

Investigation of the toxicity of
Citalopram on the fertilisation success
of the Sea Urchin *Paracentrotus lividus*



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Approved by

27/10/2022

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Investigation of the toxicity of Citalopram on the fertilization success of the Sea Urchin *Paracentrotus lividus*

Prepared for NIRAS
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1 Introduction

DHI has conducted a toxicity test assessing the effects of Citalopram to sea urchin, *Paracentrotus lividus*, fertilization test method 1008.0. The test method is found in Section 15 of EPA's Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms, Third Edition /1/.

Sperm cells were exposed to a dilution series of the test item concentrations for 1 hour. The eggs were then introduced to the test chambers which contain the sperm cells. After 20 minutes, the test was ended and the effects on exposed gametes were compared to controls to determine if the test concentrations had any effect on fertilisation.

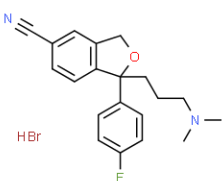
The test aimed at determining the No Effect Concentration (NOEC) level and if possible, the EC50 concentration, which results in inhibition of the fertilisation success of 50 %.

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 Appendix 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 organism

The species in the EPA Method is not available in the EU and therefore the species *Paracentrotus lividus* was used instead. Sexually mature adult echinoids (12 males and 12 females) were delivered by Ecimat, University of Vigo, Spain. The sea urchins were shipped cold and arrived within 24 hours from shipment.

The adults were shipped “dry” (wrapped in moist paper towel) and was used immediately after arrival in the laboratory as some of the sea urchins had started spawning already during transport. The male and female sea urchins were perfectly separated during shipment which means that there was no risk of fertilisation during transport.

Table 3.1 Summary of test conditions

Test guideline	US EPA fertilization test method 1008.0 /1/.
Test type	Static, non-renewal
Salinity	30‰ ± 2‰
Temperature (C°)	20°C ± 1°C
Light quality	Ambient laboratory light during test preparation
Light intensity	10 – 20 µE/m ² /s (ambient laboratory levels)
Test chamber size	Disposable (glass) liquid scintillation vials (20 mL capacity)
Test solution volume	5 mL
Number of eggs and sperm cells per chamber	About 2,000 eggs and 5,000,000 sperm cells per vial
Number of replicate chambers per concentration	4 replicates of each test concentration 8 control replicates
Dilution water	Uncontaminated source of filtered natural seawater (salinity of 31 PSU)
Test concentrations	0; 0.01; 0.03; 0.1; 0.3 and 1.0 mg Citalopram HBr/L Corresponding to: 0; 0.008; 0.024; 0.080; 0.24 and 0.80 mg Citalopram/L
Oxygen, pH, temp and salinity	Measured at the test start in test solutions
Test duration	1 hour and 20 minutes
Endpoint	Fertilization of sea urchin eggs

Test acceptability criteria	70% – 90% egg fertilization in controls
Reference test	Copper test solutions were prepared with copper sulphate. Copper concentrations: 6.25, 12.5, 25.0, 50.0, and 100.0 µg Cu/L.

3.2 Test procedure

3.2.1 Sperm collection

Sperm was collected from 2 males. 1 mL of 0.5 M KCl solution was injected by the mouth with a thin needle (26 G) distributed over 3 sites, and then the animals were gently turned a few times. The sperm was sucked up with a pipette into a vial. The sperm was kept on ice until use and was used within approx. 1 hour. The sperm suspension was counted in a Neubauer hemacytometer.

3.2.2 Egg collection

Eggs were collected from 2-4 females. 1 mL of 0.5 M KCl solution was injected by the mouth with a thin needle (26 G) distributed over 3 sites, then animals were gently turned a few times. The eggs were rinsed into a beaker with sea water, with a disposable pipette. Eggs were transferred to a plastic centrifuge tube (15 mL). The eggs were washed 3 times with seawater, by centrifuging at speed: 850 rpm for 3 min, removing the above water and putting clean seawater on. The washed egg suspension can last for a few hours at room temperature.

The egg stock solution containing approx. 2,000 eggs/mL (counted in a Sedgwick-Rafter chamber). In order to keep the eggs in suspension in the egg stock solution, a weak aeration was present in the beaker.

3.2.3 Test item preparation

A stock solution of 60 mg Citalopram HBr/L was prepared by adding 30 mg test item to 500 mL of filtered natural sea water. The pH of the stock solution was 7.9 and therefore no adjustment was needed. The stock solution was used to prepare the dilution series of 0.01; 0.03; 0.1; 0.3 and 1 mg Citalopram HBr/L corresponding to: 0; 0.008; 0.024; 0.080; 0.24 and 0.80 mg Citalopram/L. pH in all dilutions were 7.9.

3.2.4 Test set-up

At the time where the sperm solution was ready to use, 100 µL of the sperm solution was added to each test vial with 5 mL test solution and then mixed by gentle circulation of the rack. The exposure conditions were as described in Table 3.1.

After 1 hour of exposure of the sperm cells, 1 mL of egg solution was added to all vials, with a pipette where the tip is cut off, the rack was mixed again by circulation. After 20 minutes of fertilisation time the test was stopped by adding 1 mL of 1% glutaraldehyde to all vials and the rack was circulated again.

Within 48 hours, all vials were counted: 100-200 eggs per vial. During counting it was noted how many eggs were fertilized and unfertilized. A Sedgwick-Rafter chamber and a stereo microscope was used for counting.

Duplicate samples for chemical analysis were collected from each test concentration and the control at the initiation of the test. The samples were shipped on dry ice to the laboratory Molab, Kristianstad.

Two times 5 mL sample were collected (polyethylene vials (HDPE) and stored frozen at $\pm 20 \pm 2.0^{\circ}\text{C}$. 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.

4 Statistical analysis

The statistical analyses were performed using the free software R /1/. The corresponding packages used for the different analysis are described in Section 7, References.

The LOEC/NOEC values were determined by use of the Dunnett's test /3/. The NOEC values ($p > 0.05$) were determined as the highest tested concentration, at which no significant negative effect was observed compared with the control. The LOEC ($t < 0$ and $p < 0.05$) 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 (W2.3 /6/).

5 Results

5.1 Results from chemical analysis

Test item concentration in the test system was verified by analysing the lowest and the highest test concentrations (Table 5.1 and Annex B). The concentration level was satisfactory and therefore no more samples were analysed.

Table 5.1 Results from chemical analysis

Nominal concentration	Actual measured concentration ($\mu\text{g/L}$) at test start
Citalopram HBr $\mu\text{g/L}$	
10	9.4
1000	1018.1

5.2 Ecotoxicological results

The reference substance was tested in the concentration series of 6.25, 12.5, 25.0, 50.0, and 100 $\mu\text{g Cu/L}$. As no eggs were fertilised in the second highest concentration, the highest concentration of 100 $\mu\text{g/L}$ was not counted. The sensitivity of the sea urchin to the reference substance was comparable to results in the US EPA guideline /1/ in which an average EC₅₀ of 29.9 $\mu\text{g Cu/L}$ was reported. This result was an average of 5 tests

performed with a different sea urchin species in natural sea water. As the results in the present reference test are comparable to results from the guideline and no validity criteria in this respect is present, the results from the reference test are accepted.

Table 5.2 Results of the ecotoxicological test with the reference item

LOEC (µg Cu/L)	EC10 (µg Cu/L)	EC25 (µg Cu/L)	EC50 (µg Cu/L)
6.25	<6.25	<6.25	7.8 (7.1 - 8.4)

The primary data for the test with Citalopram HBr is presented in Appendix A. The results of the test are summarized below.

Significant effects on the fertilisation success after exposure to Citalopram was observed (Table 5.3 and Figure 5.1) at the three highest concentrations. LOEC and NOEC values are thus estimated to be 0.1 and 0.03 mg Citalopram HBr/L, respectively.

The EC10 and EC50 for the endpoint fertilisation success were estimated to be 0.3 mg/L and >1 mg Citalopram HBr/L, respectively.

Table 5.3 Average fertilisation success

Concentration mg/L	Average fertilisation success (%)	Std. dev. (%)
Citalopram HBr		
Control	71.4	3.9
0.01	75.5	4.3
0.03	63.8	5.5
0.1	61.0	4.7
0.3	50.2	2.5
1	45.8	6.0

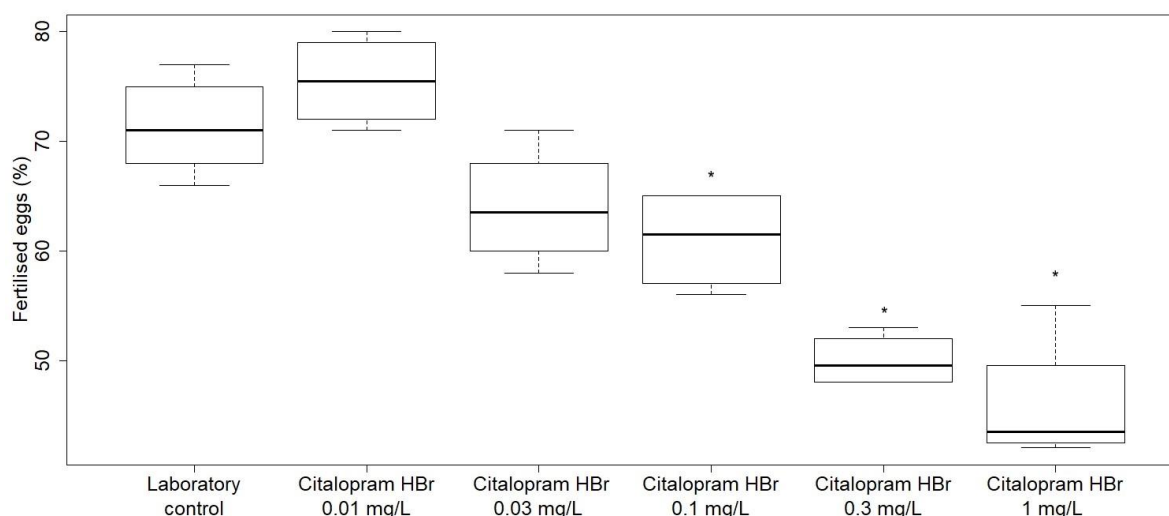


Figure 5.1 Observed percentage of fertilised eggs after exposure to Citalopram HBr. The box itself represents the middle 50% of the data. The box edges are the 25th and 75th percentiles. An asterisk in the plot indicates a significant difference between the test group and the control group.

6 Conclusion

The validity criteria of 70% – 90% egg fertilisation in controls was fulfilled (observed 71 %) and the chemical verification of the test solutions were at the expected level. The effect concentrations are presented in µg/L in Table 6.1 below.

Table 6.1 Results of the Sea Urchin fertilisation test after exposure to Citalopram (nominal concentrations).

Substance	NOEC	LOEC	EC10	EC25	EC50
Citalopram HBr (µg/L)	30	100	39 (12-67)	227 (123-330)	>1000
Citalopram (corrected for HBr in µg/L)	24	80	31 (10-54)	182 (98-264)	>800

7 References

- /1/ US EPA. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms, Third Edition, October 2002
- /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) (Dunnett'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 and statistical calculations

A Raw data and statistical calculations

A.1.1 Primary data toxicity test

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

Concentration (mg/L)		Non-fertilised eggs	Fertilised eggs	Percent eggs fertilised
0	A	26	81	76
0	B	35	67	66
0	C	36	78	68
0	D	30	74	71
0	E	26	75	74
0	F	25	83	77
0	G	35	75	68
0	H	33	82	71
0.01	A	23	83	78
0.01	B	28	77	73
0.01	C	22	87	80
0.01	D	33	79	71
0.03	A	41	77	65
0.03	B	43	69	62
0.03	C	55	75	58
0.03	D	30	72	71
0.1	A	45	57	56
0.1	B	50	69	58
0.1	C	39	73	65
0.1	D	38	70	65
0.3	A	54	62	53
0.3	B	50	52	51
0.3	C	53	49	48
0.3	D	61	57	48
1	A	67	49	42

Concentration (mg/L)		Non-fertilised eggs	Fertilised eggs	Percent eggs fertilised
1	B	47	57	55
1	C	59	44	43
1	D	57	44	44

Table A.2 pH, oxygen and salinity

Test concentration (mg/l)	Date: 03.08.2022. t = 0		
	% O ₂	‰ sal.	pH
Control	100	31	7.9
0.01	100	31	7.9
0.03	100	31	7.9
0.1	100	31	7.9
0.3	100	31	7.9
1	100	31	7.9

A.1.2 Statistical analysis

A.1.3 Determination of NOEC/LOEC for the effect on the fertilisation success

Table A.3 Experimental results, fertilisation (%)

Replicate No.	Laboratory control	0.01 mg/L	0.03 mg/L	0.1 mg/L	0.3 mg/L	1 mg/L
1	76	78	65	56	53	42
2	66	73	62	58	51	55
3	68	80	58	65	48	43
4	71	71	71	65	48	44
5	74	-	-	-	-	-
6	77	-	-	-	-	-
7	68	-	-	-	-	-
8	71	-	-	-	-	-
Count	8	4	4	4	4	4
Mean	71.4	75.5	63.8	61.0	50.2	45.8

- 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).

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	4.1	2.8	1.5	0.49	
2CIT-0.03-mg/L - CIT-0-mg/L	-7.4	2.8	-2.7	0.06	.
3CIT-0.1-mg/L - CIT-0-mg/L	-10	2.8	-3.8	0.01	**
4CIT-0.3-mg/L - CIT-0-mg/L	-21	2.8	-7.7	< 0.001	***
5CIT-1-mg/L - CIT-0-mg/L	-25	2.8	-9.2	< 0.001	***

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

The hypothesis that the mean of any test groups with Citalopram is significantly lower than the laboratory control was verified ($P < 0.05$) at 0.1 mg Citalopram HBr/L and above, which means that the LOEC is 0.1 mg/L and NOEC is 0.03 mg/L (Table A.5).

Table A.5 Endpoint: estimations of NOEC and LOEC, Dunnett's test.

Endpoint	NOEC	LOEC	Unit
Fertilisation	0.03	0.1	mg/L

A.1.4 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}) of the fertilisation success.

ECx	Citalopram HBr concentration mg/L	Std. Error	95% confidence interval	
			Lower	Upper
EC05	0.016	0.007	0.002	0.030
EC10	0.039	0.014	0.012	0.067
EC25	0.227	0.053	0.123	0.330
EC50	>1	-	-	-

Table A.7 Fertilisation success endpoint, estimations of EC10, EC50, Probit analysis.

Endpoint	EC10	EC25	EC50	Unit
Fertilisation success	0.039 (0.012 - 0.067)	0.227 (0.123 - 0.33)	>1	mg Citalopram HBr/L

APPENDIX B– Chemical analysis

Results from chemical analyses

B Results from chemical analyses

Sample ID Lab	Sample ID	Citalopram ug/L
	Sea Urchin test (Method US EPA 1008.0)	
22-33-5	DHI 11827338 Sea Urchin test Cit. 0,01 mg/l A T=0, 03.08.2022/AKA	9,4
22-33-6	DHI 11827338 Sea Urchin test Cit. 1 mg/l A T=0, 03.08.2022/AKA	1018,1
	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

Identification of test item

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



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Certificate of Analysis

Product Name and Code No. (including Salt Form): Citalopram Hydrobromide Lu 10-171-B			Citalopram, HBr Lu 10-171-B Batch: 2001976 4g Store at RT, protected from light. Expiry date: 01-Mar-2025 Sample defrosted: 01-Mar-2022/Tini H. Lundbeck A/S, Copenhagen-DK
Batch No.: 2001976	Analysis No.: 559901	Date of analysis: 30-Apr-2020	
Date of manufacture: 14-may-2003	Special storage conditions: -		

Test:	Acceptance criteria:	Results:
Description	White to off-white crystalline material	*White power
Identification		
NMR-spectrum	Conforms to structure	Conforms to structure
NIR	Conforms to standard	Conforms to standard
FT-IR spectrum	Conforms to standard	Conforms to standard
Residue on ignition, %	Max. 0.1	0.0
Heavy metals, ppm	< 20	< 20
Purity, HPLC, w/w %, 239 nm		*99.9
Impurities, HPLC, w/w %, 239 nm		
Lu 18-027	Max. 0.1	*<LOQ
Lu 18-022	Max. 0.2	*<0.02
Lu 11-305	Max. 0.1	*<LOQ
Lu 14-017	Max. 0.1	*<LOQ
Lu 29-075	Max. 0.1	*<0.02
Lu 29-215	Max. 0.1	*<LOQ
Lu 11-109	Max. 0.1	*<0.01
Unknown each	Max. 0.10	*0.03
Impurities in total	Max. 0.5	*0.08
Residual solvents, %		
Acetone	Max. 0.15	0.056
Hexan	Max. 0.06	0.015
Methanol	Max. 0.05	< LOQ
2-Propanol	Max. 0.05	< LOQ
Heptan	Max. 0.1	< LOQ
Total	Max. 0.2	0.1
Water content, KF, % w/w		
→150°	Max. 0.5	*<0.1
Melting point, DSC, °C		
Onset:		186.2
Peak max.		188.3

Drug Substance
Short Title: Lu 10-171-B
Date: 19-May-2020

Certificate of Analysis - Reference Materials

Status: Final

CMC_007654

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v. 6.0



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Test:	Acceptance criteria:	Results:
Elemental analysis (CHN), %	Theoretical:	
Carbon:	59.27	59.36
Hydrogen:	5.47	5.50
Nitrogen	6.91	6.88
Potency, %:		*99.8 (100.0–0.08–0.1–<0.1–0.0)
Comments	*Reanalysis is performed	

This Certificate of Analysis has been produced and signed electronically and is valid without a signature.

Prepared by: Corporate Product Quality Control

Controlled by: Corporate Product Quality Control

Drug Substance
Short Title: Lu 10-171-B
Date: 19-May-2020

Certificate of Analysis - Reference Materials

Status: Final

CMC_007654

v. 6.0

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Safety data sheet

according to 1907/2006/EC, Article 31

Printing date 01.03.2022

version 4

Revision: 21.06.2021

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifier

Trade name:	Citalopram.HBr
Synonyms	1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrilmonohydrobromid Lu 10-171-B
SDS number:	88
CAS Number:	59729-32-7
EC number:	261-890-6

1.2 Relevant identified uses of the substance or mixture and uses advised against

Sector of Use	SU3 Industrial uses: Uses of substances as such or in preparations at industrial sites
---------------	--

Application of the substance / the mixture	Active substance
--	------------------

1.3 Details of the supplier of the safety data sheet

Manufacturer/Supplier:	H. Lundbeck A/S Ottiliavej 9 DK-2500 Valby Tel.: +45 36 30 13 11
------------------------	---

Further information obtainable from:	This SDS is created in Lundbeck-layout by the department for Health, Safety & Environment (Corp. HS&E). For further information please contact corp.hse@lundbeck.com. Edition number: 12
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1.4 Emergency telephone number:	+45 36301311 (Opening hours Monday to Friday 9 am - 4 pm (DK time)) +45 36301311 (Opening hours Monday to Friday 9 am - 4 pm (DK time))
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SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Classification according to Regulation (EC) No 1272/2008

Acute Tox. 4	H302 Harmful if swallowed.
Skin Sens. 1	H317 May cause an allergic skin reaction.
Aquatic Chronic 1	H410 Very toxic to aquatic life with long lasting effects.

2.2 Label elements

Labelling according to Regulation (EC) No 1272/2008

The substance is classified and labelled according to the CLP regulation.

Hazard pictograms



GHS07 GHS09

Signal word

Warning

Hazard statements

H302 Harmful if swallowed.
H317 May cause an allergic skin reaction.
H410 Very toxic to aquatic life with long lasting effects.

(Contd. on page 2)

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 1)

Precautionary statements

P261 Avoid breathing dust/fume/gas/mist/vapours/spray.
P273 Avoid release to the environment.
P280 Wear protective gloves.
P301+P312 IF SWALLOWED: Call a POISON CENTER/doctor if you feel unwell.
P330 Rinse mouth.
P501 Dispose of contents/container in accordance with local regulations.

2.3 Other hazards

The substance is a solid. Dust may form explosive mixtures with air.
Citalopram hydrobromide is the active substance of antidepressant drugs with a normal daily dosage of 20 to max. 60 mg, with reduced dosage to elderly and to persons with reduced liver or kidney functions.

Results of PBT and vPvB assessment

PBT: Not applicable.
vPvB: Not applicable.

SECTION 3: Composition/information on ingredients

3.1 Substances

CAS No. Description 59729-32-7 Citalopram.HBr
Identification number(s)
EC number: 261-890-6

SECTION 4: First aid measures

4.1 Description of first aid measures

General information: When seeking medical attention, show this material safety data sheet or the packing with the label.
After inhalation: Immediately remove patient from exposure and move to fresh air. Rinse mouth and nose with water. Obtain medical attention if irritation occurs.
After skin contact: Remove contaminated clothing. Wash affected area with plenty of water. Obtain medical attention if irritation persists.
After eye contact: Remove contact lenses if any. Immediately rinse affected eye(s) with water for up to 15 minutes. Obtain medical attention if irritation/discomfort persists. Continue to rinse with water during transport.
After swallowing: Flush mouth with water and give milk or water to conscious person. Try to induce vomiting. Obtain medical attention. In case of unconsciousness provide artificial respiration.

4.2 Most important symptoms and effects, both acute and delayed

No further relevant information available.

4.3 Indication of any immediate medical attention and special treatment needed

No further relevant information available.

GB

(Contd. on page 3)

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 2)

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing agents: Water, dry chemical, CO₂ or foam.

5.2 Special hazards arising from the substance or mixture

Formation of toxic and corrosive gases is possible during heating or in case of fire (CO_x, NO_x, HF, HBr).
Avoid inhalation of fumes. Persons who have inhaled fumes must obtain medical attention (risk of delayed lung oedema).
The substance is combustible and the dust may form explosive mixtures with air.

5.3 Advice for firefighters

Protective equipment: A self-contained breathing apparatus and full protective clothing should be worn when fighting the fire.

Additional information: Evacuate area.
Remove substance/product from fire threatened area, if possible.
Stop leakage. Water from extinction of fires may be hazardous waste. Must not enter sewage or water systems.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

Use respirator, protective gloves and goggles/face shield during clean-up.
Avoid contact with skin and eyes and inhalation of dust.

6.2 Environmental precautions:

Do not allow product to reach sewage system or any water course.

6.3 Methods and material for containment and cleaning up:

Small release: Wipe up spillages with moist cloth or paper.
Major release:
Pick up mechanically and dispose of according to regulation on hazardous waste.
Dust generation may be reduced by carefully moistening or by covering with plastic film.
Wash the spillage area with plenty of water, and prevent entry into drains.

6.4 Reference to other sections

See Section 7 for information on safe handling.
See Section 8 for information on personal protection equipment.
See Section 13 for disposal information.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Persons, who handle this material, should be familiar with the hazards of the material and the necessary safety precautions, including this safety data sheet.
The substance should preferably be used in closed systems and handled under well-ventilated conditions.
Wash hands after work, before eating and after using the bathroom.
Immediately remove contaminated clothes.
Avoid inhalation of dust. Avoid contact with skin and eyes. Avoid prolonged and/or repeated exposure.

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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	
Lower:	Not determined
Upper:	Not determined
Flash point:	Not available

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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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