Phenomenological Models of Exposure and Effects in Epidemiology of the Long-Term Health Consequences of Agent Orange in Vietnam

Vladimir V. Antonyuk [a,b] and Sergei P. Poznyakov [b], (a) Dept of Medical Demography, Research Public Health Institute "MedSocEconomInform", Dobrolyubova str. 11, Moscow 127254, Russian Federation; (b) - Joint Russian-Vietnam Tropical Centre, Gia Thuy, Gia Lam, Hanoi, Vietnam

Introduction

The hormone-like pleiotropic, disregulative and disadaptive activity of dioxin-like compounds (DLC) and critical dependence of their toxycokinetics and toxycodynamics on peculiarities of exposure, large number of internal, external, and temporal effect-modifying factors result in expressed polymorphism of systemic responses in high individual, situational and temporal variability of health effects and their relationships with the parameters of exposure. These special features of the toxicology of DLC thus require: 1) investigation of sufficiently numerous groups of exposed and unexposed persons under comparable influence of effect-modifying factors in the longitudinal studies; 2) evaluation of a history of integrated exposure to DLC and other cocomittant ethiopatogenetically significant factors united in the "dioxin-containing ecotoxicological factor" (DEF) concept; 3) identification of all possible health hazards associated with exposure, including sub clinical, latent and disadaptive conditions; and 4) evaluation of biological and methodological variability and uncertainty of exposure and effects estimates and their relationships.

Typologically, the exposure to DEF and certain systemic responses may be represented as structured "phenomenological models" of exposure and effects using multidimensional statistical investigations of associations between logically, toxicologically and biologically linked direct and indirect characteristics of different constituents of DEF or/and the systems of an organism which are under investigation. This approach permits: evaluation of the comparability of exposure patterns in different situations; definition of individual exposure measures by allocating persons in typologically similar and statistically homogenous "exposure risk groups" (ERG), ranked by the characteristics of likely intensity of exposure to DLC; investigation of the ERG-based exposure-response-like relationships in a concrete situation by statistical definition of the "effects development risk groups"; identification of relatively discrete symptom complexes of health outcomes consisting of the most associated symptoms and signs ("pathologies development risk groups", PDRG); and identification of specific systemic alterations in the homeostasis using the criterion of biological plausibility [1].

The objective of this report is to illustrate methodological advantages of this "phenomenological approach" with the results of investigation of the long-term health consequences (LTHC) of Agent Orange (AO) in Vietnam.

Evaluation of past direct exposure to Agent Orange by the "phenomenological modelling"

Analytical generalization of the results of epidemiological investigations revealed serious problems in adequate reconstruction of a history of exposure to dioxin-containing chemicals using the data on residual levels of DLC in the avaliable biomaterials and methods for toxycokinetic modelling [2]. The main reasons include: 1) the dependence of toxicokinetics of DLC on exposure levels and

conditions, biological effects and toxicokinetic interactions of different congeners, as well as on a history of influence of many internal and external factors; and 2) the inability to evaluate ethiopathogenetically significant influence of other constituents of DEF. In Vietnam, more than 90% of persons who were in likely direct contact with AO have reported about manifested symptoms and signs of toxic responses from the organs of contact and systemic responses. These effects provided an opportunity to estimate the likely levels of exposure to all components of AO using retrospective self-reported characteristics of acute intoxication [3] and "phenomenological modelling". The reality of expected and toxicologically reasonable relationships between integrated characteristics ("medical equivalents of toxodose", "MET"=Σ manifestations/number of characteristics) of initial (MET1, 1-3 days postexposure) and subsequent (MET2, 3-6 months postexposure) responses is shown in fig. 1. These data, also illustrate a possibility to identify the persons with statistically atypical relations between values of indices MET1 and MET2 derived from their incorrect self-estimates of exposure or from the distinctive individual susceptibility regarding development of primary health consequences from the exposure (MET2).

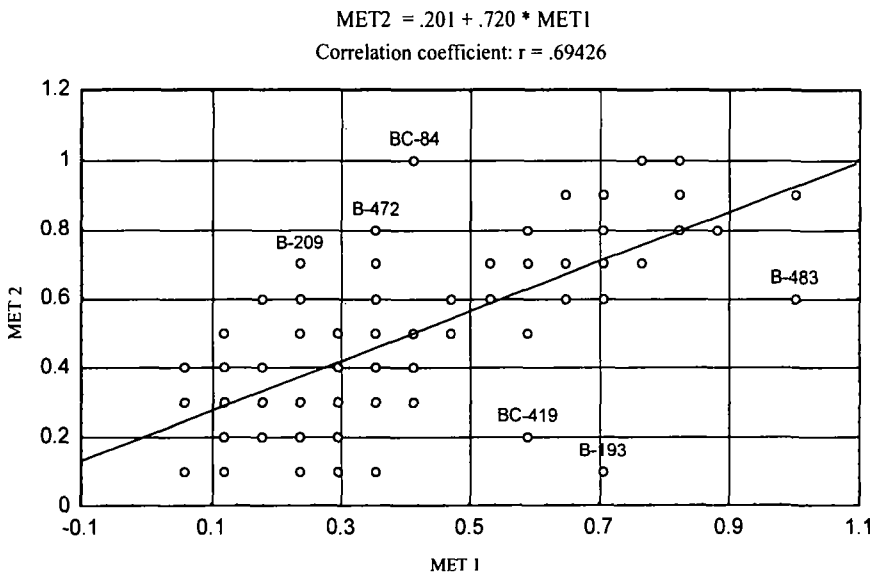

Fig. 1. Linear regression model of past direct exposure to Agent Orange in a contingent of South Vietnamese peasants (Song Be, Binh My, 1989; m, 31-50). Statistically atypical persons are marked by codes ("Intentional Statistical Analysis").

The reality of certain relationships between the values of MET1 and MET2 permits the identification of statistically reasonable individual exposure measures using the procedure of "Cluster Analysis" (fig.2). These data demonstrate a possibility to define two statistically homogenous ERG with low and high likely intensity of exposure under given conditions (sample size, individual variability and uncertainty of exposure characteristics) and to consider allocation of persons in these ERG as their individual exposure measure.

The reliability of such classification is proved by significant consistency of results obtained in groups of exposed South and North Vietnamese and by significant prevalences of identified biomedical indicators of exposure and effects in the selected ERG [3].

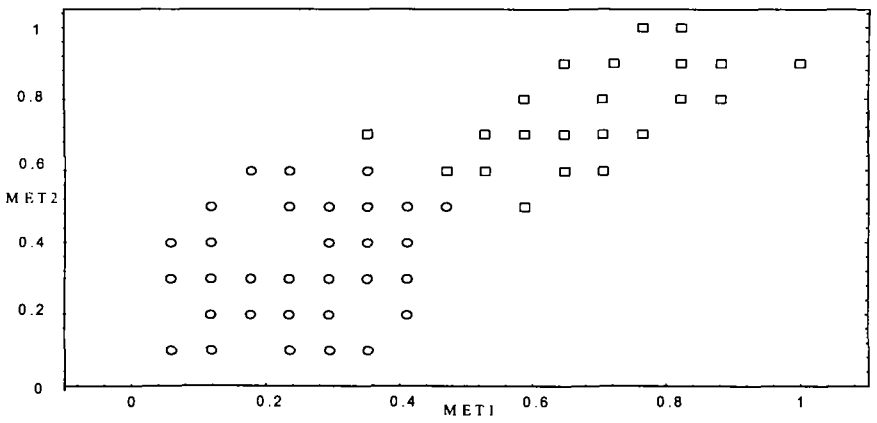

Fig. 2. Statistical definition of exposure risk groups with low (O) and high ( ) likely intensity of exposure to Agent Orange using the method for "Cluster Analysis".

The most essential features of the exposure patterns may be established using the methods for multidimensional statistical investigation of associations between all components of MET1 and MET2 (fig.3).

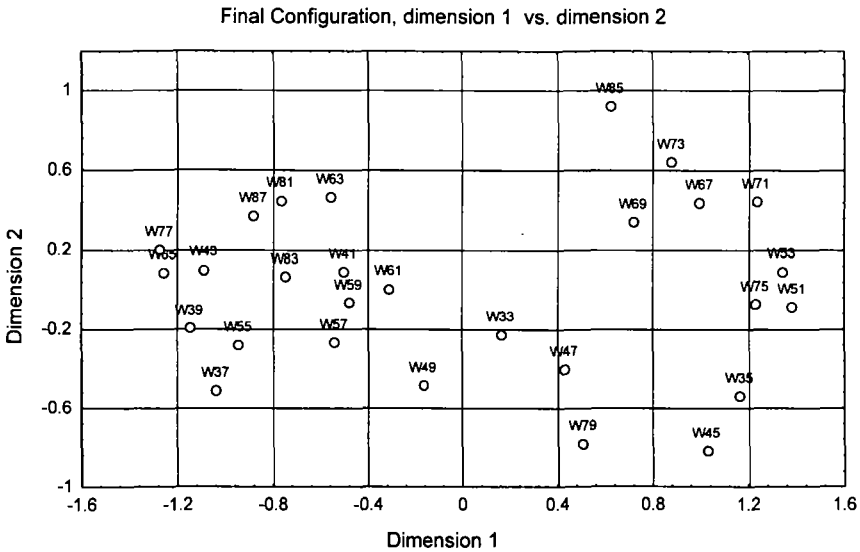

Fig. 3. Investigation of patterns of direct exposure to Agent Orange with the self-reported characteristics of the acute period of intoxication (w_i) ("Ward's method, City-block (Manhattan) distances, Multidimensional scaling").

The results of such groupings may provide information about the toxicological sense of registered exposure characteristics and permit evaluation of ethiopathogenetically important similarity of

exposure conditions in different situations. For example, the data presented in fig. 3 illustrate a possibility of allocation of the most closely associated symptoms and signs of acute intoxication into the two principal groups presented in table 1.

Table 1.

Groups of the most associated symptoms and signs of primary responses to Agent Orange

	MET1 components	MET2 components
1	w37 (nasal bleeding), w39 (nausea), w41 (vomiting), w43 (diarrhea), w55 (dizziness), w57 (skin itching), w59 (skin blisters), w61 (skin reddening), w63 (fever), w65 (fainting)	w77 (impotence), w81 (changed skin color), w83 (skin inflammation), w87 (skin blisters under the sun)
2	w51(headache), w53 (weakness)	w67 (frequent wish to lie down), w69 (high tiredness), w71 (weakness on exertion), w73 (insomnia), w75 (frequent headaches), w85 (weight loss)

These groupings permit the assumption that the components of MET1 and MET2 included in the first group reflect primary and subsequent acute toxic responses. In the second group, the close association only between indicators of some common systemic and vegetative nervous system disorders may reflect the reality of a separate syndrome which is not critically dependent on the likely intensity of exposure. Representation of the results of multidimensional scaling as the projection of distances between components of MET1 and MET2 on the main axis (dimension1/dimension2→dimension) permits presentation of the generalized characteristic of exposure patterns and investigation of their comparability in different groups of exposed South and North Vietnamese (table 2).

Table 2.

Investigation of the comparability of exposure patterns for sub groups of South (BM) and North (BH) Vietnamese with low (BM1, BH1) and high (BM2, BH2) likely intensity of exposure to Agent Orange using the "Multidimensional Scaling" and "Spearman Rank Order Correlations" methods

Exposure Risk Groups ("Cluster Analysis")	p, MET1	p, MET2
BM 1 / BM 2	< 0.000	< 0.00
BH 1 / BH 2	< 0.000	<0.00
BH 1+BH 2 (1994) / BH 1+BH 2 (1995)	0.015	0.023
BM 1 + BM 2 / BH 1 + BH 2	< 0.000	0.032
BM 1 / BH 1	0.122	0.433
BM 2 / BH 2	< 0.000	0.026
	p, (MET1+MET2)	
BM 1 + BM 2 / BH 1 + BH 2	0.065	
BM 1 / BH 1	0.112	
BM 2 / BH 2	< 0.000	

The data in table 2 indicate: 1) the significant similarity of exposure patterns for the groups of low and high-exposed peasants in each village that permits the assumption of similar mechanisms of formation of primary responses to the low and high levels of exposure; 2) the temporal reproducibility

of exposure patterns in the village Bac Hong, and 3) the comparability of exposure patterns in South and North Vietnamese only for the high exposed sub groups that can be explained by reasonably higher uncertainty of retrospective exposure self-estimates or by different conditions of low exposure in these contingents.

"Phenomenological modelling" in the investigation of nosological specificity of health outcomes

Pleiotropic activity of DLC and high dependence of their effects formation on a large number of intrinsic biological effect-modifying factors (genotype, metabolic and endocrine phenotypes of an organism) determine high polymorphism and individual variability of expected health outcomes which may be displayed, even for a given time point, age/sex-adjusted sub groups, and conditions of exposure. The complexity and multitude of the Ah-receptor-dependent and independent mechanisms of formation of systemic responses to DLC significantly limit the opportunity to forecast individual peculiarities of healt outcomes basing on the Ah-receptor-related available biomarkers of individual susceptibility to DLC and implication of methods for the toxycodynamic modelling, even under experimental conditions [4]. This problem, as well as the problem of identification of specific systemic alterations in the homeostasis may be resolved by multidimentional statistical definition of the "phenomenological models" of effects based on the epidemiological or biomedical information [1].

For example, three discrete groups of "symptom complexes" of the LTHC of AO have been identified in a group of exposed South Vietnamese using the methods for "K-means Clustering" (distance matrices) and estimation of the coefficients of reciprocal directed interactions [5] (fig.4).

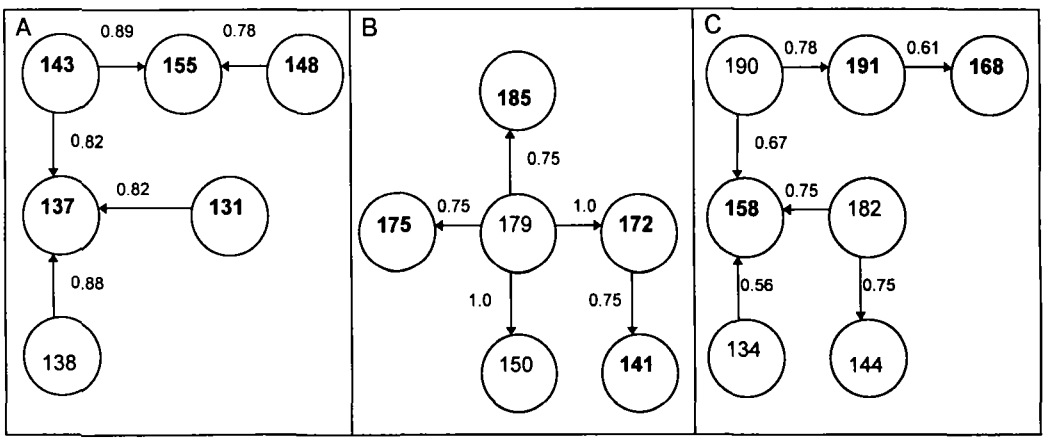

Fig. 4. Graphs for the main elements of different symptom complexes (A-C) of the long-term health consequences of Agent Orange in a group of South Vietnamese peasants. (Codes for symptoms and signs (w_i). Constituents of the exposure risk group-specific "patterns of pathological manifestations" [6] are in bold. Direction and strength of reciprocal interactions).

From this picture, we may consider formation of certain pathological states manifesting, for example, in the symptom complex "A" as w137 (pain-chest) or w155 (pain-loins) under contribution of states manifesting in the w138 (headache), w131 (cough), w143 (dyspnea, exertion) or w143 and w148 (tachycardia) symptoms and signs, correspondingly.

The results of systemic identification of biomedical indicators for discrimination of the ERG are presented in table 3 ("Pattern Recognition Ananlysis", Statex 2, Moscow, 1992; Binh My, 1989; apparenthly healthy males, 31-50, free from the strong influence of common health risk factors) [7,8].

Table 3.

Discrimination of exposure risk groups by the specific patterns of immunological status and porpyrin excretion profiles. (* - Limits of values which are critical for recognition).

Exposure Risk Groups	*CM I*	*BM II*	*BM III*
Direct exposure to AO	no	no	yes
Chronic exposure to DEF	no	yes	yes
Leucocytes, $x10^9$/L	ns	5.7* ≤ ≤ 9.20	ns
Lymphocytes, $x10^9$/L	ns	2.48* ≤ ≤ 6.53	ns
Neutrophils, %	60* ≤ ≤ 73	58* ≤ ≤ 73	ns
T-Lymphocytes, $x10^9$/L	ns	ns	.55 ≤ ≤ 1.34*
T-helpers, %	ns	30 < ≤ 64	8.0 ≤ ≤ 34*
NBT-тест, %	ns	ns	10.0* ≤ ≤ 72
CIC-termostable, u/dl	2* ≤ ≤ 177	ns	ns
Phagocytic Index, %	52* ≤ ≤ 316	6.0 ≤ ≤ 98*	ns
Ig A, мг/мл	.40 ≤ ≤ 11.9*	ns	ns
All porphyrins, pmol / 24 h	30.8 ≤ ≤ 148.2*	ns	148.2* < ≤ 442.7
Uro-, %	11.9* < ≤ 33.5	ns	4.62 ≤ ≤ 19.7*
7-COOH-, %	ns	ns	2.23* < ≤ 8.99
6-COOH-, %	0.29 ≤ ≤ 1.03*	0.08 ≤ ≤ 0.82*	0.57* < < 3.10
5-COOH-, %	0.10* ≤ ≤ 1.39*	1.24* ≤ ≤ 5.46	ns
Copro-I, %	15.6* ≤ ≤ 23.9*	23.2* ≤ ≤ 54.7	ns
Copro-III, %	ns	ns	57.2* < < 75.6
Copro-III / I, ratio	ns	2.93* ≤ ≤ 3.18*	ns

Literature cited

(1) Poznyakov, S.P.; Roumak, V.S.; Sofronov, G.A. *Organohalogen Compounds* **1997**, this issue.

(2) Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. *Veterans and Agent Orange*; Institute of Medicine; NAS, **1994**.

(3) Roumak, V.S.; Poznyakov, S.P.; Oumnova, N.V.; Sofronov, G.A. *Organohalogen Compounds* **1996**, 30, 85-90.

(4) U.S.EPA. *Health Assessment Document for 2,3,7,8-tetrachlorodibenzo-p-dioxin and Related Compounds*. **1994**. EPA/600/BP.

(5) Raushenbah G.V. *Analysis of categorical information in the sociological investigations*; Nauka; Moscow, **1985**; p.169-203.

(6) Poznyakov, S.P.; Antonyuk, V.V.; Nguyen Quoc An; Tran Xuan Thu; Kountzevitch, A.D.; Sofronov, G.A.; Roumak, V.S. *Organohalogen Compounds* **1994**, 21, 175-180.

(7) Poznyakov, S.P.; Roumak, V.S,; Antonyuk, V.V.; Nguyen Quoc An; Sofronov, G.A. *Organohalogen Compounds* **1995**, 26, 141-146.

(8) Poznyakov, S.P.; Antonyuk, V.V.; Nguyen Quoc An; Bykhovsky, V.J.; Roumak, V.S. *Organohalogen Compounds* **1993**, 13, 221-224.