
EPIDEMIOLOGICAL AND CLINICAL LABORATORY STUDIES ON HEALTH CONSEQUENCES OF AGENT ORANGE IN THE SOUTH VIETNAM

Roumak, V., Poznyakov, S., An, N., Kim Chi, H., Thu, T., Sofronov, G., Sokolov, V., Kountzevitch, A.
Soviet-Vietnam Tropical Center, Ho Chi Minh City, Vietnam
Tropical Department, Institute of Animal Evolutionary Morphology and Ecology, Russian Acad. Sci., Moscow, Russia

Large-scale realization of the US "Ranch Hand" project in S. Vietnam resulted in acute intoxication of the local inhabitants with dioxin-contaminated phytotoxicants due to the direct contacts, in wide pollution of the environment with TCDD (HxCDF), and in alterations in natural biocoenoses yielding ecotoxicologically specific regions still used for agricultural needs. There are many factors both complicating (medico-biological specificity, assesment of the remote direct exposure, complex ethiology and pathogenesis) and favoring (involvement of the sufficiently large, socio-demographically, nutritionally and toxicologically homogenous groups of rural South Vietnamese with their conservative lyfe style, no migrations, high degree of the direct exposure, durable chronic exposure from the environment, insignificant levels of dioxin-like compounds in the untreated environment, low use of drugs, pesticides and micronutrients, enough time for developing dioxin-related health outcomes) identification of health consequences of dioxin in this population.

Comparative cross-sectional epidemiological and clinical laboratory cohort designs were employed to study medico-biological posteffects of potential direct and chronic contacts with dioxin-containing phytotoxicants among villagers of the province Song Be on the background of socio-demographic, medico-biological, nutritional and toxicological features of this subpopulation /1/. The contingent under study was defined upon analysis of detailed cartographic (a computerized analog of the US "HERBS Tape", 1981), chemico-analytical (Schechter et al, 1986, 1989, 1990; Huteau et al, 1990; Klujev et al, 1991), medical (Vietnamese Committee 10/80, 1983), ecological /2/ and epidemiological /1,3/ information /1/. A basic questionnaire developed for the purposes of epidemiological study (247 items) elicited information on socio-demographic (N=5256, m/f, 21-60, 97.4-100% of the nationality "kinh", 84.1-92.4% are the peasants occupied in irrigated farming and Hevea cultivation; history of residence), medico-biological (self-reported

characteristics of morbidity and pathologic conditions for respiratory (8 questions), cardio-vascular (10), pancreatic (3), gastroenteral (12), osteoartricular (6) and urinary (4) systems, visual (7) and reproductive (6) functions; incidence of dermal (3), oncological (3), infectious and parasitic (5) diseases), and toxicological (AO: remote direct contacts - self-reported characteristics of early and subsequent (1-3 d and 3-6 m post-exposure) responses from the organs of contact and organism to inhaled (3,1), eye-irritating (3,2), skin-resorptive (3,4), and enteral (3,3) components, vegetative reactions (5,5); AO: chronic exposure - by time and history of residence on sprayed territory; frequency of contacts with certain pesticides; smoking; alcohol; drugs and micronutrients) status. The objectiveness of the recorded data was verified by personal requesting and general physical examinations, by randomly repeated inquiries, by the included contradictory items, by correlations with cartographic information, by sometimes occurred hallmarks of dioxin toxicity on skin and nails as well as by the results of subsequent clinical investigations.

Three groups of risk regarding potential contacts with AO were delineated on the basis of epidemiological study. The "control" group (I) consists of 3032 native dwellers of the village Chanh My (no contacts with phytotoxicants, no water or food exchanges with the polluted zone). The "exposed" groups included 2224 inhabitants of the village Binh My (50 km off from Chanh My) who have resided on the treated area from 5 to 25 years and had no (II) or have had the direct contacts (III) with AO. These groups were similarly supplied with macro- and microelements and were free from the impact of inorganic ecotoxicants: Cr, Ni, Be, Pb, Cd, As (hair, at. ads. spectr.)/1/.

A case-control study on reproductive pathology (N=400, f, was carried out using a specialized medico-genetic questionnaire, genealogic method and gynaecological examinations /4/.

To investigate subclinical indicators of contacts with AO, the comparative physiological, immunological, biochemical and ultrastructural studies were performed with apparently healthy, malaria and HBsAg free, socio-economically, nutritionally and toxicologically homogenous representatives of 3 risk groups (N=106-216, m, 31-50) selected from the entire subpopulation. Deeper medical and physiological examinations, clinical testing of blood and urine specimens, collection of a 24-h urine, blood and skin biopsy samples, implementation of immunological, cyt P-450-related, and cytogenetic tests with freshly isolated lymphocytes, and of loading (antipyrene, vit A) tests were carried out in the course of a 3-d hospitalization at the Central Hospital of the Province Song Be. Deeper biochemical and ultrastructural analytical studies were performed at 5 laboratories of different scientific research institutes of Russian Academy of Sciences with the preserved biomaterials.

All data obtained were supplied to the integrated data base ("R Base System Y") using a title of each patient as a

key column. The following tables were created: "Tab" (epidemiological data; integral indices of remote direct exposure to AO - "Medical Equivalents of Toxodose" based on symptomocomplexes of early "MET1" and subsequent "MET2" toxic responses; integral indices for health status - "Relative Frequency of Pathological Signs" /1,3/), "Reprod" (data on female reproductive pathology /4/), "Anthropom, Phys-CV, Psychomo" (anthropometric measurements; characteristics of physical development, of respiratory and cardiovascular functions, of physical and mental working capacities - spirometry, electro-, rheo-, and kinetocardiographic, stepergometric test PWC170, orthostatic probe, sensomotoric reactions, dark adaptation, etc. /5/), "Blood" (blood group, Hb, RBC, ESR1,2, leucocytes, lymphocytes, neutrophils, eosinophils, platelets; plasma protein, glucose, urea, creatinin, iron, bilirubin, lipids, triglycerides, cholesterol, phospholipids, b-lipoproteins and serum enzymes: AlcPhase, AST, ALT, gGT, GDH, LDH, gBDH - using "Centrifition" analytical system /1/), "Urine" (urinogramma), "Endocrin" (serum HBS Ag, insulin, thyroxin - by IEAssay), "Immunol" (B, T, Th, Ts lymphocytes, phagocytes; NBT-test, phagocytosis with DOW-latex; serum immune complexes, Igs A, M, G /6/), "P450" (basal and induced lymphocytic benz-a-pyrene hydroxylase; urinary excretion of 3-OH-Me-, 4-OH-, nor-antipyrene metabolites /7/), "Cytogen" (CA, SCE in lymphocytes /4/), "Vitam" (plasma a-tocopherol, b-carotene, carotinoids, retinol before and after administration of test and pharmacologic doses of vit A /8/), "Porphy" (urinary riboflavin, uro-, hepta-, hexa-, and pentacarboxylic-porphyrins, coproporphyrin I and III isomers, creatinine /9/; plasma porphyrins, zinc-protoporphyrin IX and protoporphyrin IX - by HPLC), "Skin" (ultrastructural characteristics of epidermis /10/. Integral indices were calculated by statistical summation. Statistical evaluations were done using a standard software package of the "Statgraphics v.3.0, the designed program for calculating Z-value based probability and a "system approach" to establish the "normal" local ranges for some biochemical parameters /1,3,8,9/.

As a whole, initial results of epidemiological studies demonstrated statistically significant increase in RFPS values for most health parameters studied including characteristics of female reproductive function (elevated number of abnormal pregnancies, still-born, and congenital malformations of non-genetic origin, delayed sexual maturation, higher incidence of gynaecological inflammatory diseases) in the III and to a lesser extent in the II risk groups as compared to the I group for all subgroups differentiated by age and sex, and by the impact of main confounding factors (nutrition, pesticides, smoking, alcohol, occupation) /1,3,4/. Statistically significant subclinical alterations in homeostasis including impaired adaptational capability of cardiovascular system, slow sensomotoric reactions, and dark adaptation /5,8/, some signs of the depressed immunity /6/, greater incidence of cyt P-450A1

activities /7/, development of anemias, hypoinsulinemia, hyposensitive hypovitaminosis A /1,8/, and of coproporphyrinuria /9/, the occurrence of ultrastructural changes in epidermis /10/ found in the clinical laboratory investigations among AO-exposed men (III > II > I) indicate that the specific effects of TCDD may be involved. These results demonstrated the efficacy of the employed approach /1,3,8/ and the occurrence of medicobiological consequences of AO (TCDD, HxCDF) both in the heavily exposed and new generations of rural South Vietnamese.

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