Agricultural Chemicals as a Risk Factor For Intrauterine Fetal Hypotrophy In The Regions With Intensive Farming

Magomed G. Magomedov
Doctor of Medical Sciences, Head of the Department of general hygiene and human ecology, e-mail: magomedov_1957@mail.ru; Tel: +7(928) 803 80 06.
Djamilya M. Magomedova
Assistant at the Department of Pediatrics
Shamayilpatimat M. Magomedova
Resident doctor at the Department of radiodiagnostics and radiotherapy
Abdurrahman M. Samedov
Student at the treatment department
Shamil M. Taymaskhanov
Student at the pediatric department
Islam S. Magomedov
Student at the pediatric department
Dagestan State Medical University
367012, 1 Lenin Square, Makhachkala, Republic of Dagestan, Russia

Abstract

The present article describes the results of the retrospective study and the evaluation of high territorial loads (TL) of pesticides on the occurrence rate and spread of intrauterine fetal hypotrophy (IUFH) on the lowland, sub-mountain, and highland areas of Dagestan that are different by the rate of the studied pathology and the amount of the applied pesticides.

A high rate of early neonatal lethality, natimortality, perinatal lethality, and the impact of the applied pesticides on IUFH in the regions of intensive farming provides the rationale for the present study.

The leading approach to the study was the evaluation, prognosis, and prevention of the development and spread of IUFH under the isolated and combined impact of different groups of chemical compounds (GCC) on women of fertile age in the farming regions with high TL.

The study includes the data on 3,190 cases of IUFH in 1993-2002 in different altitudinal belts of the Republic of Dagestan (RD) with various levels of pesticide TL.

The results of one and two-factor variation analysis of the isolated and combined impact of different GCC on the territory of lowland and highland Dagestan revealed 13 combinations of pesticide groups out of 78 with the effect of synergism and additivity that represent a high risk of the development of the studied fetus pathology.

A list and scheme of dangerous combinations of groups of pesticides provided for the specialists of local Rospotrebnadzor and medical institutions during prevention events will allow avoiding the contact of chemicals with women of fertile age involved in farming and decrease the risk of the development of IUFH.

Key words: *intrauterine fetal hypotrophy, ecological-hygienic factors, pesticides, territorial load (TL), ecological zones (EZ), infant mortality.*

Introduction

Among unfavorable factors of the environment in the farming areas, pesticides are the most significant ones in the development of maternal and fetal pathology are [15-18, 20].

A stable tendency to an increase in the territorial-populational load (TPL) of pesticides in RD from the 2000s indicates problems connected with an increase in the ecologically caused diseases as it was observed during the years of intensive pesticides and mineral fertilizers application. A retrospective study on the evaluation of the influence of different levels of pesticide TPL on the rate of IUFH would provide the prognosis and prevention of this pathology.

ISSN: 2005-4238 IJAST

A typical manifestation of even weak and moderate ecological problems is intrauterine fetal hypotrophy that occupied the 3rd place in the rank of neonate pathologies after intrauterine fetal hypoxia and distress syndromes [2, 17].

IUFH is one of the most important social-medical problems because its rate primarily determines the level of natimortality, infant mortality (perinatal, early, neonatal, and up to 1 year old), infant morbidity rate, and other parameters of potential health of the population [1, 4, 9, 25, 26, etc].

Infant mortality leads to severe irreversible losses in the population. Ecological factors have a great impact on the epidemiology of embryo and fetal pathology [14, 16 – 18, etc]. The search for scientifically grounded criteria of early identification of ecological factors that influence population health for the prevention and exclusion of possible impact is an important and acute task.

IUFH occupied a significant place among significant risk factors of mortality, retardation and degraded development of the fetus. This is confirmed by higher rates of mortality among children who were born with low body weight and IUFH in comparison with children who were born with normal weight: early neonatal mortality is higher by 17-20 times, natimortality – by 7.5 times, and perinatal mortality – by 10-12 times [4, 5, 17, 22]. Congenital hypotrophy (CH) or intrauterine growth retardation (IUGR) (by the classification of ICD-10) is the most common fetal pathology that occurs in unfavorable conditions during pregnancy. It is seen as one of the types of congenital fetal defects (CFD) [6, 7] that indicate the unfavorable influence of the environment on humans.

Infants with low body weight significantly determine perinatal mortality. In Russia, this rate is more than 60% of all the lethal cases. In Europe, 2/3 of perinatal cases of undercarried infants are observed in the perinatal period [17, 24, etc].

Some authors believe that children born with IUGR have a higher rate of neuro-psychic deviations of different degrees (even deep mental disorders). Around 30% of children up to 5 years old and older have different deviations in physical and neurological status. The rate of brain pathology in undercarried children was observed more often by 2-3.5 times than in full-term newborns.

The rate of severe complications in undercarried neonates is 10 times higher. Mild functional disorders in the cohort of undercarried neonates were observed in 1.0 – 60 cases. The development of these disorders is greatly affected by the influence of environmental factors [24-26, etc].

In the conditions of influence of chemical substances on humans, there is a direct correlation between the intensity of their application and their embryotoxic, mutagen, and carcinogenic effects. Since IUFH results not only from a hereditary pathology but also from gene and embryotoxicity, IUFH can be seen as a signal marker of a mutagenic and carcinogenic effect of harmful factors of different origins.

However, the results of the studies dedicated to this problem did not reveal the influence of the leading environmental factors on the development and outcome of pregnancy because of a lack of scientific-methodical tools of the quantitative evaluation of the influence of single risk factors and their different combinations and reliable methods of prognosis of ecologically induced pathological conditions.

The literature review showed that there are different factors among possible causes of IUFH. Their share may vary significantly depending on the territorial peculiarities of women and children health losses, which determines the necessity to perform regional-oriented ecological-hygienic and epidemiological studies [17].

Republic of Dagestan (RD) is an agrarian region with clearly identified climate-geographical, biochemical, vegetable, and soil characteristics by the peculiarities of altitudinal belts (lowland, sub-mountain, highland) [16, 17]. The contrast characteristics of altitude shifts determine significant differences in the farmed crops and the intensity of application of crop protection chemical substances, especially pesticides [17]. Before 1993, the intensity of the application of pesticides in the agrarian region of RD, wherein primarily fertile age women labor is used, exceeded the critical level of the load (CLL) manifold (3.97 – 4.5 kg/ha) [3, 15,17]. Even now, the territorial and populational loads of the pesticides exceed average parameters in Russia [3, 18, 19, 20].

For a long time, RD occupies one of the leading places among RF regions in the rank of child and infant mortality having a significant share of causes for IUFH.

The present study was aimed to predict and prevent the development of IUFH by the results of the evaluation of the isolated and combined effect of different groups of pesticides on the spread of this pathology in different ecological zones of RD.

ISSN: 2005-4238 IJAST

Materials and Methods

The data was collected from the primary records of medical institutions: History of the development of a neonate (Form №097/y) and Record journals of the department of neonates (form № 102/y).

IUFH was diagnosed by the IDC-10 [21, 24]. In total, there were 2175 cases of neonates with IUFH born from 1993 to 1996 in 24 regions (1108 – in the lowland ecological zone, 410 – in the sub-mountain zone, and 657 – in the highland ecological zone of RD) and 1015 cases in 34 regions of RD (608, 190 and 217 cases, respectively) that were born in 2000-2002.

The risk of the development of IUFH in families was evaluated by a specially developed inventory that included social-economical, ecological, genealogical, and clinical blocks of questions and collected data on previous pregnancies and deliveries and cases of giving birth to children with low body weight in the anamnesis.

Pesticide residue levels in the food products were estimated in the lab of Rospotrebnadzor of RD, State Agrochemical Center of Agrochemical Service "Dagestanskiy" and Republican Crop Protection Center.

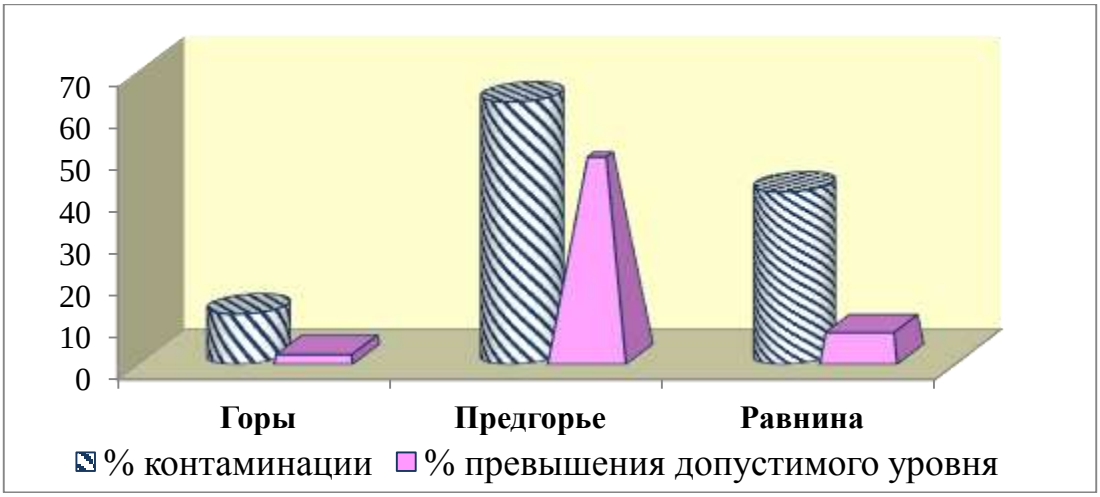
The territorial load (TL) in kg/ha of the active ingredient, the range index (RI) including the parameters of toxicity, persistence, and cumulativeness of pesticides was studied for the period of 1984 – 2000 by the method [3, 10-13]. The main sources of information were republican and regional crop protection centers and institutions of the Ministry of Agriculture of RD on the application of pesticides. The study included lowland, sub-mountain and highland ecological zones (EZ) of RD.

A two-factor variance analysis for inconsistent complexes was used with a calculation of a power of factors influence (h2) [8] on the effective feature for the study of the combined effect of TL and RI of different groups of pesticides on the occurrence rate of IUFH on the territory of the studied regions of RD (3190 families with cases of IUFH).

The obtained results were recorded in special template tables that allowed the authors to evaluate the risk of the development of the studied pathology under the isolated and combined influence of the applied pesticides on the maternal organism.

Results and Discussion

The analysis of the application of pesticides in 13 regions of lowland Dagestan showed that farming was associated with the application of highly-toxic pesticides with expressed cumulative properties.



Горы – Highlands
Предгорье – Sub-mountains
Равнина – Lowlands
% контаминации – % of contamination
% превышения допустимого уровня - % of exceedance of limits

Fig. 1. **Pesticide residue levels in food products by the ecologic zones in the Republic of Dagestan**

ISSN: 2005-4238 IJAST

The measures on the prevention of pregnancy pathologies, including IUFH, should include not only the combined effect of chemicals with unfavorable factors of non-chemical origin but also possible modifications of biological effects from the combined effect of different groups of pesticides.

The highest total TL is observed in Cu-containing pesticides (20.1%) that appear to have the most expressed effect on the development of IUFH.

The rest groups of chemical compounds in pesticides that can influence the development of IUFH are used in significantly lower amounts.

TL and RI were characterized by high levels in sub-mountain Dagestan by the annual average and progressive average parameters.
The share of total TL of pesticides in the sub-mountain area is 53.48%, in the highlands – 16.73%, and in the lowlands – 29.8%.

The list of pesticides used on the territory of sub-mountain Dagestan included potent – 0.2%, highly toxic – 3.02%, moderately toxic – 54.42%, and low toxic – 2.76% substances. During the period of the study, potent and highly toxic pesticides were used more often in the sub-mountain zone than in the highland and lowland zones of RD.

The comparative analysis of the parameters between TL and RI of pesticides and the intensity of the spread of the studied pathology showed their comparability (Table 1, 2).

Table 1. The occurrence rate of IUFH and the intensity of pesticides application by the altitudinal belts of RD (%)

		1984-1989	1989-1992	1991-1995	1994-1996	1984-1995	1989-1996	1984-2000	1989-2002
№	Altitudinal belts	TL (kg/ha) RI	IUFH %	TL (kg/ha) RI	IUFH %	TL (kg/ha) RI	IUFH %	TL (kg/ha) RI	IUFH %
1	Lowlands	93.66 145.6	8.2	5.15 5.32	8.3	51.75 74.79	8.3	32.95 47.6	8.27
2	Sub-mountain region	139.95 199.5	9.36	4.79 5.41	10.3	92.64 133.4	9.85	48.45 69.8	9.84
3	Highlands	51.63 73.7	3.06	0.61 0.76	4.3	29.02 40.07	3.95	17.44 24.1	3.77
I	P (1-2)	P<0.10; t=1.04		P<0.02; t=2.55		P<0.02; t=2.45		P<0.02; t=1.75	
II	P (1-3)	P<0.001; t=6.27		P<0.001; t=9.36		P < 0.001; t=11.9		P < 0.001; t=9.19	
III	P (2-3)	P<0.001; t=5.86		P<0.001; t=8.51		P< 0.001; t=10.48		P< 0.001; t=8.38	

In all the altitudinal belts, there was a sharp decrease in the TL and RI in 1991-1995 than in 1984-1989. In the highland zone, it decreased by 85 times, in the lowland zone – by 18 times.

Although this phenomenon is positive in terms of ecological conditions, socially economically, this demonstrates a high tempo of economical decrease in the highland zone that indirectly contributes to the spread of the studied pathology.

Although the volume of potent, highly toxic, toxic, and moderately toxic pesticides for the period of 1998-2000 by more than 80 times in comparison with 1984-1989, their share in the total TL of groups of pesticides remains significant.

Because of the fact that along with TL and RI of pesticides, the residual level of pesticides in water and food products significantly influences the population health, the authors analyzed the respective parameters. Out of 659 tests for the residual levels of pesticides in food products in the highland zones of RD, pesticides were revealed in 12.01%. In 2.2 %, there was exceedance of the permitted norms (Fig. 1). In the lowlands, the contamination of food products was 41.15 % and an exceedance of the accepted norms was 7.3. The highest residual levels of pesticides were registered in the sub-mountain ecological zone, wherein the contamination was 62.65 % and the exceedance of the permitted norms – 47.7 %

ISSN: 2005-4238 IJAST

Table 2. The rate of IUFH and the intensity of pesticide application by the altitudinal belts of RD (‰)

		1984-1989	1989-1992	1991-1995	1994-1996	1984-1995	1989-1996	1984-2000	1989-2002
№ п/п	Altitudinal belts	TL (kg/ha) RI	IUFH ‰	TL (kg/ha) RI	IUFH ‰	TL (kg/ha) RI	IUFH ‰	TL (kg/ha) RI	IUFH ‰
1	Lowlands	93.66 145.6	17.19	5.15 5.32	58.51	51.75 74.79	37.85	32.95 47.6	37,1
2	Sub-mountain region	139.95 199.5	14.2	4.79 5.41	101.4	92.64 133.4	57.6	48.45 69.8	39,81
3	Highlands	51.63 73.7	11.2	0.61 0.76	34.45	29.02 40.07	27.83	17.44 24.1	32,0
I	P (1-2)	P<0.10; t=1.04		P<0.02; t=2.55		P<0.02; t=2.45		P<0.02; t=1.75	
II	P (1-3)	P<0.001; t=6.27		P<0.001; t=9.36		P < 0.001; t=11.9		P < 0.001; t=9.19	
III	P (2-3)	P<0.001; t=5.86		P<0.001; t=8.51		P< 0.001; t=10.48		P< 0.001; t=8.38	

On the territory of Dagestan, pesticides were used that are included in the group of CLL by their properties of toxicity, persistence, and cumulativeness. Their TL values are ranked by the following scheme: sub-mountain, lowland, and highland Dagestan.

- In the sub-mountain and lowland EZ, TL of pesticides exceeded CLL by 12.2 and 8.3 times, respectively, and in the highland EZ, TL of pesticides included in CLL was much lower (3.97 kg/ha);
- The forbidden organochlorine pesticides with expressed toxicity, high stability, and cumulativeness that exert teratogenic and embryotoxic effects are still applied in certain amounts in RD.
- The levels of pesticides with expressed toxic and cumulative properties are higher in the sub-mountain zone than in the highland and lowland zones and, in the highland zones, they are lower than in the lowland and sub-mountain zones of RD.

Progressive average and mean arithmetic data obtained from the lab analysis of the environmental probes (primarily, food products) showed that highest residual levels of pesticides were observed in the sub-mountain zone - 30.56 % of probes in comparison with 22.39 % in the lowland zone and 7.44 % in the highland zone.

Table 3. The risk of the development of IUFH in the areas of isolated and combined application of different pesticides in the lowland and sub-mountain areas of RD in 1993-2002.

TL of Cu-containing compounds		S-containing chemicals	Hydrocarbons	Organophosphorous compounds	Nitro-, halogen-substituted chemicals	Carbamic acids	Carboxylic acids	Combined chemicals	Derivatives of Carb. acids	Heterocyclic compounds	Non-organic compounds	Hg-containing chemicals	Chlor-organic compounds (0.79)
TL of Cu-containing chemicals (12.4).	**Fa**	0.03	0.63	0.23		0.63	1.05	0.062	0.11	0.02	2.40	0.72	0.13
	Fb	0.75	5.89	0.29		5.89	1.46	25.65	0.33	6.32	2.80	15.1	1.92
	Fab	0.49	0.65	**5.26**		0.65	0.32	0.191	**1.68**	0.02	0.55	0	0
TL of S-containing chemicals (15.635)	**Fa**	0.06	0.05	0.03	0.03	6.66	3.076	0.03	0.24	0.01	0.04	0.03	
	Fb	6.53	2.95	723	4.18	9.54	40.29	0.59	7.62	6.45	13.1	2.49	
	Fab	1.96	0.18	0.51	0.97	7.61	3.323	0.14	0.22	1.73	0.46	0.29	
Hydrobarbons (12.695)	**Fa**	9.55	5.89		5.85	6.64	4.47	2.4	6.07	0.03	5.59		
	Fb	5.28	0.65		0.97	29.49	3.16	3.67	3.85	15.8	0.48		

ISSN: 2005-4238 IJAST

	Fab	5.36	0.65		1.5	1.37	0.57	0.08	2.46	0.10	5.35
Organophosphorous compounds (2.425)		**Fa**	1.29	6.38	3.63	0.015	2.65	1.69	2.91	4.63	5.28
		Fb	6.38	1.3	3.21	26.40	0	5.96	10.7	12.8	9.55
		Fab	0.21	0.21	0.01	0.858	0.02	1.0	1.74	4.0	5.36
Nitro- and halogen-substituted chemicals (14.32)			**Fa**		0.73	0.062	0.18	0.02	0.43	0.72	0.13
			Fb		2.86	25.65	0.33	6.32	1.88	15.1	1.92
			Fab		1.01	0.191	1.68	0.22	1.57	0	0
Carbamic acids (2.727)				**Fa**	2.16	0.878	1.14	0.91	2.45	0.02	1.24
				Fb	2.35	27.59	3.48	7.28	1.86	10.4	1.61
				Fab	0.03	3.153	1.64	0.42	**4.65**	3.18	**11.8**
Carboxylic acids (2.4)					**Fa**	0.141	2.72	3.18	3.38	1.12	2.38
					Fb	27.57	4.78	959	0.03	8.64	2.38
					Fab	0.597	0.26	0.01	0.74	0.28	0.05
Combined chemicals (2.505)						**Fa**	29.6	32.0	26.2	21.9	33.6
						Fb	0.05	9.3	2.53	11.2	1.62
						Fab	3.16	1.41	0.04	1.46	5.92
Derivatives of Carb. acids (6.895)							**Fa**	0.48	0.67	0.00	33.6
							Fb	10.8	5.31	18.7	1.62
							Fab	6.17	0.97	4.54	5.92
Heterocyclic compounds (1.408)								**Fa**	11.0	0.81	0.35
								Fb	0.98	5.7	1.97
								Fab	0.97	1.73	0.00
Non-organic compounds (0.247)									**Fa**	0.32	6.18
									Fb	8.69	1.33
									Fab	0.44	1.31
Hg-containing compounds (0.0231)										**Fa**	11.4
										Fb	1.32
										Fab	6.00
At k1:k2=1:16 and P<0.05 F_{st} =4.5; at P<0.01 F_{st} =8.2.											

The results of the lab tests by the altitudinal belts confirm the ecological burden of sub-mountain and lowland areas of RD in comparison with the highland area.

Despite the obtained data on the pesticide application, the evaluation of the risk of the development of IUFH from different chemical groups of pesticides cannot be complete without the study of the combined effect of different chemical groups of pesticides because this effect is observed in real life, especially, the regions of intensive farming.

For this reason, one and two-factor variance analysis was performed for inconsistent complexes [8, 17], wherein the authors estimated the degree of the risk of the isolated and combined effect of different groups of pesticides on the formation of IUFH.

Table 4. The scheme of conversion of a template table of values F_f into a template prognostic table

Legend and values of the template table before the conversion				Legend and number of symbols in the prognostic template after the conversion
№	F_f by the results of variance analysis	P<0.0..	Degrees of freedom (k1:k2)	Number of symbols «+++», «±» or «-»
1	$F_f < F_{st}$	0.05	1:16	«-»
2	$F_f < F_{st}$ in cases of synergism and additivity	0.05	1:16	«±»

ISSN: 2005-4238 IJAST

3	$F_f = F_{st}$	0.05	1:16	«+»
4	$F_f > F_{st}$	0.05	1:16	«++»
5	$F_f = F_{st}$	0.01	1:16	«+++»
6	$F_f > F_{st}$	0.01	1:16	«+++»

One-factor variance analysis of inconsistent complexes of the isolated effect of each chemical group of pesticides revealed a significant correlation between nearly all the chemical groups of pesticides and the rate of occurrence of IUFH in RD ($F_f > F_{st}$ at k1:k2=1:27), especially, in the lowland and sub-mountain areas ($F_f > F_{st}$ at k1:k2=1:16).

Considering the fact that in the sub-mountain and lowland areas of RD, around 30 different chemical groups of pesticides are applied simultaneously in farming and 15 of them have significant TL and RI, the authors studied the consequences of their combined application from a scientific and practical point of view. The two-factor variance analysis showed that 12 combinations of groups of chemicals out of 78 have the highest risk for the development of IUFH (Table 3). In other words, in 10 cases, the effects of additivity and synergism were observed: $F_{abf} > F_{af}$, $F_{abf} > F_{bf}$ and in 1 case, an independent effect was revealed. In other cases, the effect of antagonism was observed with the Fisher t-test (F_f) below the threshold of significance (F_{st}) (Table 4).

Table-Template 5.

F in cases of isolated and combined influence of groups of chemicals on the rate of IUGR in the lowland and sub-mountain areas of RD in 1989-2002

		Cu-containing (12.4)	S-containing chemicals (15.635)	Hydrocarbons (12.7)	Organophosphorous compounds (2.43)	Nitro-, halogen-substituted (14.323)	Carbamic acids (2.73)	Carboxylic acids (2.4)	Combined chemicals (2.51).	Derivatives carb. acids (6.9)	Heretocyclic compounds (1.4)	Non-organic compounds (0.247)	Hg-containing chemicals (0.0231)	Chlor-organic compound (1.18)
TL Cu-containing (12.4).	**F*a***	-	-	-	-		-	-	-	-	-	-	-	-
	F*b*	-	++	-			+	-	+++	-	++	-	+++	-
	F*ab*	-	-	++			-	-	-	+	-	-	-	-
TL S-containing (15.635)	**F*a***	-	-	-	-		-	++	-	-	-	-	-	-
	F*b*	++	-	++	-		-	+++	+++	-	++	++	+++	-
	F*ab*	-	-	-	-		-	++	-	-	-	-	-	-
Hydrocarbons (12.695)	**F*a***		+++	++			++	++	+	-	++	-	++	
	F*b*		++	-			-	+++	-	-	-	+++	-	
	F*ab*		++	-			-	-	-	-	-	-	++	
Organophosphorous compounds (2.425)	**F*a***			-	++		-	-	-	-	-	++	++	
	F*b*			++	-		-	+++	-	++	+++	+++	+++	
	F*ab*			-	-		-	-	-	-	-	-	++	
Nitro- halogen-substituted (14.32)	**F*a***						-	-	-	-	-	-	-	
	F*b*						-	+++	-	++	-	+++	-	
	F*ab*						-	-	+	-	-	-	-	
Carbamic acids (2,727)	**F*a***							-	-	-	-	-	-	
	F*b*							-	+++	-	++	-	+++	
	F*ab*							-	-	-	-	+	-	
Carboxylic acids (2.4)	**F*a***								-	-	-	-	-	
	F*b*								+++	+	+++	-	++	
	F*ab*								-	-	-	-	-	
Combined chemicals (2.505)	**F*a***									+++	+++	+++	+++	
	F*b*									-	+++	-	+++	

ISSN: 2005-4238 IJAST

	F*ab*	-	-	-	-	++
Derivatives carboxylic acids (6.895)		**F*a***	-	-	-	+++
		F*b*	+++	+	+++	-
		F*ab*	+	-	+	+
Heterocyclic compounds (1.408)			**F*a***	+++	-	-
			F*b*	-	+	-
			F*ab*	-	-	-
Non-organic compounds (0.247)				**F*a***	-	+
				F*b*	++	-
				F*ab*	-	-
Hg-containing compounds (0.0231)					**F*a***	+++
					F*b*	-
					F*ab*	+

* at k1:k2=1:16 P<0.05F*st*=4.5: P<0.01 F*st*=8.7. «-» at F_f = F*st* at P<0.05; «+» at F_f > F*st* at P<0.05; «++» at F_f = F*st* at P<0.01 «+++» at F_f > F*st* at P<0.01; at P<0.05 $F_{\underline{st}}$=4.5; at P<0.01 $F_{\underline{st}}$ =8.7; (k1:k2=1:16); ** TL of pesticides is presented in brackets.

An increase in TL of groups of pesticides led to qualitative changes in the manifestation of the negative influence of different combinations.

The weakening of antagonistic effect increased to 51 %, including the cases with significant negative effect (F_f>F_{st}, at P<0.05) – 11.5 %. An increase in the antagonistic effect was observed in 43.6 %. In 3 combinations (3.9 %), a transformation of the effect of antagonism into the effect of potentiation was registered, and in 1 case - weakening of the effect of synergism of the combined effect.

The analysis of possible combinations of the most dangerous pesticides by the altitudinal belts of RD showed that they are mostly observed in the lowland and sub-mountain areas. In the highland areas, such combinations are observed only in 30% of regions. Still, the possibility of negative influence of dangerous combinations even in the amounts revealed for highland areas remains acute.

It can be stated that an increase in the TL of different groups of pesticides leads to an enhancement of a negative effect of their combined influence, weakening of antagonism, and increase in the number of combinations of groups of pesticides with an increase in the threshold of the significance (Ff>Fst, at P<0.05) for the studied pathology.

The combined influence of different groups of pesticides with an increase in their TL leads to the transformation of the effect of antagonism into the effect of additivity, synergism and into an independent effect when it comes to IUFH. The obtained results on dangerous combinations can be a significant argument in the development of preventive measures in terms of safe planning and choice between the farming of crops that require toxic substances and the health of mother and child.

All the preparations of pesticides used in RD were combined into the respective groups of chemicals, their summed TL and RI were calculated, and the degree of danger for the development of IUFH was evaluated using two-factor variance analysis for the inconsistent complexes.

There are 13 cases of the isolated and combined influence of pesticides used in farming that significantly affect the development of IUFH in the lowland and subsountain territory of RD (Ff>Fst, at P<0.5).

In the highland area of RS, pesticides did not influence significantly the development of IUFH.

The analysis of the intensity of the distribution of pesticide combinations that exert the highest risk for the development of IUFH by the altitudinal belts of RD showed that they were met more often in the lowland and sub-mountain areas.

Thus, the prepared template of the indication of combinations dangerous for the intrauterine development of the fetus has not only regional significance in the prevention of the studied pathology but can also be used in other regions of intensive farming.

It should be mentioned that despite relatively high values of F(ab)f in the lowland and sub-mountain areas, the prevalence of the power of influence (h2) of the combined effect of the complexes of pesticides with additive and synergic effect is observed on the territory of RD. In other words, the growth of negative influence of the factor is observed in combination with low doses (reversion of the

ISSN: 2005-4238 IJAST

activity) and high doses (inversion of the activity). The later has a weaker effect in higher doses of mutagens due to toxic damage of a living substrate [17, 23].

The identification of the peculiarities of the combined effect by the altitudinal belts can significantly facilitate the differentiation of regional risk factors for IUFH or the identification of special parameters as a coefficient of regional risk.

For the evaluation of peculiarities of biological effects in cases of the combined activity of the same groups of pesticides, the authors performed the study in different climate-geographical areas by the altitudinal belts and in different levels of TL of groups of pesticides. Thus, excluding the studied variants of the combined effect of more than 60 preparations of pesticides by the method of two-factor variance analysis of inconsistent complexes, the authors studied 156 variants of combinations of different groups of pesticides (Table 3).

The authors revealed that an increase in the TL (sub-mountain and lowland areas of RD) in some combinations of groups of pesticides led to the transformation of biological effects towards synergism and antagonism. Thus, the transformation of the antagonistic effect (F_{abf}=0.151) into synergism (F_{abf}=5.261) was observed when organophosphorous compounds were combined with Cu-containing pesticides, carbamic acid – with non-organic compounds (F_{abf} =0.157 and F_{abf} =4.651, respectively) and organochlorine compounds (F_{abf} =0.894 and F_{abf} =11.786, respectively) (Table 3).

The antagonistic effect that developed with an increase in TL of pesticides in regards to the studied pathology was observed in the combination of Cu-containing pesticides with heterocyclic compounds (F_{abf}=2.166 and F_{abf} 0.22,), carbamic acid with combined preparations (F_{abf}=5.446 and F_{abf}=0.597), and combined preparations with heterocyclic compounds (F_{abf} =4.692 and F_{abf} =1.411).

Conclusions

1. High TL and RI of pesticides used in farming increase the risk of the development of IUFH and have a significant positive correlation.

2. An increase in TL and RI of pesticides leads to a tendency of the transformation of the effect of antagonism into the effects of synergism and additivity in regards to the formation of IUFH.

3. The list of chemical groups of pesticides used in farming in RD includes chemicals that exert dangerous effect on the development of IUFH, especially, in combinations.

4. The revealed effects of additivity and synergism of combined application of groups of pesticides in all the ecological zones of RD provide grounds for the revision of the list of groups of pesticides permitted in farming.

5. Specialists of Rospotrebnadzor, medical network and crop protection centers should initiate sanitary-educational programs that would reveal the danger of the application of pesticides that exert synergic and additive biological effects on the development of IUFH.

References

1. Buylashev T.S. Medical-social evaluation of the growth and development of children born with low body weight. Dissertation. M., 1988. p. 9-31.
2. Demin V.F., Kluychnikova S.O. Ecopathology of childhood period. Significance of technogenic and medico-social factors. III Congress of Russian Pediatricians. M., 2000. p. 20-21.
3. The study of the influence of pesticides and plant growth regulators on the population health. Temporary methodical recommendations for scientific and medical institutions that fulfilled the tasks 0.6 (program C.10). Kiev: Scientific basics of hygiene and toxicology of pesticides, polymers, and plastic masses, 1985. p. 83.
4. The concept of protection of reproductive health in Russia in 2000-2004 and the plan of events of its realization. M., 2000.
5. Kulakov V.I., Kirbasova N.N., Ponomareva L.I., Lopatina T.V. Ecological problems of reproductive health. Obstetrics and gynecology. 1993. № 1. p. 12-14.
6. Lazyuk G.I., Kirillova I.A., Novikova I.V., Arydov N.N. Anomalies in embryonal development of humans under the influence of low doses of ionizing radiation. The effect of low doses of ionizing radiation on gonads and fetus. Obninsk, 1988. p. 34.
7. Lazyuk G.I. Human teratology. M.: Medicine, 1979.

ISSN: 2005-4238 IJAST

8. Lakin G.F. Biometry: handbook for biological specialities. 3rd edition, revised and added. M.: Higher school, 1980. p. 293.
9. Magomedov M.G. The role of ecological factors in the epidemiology of the development of intrauterine development of the fetus (Experimental study). Makhachkala. 2001. p. 105.
10. Magomedov M.G. Ecological and social-economic aspects of epidemiology of congenital hypotrophy in Dagestan. Makhachkala, 2000. p. 151.
11. Magomedov M.G., Omarov S.M., Shlyakhetskiy N.S., Magomedova D.M, Isaeva Z.U. Prognosis of the development of intrauterine development of the fetus under combined effect of small doses of pesticides. Problems of quality, safety, and diagnostics in the conditions of information-oriented society. Materials of scientific and practical conference. Sochi, 2005. p. 401-403.
12. Magomedov M.G., Omarov S.M., Shlyakhetskiy N.S., Magomedova D.M, Isaeva Z.U. Statistical approach to the prognosis of the retardation of intrauterine development of the fetus under the combined effect of small doses of ionising radiation and pesticides. Issues of quality, safety, and diagnostics in the conditions of information-oriented society. Materials of scientific and practical conference. Sochi, 2005. - C. 403-406.
13. Magomedov M.G., Omarov S.M., Shlyakhetskiy N.S., Scherbo A.P. Matrix method of the identification of biological effects under radiation-chemical influence. Journal of Dagestan Scientific Center. 2005. №22. p. 55-61.
14. Magomedov M.G. Quantitative evaluation of ecological-hygienic risk factors of embryo and fetopathology in its prognosis and prevention. Methodic guidelines. Makhachkala, 2006. P. 33.
15. Magomedov M.G., Tumalaeva O.M., Magomedova D.M. Association of marker diseases and anthropophysiometric paramreters of men of army subscription age by the ecological zones of the Republic of Dagestan. South of Russia: ecology, development. 2011. V. 6. №1. p.164-177.
16. Magomedov M.G. Ecological-hygienic risk factors of the spread of the retardation of the development of intrauterine development of the fetus in the agrarian regions of the South of Russia. Dissertation. Saint-Petersburg, 2006.
17. Magomedov M.G., Scherbo A.P., Shlyakhetskkiy N.S. Prognosis of intrauterine fetus hypotrophy under the influence of ecological-hygienic risk factors. Makhachkala, 2007, p. 181.
18. Magomedov M.G., Tumalaeva O.M., Magomedova D.M., The evaluation of territory-populational load of the environmental factors by the ecological areas of the Republic of Dagestan. South of Russia: ecology and development. 2011. v. 6. №1. p.154-164.
19. Magomedov M.G., Magomedova D.M., Ibnumaskhudova P.M., Tumalaeva O.M., Gazimagomedova M.K., Magomedgadgiev B.G., Magomedova Sh.M. Agrochemicals as a risk factor for cardiovascular pathology in the regions of intensive farming. Acute issues of modern medicine: materials of III international conference of Precaspian countries. Astrakhan, 2018, p. 220.
20. Magomedov M.G., Magomedova D.M., Magomedova Sh.P. Ecological-hygienic peculiarities of the epidemiology of congenital heart disorder by the altitudinal belts of the Republic of Dagestan. Ecology and natural resource management: applied aspects. VIII International scientific and practical conference, Ufa, 2018.
21. Mogruyanu P.D., Krasinkova G.V. Prevention and treatment of background diseases in children. Kishinev, 1990. p.20.
22. Nurmagomedova S.S. Prevention and treatment of the retardation of intrauterine development of the fetus in pluripara women. Dissertation. Makhachkala, 2000.
23. Sanotskiy I.V. Issues of remote consequences of the influence of ecotoxicants. Russian Scientific conference. Medical aspects of radiation and chemical safety. Spb, 2001. p. 5-7.
24. Smiyan I.S., Labada V.F., Fedortsev O.E. Prenatal hypotrophy. Hypotrophy. Kiev: Zdorovie, 1980. p. 97.
25. Yakunin Yu.A., Yampolskaya E.I. Perinatal and prenatal damage of CNS. Clinical neuropathology of infants. M.: Medicine, 1986. p. 223-254
26. Eiser C. Effects of chronic illness on intellectual development. Arch. Dis. Childhood 55: 766-770 (1980).

ISSN: 2005-4238 IJAST