability was satisfactory and therefore no more samples were analysed.

Table 6.1 Results from chemical analysis

Nominal concentration	Actual measured concentration		Average measured concentration ($\mu\text{g/L}$)	Average measured concentration in percent of nominal
Citalopram $\mu\text{g/L}$	Test start (T=0)	Test end (T=24h)		
10	11.3	12.3	11.8	118.0
1000	1178.8	1232.7	1205.8	120.6

6.2 Ecotoxicological results

The primary data are presented in Appendix A. The results of this test are summarized below.

Significant effects on the observed percentage of abnormal larvae after exposure to Citalopram were observed (Table 6.2) at the highest concentrations. NOEC and LOEC values are thus estimated to be 0.1 mg Citalopram/L and 0.3 mg Citalopram/L, respectively.

An EC50 value of 0.52 (0.35-0.70) mg Citalopram/L was estimated.

Table 6.2 Oyster larval development after exposure to Citalopram.

Concentration (mg/L)	Percent abnormal (average)	Std. dev. (%)
Control	11.0	2.3
0.01	17.7	7.4
0.03	19.7	4.0
0.1	21.0	6.0
0.3	25.7	6.5
1	100	0

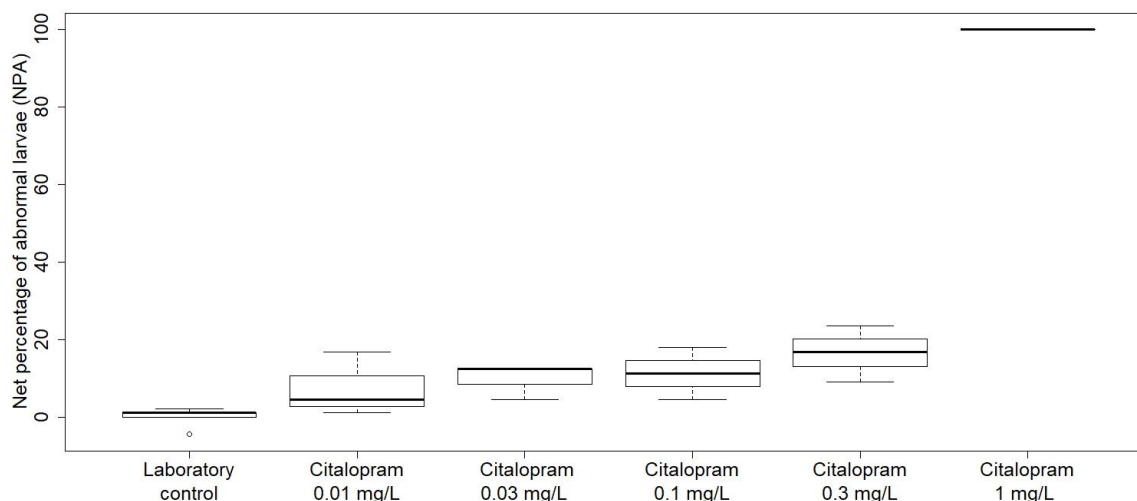


Figure 6.1 Boxplot of the observed net percentage of abnormal larvae (NPA) after exposure to Citalopram

7 Conclusion

The validity criterion was fulfilled, and the stability of the test item was satisfactory.

The EC 10 and EC50 with the reference substance was 12.1 and >24 µg Cu/L, respectively. The EC50 with the reference substance is therefore not within the expected range of 4 µg/L to 16 µg/L expressed as total copper according to the performance criteria in the guideline. However, the EC10 was comparable to an EC10 of 12.0 (10.9-13.2) µg Cu/L observed in a reference test performed in May 2022 at DHI with oysters from the same source. The results obtained with the test substance Citalopram is therefore considered acceptable.

Table 7.1 Results of the Oyster larval development toxicity test after exposure to Citalopram

Endpoint	NOEC	LOEC	EC50
Embryo-larval development	0.1 mg Citalopram/L	0.3 mg Citalopram/L	0.52 (0.35-0.70) mg Citalopram/L

8 References

- /1/ DS/ISO 17244 "Water quality - Determination of the toxicity of water samples on the embryo-larval development of Japanese oyster (*Crassostrea gigas*) and mussel (*Mytilus edulis* or *Mytilus galloprovincialis*). First edition. 2015.09.15.
- /2/ R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>.
- /3/ Frank Bretz, Torsten Hothorn and Peter Westfall (2010) (Dunnnett's test), Multiple Comparisons Using R, CRC Press, Boca Raton.

- /4/ Fox, J. (2005) The R Commander: A Basic Statistics Graphical User Interface to R. *Journal of Statistical Software*, 14(9): 1–42
- /5/ Fox, J. and Weisberg, S. (2011) *An R Companion to Applied Regression*, Second Edition, Sage.
- /6/ Ritz, C (2010). Towards a unified approach to dose-response modelling in ecotoxicology. *Environmental Toxicology & Chemistry*, 29, 220–229.

APPENDICES

APPENDIX A

Raw data Raw data and statistical evaluation

A Raw data toxicity test

A.1.1 Primary data toxicity test

Table A 1 Raw data generated in the toxicity test with Citalopram.

Concentration Citalopram(mg/l)		Total abnormal larvae	Total D-larvae	Total number	NPA
0	A	12	88	100	1.1
0	B	13	87	100	2.2
0	C	7	93	100	-4.5
0	D	12	88	100	1.1
0	E	11	89	100	0.0
0.01	A	26	74	100	16.9
0.01	B	12	88	100	1.1
0.01	C	15	85	100	4.5
0.03	A	22	78	100	12.4
0.03	B	15	85	100	4.5
0.03	C	22	78	100	12.4
0.1	A	15	85	100	4.5
0.1	B	27	73	100	18.0
0.1	C	21	79	100	11.2
0.3	A	32	68	100	23.6
0.3	B	19	81	100	9.0
0.3	C	26	74	100	16.9
1.0	A	100	0	100	100
1.0	B	100	0	100	100
1.0	C	100	0	100	100

Table A 2 pH, oxygen and salinity

Test concentration (mg/l)	Date: 7 September 2022 t = 0			Date: 8 September 2022 t = 24h		
	% O ₂	‰ sal.	pH	% O ₂	‰ sal.	pH
Laboratory control	100	31.5	7.8	100	33.2	8.1
0.01	100	31.4	7.8	100	33.0	8.1
0.03	100	31.3	7.8	100	32.9	8.1
0.1	100	31.4	7.8	100	32.9	8.1
0.3	100	31.3	7.8	100	33.0	8.1
1	100	31.4	7.8	100	33.2	8.1

A.2 Statistical analysis

A.2.1 Determination of NOEC and LOEC for the effect on the larvae abnormality

Table A 3 Experimental data of the abnormal larvae (%)

Replicate No.	Laboratory control	0.01 mg/l	0.03 mg/l	0.1 mg/l	0.3 mg/l	1.0 mg/l
1	12	26	22	15	32	100
2	13	12	15	27	19	100
3	7	15	22	21	26	100
4	12	-	-	-	-	-
5	11	-	-	-	-	-
Count	6	3	3	3	3	3
Mean	11	17.7	19.7	21.0	25.7	100

- Dunnett's test

Dunnett's test tests the null hypothesis that the averages of each test group are not different from the control group.

Table A 4 Multiple comparisons of means: Dunnett's contrasts.

Mean Comparisons	Estimate	Std. Error	t value	Pr(> t)	Significance ¹⁾
1CIT-0.01-mg/L - CIT-0-mg/L	6.67	3.491	1.909	0.274	
2CIT-0.03-mg/L - CIT-0-mg/L	8.67	3.491	2.482	0.104	
3CIT-0.1-mg/L - CIT-0-mg/L	10	3.491	2.864	0.052	.
4CIT-0.3-mg/L - CIT-0-mg/L	14.67	3.491	4.201	0.004	**
5CIT-1-mg/L - CIT-0-mg/L	89	3.491	25.491	< 0.001	***

1) Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 (Adjusted p values reported - single-step method)

The two highest concentrations were significantly different from the control group.

Table A 5 Endpoint: estimations of NOEC and LOEC.

Endpoint	NOEC	LOEC	Unit
Embryo-larval development	0.1	0.3	mg Citalopram/L

A.2.1 Results of the Probit analysis

The ECx values were estimated by use of the probit analysis.

Table A 6 ECx estimates, Probit analysis with R (W2.3 {drc}) /6/ of the embryo-larval development

ECx	Citalopram HBr concentration mg/L	Std. Error	95% confidence interval	
			Lower	Upper
EC05	0.226	0.042	0.136	0.315
EC10	0.285	0.040	0.201	0.369
EC25	0.395	0.047	0.296	0.493
EC50	0.525	0.081	0.353	0.697

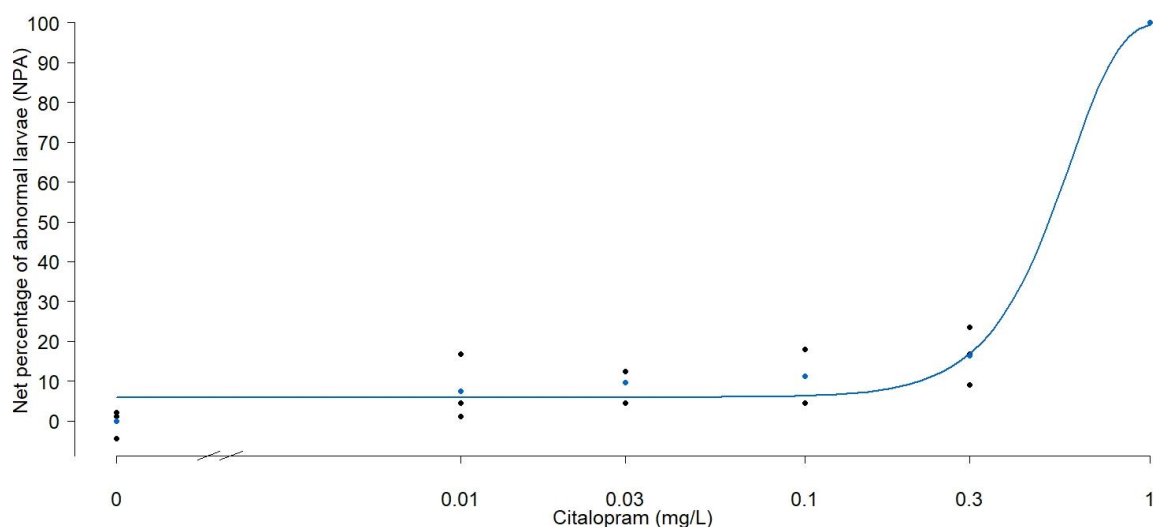


Figure A.1 Effect of Citalopram on the net percentage of abnormal larvae. In blue, the dose response curve established by use of the free software R, (W2.3 {drc}). The blue points correspond to the average NPA of each concentration. The black points correspond to the NPA of each replicate.

Table A 7 Embryo-larval development endpoint, estimations of EC10, EC50, Probit analysis.

Endpoint	EC10	EC50	Unit
Embryo-larval development	0.28 (0.20-0.37)	0.52 (0.35- 0.70)	mg Citalopram/L

A.3 Validity criterion

The average ratio of D larvae in the laboratory controls was 89% and therefore the validity criterion of $\geq 80\%$ was fulfilled.

B Raw data toxicity test with reference test

B.1 Primary data toxicity test

Table B.1 Raw data generated in the toxicity test with CuSO₄·5H₂O.

Concentration CuSO ₄ ·5H ₂ O as µg Cu/l		Total abnormal larvae	Total D-larvae	Total number	NPA
0	A	12	88	100	1.1
0	B	13	87	100	2.2
0	C	7	93	100	-4.5
0	D	12	88	100	1.1
0	E	11	89	100	0.0
1.5	A	12	88	100	1.1
1.5	B	12	88	100	1.1
1.5	C	20	80	100	10.1
3	A	10	90	100	-1.1
3	B	11	89	100	0.0
3	C	17	83	100	6.7
6	A	20	80	100	10.1
6	B	22	78	100	12.4
6	C	19	81	100	9.0
12	A	12	88	100	1.1
12	B	12	88	100	1.1
12	C	31	69	100	22.5
24	A	26	74	100	16.9
24	B	20	80	100	10.1
24	C	25	75	100	15.7

Table B.2 pH, oxygen and salinity

Test concentration (µg/l)	Date: 7 September 2022 t = 0			Date: 8 September t = 24h		
	% O ₂	‰ sal.	pH	% O ₂	‰ sal.	pH
0	100	31.5	7.8	100	33.2	8.1
1.5	100	31.3	7.8	100	32.4	8.1
3	100	31.3	7.8	100	31.9	8.1
6	100	31.3	7.8	100	32.4	8.1
12	100	31.3	7.8	100	32.1	8.1
24	100	31.3	7.8	100	32.7	8.1

B.2 Statistical analysis

B.2.1 Determination of NOEC and LOEC for the effect on the larvae abnormality

Table B.3 Experimental data of the abnormal larvae (%)

Replicate No.	Laboratory control	1.5 µg Cu/L	3 µg Cu/L	6 µg Cu/L	12 µg Cu/L	24 µg Cu/L
1	12	12	10	20	12	26
2	13	12	11	22	12	20
3	7	20	17	19	31	25
4	12	-	-	-	-	-
5	11	-	-	-	-	-
Count	5	3	3	3	3	3
Mean	11	14.7	12.7	20.3	18.3	23.7

- Dunnett's test

Dunnett's test tests the null hypothesis that the averages of each test group are not different from the control group.

Table B.4 Multiple comparisons of means: Dunnett's contrasts.

Mean Comparisons	Estimate	Std. Error	t value	Pr(> t)	Significance ¹⁾
1 - Copper-1.5-µg/L - Copper-0-µg/L == 0	4.12	4.163	0.99	0.8121	
2 - Copper-3.0-µg/L - Copper-0-µg/L == 0	1.887	4.163	0.453	0.9905	
3 - Copper-6.0-µg/L - Copper-0-µg/L == 0	10.52	4.163	2.527	0.0961	.
4 - Copper-12-µg/L - Copper-0-µg/L == 0	8.253	4.163	1.983	0.2439	
5 - Copper-24-µg/L - Copper-0-µg/L == 0	14.253	4.163	3.424	0.0178	*

1) Signif. codes: 0 '****' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 (Adjusted p values reported - single-step method)

The highest exposure group, was significantly different from the control group.

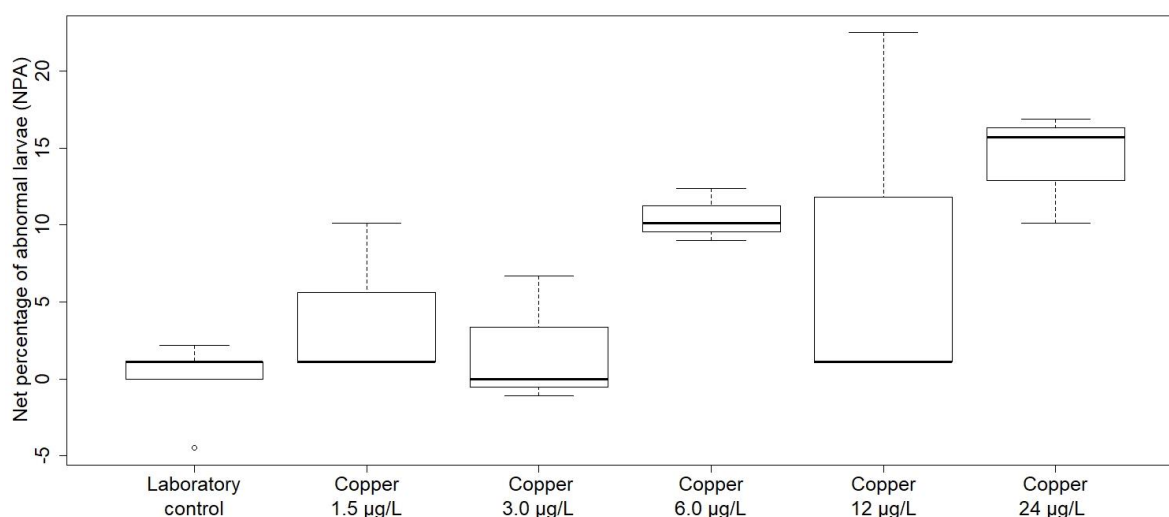


Figure 8.2 Observed net percentage of abnormal larvae (NPA) after exposure to Copper.

Table B.5 Endpoint: estimations of EC50, NOEC and LOEC

Endpoint	NOEC	LOEC	EC10	EC50	Unit
Embryo-larval development	12	24	12.1	>24	µg Cu/L

B.3 Validity criteria and performance evaluation

The average ratio of D larvae in the laboratory controls was 89% and therefore the validity criterion of $\geq 80\%$ was fulfilled. The EC50 with the reference substance was >24 µg Cu/L which was not within the required range of 4 µg/L to 16 µg/L expressed as total copper according to the standard. However, the EC10 was comparable to an EC10 of 12.0 (10.9-13.2) µg Cu/L observed in a reference test performed in May at DHI with oysters from the same source.

APPENDIX C– Chemical analysis

Results from chemical analyses

C Results from chemical analyses

Sample ID Lab	Sample ID	Citalopram ug/L
	Oyster larvae test (DS/ISO 17244)	
22-33-1	DHI 11827338 Oyster larvae test Cit. 0,01 mg/l A T=0, 07.09.2022/JAB	11,3
22-33-2	DHI 11827338 Oyster larvae test Cit. 1 mg/l A T=0, 07.09.2022/JAB	1178,8
22-33-3	DHI 11827338 Oyster larvae test Cit. 0,01 mg/l A T=24, 08.09.2022/JAB	12,3
22-33-4	DHI 11827338 Oyster larvae test Cit. 1 mg/l A T=24, 08.09.2022/JAB	1232,7
	LOQ (ng/L)	1,2
	RS (%)	1,8

Analysis by Ola Svahn (PhD), MoLab, Stridsvagnsvägen 14, Kristianstad (2022-09-28)

Method description: Thawing of frozen samples. Analysis of the samples were performed using chromatography in combination with mass spectrometry (UPLC-MS/MS). The analysis method for citalopram is developed as described by Svahn, O., & Björklund, E. (2016)* and validated according to Standard method 1694 (US EPA, 2007).

*) Svahn, O., & Björklund, E. (2016). *Increased electrospray ionization intensities and expanded chromatographic possibilities for emerging contaminants using mobile phases of different pH. Journal of Chromatography B*, 1033, 128-137.

APPENDIX C – CoA

Identification of test item (CoA)

D Certificate of Analysis (CoA) and Material Safety Data Sheet (MSDS)

Safety data sheet according to 1907/2006/EC, Article 31

Printing date 01.03.2022

version 4

Revision: 21.06.2021

Trade name: Citalopram.HBr

(Contd. of page 3)

Information about fire - and explosion protection:

Prevent formation of dust.

If hazardous, explosive atmospheres may form, the work area must be classified and organised according to the regulations on hazardous, explosive atmosphere. All work must be carried out in compliance with these regulations.
Dust can combine with air to form an explosive mixture (dust explosion).

7.2 Conditions for safe storage, including any incompatibilities

Storage:

General requirements:

Store in a well-closed container.
Must be stored securely and separate from food, feedstuff, medicine and the like.
Store separated from substances that may cause hazardous reactions (see section 10).

7.3 Specific end use(s)

No further relevant information available.

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with limit values that require monitoring at the workplace:

No occupational exposure limits were found.

8.2 Exposure controls

Appropriate engineering controls

For further information - see item 7 (Information for safe handling).

Individual protection measures, such as personal protective equipment

Respiratory protection:

In case of insufficient ventilation, use a self-contained breathing apparatus or mask (with filter P2). The filters have a limited usage time and should be changed regularly.

Hand protection

Use gloves e.g. of the type: nitrile or butyl rubber.

Eye/face protection

Use safety glasses/goggles or face shield at the risk of eye contact.

Body protection:

Use protective clothing at the risk of skin contact.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

General Information

Physical state

Solid

Colour:

White to off-white

Odour:

Weak

Odour threshold:

Not determined

Melting point/freezing point:

185-188 °C

Boiling point or initial boiling point and boiling range

Not available

Flammability

Not determined

Lower and upper explosion limit

Not determined

Lower:

Not determined

Upper:

Not determined

Flash point:

Not available

(Contd. on page 5)

GB

Safety data sheet according to 1907/2006/EC, Article 31

Printing date 01.03.2022

version 4

Revision: 21.06.2021

Trade name: Citalopram.HBr

(Contd. of page 4)

Auto-ignition temperature:	Not determined.
Decomposition temperature:	Not determined
pH	Not applicable
Viscosity:	
Kinematic viscosity	Not applicable
Dynamic:	Not applicable
Solubility	30 mg/ml (water), 50 mg/ml (ethanol), 270 mg/ml (chloroform)
Water:	Not determined
Partition coefficient n-octanol/water (log value)	Not determined
Vapour pressure:	Not applicable
Density and/or relative density	
Density:	Not determined.
Relative density	Not determined
Vapour density	Not applicable

9.2 Other information

Appearance:	
Form:	Crystalline
Auto-ignition temperature:	Not determined
Explosive properties:	High concentrations of dust increases the risk of dust explosion.
Change in condition	
Softening point/range	
Oxidising properties	Not determined
Evaporation rate	Not applicable

Information with regard to physical hazard classes

Explosives	None
Flammable gases	None
Aerosols	None
Oxidising gases	None
Gases under pressure	None
Flammable liquids	None
Flammable solids	None
Self-reactive substances and mixtures	None
Pyrophoric liquids	None
Pyrophoric solids	None
Self-heating substances and mixtures	None
Substances and mixtures, which emit flammable gases in contact with water	None
Oxidising liquids	None

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Oxidising solids	None
Organic peroxides	None
Corrosive to metals	None
Desensitised explosives	None

SECTION 10: Stability and reactivity

10.1 Reactivity	No further relevant information available.
10.2 Chemical stability	Stable at normal temperature and pressure.
10.3 Possibility of hazardous reactions	The substance is expected to be combustible. Dust may form explosive mixtures with air.
10.4 Conditions to avoid	No further relevant information available.
10.5 Incompatible materials:	No further relevant information available.
10.6 Hazardous decomposition products:	Formation of toxic and corrosive gases is possible during heating or in case of fire (COx, NOx, HF, HBr).

SECTION 11: Toxicological information

11.1 Information on hazard classes as defined in Regulation (EC) No 1272/2008

Acute toxicity	The substance can be absorbed by inhalation, skin contact and ingestion. The substance can be absorbed by inhalation and ingestion. Pharmacological effects occur at an exposure far lower than acute toxicity effects. Harmful if swallowed.
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Acute toxicity - data

Oral	LDlow	9.8 mg/kg (Rat)
	LD50	900-1,710 mg/kg (Rat)

Symptoms of exposure:	Nausea, hand tremor, disturbed sleep, dizziness, lethargy, loss of consciousness.
Skin corrosion/irritation	Based on available data, the classification criteria are not met.
Serious eye damage/irritation	Based on available data, the classification criteria are not met.
Respiratory or skin sensitisation	May cause an allergic skin reaction.

11.2 Additional toxicological information:

IARC (International Agency for Research on Cancer)	Persons under treatment with or exposed to isocaboxazide should not be exposed Substance is not listed.
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Sensibilisation - data

Sensitisation	Skin sensitization	1.2-8.9 - (Mouse) (OECD 429)
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Endocrine disrupting properties

Substance is not listed.

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SECTION 12: Ecological information

12.1 Toxicity Very toxic to aquatic life with long lasting effects.

EC50	5.19 mg/l (Alga) (Algae toxicity, OECD 201 (72h))
NOEC	0.921 mg/l (Alga) (Algae toxicity, OECD 201 (72h))
	0.105 mg/l (Daphnia) (Daphnia toxicity, OECD 211 (21 days))
	0.0268 mg/l (Fish) (Fish toxicity, OECD 210 (28 days))

12.2 Persistence and degradability The substance is not readily biodegradable.
Not determined. Not to be released to the environment.

biodegradability (-) (Biodegradability (OECD 301))

12.3 Bioaccumulative potential Log Kow < 3, indicates that the substance does not bioaccumulate.

Log Kow 1 (-) (Partition Coefficient, shake flask method)

12.4 Mobility in soil No further relevant information available.

12.5 Results of PBT and vPvB assessment

PBT: Not applicable.

vPvB: Not applicable.

12.6 Endocrine disrupting properties For information on endocrine disrupting properties see section 11.

12.7 Other adverse effects

Bioaccumulation potential:

General notes: Water hazard class 3 (German Regulation) (Self-assessment):
extremely hazardous for water
Do not allow product to reach ground water, water course or
sewage system, even in small quantities.
Danger to drinking water if even extremely small quantities leak
into the ground.

SECTION 13: Disposal considerations

13.1 Waste treatment methods The product should be disposed of according to local regulations.

SECTION 14: Transport information

14.1 UN number or ID number ADR, IMDG, IATA	UN3077
14.2 UN proper shipping name ADR IMDG, IATA	3077 ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (Citalopram.HBr) ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (Citalopram.HBr)
14.3 Transport hazard class(es) ADR, IMDG, IATA Class Label	- 9 Miscellaneous dangerous substances and articles. 9

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14.4 Packing group ADR, IMDG, IATA	III
14.5 Environmental hazards:	Environmentally hazardous substance, solid
14.6 Special precautions for user Hazard identification number (Kemler code): EMS Number: Stowage Category Stowage Code	Warning: Miscellaneous dangerous substances and articles. 90 F-A,S-A A SW23 When transported in BK3 bulk container, see 7.6.2.12 and 7.7.3.9.
14.7 Maritime transport in bulk according to IMO instruments	Not applicable.
Transport/Additional information:	
ADR Limited quantities (LQ) Excepted quantities (EQ) Transport category Tunnel restriction code	5 kg Code: E1 Maximum net quantity per inner packaging: 30 g Maximum net quantity per outer packaging: 1000 g 3 E
IMDG Limited quantities (LQ) Excepted quantities (EQ)	5 kg Code: E1 Maximum net quantity per inner packaging: 30 g Maximum net quantity per outer packaging: 1000 g
UN "Model Regulation":	UN 3077 ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (CITALOPRAM.HBR), 9, III

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

Australian Inventory of Industrial Chemicals	This safety data sheet has been prepared according to Regulation (EU) no. 1907/2006.
Substance is not listed.	
Directive 2012/18/EU	
Named dangerous substances - ANNEX I	Substance is not listed.
Seveso category	E1 Hazardous to the Aquatic Environment
Qualifying quantity (tonnes) for the application of lower-tier requirements	100 t
Qualifying quantity (tonnes) for the application of upper-tier requirements	200 t
National regulations:	
Information about limitation of use:	Not available

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15.2 Chemical safety assessment: A Chemical Safety Assessment has not been carried out.

SECTION 16: Other information

This information is based on our present knowledge of the substance/product.

Department issuing SDS: Corp. HS&E

Abbreviations and acronyms: ADR: Accord relatif au transport international des marchandises dangereuses par route (European Agreement Concerning the International Carriage of Dangerous Goods by Road)
IMDG: International Maritime Code for Dangerous Goods
IATA: International Air Transport Association
GHS: Globally Harmonised System of Classification and Labelling of Chemicals
EINECS: European Inventory of Existing Commercial Chemical Substances
CAS: Chemical Abstracts Service (division of the American Chemical Society)
LC50: Lethal concentration, 50 percent
LD50: Lethal dose, 50 percent
PBT: Persistent, Bioaccumulative and Toxic
vPvB: very Persistent and very Bioaccumulative
Acute Tox. 4: Acute toxicity – Category 4
Skin Sens. 1: Skin sensitisation – Category 1
Aquatic Chronic 1: Hazardous to the aquatic environment - long-term aquatic hazard – Category 1

Sources Investigators Brochure report for Citalopram, January 2000.

Data compared to the previous version altered. See * marking.

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