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Research article

De novo congenital malformation frequencies in children from the Bryansk region following the Chernobyl disaster (2000–2017)

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A R T I C L E I N F O

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A B S T R A C T

Background: Ionizing radiation and chemical pollution can disrupt normal embryonic development and lead to congenital malformations and fetal death. We used official government statistical data for 2000–2017 to test the hypothesis that radioactive and chemical pollutants influenced the frequency of *de novo* congenital malformations in newborns of the Bryansk region of southwest Russia.

Methods: A variety of statistical approaches were used to assess congenital malformation frequencies including the Shapiro-Wilk test, White's homoscedasticity test, Wilcoxon T-test, Spearman's rank correlation test, and the inversely proportional regression.

Results: We found that the frequency of polydactyly, multiple congenital malformations, and the frequency of *de novo* congenital malformations in newborns were significantly higher ($p = 0.001–0.054$) in regions with elevated radioactive, chemical and combined contamination. Polydactyly, multiple congenital malformations, and the sum of all congenital malformations were 4.7–7.4 times, 2.5–6.8 times, and 3.5–4.6 times higher in contaminated regions in comparison with the control group. The combination of both radioactive and chemical pollutants led to significantly higher frequencies of multiple congenital malformations when compared to regions with only one pollutant (radiation alone: 2.2 times, $p = 0.034$; chemical pollutants alone: 1.9 times, $p = 0.008$) implying that the effects of these stressors were at minimum additive. Although there was a trend for decreasing frequencies of multiple congenital malformations during the 2000–2017 period in areas of combined pollution, the opposite was true for regions with radioactive or chemical pollutants alone. However, overall, our models suggest that the frequency of multiple congenital malformations in areas of combined pollution will significantly ($p = 0.027$) exceed the frequencies observed for regions containing radioactive or chemical pollutants alone by 39.6% and 45.7% respectively, by 2018–2023.

Conclusion: These findings suggest additive and potentially synergistic effects of radioactive and chemical pollutants on the frequencies of multiple congenital malformations in the Bryansk region of southwestern Russia.

1. Introduction

In humans, there are more than 8000 genetically caused developmental anomalies (McKusick, 1998). Even healthy newborns have 3–5 such anomalies. In addition to small anomalies, large congenital malformations (CM) are sometimes seen. The main factors associated with development abnormalities are genetic and environmental factors including the influence of pollution, background radiation, diet, disease and parasites. Genetic mutations and other forms of genetic damage are also influenced by the chemical and physical environment and radiation and chemical pollutants are well known teratogens (Gilbert-Barness, 2010). Therefore, CM rates can be considered as indicators of adverse factors in the environment (Bochkov and Chebotaryov, 1989).

For example, about 3.3% of live births in the United States have a major birth defect associated with CM (Parker et al., 2010). Major CMs account for 20% of US infant deaths as well as 2.3% of premature death and disability (McKenna et al., 2005). According to EUROCAT, an overall frequency of CM lower than 20 per 1000 is likely the result of incomplete identification or underestimation of malformations (EUROCAT, 2011). These defects are thought to originate in the first trimester of pregnancy

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as a result of inherited disease or environmental interactions (Brent, 2004*)*. Environmental risk factors for birth defects include folate deficiency, maternal smoking, alcohol abuse and radiation.

Ionizing radiation can disrupt normal embryonic development and lead to both fetal death and congenital malformations (CM) including physical abnormalities, metabolic disorders, as well as genetic defects (ICRP, 2003; BEIR, 2006). The formation of these pathologies depends on the level of irradiation (i.e. dose) and the stage of embryonic development at which exposure occurs. Ionizing radiation causes mutations in the germ cells of parents and can interfere with the processes of prenatal development in its early stages. The radionuclides incorporated in the maternal parent can cause embryonic dysplasia, structural, and functional changes in the developing organs and tissues of the embryo and fetus, which can lead to stillbirth of the fetus (in cases of higher exposure) and to the appearance of CM (ICRP, 2003; BEIR, 2006).

Even 32 years after the Chernobyl disaster, many parts of Ukraine, Belarus and Russia remain heavily contaminated with radioactivity, caused mainly by the long-lived isotopes of Cs-137 and Sr-90 (half-lives of 30y and 29y, respectively). This contamination is radiologically significant and will remain significant for decades if not centuries (Izraehl' and Bogdevich, 2009; Onishchenko, 2009; National Report of Ukraine, 2011; National Report of the Republic of Belarus, 2016; Russian national report, 2016; Yablokov et al., 2016; Brechignac et al., 2016).

There are currently 316,000 people spread across 749 settlements living in radioactively contaminated areas of the Bryansk region (Decree of the Government of the Russian Federation of 10.08.2015 No. 1074). Monitoring of the radiation situation for 30 years after the disaster shows that the processes of soil self-purification from long-lived radionuclides are slow. In some districts, the soil contamination density by Cs-137 and Sr-90 in the southwest territories (SWT) of the Bryansk region in 2015 exceeds regulatory limits (37 kBq/m^2 for Cs-137 and 5.6 kBq/m^2 for Sr-90) by ten times (up to 2116 kBq/m^2 for Cs-137 and up to 60 kBq/m^2 for Sr-90) (Data on radioactive contamination of the territory of populated areas of the Russian Federation, 2015). The average cumulative effective doses of exposure to residents of radiation-contaminated areas of the Bryansk region (1986–2016) vary up to hundreds of mSv, and the maximum calculated dose is 299 mSv which was noted for residents of the village of Zaborie, Krasnogorsky district (Bruk et al., 2017).

Although a number of authors have suggested that there are no convincing population-epidemiological data on the effect of radiation contamination at low doses on the frequency of CM (Dolk and Nichols, 1999; Dolk, 2004; Bochkov, 2008; Demikova et al., 2010), population-ecological data show that the frequency of CM increased in the Republic of Belarus for 15 years after the disaster by a factor of 1.7 times (National Report of the Republic of Belarus, 2016; Yablokov et al., 2016), and in Ukraine – by 5.7 times (National Report of Ukraine, 2011; Yablokov et al., 2016). Especially significant was the increase in CM in areas with a level of Cs-137 contamination of more than 555 kBq/m^2 in the Gomel and Mogilyov regions of Belarus, with the maximum occurrence of CM in the Gomel region in 1994, of six times higher than the 1986 level (Lazyuk et al., 1999a). The total frequency of CM in the radiation-contaminated areas of Zhytomyr region of Ukraine in 2000–2010 was significantly higher than in control areas (Timchenko et al., 2014), and in 2005–2008 in the radiation-contaminated areas of the Ukrainian Polesie (Rivne, Volyn, Zhytomyr, Kiev, Chernihiv and Sumy regions) showed an excess of 1.8 times the frequency of CM of neural tube defects compared with the average for European data (2.6 times for microcephaly, 2.2 times for congenital cataract, 2.1 times for anencephaly and 1.6 times for microphthalmia) (Dancause et al., 2010). The incidence of teratoma in the Rivne region of Ukraine in 2000–2009 is 2.5 times higher, and of conjoined twins is three times higher than the average in European countries (Wertelecki, 2010; Wertelecki et al., 2014). In addition, the frequency of occurrence of multiple congenital malformations (MCM) and previously rare CM (including polydactyly, deformed internal organs, limb reduction defects, cessation of the growth) were significantly increased compared with the control districts (National Report of Ukraine, 2011; Yablokov et al., 2016).

According to the Russian State Medical and Dosimetry Registry, which includes data for more than 30,000 children, 46.7% of the children born to liquidators of the Chernobyl disaster had CM and genetic diseases (with a predominance of the musculoskeletal system), and the prevalence of CM among children of liquidators is 3.6 times higher than the national indicators (Ivanov, 2002; Yablokov et al., 2016).

Ten years after the Chernobyl disaster, the incidence of CM for radiation-polluted SWT of the Bryansk region was 1.5 times higher than for the whole region, and the proportion of CM was almost five times higher than the average value of this indicator across Russia for cases of infant mortality (Zhilenko and Fedorova, 1999; Yablokov et al., 2016). A significant excess of the total and primary morbidity rates of the total frequency of all CM of children in the SWT was found in comparison with the same indicators of ecologically safe territories of the Bryansk region for 1990–2009 (Korsakov et al., 2014). In addition, within the SWT, the highest frequency of incidence of polydactyly, limb reduction defects (LRD) and MCM in 1999–2014 was identified in areas with a higher level of radioactive contamination (more than 370 kBq/m^2) (Korsakov et al., 2016a).

Some CM are the result of so-called *de novo* mutations which arise in the population. De novo mutations arise during gametogenesis or during early embryonic development and can determine the expression of CM such as polydactyly, LRD and MCM in offspring (Lazyuk et al., 1999; Yablokov et al., 2016; Holtgrewe et al., 2018). It was found that these de novo CM are found significantly more often in areas with a concentration of Cs-137 contamination of more than 555 kBq/m^2 (Lazyuk et al., 1999; Yablokov et al., 2016). Therefore, we studied precisely these de novo CM (polydactyly, LRD, and MCM).

Chemical pollution of the environment as well as radioactive contamination can disrupt embryonic development and lead to the formation of CM (Brent, 2004; Antonov et al., 2008; Antonova et al., 2010). Analysis of environmental monitoring data of air and soil pollution by various pollutants has revealed negative effects on the frequency of formation of CM (Antonov et al., 2008; Verzilina et al., 2008, 2015; Trifonova and Marcev, 2015).

Antonov et al. (2008) analyzed the relationship between indices of the frequency of newborns with CM and the average annual concentrations of pollutants in the atmosphere of the city of Omsk, and found significant correlations between the frequency of MCM and concentrations of carbon monoxide, phenol, inorganic dust and sulfur dioxide ($r = 0.6–0.9$), and with the fraction of samples exceeding the maximum permissible concentration (MPC) ($r = 0,71$). Verzilina et al. (2015) found that under conditions of high air pollution in the city of Belgorod (4–10 MPC), there was a negative impact of 56 atmospheric pollutants on the incidence rate of CM in newborns. The authors also established significant indicators of the relative environmental risk for the incidence of neonatal CM of musculoskeletal and urinary systems and the MCM of the Belgorod region under conditions of increased load of mineral fertilizers on the arable land (Verzilina et al., 2015). There were also significant correlations between the total frequency of CM and chemical emissions into the atmospheric air of the Vladimir region *(*Trifonova and Marcev, 2015*)*. In addition, maternal involvement in agricultural activities during the first trimester of pregnancy was a significant risk factor for CM (Garcia et al., 1999; Stemp-Morlock, 2007). In particular, it was found that organochlorine pesticides and organic solvents are potential risk factors for congenital heart defects (Gorini et al., 2014).

In the Bryansk region, in addition to areas with intense radiation pollution after the Chernobyl disaster (Data on radioactive contamination of the territory of populated areas of the Russian Federation, 2015*)*, territories of combined radiation and chemical pollution are common (Korsakov and Mihalev, 2010; Geger, 2012).

It should be noted that in 2016 in the Bryansk region, the total amount of gaseous chemical emissions into the atmosphere was 199.9 thousand tons, 57.6 million cubic meters of untreated wastewater was discharged into water bodies, the amount of production and consumption wastes exceeded 1.3 million tons, the volume of application of herbicides increased by 23% compared with 2015, and mineral fertilizer use increased by 30% (On the state and environmental protection of the Russian Federation in 2016, 2017) . In addition, the Bryansk region is among the regions of the Russian Federation with the greatest loss of forests (1000 ha in 2015 and 700 ha in 2016) (On the state and environmental protection of the Russian Federation in 2016, 2017) and according to the rating of the ecological development of Russian cities in 2017 (Environmental development rating of Russian cities in 2016, 2017Environmental development rating of Russian cities in 2016, 2017), it is classified as an underdeveloped region by indicators such as air quality, water quality, waste management, land use, transportation, energy consumption and environmental management.

At the same time, despite the known geographic distribution of radioactive pollutants in the Bryansk region, the consequences of the Chernobyl disaster are still relatively understudied and there has been no consideration of possible additive and synergistic effects of chemical pollutants under the combined action of physical and chemical environmental factors (Korsakov and Mihalev, 2010; Geger, 2012).

The study of the frequency of malformations in newborns under such conditions is extremely important, not only for assessing the effect of low-level Chernobyl-derived radioactive contamination, but also for assessing the effectiveness of the contribution of concomitant chemical pollution of the environment to the frequency of formation of CM in radioactively contaminated areas affected by the Chernobyl disaster. The frequency of *de novo* CM (polydactyly, LRD and MCM) in newborns with such multi-factor environmental contamination has not been studied before and is the main topic of this ecological research.

2. Methods

Data for 2000–2017 concerning the frequencies of polydactyly (Q69), LRD (Q71-Q73) and MCM (Q87, Q89.7, Q91.0, Q91.4) for children born polluted areas were compared with data for control areas (Kletnyansky and Mglinsky). Data concerning CM frequencies were obtained from official publications of the Bryansk region (sectoral statistical reporting form No. 60, form No. 025-11/y-98) given by the Bryansk Clinical Diagnostic Center. Data on the occurrence of CM are obtained from the automated information-analytical system “Monitoring CM” (computer screening), which is a database of all newly diagnosed cases of CM in children and fetuses registered in the Bryansk region. The study was based on data from obstetric institutions and gynecological clinics in the region, children's clinics and hospitals, and women's clinics. The monitoring registered *de novo* CM detected during the neonatal period, such as polydactyly, LRD and MCM, which, in accordance with the International Classification of Diseases of the 10th revision, fall into the XVII class “Congenital malformations, deformations and chromosome disorders". The period of the statistical study was 18 years (2000–2017). The subsequent calculation of the absolute values of the *de novo* CM frequency (polydactyly, LRD and MCM) were conducted according to the recommendations of EUROCAT as the ratio of the number of live and stillborn children with developmental defects (including induced abortions weighing ≥500 g at 22 or more weeks gestation) to the total number of live and stillbirths, multiplied by 1000 (EURO-PERISTAT Project, 2008).

In total, for 2000–2017, 476 cases of *de novo* CM were registered in the Bryansk region, including 187 cases of polydactyly, 73 cases of LRD, and 216 cases of MCM.

The density of radioactive contamination of the territories (Cs-137 and Sr-90) due to the Chernobyl disaster was estimated according to “Data on radioactive contamination of the territory of populated areas of the Russian Federation, 2015”. The average annual effective dose to the population from the Chernobyl component was estimated according to the data of information guide Trapeznikova (2018). It should be noted that the level of natural background radiation (exposure dose rate of gamma radiation) in all uncontaminated districts of the Bryansk region does not exceed 0.20 μSv/hour and in radiation-contaminated areas it often exceeds 0.30 μSv/hour and in some settlements the exclusion and resettlement zones values reach 0.8–1.6 μSv/hour (Trapeznikova 2018). Data for chemical pollution was acquired from reports on emissions of chemicals into the atmosphere from stationary sources (Muratova, 2018). Recalculation of the amount of gross emissions of chemicals into the atmosphere (tons/year per km^2) was converted to g/m^2 according to Muratova (2018).

Statistical analyses were conducted using the Stata package (Stata/SE version 14). First, we checked the normality of the distribution of the frequency of the CM in all groups. Due to the small sample size ($n = 18$), we applied the *Shapiro-Wilk criterion* that is widely used in such situations. This analysis suggested that the measurements were not normally distributed ($p > 0.20$) and so we used the *Wilcoxon nonparametric T-test* for our analyses.

Initially, many of our analyses used a linear regression of the frequency of de novo CM in newborns in relation to contamination levels in different areas of the Bryansk region during the period 2000–2017. However, these initial tests indicated that linear regression unsatisfactorily approximates the available data: the standard deviation is large, and the subsequent predictions are not reliable. Therefore, we applied the inversely proportional regression (Hansen, 2019) which is more flexible and more closely matches the original data.

We tested for homoscedasticity in the data using the *White test* (Hansen, 2019). We found that in most cases homoscedasticity is satisfactory and thus allows the use of standard statistical methods recommended for such situations. Since the normality of the distribution of the *de novo* CM is violated, we used non-parametric statistical analyses (*Spearman's rank correlation test)* for testing the hypothesis that the frequency of polydactyly, LRD and MCM varied among years. Calculations of 95% confidence intervals were carried out for the coefficient a (see below), showing the direction of the trend.

Based on the statistical data available for 2000–2017, we calculated a predicted frequency of polydactyly, LRD and MCM in the studied areas. For this, we used the least squares method (using the linearization technique) inversely proportional function $y = a\overline{x}+b$, where $\overline{x} = 6/x$. Coefficient 6 is very important here, since we investigated six three-year periods ($x = 1,2,\ldots,6$) and without it, the interval for $\overline{x}$ on the abscissa axis would decrease six times, which would lead to an artificial increase in errors and confidence intervals. Using the obtained function, we calculated a forecast for two upcoming three-year periods (2018–2020 and 2021–2023).

3. Results

Data on the density of radioactive contamination with Cs-137, Sr-90 and the level of chemical pollution with the main gaseous pollutants varied widely in districts of the Bryansk region (Table 1). Cs-137 varied from 5.5 to 466 kBq/m^2, while Sr-90 varied from 0.5 to 16.7 kBq/m^2 (Data on radioactive contamination of the territory of populated areas of the Russian Federation, 2015). The average annual effective doses to the population from the Chernobyl component varied from less than 0.1 up to 2.1 mSv per year (Trapeznikova, 2018). Thus, cumulative doses over an 18-year period (2000–2017) in radiation-contaminated areas ranged from 12.1 to 37.9 mSv. Gross contamination levels resulting from gaseous pollutants into the atmospheric air per area of the region (g/m^2) varied from 22.6 to 29600, of which carbon monoxide (CO) ranged from 2.3 to 12600, nitrogen oxides (NO_x) ranged from 0.5 to 10700, sulfur dioxide (SO_2) ranged from 0.0 to 2660 and volatile organic compounds (VOC) ranged from 0.7 to 3620 (Muratova, 2018).

We ranked the territories of the Bryansk region based on the levels of radioactive and chemical pollution over the 18 year study period (2000–2017) (Table 1). Thus, in the group of ecologically safe (control) territories, the density of radioactive contamination with Cs-137 and Sr-90 was 5.5–6.8 and 0.5–0.6 kBq/m^2 respectively, which is several times less than regulatory limits (no more than 37 kBq/m^2 for Cs-137 and 5.6

Table 1. Ranking of areas within the Bryansk region by the level of radiation and chemical pollution (2000–2017).

N	Districts of the Bryansk region	Main gaseous air pollutants					Cs-137 contamination density, kBq/m^2	Sr-90 contamination density, kBq/m^2	Average annual effective dose, mSv
		Total	Of them:						
			VOC*	NO_x	SO_2	CO			
		Gross emissions of gaseous pollutants per area, g/m^2							
Ecologically safe territories (control)									
1	Kletnyansky *(n = 20861)*	22.6	0.7	6.6	7.2	8.0	5.5	0.5	<0.1
	Mglinsky *(n = 20382)*	28.6	5.4	8.8	1.9	12.4	6.8	0.6	<0.1
Territories of chemical pollution									
2	Dyatkovsky *(n = 76012)*	9460	346	3790	2000	3310	39.3	1.1	0.2
	Bryansk city *(n = 439901)*	29600	3620	10700	2660	12600	9.0	6.1	<0.1
Territories of radioactive contamination									
3	Novozybkovsky *(n = 12849)*	9.0	5.0	0.5	0.0	2.3	470	8.6	2.1
	Krasnogorsky *(n = 14472)*	18.0	0.7	7.5	0.7	9.1	310	9.5	1.4
	Gordeevsky *(n = 12526)*	39.6	3.0	16.8	0.0	19.8	335	5.1	1.3
	Zlynkovsky *(n = 13180)*	56.2	4.1	17.3	7.2	27.6	421	16.7	1.8
	Klimovsky *(n = 31273)*	66.1	1.1	10.6	20.5	33.9	142	6.5	0.7
Territories of combined radiation-chemical contamination									
4	Klintsy city *(n = 71915)*	8170	1330	3650	165	3020	200	3.0	1.2
	Novozybkov city *(n = 41608)*	8220	1080	3180	771	3180	466	10.0	2.0

* Volatile organic compounds (VOC).

kBq/m^2 for Sr-90). The average annual effective doses to the population from the Chernobyl component is less than 0.1 mSv per year. The level of chemical contamination due to air pollution ranged from 22.6 to 28.6 g/m^2. Given these relatively low levels of contaminants, we have classified these areas as ecologically safe (control).

We have classified some areas as chemically polluted where gross emissions of gaseous pollutants per area of the region exceeded those of the control areas by hundreds to thousands of times, ranging widely from 9460 to 29600 g/m^2, of which CO varied from 3310 to 12600 g/m^2, NO_x varied from 3790 to 10700 g/m^2, SO_2 varied from 2000 to 2660 g/m^2, and VOC varied from 346 to 3620 g/m^2. In these regions the density of radioactive contamination ranged from 9.0-39.3 kBq/m^2 for Cs-137 and 1.1–6.1 kBq/m^2 for Sr-90, which are relatively low and thus these territories are classified as chemically contaminated alone. It should be noted that the average annual effective doses to the population from the Chernobyl component were very small values ranging from less than 0.1–0.2 mSv per year.

A third group of territories had densities of Cs-137 and Sr-90 that exceeded the established limits by 3.9–12.7 times for Cs-137 (up to 470 kBq/m^2) and 1.2–3.0 times for Sr-90 (up to 16.7 kBq/m^2). Therefore the average annual effective doses to the population from the Chernobyl component varied from 0.7 to 2.1 mSv per year. In these regions, the level of chemical pollution of atmospheric air was comparable to control areas, ranging from 9.0 to 66.1 g/m^2. Thus, we refer to these areas as "territories of radioactive contamination".

In the territories of combined radiation and chemical pollution, the density of radioactive contamination, as with radiation-contaminated areas, exceeds regulatory limits tenfold: up to 466 kBq/m^2 for Cs-137 and slightly less (up to 10 kBq/m^2) for Sr-90. The average annual effective doses to the population in these territories from the Chernobyl component varied from 1.2 to 2.0 mSv per year. At the same time, in addition to the high level of radioactive contamination, the level of chemical pollution by gaseous pollutants was hundreds of times higher than the values of radiation-contaminated areas, amounting to 8170–8220 g/m^2, which allows us to classify them as combined radiation-chemical areas (Table 1). Table 1 also indicates the average population of a city or district (n) during 2000–2017. This ranges from 12526 to 439901 on average per year.

Dynamics of the number of newborns in ecologically different territories of the Bryansk region in 2000–2017 presented in Table 2. The data in Table 2 indicates the number of newborns in the territories of chemical pollution varied from 4038 to 6230 per year, in the territories of radioactive contamination and from 705 to 1146 in the territories of combined contamination – from 991 to 1351 and in ecologically safe territories – from 300 to 454.

The dynamics of the frequency of *de novo* CM in newborns of ecologically different territories of the Bryansk region in the period 2000–2017 shows that the values range from 0 to 3.99 (the frequency of total CM reaches up to 6.57), although frequencies vary over the years, especially in areas of radioactive and combined contamination, both in polydactyly and in LRD and MCM (Table 3).

The average frequency of *de novo* CM in newborns in the Bryansk region in the period 2000–2017 are presented in Table 4. Table 4 also indicates the total number of births *(n)* for 2000–2017. Thus, the total number of births in ecologically safe territories amounted to 6553 births, for areas of chemical pollution – 93581, for areas of radioactive contamination – 16573 and for areas of combined contamination – 21009 births.

In the rest of the table, p means significance level while checking the hypothesis about differences between the ecologically unfavorable territories with control.

Table 2. Dynamics of the number of newborns in ecologically different territories of the Bryansk region in 2000–2017.

Years	Territories*			
	CP	RC	CC	ES
2000	4038	959	1018	422
2001	4080	915	1004	390
2002	4210	857	991	353
2003	4626	840	1100	398
2004	4989	810	1119	380
2005	5115	814	1131	361
2006	4990	790	1062	329
2007	5009	705	1024	351
2008	5415	879	1139	381
2009	5642	1012	1195	454
2010	5827	966	1263	399
2011	5511	970	1182	368
2012	5500	985	1302	334
2013	5723	1074	1309	340
2014	5465	1104	1351	367
2015	5209	1146	1332	300
2016	6230	940	1268	325
2017	6002	807	1219	301

* Territories: CP – chemical pollution; RC – radioactive contamination; CC – combined contamination.; ES – ecologically safe.

Table 4 indicates that in the control group, the frequency of polydactyly, MCM and the total of *de novo* CM in newborns was significantly lower than in the territories of radioactive, chemical, and combined pollution ($p = 0.001–0.054$). Rates of polydactyly were lower by 4.7–7.4 times, MCM was lower by 2.5–6.8 times, and total CM was lower by 3.5–4.6 times. The number of LRD is also lower in the control group compared to polluted territories (1.5–1.8 times), but the differences reached statistical significance only in comparison with areas of chemical pollution likely because of the high variability among different locations.

There were no statistically detectable differences in the frequency of polydactyly, LRD and the total of CM in newborns among the territories of radiation, chemical and combined environmental pollution; all showed dramatically higher frequencies than control regions. However, significant differences were found in the occurrence of MCM in conditions of combined pollution (1.48 ± 0.30), exceeding the levels for both radioactive (2.2 times, $p = 0.034$) and chemical pollution sites (1.9 times, $p = 0.008$) (Table 4).

It should be noted that under the influence of various factors of environmental stress, we found certain regularities. Our data suggest that MCM and polydactyly are more variable than LRD (Table 4). The maximum occurrence of MCM is detected under conditions of combined pollution (1.48 ± 0.30), while polydactyly varies more under conditions of radioactive contamination (1.01 ± 0.27). The frequency of the LRD is similar under all contaminant conditions ranging from 0.40 to 0.44 (Table 4).

Since the dynamics of *de novo* CM frequency in newborns varies considerably among years (Table 3), we calculated the inverse proportional regression over three-year periods (2000–2002, 2003–2005, 2006–2008, 2009–2011, 2012–2014, 2015–2017) and used this model to forecast CM rates for the subsequent six-year periods (2018–2020 and 2021–2023) (Figures 1, 2, and 3).

As seen in Figure 1, this analysis demonstrates an increase in the multi-year trend in the frequency of polydactyly during the eighteen-year period (2000–2017) in the territories of the chemical (from 0.69 in 2000–2002 to 0.93 in 2015–2017) and combined (from 0.55 to 0.74) pollution, but a decrease (from 0.64 to 0) in unpolluted areas. However, both the decreasing and increasing trends were not statistically significant, reaching maximum values in unpolluted areas ($\rho = -0.65$, $p = 0.16$). In the radioactively polluted territories, the values of the multi-year trend (including forecasts) changed little, amounting to 1.0–1.01 ($y = -0.01/x+1,014$). The predicted values of the frequency of polydactyly in 2018–2023 (Figure 1) in the areas of chemical pollution exceed the average values for 2000–2017 (Table 4) by 9.3% (0.94 and 0.86), and in the areas of combined pollution by 9.6% (0.745 and 0.68). A similar forecast for 2018–2023 in unpolluted areas would be 0.01 per 1000 births, with an average 0.12 in 2000–2017.

The results of the analysis of the frequency of the LRD in newborns of ecologically different areas of the Bryansk region showed a non-significant increase of the multiyear trend in the areas of combined pollution (from 0.09 in 2000–2002 to 0.53 in 2015–2017) and in control areas (with 0–0.22), but a decrease in the territories of radioactive (from 1.05 to 0.19) and chemical (from 0.70 to 0.33) pollution. The predicted values for 2018–2023 in the territories of combined pollution exceed the observed values for 2000–2017 by 36.3% (0.545 and 0.40), while conversely, in the territories of radioactive and chemical pollutants, are predicted to decrease by 2.8 (0.16 and 0.44) and 1.4 times (0.31 and 0.43), respectively. The forecasted frequency of LRD in the control areas is small in comparison with other areas for 2018–2023 (0.235 per 1000 births), but it is predicted to exceed the average values of 2000–2017 (0.16) by 1.5 times (Figure 2).

The analysis of MCM dynamics in newborns in the Bryansk region showed no significant change in the long-term trend of MCM frequency across all regions regardless of environmental conditions (Figure 3). An increase in the multiyear trend from 0.29 to 0.83 and from 0 to 0.28 was found for territories of radioactive contamination and control, while in areas of chemical contamination there was a slight increase (from 0.71 to 0.81). A decrease in the multiyear trend by 1.73 times (from 2.11 to 1.22) was observed in the territories of combined pollution. Nevertheless, the predicted values of the MCM frequency in 2018–2023 will still be significant ($p = 0.027$) and exceed the average indicators of the territories of radioactive and chemical pollution by 39.6 and 45.7% respectively (1.18 versus 0.845 and 0.81 respectively). The predicted values for 2018–2023 under conditions of combined pollution will be less than the values for 2000–2017 by 20.3% (1.18 and 1.48), while under conditions of radioactive and chemical pollutants, predicted values will increase by 26.1% and 3.8% (0.845 and 0,67; 0.81 and 0.78). However, the forecast frequency of MCM for 2018–2023 will exceed the average values for 2000–2017 by 1.6 times (0.295 and 0.19) (Figure 3).

In addition to analyzing the temporal dynamics of the *de novo* CM for 2000–2017 (Figures 1, 2 and 3), we calculated the relationship among territories relative to environmental conditions, which revealed interesting regularities. There was a high and significant direct correlation of the frequency of the MCM among the territories of chemical and combined pollution ($\rho = 0.89$, $p = 0.019$), but there was no dependence in the territories of radioactive and combined pollution ($\rho = 0.09$, $p = 0.872$). With respect to LRD, a high and significant inverse correlation was also found among the territories of chemical and combined pollution ($\rho = -1.0$, $p = 0.001$), but a lack of dependence between the territories of radioactive and combined pollution ($\rho = -0.07$, $p = 0.910$). No significant dependencies were found among the regions for the frequency of polydactyly.

4. Discussion

The WHO and IAEA have suggested that levels of radioactive pollution caused by the Chernobyl accident are too low to cause a statistically significant increase in the frequency of congenital malformations (CM) (Chernobyl Joint News Release, 2005; IAEA, 2006). However, a review of the literature suggests a different story. For example, many studies have suggested a link between exposure to Chernobyl-derived fallout and the incidence of CM including Down syndrome, anencephaly, polydactyly, limb reduction defects, CM of the central nervous system, and multiple CM(e.g. Lazyuk et al., 1999; Zhilenko and Fedorova, 1999; Ivanov, 2002;

Table 3. The frequencies of *de novo* CM in newborns of ecologically different territories of the Bryansk region (per 1000 births) during 2000–2017.

Years	Polydactyly				LRD			
	Territories*				Territories*			
	CP	RC	CC	ES	CP	RC	CC	ES
2000	0.17	1.09	0.88	0.00	1.42	1.09	0.00	0.00
2001	0.70	0.00	0.00	2.20	0.29	0.00	0.00	0.00
2002	1.05	2.91	0.00	0.00	0.75	1.50	0.00	0.00
2003	0.93	0.67	1.89	0.00	0.00	3.52	0.00	0.00
2004	1.23	0.00	0.00	0.00	0.24	0.00	2.00	0.00
2005	0.65	0.67	1.20	0.00	0.00	0.00	0.00	0.00
2006	0.93	0.00	1.22	0.00	0.24	0.78	0.00	1.50
2007	1.00	0.00	0.00	0.00	0.33	0.00	0.53	0.00
2008	1.03	1.32	1.76	0.00	1.40	0.00	0.00	0.00
2009	0.63	1.33	1.28	0.00	0.10	0.00	0.00	0.00
2010	1.21	1.52	1.05	0.00	0.33	0.00	1.80	0.00
2011	0.39	0.00	2.07	0.00	0.22	0.00	0.00	0.00
2012	0.91	3.45	0.00	0.00	0.57	0.00	0.00	0.00
2013	0.61	0.94	0.98	0.00	0.11	0.00	1.60	0.00
2014	1.67	0.00	0.00	0.00	0.11	0.00	0.00	0.00
2015	0.61	1.12	0.00	0.00	0.83	0.00	0.00	0.00
2016	0.87	3.17	0.00	0.00	0.11	0.00	1.30	0.00
2017	0.87	0.00	0.00	0.00	0.71	1.11	0.00	1.30
Years	MCM				Total CM			
	Territories*				Territories*			
	CP	RC	CC	ES	CP	RC	CC	ES
2000	1.42	0.00	3.51	0.00	3.01	2.17	4.39	0.00
2001	0.43	0.00	1.90	0.00	1.42	0.00	1.90	2.20
2002	0.40	1.41	1.77	0.00	2.20	5.82	1.77	0.00
2003	0.73	0.00	0.00	0.00	1.66	4.19	1.89	0.00
2004	1.06	0.00	1.37	0.00	2.53	0.00	3.37	0.00
2005	0.24	0.00	0.00	0.00	0.89	0.67	1.20	0.00
2006	0.35	0.00	1.74	0.00	1.52	0.78	2.96	1.50
2007	0.78	1.44	1.67	0.00	2.11	1.44	2.20	0.00
2008	0.64	1.77	1.48	0.00	3.07	3.09	3.24	0.00
2009	0.61	0.00	1.14	0.00	1.34	1.33	2.42	0.00
2010	1.08	0.56	1.76	0.00	2.62	2.08	4.61	0.00
2011	0.44	1.30	3.42	1.75	1.06	1.30	5.49	1.75
2012	0.79	2.30	0.64	0.00	2.27	5.75	0.64	0.00
2013	3.16	0.94	3.99	1.60	3.89	1.88	6.57	1.60
2014	1.40	0.00	2.18	0.00	3.18	0.00	2.18	0.00
2015	0.00	1.25	0.00	0.00	1.44	2.37	0.00	0.00
2016	0.11	0.00	0.00	0.00	1.09	3.17	1.30	0.00
2017	0.34	1.12	0.00	0.00	1.92	2.23	0.00	1.30

* Territories: CP – chemical pollution; RC – radioactive contamination; CC – combined contamination; ES – ecologically safe.

Table 4. The frequency of *de novo* CM in newborns of the Bryansk region (per 1000 births, M ± m) in the period 2000–2017 according to environmental conditions.

Territories	CM *de novo*, M ± m			
	Polydactyly	LRD	MCM*	Total CM
Chemical pollution *(n = 93581)*	0.86 ± 0.08	0.43 ± 0.10	0.78 ± 0.17	2.07 ± 0.20
	p = 0.003	p = 0.016	p = 0.002	p = 0.001
Radioactive contamination *(n = 16573)*	1.01 ± 0.27	0.44 ± 0.22	0.67 ± 0.18	2.13 ± 0.41
	p = 0.008	p = 0.540	p = 0.054	p = 0.007
Combined contamination *(n = 21009)*	0.68 ± 0.18	0.40 ± 0.17	1.48 ± 0.30	2.56 ± 0.43
	p = 0.023	p = 0.231	p = 0.001	p = 0.001
Ecologically safe (control) *(n = 6553)*	0.12 ± 0.12	0.16 ± 0.11	0.19 ± 0.13	0.46 ± 0.19

*Significance level while checking the hypothesis about differences in the frequency of MCM between the territories of radioactive contamination and combined contamination (p = 0.034); chemical pollution and combined contamination (p = 0.008) according to the Wilcoxon T-test.

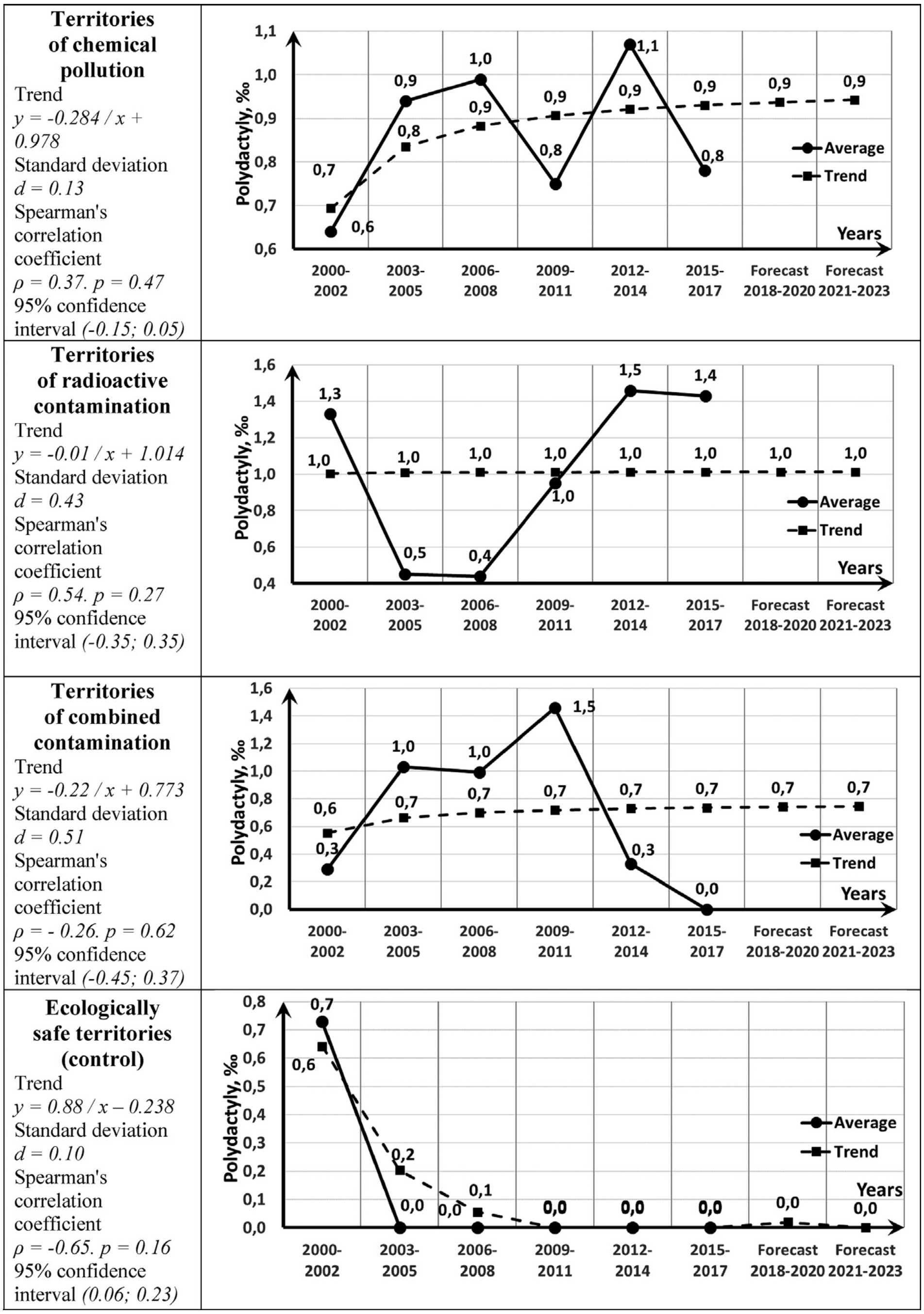


Figure 1. Dynamics of polydactyly frequency in newborns of ecologically different territories of the Bryansk region with a long-term trend line for three years in the period in 2000–2017 and forecast for 2018–2023 (per 1000 births).

Busby et al., 2009; TORCH, 2006, 2016; Dancause et al., 2010; Wertelecki, 2010; Wertelecki et al., 2014; Timchenko et al., 2014; Korsakov et al., 2014, 2016; Yablokov et al., 2016; Schmitz-Feuerhake, 2020).

WHO and IAEA experts have suggested that radiation doses due to Chernobyl are insufficient to induce CM, and have stated that "*Small, but steady increase in messages on congenital defects … belongs to the better statistics, not radiation*" (IAEA, 2006). However, others have suggested that the real cumulative doses are significantly higher than calculated (e.g. Datesman, 2020) and that even low levels of chronic radiation can generate significantly higher effects than the official radiation risk models employed by UNSCEAR and ICRP (Fairlie, 2005; TORCH, 2006; 2016; Busby et al., 2009; Yablokov et al., 2016; Korsakov et al., 2016; Schmitz-Feuerhake, 2020).

Perhaps the main reason for the lack of acknowledgement by WHO, IAEA, and UNSCEAR experts (Dolk and Nichols, 1999; ICRP, 2003; 2007; NCRP, 2013) of a relationship between the frequency of CM and radiation exposure from the Chernobyl accident is the perceived lack of correlation between the CM frequencies and dose. However, the dose reconstruction methods that were employed were inconsistent and inaccurate with enormous errors that failed to capture the relevant variation for the affected populations (Yablokov et al., 2016; Korsakov et al., 2016). The IAEA and WHO (Chernobyl Forum, 2005) estimate the collective dose for Belarus, Ukraine and European Russia at 55000 person-Sv. According to other estimates (CERRIE, 2004; Fairlie, 2005; TORCH, 2006, 2016), this collective dose reaches 326000 person-Sv. According to the National Report of Belarus (2016), only for Belarus

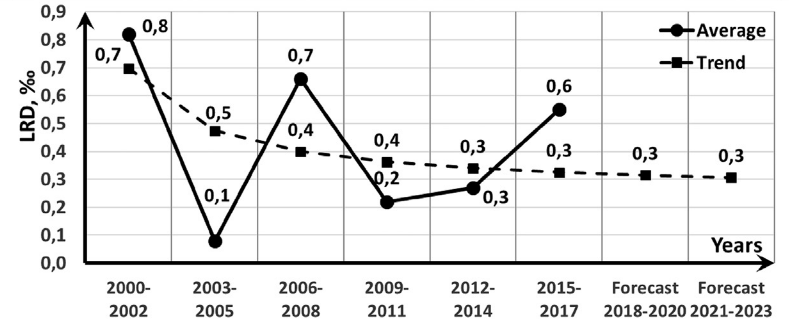
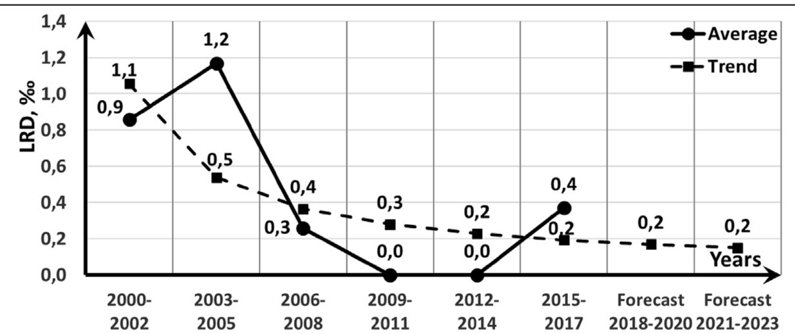
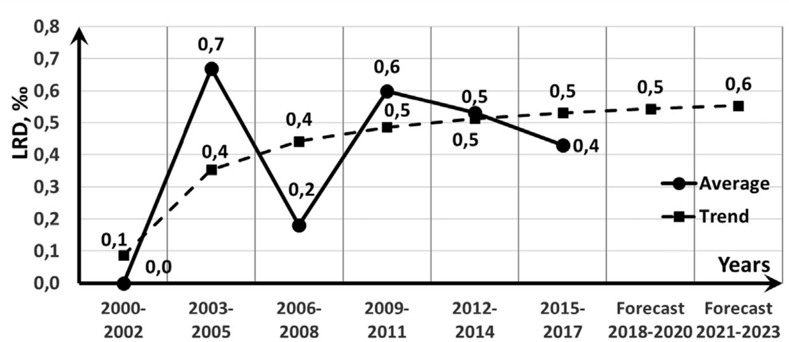
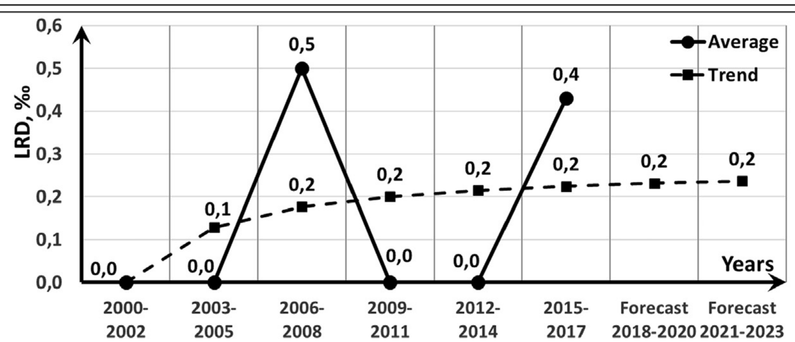
Territories of chemical pollution Trend $y = 0.446 / x + 0.251$ Standard deviation $d = 0.23$ Spearman's correlation coefficient $\rho = -0.20.\ p = 0.70$ 95% confidence interval *(-0.11; 0.26)*	
Territories of radioactive contamination Trend $y = 1.033 / x + 0.022$ Standard deviation $d = 0.32$ Spearman's correlation coefficient $\rho = -0.58.\ p = 0.23$ 95% confidence interval *(-0.09; 0.43)*	
Territories of combined contamination Trend $y = -0.532 / x + 0.619$ Standard deviation $d = 0.18$ Spearman's correlation coefficient $\rho = 0.20.\ p = 0.70$ 95% confidence interval *(-0.24; 0.06)*	
Ecologically safe territories	
(control) Trend $y = -0.288 / x + 0.273$ Standard deviation $d = 0.20$ Spearman's correlation coefficient $\rho = 0.30.\ p = 0.56$ 95% confidence interval *(-0.21; 0.12)*	

Figure 2. Dynamics of limb reduction defects frequency in newborns of ecologically different territories of the Bryansk region with a long-term trend line for three years in the period in 2000–2017 and forecast for 2018–2023 (per 1000 births).

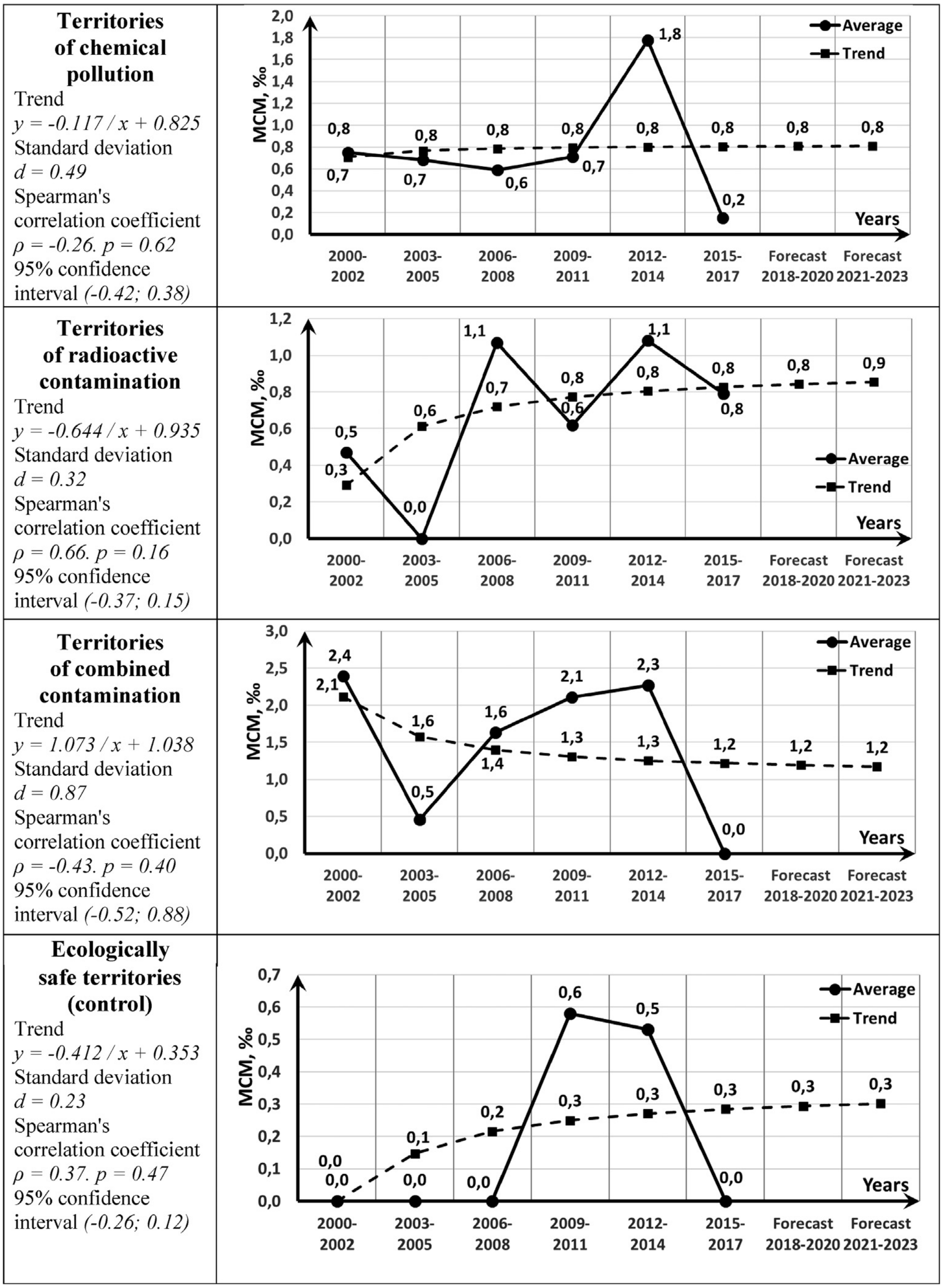


Figure 3. Dynamics of multiple congenital malformations frequency in newborns of ecologically different territories of the Bryansk region with a long-term trend line for three years in the period in 2000–2017 and forecast for 2018–2023 (per 1000 births).

this dose is 514000 person-Sv. Collective doses for Western Europe were also high and estimated (CERRIE, 2004; Fairlie, 2005) to be over 500000 personSv. For the whole world, the collective dose from the Chernobyl disaster can reach 930 000 person-Sv (TORCH, 2006, 2016). Therefore in practice, it is far more reasonable to use the actual measured levels of environmental contamination where people live, drink, eat and breath. When such direct approaches are used, relationships between contamination levels and biological effects are often observed (Yablokov et al., 2016).

Other areas of Europe were also affected by the Chernobyl disaster. For example, it has been reported that there were 1000–3000 additional cases of CM in Bavaria, Germany, during the five years after accident (Scherb and Weigelt, 2003). In addition, up to 2500 CM cases in newborns per year were reported in Belarus following the accident (Lazyuk et al., 1999a). Based on these findings, it is possible to predict that in areas across Europe contaminated with $\geq$37 kBq/m^2 there could be 10–13 thousand newborns with CM annually in the first five years after Chernobyl accident, about 6–8 thousand per year in years six to ten, about 3–5 thousand annually during the second decade after accident. . Thus, over the 30 years that have passed since 1986, the total number of newborns with congenital malformations could range as high as 140–170 thousand people (Yablokov et al., 2016; Korsakov et al., 2016).

Independent of the findings presented here, it should be noted that there is a tendency for increasing frequencies of CM, not only in the Bryansk region, but also for Russia in general, and the rest of the world, and this may reflect general trends similar to those observed for cancer incidence globally (Jemal et al., 2011; Yablokov, 2015; Torre et al., 2016). Some have suggested that this may reflect an increase of the genetic load in human populations due to the increase in chemical and radiation contamination of the biosphere by "global" (rapidly spreading from the place of pollution throughout the biosphere) and "eternal" (half-lives of which are more than a hundred years) pollutants (Yablokov, 2015). The International Commission on Radiological Protection claims that the genetic radiation risk is nearly negligible and radiation-induced effects after exposure in utero will not occur below doses of 100 mSv (ICRP, 2007). However, Schmitz-Fuerhake et al. (2016) discussed the clash between the current risk model and these observations on the basis of biological mechanisms and assumptions about linear relationships between dose and effect in neonatal and fetal epidemiology. Nearly all types of hereditary defects can be found at doses as low a 1–10 mSv indicating that current radiation risk models are inadequate for low dose environments.

It should be noted that potentiation and synergy among environmental stressors have been frequently observed (Koterov et al., 1997; Dergacheva et al., 1997; Sharetsky et al., 1997; Altenburger et al., 2003; Geras'kin et al., 2005; Barantseva et al., 2009; Komarova, 2009; Mirzoev, 2010; Nagai and Schamphelaere, 2016; Versieren et al., 2016; Deruytter et al., 2017; Aronzon et al., 2020; Isaza et al., 2020), but very rarely have they been studied under realistic conditions (Korsakov et al., 2015). Most studies are conducted in animal experiments with massive, highly unrealistic radiation exposures (of the order of 0.5–1 Gy or more), and no less massive exposures to chemicals (tens and hundreds of maximum permissible concentrations and doses) (Koterov et al., 1997; Dergacheva et al., 1997; Sharetsky et al., 1997; Geras'kin et al., 2005; Barantseva et al., 2009; Komarova, 2009; Mirzoev, 2010). At the same time, at such radiation doses that are considered to be small doses in the experiment, in combination with cadmium chloride (Koterov et al., 1997), cadmium nitrate (Mirzoev, 2010), cadmium, plumbum and dichlorophenoxyacetic acid (Geras'kin et al., 2005), benzene (Sharetsky et al., 1997), sodium nitrite and nitrate (Dergacheva et al., 1997), acetaldehyde, ethanol and acetone (Barantseva et al., 2009), aminobenzamide (Komarova, 2009), there is a significant increase in both deterministic and stochastic effects (mortality of experimental animals, chromosomal breakdowns, activation of the process of free radical lipid peroxidation, decrease in membrane permeability, etc.).

The present study indicates not only a significantly lower occurrence of polydactyly and multiple CM in control areas, but also significant differences in the frequency of multiple CM under conditions of combined environmental pollution in comparison with similar indicators in areas of radioactive and chemical pollution, which may indicate a synergistic interaction between radiation and chemical contaminants. In addition, the estimated values for multiple CM in the combined contamination areas by 2018–2023 is predicted to still be significantly ($p = 0.027$) higher than the territories of radioactive and chemical contamination by 39.6% and 45.7%, respectively, which reflects continuing synergistic interactions between radiation and chemical factors.

A study of the effect of pollutants on the frequency of CM *de novo* over the course of 18 years (2000–2017) revealed that the prevalence in the frequency of polydactyly, limb reduction defects, and multiple CM is determined by the combined effect of nitrogen oxides, carbon monoxide, sulfur dioxide, and volatile organic compounds in combination with the contamination by long-lived radionuclides (Cs-137 and Sr-90) with their isolated and combined effects.

It should be noted that there are many exogenous and endogenous factors that can influence the expression of CM. Among the main risk factors for the occurrence of CM, one can point to socio-economic status, working and living conditions, the state of the healthcare system and its the effectiveness (e.g. the detection of CM in the early stages) and environmental pollution. Also an increased risk of CM is associated with endocrine and metabolic diseases of the mother (most often CM development is observed in diabetes mellitus, virializing tumors of the genital glands and adrenal cortex, phenylketonuria), abnormalities of germ cells (the result of impaired spermatogenesis, oogenesis), the age of the father and mother (for example, CM of the respiratory system are more often observed in young mothers, and in mothers older than 35 years, the frequency of birth of children with genomic mutations, including Down syndrome) is increased, the use of certain drugs (tranquilizers, anticonvulsants) etc. (Khanum et al., 2004; Al-Sabbak et al., 2012; Canals et al., 2014; Persson et al., 2017; Harris et al., 2017; Morris et al., 2018; Xiaoqing et al., 2018; Savabieasfahani et al., 2020).

In our opinion, the factors that contributed to the increase in the incidence of *de novo* CM in newborns in polluted areas of Bryansk require further study. However, our preliminary studies suggest progress in the following areas are needed:

1. Better measurements ofradioactive and chemical pollution in the environment;
2. Better estimates of accumulated radiation doses in the population (primarily Cs-37 and Sr-90);
3. Betteranalysis of the distribution of sources of air pollution and the deposition of emissions from gaseous pollutants, taking into account meteorological factors;
4. Better analysis of the socio-economic situation in the region (for example, production index, retail trade turnover, consumer price index, average wage, fertility, mortality and natural growth rates and other indicators).

In future studies, it would be important to consider the following:

1) The dynamics of additional types of CM should also be assessed (e.g. nervous system, circulatory system, digestion, respiratory organs, urogenital, small and large CM);
2) The frequency of CM should also be assessed in other regions of the Russian Federation, Ukraine and the Republic of Belarus affected by the Chernobyl disaster;
3) Further analyses should also consider the embryotoxic effects of radioactive contamination associated with transuranic radionuclides, in addition to Cs-137 and Sr-90;
4) Follow-up studies are needed to asses any association between medical abortions and contaminated areas of the Bryansk region that may have been linked to prenatal identification of large CM. This is particularly important given the potential for abortions to obscure the statistical analysis of CM in general.

5. Conclusions

1. We found that the frequency of polydactyly, MCM and the frequency of *de novo* CM in newborns were significantly higher ($p = 0.001–0.054$) in regions with elevated radioactive, chemical and combined environmental pollution compared to ecologically safe (control) territories.
2. Significant increases in the frequency of MCM were found under conditions of combined radioactive and chemical pollutants, exceeding that observed for radioactively (2.2 times, $p = 0.034$) and chemically (1.9 times, $p = 0.008$) contaminated areas.
3. Our models suggest that the frequency of MCM in areas of combined pollution will significantly exceed the frequencies observed for regions containing radioactive or chemical pollutants alone by 39.6% and 45.7% respectively, by 2018–2023.
4. Overall, our findings suggest additive and potentially synergistic effects of radioactive and chemical pollutants on the frequencies of MCM in the Bryansk region of southwestern Russia.

Declarations

Author contribution statement

Anton Korsakov: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Emilia Geger: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Dmitry Lagerev, Leonid Pugach, Timothy Mousseau: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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