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## Increased prevalence of pathologic states for different systems of organism associated with Agent Orange sprayings in Vietnam

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### 1. Introduction

The Ah-receptor-mediated hormone-like interference of 2,3,7,8-TCDD and related compounds in the normal processes of cell- and tissue-specific gene expression determines variety of their primary effects in target cells. On the organism's level, the pleiotropic and dysregulating dioxin's activity, the interaction of various primary and adaptive responses, the dependence of dioxin's activity upon exposure conditions, individual genetic and biologic features of the organism, factor of time, and concomitant influence of other factors may result in the formation of various health outcomes. Depending upon all the above mentioned factors, the possible effects of dioxin-containing chemicals may vary from manifested toxic and systemic responses, including developmental alterations and cancer end-points, to the more or less expressed hystological, biochemical, immunological, endocrinological, and cytogenetic alterations, to the premorbid and disadaptive pathologic states. During the last decades, numerous studies have identified several rare diseases with sufficient or limited/suggestive evidences of associations with heavy exposure of humans to dioxin-contaminated chemicals and the number of certain rare diseases and health outcomes with inadequate/insufficient evidence of the associations. At the same time, it becomes evident that a broad range of characteristics of health status should be investigated in the longitudinal studies, and the principles of reconstruction of a history of exposure to all toxicokinetically and pathogenetically significant factors should be applied to reveal the reality and biomedical significance of all possible health outcomes<sup>1)</sup>. On population level, these health effects may be manifested in the population-, time- and situation-dependent increase in the occurrence of common diseases and their untypical development, changes in the morbidity patterns, and increased prevalence of sub clinical pathological states for different organism's systems. One of the most striking and poor investigated features of dioxin's toxicology is a possibility to induce the long-lasting and remote health consequences manifesting decades postexposure (the Long-Term Health Consequences, LTHC). A latent period of more than 15 years has been identified for several cancer end-points of heavy occupational exposure to dioxin-containing chemicals. Several long-lasting chronic dermatological, ocular, immunological, endocrinological, and biochemical alterations of different medical significance has been registered in patients of the Yusho, Yu-Cheng, Missouri, and other accidents. By certain methodologic considerations the population of rural Vietnamese directly exposed to Agent Orange (AO) and/or residing on the dioxin-contaminated and chemically affected territories after the wartime (Dioxin-

containing Ecotoxicologic Factor, DEF) appeared to be one of the most appropriate objects for investigation of the LTCH of dioxin-contaminated herbicides application <sup>2-4</sup>).

## 2. Objective

The aim of this study was to investigate the prevalences of current pathologic states for different systems of organism in contingents of rural Southern and Northern Vietnamese in association with a history of their past direct contacts with AO, durable residence on the sprayed territory, and an influence of common health risk factors.

## 3. Contingents, materials and methods

The characteristics of exposure to AO and DEF and of health status have been taken from the results of cross-sectional epidemiologic investigations (structured questionnaire, primary medical examination) carried out in the contingents of rural Southern (1989; Song Be province, villages Binh My and Chanh My) and Northern (1993-1995; Dong Anh province, village Bac Hong) Vietnamese. Classification of likely degree of past direct exposure to

AO and evaluation of integrated chronic exposure to dioxin and other place-specific factors from the chemically affected environment (DEF) have been performed as described in other communications <sup>4-6</sup>) basing on the symptoms and signs of primary toxic responses of the organs of contact and organism, toxicologically and statistically grounded definition of the Exposure Risk Groups (ERGs), and on a history of residence on the sprayed territory. The following population groups consist of adult males with different conditions of likely exposure to AO and DEF have been specified: 1) peasants from the sprayed village Binh My with a validated history of direct contacts with AO during the war-time and residence on sprayed territory more than 15 years up to the moment of investigation (m, 31-50; ERG: BM III - exposure to AO and DEF); 2) peasants, living on the sprayed territory after the war-time more than 15 years (m, 31-50; ERG: BM II - exposure to DEF); 3) peasants from intact village Chanh My (40 km away) with the same social and demographic structures, and the history of agricultural chemicals' applications (m, 31-50; ERG: CM I - the external referent group); 4) war veterans living in the village Bac Hong (North Vietnam) after the war-time (m, 40-60) with a validated history of exposure to AO (ERG: BH II - exposure to AO) and unexposed (ERG: BH I - internal referent group). The investigated standardized batteries of symptoms and signs that could indicate alterations in the respiratory (RES), cardiovascular (CV), osteoarticular (OSAR), pancreatic (PAN), gastroenteral (GENT), urine excreting (URIN), and visual (VIS) systems of organism have been developed in Russia for hygienic health screening and adapted to Vietnam conditions during a pilot study <sup>2-6</sup>). The persons with the complete sets of medical problems indicating pathologic states of corresponding organism's systems have been considered as the most likely "cases" (Epidemiologic Indicators of pathologic states, EI). Increased occurrence of frequent upper respiratory diseases (>4 times/year) has been considered as an indicator of immunological dysfunctions (IMMUNE). The associations between exposure measures developed for AO and DEF, and between the characteristics of common health risk factors influence and prevalences of the EI have been investigated by stratified analysis.

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## 4. Results

Significant deterioration of general health status associated with a validated history of past direct contacts with AO (a membership in the ERGs: BM III and BH II)<sup>4-7</sup> and durable residence on the sprayed territory (DEF > 15 years, BM II) is presented in fig. 1. These data, also, indicate significant deterioration of subjective health associated with an influence of several risk factors which are common for the population under analysis.

**Fig. 1. Deterioration of general health status in contingents of rural Southern (1989; province Song Be, villages Chanh My and Binh My; m, 31-50) and Northern (1993; province Dong Anh, village Bac Hong; m, 40-60) Vietnamese associated with an influence of different health risk factors**

ERG	N	AO	DEF	IHS	p
CM I	291	no	no	.103 - .127 (.115)	AO***, DEF**, M**, N**
BM II	194	no	yes	.162 - .191 (.176)	
BM III	110	yes	yes	.266 - .304 (.285)	
BH I	176	no	no	.183 - .230 (.207)	AO***, M*, N**, A*
BH II	96	yes	no	.354 - .417 (.385)	

**Abbreviations:** ERG - Exposure Risk Groups: persons with validated history of direct exposure to Agent Orange (AO) and Dioxin-containing Ecotoxicologic Factor (DEF). IHS - Index of health status, total sum of medical problems / number of characteristics, 0 → 1 deterioration; MANOVA, 95% C.I., means with factors: AO, DEF, history of malarial diseases "M", inadequate protein nutrition "N" - <100 g meat/week, high alcohol consumption "A" - > 200 ml/week, intensive smoking - ≥ 20 cigarettes/day; persons with a history of frequent contacts and intoxication with pesticides are excluded). \*, \*\*, \*\*\* - p for the main effects: 0.05 << 0.01, 0.01 << 0.001, < 0.001.

Specific patterns of pathologic manifestations associated with strong separate influence of different health risk factors in the contingent of rural Southern Vietnamese are presented in fig. 2. These data show significantly increased prevalences of EI for almost all organism's systems under the study found in sub groups of persons with validated history of past direct exposure to AO on the background of DEF (column 1) using internal comparison (ERGs: BM III / BM II). Also, the data demonstrate relative specificity of health outcomes associated with an influence of different health risk factors that is consistent with the reality of specific patterns of pathologic manifestations established with separate symptoms and signs in the previous study<sup>4-6</sup>. The effect-modifying activity of DEF may be considered from different manifestations of health consequences of past malarial diseases (M, column 5), inadequate protein nutrition (N, column 8), and intensive smoking (S, column 10) in corresponding stratified sub groups of peasants selected in the village Binh My (ERG: BM II, DEF=1) or in the village Chanh My (CM I, DEF=0).

The results of two subsequent epidemiologic studies carried out in another contingent of peasants (Northern Vietnamese, war veterans) in 1993 and 1995 confirmed consistency and relative specificity of established associations between validated history of past direct contacts with AO and increased prevalences of EI of pathologic states for different organism's systems as well as the greater medical significance of this exposure comparing to the past malarial diseases (Fig. 3) and chronic influence of other common health risk factors (not shown).

In general, these findings demonstrate reality, consistency and relative specificity of strong associations between the EI of pathologic states for different organism's systems and validated history of acute intoxication with AO and durable residence on the sprayed territory (DEF). The reality and biological plausibility for some of these effects is confirmed by the results of matched clinical and laboratory investigations in a hospital-based trial (dysfunctions of cardiovascular and respiratory systems: test PWC<sub>170</sub>, (rheo)ECG, spirometry; significant alterations in certain clinical immunological characteristics) <sup>2-6</sup> as well as by the increased susceptibility to acute pneumonia and tuberculosis (depressed immunoresistence) found among AO-exposed persons in special epidemiologic investigation <sup>8</sup>). These facts allow to consider increased prevalence of functional abnormalities in different organism's systems as the characteristic feature of the LTHC which may be developed and maintained under the strong pressure of DEF and common health risk factors in this population.

## 6. References

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**Fig. 2. Specific patterns of pathologic manifestations for different organism's systems associated with validated history of past direct contacts with Agent Orange (AO), durable residence on the sprayed territory (DEF), and strong separate influence of common health risk factors in a contingent of rural Southern Vietnamese (Song Be, 1989, m, 31-50)**

Odds-ratios for persons with the complete sets of medical problems indicating the most likely functional alterations in gastroenteral (GENT), cardiovascular (CV), immune (IMMUNE, frequent upper respiratory diseases), osteoartricular (OSAR), visual (VIS, total), pancreatic (PAN), respiratory (RES), and urine excreting (URIN) systems; stratified analysis, no significant differences between fractions of persons with an influence of other risk factors in comparison groups, MH-OR, 95% C.I. excludes 1.0; +, \*/\*, \*\*/\*\*, \*\*\*/\*\* -  $p < 0.10$ , 0.05, 0.01, 0.001. "DEF" - Dioxin-containing Ecotoxicologic Factor (>15 years of residence on the sprayed territory); "M" - past malarial diseases; "N" - inadequate protein nutrition (<100 g meat/week); "S" - intensive smoking ( $\geq 20$  cigarettes/day); **X** - an influence of risk factors on the background of DEF.

Columns	1	2	3	4	5	6	7	8	8	9	10
Risk Factors	AO <sup>X</sup>	DEF	M <sup>X</sup>	M	3 / 4	N <sup>X</sup>	N	6 / 7	S <sup>X</sup>	S	8 / 9
Comparison Groups, N	BM III/II 110/194	BMII/CMI 194/291	BMII+/- 26/168	CMI+/- 38/253	M+/ 26/38	BMII+/- 48/83	CMI+/- 51/169	N+/ 99/51	BMII+/- 72/122	CMI+/- 166/125	S+/ 72/166
<b>GENT</b>	5.81***	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
<b>CV</b>	4.13***	4.56**	ns	ns	ns	5.33*	ns	*	ns	ns	**
<b>IMMUNE</b>	3.01***	ns	ns	ns	ns	9.90***	ns	*	ns	ns	ns
<b>OSAR</b>	2.49**	ns	ns	ns	**	5.44***	ns	*	ns	ns	**
<b>VIS, total</b>	2.33**	2.07***	3.62**	ns	+++	4.23**	3.32***	ns	2.75**	3.27***	##
<b>Diplopia</b>	3.25**	7.03**	ns	ns	ns	ns	ns	ns	ns	ns	ns
<b>Spots, eyes</b>	2.54**	7.69***	4.53**	ns	**	ns	ns	ns	ns	ns	**
<b>Mesopic vis.</b>	2.17*	ns	7.76**	ns	ns	4.71 <sup>+</sup>	ns	ns	11.3***	7.95**	ns
<b>Blurred vis.</b>	2.07**	3.26***	2.43*	ns	*	ns	ns	ns	ns	ns	**
<b>Dark adapt.</b>	ns	ns	8.35***	ns	***	2.99**	6.89***	ns	9.17***	5.95***	**
<b>Hemeralopia</b>	ns	ns	3.97*	ns	**	ns	ns	ns	6.16***	5.57**	ns
<b>PAN</b>	2.19**	1.83**	2.66*	ns	ns	3.53**	ns	ns	2.02*	ns	**
<b>RES</b>	2.21 <sup>+</sup>	ns	8.10**	ns	*	ns	ns	ns	ns	ns	*
<b>URIN</b>	2.11*	2.32*	4.62**	ns	**	2.86*	11.9***	ns	ns	ns	**

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**Fig. 3. Specific patterns of pathologic manifestations for different organism's systems associated with validated history of past direct contacts with Agent Orange (AO) and a history of malarial diseases (M) in a contingent of Northern Vietnamese (1993 and 1995, Dong Anh, Bac Hong, m, 40-60)**

Risk Factors	AO <sup>x</sup> (M=0) 1993	AO <sup>x</sup> (M=1) 1993	M <sup>x</sup> (AO=0) 1993	AO <sup>x</sup> (M=1) 1995
Comparison Groups, N	BH II/BH I 16/109	BH II/BH I 62/67	BH I +/- 67/109	BH II/BH I 29/112
<b>GENT</b>	3.49*	2.62*	ns	2.94*
<b>CV</b>	4.21*	2.18 <sup>+</sup>	2.75*	3.16*
<b>IMMUNE</b>	4.85*	2.52*	ns	4.19 <sup>+</sup>
<b>OSAR</b>	ns	ns	1.92 <sup>+</sup>	ns
<b>VIS, total</b>	7.4*	3.17*	ns	3.89*
<b>Diplopia</b>	3.26*	3.70**	ns	2.46 <sup>+</sup>
<b>Spots, eyes</b>	9.11***	2.30*	ns	2.44 <sup>+</sup>
<b>Mesopic vis.</b>	ns	2.42*	ns	5.69***
<b>Blurred vis.</b>	4.10*	ns	2.44*	2.36 <sup>+</sup>
<b>Dark adapt.</b>	ns	ns	1.93 <sup>+</sup>	ns
<b>Hemeralopia</b>	3.29 <sup>+</sup>	ns	ns	3.14*
<b>PAN</b>	ns	ns	ns	ns
<b>RES</b>	2.91 <sup>+</sup>	ns	1.95 <sup>+</sup>	3.08*
<b>URIN</b>	3.36*	2.85*	ns	ns

Stratified analysis, MH-OR, 95% C.I. excludes 1.0; <sup>+</sup>, \*, \*\*, \*\*\* -  $p < 0.10, 0.05, 0.01, 0.001$ ; Yates correction; exact Fisher 2-tailed  $p$  values. <sup>x</sup> - No significant differences in fractions of persons with an influence of other risk factors in comparison groups.