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Comprehensive assessment of unutilized and obsolete pesticides impact on genetic status and health of population of Almaty region

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ABSTRACT

The group of persistent organic pollutants (POPs) are particularly dangerous for the environment and by consequence for human health because of the risk to be transmitted in the food chain. Among them, the urgent problem of obsolete and forbidden organochlorinated pesticides (OCPs) needs a rigorous management in many countries, including Kazakhstan.

The aim of our study was to evaluate the effect of pesticides content in food products on the genetic status and health of the population living on the contaminated areas near destroyed warehouses for OCPs (4 villages of Talgar district and 1 control site, Almaty region).

The food products sampled in Taukaraturyk (control site), and in 4 villages where non-utilized obsolete pesticides were discovered: Beskainar, Kyzylkairat, Amangeldy, and Belbulak. The contents of 24 pesticides in food products from plant (apples, pears, tomatoes, cucumbers, sweet peppers) and animal (beef meat, cow milk, honey) origin, that grown in places of localization of non-utilized OCPs, were determined, sometimes in high and unacceptably high concentrations (before 2500 times over MRL). In pears, the pesticides content (especially DDT, γ-HCH, β-HCH, endosulfan, and aldrin pesticide group), was higher than in other fruits. Among vegetables, the highest levels of all groups of pesticide were found in cucumbers. Beef meat samples demonstrated increased contents of β-HCH, γ-HCH, endrin and dieldrin. In cow milk samples only the high concentration of dieldrin was found. The content of pesticides in meat was 4–5 times higher than in milk. The medical examinations, carried out among the cohorts living around the polluted by pesticides territories and control cohort from ecologically favorable village, showed that there were more individuals with high and middle levels of somatic health in the control group than in groups exposed to OCPs. The long-term effect of the pesticide contamination of the environment on genetic status of the population was assessed by chromosomal aberration (CA) frequencies. The highest level of chromosomal aberrations was identified for the examined residents of Kyzylkairat (41%) and Belbulak (38%), a high level in Amangeldy (12%), and middle level in Beskainar (6.5%). The association between the CA frequency, health status and the pesticides contents in food were assessed by a Spearman rank correlation. The low indicators of somatic health status were strictly associated with high levels of CA, and good health status indicates that the CA rates did not exceed the spontaneous level of mutagenesis. The strongest correlation was shown between high levels of chromosomal aberrations and the content of different pesticides in pears (Cr = 0.979–0.467), tomatoes (Cr = 0.877–0.476), cucumbers (Cr = 0.975–0.553) and meat (Cr = 0.839–0.368). The obtained results highlight the need to improve health protection by increasing the public

Abbreviations: POPs, persistent organic pollutants; OCPs, organochlorinated pesticides; MRL, maximum residue level; MPC, maximum permissible concentration; CA, chromosomal aberration; Hexachlorobenzene, HCB; Hexabromobenzene, HBB; Hexachlorocyclohexane, HCH; Heptachlor, HC; Heptachlor epoxide, HCE; VLC, vital lung capacity; VI, vital index; RI, Robinson index; OHA, overall health assessment; Cr, rank correlation index.

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awareness to the security of the storage of obsolete OCPs in order to strengthen food safety by efficient control services.

1. Introduction

Intensive anthropogenic pollution of the environment affects the populations of plants and animals, and ultimately influence on human health. Environmental pollutions are one reason of mutation process and genetic load increasing in human populations (WHO, 2018; Sharabchiev, 2015). Human, his environment, and the public health have always been the state priority. It is known that human health depends on quality of health care system, genetic predisposition and the life style including nutrition and the ecological environment (Bircher and Kuruvilla, 2014).

An increase of the number of hereditary and multifactorial diseases, congenital pathologies and malformations especially is expressed in ecologically unfavorable regions (Parrón et al., 2014; Teodoro et al., 2019). Among the chemical pollutants of the environment, persistent organic pollutants (POPs) are particularly dangerous. The Stockholm Convention is an international agreement to protect human health and the environment from POPs. It was adopted in 2001 and entered into force in 2004 initially for 12 POPs. Currently, 16 additional POPs have been added to the Stockholm Convention in 2017 (http://chm.pops.int/TheConvention/ThePOPs/TheNewPOPs). The most dangerous substances were: organochlorine pesticides (OCPs) and their metabolites (aldrin and dieldrin, DDT, hexachlorobenzene, hexachlorocyclohexane, lindane, heptachlor, heptachlor epoxide); organophosphorus pesticides (bazudine, malathion, thiophos, metaphos); polychlorobiphenyls; aflatoxins; cadmium and lead. The danger of pesticide influence is increased due to the fact that numerous initially nontoxic pesticides compounds can be transformed in soil into persistent toxic metabolites. Then, they can accumulate in food products during a very long time and in a multiple manner, transmitted through the food chain, accumulate in the human body and thereby affect the genetic status and health of the population (Gilden et al., 2010; Hernández et al., 2013; Mostafalou and Abdollahi, 2013; Sagiv et al., 2019).

The use of organochlorine pesticides has been stopped by many countries because of their toxicity in Human (Rodrigues et al., 2011; Mostafalou and Abdollahi, 2017). Therefore, these pesticides have been banned by the Stockholm convention, signed by 183 countries all over the world, among them the Republic of Kazakhstan. From 1960 to 1990, OCPs were widely used in agriculture in Kazakhstan and other countries of Central and East Asia. Their usage was officially stopped in the 70s years, but DDT stocks continued to fill unused storage facilities, from where they could contaminate the soil and water of Central Asian rivers (Khadzhamberdiev et al., 2010). In this regard, the Aral Sea basin is the most environmentally unfavorable region in Central Asia. Most studies of the effects of POPs (especially OCPs) on public health have been conducted in this region. The presence of toxic concentrations of POPs in food products (Diacono et al., 2008; Konuspayeva et al., 2009; Muntean et al., 2003), in human blood and breast milk (Ataniyazova et al., 2001; Zetterstrom, 1998) were detected. Research conducted in Kazakhstan, reported about traces of hexachlorocymclohexane, lindane, hexane chlorothalonil, polychlorinates, and lead in camel milk that consuming by human (Konuspayeva et al., 2011a,b; Konuspayeva et al., 2011 a; Meldebekova et al., 2008; Nurseitova et al., 2016).

The negative impact of POP's on the mental health (Crighton et al., 2003), increased risk of acute infectious and inflammatory diseases of the genitourinary system (Sitdykova et al., 2010), and cancer development (Sailaukhanuly et al., 2016) have been revealed in the inhabitants of the Aral zone. Pesticides induce reproductive and endocrine system disorders (Evangelou et al., 2016; Bretveld et al., 2006), cancer and respiratory failure, delayed development of the nervous and immune systems, and inborn defects (Gilden et al., 2010; Guyton et al., 2015). Most of pesticides have skin-resorptive toxicity (Mesnage and Séralini, 2018), immunotoxicity (Galloway and Handy, 2003), and induce mutagenic, antimitotic and embryotoxic effects (Mohamed and Mohamed, 2015). Similar studies have been conducted in other Asian countries, such as Japan, China, Philippines, Vietnam, Cambodia, India, Malaysia, Indonesia, Pakistan (Ali et al., 2020; Dewan et al., 2013; Pathak et al., 2010; Tanabe and Kunisue, 2007).

In accordance with the Stockholm Convention, Kazakhstan has committed not to produce, not use, and dispose the stockpiles of chemicals as OCPs considerate as especially dangerous for humans. However, the problem of obsolete, unusable pesticides in Kazakhstan is the necessity to organize the environmental remediation measures and the disposal of uncontrolled pesticide stocks that have been polluting the environment for a long time. According to the data of Ministry of agriculture of Republic of Kazakhstan, dated by 2012, about 6931.4 tons of obsolete, banned and unusable pesticides were stored in warehouses of various regions all over the Republic https://www.gov.kz/memleket/entities). There are 64 abandoned pesticide warehouses, which have been detected only on the territories of 10 districts of the Almaty region. Approximate assessment revealed about 68.443 kg of obsolete and unusable pesticides (class of sym-triazine, organophosphorylated organic chlorinated or organic fluorinated compounds, thiocarbamate) of German and Chinese origin (Nurzhanova et al., 2018) on these sites. The former storage facilities of POPs were in fact abandoned or became private properties with the land on which they were located. As a result, almost all the warehouses were completely or partially destroyed, the containers rotted, the chemicals were scattered randomly, and pesticides penetrate the soil, contaminating surface and groundwater sources. Previous monitoring studies revealed that soil around the former repositories was contaminated by OCPs in concentrations much higher than the maximum permissible levels (Berkinbaev, 2012; Nurzhanova et al., 2008, 2010, 2013bib_Nurzhanova_et_al_2013bib_Nurzhanova_et_al_2008bib_Nurzhanova_et_al_2010). However, there are no studies carried out in these contaminated regions on contents of the different OCP compounds in food products of plant and animal origin and their influence on human health. The objectives of our study were following: (1) To determine the content of non-utilized pesticides in food products of plant and animal origin grown in the pesticides burial areas of the Almaty region; (2) To establish the level of somatic health and cytogenetic status of the population in this sites; (3) To assess the impact of high concentrations of pesticides in food products to genetic status of population living near the polluted territories.

2. Materials and methods

The study was carried out respecting existing ethical standards according to the decision of the local ethical commission of the Kazakh-Russian Medical University (protocol No. 52 of September 5, 2017). Peripheral blood samples were collected from volunteers of study with signed informed consents and questionnaires.

2.1. Study sites and objects

The study was carried out in the Talgar district of the Almaty region ($43^0$20 ′N $77^0$25′E) located 50 km East from the town Almaty. This region occupies an area of 3.8 thousand square kilometers with a population of 196.567 inhabitants. The climate of the region is sharply continental. Almost all landscapes, from glaciers to semi-deserts, are represented on this territory. Talgar district includes 10 rural districts and 53 villages, whose residents are mainly employed in the agricultural sector.

The samplings of the study were carried out in 4 villages of the Talgar district (Beskainar, Kyzylkairat, Amangeldy, Belbulak), where the burial sites of the obsolete pesticides had been previously identified. The village Taukaraturyk, that located in Enbekshikazakh district of Almaty region, was selected as a control site. The former storage facilities for chemical plant protection products in Taukaraturyk were not listed in the data of the regional and district Territorial Administration and the Ministry of Ecology of the Republic of Kazakhstan. The nearest warehouse from Taukaraturyk is at a distance of 60–70 km. The location of studied settlements is indicated in Fig. 1.

All former storage facilities and territories around have today private owners. In Kyzylkairat, two warehouses of pesticides, located side by side, were discovered. One had been destroyed and in the second, a residential private house was installed. About 10000 kg of obsolete pesticides were took out and used by the residents, as evidenced by the presence of empty containers in private households. In Belbulak there was 1 warehouse of pesticides, which has been currently disposed of, and a new plant producing animal feed was built on this territory. In Amangeldy, 2 obsolete stocks of pesticides were detected on the territory of agricultural college. One of them is a room of 10 m^2, where about 450 kg of pesticides mixture were found out. The second one (about 30000 kg of pesticides mixture) has been buried in concrete water scoop or distributor located near the training field. The pesticide warehouse in Beskainar was destroyed by the owner, and unused waste pesticides were buried nearby, as evidenced by the strong smell. Pesticide containers are used as drinking bowls for animals. The territory is going to be used for the construction of holiday cottages. According to the Talgar District Territorial Administration official data, the following pesticides should be stored there: phasolone, chlorophos, granosan, nisaran, decis, nitrofen, zinc phosphide, metaphos, sevin and phosphamide. In all studied points, local residents grow fruits (apples, pears), vegetables (tomatoes, cucumbers, sweet peppers) and contain livestock (cattle). Grown food products are sold in free trade and are consumed by local residents. Pesticide containers are used in the household.

The study objects were food products of plant and animal origin, and population living close to these former pesticide warehouses. Table 1 and Supplement A (Fig.S.A1-A.4) represents data about locations and quantity of biosamples.

2.2. Determination of pesticide contents in products of plant and animal origin

The determination of pesticides was carried out in products of plant (apples, pears, tomatoes, cucumbers, sweet peppers) and animal (beef meat, cow's milk, honey) origin. Meat, milk and honey were sampled in May–June 2019, vegetables and fruits - in late July-early August 2019, when they reached full ripeness. Food products were sampled in private households or bought at small shops, spontaneous markets located close to former pesticides warehouses after getting the evidences of local residents consume this kind of product. For this, residents and sellers were questioned, and only local food samples were taken for the analysis. In each village, products were sampled at three different points located in proximity to the former pesticide warehouse (radius of 1–2 km). Three sites of food products sampling was selected near each former warehouse locality (Supplement B, Fig.S.B1). Each kind of vegetable or fruit was sampled in 5 replicates (500–800 g), meat and honey - 300 g of each, and milk - 1 L. For an example, if several fruit trees grew on the territory of one point, then the 5 fruit replicates to constitute 1 sample were picked from different trees.

The chemical analysis of pesticides content in food products of plant and animal origin was carried out in a certified laboratory of the Scientific Analytical Center LLP (Accreditation certificate No. KZ. T.02.0926 from 08.24, 2018) in accordance with international, and Kazakhstani standards (GOST 30349-96, 1998; GOST 23452-79, 1986; GOST 32689.1-2014, 2016). Determination of pesticide residues and their decay products in food of plant and animal origin (van Zoonen, 1996) was carried out by capillary gas chromatography with an electron capture detector (Agilent 6890N chromatograph with MSD 5975C, Agilent technologies, USA), photometric analysis (liquid analyzer Fluorat-02, LUMEX, Russia), and atomic absorption spectrometry with electrothermal atomization (ACME 9000 HPLC with UV/VIS detector, Kunash Instruments, UK). The minimum detected concentration in animal products was 0.005 mg/kg (absolute total error - 0.0025 mg/kg) for 4.4′-DDT, 4.4′-DDD, 4.4′-DDE, 0.008 mg/kg (total error - 0.004 mg/kg) for HCH isomers, and 0.005 mg/kg (total error −0.0025 mg/kg) for heptachlor. The minimum concentration of residual amounts of organochlorine pesticides measured in samples of vegetables and fruits for γ-HCH is 0.001 mg/kg, for dicofol and hepatlor - 0.005 mg/kg, for DDT and its metabolites - 0.007 mg/kg. Using these methods for any kind of

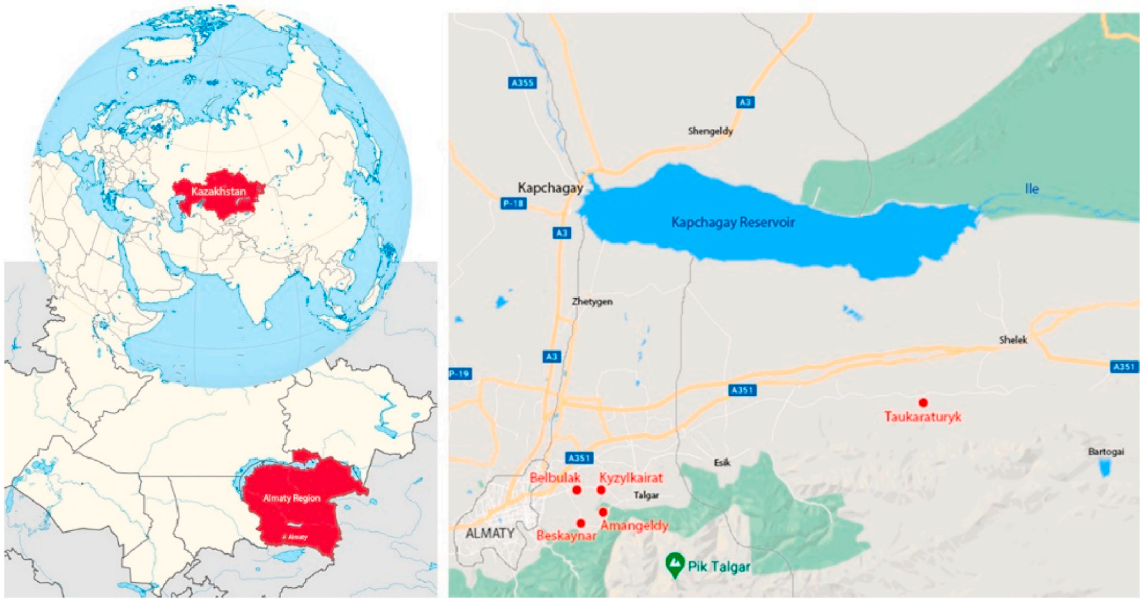


Fig. 1. The location of the studied villages. Taukaraturyk (N 43°29′51″ E 78°01′15″); Kyzylkairat (N 43°18′27′′E 77°11′27″); Amangeldy (N 43°17′43′′E 77°12′36″), Belbulak (N 43°18′52′′E 77°06′03″); Beskainar (N 43°13′03′′E 77°06′06″). The Google Maps resources were used for demonstration of locations.

Table 2
The pesticides contents (times of MRL exceeding) in food products of plant and animal origin from the different villages.

	Apples		Pears		Tomatoes		Cucumbers		Sweet Pepper		Meat		Milk	
	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding*	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples sover MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding *
Kyzylkairat														
Group 1 MRL – *0.*05 mg/kg *(EU) MPC - 0.*05 mg/kg *(CU)*														
4,4 DDT	2	99	3	232	2	266	3	200	3	94	1	83	3	10
4,4 DDD	1	1.2	1	18	–	–	1	14	–	–	2	66	3	10
4,4 DDE	–	–	3	3	–	–	1	2	–	–	–	–	1	1.4
2,4 DDD	1	16	2	7	1	2	1	1.4	–	–	2	22	3	4
Group 2 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
HCB	3	9	3	14	3	7	3	7	2	3	–	–	2	4
HBB	–	–	–	–	–	–	–	–	–	–	1	822	1	206
Group 3 MRL – *0.*01 mg/kg *(EU) MPC - 0.*05 mg/kg *(CU)*														
α HCH	1	8	3	17	1	10	2	5	1	5	–	–	–	–
γ HCH	3	11	3	26	3	16	3	21	2	14	3	143	3	27
β HCH	3	5	3	56	3	60	3	16	2	16	3	299	3	19
δ HCH	–	–	1	16	–	–	–	–	–	–	–	–	–	–
Group 4 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
Aldrin	2	2	3	58	3	42	3	3	2	2	–	–	–	–
Endrin	3	49	3	95	2	15	2	30	1	2	1	384	2	66
Dieldrin	2	28	3	15	3	9	3	5	1	3	2	194	3	35
Endrin aldehyde	3	52	3	89	3	97	3	147	2	67	2	124	3	6
Group 5 MRL – *0.*05 mg/kg *(EU) MPC - 0.*05 mg/kg *(CU)*														
Endosulfan 1	–	–	2	6	1	2	2	2	1	1.2	1	40	2	6
Endosulfan 2	3	9	3	29	3	4	3	21	1	1.4	–	–	–	–
Endosulfan sulfate	3	30	3	46	3	44	3	45	2	23	1	490	3	1.3
Group 6 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
HC	–	–	2	81	1	32	2	22	2	22	–	–	–	–
HCE	3	4	3	40	3	16	3	12	2	8	–	–	–	–
Another														
Dikofol [a]	–	–	–	–	1	10	–	–	–	–	–	–	–	–
Chlordane[b]	3	2	3	21	3	5	3	4	2	3	3	318	3	19
Metoxichlor [c]	–	–	–	–	–	–	–	–	–	–	–	–	1	47
Beskainar														
Group 1 MRL – *0.*05 mg/kg *(EU) MPC - 0.*05 mg/kg *(CU)*														
4,4 DDT	1	67	2	508	2	315	3	846	ns	–	1	598	2	13
4,4 DDD	2	131	3	191	1	69	3	179	ns	–	–	–	2	6
4,4 DDE	–	–	2	2	–	–	1	5	ns	–	–	–	–	–
2,4 DDD	2	2	1	2	1	2	1	13	ns	–	–	–	–	–
Group 2 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
HCB	3	18	3 4		2	3	2	18	ns	–	–	–	1	4
HBB	–	–	– –		–	–	–	–	ns	–	–	–	–	–
Group 3 MRL – *0.*05 mg/kg *(CU); 0,*01 mg/kg *(EU)*														
α-HCH	2	15	1 3		–	–	2	11	ns	–	–	–	1	3
γ-HCH	3	12	3 7		–	–	2	16	ns	–	3	241	3	17
β-HCH	3	35	3 7		2	5	3	221	ns	–	2	218	3	13
δ-HCH	–	–	– –		–	–	–	–	ns	–	–	–	–	–
Group 4 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
Aldrin	2	85	1 2		1	1.4	2	129	ns	–	–	–	–	–
Endrin	3	92	– –		1	58	1	108	ns	–	1	419	2	59
Dieldrin	1	5	2 3		1	2	2	59	ns	–	3	273	2	530

(*continued on next page*)

Table 2 (*continued*)

	Apples		Pears		Tomatoes		Cucumbers		Sweet Pepper		Meat		Milk	
	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding*	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples sover MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding *
Endrin aldehyde	3	575	–	–	–	–	–	–	ns	–	–	–	2	5
Group 5 MRL – *0.*05 mg/kg *(EU) MPC - 0.*05 mg/kg *(CU)*														
Endosulfan 1	–	–	–	–	1	1.3	1	13	ns	–	1	32	2	4
Endosulfan 2	2	17	1	56	2	86	1	61	ns	–	–	–	–	–
Endosulfan sulfate	2	64	3	458	3	183	2	317	ns	–	–	–	1	2
Group 6 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
HC	1	15	1	3	–	–	1	5	ns	–	–	–	–	–
HCE	3	11	3	3	2	3	2	176	ns	–	–	–	–	–
Another														
Chlordane[b]	3	6	3	2	3	3	2	5	2	136	3	6	3	2
Metoxichlor[c]	–	–	–	–	–	–	1	185	ns	–	–	–	–	–
Belbulak														
Group 1 MRL – *0.*05 mg/kg *(EU) MPC - 0.*05 mg/kg *(CU)*														
4,4 DDT	3	115	1	83	–	–	–	–	2	73	1	121	3	7
4,4 DDD	1	10	–	–	–	–	1	13	1	22	1	93	2	9
4,4 DDE	–	–	–	–	–	–	–	–	1	1.2	1	9	1	2
2,4 DDD	1	1.4	–	–	–	–	–	–	1	16	3	37	3	4
Group 2 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
HCB	3	8	2	2	3	2	3	9	3	6	–	–	3	3
HBB	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Group 3 MRL – *0.*05 mg/kg *(CU); 0,*01 mg/kg *(EU)*														
α HCH	2	13	–	–	–	–	2	24	3	5	1	39	–	–
γ HCH	3	18	1	15	1	16	2	21	3	7	3	242	3	11
β HCH	3	61	1	8	1	7	2	36	3	55	3	171	3	21
δ HCH	–	–	–	–	–	–	1	19	–	–	–	–	–	–
Group 4 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
Aldrin	3	27	–	–	1	2	2	24	3	15	–	–	–	–
Endrin	2	13	–	–	–	–	1	15	2	22	1	285	2	49
Dieldrin	3	6	1	2	1	2	2	8	3	33	3	389	3	77
Endrin aldehyde	3	83	1	60	1	4	2	103	3	50	3	82	3	3
Group 5 MRL – *0.*05 mg/kg *(EU) MPC - 0.*05 mg/kg *(CU)*														
Endosulfan 1	2	2	1	3	–	–	1	2	1	6	1	34	3	3
Endosulfan 2	3	13	2	8	3	3	3	13	3	10	–	–	–	–
Endosulfan sulfate	3	29	1	20	1	5	2	24	3	19	1	26	2	2
Group 6 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
HC	3	98	–	–	–	–	1	53	1	68	1	384	1	14
HCE	3	16	2	12	1	3	1	27	3	43	–	–	–	–
Another														
Dikofol[a]	2	13	–	–	–	–	–	–	3	11	–	–	–	–
Chlordane[b]	3	4	1	2	3	3	2	11	2	15	3	198	3	20
Metoxichlor[c]	–	–	–	–	–	–	1	21	2	18	2	168	–	–
Amangeldy														
Group 1 MRL – *0.*05 mg/kg *(EU) MPC - 0.*05 mg/kg *(CU)*														
4,4 DDT	–	–	1	35	–	–	–	–	–	–	3	284	3	14
4,4 DDD	–	–	1	12	–	–	–	–	–	–	–	–	2	8
4,4 DDE	–	–	1	35	–	–	–	–	–	–	–	–	–	–
2,4 DDD	–	–	–	–	–	–	–	–	–	–	1	5	2	4
Group 2 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
HCB	–	–	1	4	2	2	–	–	1	5	1	194	1	2

(*continued on next page*)

Table 2 (*continued*)

	Apples		Pears		Tomatoes		Cucumbers		Sweet Pepper		Meat		Milk	
	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding*	Number of samples over MRL*	Maximum MRL exceeding *	Number of samples sover MRL*	Maximum MRL exceeding *	Number of samples over MRL*	Maximum MRL exceeding *
HBB	–	–	1	4	–	–	–	–	–	–	1	414	1	17
Group 3 MRL – *0.*05 mg/kg *(CU); 0.*01 mg/kg *(EU)*														
α HCH	–	–	1	3	–	–	1	2	–	–	–	–	1	1.5
γ HCH	–	–	1	2	–	–	–	–	–	–	3	158	3	4
β HCH	–	–	2	44	1	3	–	–	1	4	3	240	3	11
δ HCH	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Group 4 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
Aldrin	–	–	1	20	–	–	–	–	–	–	–	–	–	–
Endrin	2	1.4	2	4	–	–	1	2	2	2	2	352	1	53
Dieldrin	–	–	1	3	–	–	–	–	–	–	2	348	2	2780
Endrin aldehyde	1	2	1	13	–	–	1	3	–	–	2	94	2	10
Group 5 MRL – *0.*05 mg/kg *(EU) MPC - 0.*05 mg/kg *(CU)*														
Endosulfan 1	–	–	1	5	–	–	1	2	1	2	–	–	3	5
Endosulfan 2	1	3	2	4	–	–	–	–	–	–	–	–	–	–
Endosulfan sulfate	–	–	1	10	1	10	2	14	2	5	–	–	3	2
Group 6 MRL – *0.*01 mg/kg *(EU) MPC - 0.*01 mg/kg *(CU)*														
HC	–	–	–	–	–	–	–	–	1	3	–	–	–	–
HCE	–	–	1	28	–	–	–	–	–	–	–	–	–	–
Another														
Chlordane[b]	1	2	1	8	–	–	–	–	–	–	2	114	3	20
Chlorobenzilate[d]	–	–	1	10	–	–	1	3	–	–	1	287	–	–

Note:

[a] Dikofol; MRL – 0.02 mg/kg (EU, CU);

[b] Chlordane: MRL – 0.01 mg/kg (EU), 0.02 mg/kg (CU);

[c] Metoxichlor: MRL 0.01 mg kg–1 (EU);

[d] Chlorobenzilate: MRL – 0.02 mg/kg (EU), ns – no samples; *The MRL (maximum residual level) used for EU standarts, MPC (maximum permissible concentration) used for countries for CU.

Table 1
Location and characteristic of study objects.

Village	Total number of inhabitants (males/females)	Number of exposed persons (males/females)		Average age	Geographical coordinates of warehouses	Number of samples at each site		Quantity of pesticides, kg
		Cytogenetic status	Health status			Fruit, Vegetables	Meat, Honey, Milk	
Taukaraturyk (Control)	1852 (951/901)	30 (12/18)	103 (27/76)	52.3	–	15	9	no known deposit
Kyzylkairat	6582 (3281/3301)	32 (10/22)	41 (11/30)	48.6	2 (nearby) N 43°17′58′′78 E 77°11′40′′21	15	9	10 000 Warehouse destroyed, but contaminated soil
Amangeldy	667 (321/346)	25 (14/11)	21 (2/19)	50.7	1. N 43°17′57′′98 E 77°11′30′′72 2. N 43°18′00′′97 E 77°12′37′′06	15	9	30 500 Mixture of pesticides
Belbulak	8510 (4209/4301)	26 (5/21)	43 (6/37)	49.5	N 43°19′25′′95 E 77°06′19.63′′	15	9	500 Mixture of pesticides
Beskainar	2008 (987/1021	31 (7/24)	44 (10/34)	52.8	N 43°13′16′′36 E 77°06′49′′78	15	9	50 Mixture of pesticides

measuring sample, the limits of possible systematic error values influencing by different factors estimated as ± 0.15 (DG-SANCO, 2007).

In total, the 24 organochlorine pesticides were analyzed in food products. All pesticides were divided into 6 groups depending on the chemical structure of active compounds: group 1 DDT: 4.4 DDT; 4.4 DDD; 2.4 DDD; 4.4 DDD, DDE; group 2 hexahalogenated benzene (HCB): hexachlorobenzene and hexabromobenzene; group 3 hexachlorocyclohexane (HCH): α- HCH, γ-HCH, β-HCH, δ-HCH; group 4 Aldrin: aldrin, endrin, dieldrin, endrin aldehyde; group 5 endosulfan: endosulfan 1, endosulfan 2, and endosulfan sulfate; and finally group 6 heptachlor: heptachlor and heptachlor epoxide. Measured concentrations of pesticides in food were compared to Europe Union and Custom Union standards (EU - Pesticides database, 2009; Unified sanitary and epidemiological and hygienic requirements for products, 2010).

2.3. Assessment of the general health status of residents

The general health status was examined in 149 residents of the studied region: 44 from Beskainar, 41 from Kyzylkairat, 43 from Belbulak and 21 from Amangeldy. The control group included 103 residents of Taukaraturyk (Table 1). Invited to the study persons were the residents of surveyed villages living close to the former pesticide warehouses. This explains the different ratios of study cohorts by gender, age, and ethnicity. Total population cohort was aged between 20 and 70 years. People lived in these localities since at least 10 last years, but some of them about 50 years.

The level of somatic health of residents was determined by the current state of the body's functional capabilities (7 tests for physical activity and functional state) using the express method scoring system (Onishchenko et al., 2014).

The study of overall health assessment (OHA) was carried out according to a scoring system of ratings: group 1- low level of health (>3 points); group 2 - average level of health (4–11 points); group 3- high level of health (12 points and above) (Apanasenko, 2004). The measurement of vital lung capacity (VLC) was carried out for the assessment of adaptive capabilities of the human cardiorespiratory system. To estimate the physiological interaction between circulatory and respiratory systems vital index (VI) was determined. The main indicators of OHA were: vital lung capacity (VLC), power index, Robinson index (RI). The physiological norm of VLC is 2500–3000 cm^3 for women, and 3500–4000 cm^3 for men and a deviation of 15% is tolerated. VLCs were measured with a Spiro S-100 spirometer (Altonika, Russia) and the vital index (VI) was calculated by the following formula:

$$VI = VLC/Body\ Weight\ (cm^3/kg) \quad (1)$$

Physiological norm of VI is considered as 65–70 mL/kg for men, 55–60 mL/kg for women. The VI of 15–20% less than norm reflects functional insufficiency of the respiratory system, most often associated with underdevelopment of the lungs or overweight.

The power index showing the harmonious development of the muscular system was determined using carpal dynamometry as a percentage of body weight (kg). The level of metabolic and energy exchange during the exercise stress and cardiovascular system functionality were determined by the Robinson index (RI) in combination with the recovery time of the heart rate and pulse after a fixed physical load (20 deep squats in 30 s). The recovery time of the pulse after a fixed cardiac exercise stress reflects the state of the reserve capabilities of the cardiovascular and respiratory systems, their ability to regulate the blood supply to the myocardium. The recovery time of the pulse after an exercise stress of less than 1 min was estimated as a high level of rehabilitation, and the restoration of heart rate of more than 3 min indicates cardiac dysfunction associated with chronic disorders in the circulatory system.

The Robinson Index (RI) was calculated $RI = HR \times Ps /100$ (2)

where HR is the heart rate, Ps is systolic blood pressure (mm Hg).

2.4. Cytogenetic analysis of metaphase chromosome spreads of human peripheral blood lymphocytes

The samples of the heparinized peripheral blood of persons living in the studied villages, in close proximity to the former pesticide warehouses, were collected to determine the genetic status. 144 volunteers (48 men, 96 women) were examined in Belbulak (26 persons), Amangeldy (25 persons), Kyzylkairat (32 persons), and Beskaynar (31 persons). The control group included 30 inhabitants of Taukaraturyk. It should be noted that among all surveyed persons, 78 volunteers were examined for OHA and cytogenetic status. Blood samples collected in heparinized tubes were transported during 2–5 h in closed refrigerated containers. Lymphocyte cultures were prepared from freshly peripheral blood samples with using of 85% RPMI 1640 medium (Gibco & Sigma Aldrich) was supplemented with 15% of bovine serum albumin (Sigma Aldrich, USA), 50U/mL of penicillin, 100U/mL streptomycin and 2% of PHA (Sigma Aldrich, USA). The cell cultures were incubated for 48 h in CO2-incubator (Binder, Germany) at 37°C and 1.25 μM of colchicine (Sigma Aldrich) was added 2 h before harvesting. Chromosome slides were made by hypotonic treatment (0.075M KCl) at 37 °C for 15 min, followed by fixation in methanol/acetic acid 3:1, air-drying and staining by Giemsa (MiniMed-R, Russia) for 20 min. The slides (16562 metaphase plates) were analyzed under the Leica DM LS2 (Leica Wetzlar GmbH, Leica Microsystems, Germany) and Lomo DV 1000 (Russia) microscopes using oil immersion at a magnification of 10x100. All types

of chromosomal aberrations detected during routine staining (chromatid breaks, single fragments, chromosomal breaks, paired fragments, dicentrics, rings and exchanges) were taken into account. Microscopic examination of metaphase plates was carried out accordingly standard criteria (Zakharov et al., 1982).

2.5. Statistics

The significance of differences of cytogenetic indicators between control and experiment was estimated using Chi2 ($\chi 2$) and the Student's t-test. Signification was declared at $p < 0.05$. The calculation of the proportion of cells with chromosome aberrations from the total number of analyzed cells was calculated by the formula:

$$p = X/N \times 100\% \quad (3)$$

where X-number of cells with aberrations, N-number of studied metaphase cells.

The Spearman's rank correlation method was used to assess the association between the frequency of chromosomal aberrations, health state, and the concentration of pesticides in food products. The excess of MRL was calculated for each group of pesticides and for each food product. For association of chromosomal aberration (CA) level with pesticides content in food products the three ranks were used. The first rank included data with a maximum excess of the MRL and a CA rate of more than 2%. The second rank included data with an average exceeding and a CA rate of 1–2%. The third rank was made by the group with a minimum excess of MRL and a frequency of chromosomal aberrations of 0–1%.

Three ranks criterions (norm limits, below norm level, and excess of norm) were used for association analysis between health status and the content of pesticides in food products. For level of OHA (points) the following rank correlation was used: 0–3 low, 4–11 – medium, 12 and above – high. The reliability of the Spearman' rank correlation indexes were determined by the unpaired Fisher-Student test. The rank correlation index value over than critical point (Tkr) was regarded as statistically significant. Value of coefficient Cr were positive or negative. The strength of the correlation: *Cr* = 0.20–0.39 – weak correlation; *Cr*= 0.40–0.69 – moderate correlation; *Cr*= 0.70–1.00 – strong correlation (https://math.semestr.ru/corel/spirmen.php).

3. Results

3.1. Determination of pesticides in foods of plant and animal origin

The content of 24 pesticides in food products of plant (apples, pears, tomatoes, cucumbers, sweet peppers) and animal (beef meat, cow milk, honey) origin were determined at 3 sampling points located around each former warehouses (see Materials and methods). The detailed information is presented in Supplement B (Fig.S.B1). Table 2 represents data on MRL exceeding for different groups of pesticides in food products from surveyed villages.

In food products of plant and animal origin sampled in Kyzylkairat, high concentrations were noted for all groups of pesticides generally at all three sampling sites. The highest concentrations of pesticides from the DDT and aldrin groups were detected in the pears and tomatoes. For example, the DDT content in pears exceeded the MRL by 232 times, and in tomato - by 266 times. Exceeding of MRLs by the aldrin pesticides group were detected for all aldrin derivatives, but endrin revealed the highest levels. Endrin aldehyde content in pears was 89 times higher than MRL, in tomatoes - 97 times, and in cucumbers - even 147 times. For hexachlorobenzene and HCH, the excess of MRL was not so significant, with the exception of γ-HCH and β-HCH. For products of animal origin, an increased content of all organochlorine pesticides was also noted, except the heptachlor group. In honey samples, a slightly increased content of 4.4 DDDT, endrin aldehyde and endosulfan sulfate was found. The content of pesticides in meat was for 4–5 times higher than in milk. For example, in one of the studied sites, the content of hexabromobenzene in meat was 822 times MRL, and in milk −206 times. Multifold excess of MRL was also typical for β-HCH, γ-HCH, 4.4 DDD, 4.4 DDT, endrin, dieldrin, endrin aldehyde, endosulfan sulfate (Table 2).

In foods products sampled in Beskainar, the highest concentration levels of the DDT (especially 4.4 DDT and 4.4 DDD), HCH, endosulfan, and aldrin pesticides groups were observed. In pears the concentration of pesticides was higher, than in another fruits. Among vegetables, cucumbers revealed the highest levels of accumulated pesticides belonging to the different groups. For example, an unacceptably high content of 4.4 DDT was found in cucumbers (>800 times MRL), and pears (>500 times MRL). The increased content was observed mainly in 2–3 studied points. The concentration of 4.4 DDD of fruits and vegetables was slightly lower than 4.4 DDT. The maximum exceeding of 4.4 DDD in fruits was approximately 200 times MRL. Among vegetables, the minimum levels of 4.4 DDD concentration were in tomatoes (>60 times MRL), and the highest in cucumbers (179 times MRL). Concerning endosulfan group, the content of endosulfan sulfate exceeded maximum levels in pears (458 times MRL), and in cucumbers (317 times MRL). Pesticides of the aldrin group, especially endrin and endrin aldehyde, were more concentrated in apples. For example, the content of endrin aldehyde in apples achieved 575 times MRL. Among vegetables, the cucumbers revealed the highest levels of pesticides of aldrin group. Contrarily, endrin aldehyde presence in vegetables was no detected, while endrin contents exceeded the MRL by 58–108 times. Hexachlorobenzene, heptachlor, heptachlor epoxide, HCH and its derivatives have been detected in vegetables and fruits in insignificant concentrations. However, in one surveyed site, the content of β-HCH in cucumbers exceeded the MRL more than 200 times (Table 2). In animal products from Beskainar, the increased contents of pesticides, with the exception of endrin aldehyde, were detected mainly in meat samples. In one of three sites, the 4.4 DDT content in meat reached >600 times MRL. Meat samples demonstrated the increased contents of β-HCH, γ-HCH, endrin and dieldrin. In milk samples only the high concentration of dieldrin had shown (>500 times MRL). Hexachlorbenzene, hexabromobenzene, heptachlor, heptachlor epoxide, endosulfan 2, aldrin, dicofol, and chlorobenzilate were not detected in animal products.

Food products from Belbulak showed lower concentrations of pesticides compared to Kyzylkairat and Beskainar. In Belbulak, samples of apples, cucumbers, sweet peppers and meat detected the most critical concentrations of pesticides. The content of 4.4 DDT and heptachlor in apples exceeded the MRL by almost 100 times, endrin aldehyde - by 80 times, HCH and its derivatives by more than 60 times (Table 2). A high concentration of endrin aldehyde were in cucumbers (>100 times of MRL) and sweet peppers (>50 times of MRL). Unacceptably high levels were observed in meat samples for following groups: HCH, DDT, aldrin, heptachlor, chlordane and chlorobenzylate. For example, the MRL exceeding for the very dangerous γ-HCH varied from 57 to 242 times over MRL. The content of dieldrin and endrin were more than 389 times MRL and 285 times MRL, respectively. The heptachlor content was 384 times MRL, chlordane and chlorobenzylate - more than 160 times MRL, 4.4 DDT 121 times MRL. The content of endrin, dieldrin in milk were increased, but lower than in meat in 5 times. The MRL exceeding of dieldrin and endrin were 50–80 times. It should be noted that in food sampled in Belbulak pesticides as dicofol, chlordane and chlorobenzilate were detected contrarily to Kyzylkairat and Beskaynar. Moreover, dicofol content was the highest in apples, but chlordane and chlorobenzilate - in cucumbers and sweet peppers, and chlordan - in milk. In honey samples, the pesticides were not detected, except some traces of endosulfan.

Among all surveyed sites, the pesticide contamination of fruits and vegetables from Amangeldy was the lowest. Only in pears, 4.4 DDT, 4.4 DDD, β-HCH, aldrin, endrin aldehyde, endosulfan 1, heptachlor epoxide and chlorobenzilate exceeded MRLs. The maximum MRL exceeding was

stated for β-HCH (by 44 times) and 4.4 DDT (by 35 times). However, these OCPs were found only in one of three sites, most closely located in the proximity to the former pesticides warehouse. Animal products of Amangeldy contained high concentrations of pesticides such as dieldrin, endrin, hexachlorobenzene, hexabromobenzene, chlorobenzilate, HCH derivatives and 4.4 DDT. The content of dieldrin was an unacceptably high, in milk samples (2780 times MRL), but also in meat (348 times MRL) (Table 2). Unacceptably high contents of 4.4 DDT (284 times MRL), hexachlorobenzene (194 times MRL), hexabromobenzene (414 times MRL), chlorobenzylate (287 times MRL), γ-HCH (158 times MRL), and β –HCH (240 times MRL) were measured only in meat samples. The pesticides were not determined in honey sample from Amangeldy. Among all studied organochlorine pesticides, only dibutylene and methoxychlor were not detected in products taken from surveyed villages.

So, of the products of plant origin, the highest content of all groups of pesticides has been detected in pears, and of products of animal origin - in meat.

3.2. Cytogenetic analysis of the human population

The highest frequencies of chromosomal aberrations (CA) were observed among residents of Belbulak (3.00 ± 0.33%) and Kyzylkairat (2.84 ±0,37%), that significantly differ ($p < 0.001$) from CA frequencies detected in residents of Amangeldy (1.96 ± 0.27%, $p \leq 0.001$) and the control group of Taukaraturyk (0.85 ± 0.12%). The average CA frequency in residents of Belbulak significantly exceeds the control group (Taukaraturyk) by 1.4 times ($p < 0.001$), Kyzylkairat by 1.09 times ($p < 0.001$). Residents of Beskaynar also demonstrated increased cytogenetic indices (1.88 ± 0.23%). The statistical data indicate an excess of the CA frequency in this cohort by 1.2 times ($p < 0.1$) compared to the control group (Table 3). The average age of the examined individuals was 50 years. There were no statistically significant differences in the frequency of chromosomal aberrations among both sexes and age categories (persons before and after 50 years) from all localities.

A shift towards chromatid mutations, that testifies the chemical mutagenesis, was detected for all surveyed cohorts with exception of residents from Amangeldy, where the frequencies of chromosomal and chromatid aberrations were not significantly different. The most representative and interesting types of aberrations are presented in Supplement C (Fig.S.C1).

The surveyed population was divided into three groups: individuals with chromosomal aberrations in peripheral blood lymphocytes up to 2% (spontaneous level), from 2 to 4% (elevated) and equal or more than 4% (high). Nineteen percent of the surveyed residents of Belbulak, 32% of Amangeldy, 45% of Beskainar, 34% of Kyzylkairat, and finally 82% inhabitants of Taukaraturyk demonstrate the CA frequencies, which did not exceed the general population spontaneous level for Kazakhstan. An increased level of the chromosomal aberrations frequencies characterizes 42% of the Belbulak cohort, 56% of Amangeldy, 48% of Beskainar, 25% of Kyzylkairat, but only 10% of the control cohort from Taukaraturyk (Fig. 2).

The highest level of chromosomal aberrations was identified for the examined residents of Kyzylkairat (41%) and Belbulak (38%). Only 12% of the surveyed population of Amangeldy and 6.5% of Beskainar cohort revealed a high level of chromosomal aberrations. In a control cohort of Taukaraturyk residents, there were no individuals with a high level of CA frequency.

3.3. Analysis of somatic health level of the population

The overall health assessment, determined by the method of Apanasenko, where determination of the vital index (VI) which is based on 7 tests for physical activity and functional state, and mostly associated with the physiological interaction of the circulatory system and respiration (see also Materials and methods).

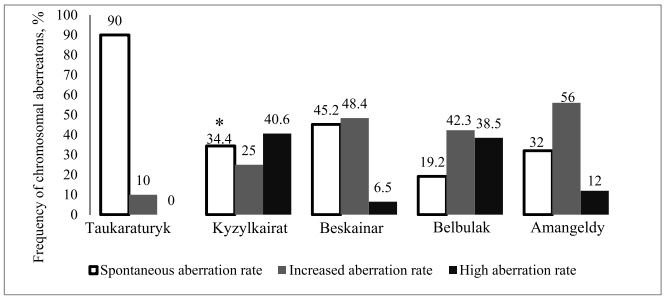


Fig. 2. Distribution of the studied cohorts according to the level of frequency of chromosomal aberrations.

Table 3
Cytogenetic indicators of surveyed population.

Location Cytogenetic data	Taukaraturyk (control)	Kyzylkairat	Beskaynar	Belbulak	Amangeldy
Persons examined (males/females)	30 (12/18)	32 (10/22)	31 (7/24)	26 (5/21)	25 (14/11)
Average age	52.30±2.34	48.59±2.79	52.80±1.81	49.53±3.,58	50.68±2.79
Spreads studied	6108	2004	3350	2600	2500
Aberrations per cell.	0.008	0.02	0,02	0.03	0.02
Aberration frequency,%					
Chromatid gaps	–	0.05±0.05	–	0.19±0.08*	0,04±0,04
Chromatid breaks	0.61±0.09	0.85±0.21	–	0.69±0.16	0.24±0.09**
Single fragments	0.04±0.02	1.09±0.23***	0.12±0.06	1.03±0.19***	0.72±0.17***
Chromatid type aberration frequency	0.65±0,10	1.94±0.31***	1.04±0.18	1.73±0.25***	0.92±0.19
Chromosome gaps	–	–	–	0.15±0.07*	0.20±0.08**
Chromosome breaks	0.09±0.04	0.29±0.12	0.53±0.12***	0.23±0.09	0.16±0.08
Paired fragments	–	0.45±0.15	0.06±0.04	0.81±0.17	0.60±0.15
Dicentrics	–	0.1±0,07	0.03±0.03	0.15±0.07*	0.20±0,08**
Rings	0.01±0.01	0	0.21±0.08**	0.07±0.05	0.04±0.04
Chromatid exchange	0.01±0.01	0.05±0.05	–	–	–
Chromosome type aberration frequency	0.19±0.05	0.89±0.21***	0.84±0.15***	1.27±0.22***	1.12±0.21***
Total aberrations	52	57	62	78	49
Number of analyzed cells	6108	2004	3350	2600	2500
Frequency of cells with aberrations	52	49	63	73	44
Number of cells with aberrations	0.85±0.12	2.44±0.34***	1.85±0.23***	2.80±0.32***	1.76±0.26***
Total CA frequency	**0.85±0.12**	**2.84±0.37*** **	**1.88±0.23*** **	**3.00±0.33*** **	**1.96±0.27*** **

Note: *** - p ˂0.001, the difference is highly reliable; ** - p ˂0.01, the difference is moderately significant; * - p˂0.05, the lower confidence limit; p˃0.05 - the difference is not significant.

The VC is considered to be the norm from 2500 to 4000 mL, VI from 55 to 60 mL/kg and above. Values of vital index less than 50 mL/kg showed functional insufficiency of the respiratory system associated with a small volume of vital capacity of the lungs or overweight. In Taukaraturyk (control site) more than 43.7% of residents had a high and middle level of VI. The same indicator for pesticide-contaminated sites was 19.4%.

The low VI rates, less than 58%, were observed in control group, whereas exposed by pesticide cohort had more than 80% residents showing low health status. The Robinson index is used to assess the level of metabolic and energy processes in the human body according to the systolic pressure at the height of physical activity. A low level of compensatory-adaptive reactions in the blood supply system of the heart (values greater than 111 units) was detected in 23% of the residents from the control group and in 33% of residents from the contaminated by pesticide sites. The indicators of half of the examined in both groups fluctuated at an middle level, but the number of people with high rates of compensatory activity of the cardiovascular system under load in the control group was 10% higher than the number of people with this indicator in the pesticide-contaminated sites (Table 4). Exposed cohorts were characterized by 2% of OHA high level, 25.5% OHA middle level, and 72.5% by low level of OHA (Table 5).

Our overall health assessment showed that there were more individuals with high and middle levels of health in the control group than in the exposed by POPs group.

3.4. Analysis of the association between cytogenetic and general health indicators

The analysis was carried out taking into account the individual characteristics of 78 volunteers who were examined cytogenetically and for health status. Spearman's correlation was used for evaluation of the association. Fig. 3 shows the accordance of the individual frequency of chromosomal aberrations with the level of health (using the point system).

It should be noted that among these 78 surveyed individuals 76.9% (59 persons) were characterized by low level of health and the 24.3% (19 persons) demonstrated pure genetic status by high level of chromosomal aberrations. The middle OHA level was characterized for 20.5% (17 persons) and the average level of CA was in 41.0% (32 persons). Only 2.6% (2 persons) of these cohort have been characterized by high level of health and 34.7% (27 persons) marked by complete absence of chromosomal aberrations, that indicates the good genetic status. The Spearman's rank correlation index showed the presence of an association between the level of health with the presence of chromosomal abnormalities. Moreover, the rank correlation index was statistically significant and reliable (P‹0.05). Thus, the low indicators of somatic health status are strictly associated with high level of CA frequency, and good health status indicates that the CA rates are not exceeded the spontaneous level of mutagenesis.

Table 5
Indicators of overall health assessment (OHA) for the studied residents, %.

Group	Number of persons	OHA index		
		High 12–18 points	Average 4–11 points	Low 3 points and below
Control cohort - Taukaraturyk	103	7.8% (8 persons)	41.7% (43 persons)	50.5% (52 persons)
Exposed Cohorts	149	2.0% (3 persons)	25.5% (38 persons)	72.5% (108 persons)

3.5. Analysis of the association between the frequency of chromosomal aberrations and the accumulation of pesticides in food

The detection of pesticides in food products revealed sharp differences of pesticides contents between the three sampling points in the same location (Supplement D – Tab.S.D1; Tab. S.D2). The excess of MRL and average values were calculated for each group of pesticides and for each food product. The correlation analysis by the average values of each village did not established a reliable result due to the spotted distribution of pesticides at different points around the warehouses (Supplement E – Tab.S.E1). For example, in Beskainar, the excess of MRL by 4.4 DDT in pear in the three studied points varied from 0 to 508 times. Therefore, we used the Spearman's rank correlation to estimate the influence of pesticides on the health and genetic status of the population. The ranking was done according to the frequency of chromosome aberrations and the content of pesticides in food products (Materials and Methods). Detailed data on association between the CA frequency of population probably consuming the pesticides with food and the pesticide content in food products of animal and plant origin are presented in Supplement F (Tab. S.F1).

For all pesticide groups, the strongest direct correlation ($p > Tkr$) between the CA frequency and the pesticide content had been detected in food of plant origin, especially expressed in pears, tomatoes, and cucumbers from Kyzylkairat, Beskainar and Amangeldy.

The high frequency of CA in human lymphocytes is significantly correlated with content DDT group pesticides in apples (Kyzylkairat – Cr = 0.97***, Beskainar – Cr = 0.69**), pears (Kyzylkairat – Cr = 0.51**) cucumbers (Kyzylkairat – Cr = 0.59***, Beskainar – Cr = 0.88***), tomatoes (Kyzylkairat – Cr = 0.49**, Beskainar – Cr = 0.77*), and beef meat (Beskainar – Cr = 0.84***, Kyzylkairat – Cr – 0.70***, Amangeldy – Cr = 0.81***).

Pesticides of HCB group were associates with induction of CA at population consuming apples (Kyzylkairat – Cr = 0.66**), pears (Beskainar – Cr = 0.92***, Kyzylkairat – Cr = 0.47**), tomatoes Amangeldy–Cr = 0.80***, Kyzylkairat – Cr = 0.48**, Beskainar– Cr = 0.6*), cucumbers (Kyzylkairat (Cr = 0.96, Belbulak – Cr = 0.77**, Beskainar – Cr–0.73*), beef meat (Kyzylkairat – Cr = 0.46**), and milk (Kyzylkairat – Cr = 0.46**).

HCH group of pesticides presence in food products revealed the correlation with induction of CA in human lymphocytes for apples (Kyzylkairat – Cr = 0.39***), pears (Amangeldy – Cr = 0.98***, Kyzylkairat – Cr = 0.64**, Beskainar – Cr = 0.37*), cucumbers

Table 4
Indicators of vital index and Robinson index, %.

Villages	Number of person	Vital index (VI), %			Robinson index (RI)		
		High (≥51 mL/kg)	Average (41–50 mL/kg)	Low (≤40 mL/kg)	High (70–84 units and lower)	Average (85–110 units)	Low (more than 111 units)
Control cohort - Taukaraturyk	103	9.7	32.0	58.3	33.,3	43.7	23.3
Exposed Cohorts:	149	5.3	14.1	80.5	19.5	47.6	32.9
Beskaynar	44	2.0	3.3	24.1	7.4	13.4	8.7
Kyzylkairat	41	1.3	4.7	21.5	5.4	10.7	11.4
Belbulak	43	2.0	3.4	23.5	4.7	14.8	9.4
Amangeldy	21	0	2.7	11.4	2.0	8.7	3.4

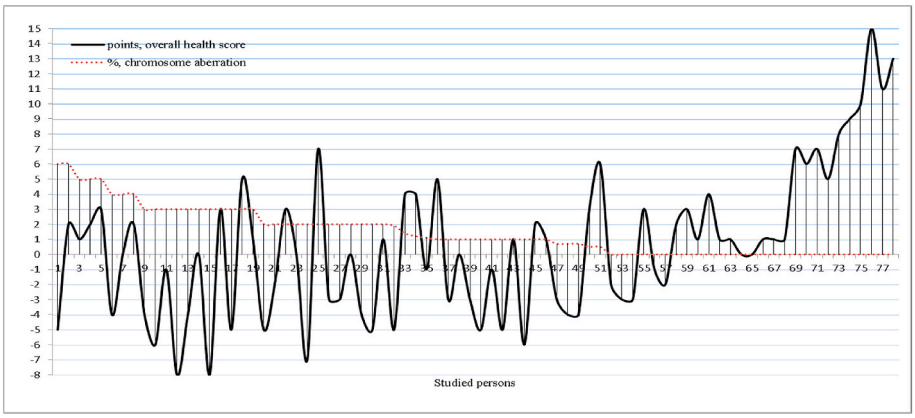


Fig. 3. Correlation between the overall health assessment (OHA) and the frequency of chromosomal aberrations of residents in studied villages. Y-axis: the level of OHA (points): 0–3 - low, 4–11 - medium, 12 and above - high. The frequency of chromosomal aberrations (%): above 3% - high; 0–2% - average; 0–1% - low; X-axis: number of persons examined.

(Beskainar – Cr – 0.84***, Kyzylkairat – Cr = 0.96**, Belbulak – Cr = 0.69**), tomatoes (Beskainar – Cr = 0.60*), sweet peppers (Beskainar – Cr = 0.78*).

There were significant correlation of increasing of CA frequency with content of aldrin group of pesticides in apples (Kyzylkairat –Cr = 0.70***, Amangeldy – Cr = 0.95***), in pears (Kyzylkairat – Cr = 0.70***, Beskainar – Cr = 0.62**), in tomatoes (Beskainar – Cr = 0.85***, Beskainar – Cr = 0.85**), in cucumbers (Kyzylkairat – Cr = 0.55***, Amangeldy – Cr – 0.96***, Beskainar – Cr–0.83**), in beef meat (Beskainar – Cr = 0.37***, Amangeldy – Cr = 0.83***), and in milk (Amangeldy – Cr = 0.78***, Kyzylkairat – Cr – 0.54**, Belbulak – Cr = 0.54*).

Endosulfan group of pesticides content in food products revealed the correlation with human lymphocytes CA frequency for pears (Amangeldy – Cr = 0.98***, Kyzylkairat – Cr = 0.55**), cucumbers (Kyzylkairat – Cr = 0.57***), tomatoes (Amangeldy – Cr = 0.88***, Kyzylkairat – Cr = 0.48**), sweet peppers (Beskainar – Cr = 0.78***). For products of animal origin, a significant correlation was observed only for meat from Beskainar (Cr = 0.84***).

HC group of pesticides presence in food products revealed the correlation with induction of CA in human lymphocytes for pears (Beskainar – Cr = 0.92***, Amangeldy – Cr = 0.98***), apples (Kyzylkairat – Cr = 0.26*), tomatoes (Kyzylkairat – Cr = 0.58***), cucumbers (Kyzylkairat – Cr = 0.74**). For products of animal origin, a significant moderate correlation of HC group of pesticides was observed only for meat from Amangeldy (Cr = 0.58**) and Kyzylkairat (Cr = 0.69**).

4. Discussion

4.1. Pesticides content in food products of plant and animal origin

The most POPs pesticides were no longer used in the EU, but in most developing countries the POPs have not been disposed of and they enter in the human food chain through soil, water and food. According to the EU's Pesticide Action Network, in 2008, about 350 different pesticides were found in food products made in the EU. More than 5% of products contained pesticides at levels exceeding the EU standards of MRL (Fenik et al., 2011). The results of organoclorine pesticides determining in soil samples in Almaty region, have demonstrated that soil was contaminated by metabolites of 2.4 DDD; 4.4 DDD; 4.4 DDT; 4.4 DDE and isomers of hexachlorane. The most polluted regions were Eskildinsky, Talgar, Karasai, Enbekshi-Kazakh districts and the presence of pesticides was unacceptable (Nurzhanova et al., 2010, 2013).

POPs through the food chain accumulate in food products ranging from meat, poultry and fish, to vegetable oils, nuts and various fruits and vegetables. All pesticides and their decay products cause an imbalance of nutrients, a decrease in the quantity of agricultural products (Bourn and Prescott, 2002; Petraitis et al., 2013) and affect the human health. Most studies of pesticides content in food products were carried out with aim to estimate the pesticides quantity in imported or local food products for development the monitoring systems and strict regulation norms (Le Doux, 2011; Li et al., 2014; Man Zhanga et al., 2017). However, there is no sufficiently argued data on the accumulative capacity of food products grown in contaminated areas.

Our studies on the accumulation of pesticides in food products of plant and animal origin grown in places of localization of non-utilized OCPs revealed products and groups of pesticides that accumulate in high and unacceptably high concentrations. DDT pesticides in plant products were mainly detected in pears, cucumbers, from animal products - in meat. Pesticides of the hexachlor group in the products of plant and animal origin detected in minimal amounts. However, in some of the studied points an unacceptably high HBB content was observed in meat samples. The concentration on maximum levels of HCH pesticides group (especially β-HCH), was detected in pears, tomatoes, cucumbers and meat. The results evidenced that pesticides of the aldrin group more accumulate in plant products than in animal products. Unacceptably high levels of endrin and dieldrin were found in meat and milk. Endosulfan and endosulfan 2 were mainly detected in plant products. In animal products, pesticides of the endosulfan group detected in small amounts. The high concentration of pesticides of the heptachlor group was found in pears, sweet pepper and beef meat, moreover heptachlor and heptachloroepoxide accumulate in plant products, while, in meat, only heptachlor was detected. These results were consistent with other investigations (Crinnion, 2009; Zikankuba et al., 2019; Reeves et al., 2019). In previous studies regarding the presence of organic pollutants in camel milk from different regions of Kazakhstan, traces of hexachlorocyclohexane, lindane, hexanechlorothalonil were found (Konuspayeva et al., 2011a,b). In addition, high content of pesticides, such as chlordane and chlorobenzylate, was found in animal products. Similar studies, done by Lesa A. Thompson et al. (2017), also showed that

products of plant and animal origin have different accumulating capacity for one or another group of pesticides. Studies in Karakalpakstan (Uzbekistan) show that a number of commonly consumed foods contain high levels of α-HCH, β-HCH, γ-HCH, DDE and dioxins, especially the most toxic dioxin, 2.3.7.8-TCDD. Among the samples analyzed, the highest levels of contamination were found in foods rich in lipids, such as lamb and chicken fat, eggs, and cottonseed oil, which are important local foods (Muntean et al., 2003).

4.2. Influence of pesticides on chromosomal aberrations frequency and health status

It is known that due to their high mutagenic potential, pesticides affect human health. A number of studies on the effects of pesticides have shown that there is a correlation with the occurrence of certain human pathologies, including hepatotoxicity (Buczynska and Szadkowska-Stanczyk, 2005), an increased risk of various types of cancer (Asghar et al., 2016; Purdue et al., 2007; Ruder et al., 2006), neurodegenerative diseases such as Parkinson's disease (Alavanja et al., 2004; Chade et al., 2006), deficiencies in brain development, immune system (Colosio et al., 2005), reproductive defects (Nicolopoulou et al., 2001), aging and changing genetic status (Chatterjee et al., 2018).

An analysis of the statistical data on the morbidity of residents of the Almaty region from 2011 to 2017 showed that the Talgar district is characterized by an excess of the average regional indicators for diseases of the respiratory system and cardiovascular system. In 2011, the incidence of the Talgar region's population with these diseases exceeded the average republican by 50%, in 2017 already by 67% (http://dps.medinfo.kz/). Based on this, our rating scale took into account the data for respiratory and cardiovascular system. Our studies have shown that among residents of the Talgar district of the Almaty region, living on the contaminated by pesticides territories for a long time, the disturbance in the function of the respiratory and cardiovascular systems had registered. More than 80% of residents had low vital capacity of the lungs and low level of compensatory-adaptive reactions of the cardiovascular system. These results are consistent with the other investigations that have shown that pesticides decrease the respiratory function (Chakraborty et al., 2009; Hernandez et al., 2008; Hoppin et al., 2002; Sapbamrer et al., 2020; Zolotnikova et al., 2018) and increase the risk of cardiovascular diseases (Phillip and Mary, 2009; G.Wahab et al., 2016). The medical examinations, carried out among the cohorts living around the polluted by pesticides territories and control cohort from ecologically favorable village, showed that there were more individuals with high and middle levels of health in the control group than in the exposed by POPs group. Since we surveyed the populations living in close proximity to the non-utilized stocks of pesticides, the study cohorts were very heterogeneous by individual characteristics. However, we tried to match exposed by POPs human cohort to control group taking into account individual characteristics - age, sex, ethnicity, life style, physical activity.

The individual general level of health correlates with the level of chromosomal aberrations frequency (Fig. 3). Thus, high frequency of chromosomal aberrations correlates with poor somatic health, and good health status indicates that the CA rates are not exceeded the spontaneous level of mutagenesis. Based on literature data (Andersson, 1993; Rössner et al., 1998; Menasha et al., 2005; Nefic and Musanovic, 2014), the CA frequency up to 2% was taken as a spontaneous mutagenesis level. Thus, the data on the cytogenetic analysis of a healthy populations from different regions of Kazakhstan (Karaganda, Pavlodar, Akmola, North Kazakhstan, Almaty region and Almaty city) indicate that spontaneous frequencies of chromosomal aberrations range from 1.3% to 2.2% (Bolegenova et al., 2009; Gubitskaya et al., 2007; Vishnevskaya et al., 1995). Numerous numbers of other researches have shown that a substantial, constant and steady pesticide contamination of agricultural areas significantly increases the frequency of chromosomal aberrations. Studying the genotoxic effect of the pesticides mixture on agricultural workers employed in cotton fields in India, Venkata et al. (2017), showed an increased frequency of chromosome aberrations in the study group, especially expressed in the prevalence of acentric fragments in comparison with the control group. At the same time, the age and longevity of pesticides pollution did not affect to the frequency of different types of chromosome aberrations. Jonnalagadda et al. (2012) showed that farmers who spray pesticide mixtures when growing cotton crops show an increase of CA frequencies up to 2.8% compared with the control group (0.72%). Zeljezic et al. (2009) studied 32 individuals working with pesticides which simultaneously exposed to various active substances. The genomic frequency of translocations was also significantly increased.

It is known that cytogenetic indicators can depend on age and sex. However, we could not analyze the age or sex dependent correlations because our cohorts were formed from all residents living on the polluted localities. The results of cytogenetic analysis of populations living in the proximity to the exposed by pesticides areas showed a high level of chromosomal aberrations among residents of Belbulak and Kyzylkairat, increased - among residents of Amangeldy and Beskaynar, low - for the cohort of Taukaraturyk (Fig. 2). Ratio of chromosomal (chromosome gaps, chromosome breaks, paired fragments, dicentrics, rings) and chromatid aberrations (chromatid gaps, chromatid breaks, and single fragments) indirectly indicates the type of mutagenic effect. In spontaneous mutagenesis, the frequency of chromosomal abnormalities is lower or equal to the frequency of chromatid ones (Bender and Setlow, 1994). The prevalence of chromosomal type mutations over chromatid ones may indicate radiation exposure. A shift towards chromatid mutations, as in the case of a survey of Kyzylkairat residents, where the frequency of chromatid type aberration was 2.2 times higher than the frequency of chromosomal type aberrations, testifies the chemical mutagenesis.

The further analysis was conducted taken into account the content of pesticides in food and the level of chromosomal aberration frequency in the studied cohorts of the population. We cannot state with certainty that the products taken for research were consumed by human volunteers of the research. However, for chemical analysis, we've tried to sample products directly from gardens of the surveyed residents or in nearby markets.

The correlation between high frequencies of chromosomal aberrations and high content of pesticides in food was registered for all pesticide groups (Supplement F) in all studied locations. However, the pesticide contents in food of plant and animal origin were different. Strong positive correlation was observed for the group of HCB pesticides in pears, tomatoes, and cucumbers (Kyzylkairat, Beskaynar, Belbulak) for which the excess of MRL is insignificant (2–14 times). This is possibly connected to the fact that this pesticides group has a strong effect on the frequency of chromosomal aberrations, even in low doses. At the same time, in meat, an unacceptably high excess of MRL for HBB (more than 800 times) and the strong correlation with the frequency of chromosomal aberrations have been observed.

The maximum MRL excess for pesticides of DDT and HCH groups (especially β-HCH) was noted in Kyzylkairat (pears, tomatoes, and cucumbers), Beskainar (pears, tomatoes, cucumbers, meat), Amangeldy (pears, meat). For these pesticides groups, high values of the correlation indexes were noted, which indicates their greatest possible effect on the frequency of chromosomal aberrations.

A strong positive correlation between the content of pesticides in products of animal origin and the frequency of chromosomal aberrations was noted for the aldrin group of pesticides. A negative correlation was mainly found for the accumulation of pesticides of the aldrin group in vegetables and fruits. That probably indicates the cytogenetic damage caused by the action of this group of pesticides was not high enough to provoke permanent induction of mutations or mitosis brake. Similar studies by Jean et al., 2011 showed that the absence of significant structural and quantitative chromosome aberrations under the action of pesticides mixtures have been associated with possible effective DNA

reparation.

In our studies for endosulfan pesticide group, a strong correlation between the frequency of chromosomal aberrations and the content of pesticides in plant products was shown. According to the concentration of heptachlor and decay products, a positive strong (tomatoes, pears) and moderate (sweet pepper) correlation was observed. It should be noted that in Belbulak, the highest percentage of the frequency of chromosomal aberrations in population was detected. However, the contamination of food products by pesticides was not high in comparison with other sites. This could be related to the location of this village, on the territory of which the complete disposal of pesticides was carried out, but currently there are deposits of household garbage in the warehouse. The radiation background in this village does not exceed the norm. In addition, in the Belbulak mainly live repatriates from China and Mongolia with low social status.

The pesticides influence on human health are complex and still poorly studied, since it is not easy to assess the risk of any toxic effects of chemicals on human health without strict experiment. Studies of the genotoxic effect of various groups of pesticides carried out on human and animal cell cultures showed that DDD (Perry et al., 2016), HCH (Pool-Zobel et al., 1994), aldrin (Dulout et al., 1985), endosulfan 2 (Rani and Reddy, 1986) and chlordane ((Sarkar et al., 1993) cause various types of chromosomal aberrations and DNA damages. It should be noted, that the genotoxic effect of HCB and HBB has been studied extremely poorly. In animal experiment conducted in 1960–1990, the lethal doses of DDD, DDT, DDE (Ben-Dyke et al., 1970; Tomatis et al., 1974), HCH, aldrin, deldrin, chlordane (Gaines, 1960; Lu et al., 1965; Usharani and Reddy, 1986), HCB (Cantoni and Comi, 1997; Cuomo et al., 1991), derivatives of endosulfan (Hoechst, 1982) and dicofol (Deichmann and Keplinger, 1970) were determined.

A number of studies report the effects of pesticides on the cardiovascular and circulatory system. For example, exposure to HCB, HBB, aldrin, deldrin, endosulfan, and chlordane can result in cardiovascular disorders such as tachycardia, hypertension, and strokes (Gralla et al. (1977), Kalender et al., 2004; Jalil et al., 2007, Wang and MacMahon, 1979). Few data show increased a weak correlation of exposure of DDT or similar compounds with effect on cardiovascular system (Lee et al., 2012; Lind et al., 2014). Animal and human studies revealed a haematological effect of DDT (Serdar et al., 2014), γ-HCH (Joseph et al., 1992), HCB (Kuiper-Goodman et al., 1977), endosulfan 2 (Lo et al., 1995) and chlordane (Jonson et al., 1986). The effects of HCE on rats and rabbits led to histological and anatomopathological abnormalities (Weeks et al., 1979; Gorzinski et al., 1985). Most of studies on pesticides genotoxicity were done in animal models. However, there were some reports on human populations that POPs can induce the disorders of reproductive (Bretveld et al, 2006) and endocrine system (Evangelou et al., 2016), cancer (Guyton et al., 2015), respiratory failure (Sapbamrer et al., 2020), delayed development of the nervous and immune systems (Galloway and Handy, 2003), embryotoxicity (Gilden et al., 2010; Mohamed et al., 2015), and skin-resorptive effect (Mesnage and Séralini, 2018).

Taking into account the extremely small number of comprehensive studies on pesticides influence on human food chain and mechanisms of disease induction, and also the absence of projects for study of POPs long-term effects on human populations, we hope, that our primary results will promote the further investigations of pesticides influence on health and genetic status of population living on the polluted territories.

5. Conclusion

Our pilot study revealed that forbidden obsolete pesticides spread out of the ancient storage warehouses in the environment and contaminated the food chain in the concerned villages. Indeed food products sampled in these villages were contaminated, sometimes several hundred times over MRL, as well as food from plant as from animal origin.

Indeed, we have to deal with the uncertain effects of hazard pesticides mixtures that for many years pollute the environment, the food chain and affect the genetic status and human health. The results indicate the association of pesticides content in food of plant and animal origin with cytogenetic damages and somatic health status. Research will continue to get more information about the soil, water contamination, assessment of pesticides genotoxicity using model experiments, study the effects on the fodder plants and farm animals. Perhaps, more complete data allow us to conduct the principle component analysis and elucidate the mechanisms of separate pesticide groups action. We anticipate that our pioneer research will contribute to further studies of the long-term effects of pesticides on the human environment, food chain, and health.

The results of our research raise the question of necessity to promote public awareness regarding the practice of pesticides using and strengthen the food safety control services as a measures to protect public health. To ensure that there is no threat to public health, it is important to involve the regional administrative resource and private land owners to the joint utilization of unused banned pesticides stocks, land remediation, recultivation, and regulation the control system of food safety from pesticide contamination.

Credit author statement

Erika Djangalina: Conceptualization, Writing - original draft. Nazym Altynova: Conceptualization, Writing - original draft: Investigation, Writing - original draft preparation. Unzira Kapysheva: Investigation, Writing - original draft. Bolat Zhaksymov: Data curation, Formal analysis. Elvira Shadenova: Resources, Investigation. Mukhtar Baizhanov: Resources, Investigation. Oraz Sapargali: Resources, Software. Alexander Garshin: Methodology, Data curation. Akerke Seisenbayeva: Methodology, Investigation. Matthieu Delannoy:Validation, Formal analysis. Stefan Jurjanz:: Conceptualization, Writing-Reviewing and Editing. Elmira Khussainova: Project administration. Bakhytzhan Bekmanov: Resources, Supervision. Leyla Djansugurova: Conceptualization, Writing-Reviewing and Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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