

## The Assessment of Halogenating Stress in Population by the Environmental and Health Monitoring

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### ABSTRACT

This study aimed to find out the dependence of myeloperoxidase content in patients living in the environmentally unfriendly region of Kazakhstan (Taraz), on the PCBs content in the air. During this study, 324 patients were examined to solve the clinical problem. The content of myeloperoxidase fluctuated significantly depending on the age of the experimental subjects. Statistically significant increase in the enzyme was observed in 23.0% of children aged 6-7 years, 33.4% of adolescents aged 14-17 years and 39.2% of adults aged 50-59 years. At the same time, significantly low content of myeloperoxidase was largely verified in children, adolescents, as well as in groups of the experimental subjects aged between 18-29 and 30-39 years. The largest number of people with low activity of myeloperoxidase was observed in groups aged between 40 and 49 years, which made 77.5% of the total. Research results showed significant inverse correlation between the low activity of myeloperoxidase and the PCBs concentration, which ranged from  $r = -0,55$  to  $r = -0,91$  ( $p < 0,05$ ). Therefore, the most significant correlation between the laboratory and hygienic indices was detected among subjects aged between 50-59 years ( $r = -0,9$ ).

### KEYWORDS

Ecological Parameter Monitoring, environmental monitoring, myeloperoxidase, polychlorinated biphenyls, Proteins, toxins

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### Introduction

Chemical pollution of the environment stands among the present global challenges (Revich, Sergeyev & Hauser, 2006). It is well known that long-term impact of the "low intensity" chemical factors lead to significant changes in health status, which is not always recognized by the official medicine. According to Nicholas E. Ashford and Claudia S. Miller et al. (Revich, Sergeyev & Hauser, 2006; Titov, 2007), "diseases of the 21<sup>st</sup> century associated with low-level exposure to chemicals include birth defects, various diseases of the immune system, attention deficit, hyperactivity disorders, depression and asthma, diseases of the cardio-vascular system, various hormonal disturbances, particularly related to the reproductive system, encephalopathy, certain forms of cancer and other diseases. Specific features of these diseases include their development primarily within body systems and fluids, rather than within

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specific afflicted organs. This refers primarily to the endocrine, immune and nervous systems. In addition, significantly smaller concentrations of chemical agents as compared with those that would normally cause classic toxic effects in specific organs, could lead to possible disorders in the key body systems (Rakhmanin, & Litvinov, 2004; Titov, 2007).

Currently, there is a huge number of new highly toxic substances circulating in the biosphere, which the human body did not come across in the course of evolution. Therefore, obviously, no human body has perfect mechanism of their neutralization, and maintenance of homeostasis. The most dangerous toxicants are the so-called persistent organic pollutants (POPs). According to the UN initiative, these toxicants are subject to destruction their production and use is prohibited (the Stockholm Convention on Persistent Organic Pollutants, 2001). POPs present a group of 12 highly toxic and highly stable compounds that are capable of cross-border long-range transfer and accumulation in various objects of the geosphere and in living organisms (Rakhmanin, & Litvinov, 2004). This group of toxicants includes polychlorinated biphenyls (PCBs) – a separate class of halogenated hydrocarbons. PCBs are characterized by a broad-spectrum biological impact; even taken in very small concentrations, these substances can lead to serious disorders of the nervous, immune and hormonal systems, causing carcinogenic and mutagenic effects.

Today, much attention is paid to the endogenous formation of reactive halogens (RH) or reactive halogen compounds (Hal). Primary RH products (HOCl and HOBr) are formed in the oxidation reaction, by Cl<sup>-</sup> and Br<sup>-</sup> hydrogen peroxides respectively, catalyzed by the myeloperoxidase enzyme (MP) P.G. Furtmüller, U. Burner and C. Obinger (1998). Myeloperoxidase is mainly found in the azurophilic granules of neutrophils and in the lysosomes of monocytes and then gradually disappears during their transformation into macrophages (Kettle, & Winterbourn, 1997) MP can catalyze the oxidation of halides (Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>) forming highly reactive hypohalites (OHaI<sup>-</sup>) (Ruf, & Carayon, 2006). The halogen atom is an oxidant in a hypohalite molecule, when it takes two electrons and turns into a halide.

Free radicals react with the fatty acids that form part of membrane lipids, initiating a chain reaction of peroxidation. Reactive oxygen species (ROS) cause formation of lipid peroxidation products. Leukocytes are one of the most powerful factors that cause ROS generation. During phagocytosis, bacterial digestion begins after absorption of phagocytes, accompanied by burst of cell metabolic activity, increased production of reactive oxygen species and other pro-oxidants. In the light of modern ideas, violation of properties of membrane lipid layer as a barrier and as an important cell structure not only accompanies

the course of many diseases, but also in many cases is the root cause of their development.

Hypohalites are not only strong two-electron oxidants; these compounds are also included in adjoining, substitution, halogenation and other processes by modifying functional groups of various vital molecules (Malle, Marsche & Arnhold, 2006; Pattison & Davies, 2006). It is believed that the RH can cause stress like the excessive production of reactive oxygen and nitrogen. Reaction of the human body to the RH impact is regarded as halogenating stress (Panassenko, et. al., 2005; Panassenko, Osipov & Schiller, 2002). It is known that MP activity is interrelated not only with the cellular response effectiveness but also with the damaging impact of HOCl, HOBr and other oxidants on the body's own cells, tissues and organs (Galijasevic, Abdulhamid & Abu-Soud, 2008).

The impact of aggressive external factors on the immune system is becoming extremely relevant today. At the same time, the available data related to the impact of PCBs on the human cellular immunity are contradictory and do not provide comprehensive insight into the molecular mechanisms of these immunotoxic compounds. Toxins cause cell damage and death through the lack of energy triggered by the increased energy consumption (functioning of detoxification systems, transfer ATPase activation aimed at compensating shunt flow of ions in the damaged areas of biomembranes), and inadequate synthesis of macroergic substances in the cell (affected mitochondrial membranes, biological oxidation enzymes, oxidative phosphorylation) (Klebanoff, 2005).

Prolonged impact of adverse environmental factors may lead to a critical RH level in the human body. Specific attention should be paid to health assessment as regards the population living in urban areas, due to the advanced industrial development along with air, water and soil pollution. Both domestic and foreign leading experts lay emphasis on rapid growth in the number of patients with chronic diseases (Klebanoff, 2005). Moreover, these processes have developed significantly among children and youth (Rakhmanin, & Litvinov, 2004). It was found that the decrease in the MP activity of neutrophils correlates with the rising frequency of infectious complications in patients with atherosclerosis (Klebanoff, 2005). The decreased peroxidase activity in mature granulocytes was observed in cases of infectious leukocytosis, Hodgkin's disease and certain metastatic tumors. Abnormality of enzyme activity was observed during long-term exposure to low doses of radiation; its absence was observed in acute myeloid leukemia (Konkabaeva, & Bazelyuk, 2002).

Myeloperoxidase activity in peripheral blood neutrophils can be regarded as one of the Hal-markers of the human body. As regards rapid diagnostic of adaptive capabilities of the human body, MP activity may be used in population analysis, mass screening studies in the context of ecological trouble. It was found that the decrease in adaptive capacity of the human body provided long-term impact of chemical factors having "low intensity" occurs in the setting of granulocytopenia, pronounced reduction of blood bactericidal properties, oppression of phagocytic mechanism of cell protection and the antibody synthesis reduction (Kutter et al., 2000; Rakhmanin, & Litvinov, 2004; Titov, 2007). In order to assess the reactions that occur at the cellular level, cytochemical method was applied to determine MP (Konkabaeva, & Bazelyuk,

2002). This method provided the possibility to quantify the MP activity in the blood cells and to determine the peroxidase activity.

Myeloperoxidase (donor:  $H_2O_2$  oxidoreductase; KF 1.11.1.7) is a hemoprotein enzyme, reducing hydrogen peroxide by means of electrons having different chemical nature. The application of cytochemical techniques and electron microscopy along with biochemical methods and labeled precursors found that MP was formed at early stages of neutrophil formation in the endoplasmic reticulum, and then enters the Golgi complex, from which bubbles accumulating MP are constricted. After confluence of these bubbles, azurophilic granules are formed at the promyelocytic stage. The process is marked by intensive production of porphyrin at the myeloblast stage. Termination of MP synthesis coincides with the termination of the azurophilic granules' formation and cell transition to the next stage (Nauseef, 2014; Shiohara, & Komiyama, 2000).

Biochemical methods using  $^3H$  leucine showed that only previously accumulated enzyme functioned in case of inflammation. Thus, the latest data suggest phasic MP synthesis. The presence of  $H_2O_2$  in the system at higher concentration than required for the catalytic cycle, the bulk of the enzyme turns into the relatively inactive form III of the compound, which dramatically slows down the speed of the overall process. The active enzyme center in the redox state of MP III has ferric structure (Fe II).

Some data suggest that the subunits of the MP molecule are different according to some criteria. First, prosthetic groups of each subunit are bound in varying degrees to apoenzyme; the heme related to one of the subunits is weakly bound to protein and can be separated from the protein part by ethyl acetate. Second, these non-equivalent components of the enzyme interact with the substrate at different speed in the formation of the oxidized MP II.

The peculiarity of the enzyme lies in the fact that when it interacts with  $H_2O_2$  in the equimolar ratio, the oxidized states MP I and MP II are formed only in one of the two active centers, the other center does not react with  $H_2O_2$ . The neutrophil MP is an integral part of a complex protection system of the human body. In the viable leukocytes, MP (due to its functional characteristics) is able to protect cells from the toxic effect of the intracellular hydrogen peroxide;

However, there are very few studies related to energy production processes in the testicle tissues during intoxication caused by polychlorinated biphenyls. This necessitates a detailed study of these processes to development the principles aiming at correction and prevention of pathological changes.

Prolonged exposure to organic pollutants, which include PCBs, can cause halogenating stress, which can be determined by the activity of myeloperoxidase in blood neutrophils.

The objective of this research was to determine the activity of myeloperoxidase in neutrophils of the peripheral blood in different urban groups as an indicator of halogenating stress.

#### Aim of the Study

The aim of the study was to find out the cause of specific diseases that arise in the results of chemical environmental pollution, the content of myeloperoxidase and their effect. The consequences of prolonged exposure to adverse environmental factors on the human body. Special attention to the health of the population living in develop cities.

#### Research questions

The main research question of the study was the following: What is the relationship between the level of myeloperoxidase in patients living in ecologically unfavorable regions?

#### Methods

The study was conducted among residents of the city of Taraz, located in the South Kazakhstan Region. Hygiene studies found excessive concentrations of polychlorinated biphenyls (PCBs) in the composition of suspended air particles (TSP) in all observation posts. TSP air monitoring results (PM<sub>10</sub> and PM<sub>2.5</sub>) showed that maximum permissible concentration of PCBs was exceeded by 2 -3 times. Other indicators related to gases (CO, SO<sub>2</sub>, NO) did not go beyond the acceptable level. PCBs refer to persistent organic pollutants, which pose a serious threat, since they can cause chronic intoxication, carcinogenic, immunosuppressive, allergenic effects along with their negative impact on the human reproductive function (Rakhmanin, & Litvinov, 2004; Titov, 2007). This circumstance determined mass screening of different population groups. The inclusion criteria for this study were the occupancy time (not less than 10 years) and the lack of adult contact with harmful production factors. Adult groups were formed with regard to stratification (by age) and a quota-related sampling in the following groups: children aged between 5 and 7 years (51 person); 14-16 years (66 persons); adults aged between 20-29 years (56 persons); 40-49 years (49 persons), 50-59 years (46 persons). In general, 324 people were examined. All persons included into these groups were subject to cytochemical study of peripheral blood neutrophils with a view to determine the myeloperoxidase activity by the Graham – Knoll method modified by Z. I. Namazbaeva and L. T. Bazelyuk (2014). The physiological limits of enzyme activity variation were practiced for 20 years, standardized in healthy persons living in ecologically safe regions of Kazakhstan. The analysis was carried out with regard to the mean value of enzyme activity, the parameters of cell distribution in the cell population: variation coefficient – cell heterogeneity degree by the enzyme activity, the asymmetry ratio – the balance of pools with high and low enzyme activity, the excess coefficient – cells with typical enzyme activity (Namazbaeva, & Bazelyuk, 2014). Shifts of cellular homeostasis in risk groups were considered with regard to quantitative and qualitative (frequency of occurrence in the population) characteristics of the enzyme activity. Quantitative analysis of MP activity was evaluated by its comparison with the physiological limits. Qualitative analysis was evaluated by the proportion or frequency of change occurrence (%) as regards the MP activity in different population groups.

Research protocol was approved at a joint administrative meeting held between the clinics of H. A. Yasavi International Kazakh-Turkish University. (South-Kazakhstan branch of the National Centre for Occupational Health and Occupational Diseases, Public Health Ministry of the Republic of Kazakhstan, Shymkent) and the Republican State Enterprise "National Centre for Occupational Health and Occupational Diseases" (Public Health Ministry of the Republic of Kazakhstan, Karaganda), pursuant to Protocol No. 13 dated April 21, 2010. The Protocol was made up pursuant to the basic principles of the Helsinki Declaration on Biomedical Research (1974), adapted at the 41<sup>st</sup> International Assembly in Hong Kong (September, 1989), which considers a person as a research object.

This document is based on a number of key principles, such as respect of the person's honor and dignity, awareness of the patient, harm and benefit risk assessment. Overall, this study reflects the ethical principles in relation to people who act as subjects of research, set out in the Belmont Report (The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research dated 18 April 1979) and the Russian Bioethics Committee at the Commission of the Russian Federation for UNESCO. In accordance with the protocol, informed consent was obtained in all subjects.

Statistical processing of quantitative variables with normal distribution was carried out by means of calculating arithmetic mean, error and the 95% confidence interval (CI). Differences between groups were detected by methods of parametric statistics. Linear dependencies were detected by using Pearson's pair correlation coefficient.

## Results

The distinctive feature of research results lies in a significant change in the activity of MP enzyme in all groups (Table 1). The analysis of MP activity in neutrophils of the peripheral blood showed that in children (aged 6-7 years) this activity increased from 23% up to  $2,48^{\pm 0,07}$  c.u., while the proportion of reduced activity (up to  $0,68^{\pm 0,07}$  c.u. made 46.2% among patients. In 42.4% of teenagers, low MP activity was found, its proportion amounted to  $1,39^{\pm 0,12}$  c.u.

**Table 1.** Myeloperoxidase activity in peripheral blood neutrophils in different population groups living in Taraz

<i>Subjects of research in Taraz (groups, quantity)</i>	Physiological limits		Excess activity		Decreased activity	
	M±m	95% CI	M±m	95% CI	M±m	95% CI
1.Children	1,53±0,02	1,47-1,59	2,48±0,07*	2,32-2,64	0,68±0,07*	0,52-0,82
2. Adolescents	2,17±0,35	2,08-2,25	2,39±0,49	2,25-4,54	1,39±0,12*	1,14-1,65
3.Adults (18-29 years)	2,17±0,35	2,08-2,25	2,90±0,03	2,51-3,28	1,31±0,15*	0,97-1,66



4. Adults (30-39 years)	2,17±0,35	2,08-2,25	2,85±0,51	0,00-8,52	0,97±0,10*	0,76-1,18
5. Adults (40-49 years)	2,17±0,35	2,08-2,25	-	-	0,57±0,10*	0,35-0,78
6. Adults (50-59 years)	1,53±0,02	1,47-1,59	2,48±0,07	2,32-2,64	0,68±0,07*	0,52-0,82

Note \* - reliable data as compared with physiological parameters, p<0,01

In 50% of the population aged between 18 and 29 and between 30 and 39, the study found low enzyme activity, which is 40% and 54% below the limits of physiological fluctuations, respectively (Table 2). The largest number of people with low MP activity was observed in subjects aged between 40 and 49 and made 77.5% of the total quantity. The enzyme activity in that group was reduced by 74% and amounted to  $0,57 \pm 0,10$  c.u. However, the group of subjects aged between 50 and 59 was characterized by the smallest number of individuals with low enzyme activity, which made 13.4%.

**Table 2.** The frequency of changes in myeloperoxidase activity in peripheral blood neutrophils in different population groups living in Taraz

Subjects of research	Standard		Number of subjects with excess concentration,		Number of subjects with decreased concentration	
	1,07-2,07 c.u. (6-7 years)	1,6-2,2 c.u. (14-16 years)	2,08-3,02 c.u. (6-7 years)	2,3 -3,02 c.u. (1-4 and 16 years); adults - 2,8-3,8 c.u.	0,6 7-1,06 c.u. (6-7 years)	0,65 -1,6 y.e. (1-4 and 16 years), adults - 1,99-0,2 c.u.
	Number of subjects	% related to the number of subjects	Number of subjects	% related to the number of subjects	Number of subjects	% related to the number of subjects
1. Children	12	30,8	12	23	22	46,2
2. Adolescents	16	24,2	22	33,4	28	42,4
3. Adults (18-29 years)	27	48,2	3	5,3	28	50
4. Adults (30-39 years)	24	42,8	4	7,2	28	50
5. Adults (40-49 years)	8	16,3	3	6,2	38,0	77,5
6. Adults (50-59 years)	22	47,83	18	39,2	6,0	13,04

The proportion of subjects living in Taraz, whose MP activity did not exceed physiological limits ranged from 16.3% to 48.2% depending on their age. The highest incidence of subjects with normal MP activity was found in persons aged between 18 and 29 years (48.2%), as well as in persons aged between 50 and 59 years (47.8%).

### Discussion and Conclusion

The authors carried out hygienic and clinical research, analyzed the dependence of MP content on the age of subjects living in the ecologically unfavorable regions of Kazakhstan (Taraz) through cytochemical study of peripheral blood neutrophils. Observation provided the following results:

1. Health studies in Taraz revealed an excess of PCBs in the suspended air particles at all observation posts ( $p < 0,05$ ).

2. The statistically significant increase in the MP content in 23.0% of children, 33.4% of adolescents aged 14 – 17, 39.2% of adults aged 50-59 years shows stress in their compensatory mechanisms.

3. The revealed statistically significant increase in the MP activity in most examined groups (46,2 % – children; 42,4 % – adolescents; 50% – adults aged 18-29 and 30-39; 77,5% – adults aged 40-49), indicates depletion of their compensatory mechanisms and activation of halogenating stress.

4. Halogenating stress in the population is observed provided long-term and chronic exposure to PCBs.

5. The level of MP activity may serve as an indicator that can be used to evaluate halogenating stress and indicates a change in the metabolic processes at the cellular level in the general adaptation reaction.

6. Correlation analysis showed that the accumulation of PCBs in the suspended air particles had a negative impact on myeloperoxidase activity in blood neutrophils.

The study revealed inverse significant correlation between low MP activity and the concentration of PCBs, which ranged from  $r = -0,55$  to  $r = -0,91$  ( $p < 0,05$ ). At the same time, the most significant correlation between the laboratory and hygienic indicators was detected in subjects aged between 50 and 59, ( $r = -0,9$ ).

Practical recommendations:

The level of myeloperoxidase indicates its sensitivity to xenobiotics, depending on the duration of exposure, which is a risk factor for the immune system disorders and demonstrates the pathogenetic mechanisms of human adaptation to chemical loads.

The enzyme activity may serve as a biological indicator at the intracellular and population cell levels, indicating oxidation, carbonyl and nitrating stress.

The study of the MP level in neutrophils may be used as a screening method and preclinical diagnosis of ecology-dependent disorders in the population.

### **Implications and Recommendations**

Correlation analysis showed that the accumulation of PCBs in suspended particles negatively affects the activity of myeloperoxidase in neutrophils of blood. The study found the reverse correlation between low MP activity and the concentration of PCBs in the air, which ranged from  $R = -0,55$  and  $R = -0,91$ ,  $p < 0.05$ . The degree of correlation depends on the age of the subjects. The most



significant relations between the studied parameters were found in individuals between the ages of 50 and 59 ( $R = -0,9$ ). Changes in MP activity is a risk factor associated with immune system disorders. High concentrations of MP-this is more physiological than the lower; this indicates the presence of compensatory processes in the target population. A decrease in the activity of the MP can indicate the presence of endotoxemia and contributes to the development of metabolic disorders. Deviations of the MP properties can lead to metabolic instability and pathological changes. The results indicate long-lasting toxic effects of environmental factors on the system, which provide stable functioning of neutrophils

### Disclosure statement

No potential conflict of interest was reported by the authors.

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