



Effective extraction methodology for the isolation of antidepressants from human blood

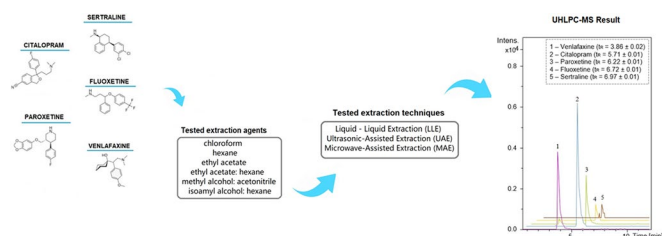
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Abstract

The objective of this study is to choose the best methodology containing a high-efficiency extraction technique and an extraction agent for the isolation of antidepressants, such as citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine, from human blood samples. In this research, various extraction agents have been examined to achieve the highest efficiency of the conducted process. Moreover, the following most available extraction techniques have been investigated and compared: liquid–liquid extraction, ultrasound-assisted extraction, and microwave-assisted extraction. The obtained extracts have been analysed with the application of the ultra-high performance liquid chromatography with mass spectrometry. The conducted research has confirmed that the microwave-assisted extraction with ethyl acetate—the average extraction efficiency is $77.4 \pm 2.7\%$ —constitute the most promising extraction method and the agent. Furthermore, the developed method was successfully applied to the analysis of the whole blood samples collected from patients treated with the analysed drugs. It should be emphasised that choice of extraction and solvent methods are the first steps to develop the methods allowing for determination of antidepressants in whole blood for toxicological and clinical purposes.

Graphic abstract



Keywords Antidepressants · Real clinical samples · Extraction methods · UHPLC-MS

Introduction

Selective serotonin reuptake inhibitors (SSRI) are the first-line antidepressants, applied in the treatment of mood disorder. They are called selective because they seem to affect primarily serotonin, not other neurotransmitters. Their main

mechanism of action is to inhibit the reabsorption (reuptake) of serotonin. All drugs in this group work in a similar way and they can cause similar side effects, despite better overall safety and tolerability in comparison to older antidepressants. Due to their positive properties and high treatment effectiveness as regards patients with mood disorder, the most frequently used ones include citalopram, fluoxetine, paroxetine, and sertraline [1–6].

There is a drug similar to SSRIs in terms of both desired and side effects—venlafaxine. It belongs to the serotonin–norepinephrine reuptake inhibitors (SNRI). In spite of this, the effect of venlafaxine at low doses is significantly lower on norepinephrine than on serotonin. It is also one

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of the most popular antidepressant used in the treatment of mood disorder [7, 8]. The selected properties of SSRIs and SNRIs are presented in Table 1.

The SSRIs and SNRIs are the most used antidepressants. Their efficacy after administration as first-line drugs is approximately 60%, where only 15% of patients do not achieve remission after several subsequent treatment attempts (STAR-D study) [9, 10]. One of the most significant reasons for the lack of response to treatment is poor collaboration, which results in a lack of adequate drug levels. Individual differences in drug metabolism may also play an important role here [11]. Hence, it is crucial to control the concentration of these drugs in biological material. New methods are still being sought for determining the concentration of medicines, which would facilitate the therapeutic drug monitoring of the patient. It is useful for better adjustment of doses to the treatment of an individual patient. Nevertheless, the extraction procedure is the main step in the analysis of human fluids and tissues. If the extraction efficiency is high, it guarantees the proper isolation of drugs and, consequently, accurate results. What is more, the extraction technique should be accordance with the principles of green analytical chemistry. Within this green extraction concept, an extract should be obtained in such a way to have the lowest possible impact on the environment. Armenta et al. [14] suggest remarking the green extraction aspects of the currently used methods based on miniaturization, automation, voiding the use of single-use plastic consumables, reducing exploration costs, and avoiding toxic residues accumulation. Due to this, each proposed methodology applied for determination and isolation of SSRIs and SNRIs drugs must be more innovative, ecologic, and economic [12–14].

Some of the most frequently used and available techniques for isolation analytes from biological material include liquid–liquid extraction (LLE), ultrasonic-assisted extraction (UAE), and microwave-assisted extraction (MAE). However, each of these techniques has both its advantages and disadvantages. The LLE extraction is characterized by simplicity, universality, and it does not require expensive apparatus. Remane et al. [15] described LLE extraction as a fast and

simple procedure used for analyzed drugs from different classes. The wide range of different classes covered with acceptable results for 119 analytes, including SSRIs and SNRIs drugs, constitutes the major advantage and novelty. Unfortunately, the LLE extraction has disadvantages as well. For example, it often produces an emulsion that is difficult to remove or separate [15, 16].

Nowadays, extraction methods seek an increase in extraction yield and reproducibility of operations, and the reduction of extraction time and solvent consumption, which implies a significant improvement in cost saving and environmental benefits. Thus, LLE extraction is gradually being replaced in analytical laboratories by UAE and MAE techniques [12, 14]. Both UAE and MAE are easy to handle, safe, and economical. They constitute automated extraction technique where it is possible to control the extraction time and temperature. Moreover, they are the optimal technique for thermolabile compounds, where at the same time, it is possible to prepare multiple (up to 40) samples. The application of the microwave-assisted extraction as an isolation technique provides a significant decrease in the required time of extraction as suggested by Wietecha-Posłuszny et al. [17], who have used MAE extraction in a new screening methodology for the identification of 30 psychoactive drugs, including antidepressants [8, 17, 18].

There are numerous publications on the extraction of antidepressants from biological material using more advanced (sometimes more expensive) extraction techniques such as solid-phase microextraction procedure [19], protein precipitation [6], or dispersive liquid–liquid microextraction [18]. However, not every laboratory can afford to use modern techniques. Therefore, the aim of the research has been to select the most effective first-line extraction method—among LLE, UAE, and MAE extraction techniques—that is useful to isolate antidepressants from SSRI and SNRI groups from whole blood. The crucial element was to choose an optimal extraction agent for extraction citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine. The research allows to uniquely choose high-efficiency extraction technique characterized by its simplicity, automation, and environmental friendliness. Furthermore, the suggested methodology has been applied to the analysis of real blood samples taken from patients with a mood disorder. This was a group of patients (female and male at different ages) treated with SSRIs or SNRIs drugs.

Table 1 Selected properties of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors drugs

| Drug | Class of drugs | pK_A | $\text{Log}P$ | Drug mass [M+H] ⁺ |
|-------------|---|--------|---------------|------------------------------|
| Citalopram | Selective serotonin reuptake inhibitors (SSRI) | 9.50 | 3.74 | 325.171 ± 0.001 |
| Fluoxetine | | 10.3 | 4.05 | 310.141 ± 0.001 |
| Paroxetine | | 9.90 | 3.95 | 330.150 ± 0.001 |
| Sertraline | | 9.48 | 5.29 | 306.081 ± 0.001 |
| Venlafaxine | Serotonin–norepinephrine reuptake inhibitors (SNRI) | 10.1 | 3.28 | 278.212 ± 0.001 |

Results and discussion

Selection of extraction agent and technique

In the case of extraction from whole blood, no obvious statements may be made as to which extraction technique and

agents are excellent for SSRIs and SNRIs drugs. The aim of this stage was to select the extraction agents which tested compounds, extracted from the blood in undissociated form, passing more efficiently to the organic phase, as a result. Due to these different extraction agents such as: chloroform, hexane, ethyl acetate, ethyl acetate: hexane (10:90, v/v) methyl alcohol: acetonitrile (1:1, v/v), and 3-methylbutan-1-ol: hexane (1:99, v/v) were selected and compared. Each solvent was tested using three extraction techniques: LLE (extraction parameter: 10 min), UAE (extraction parameters: 10 min, 25 °C), and MAE (extraction parameters: 10 min, 50 °C, 800 W). The samples were prepared according to the procedure described in the section “Sample preparation”, at the drug concentration 500 ng/cm³. Moreover, for each sample, 0.6 M NaOH (pH = 13.5) was added. Under these conditions, the pH value is higher than the pKa value of the analysed drugs (see Table 1). The formation of a strongly alkaline environment during the extraction resulted in the citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine being mostly in uncharged form, and thus showing a greater affinity for the organic phase.

In the preliminary research, two of them (chloroform and methyl alcohol: acetonitrile) were rejected due to a problem in a blood preparation step where observed the protein precipitation (coagulation) which prevented further analysis. Therefore, in the further analysis, only hexane, ethyl acetate, ethyl acetate: hexane (10:90, v/v), and 3-methylbutan-1-ol: hexane (1:99, v/v) were used. Each time, three samples were prepared and analysed three times using UHPLC-MS technique. The results were compared by means of the extraction efficiency (EE) relating to an analyte. It was calculated as regards, the ratio of the relative peak area obtained for an extracted (A) sample $\left(\frac{I_A}{I_{IS}}\right)_A$ in comparison to the relative

peak area obtained for the standard drug (B) solution $\left(\frac{I_A}{I_{IS}}\right)_B$ —see Eq. (1).

$$EE = \frac{\left(\frac{I_A}{I_{IS}}\right)_A}{\left(\frac{I_A}{I_{IS}}\right)_B} \times 100\%, \quad (1)$$

The obtained extraction efficiency of citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine isolated from whole blood with the use of the LLE, UAE, and MAE extraction and various extraction solvents, have been summarized in Table 2.

As can be seen, each solvent extracted all investigated antidepressants; however, their optimum extraction parameters are completely different. For instance, citalopram, sertraline, and venlafaxine are best when extracted in the mixture consisting of 3-methylbutan-1-ol and hexane (1:99, v/v), in contrast to fluoxetine that is best isolated with application of hexane. In the case of paroxetine, the best efficiency was obtained using ethyl acetate. Moreover, the extraction efficiency (see Table 2) in the same extraction agent is different for the analysed extraction techniques. For example, taking into consideration the LLE extraction and UAE extraction, the best results were obtained using 3-methylbutan-1-ol: hexane, yet, higher performance was obtained for UAE—the $\overline{EE} = 50.9 \pm 4.9$ for LLE and $\overline{EE} = 63.9 \pm 1.9$ for UAE. It was observed that ethyl acetate allows for achievement of the best extraction efficiency ($\overline{EE} = 77.4 \pm 2.7$) with the application of MAE extraction. Both SSRIs and SNRIs have satisfactory EE, which is certainly due to the character of the performed process, as the action of the microwave prompts the destruction of the blood cells (from the inside). Thus, this effective procedure—MAE extraction and ethyl

Table 2 Summary of the extraction efficiency obtained based on the liquid–liquid extraction (LLE), ultrasonic-assisted extraction (UAE), and microwave-assisted extraction (MAE) techniques and different extraction agents

| Extraction technique | Extraction agent | Extraction efficiency (EE) /% (n = 5) | | | | | Average extraction efficiency (EE) /% |
|----------------------|--|---------------------------------------|------------|------------|------------|-------------|---------------------------------------|
| | | Citalopram | Fluoxetine | Paroxetine | Sertraline | Venlafaxine | |
| LLE | Hexane | 33.0 ± 6.7 | 38.4 ± 3.4 | 58.5 ± 9.6 | 38.4 ± 1.9 | 40.1 ± 1.3 | 41.7 ± 4.6 |
| | Ethyl acetate | 30.2 ± 2.5 | 35.4 ± 2.1 | 25.8 ± 1.7 | 29.8 ± 3.2 | 38.3 ± 1.1 | 31.9 ± 3.9 |
| | Ethyl acetate: hexane (10:90, v/v) | 50.9 ± 4.8 | 45.1 ± 3.3 | 48.6 ± 5.9 | 51.3 ± 1.2 | 47.2 ± 5.4 | 48.6 ± 4.2 |
| | 3-Methylbutan-1-ol: hexane (1:99, v/v) | 81.0 ± 3.8 | 36.0 ± 5.4 | 30.1 ± 6.0 | 38.1 ± 5.2 | 69.4 ± 4.0 | 50.9 ± 4.9 |
| UAE | Hexane | 47.2 ± 2.9 | 23.9 ± 0.4 | 76.6 ± 1.4 | 57.0 ± 2.1 | 18.0 ± 1.3 | 44.5 ± 1.6 |
| | Ethyl acetate | 56.3 ± 2.0 | 28.6 ± 1.1 | 13.6 ± 3.7 | 68.2 ± 0.8 | 24.5 ± 0.6 | 38.2 ± 1.4 |
| | Ethyl acetate: hexane (10:90, v/v) | 26.5 ± 2.1 | 78.9 ± 2.1 | 19.7 ± 3.7 | 49.7 ± 1.9 | 69.3 ± 2.9 | 48.9 ± 2.5 |
| | 3-Methylbutan-1-ol: hexane (1:99, v/v) | 62.4 ± 2.1 | 59.1 ± 1.3 | 44.2 ± 3.7 | 90.4 ± 0.3 | 63.2 ± 2.4 | 63.9 ± 1.9 |
| MAE | Hexane | 26.9 ± 5.9 | 84.9 ± 2.2 | 34.0 ± 1.3 | 71.9 ± 1.4 | 76.4 ± 0.9 | 58.8 ± 2.3 |
| | Ethyl acetate | 60.8 ± 3.2 | 81.4 ± 2.4 | 79.4 ± 1.8 | 77.2 ± 1.9 | 88.4 ± 4.3 | 77.4 ± 2.7 |
| | Ethyl acetate: hexane (10:90, v/v) | 54.1 ± 1.2 | 73.2 ± 5.0 | 47.3 ± 2.7 | 56.9 ± 4.9 | 59.5 ± 2.2 | 58.2 ± 3.2 |
| | 3-Methylbutan-1-ol: hexane (1:99, v/v) | 57.2 ± 2.3 | 81.0 ± 1.5 | 65.7 ± 3.6 | 73.8 ± 2.6 | 91.9 ± 3.7 | 73.9 ± 2.6 |

acetate—may be successfully used in clinical patients' blood samples. Moreover, the suggested methodology constitutes a good alternative to fast, easier and cheaper method of the drugs employed in clinical examinations. In addition, it may be useful for comparison with novel extraction techniques.

Validation procedure

The validation procedure of the suggested extraction methodology was carried out according to the literature guidelines [8, 20]. Validation parameters, such as linearity, the limit of detection (LOD), the limit of quantitation (LOQ), and precision (CV) obtained with the application of the microwave-assisted extraction method and ethyl acetate as the extraction agent are presented in Table 3.

The linearity of the optimized method was tested in the range with concentration points: 25, 50, 100, 150, 200, 250, and 300 ng/cm³, for each of the drugs. Calibration curves were based on a linear regression model that took into account the ratio of the peak area of each compound to that of the IS. Deuterated compounds from the same groups of drugs as the studied compounds, such as fluoxetine-D₅ for fluoxetine and sertraline, paroxetine-D₅ for paroxetine and citalopram, and venlafaxine-D₅ for venlafaxine, were used. The concentration of each IS (added to the samples before the extraction process) was constant and amounted to 150 ng/cm³.

The limits of detection (LOD) and quantification (LOQ) were calculated as the ratios of three times and ten times the standard deviation of the analytical signal measured at 50 ng/cm³ to the slope of the calibration graph, respectively. The calculated LOD and LOQ values indicate the possibility of determining the studied compounds at the low concentration.

As for precision, this was determined at medium (150 mg/dm³) levels. For intraday precision ($n=9$), three samples containing analytes of the concentration were analysed and each analysis was repeated three times. The interday precision ($n=27$) was evaluated by repeating the analysis for three consecutive days. The obtained results confirm that

for analysed drugs, the intraday precision was lower than 9.6% and interday precision was lower than 13.7% for each analyte. It is in accordance with the accepted criteria (see Table 3)—less than $\pm 15.0\%$ [20]. Moreover the obtained precision was similar to isolation of SSRIs and SNRIs with the application of the novel extraction techniques—dispersive liquid–liquid microextraction [18], which further emphasizes the possibility of using traditional MAE extraction. The obtained results were better than protein extraction to determine sertraline. The intraday precision of the developed method was lower than 12% [21].

The satisfying results for validation of the proposed methodology of isolation of citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine from whole blood using the MAE extraction and ethyl acetate guarantee the possibility of its application for the analysis of the blood samples of the patients.

Case samples

The validated method based on the combination of MAE extraction and ethyl acetate (such as extraction agent) was applied for the analysis of real samples collected in vivo. The clinical samples were provided by the Department of Adult Psychiatry at the Jagiellonian University Medical College. The whole blood samples were collected from patients treated by SSRIs and SNRIs drugs. The first patient (case #I) was a 61-year-old male treated with 150 mg of venlafaxine (venlafaxine). Case #II (51-year-old male), case #IV (41-year-old male) and case #V (47-year-old female) were treated with 75 mg of effectin ER (venlafaxine). Case #III was collected from a female who was treated with 20 mg paroxen (paroxetine). Each patient suffered from a mood disorder—bipolar disorder or depression. The obtained results are presented in Table 4.

As can be seen in Table 4, in each case #I–V samples were successfully used in identifying the analysed drugs in therapeutic concentration—paroxetine in the range 10–75 ng/cm³ and venlafaxine 250–750 ng/cm³ [22]. On this basis, it can be concluded that the patient takes this

Table 3 Validation parameters obtained with the application of the microwave-assisted extraction method and ethyl acetate as the extraction agent

| Parameter | Results | | | | |
|------------------------------------|------------|------------|------------|------------|-------------|
| | Citalopram | Fluoxetine | Paroxetine | Sertraline | Venlafaxine |
| Linearity range/ng/cm ³ | LOQ-300 | | | | |
| R ² | 0.9902 | 0.9876 | 0.9708 | 0.9820 | 0.9886 |
| Slope | 0.0044 | 0.0010 | 0.0014 | 0.0023 | 0.0175 |
| LOD/ng/cm ³ | 4.1 ± 2.0 | 4.6 ± 5.0 | 3.6 ± 4.3 | 3.7 ± 4.1 | 1.8 ± 0.6 |
| LOQ/ng/cm ³ | 13.5 ± 6.6 | 15.3 ± 6.7 | 11.9 ± 3.8 | 12.3 ± 3.5 | 5.9 ± 2.0 |
| Precision, CV/% | | | | | |
| Intraday ($n=9$) | 6.8 | 4.7 | 9.6 | 7.9 | 8.6 |
| Interday ($n=27$) | 10.6 | 8.8 | 13.7 | 11.6 | 9.8 |

Table 4 Results obtained from analysis of real case samples

| Parameters | Case #I | Case #II | Case #III | Case #IV | Case #V |
|--|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug | Venlafaxine | Venlafaxine | Paroxetine | Venlafaxine | Venlafaxine |
| t_R /min | 3.84 ± 0.01 | 3.85 ± 0.01 | 6.23 ± 0.01 | 3.84 ± 0.01 | 3.88 ± 0.02 |
| Final concentration/ng/cm ³ | 287.5 ± 2.3 | 386.3 ± 2.0 | 54.6 ± 1.3 | 406.8 ± 3.1 | 265.2 ± 1.6 |

medication according to the psychiatrist's recommendation. It may be a good preliminary step to develop the analytical and quantitative research for a larger group of drugs.

Conclusion

In the proposed research, three most common extraction techniques—LLE, UAE, and MAE extraction have been compared. The main goal was to choose the easiest and high-efficiency methodology for isolation of SSRIs and SNRIs drugs from human blood. As it has been presented, the best results are obtained by means of the ethyl acetate in conjunction with MAE extraction. Moreover, the suggested MAE extraction technique is rapid and easy to handle as well as it moderates solvent consumption. It enables the isolation of drugs with high efficiency, which is important in qualitative analysis. The results of the analyses of real samples indicate the possibility of using the suggested methodology based on the combination of MAE extraction and ethyl acetate for the isolation of SSRIs and SNRIs drugs from blood. It may prove to be a useful contribution to development of the new methods for therapeutic drug monitoring (i.e., patients with depression) or in forensic and toxicology analysis.

Experimental

Chemicals and materials

Drug standards and their deuterated analogue at a concentration of 1 mg/cm³: citalopram, fluoxetine, paroxetine, sertraline, venlafaxine, fluoxetine-D₅, paroxetine-D₅, and venlafaxine-D₅ were purchased from Lipomed AG (Switzerland). Each standard solution was stored in methyl alcohol in a freezer at -20 °C. The other chemicals used throughout the experiments, such as: chloroform, formic acid, hexane, acetic acid, and sodium tetraborate decahydrate (borax), were purchased from Sigma-Aldrich (USA). Acetonitrile, 3-methylbutan-1-ol, and methyl alcohol were supplied by Fluka Analytical (Germany), whereas the 3-methylbutan-1-ol was obtained from Chempur (Poland). Ethyl acetate was purchased from Avantor Performance Materials POCH (Poland). Ultrapure water (18.2 MΩ cm, < 3 ppb TOC) which was used to prepare all aqueous solutions was

generated with the Milli-Q system by Merck-Millipore (Darmstadt, Germany).

Instrumentation

The measurements were carried out using UltiMate 3000 RS liquid chromatography system (Dionex, USA) coupled with a mass spectrometer MicrOTOF-Q II with a time of flight mass analyser (Bruker, Germany). The mobile phase consisted of 0.1% formic acid in ultrapure water (A) and acetonitrile (B). The following gradient programme (B) at the flow rate of 0.4 cm³/min was used: 0 min - 5%; 14 min - 70%; 16.5 min - 5%; 20 min - 5%. Separation was carried out in a Hypersil Gold Phenyl column (50 mm × 2.1 mm I.D., particles 1.9 μm, injection: 5 mm³, Dionex) at 20 °C. The ESI ion source conditions were as follows: nebulizer pressure: 2.5 bar, dry gas: 5.5 dm³/min heated to 200 °C. Data were recorded in the positive ion mode and profile spectra were acquired in the mass range 100–1000 *m/z*. Cluster mass calibration was performed using a mixture of 10 mM sodium formate and isopropanol before each run.

For the extraction of drugs from human blood ultrasonic bath SONIC-3 (Polsonic, Poland), which works at the frequency of 40 kHz. and a MARS 5 microwave-assisted sample preparation system (CEM Matthews NC, USA) equipped with 24 Xpress PHA vessels (75 cm³) were used.

Blood collections

In the present study, whole human blood (drug free) was provided by at local blood bank (Krakow, Poland). The real case samples from patients (case #I–V), who took the analysed drugs were kindly provided by the Department of Adult Psychiatry at the Jagiellonian University Medical College (according to the Bioethical Commission Approval no 1072.6120.302.2018). All the samples were stored at the temperature of -20 °C prior to the analysis in accordance with the standard laboratory practice.

Sample preparation

The solutions of citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine were prepared at a concentration of 100 ng/cm³ in methyl alcohol with the application of stock solutions at a concentration 1 mg/cm³. Subsequently, it

evaporated under nitrogen at the temperature of 40 °C. Then, 300 mm³ of whole blood and 300 mm³ of borate buffer (pH=9.5) were added to each probe and vortexed (Vortex Heidolph, Germany) for 5 min. The prepared samples were extracted using three techniques—LLE, UAE, and MAE—and for testing six different extraction solvents: chloroform, hexane, ethyl acetate, ethyl acetate: hexane (10:90, v/v), methyl alcohol: acetonitrile (1:1, v/v), and 3-methylbutan-1-ol: hexane (1:99, v/v). The amount of 1 cm³ of extraction solvent (during analyses) was added and these prepared samples were gently agitated for 10 min using at platform shaker (LLE) or sonicated for 10 min at 25 °C (UAE). The MAE extraction was performed with the application of 3 cm³ of extraction solvent using the following parameters: 10 min, 50 °C and 800 W. Next, for each sample, the amount of 1 cm³ of 0.6 M NaOH was added, then vortexed for 2 min and filtrated using PTFE filters (0.25 µm). Finally, the supernatant was transferred to a new probe and evaporated under nitrogen. Prior to UHPLC-MS analysis, 100 mm³ of mobile phase (acetonitrile 0.1% formic acid, 1:9, v/v) was added.

In respect of case #I–V samples, 300 mm³ of whole blood was taken and 300 mm³ of borate buffer was added (pH=9.5). The prepared samples were extracted using only the MAE technique (10 min, 50 °C, and 800 W) and ethyl acetate as an extraction agent. Other activities were carried out analogically as described above.

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