IS IT NECESSARY TO EXPECT NEW HEALTH EFFECTS OF LOW DOZES OF MERCURY?

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"**Toxicity of mercury** and **poisoning** — reality with which it is necessary to collide to each American. Both EPA and National Academy of sciences declare, that 8 - 10 % of American women have level of Hg, leading to occurrence of neurologic frustration for any child born by them. According to the Center to the control of diseases (CDC), each sixth child in the USA has infringements in development of neurologic character".
Boyd Haly, Kentucky University.

All people now are exhibited by mercury and its compounds as a result of natural and anthropogenous emissions. The natural level of influence of mercury is about 2000; it is probable, that all of alive organisms on the Earth are adapted for this influence - otherwise the life on our planet would stop. Almost double excess of this level is connected with anthropogenous activity - up to 3900 t/year (http://www.econ-hg.ru/doc-html/rtut.htm), that, basically, can reach borders of natural tolerance to mercury of different biological species.

Recent studies show that mercury exposure may occur in the environment, and increasingly in occupational and domestic settings. Several sources of toxic Hg exposure in human have been reported in biomedical literature: (1) methylmercury, the most widespread source of Hg exposure, is most commonly the result of consumption of contaminated foods, primarily fish; (2) ethylmercury, which has been the subject of recent scientific inquiry in relation to the controversial pediatric vaccine preservative thimerosal; (3) elemental Hg vapor exposure through accidents and occupational and ritualistic practices; (4) inorganic Hg through the use of topical Hg-based skin creams and in infant teething powders; (5) metallic Hg in dental amalgams, which release Hg vapors, and Hg2+ in tissues [1].

Regulatory Standards and Advisories for Hg^0 :

The occupational exposure limit set by the U.S. Occupational Safety Health Administration is 100 μg/m^3 as a time-weighted average (TWA) for 8 hr/day, 5 days/week (NIOSH 1997 [2]). The American Conference of Governmental and Industrial Hygienists (ACGIH) recommends a maximum Hg^0 concentration of 25 μg/m^3 as a TWA for the same exposure duration (ACGIH 1994 [3]). Because children are more sensitive than adults to mercury, occupational standards do not apply to them. For Hg^0, the recommended limit for continual habitation by children is 0.2 μg/m^3, according to the ASTDR (1999) [4]. However, this concentration is very hard to achieve after an Hg^0 cleanup. For the natural gas regulator spills, the ATSDR and U.S. EPA worked with IDPH to develop suggested action levels for mercury vapors, 1 μg/m^3 for clearance and a home evacuation level of 10 μg/m^3 in living areas (ASTDR 2002, 2004 [5,6]).

Maximal concentrations of Hg in air, detected in Central Europe, were: from 2.5 ng/м3 - open air; till 5 -15 ng/м3 – in industrial zones; for Northern-East Atlantic - 1.6 ng/м3 (www.helcom.ru/doc/vv6.pdf). Are they dangerous?

In accordance with FDA, WHO, ATSDR and EPA, the safety level of Hg's daily intake decreased during last 30 years more than in 1000 times (Fig.1). Scientists report that now level of Hg, associated with harmful effects, achieve the lowermost - EPA - regulatory standard

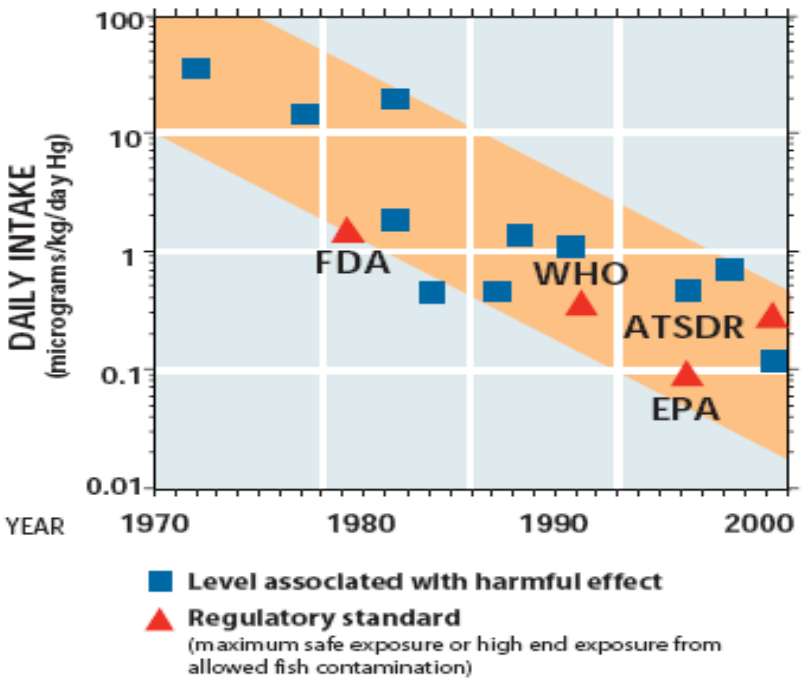

Fig.1 **"What mercury levels are safe for me?" – by the data of University of Minnesota** (http://www.noharm.org).

In an organism mercury is distributed, practically, in all tissues and subcellular structures, but most of all was find out in blood, liver, kidneys and brain. In cells non-random distribution of mercury is observed: 54 % collect in soluble fraction, 30 % - in nuclear, 11 % - in mitochondrial, 6 % - in microsomal [7].

These data allow suppose that Hg may induce mutations, influence to generation and distribution of power in cell and effects to systems of detoxification.

Blood mercury levels of <10 µg/dL and 300 µg/dL corresponded to mild effects and death, respectively [8]. Teratogenic effects due to organic or inorganic Hg do not well documented for humans or animals, although some evidence exists for mercury-induced menstrual cycle disturbances and spontaneous abortions, congenital abnormalities and reduced fertility is limited [7, 9, 10]. *Ionic Mercury* induces C-mitosis with inactivation of mitotic spindle resulting in aneuploidy and polyploidy, chromosomal aberrations and micronuclei in peripheral lymphocytes and increase frequency of sister chromatid exchanges. Effects of *Methylmercury* connect with abnormal mitosis, single-strand breaks in cellular deoxyribonucleic acid and spindle disturbances. For example, 0-25 x 10^{-6} M methyl-Hg and 0-434 x 10^{-6} M dimethyl-Hg induced dose-depending increase of frequency of chromosomal aberrations in culture of human blood lymphocytes as well as induction of C-mitosis with inactivation of mitotic spindle resulting in aneuploidy and polyploidy [11]. All of the effects, enumerated above, may be connected with development of tumor diseases and cancer, so they are first group of illnesses, new for mercury.

Next, mercury may influence to resistance of an organism to other exposures. So, [12] Brown Norway rats display a relative resistance to experimental Chlamydia-induced arthritis. Mercuric chloride modulated this innate resistance to arthritis: mercury-exposed rats had a marked exacerbation of the histopathological severity of the arthritis, and the infiltration was predominantly neutrophilic. Mercury exposure was also associated with marked enhancement in IgE levels and an alteration in IgG2a/IgG1 ratio, reflecting a Th2 shift. The local cytokine profile in the joint was markedly altered after mercury exposure, with a suppression of tumor necrosis factor-alpha and interferon-gamma but an enhancement of vascular endothelial growth factor. This was associated with decreased host clearance capacity reflected in enhanced bacterial load

in both the spleen and the joint and was accompanied by enhanced detection of microbial antigens in the synovial tissues by immunohistological staining. I.e, genetically defined cytokine production in the joint defines the severity of reactive arthritis by dictating the local clearance of the pathogen. This interplay can be altered dramatically by mercury exposure, which results in suppression of protective cytokines in the microenvironment of the joint and may cause the other type of Hg-dependent diseases - immunologic.

Experiments on rats (Tabl 1) demonstrated, that Hg0 vapor exposure increased the expression of genes encoding inflammatory responses, such as chemokines, tumor necrosis factor-alpha (TNFalpha), TNF-receptor-1, interleukin-2 (IL-2), IL-7, prostaglandin E2 receptor, and heat-shock proteins. As adaptive responses, glutathione S-transferases (GST-pi, mGST1), metallothionein, and thioredoxin peroxidase were all increased in response to Hg exposure. Some transporters, such as multidrug resistance-associated protein (MRP), P-glycoprotein, and zinc transporter ZnT1, were also increased in an attempt to reduce pulmonary Hg load. The expression of transcription factor c-jun/AP-1 and PI3-kinases was suppressed, while the expression of protein kinase-C was increased. Expression of epidermal fatty acid-binding protein was also enhanced. Real-time RT-PCR and Western blot analyses confirmed the microarray results. In summary, genomic analysis revealed an array of gene alterations in response to Hg0 vapor exposure, which could be important for the development of pulmonary adaptation to Hg during Hg0 vapor inhalation [13]

Effect of mercury vapor exposure on rat's **gene expression** (by **Jie Liu et al, 2003)**

Inflammation-related genes	***Effect (folds)***	***Transporter and related genes***	***Effect (folds)***
CXC chemokine LIX	14.47	Multidrug resistance protein (MRP2)	1,63
TNF- alpha	2.52	P-glycoprotein-1	2,95
TNF-R1	2,06	Zinc transporter ZnT-1	1,72
Macrophage inflammatory protein-1	2,88	Organic cation transporter OCT1	2,25
Interleukin-2	2,12	***Signal transduction-related genes***	
Interleukin-7	1,71	c-jun/AP-1	0,48
Prostaglandin E2 receptor	2,73	Phosphatidylinositol-3-kinase p85	0,53
Glutathione system and antioxidants		Nur77 early response protein	0,28
Glutathione S-transferase GST-pi	2,74	Protein kinase C alpha	2,71
Microsomal GST1	1,53	Protein kinase C gamma	2,08
Glutathione reductase	1,70	Other genes of interest	
Heat shock protein-60	1,50	Epidermal fatty acid-binding protein	2,34
Thioredoxin peroxidase	2,26		
Cu,Zn-superoxide dismutase	1,24		

So, next group of mercury induced diseases are pulmonary ones, and, probably, tumors of lung.

From the other hands, demonstrated data shown that mercury expresses groups of genes, responsible for both - common and special reactions.

As mercury is natural toxic factor, for preservation of life on the Earth evolution should arise the inherited mechanism for protection of alive organisms. For this reason protection should be determined genetically and to search for iti is necessary in the certain combination of polymorphic variants of the genes responsible for transformation of mercury and detoxification. Now it is known already more than 200 of " genes of an environment ". For many of them are

revealed genetic polymorphism, influencing on functional activity of alleles. It is essential, that in each group of the enzymes participating in detoxification, are found out mutant isoforms which function can be broken in comparison with normal alleles. And these functionally defective alleles meet among persons with various diseases much more often, in etiology which important role play adverse exogenous factors. The genes having such alleles, also it is possible to consider as "genes of predisposition" to those or other diseases.

Whether all people are equally sensitive to mercury and its compounds? Differently, whether it is possible to suppose, what unconditional observance of specifications will keep health to mankind?

Because detoxification of the most of dangerous organic compounds of Hg in human body requires reduced glutathione, all people with mutations in one of big glutathione S-transferases gene family (GSTs) are the most of sensitive to very low level of Hg and its compounds. By different data, frequency of mutations in GST genes varies from 35 to 50% among Euro-Asian human population - all of them are candidate in risk group. For example, relatively new disease, linking with Hg - autism - connects with GSTs polymorphism, too. Some light to the connection between GST polymorphism and metallothionein expression in context of body levels mercury throw study among students in Austria [14]. Authors has shown that hair mercury concentrations are significantly increased in persons with the double deleted genotype (GSTT1-/- and GSTM1-/-) as compared to persons with the intact genotype, and b) MT1X expression is higher in persons with the intact genotype (GSTT1+/+ and GSTM1+/+). They concluded that the epistatic effect of the GSTT1 and the GSTM1 deletion polymorphism is a risk factor for increased susceptibility to mercury exposure. The relationship between MT gene expression and GST gene polymorphisms needs further investigation. If MT expression depends on GST polymorphisms it would have important implications on the overall metal detoxification capability of the human organism.

Level of mercury in human biosubstrata, usually, is not high [15, 16]. However influence of these dozes on health very difficultly to determine because for more than 100 years of research of these compounds well studied are only effects of very high (toxic) dozes. Therefore the main task of modern researches is studying health effects of small dozes of mercury and itscompounds.

The special attention should be turned on that fact, that the structure of a complex of a protective combination of genes (a protective genotype) should include not only certain alleles of the genes connected with detoxification directly, but also the genes determining character of general reactions, for example, connected with development of stress - nonspecific response of all organism to any influence.

Thus, here the main is the question - which genotype is protective, and what combination of other alleles the same genes strengthens toxic effect of mercury and its compounds, or is connected with increase of individual sensitivity of an organism. Besides this it is represented rather important to estimate capacity (efficiency) of protective genotype, because the situation when the protective genotype is sufficient for long (during all life of an organism) oppositions of a natural exposition is rather probable, but it is ineffective at a greater level of influence.

The analysis of prevalence of the protective genotype in human populations also is one of priorities of the present stage of researches on a problem " Mercury and health of the person ", including as it is directly connected with features of influence of mercury and its compounds on health of autochthonous populations of Northern countries.

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