The Long-Term Health Consequences of Agent Orange in Vietnam: Evidences of the Reality and Medical Significance

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By certain substantial reasons, Vietnam unfortunately provides a unique opportunity to study the long-term health consequences of war dioxin-contaminated herbicides in high exposed human contingents on population level. The evidences of the reality and medical significance of specific health outcomes associated with a history of direct contacts with Agent Orange (AO) and long residence on the herbicide sprayed territory have been obtained in Joint Vietnam-Russian Tropical Center in the course of specialized epidemiological, clinical laboratory and statistical investigations (Song Be province villagers; m, f, 2235)[1-7].

Statistical analysis of interrelations between questionnaire-derived retrospective characteristics of primary responses to AO from the organs of contact and the organism (Medical Equivalents of Toxodose; MET1: inhalative, eye-irritating, skin-resorptive and enteral components, relevant symptoms, 1-3 d postexposure; MET2: systemic responses, 3-6 m postexposure) allowed: to define the likely extent of the exposure (Exposure Risk Groups; "Statistical Grouping"; "Intentional Statistical Analysis" and "Cluster Analysis"), to evaluate pathogenetic significance of different ways of AO entering the organism, and to select untypical subjects with false self-estimates of the exposure or with distinctive susceptibility to AO regarding development of primary toxic responses (Fig.1)[1,2,4].

Fig.1. A questionnaire-based method designed for evaluation of past direct exposure to Agent Orange (m, 31-50, N = 110).

Practicability: number of persons who were able to characterize primary responses:	**86 / 110 = 78.18%**
A linear regression model of the exposure "Intentional Statistical Analysis" $R^2 = 0.655$:	
MET2 = 0.829xMET1 + 0.157	
Number of selected untypical subjects:	**6**
Persons fitted for the exposure model:	**80 / 86 = 93.02%**
Statistically defined ERG: number of clusters for definite MET1/MET2 relationships:	**2**
MET1/MET2 values in the ERG I:	0.06-0.53 / 0.10-0.70
MET1/MET2 values in the ERG II:	0.53-0.82 / 0.50-0.90

A history of residence on the sprayed territory has been accounted to evaluate potential influence of Dioxin-containing Ecotoxicological Factor (environmental dioxin, other health risk factors produced by the "Ranch Hand Operation").
Strong consistent associations between the ERG-based measures of the exposure and relative frequencies of current medical problems (symptoms and signs of pathological conditions for different systems of the organism) were found for 11 characteristics of health status in all sex and age-adjusted sub groups and for 24 characteristics in certain sub groups. Significant excess of prevalences for, approximately, 20 exposure-associated health problems was established in the exposed groups using internal and external comparisons (M-H weighted odds-ratios, age and sex-stratified). Significant deterioration of current general health status (integrated Index of Poor Health Status consists of exposure-associated complaints) was found in all age and sex-adjusted sub groups of persons exposed to AO and in certain sub groups of persons exposed to DEF ("Mann-Whitney Rank Test)[1]. The reality of definite associations between MET1, MET2 and IPHS values established in the selected group of AO-exposed subjects indicated a possibility: to define certain statistically homogenous Effect Development Risk Groups (Fig.2, "Cluster Analysis"), to demonstrate the existence of exposure-effect-like relationship, and to select untypical subjects with the erroneous results of medical examination or with distinctive susceptibility to AO in terms of untypical development of exposure-associated health outcomes that may be useful for further investigation of genetic background and external factors involved in this effect formation[2].

Fig. 2. Statistical definition of the EDRG (m, 31-50: +AO, -M*, -S*, -P*; fitted for the regression model of the exposure. Averages for a whole contingent: MET1 = 0.365, MET2 = 0.464, IPHS = 0.276).

Indices:	Effect Development Risk Groups			
% of averag.	I	II	III	IY**
MET1	- 41%	- 8%	+ 92%	+ 60%
MET2	- 45%	+ 6%	+ 68%	+ 7%
IPHS	- 21%	+ 8%	+ 35%	- 62%

* Past malarial diseases, intensive smoking, frequent contacts with pesticides.
** Untypical (hyposensitive?) subject.

Special features of current medical conditions associated with past exposure to AO are evident from specific sub clinical pathological profiles (Fig.3) established in groups with separate influence of main risk factors and from the results of satisfactory identification of AO-exposed persons (Fig.4) in the entire population sample carried out using Bayesian's classification procedure and AO-specific pathological pattern. The results obtained by a "Multifactor ANOVA" method confirmed the leading role of past direct contacts with AO in significant deterioration of current general health status (IPHS) and demonstrated additive contribution of intensive smoking and consequences of past malarial diseases to this effect[2].

Systemic statistical analysis of collected clinical laboratory data also revealed certain significant sub clinical alterations in the homeostasis associated with a history of exposure to AO/dioxin. For example, certain alterations in humoral and cellular (T-cells, T-helpers, NBT-test; "Pattern Recognition Analysis") immunity found in a group of AO-exposed subjects[3] were consistent with significantly increased prevalences of upper respiratory diseases and infectious pulmonary diseases registered in this population group[4]. Significantly increased prevalences of "hyposensitive" hypovitaminosis A and of coproporphyrinuria found in a group of AO-exposed subjects were coincided with the increased excretion rates of 4-hydroxy-antipyrine and were not associated with an influence of other risk factors or impaired liver functioning[5]. Significant ultrastructural alterations in skin which may be attributed to the consequences of chloracne development and impaired differentiation of keratinocytes were also found by scanning electron microscopic examination only among AO-exposed subjects[6]. Some hidden disadaptive conditions that are characteristic of dioxin's effect were revealed in the exposed subjects using certain physical, biochemical and cytogenetic loadings[7].

In terms of biological plausibility the established health effects of AO may result from: 1 - pathological conditions induced by acute intoxication and permanently developing under the strong influence of other risk factors in this population, 2 - long-lasting consequences of stem-cells damage caused by acute intoxication, 3 - the hormone-like activity of dioxin residuals in target cells, and 4 - long-lasting preservation of exposure-induced state of the homeostasis that is characteristic of the population with a homeostatic strategy of adaptation.

References

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Fig. 3. SPECIFIC PATTERNS OF PATOLOGICAL MANIFESTATIONS ASSOCIATED WITH EXPOSURE TO DIFFERENT HEALTH RISK FACTORS (M-H weighted odds ratios / Attributable Risk = (RR-1) / RR, %).

Risk factors	AO	Nutrit.	DEF	S	M ± S	Alcohol	P ± M± S	P ± M± S
E R G	BM III / BM II	BM II + / –	BM II + / –	BM II + / –	BM II + / –	CM I + / –	BM II + / –	BM III + / –
N, males, 31-50	70 / 121	150 / 93	142 / 43	64 / 121	29 / 168	32 / 125	16 / 345	14 / 163
148 Tachycardia	6.22* / 84	1.01	1.10	2.17* / 54	1.58	1.30	1.20	1.13
172 Vomiting	5.95* / 83	0.79	0.95	2.36	2.43* / 59	2.39	1.47	0.42
175 Constipation	5.77* / 83	2.52* / 60	1.27* / 21	1.40	4.38* / 77	1.80	0.64	0.48
143 Dyspnea, exertion	3.29* / 70	1.61	0.96	1.59	2.41* / 59	3.71* / 73	2.88* / 65	0.52
137 Pain-chest	2.76* / 64	1.80	1.13	1.89	4.45* / 78	3.91* / 74	2.79o / 64	0.59
191 Spots before the eyes	2.68* / 63	0.36	0.90	0.70	4.55* / 78	2.42o / 59	--	0.30
158 Pain-legs, rest	2.62* / 62	0.90	0.99	0.70	0.62	2.10	3.57* / 72	1.07
168 Increased appetite	2.62* / 62	1.21	0.93	0.27	0.99	--	--	--
169 Thirst, permanent	2.38* / 58	1.80	1.09	3.03* / 58	3.96* / 75	1.26	1.13	0.72
131 Cough, total	2.24* / 55	2.34* / 57	1.26	1.65	1.10	2.67* / 63	0.83	0.84
157 Pain-legs, walk	2.24* / 55	3.58* / 72	1.53* / 35	0.59	0.91	2.03	--	1.46
150 Pain-heart	2.19* / 54	2.40* / 58	1.23	1.30	1.36	6.41* / 84	1.25	0.88
185 Blurred vision	2.14* / 53	1.21	1.05	1.24	2.44* / 59	2.34o / 57	1.64	1.64
155 Pain-loins	1.93o / 48	1.97	1.23	1.21	2.90* / 66	0.75	1.58	1.35
163 Weight loss	1.92o / 48	1.74	0.72	0.82	2.27	2.93* / 66	2.20	0.63
196 Frequent URD	1.86o / 46	4.28* / 77	0.92	0.85	1.03	2.10	--	0.43
141 Headache, frequent.	1.70	1.93	0.90	2.99* / 67	3.39* / 71	1.89	2.88* / 65	1.36
133 Cough, at night	1.64	3.18* / 69	1.85* / 46	1.56	2.11	1.49	1.52	1.85
170 Thirst, frequent.	1.36	0.58	1.61* / 38	0.15o	--	7.67* / 87	--	--
161 Pain-joints	1.10	1.59	1.05	1.00	1.61	1.63	0.82	0.71
180 Anal bleeding	1.05	--	1.06	1.19	1.80	0.33	0.71	0.76
192 Dark Adaptation.	0.74	1.96* / 49	.67	9.39* / 89	8.35* / 88	0.53	8.64* / 88	5.25* / 81

* 95 % confidence interval excludes 1.0; o Chi-square test, p<0.05 (Epi Info 5.01); Nutrit.- <100 g meat / w; DEF - >15 y; Smoking "S" - >10 cigarettes / day; Malaria "M" - history of malarial diseases; Alcohol - >0.5 l / w; Pesticides "P"- >10 contacts / y, cases of intoxication. +/- : sub groups of subjects exposed / unexposed to the health risk factor. BM III / II (Binh My; AO - yes / no), CM I (Chanh My; AO, DEF - no).

Fig.4. IDENTIFICATION OF PERSONS EXPOSED TO AGENT ORANGE IN THE VILLAGE BINH MY

BAYESIAN'S WEIGHTS FOR SYMPTOMS AND SIGNS ASSOCIATED WITH EXPOSURE TO AGENT ORANGE

$$\text{Log}\ [\ Pr(\ x_i \mid \text{BM III}\ ) / Pr(\ x_i \mid \text{BM II}\ )\ ]$$

A priori probability constant : $\text{Log}\ (\ N_{\text{BM III}} / N_{\text{BM II}}\ ) = -0.24$

REFERENCE GROUPS	BM III / BM II
Past direct exposure to Agent Orange	yes / no
Dioxin-containing Ecotoxicolocical Factor	yes / yes
M, 31-50; "N" / "S" / "M" / "P"/ "A" - no	70 / 121

SYMPTOMS AND SIGNS	YES	NO
148 Tachycardia	0.53	- 0.32
172 Vomiting	0.68	- 0.06
175 Constipation	0.59	- 0.19
143 Dyspnea, exertion	0.32	- 0.19
137 Pain-chest	0.22	- 0.25
191 Spots before the eyes	0.42	- 0.09
158 Pain-legs, rest	0.33	- 0.07
168 Increased appetite	0.36	- 0.07
169 Thirst, permanent	0.24	- 0.10
131 Cough, total	0.17	- 0.21
157 Pain-legs, walk	0.27	- 0.07
150 Pain-heart	0.22	- 0.12
185 Blurred vision	0.21	- 0.09
155 Pain-loins	0.07	- 0.18
163 Weight loss	0.19	- 0.09
196 Frequent upper respiratory diseases	0.18	- 0.08

PROBABILITIES OF MISSCLASSIFICATION:

Pr (BM II → BM III)	22.2 % (43 / 194)
Pr (BM III → BM II)	22.7 % (24 / 108)

Main health risk factors: "N" - nutrition, "S" - smoking, "M" - past malarial diseases, "P" - pesticides, "A" - alcohol (fig.3).