Methodologic Considerations in Evaluating the Long-Term Health Consequences of Agent Orange in Vietnam

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Introduction

Initial domestic investigations on the long-term health consequences (LTHC) of Agent Orange (AO) in Vietnam indicated a possibility of lot adverse health outcomes, including some rare diseases and different disorders. However, methodologic weaknesses of these studies did not allow to rich reliable conclusions[1)]. The most successive international chemical analytical investigations clearly document: 1) significantly elevated residual levels of TCDD in sporadically collected environmental samples and human tissues in sprayed areas; 2) some of the lowest dioxin levels in human tissues reported worldwide to date in unsprayed territories, and 3) relatively high contamination of the environment with persistent agricultural organochlorines in some localities. The results of cooperative epidemiologic studies on hepatocellular carcinoma, hydatidiform mole, goiter, congenital malformations and other reproductive abnormalities revealed high incidence of the diseases in population of rural South Vietnamese, more or less increased risk in sprayed areas, the demands for more reliable and feasible exposure assessment methods, and a necessity to account significant influence of many intervening factors[2-4)]. Moreover, these episodic studies did not embrace various health outcomes, which are expected from the results of recent generalizations[5,6)]. Since 1988, the Joint Russian-Vietnamese Tropical Center conducts integrated multilevel ecotoxicologic, epidemiologic and biomedical investigations of all posible health effects of AO/dioxin in sub populations of rural southern and northern Vietnamese aiming at the development of methodologic basis for identification, evaluation, and treatment of the LTHC on population and individual levels. Here, we present some general methodologic considerations concerning these problems.

Conditions for investigation of the LTHC of war herbicides in Vietnam

Vietnam, unfortunately, provides a unique opportunity to investigate the LTHC of intoxication with dioxin-containing herbicides and continuos residence in the dioxin-contaminated environment. Besides detailed description of spraying missions, there are many toxicologically and methodologically significant prerequisites favoring these studies. They include: 1) substantially higher levels of exposure than that observed in foreign veterans of Vietnam war or in the dominant proportion of general population in the industrialized countries; 2) availability of numerous, sociodemographically constant, and non-migrating contingents of exposed and unexposed rural Vietnamese living in one and the same or in the closely located communities in

very similar conditions that permits investigation of various health outcomes and intervening factors with the most adequate internal and external comparisons; 3) conservative life style, relatively high and historically unvariable influence of health risk factors, and poor special medical aid that simplify historic reconstruction of exposure and favoring development of different pathologic conditions; 4) sufficient duration of postexposure period and an opportunity to investigate potentially exposed subsequent generation. At the same time, there are many local conditions impeding the investigations. They include: 1) a necessity to account a history of an influence of various confounding, pathogenetically significant, and relevant common health risk factors; 2) an influence of socioeconomic and environmental factors originated from the long-lasting ecocydic consequences of the "Operation Ranch Hand" in some communities; 3) poor informativity of residual dioxin levels; often incomplete and unreliable local documentary information; absence of retrospective medical records and death certificates, and likely problems with recall bias; and 4) poorly investigated biomedical features of Vietnamese.

Exposure assessment

Besides the acute and/or chronic intoxication with herbicides/dioxin, health status of rural Vietnamese in sprayed areas might be compromized by several other factors, which also closely related to the sprayings. They include: 1) significant compulsory changes in habitual lyfe style, occupation, nutrition, and socioeconomic status, and 2) appearance of additional physical and biogenic hazardous factors. By this reason we introduced a new concept of ethiologic "Dioxin-containing ecotoxicologic factor" (DEF) integrating exposure to the environmental dioxin and an influence of both measurable and unidentified health risk factors in sprayed areas. Generalizing the likely histories of exposure we may define the following "exposure risk contingents": 1) native population in sprayed villages maintained habitual lyfe style after sprayings; 2) the population and migrants who changed significantly their habitual lyfe style and undergone significant influence of additional socioeconomic and environmental health risk factors; 3) war veterans who undergone single/frequent acute exposures to herbicides/dioxin on the background of hard military service conditions and after the wartime returned to the dioxin-free native villages in northern Vietnam or migrated to the sprayed/unsprayed regions in southern Vietnam. At present, it becomes evident that such traditional exposure biomarkers as current serum dioxin levels and chloracne are not practical and relevant for evaluation of exposure to AO/dioxin at the individual level[6]. Therefore, historic reconstruction and classification of exposure may be based mainly on the self-reported data, some available records, and residual ecological and chemical markers at the group level. Obviously, such exposure measures may be expressed only in probabilistic terms and there is a need of more sophisticated techniques for their internal validation. For this purpose we developed a new concept of "phenomenological models of exposure" to investigate essential typological features of associations between informative datasets of different exposure characteristics. Thereby, statistical investigation of toxicologically reasonable associations between the prominent, well-remembered, and relatively consistent self-reported symptoms and signs of acute intoxication with AO enabled us to develop individual indices of the exposure; to define statistically homogenous sub groups with different likely exposure intensity ("exposure risk groups"); to consider the allocation of a person in one of these groups as the statistically reasonable individual exposure measure; to investigate exposure conditions in different contingents; and to reveal statistically atypical persons with the likely wrong self-estimates of exposure, distinctive susceptibility or exposure conditions. The phenomenological modelling also appear to be useful in assessing complex exposure to all ethiopathogenetically significant DEF constituents, in particular,

for considerations on causality. It allows selection of statistically homogenous sub groups of persons with definite patterns of associations between characteristics of exposure to all these factors within a given time period. These sub groups may be further stratified by individual indices of the likely degree of exposure to dioxin, which may be derived by summation of individual exposure opportunity scores. That permits to classify the likely degree of exposure to dioxin on the background of accountable influence of other ethiopathogenetically significant factors under the study and vice versa, to evaluate potential significance of these factors on the background of different likely levels of dioxin exposure [7-9].

Health effects

Basing on recent knowledges we may expect very wide spectrum of different LTHC of AO/dioxin in Vietnam due to heavy past exposure; pleiotropic, disregulating, and disadaptive biological activity of dioxins; utmost strong influence of various predisposing factors, and homeostatic strategy of adaptation of Asians. The LTHC may cover not only increased incidence of a limited number of certain rare diseases and disorders with "sufficient, limited/suggestive or inadequate/insufficient" evidences of associations with exposure[6] but also various, more or less specific and manifested disorders and dysfunctions, which may differ from that observed in other exposed populations. In fact, we obtained the evidences of reality, specificity, and medical significance of polymorphic alterations in current health status and homeostasis in exposed adult southern and northern Vietnamese. They include increased susceptibility to the infectious respiratory diseases[10], increased prevalence of manifested and subclinic pathologic and disadaptive conditions for different systems of an organism[7-9,11,12], some ecogenetic effects and reproductive outcomes[13,14], and a number of certain immunologic and biochemical alterations[7,8]. These remote responses may result from: 1) systemic health consequences of heavy initial exposure which were permanently developing under the strong continuous pressure of local hazardous factors; 2) the stem cells damage in different tissues caused by acute intoxication; 3) the hormone-like activity of residual dioxin in different target cells; and 4) long-lasting conservation of the exposure-induced state of homeostasis in population with a homeostatic strategy of adaptation. We found that all health problems associated with herbicides sprayings should be taken into consideration in evaluating medical and social significance of the LTHC. Preliminary evaluations performed in terms of the "qualitative scale of well-being" show that even the current LTHC-related sub clinic conditions may determine the loss of 1-1.5 person-years of life in a state of well-being every 10 years in adult rural South Vietnamese. Investigations of the LTHC should involve sufficiently numerous contingents to account various health outcomes and intervening factors, which may be different in different localities, time periods, and individuals. That demands solution of methodologic problems pertaining to the identification of polymorphic health outcomes and exposed persons with the LTHC-related alterations in health status manifestating side by side with other concomittant medical problems. To solve these tasks we registered the standard sets of pathognomonic symptoms and signs indicative of more or less pronounced pathologic conditions for different systems of an organism and investigated the most essential typological features and the likely biomedical sense of their associations in sub groups with different exposure opportunities. By this approach we defined sub groups of exposed peasants with three relatively discrete syndromes of the LTHC. They indicated the likely and dominating occurence of some circulatory, gastroenteral, and one unclear systemic disorders or dysfunctions ("*pathologies* development risk groups"). Further application of Bayesian classification procedure

allowed us to select individuals with one of these particular syndromes for special medical examinations[8]. In fact, high prevalence of hidden disadaptive state of the cardio-vascular system in exposed persons was confirmed by clinical examination[7,11]. Such "phenomenologic approach" also proved to be useful for identification of specific systemic alterations in homeostasis. That may be particularly useful in studying a population with unknown local reference values, compensatory, and adaptive responses. For example, application of "Pattern Recognition Analysis" to the joint datasets of clinical immunological and biochemical investigations allowed us to reveal discriminating characteristics of the immune status and porphyrin metabolism in sub groups of apparantely healthy exposed peasants. Furthemore, such systemic investigations allow to hypothesize the mechanisms of effects formation and propose special remedial procedures[8,9].

Associations

The multifunctional Ah-receptor system mediates polymorphic responses to dioxins in close interactions with a large number of cell/tissue-specific regulatory systems, internal, and external factors. All these result in, sometimes, the critical dependence of effects formation upon peculiarities of exposure; essential biological features of an effect; relevant biomedical features of population and individuum; place-specific environmental factors, and observation period. Thus, at least the most significant effect-modifying factors should be revealed and taken into consideration in the identification of adverse effects and evaluation of the exposure-response-like relationships. For example, significant contribution of several biogenic and occupation factors and anamneses to increased risk of hepatocellular cancer and hidatidiform mole in sprayed areas is shown in French-Vietnamese studies[3]. We found different somatic responses to AO/DEF in exposed adult males and females[15]; significant specific influence of common unfavorable factors on health characteristics under the study; and sometimes the effect-modifying influence of exposure to DEF on health outcomes associated with these factors. Nevertheless, we show an applicability of epidemiologic criteria for causal inference for the LTHC after their modification according to the peculiarities of dioxin's toxicology. Hereby, we evaluated specificity and consistency of associations for polymorphic responses; estimated the exposure-response-like relationships, which seems to be appropriate only for a given exposure conditions, situation, contingent, and time point; and demonstrated a leading role of the criterion of biologic plausibility in the identification of dioxin-related health outcomes[9].

Conclusions

Evaluation of the LTHC of war herbicides in Vietnam should involve investigation of complex associations between the characteristics of potentially causal hazardous chemical, socioeconomic, and environmental factors originated from the "Operation Ranch Hand", various intervening factors influence, and diverse and sometimes hidden health outcomes. We have developed and tested some new biologically reasonable and feasible methodologic approaches to solution of this problem. They are based on historic exposure reconstruction and multidimensional statistical investigation of associations between informative number of logically, toxicologically or biologically interconnected direct and indirect characteristics of exposure, intervening factors, and health status. Such "phenomenologic modelling" of complex exposure, polymorphic health outcomes, and exposure-response-like relationships seems to be a practicable way to evaluation of the LTHC in epidemiologic studies at the population and individual levels.

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