NATIONAL CENTER OF PUBLIC HEALTH

THE MINISTRY OF HEALTH OF THE REPUBLIC OF KAZAKHSTAN

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ANALYTICAL REPORT

ON THE RESULTS OF STUDY

On lead in children as part of the implementation of the joint work plan of NCPH with the United Nations Children's Fund (UNICEF) in the Republic of Kazakhstan for 2018-2020 WP/ KAZ/2018/014/2020 " Equity and Inclusion for Children, Adolescents and Families" and "Child Friendly Social Environment"

NUR-SULTAN
2022

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NUR-SULTAN
2022

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The analytical report was approved by the Acting Chairman of the Board of the RSE at the National Center for Public Health of the Ministry of Health of the Republic of Kazakhstan on March 09, 2022, Ph.D. Zh. Kalmakova

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ABSTRACT

Report 36 p., 10 figures, 7 tables, 10 sources, 5 annexes.

KEYWORDS **ENVIRONMENT, PUBLIC HEALTH, OBJECT OF POLLUTION, EXPOSURE LEVEL, CONCENTRATION, HEALTH RISK ASSESSMENT, CARCINOGENIC POTENTIAL, ACCEPTABLE RISK LEVEL, RISK MANAGEMENT AND EPIDEMIOLOGIC STUDIES**

The objects of the study were 4 cities: Nur-Sultan, Almaty, Shymkent – cities of republican significance and the regional center – city of Karaganda. During field work of the study, we took blood samples from children and asked questions to their official guardians in outpatient clinics of the mentioned cities.

The aim of the study was to assess the epidemiologic situation of the prevalence (presence) of lead intoxication among children.

The study methodology consisted of venous blood sampling from children with questioning of their official guardians using a pre-designed questionnaire and informed consent. The obtained data will undergo statistical analysis in Epi info program.

Three null hypotheses were considered when planning the study:

1) In industrial regions and regions of the country where there is a large concentration of motor vehicles, the population is most susceptible to chronic intoxication with heavy metals, including lead;

2) lead poisoning has no differences by sex; and

3) household utensils, children's toys, cosmetics, and other household items can be sources of lead poisoning.

The novelty of this study lies in the fact that no such studies have been conducted in Kazakhstan over the past 30 years, as evidenced by the review of articles on the subject conducted within the framework of this study.

The results of the study show the need to screen children for lead in their bodies.

We have concluded and recommend an expanded nationwide study to assess risk factors like heavy metal salts in the environment (soil, water, air, vegetable products, food) associated with urbanization and industrialization of regions.

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ACRONYMS AND ABBREVIATIONS

MoH RK	Ministry of Health of the Republic of Kazakhstan
NCPH	National Center of Public Health
MUA JSC	Medical University of Astana Joint-stock Company
CRH JSC	Central Road Hospital Joint-stock Company
RSE on REM	Republican state enterprise on the rights of economic management
LLP	Limited Liability Partnership
PhD	Philosophiæ Doctor – Doctor of philosophy (academic degree)
D.med.sci.	Doctor of medical sciences
CNS	Central nervous system
IHME	Institute for Health Metrics and Evaluation
USA	United States of America
KazNMU	Asfendiyarov Kazakh National Medical University
mcg/dL	Micrograms per deciliter (unit of measure)
Epi situation	Epidemiologic situation
ZPP	Zinc protoporphyrin
ALAD	Aminolaevulinic acid dehydratase
EPP	Erythroprotoporphyrin
BLL	Blood lead level
RGF	Rg-fluorometry

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The contribution of the following international experts recommended by UNICEF to the project should be noted:

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We express our sincere gratitude to the outside experts who assisted in the preparation of this report:

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Berik Toleubekov – PhD(c) in Medical Sciences, Lund University, Lund, Sweden, general surgeon.

INTRODUCTION

Lead is a naturally occurring toxic metal found in the Earth's crust. Its widespread use has resulted in adverse effects on humans and significant public health issues in many parts of the world.

Important sources of environmental pollution include lead mining, smelting, its use in industrial production, recycling, and, in some countries, the continued use of lead-based paints and leaded aviation fuel. The production of lead-acid batteries for motor vehicles accounts for more than three quarters of global lead consumption. Lead is used in many other products, such as pigments, paints, solder, stained glass, lead crystal glassware, ammunition, ceramic glazes, jewelry, toys, and in some cosmetics and traditional medicine.

Young children are particularly vulnerable to the toxic effects of lead, and their health may be impacted due to profound and permanent negative effects on CNS development.

There is no 'safe' blood lead concentration; even blood lead levels as low as 5 mcg/dL can cause cognitive decline, behavioral disorders, and learning difficulties in children. As blood lead concentrations increase, the range and severity of symptoms and effects also increase.

In 2019, the Institute for Health Metrics and Evaluation (IHME) estimated that 900,000 deaths and 21.7 million lost disability-adjusted life years (DALYs) were associated with long-term harmful lead exposure worldwide. The greatest burden was in low- and middle-income countries. In addition, IHME estimated that in 2019, lead exposure was responsible for 62.5% of the global burden of idiopathic developmental intellectual disability, 8.2% of the global burden of hypertension-related heart abnormalities, 7.2% of the global burden of ischemic heart disease, and 5.65% of the global burden of stroke.

WHO on lead:

1. Lead is a poisonous substance the accumulation of which affects multiple body systems and is particularly harmful to young children.
2. Lead in the body is distributed to the brain, liver, kidney and bones. It accumulates in the teeth and bones over time. Human exposure is usually assessed through the measurement of lead in blood.
3. Lead accumulated in bones is released into blood during pregnancy and becomes a source of exposure to the developing fetus.
4. There is no concentration of lead that i s known to be without harmful effects.
5. Lead exposure is preventable [1].

The Republic of Kazakhstan is an industrially developed country, where many minerals, including lead, are extracted and refined. A number of regions of Kazakhstan specialize in metallurgical industry. In regions of Kazakhstan such as East Kazakhstan, Pavlodar, Karaganda (Zhezkazgan), Turkestan (Shymkent) and other regions there are metallurgical deposits, mining and processing

plants, and processing enterprises.

For instance, in East Kazakhstan region, Ust-Kamenogorsk city, there are industrial facilities of "Aluminum of Kazakhstan" JSC and "KazZinc" JSC, which produce harmful emissions into the atmosphere containing, among others, lead. It was determined that lead, contained in the atmospheric air of Ust-Kamenogorsk city, is critical for respiratory organs in terms of danger of developing non-carcinogenic effects due to both acute and chronic inhalation, as per established reference concentrations [2].

Relevance

In 2018, UNICEF, together with the National Statistical Office of Georgia, conducted the largest study of childhood lead poisoning. The results were extremely alarming: across Georgia, 41 percent of children had blood lead levels equal to or greater than 5 mcg/dL. Sixteen percent of Georgian children had lead levels exceeding 10 mcg/dL [3].

Table 1 provides information on overall childhood morbidity for 2018 - 2020. Lead poisoning may also have contributed to the occurrence of these diseases.

Given that lead is a 'silent poison' that has no recognizable symptoms, requires a venous blood test to detect it in the body, and chelation therapy to remove lead from the human body has strong negative side effects and is only used in severe cases of intoxication, the only real way to save children from lead is through prevention.

This study will analyze the epidemiological situation on the prevalence of lead intoxication in the study population.

Table 1

Overall morbidity of population of the Republic of Kazakhstan in 2018 – 2020

Nosology	Reporting period								
	2018			2019			2020		
	0-14 years	15-17 years	18 years	0-14 years	15-17 years	18 years	0-14 years	15-17 years	18 years
Diseases of the respiratory system	59 920,3	42 164,7	14 472,0	52 667,2	33 471,6	10 141,5	45 715,7	27 445,2	13 027,9
Diseases of the digestive system	9 420,1	11 241,7	7 923,0	6 865,9	6 566,2	2 956,5	6 947,5	6 864,3	2 794,8
Diseases of the nervous system	6 201,4	7 730,3	3 542,7	3 245,4	3 070,6	1 213,6	2 897,1	2 553,8	1 326,6
Diseases of the circulatory system	520,1	2 611,1	23 785,2	239,3	1 109,0	4 003,5	191,6	947,8	4 378,6
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	6 112,9	6 748,5	2 289,6	3 447,3	3 111,6	848,3	2 536,0	2 502,8	870,0
Endocrine, nutritional and metabolic diseases	1 568,6	4 183,9	6 006,8	752,8	1 646,0	1 023,5	588,0	1 279,2	1 162,4
Injury, poisoning and certain other consequences of external causes	2 681,0	5 064,6	3 021,7	2 549,0	4 840,8	2 968,1	2 362,6	4 164,8	2 870,3
Total	**86 424,4**	**79 744,8**	**61 041,0**	**69 766,9**	**53 815,8**	**23 155,0**	**61 238,5**	**45 757,9**	**26 430,6**

Note: diseases were selected taking into account the possible physiological effects of lead on the body

Review of previous studies on the impact of lead on children in the world and the Republic of Kazakhstan (Discussions with similar publications)

Reviews of studies in the USA have shown (2012, 2015) that although various occupational health and safety measures have been taken to control lead exposure, cases of lead poisoning are still being reported. Lead poisoning has been recognized as a serious public health risk, especially in developing countries. Exposure to lead has various harmful effects on the blood-forming, renal, reproductive and central nervous system, mainly through increased oxidative stress. These changes play an important role in the manifestations of the disease. Although the use of lead is controlled to some extent in countries such as the United States and Canada, it is still heavily used in developing countries. This is primarily due to the fact that lead has unique physical and chemical properties that make it suitable for a large number of applications in which people have utilized its benefits since ancient times, and thus it has become a common environmental pollutant [4, 5].

The results of clinical studies by Russian scientists have shown that lead easily passes through the placenta at all stages of pregnancy and accumulates in the fetus. Breast milk from mothers who have had prolonged contact with lead can also become a source of poisoning for the child [6].

In her study of 2006, Dr. T.S. Chernyakina reports that the amount of pollutant emissions into the environment of St. Petersburg increases annually due to motor vehicle emissions and extends to all administrative districts. Lead is one of the priority pollutants. At the same time, children in the central part of St. Petersburg are exposed to the most unfavorable conditions of chronic exposure to atmospheric air pollutants. All children in the city are at risk of exposure to chemicals contained in hot tap water [7].

In 2008, the city of Flint (Michigan, USA) was hit hard by the financial crisis. In an attempt to save money, the city government temporarily began using water from the Flint River, foregoing the quality water of Lake Huron. The Flint River had been used for decades to discharge industrial wastewater. It had high concentrations of chloride and other harmful substances, was nineteen times more corrosive than Lake Huron water. Scientists soon tested nearly 300 samples of drinking water in Flint, and approximately thirty samples showed excessive levels of lead. As a result, doctors confirmed lead poisoning in 12,000 children between the ages of 1 and 18 who lived in the city. Studies showed that lead exposure impaired the health of at least 6,000 children. The number of residents exposed to contaminated water is in the dozens of thousands [8].

Unfortunately, in Kazakhstan over the last decade, perhaps even since independence, there have been few publications on lead poisoning issues.

However, during the publication review period, we were able to find some articles on clinical trials 'involving' lead.

The results of the KazNMU study conducted in 2012 in Shymkent city showed that children have an average blood lead content of 10 mcg/dL, 53% have a significant excess of lead up to 13.0 ± 0.5 mcg/dL. In adolescents in Shymkent city, blood lead content in 18 out of 48 people exceeds the permissible level, i.e., is over 10 mcg/dL.

The blood test for lead presence showed that in children the average lead content was within 10.9 ± 0.5 mcg/dL. At the same time, 53% of the examined children had a blood lead content of 13.0 ± 0.44 mcg/dL, which was 8% higher than the normative values. In adolescents, the mean blood lead content was within 8.48 ± 2.1 mcg/dL, and in 40% of adolescents it was at 12.3 ±2.2 mcg/dL. At the same time, the report indicates that there is no sanitary protection zone around the Shymkent Lead Plant, and residential areas, schools and preschool institutions are immediately adjacent to the industrial territory and the level of lead in the blood of preschool children (6-7 years) and school children (adolescents 14-16 years) exceeds the permissible level, i.e., is above 10 mcg/dL [9].

It should be noted that many of the articles we reviewed addressed the presence of lead in the body in one way or another. However, these articles did not address the prevalence of lead intoxication among children. An example of this is the article «Influence of lead and alcohol on cerebrospinal fluid production of the brain at isolated and combined exposure» [10].

Null hypotheses

During the planning period of this study, we put forward the following main Null Hypotheses:

1. In industrial regions and regions of the country where there is a large concentration of motor vehicles, the population is most susceptible to chronic intoxication with heavy metals, including lead;
2. Lead poisoning has no differences by sex;
3. Household utensils, children's toys, cosmetics, and other household items can be sources of lead poisoning.

Limitations of the study

- A coronavirus pandemic (COVID-19 pandemic) has been declared worldwide at the time of this study.
  - There are mobility restrictions in the regions that are the most interesting for the study.
  - As a consequence, the cities of Ust-Kamenogorsk, Pavlodar, Temirtau, Zhezkazgan and Kokshetau (as a reference city) were excluded from the study.
- An upsurge in anti-vaxxer campaign activity, which consequently caused distrust on the part of the population towards the study and led to negative

publications on social media.

- The resources of the study could not cover some of the costs.
  - There was no funding provided for renumeration of study participants.
  - There is no funding for traveling to households of interviewers and phlebotomists (health workers who collect blood).
- Due to mobility and gathering restrictions by government authorities due to the COVID-19 pandemic, the representativeness of the sample is not ideal.
  - Biological fluids (blood) were collected, and questionnaires were administered in outpatient clinics in the cities selected for the study when the population was willing to participate in the study.
  - It was not possible to recruit the planned number (1000 people) of respondents in the required age range. Therefore, it was decided to increase the age range of children.
- The study was conducted only in four cities in Kazakhstan, so its results cannot be extrapolated to the entire urban pediatric population. Recruitment of participants was based on their own application after they learned about the study from different sources. That is, the sampling was not randomized.

Aim of the study

To assess the epidemiologic situation of prevalence (presence) of lead intoxication among children of the Republic of Kazakhstan.

Study objectives

- To determine the proportion of children with venous blood lead levels above thresholds (5 and 10 mcg/dL).
- To assess the prevalence of risk factors for lead poisoning among children.
- To determine the association of elevated childhood lead levels with demographic traits and risk factors.

Stages of works, required to achieve the aim and objectives

- Fieldwork for data collection.
  - Conducting briefing (training) of interviewers and phlebotomists on the aspects of blood collection and questionnaires in the framework of this study.
  - Determining blood lead levels in children clinically by collecting blood from outpatient organizations for laboratory tests;
  - Conducting a sociological survey by asking questions to the official guardians of children whose blood has been collected for laboratory testing, using a pre-designed questionnaire.
- Conducting analysis of laboratory data.

- Conducting analysis of the results of sociological survey (responses to the questionnaires).
- Conducting comparative analysis of laboratory and questionnaire data by comparing the results obtained.
- Analyzing hygienic indicators of the environment using Kazhydromet data by territories.
- Provide practical recommendations on the prevention of lead intoxication among children in the Republic of Kazakhstan.

Scientific novelty

For the first time in the Republic of Kazakhstan, a study was conducted to assess the epidemiological situation of lead intoxication among children.

Practical significance

This study will make it possible to assess the epidemiological situation with regard to the prevalence of lead intoxication in the selected regions and to identify the sanitary and hygienic problems that lead to such intoxication.

Based on the obtained results of clinical and sociological studies on the level of lead intoxication, practical recommendations for preventive measures have been developed.

Methods and study object

The methodology of the study consisted of venous blood sampling from children with questioning of their official guardians using a pre-designed questionnaire with informed consent. Laboratory tests were performed in the laboratory of Invitro network by inductively coupled argon plasma mass spectrometry (ICP MS). Chronic lead poisoning was defined by its concentration in a venous blood sample if it was equal to or greater than 5 micrograms per deciliter (5 mcg/dL).

The objects of the study are 4 cities: Nur-Sultan, Almaty, Shymkent – cities of republican significance and a regional center, the city of Karaganda. During field stage of the study, blood sampling from children and questioning of their official representatives were carried out in outpatient clinics of the above-mentioned cities.

The statistical method consists of applying the statistical analysis program Epi info to process the obtained data.

MAIN PART

Fieldwork

Field work involves conducting questionnaires and sampling biological fluids (in our case venous blood) in the areas selected for the study, among population groups selected according to certain criteria (in our case, age).

We planned to enroll children aged 5 to 7 years in the study. However, at the time of fieldwork, starting in November 2021, due to the epidemiologic situation related to the COVID-19 pandemic, we faced certain barriers in conducting the study.

Ways to address the limitations during fieldwork.

1. In order to address the challenges related to the organization of work in outpatient clinics, we requested assistance from the territorial health departments. As a result, the work progressed faster.
2. We launched an awareness-raising campaign by publishing informational materials on the study.

Communication materials were developed in the form of informational leaflets as handouts (Figure 1) and a video clip as the main advertisement of the study. Both products were published on the official internet resources of the NCPH in Kazakh and Russian languages (https://media.hls.kz/ru/videos?start=20).

A story with participation of the invited expert toxicologist Bashinskaya G.N. (chief freelance toxicologist of Astana) was published on the page of NCPH on Facebook.

Khabar TV channel (https://www.youtube.com/watch?v=_leomDuHL-I) broadcasted a report on this study with the participation of the director of "International Clinic of Asia" Narbaev A.E., the partner organization of the study in the program of the news of the day at 21:00 of 21.01.2021 (11th-15th minutes).

Figure 1. Handout in the form of leaflet in 2 languages (Kazakh and Russian) about the study

3. As mentioned above, there were difficulties in recruiting the required number of respondents (1,000 children) in the planned age category.

Taking into account such circumstances as the novelty of the study, as well as the willingness to participate in the study of parents whose children were younger or older than the planned age, with the consent of the UN Children's Fund UNICEF, the age range was expanded.

Thus, according to the results of analyzing the obtained data, a total of 1000 people aged 0 to 20 years participated in the study (see Figure 3).

At the same time, during the survey, the cities of Shymkent and Karaganda, where the number of respondents amounted to only 27 and 41 people, respectively, practically "dropped out" of the study. Therefore, in coordination with UNICEF a decision was made to fill the missing number of respondents from the cities of Nur-Sultan and Almaty.

Field work was completed on April 30, 2021, instead of the planned date of December 2020.

As a result of fieldwork, a database was generated, representing information from the questionnaire and results of laboratory tests of children's venous blood for lead content.

Distribution of participants by cities: Nur-Sultan – 511, Almaty – 421, Shymkent – 27 and Karaganda – 41 people (see Figure 2).

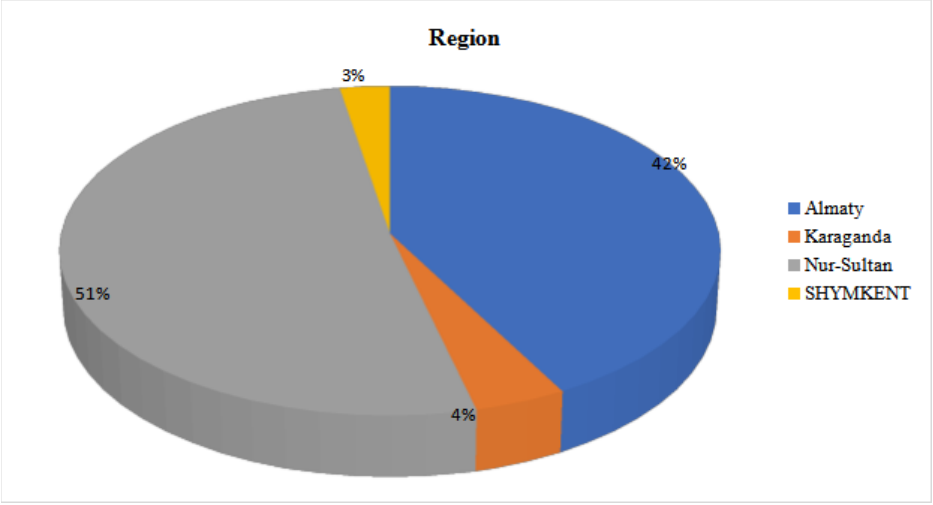

Figure 2. Proportion of regions which took part in the study

This study was anonymous. Therefore, personal identification data of the participants (respondents) were not included in the analytical part and are not disclosed.

Description of the obtained data analyzed using Epi info statistical analysis software

We should note that not all respondents answered all questions. In this regard, in some contingency tables the number of received answers is less than the number of respondents (less than 1000 people).

The survey was conducted between November 2020 and April 2021.

The age composition of the interviewees ranges from less than 1 year to 20 years old. Due to the fact that 19- and 20-year-olds did not fall within our study population, they were not included in the analysis. Thus, a dataset of 998 records was analyzed.

The column "Age" was filled out by all respondents. The greatest number of respondents who answered this question fell in the following age groups: 5 years – 126 people (12.6%), 7 years – 123 people (12.3%), 6 years – 117 people (11.7%) and 4 years – 93 people (9.3%).

One of the null hypotheses of this study was that "sex does not affect blood lead concentrations when lead is ingested by a child over a long period of time". That is, both boys and girls are equally susceptible to lead poisoning. The sex distribution of respondents is shown in Figure 4. The linear regression table shows that the P-value is less than 0.005, which confirms the null hypothesis.

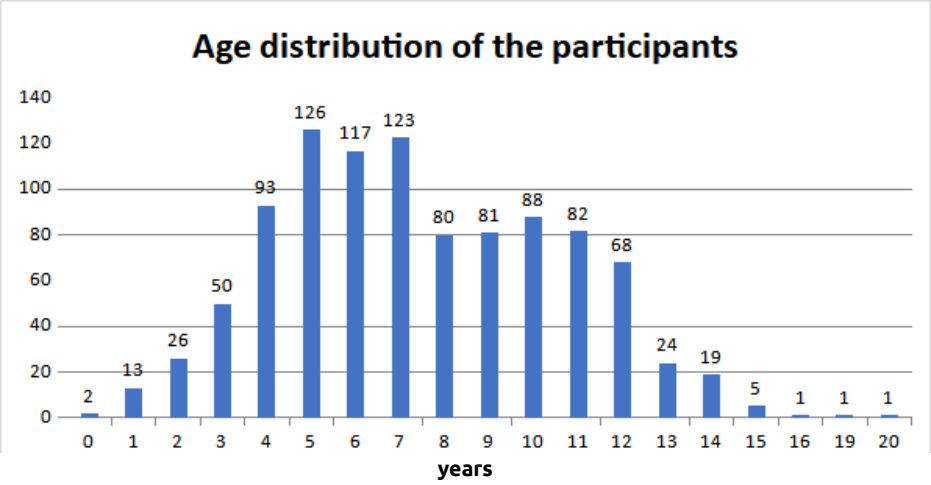

Figure 3. Histogram of age distribution of study participants

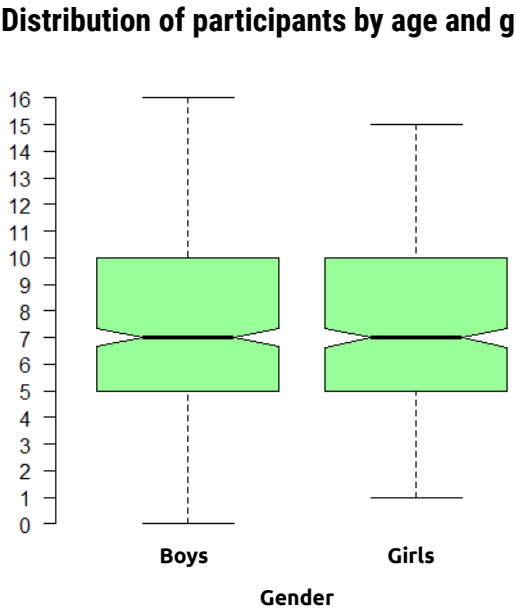

Figure 4. Box plot of age among boys and girls

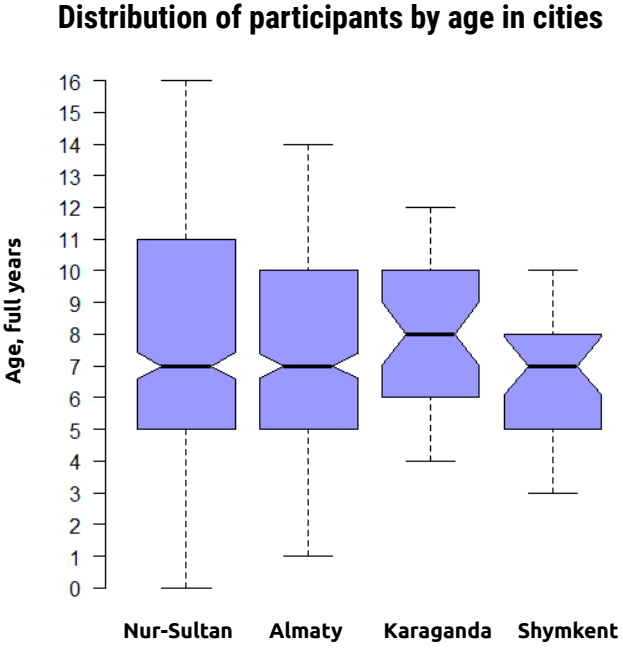

Figure 5. Box plot of age by cities studied

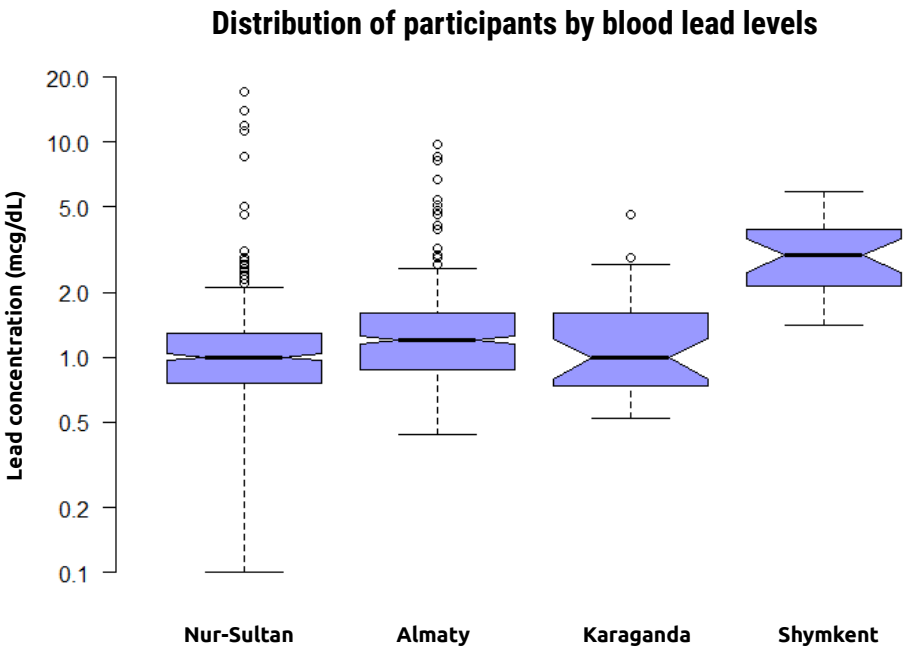

Figure 6. Box plot of blood level concentration by study location

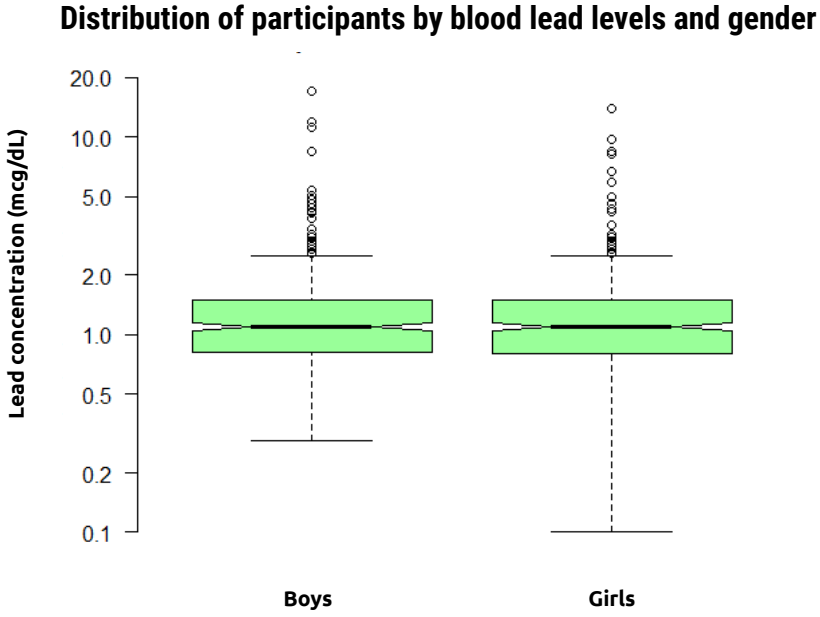

Figure 7. Box plot of blood lead concentration by sex

Analysis of the distribution of data in the frequency tables (Annex 2) for questions related to risk factors for lead intoxication showed that there is prevention of children's contact with potential sources of lead.

However, analysis on some questions was difficult because of non-response to many follow-up questions.

For example, question «17. Do you or your children live near large roads?» had 2 response options: «Yes/No». Number of respondents who answered this question was 987. Of them, 788 – 80% answered «Yes». However, only 203 respondents answered the follow-up question «18. If yes, then how long?». At the same time, we need to point out that the 203 (20%) people who answered this question are not necessarily the same ones who answered the previous question.

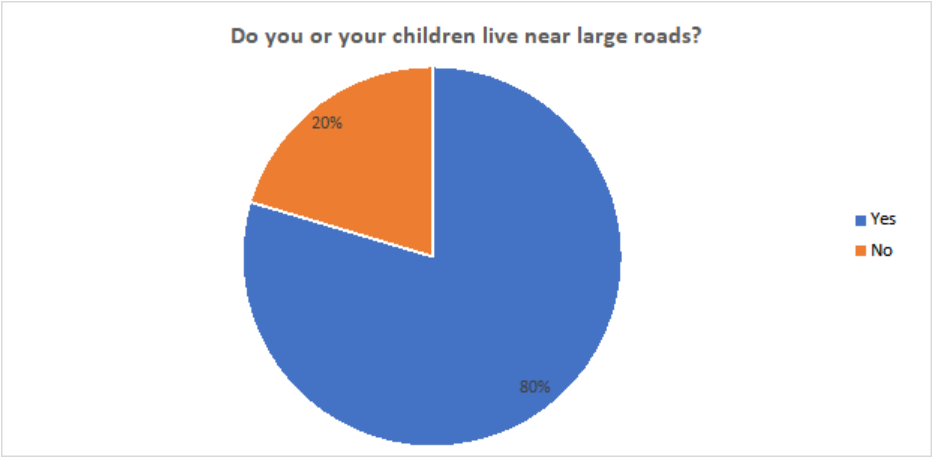

Figure 8. Example of questionnaire question

Thus, we see that more respondents are required for representativeness in order to obtain a statistically significant number of responses.

Linear regression analysis was done by sex, region and data obtained.

This analysis has shown that sex does not affect lead intoxication: both girls and boys were similarly exposed to lead.

Meanwhile, the overall analysis showed that there was no association between the analyzed variables, and the obtained blood test results.

Blood was analyzed for lead content in laboratory conditions. Normally, lead in the body should be less than 1 microgram per milliliter (mcg/mL).

Collected results of blood tests show that there were 4 results exceeding normal values (comprising 0.4%), and 3 borderline results (comprising 0.3%).

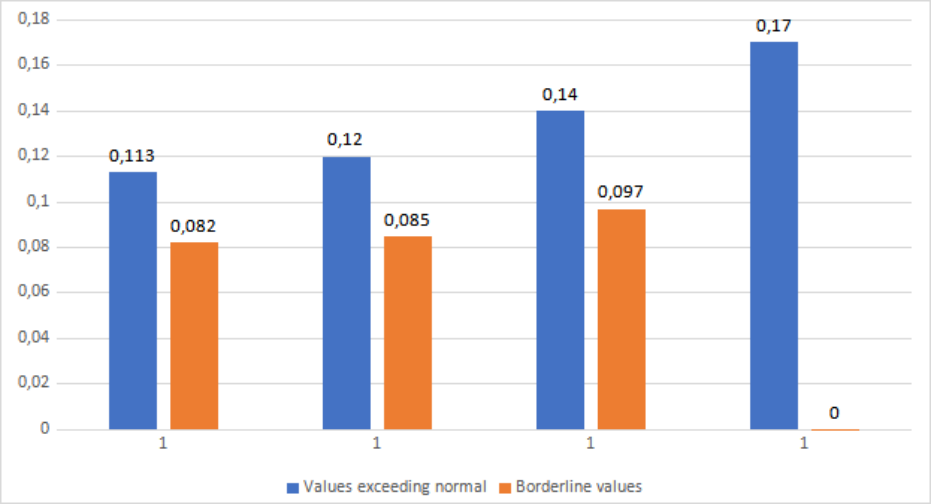

Figure 9. Values exceeding normal and borderline values, mcg/ml

However, these data, even in our small sample, are negligible to trace the association between the analyzed variables: risk factors and the obtained blood lead values in children.

Lack of association between variables was also shown in contingency tables (Annex 3).

The SPSS program was used to verify the statistical analysis performed in the Epi info program. The results were identical.

The following set of questions was also analyzed.

1. How often do your children put toys and other items in their mouth?

There were 991 responses to this question, which is almost 100% of the study population.

The answers to this question looked as follows: «Always» – 9 people, or 0.91%. «Never» – 377 people (38.04%); «Rarely» – 399 people (40.26%); «Moderately» – 124 (12.51%); «Often» – 82 people (8.27%).

Thus, we can see that the answers "Never" and "Rarely" account for the largest share of answers (40% on average). The smallest share of answers was for the "Always" option (less than 1%).

In this case, we are inclined to assume that parents are closely supervising children of younger age to avoid such a situation (see question). At the same time, the majority of respondents were beyond the age of such a risk.

2. How often are your children exposed to batteries?

This question was also answered by almost 100% of respondents (994 people),

There were 4 people who answered "Always" to this question, which amounted to – 0.4%. "Never" – 434 people (43.66%); "Rarely" – 470 people

(47.28%); "Moderately" – 65 people (6.54%); "Often" – 21 people (2.11%).

Distribution of answers for this question is not much different from the previous one, which allows us to make similar inferences.

Questions 3. How often do your children drink tap water?; 4. How often are your children exposed to radiators, pipes?; 5. How often are your children exposed to paint at home?; 6. How often are your children exposed to paint outside?; have similar distributions of answers as the previous questions, where majority of the answers fall under categories «Never» and «Rarely». So, parental vigilance about exposing children to potential risk factors is evident.

7. How often do you wet clean your home?

This question was answered by 991 people, which is almost 100% of the study population.

There were 375 people who answered "Always" to this question, which amounted to 37.84%. "Never" – 16 people (1.61%); "Rarely" – 42 people (4.24%); "Moderately" – 173 people (17.46%); "Often" – 385 people (38.85%).

The response options "Always" and "Often" account for the largest share of responses (38% on average). This suggests that in most cases one of the precautions against lead intoxication – frequent wet cleaning – is being followed.

8. How often do you wash children's toys?

A total of 986 people responded to this question, which is practically 98.6% of the study population.

The distribution of answers to this question was slightly different: 264 people answered "Always", which amounted to 26.77%; "Never" – 33 people (3.35%); "Rarely" – 177 people (17.95%); "Moderately" – 257 people (26.06%); "Often" – 255 people (25.86%).

In this case we see that "Always," "Often," and "Moderately" each accounted for a quarter of all responses. However, about 18% answered "Moderately" and more than 3% answered "Never". In this instance we can see that not enough attention is paid to the cleanliness of toys.

9. How often do your children play with cosmetics?

Of the 980 people who responded to this question, 431 respondents indicated "Never" (43.98%), and 412 respondents indicated "Rarely" (42.04%). It follows that in 843 cases (84.3%) there is practically no constant or long-term contact of the study population with cosmetics, which indicates that there is no association (correlation) between cosmetics and chronic lead intoxication.

10. How often are your children exposed to and play with ceramic items?

This question was answered by 980 people (98%). The answer "Always" amounted to 0.1%. The answer "Often" was chosen by 20 people (2%). The largest number of answers falls on the options "Never" – 49.18% (482 respondents) and "Rarely" – 36.63% (359 respondents). 118 people responded "Moderately" (12.04%). In this case we also see that there was no correlation of the obtained answers with lead intoxication in the studied population.

11. How often do you check chemical composition when buying baby

food and general food items?

Concern arises when analyzing the responses to this question.

Always – 165(16.8%), Never – 255 (25.97%), Rarely – 294 (29.94%), Moderately – 167 (17.01%) and Often – 101 (10.29%). There was a total of 982 responses to this question (98.2%).

In this case, we see that only 16.8% of respondents pay attention to the chemical composition of food products. On average, in 25% of all cases there is no vigilance. Nevertheless, we can suppose that the population of the country has trust in the food products sold on its territory.

Questions 12. How often do your children eat canned food, unwashed vegetables and fruit?; 13. How often do you use brightly colored (painted) kitchenware for children? have similar response patterns. In these cases, we also see that there is no association between these variables and lead intoxication.

14. How often do your children play outside near cars and parking lots?

Total number of responses 983 (98,3%).

Always – 30 (3.05%), Never – 120 (12.21%), Rarely – 338 (34.38%), Moderately – 357 (36.32%), Often – 138 (14.04%). Distribution of answers clearly shows that in this case children are not near cars. Nevertheless, we do not rule out the possibility that this question may have been misunderstood by parents. After all, cars and parking lots have long become an integral part of our life.

15. How often do your children spend time in a car?

Total number of responses 980 (98%).

Always – 32 (3.275%), Never – 34 (3.47%), Rarely – 213 (21.73%), Moderately – 401 (40.92%), Often – 300 (30.61%). In this instance, we see that more than 30% of parents mostly use motor vehicles to transport their children. About 62% of parents Rarely use motor vehicles. However, here again we tend to believe that the question was not fully understood, as motor transport is used daily and all big cities, which all the cities participating in the survey are, are associated with road traffic.

However, we can see that in most cases there is prevention of children's contact with potential sources of lead (see Figure 7).

We should note that laboratory results for lead concentrations in blood samples were originally reported in micrograms per milliliter (mcg/mL). However, in clinical protocols and other studies, lead concentrations are expressed in micrograms per deciliter (mcg/dL). To ensure comparability and comparability of our study data with reference values used in clinical protocols and other studies, a conversion was performed using the following formula: 0.1 μg/mL=10 mcg/dL.

Estimating the proportion of children with high blood lead levels (≥5 mcg/dL) is one of the most important research questions. According to the results of the study, the proportion of children whose blood lead concentration was equal to or greater than 5 mcg/dL was 1.4% (14 of 998 children tested). At the same time, there were no significant differences by sex, age, and location ($p>0.05$).

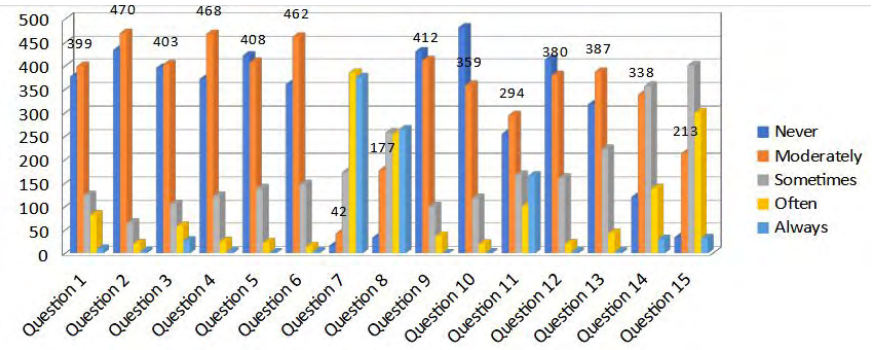

Figure 10. Main set of questions.

Table 2 **Prevalence of high blood lead concentrations by sex, age and study site**

	High level of lead concentration (≥5 mcg/dL) n (%)	Normal level of lead concentration (<5 mcg/dL) n (%)
TOTAL	14 (1.4)	984 (98.6)
Gender(p=0.57)		
Boys	6 (1.2)	498 (98.8)
Girls	8 (1.6)	486 (98.4)
Age(p=0.53)		
0—4	1 (.5)	183 (99.5)
5—9	8 (1.5)	519 (98.5)
10—16	5 (1.7)	282 (98.3)
City (p=0.65)		
Nur-Sultan	7 (1.4)	504 (98.6)
Almaty	6 (1.4)	413 (98.6)
Karaganda	0 (0)	41 (100.0)
Shymkent	1 (3.7)	26 (96.3)

Prevalence of potential risk factors for lead poisoning and their association with blood lead concentration levels

Children, as reported by their parents or legal guardians, in most cases experience infrequent or moderately frequent exposure to modifiable potential risk factors (Table 2). The highest frequency is observed for such factors as being inside a car ("often" and "always" – 34%) and being on the street near cars and parking lots ("often" and "always" – 17.2%).

Table 3 **Distribution of children according to frequency of exposure to behavioral factors potentially associated with lead poisoning.**

	Never	Rarely	Moderately	Often	Always
1. How often do your children put toys and other items in their mouth?	38.1%	40.2%	12.4%	8.3%	0.9%
2. How often are your children exposed to batteries?	43.5%	47.4%	6.6%	2.1%	0.4%
3. How often do your children drink tap water?	39.9%	40.8%	10.6%	5.9%	2.7%
4. How often are your children exposed to radiators, pipes?	37.4%	47.4%	12.3%	2.5%	0.3%
5. How often are your children exposed to paint at home?	42.4%	41.2%	13.9%	2.3%	0.2%
6. How often are your children exposed to paint outside?	36.4%	46.9%	14.9%	1.5%	0.3%
7. How often do you wet clean your home?	1.6%	4.2%	17.5%	38.9%	37.7%
8. How often do you wash children's toys?	3.4%	18.0%	26.1%	25.9%	26.6%
9. How often do your children play with cosmetics?	43.9%	42.1%	10.2%	3.8%	0.0%
10. How often are your children exposed to and play with ceramic items?	49.1%	36.7%	12.1%	2.0%	0.1%
11. How often do you check chemical composition when buying baby food and general food items?	26.0%	30.0%	17.0%	10.3%	16.6%
12. How often do your children eat canned food, unwashed vegetables and fruit?	42.2%	38.9%	16.5%	2.1%	0.3%
13. How often do you use brightly colored (painted) kitchenware for children?	32.5%	39.9%	22.9%	4.4%	0.3%
14. How often do your children play outside near cars and parking lots?	12.1%	34.4%	36.4%	14.1%	3.1%
15. How often do your children spend time in a car?	3.5%	21.7%	40.9%	30.7%	3.3%

Among environmental risk factors, children were most exposed to home renovation in the presence of the child (24.2%) and living near large roads (20.2%).

Table 4

Existence of potential environmental risk factors for lead poisoning

	Yes	No
Have you ever made any home renovations while the child was in the home?	24.2%	75.8%
Do you and your children live near large roads?	20.2%	79.8%
Do you and your children live near industrial plants and factories?	2.9%	97.1%
Do you and your children live near construction areas?	14.6%	85.4%

The association between the frequency of exposure to different risk factors and blood lead concentration levels was assessed using analysis of variance. The results of the study showed no statistically significant association in any of the modifiable risk factors ($p>0.05$) (Table 4).

Table 5

Mean blood lead concentrations depending on the frequency of exposure to behavioral risk factors.

	Never	Rarely	Moderately	Often	Always	p-value
1. How often do your children put toys and other items in their mouth?	1.37	1.35	1.48	1.28	1.05	0.69
2. How often are your children exposed to batteries?	1.35	1.37	1.25	1.92	0.93	0.20
3. How often do your children drink tap water?	1.43	1.25	1.41	1.47	1.67	0.14
4. How often are your children exposed to radiators, pipes?	1.42	1.33	1.36	1.31	0.80	0.77
5. How often are your children exposed to paint at home?	1.45	1.33	1.25	1.16	1.46	0.34
6. How often are your children exposed to paint outside?	1.42	1.36	1.23	1.36	0.70	0.47
7. How often do you wet clean your home?	1.95	1.40	1.43	1.31	1.36	0.26

	Never	Rarely	Moderately	Often	Always	p-value
8. How often do you wash children's toys?	1.27	1.38	1.37	1.33	1.40	0.96
9. How often do your children play with cosmetics?	1.34	1.30	1.51	1.67	1.35	0.12
10. How often are your children exposed to and play with ceramic items?	1.33	1.31	1.56	1.39	0.73	0.30
11. How often do you check chemical composition when buying baby food and general food items?	1.31	1.31	1.37	1.60	1.32	0.21
12. How often do your children eat canned food, unwashed vegetables and fruit?	1.36	1.31	1.43	1.27	1.36	0.24
13. How often do you use brightly colored (painted) kitchenware for children?	1.34	1.36	1.41	1.08	1.40	0.54
14. How often do your children play outside near cars and parking lots?	1.35	1.35	1.36	1.31	1.39	0.99
15. How often do your children spend time in a car?	1.13	1.33	1.36	1.38	1.29	0.80

However, a statistically significant association was found between a child's stay in the home during renovation and blood lead concentrations (Table 5).

Table 6

Mean blood lead concentrations depending on the presence of exposure to environmental risk factors.

	Yes	No	p-value
Have you ever made any home renovations while the child was in the home?	1.49	1.31	0.036 *
Do you and your children live near large roads?	1.47	1.33	0.11
Do you and your children live near industrial plants and factories?	1.23	1.36	0.56
Do you and your children live near construction areas?	1.30	1.36	0.54

** $p<0.05$*

RESULTS OF THE STUDY

We conducted the work with the population in the context of a pandemic. The solutions to the constraints (barriers) we faced were dictated by generally accepted moral and ethical standards, available resources, and the desire to see the work through to its logical conclusion.

In the course of the study, we managed to realize all the set objectives except for the recruitment of the required number of respondents in the initially planned age range and quantitative distribution by cities (260 people each in all 4 participating cities).

At the same time, the analyzed data allow us to say that our pilot study fulfilled its purpose.

We were able to see what limitations and challenges we might face in conducting a larger (country-level) study.

We should recognize that we were not able to see the picture of chronic lead intoxication in the results of the study among the participating population. However, we realize that the representativeness of the sample, rapid measures to address the barriers, activities of antivaxxer campaigns, distrust of the population due to their activity and many other factors influenced the course of the study and its results.

At the same time, the analysis of objective data provided by Kazhydromet indicates that lead is present in the air. Lead is present in almost all industrial regions of the country, which gives us the right to say that it is necessary to expand this study.

When discussing the need to conduct studies on long-term lead exposure, i.e., to expand this study, we rely on the following objective reasons:

1. Residential housing: 60% of the buildings were built before 1980 (according to the existing GOST (building codes), lead was added to paint; in 1978, the GOST was changed to prohibit lead additives. According to unreliable data, the use of lead paint continued until 1990);
2. Increase in the number of cars (according to the Association of Kazakhstan Auto Business, there are 4 million 566 thousand vehicles of all types registered in Kazakhstan, more than half of them are older than 20 years, which is 2 million 485 thousand units), which increases the emission of exhaust gases into the atmosphere;
3. Presence of metallurgical and chemical industry enterprises (physical volume index – 104.7%) [11];
4. According to the data of biomonitoring of atmospheric air, in a number of cities some indicators are exceeding permissible values ("Kazhydromet" data: in Nur-Sultan city 973 cases of exceeding the maximum permissible limits of harmful substances in the air were recorded, the most polluted areas are Akzhol street, Shapagat communal market area and "Koktal-1" micro district; in Almaty city 726 cases, in Ust-Kamenogorsk city – 786, in

Karaganda city – 187);

5. there are statistical data on changes in the incidence of respiratory diseases in the population of cities where increased air biomonitoring indicators are registered (in 2017 respiratory diseases were registered in 5 million 222 thousand Kazakhstani citizens, in 2018 this figure amounted to 5 million 188 thousand 805 cases, but mortality rates cause alarm: in 2009, 48.52 cases per 100 thousand people were registered, in 2015 there were 105 cases per 100 thousand people, and in 2018, there were 87.08 cases per 100 thousand population). Data are shown on a national scale;
6. Climatic conditions entail movement of contaminated objects (soil, water, atmospheric emissions).

Additionally, there are difficulties in conducting such studies as well as organizing health sector's response to the situation:

1. Toxico-chemical studies are not available to the general population (lack of chemical-toxicological laboratories within the health care facilities);

Lack of screening tests for lead contamination in the pediatric population.

2. The National Drug Formulary does not include medications that are used to treat conditions arising from lead poisoning (antidotes).

Let's focus on methods of diagnosing chronic lead intoxication.

As part of this study, we reviewed the clinical protocols/algorithms for diagnosing lead intoxication in Kazakhstan. There are 3 of them.

1. Algorithm of diagnostics of chronic intoxication (standard of organization of rendering toxicological service in the Republic of Kazakhstan № 18273 dated 06.02.2019);

2. Clinical protocol for diagnosis and treatment of toxic effects of substances, mainly of non-medical nature (adults and children). Recommended by the Expert Council of the RSE on REM "Republican Center for Healthcare Development" of the Ministry of Health and Social Development dated October 30, 2015, Protocol No. 14;

3. Clinical protocol for diagnosis and treatment of chronic lead intoxication. Approved by the Joint Commission on Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan dated June 29, 2017, Protocol No. 24.

We deem it necessary to update these documents.

In this regard, we have proposed a revised clinical protocol for the diagnosis and treatment of lead intoxication in Annex 3.

Table 7. Diagnostic methods of chronic lead intoxication.

BLL (blood lead level) - Atomic absorption spectrometry and/or electrochemical technique (potentiometry)	Significant: > 10 mcg/dL Indications for chelate treatment: > 45 mcg/dL
Zinc protoporphyrin (ZPP) or erythroprotoporphyrin (EPP)	BLL > 20 mcg/dL
Aminolaevulinic acid dehydratase (ALAD)	BLL > 5-10 mcg/dL
Lead in bones	«Lead lines» (> 45 mcg/dL for over 2 months) Rg- fluorometry (RGF)
Lead in urine	After chelate treatment

CONCLUSIONS

It is worth noting that all stages of the study were conducted against the backdrop of the COVID-19 pandemic. The research team had to face barriers and address them promptly.

At the same time, we saw the need to screen for lead in children's bodies.

Why is it necessary?

- Poisoning symptoms are **NON-SPECIFIC**;
- Lead poisonings are often **SUBCLINICAL**;
- Diagnosis is based on laboratory screening.

Screening results will allow to identify subclinical, asymptomatic forms of lead intoxication, to determine measures to improve the health and quality of life of the child population.

We can draw the following conclusions and recommendations based on the results of our work:

Findings

The project was designed to conduct a pilot analysis of the epidemiological situation of lead poisoning among children in the Republic of Kazakhstan, taking into account possible barriers.

This project allowed us to realize that we need to expand the category of children studied, the scope of the study and its components.

Children, as reported by their parents or legal guardians, in most cases experience infrequent or moderately frequent exposure to modifiable potential risk factors. The highest frequency was associated with factors such as being inside a car and being on the street near cars and parking lots. Among environmental risk factors, children were most frequently exposed to home renovations in the presence of the child (24.2%), as well as living near large roads (20.2%).

The results of the study showed no statistically significant association with lead concentration for any of the modifiable risk factors. However, a statistically significant association was found between a child staying in the home during renovation and blood lead concentrations.

The mean blood lead concentration level was 1.36 mcg/dL, with a median of 1.1 mcg/dL. The highest mean level of lead in children's blood was observed in Shymkent city (3.1 mcg/dL), and in Almaty, Nur-Sultan and Karaganda cities it ranged from 1.24 mcg/dL to 1.42 mcg/dL. We found no significant differences in the mean blood lead concentration level by sex and age ($p>0.05$). The excess of lead content among children of Shymkent city can be explained by environmental pollution by the Lead Plant, which operated between 1934 and 2018.

The proportion of children whose blood lead concentration was equal to

or greater than 5 mcg/dL, indicating lead poisoning, was 1.4% (14 out of 998 children examined). There were no significant differences in the prevalence of lead poisoning by sex, age, and location ($p>0.05$).

Recommendations

1. To review the sample size and increase the number of respondents.
2. Adjust the approach to sample size by households in the regions by obtaining the necessary data from the register of the population registered with outpatient clinics.
3. To ensure representativeness of the data collected, it is necessary to adjust the study design. Namely, a combined design should be envisioned, where the principles of cross-sectional study can be used, but with at least two cohorts of respondents.

This approach would expand the number of variables to be studied and allow for their comparison.

4. It is recommended to conduct a nationwide study with expansion of assessed risk factors (content of heavy metal salts in the environment (soil, water, air, vegetable products, food), industrialization of regions and its impact, etc.).

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ANNEXES

1. Annex A – summary table.
2. Annex B– frequency tables (proportions).
3. Annex C– proposed clinical protocol for the diagnosis and treatment of chronic lead intoxication.
4. Annex D – study protocol.
5. Annex E – questionnaire template.

$4f^{14}\ 5d^{10}\ 6s^2\ 6p^2$