Increased Susceptibility to the Infectious Respiratory Diseases in Rural Vietnamese Exposed to Agent Orange

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Introduction: Taking into account the hormone-like, dysregulative and disadaptive mode of dioxin's biological action, it is reasonably to consider that exposure to dioxin-like compounds may produce not only the development of certain rare diseases associated with high levels of the exposure but, at first turn, creates a favourable background for the development of a broad variable range of sub clinical pathological conditions in the low or moderately exposed populations. Depending upon peculiarities and duration of exposure, concomitant influence of other chemicals and health risk factors, genetic and population features, these often hidden chronic health outcomes may be manifested in a time- and situation-dependent manner by various homeokinetic shifts indicating dysadaptive state of the organism, by individual- and population-specific characteristics of deterioration of general health status, by impaired mental and working capacity and, also, by increased occurence of common diseases in the exposed contingent. Due to considerable subjectivity and limited informativity of health characteristics employed in sub clinical state epidemiological studies, epidemiological detection of the last effect, particularly in epidemic situation, appeared to be a promising approach to more objective assessment of hidden health consequences of exposure to dioxin-containing chemicals and to evaluation of their medical significance in a real life situation.

Objective: The aim of this study was to investigate the occurence of infectious respiratory diseases in rural Vietnamese exposed to Agent Orange (AO) as an indicator of the reality and medical significance of the long-term health consequences of past direct contacts with the dioxin-containing defoliant.

Methods: The questionnaire-derived characteristics of main health risk factors influence including a history of past direct contacts with AO confirmed by the US HERBS tape data and typical associations between characteristics of primary toxic responses from the organs of contact and organism ("Medical Equivalents of Toxodose 1,2"; Exposure Risk Groups, "ERG") and an information about the occurence of upper respiratory diseases ("URD") have been taken from the results of community-based cross-sectional epidemiological studies conducted with apparently healthy persons in the villages Chanh My and Binh My ("CM", "BM", South Vietnam, Song Be, 1989) and Bac Hong ("BH", North Vietnam, Dong Anh, 1993)[1-3]. In the end of 1992, an outbreak of infectious pulmonary disease has been registered in the villages Binh My (AO-treated) and Phu Hoa ("PH", Song Be, untreated). All persons with prolonged expectorating cough in these

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communities have been examined by physicians from the Song Be Social Diseases Center and Song Be MCH Center using a method for active detection of pulmonary tuberculosis[4] and interviewed using a basic questionnaire developed for the purposes of AO-study. The results of clinical immunological and biochemical investigations carried out in 1990 with representative groups of exposed and non exposed apparently healthy Binh My and Chanh My villagers[5,6] were taken for relevant considerations.

Results: Increased prevalence of frequent URD (>4 times/y, complaints) in different contingents of rural Vietnamese exposed to AO is shown in the following table ("DEF" - place specific dioxin-containing ecotoxicological factor, >15 y of residence on AO-treated territory; "M"- past malarial diseases, > 5 y after the last case; "S" - smoking, no significant differences in smoking habit between sub groups of comparison; persons with high exposure to pesticides and alcohol consumption are excluded; M-H OR , 95% C.I., Epi Info 5.01):

Males (30-60, Song Be, 1989)				
ERG	**AO / DEF**	**M ($\pm$S)**	**BM 1**	**BM 2** (N=167)
AO / DEF			no / yes	yes / yes
CM (N=357)	no / no	$\pm$	1.07<**1.65**<2.55	1.93<**3.01**<4.72
		+	0.99<**5.93**<45.6	1.59<**8.86**<64.8
		−	ns	1.76<**2.85**<4.62
BM 1 (N=238)	no / yes	$\pm$	−	1.15<**1.82**<2.88
		+	−	1.59<**8.86**<64.8
		−	−	1.16<**1.91**<3.15

Females (30-50, Song Be, 1989)				
ERG	**AO / DEF**	**M ($\pm$S)**	**BM 1**	**BM 2** (N=75)
AO / DEF			no / yes	yes / yes
CM (N=259)	no / no	$\pm$	ns	1.19<**2.57**<5.50
		+	−	−
		−	ns	1.22<**2.72**<6.02
BM 1 (N=272)	no / yes	$\pm$	−	ns
		+	−	ns
		−	−	ns

Males (40-60, Bac Hong, 1993)				
ERG	**AO / DEF**	**M ($\pm$S)**	**BH 1**	**BH 2** (N=71)
AO / DEF			no / no	yes / no
BH 1 (N=183)	no / no	+	−	1.40<**2.84**<5.76

These data show a reality of significant consistent associations between a history of past direct contacts with AO and increased prevalence of frequent URD in the exposed rural Vietnamese. This effect is more expressed in male contingents even on the background of past malarial disease - the next to AO main risk factor determining significant deterioration of general health status in this population[1-3].

The results of comparative evaluation of the occurence of infectious pulmonary diseases during an epidemic period that have been classified as pneumonia "P" (cases) and pulmonary tuberculosis "T" (cases) in contingents with different histories of exposure to AO and residence on AO-treated territory are presented in the following table (M-H OR, Epi Info 5.01):

ERG	AO / DEF	Age, y	N, m+f	P	OR(P)[X]	T	OR(T)[X]
PH	no / no	21-40	1440	12	--	1	--
		41-60	1177	17	--	1	--
		> 60	448	19	--	2	--
BM 1	no / yes	21-40	782	7	1.07	1	
		41-60	645	10	1.07	1	1.37
		> 60	245	12	1.15	1	
BM 2	yes / yes	21-40	439	13	3.34*	0	
		41-60	338	28	5.74*	4	4.98**
		> 60	118	18	3.49*	4	

[X] - M-H Odds Ratios for P and combined T cases: BM 1 / PH, BM 2 / BM 1.
*,** - 95% C.I. excludes 1.0, Fisher exact 2-tailed value - $p<0.05$.

Comparative analysis of several symptoms and signs recorded for cases of pneumonia in age-adjusted ERGs (proportion of persons within each ERG, %) did not reveal any ERG-specific features of the disease manifestation ("Spearman Rank Correlations", $p<0.001$) :

Age groups, m+f	40 - 60 y			> 60 y		
Symptoms and signs	PH	BM 1	BM 2	PH	BM 1	BM 2
Expectorating cough	100	100	100	100	100	100
Weight loss	62.5	90.9	77.8	63.0	100	82.4
Decreased appetite	50.0	72.7	77.8	63.0	70.0	76.5
Pain-chest-aggr. by cough	50.0	72.7	72.2	63.0	70.0	76.5
Elevated temperature	50.0	63.6	66.7	37.0	60.0	64.7
Insomnia	37.5	81.8	55.6	55.6	70.0	76.5
Pain-lower-back	37.5	45.5	61.1	22.2	60.0	29.4
Constipation	37.5	0	16.7	7.4	20.0	5.9
Haemoptisis	25.0	27.3	11.1	7.4	10.0	11.8
Pain joints	25.0	18.2	16.7	7.4	10.0	5.9
Sweating +	12.5	18.2	55.6	18.5	50.0	23.5
Diarrhea	12.5	0	5.6	14.8	0	5.9
Sputum purulent	0	0	5.6	0	0	5.9

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No significant differences have been found in a contingent of ill patients between proportions of persons with a history of malarial diseases ("M") and intensive smoking ("S", > 20 cigarettes/d) in the ERGs BM 1 and BM 2 as well as in the age-adjusted sub groups within each ERG ("Contingency tables", Fisher exact values, Woolf's chi-square test):

ERG	BM 1		BM 2	
Age groups	M, %	S, %	M, %	S, %
21-40 y	42.9	33.3	46.1	30.8
41-60 y	10.0	40.0	14.3	35.7
> 60 y	25.0	42.0	11.0	22.2

Also, the better nutrition of AO-exposed persons with pneumonia in the year of illness in comparison with healthy persons from the same ERG has been estimated using a "Cluster analysis"- based classification performed in each age-adjusted sub group ("1" - "3": joined classes with "Poor" - "Good" nutrition status):

ERG	BM 1			BM 2		
Nutrition status [x]	"1" %	"2" %	"3" %	"1" %	"2" %	"3" %
Healthy	67.5	24.4	8.1	65.0	29.4	5.6
Pneumonia	52.9	29.4	17.7	34.1	29.3	36.6
P, chi-square	0.236			4.8×10^{-8}		

[x] - Averaged weekly consumption of rice, meat and oil.

These data indicated a possibility of increased susceptibility to pneumonia in AO-exposed persons, allowed to hypothesize direct or indirect causality and to assess Attributable Risk Fractions (ARF, %) for the disease[8]:

Age Group	ARF for DEF	ARF for AO	
Comparison Groups	BM 1 / CM	BM 2 / CM	BM 2 / BM 1
21-40	0.8<1.1<1.4	21.0<**21.6**<22.1	17.5<**17.8**<18.0
41-60	0.7<1.1<1.5	30.2<**31.0**<31.8	24.6<**25.8**<27.0
> 60	1.1<2.1<3.1	20.7<**22.0**<23.3	16.5<**18.5**<20.5

The following effects that have been registered in the same contingent of Chanh My and Binh My villagers support a biological plausibility of the results presented in this study:
1 - significant alterations in cell-mediated immunity apparently originating from the non lethal damage of stem cells during acute intoxication with AO[5] consistent with observations of other authors[7],

2 - specific development of "hyposensitive" hypovitaminosis A in AO-exposed group[6],
3 - specific increase in MET 1 values for inhalative component of the exposure in a sub group of ill persons indicating a possibility of lung tissue deterioration by AO[4].

Conclusions: The results of this study confirmed a reality and medical significance of the long-term health consequences of past direct exposure to AO in Vietnam, on the one hand, and illustrated a practicability of the employed approach to identification of hidden health consequences of the exposure, on the other hand. Thus, an increased prevalence of certain common infectious diseases in contingents exposed to dioxin-containing chemicals, that may be easily registered in an epidemic situation, may serve as an objective epidemiological indicator of exposure-related health outcomes. Also, a possibility of such effects must be taken into account in the assessment of health hazards associated with the exposure.

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