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MEDICINAL PRODUCTS AS A CAUSATIVE AGENT OF OCCUPATIONAL DISEASES IN PHARMACEUTICAL WORKERS (literature review)

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Abstract. Medicinal products as a causative agent of occupational diseases in pharmaceutical workers (literature review). Kuzminov B.P., Zazulyak T.S. *The issue of occupational diseases in chemical and pharmaceutical workers is urgent because it stems from the rapid pace of development, the functional features, and the high biological activity of raw materials used by that industry. The study is aimed at summarizing the information on preconditions and nature of occupational diseases among chemical and pharmaceutical workers based on the analysis of literature data. An important prerequisite for the emergence of occupational diseases is the shortcomings in the production process, leading to pollution of surfaces and workspace air with chemicals through the use of semi-automatic equipment in particular. The harmful substances then enter the bodies of workers through the respiratory system, which is the main and most harmful way. The most dangerous processes are the production and processing of substances with high pharmacological activity, and thus the active pharmaceutical ingredients maybe considered to be the leading causative agents of occupational diseases in the industrial production of medicinal products. The range of diseases diagnosed in pharmaceutical workers is diverse and includes acute intoxication, effects on internal organs, reproductive function, changes in hormonal status, and changes in the hemic system and nervous system. The most common are diseases of respiratory organs and diseases of allergic origin. As a result, influential international organizations and many authors emphasize the need to develop criteria and methods for assessing the harmful effects of medicinal products on the health of workers when authorizing their production.*

Реферат. Лікарські засоби як етіологічний чинник професійних захворювань робітників фармацевтичних підприємств (огляд літератури). Кузьмінов Б.П., Зазуляк Т.С. *Стрімкі темпи розвитку, особливості функціонування та висока біологічна активність сировинних матеріалів, що застосовуються, зумовлюють актуальність проблеми професійної захворюваності в працівників хіміко-фармацевтичного виробництва. Метою дослідження було узагальнення інформації про передумови та характер професійної захворюваності серед робітників хіміко-фармацевтичного виробництва, яке проводилось на основі аналізу літературних даних. Показано, що вагомою передумовою виникнення професійних захворювань є недосконаліть технологічного процесу виробництва, що призводить до забруднення поверхонь та повітря робочої зони хімічними речовинами за рахунок використання, зокрема, напівавтоматизованої праці. При цьому надходження шкідливих речовин в організм робітників через органи дихання є основним і найбільш небезпечним шляхом. Найбільша небезпека існує під час отримання та переробки субстанцій, що пояснюється високою фармакологічною активністю останніх, і тому саме активні фармацевтичні інгредієнти можна вважати провідним етіологічним чинником професійних захворювань при промисловому виробництві ліків. Спектр захворювань, які фіксувались у робітників фармацевтичних підприємств, є досить різноманітним і включає гострі отруєння, вплив на роботу внутрішніх органів, на репродуктивну функцію, зміни гормонального статусу, зміни в роботі системи крові та нервової системи. Проте найпоширенішими є патології органів дихання та захворювання алергічного генезу. З огляду на це впливовими міжнародними організаціями та багатьма авторами наголошується, що при авторизації лікарських препаратів мають бути одночасно розроблені критерії та методи оцінки їх шкідливого впливу на здоров'я робітників.*

Occupational diseases in Ukraine today are a complex of socioeconomic, medical and hygienic problems. Chemical and pharmaceutical production is among leading high-technology industries that make a significant economic impact and determine the security strategy of modern states [1, 21]. The

pharmaceutical industry of Ukraine, in particular, in recent years has shown a steady upward trend in production of medicinal products, producing as of early 2021 about 4200 names of medicinal products of almost all pharmacotherapeutic groups. Public employment in the production of medicinal products is 0.15% [4, 5]. By its nature, medicinal products are developed to interact with the human body's organs and affect their functioning. Substances used in finished pharmaceutical products and with a pharmacological or other direct effect on the human body are active pharmaceutical ingredients (substances) [13, 14, 36]. Although the above effects are generally desirable for patients, any changes in body functions under the influence of medicinal products, positive or negative, is an unacceptable effect for workers in the pharmaceutical industry and can be a causative factor of occupational diseases [15, 38]. Despite the fact that there is sufficient evidence for the epidemiological characteristics of occupational diseases of chemical etiology, both domestic and foreign authors have repeatedly noted that insufficient attention had been paid to chemical safety of pharmaceutical workers, and as a result this issue determined the objective of this paper [9, 35, 36].

The research objective is to summarize the information on preconditions and nature of occupational diseases among chemical and pharmaceutical workers.

Chemical and pharmaceutical production is one of the most material-intensive industries and is distinguished by a number of features. The small production scale of most medicinal products, high consumption of raw materials and supplies due to the multistage character and complexity of the substances' synthesis process, rapid updating of the range of medicinal products, the use of the same facilities to produce different medicinal products, and the fragmentary nature of the processes have led to the spread of combined technological production schemes that allow the release of 2-3 or more types of medicinal products per year [1, 35, 39].

The industrial production of medicinal products is based on extensive application of organic synthesis and processes of isolation and purification of compounds, where gaseous substances can be released from the reaction containers. Subsequent extraction, drying, grinding, granulation, packaging of substances often leads to contamination of air on the production floor and work surfaces with these substances [36, 39].

Evaluation of the levels of chemical pollution of work area air of pharmaceutical enterprises based on observation cards data showed that the content of substances in the work area air can exceed the hygienic standards by 1.4 to 5 times. Equipment operators are among those most affected by harmful influence of aerosolized chemical agents when dosing raw materials, combining the ingredients according to the specified ratios, and loading and unloading of products from manufacturing vessels [2, 11]. Some substances generate dust that contains up to 98% of particles less than 5 μm in size, thereby facilitating their penetration into the body via the respiratory tract. Additionally, many substances such as camphor, iodine, salicylic acid, as well as a number of cytostatic agents are capable of sublimating under normal conditions, drastically increasing the risk of chemical pollution of workspace air [29].

The high requirements for quality of reaction masses and raw materials require the use of sampling and purification of compounds operations during substance production. On average, sampling during production occupies 3-5% of working time, and the concentration of hazardous substances in works pace air may exceed the hygienic standards by 2 to 28 times. Filtration and washing of semi-finished products is carried out, typically with the help of solvents and is 12-15% of the working time of the operator [3, 19].

Legally defined, a medicinal product is "any substance or combination of substances (one or more active pharmaceutical ingredients and excipients) that has properties and is intended to treat or prevent diseases in humans,… restore, correct or alter physiological functions by performing a pharmacological, immunological or metabolic action" [12]. Due to the action of active ingredients, each therapeutic class of medicinal products has certain biochemical targets, and most medicinal products are likely to have several targets/receptors. Another important pharmacokinetic property of medicinal products is bioavailability. Current knowledge about the mechanisms of interaction of xenobiotics with the body holds that the toxic effect of the substance is largely determined by its concentration in the area of the biological target, which is strongly associated with its bioavailability. The bioavailability of a substance depends on many factors and, first of all, on the speed of penetration of the chemical agent into various tissues and cellular barriers, to reach the required concentration of the substance in the target organ, where the relevant toxic effect occurs. The speed at which the substance overcomes various barriers depends on the physicochemical properties of the chemical agent itself (ability to ionize, dissociate, dissolve in lipids, bind to blood plasma proteins, intercellular space proteins, intracellular proteins, etc.). Accordingly, medicinal products show their physiological effect at the subcellular, cellular and tissue levels. At the same time, new therapeutic agents

are being developed, taking into account new aspects of human cell functioning and the relationship between gene activity and the functions of the proteins they produce (genomics and proteomics). With these methods, it is possible to obtain compounds that can fundamentally change the function of cells as compared to traditional chemical therapeutic agent [27, 48].

The therapeutic action of pharmaceutical products, which is dominant, is called the main effect. From a therapeutic point of view, this is a very desirable action. Adverse effect is any undesirable effect caused by the pharmacological properties of the medicinal product presented only when a particular medicinal product is used at recommended dosage. Adverse reaction is undesirable for human health and dangerous whenever the causal relationship between this reaction and the use of medicinal product is absent [8, 40, 42]. Pharmacovigilance data on adverse effects of medicinal products are important for predicting the nature of their harmful effect on production and the development of preventive measures [8, 22, 35]. The toxicity class and appropriate preventive measures in production are determined in accordance with the nature of adverse effects and the values of toxicity parameters of substances [7, 36]. Thus, according to the classification proposed by The International Academy of Compounding Pharmacists (IACP), a substance is classified as hazardous if it:

- is pharmacologically active at a dose below 150 μg/kg of adult body weight;
- has an occupational exposure limit value of up to 10 μg/kg;
- has high selectivity to a certain receptor or is able to inhibit the work of enzymes;
- has a carcinogenic, mutagenic effect;
- is highly toxic at or below the therapeutic dose.

Moreover, according to the IACP, a new substance with unexplored pharmacological potential and toxicity is considered hazardous.

The major routes of entry of hazardous substances into the bodies of workers are the respiratory tract and the skin. The main and most dangerous route of entry of hazardous substances into the body is through the respiratory system (inhalation route). The surface of the pulmonary alveoli when stretched at an average (*i.e.* calm, even breathing) is 90-100 m^2, the thickness of the alveolar wall ranges from 0.001 to 0.004 mm, and this creates the most favorable conditions in the lungs for the penetration of gases, vapors, dust directly into the blood [17].

The most harmful consequences of exposure to medicinal products on the health of workers were manifested as a result of adverse effects. Examples are acute intoxication of the operator during production of glibenclamide, resulting in a hypoglycemic coma, as well as poisoning with barbiturates [16, 18].

The development of adverse pharmacological effects is not the only problem associated with exposure to pharmaceuticals. It has been observed that penicillin and cephalosporin-class antibiotics and enzymes have sensitizing effect when entering the body through inhalation. Other chemical therapeutic agents that cause such problems include cimetidine, lisinopril, α-methyldopa and salbutamol. However, it is not always clear in these cases whether the effect was sensitization or the consequences of a direct pharmacological effect caused by an action of compounds on the respiratory tract.

A particular problem is posed by the association of bronchoconstriction with the effect of opiates, which have a histamine releasing effect [27]. Occupational asthma can develop during the production of medicinal products or substances such as ranitidine, omeprazole, lisinopril, 5-chloro-1-methyl-4-nitroimidazole, 2-amino-thiophenol, a number of antibiotics, as well as under the influence of opioids – dihydroxycodeine, oxycodone, etc. [23]. Inhalation of peptidase and lysozyme, which are anti-inflammatory drugs, can cause IgE-mediated bronchoconstriction [33]. Pharmaceutical workers exposed to medicinal products, and especially to antibiotics had a significantly higher prevalence of chronic respiratory symptoms [49].

Allergic reactions in the form of contact dermatitis have been reported in workers exposed to proton pump inhibitors, as well as cytotoxic drugs, including mechlorethamine, mitomycin C, carmustine, and melphalan and chlorambucil. Acute erythema multiforme was caused by H2-receptor antagonists, ranitidine, as well as an by-product used in the production of cimetidine [24, 25, 45].

Allergic skin reactions, primarily contact dermatitis, have been reported in workers involved in the production of acid blockers [20, 32, 37] and azithromycin powder [31].

Data on other adverse health effects in pharmaceutical workers have been documented, including accelerated blood clotting; hypoglycemia due to exposure to antidiabetic medicines, diuretic and antihypertensive drugs; and effects associated with the production of antihypertensive medicines [20, 23, 43].

Occupational exposure to aromatic hydrocarbons and some medicines (sulfonamides, pyrazolone derivatives, other non-steroidal anti-inflammatory drugs, cytostatics) may affect the hemic system. It has been established that such substances as nicotinic acid, chloral hydrate and their combinations with other compounds (antibiotics, vitamins, pancreatine, lidocaine, salicylates, formaline, dibasol) have a marked irritant action [10].

Of particular concern are the effects of cytostatic drugs on pharmaceutical workers, which include acute symptoms such as nausea, vomiting, headaches and hair loss, reproductive health problems and the risk of cancer development, as well as kidney, central nervous system diseases, allergic reactions leading to asthma [17].

Pharmaceutical workers involved in the production of levomycetin and azathioprine showed a significant decrease in the average level of reticulocytes and neutrophils in the blood, which may indicate the myelotoxic potential of the compounds [28].

Reproductive organ dysfunction in pharmaceutical workers is associated with the presence of substances such as solvents and corticosteroids [26, 44]. When assessing the reproductive function of the wives of 300 pharmaceutical workers exposed to sulfonamides, a significant increase in the percentage of abortions and stillbirths was recorded as compared to the control group [34].

When comparing the mortality rate of 672 workers of British pharmaceutical companies working between 1973 and 1981 with two reference groups (the total population of England and a group of workers), a significantly higher mortality rate was found in the study group. Regarding cancer mortality, a significant difference was observed in mortality only among men and the largest number of pathologies was represented by pancreatic changes [30, 38].

The effect of occupational exposure to chemical agents of pharmaceutical production on liver function has been studied in a group of workers aged 21 to 56 years in the area of production of antihistamines, antibiotics, disinfectants, cortisone. At the same time, significant deviations from the standard biochemical parameters of liver function were found, which were similar in all workers of the study group [46].

Analysis of the results of a comprehensive medical examination conducted at OJSC “Organica” in 2009-2016 revealed very specific problems in chemical and pharmaceutical production: from 47% to 88.5% of workers suffer from ENT disorders (rhinitis, laryngitis, pharyngitis and their combined forms of vasomotor, allergic, subatrophic and atrophic nature) directly associated with the action of production and, above all, chemical factors. Liver and biliary tract diseases are almost 3 times as common in workers constantly exposed to chemical production factors. Respiratory diseases were registered in 5.7% to 13% of workers. 12% of workers were affected with dermatitis confirmed by skin tests with solutions of substances used in production, accelerated destruction of erythrocytes and hemoglobin, reduced cellular immune function, which indicates a certain tension of adaptation processes in the body. Moreover, workers have the altered vitamin balance and hormonal state [3, 47].

The indicators of morbidity with temporary disability at CJSC “Darnitsa Pharmaceutical Company” are the following: 13.9-7.9 cases per 100 workers were registered in the sixth nosological group (nervous system disorders) in 1996-2000, and 5.5-3.6 cases in 2006-2010. There were 11.5-3.7 and 4.0-2.3 cases registered in the ninth nosological group (circulatory diseases). The tenth nosological group (respiratory diseases) included 53.3-31.7 and 37.0-29.7 cases, which is the highest rate [6].

According to studies carried out by such influential international organizations as the US Food and Drug Administration, the European Medicines Agency, and the Japanese Ministry of Health, Labor and Welfare, which are responsible for scientific evaluation, supervision and monitoring of medicines, the impact of substances on the health of pharmaceutical workers is studied and covered in scientific reports insufficiently, even though there is evidence of increased morbidity and mortality in this population stratum [23]. It is emphasized that introduction of the requirements of Good Manufacturing Practices, Good Laboratory Practice and Good Clinical Practice should only be a part of the pharmaceuticals authorization process. When authorizing pharmaceuticals, developing criteria and methods for assessing the harmful effects of medicines on the health of workers, although mandatory, is not typically done in practice [22, 23, 41]. It is noted that along with the intensive development of the pharmaceutical industry in European countries, there is a lack of detailed information confirming the relationship between the levels of pollution of working zone air and the morbidity rate among pharmaceutical workers. This emphasizes the importance of large-scale epidemiological studies that could characterize the changes and, in particular, the long-term effects of medicines on workers' health. Therefore, currently there is an issue of determining ways to assess occupational risks in pharmaceutical companies, as well as the implementation of appropriate preventive measures and production control [6, 35, 36].

CONCLUSIONS

The performance features of chemical and pharmaceutical enterprises create the preconditions for the release of chemical compounds into workspace air and its impact on the workers’ health. These chemical compounds include both raw materials used to synthesize and purify substances as well as active pharmaceutical ingredients of finished pharmaceutical products. The latter, due to their intended purpose, have high biological potency reflected primarily through affinity to certain receptors in the human body, and bioavailability, and therefore it is the active pharmaceutical ingredients that can be considered the leading causative agent of occupational

diseases in the industrial production of medicines. As for the nature of pathologies, a fairly wide range of diseases can be observed, but the most common are respiratory disorders and allergic diseases. Despite this, as has been noted by many authors, the issue of occupational morbidity of chemical and pharmaceutical workers received insufficient attention, and this brings the issue of occupational risk assessment at pharmaceutical enterprises, as well as the implementation of appropriate preventive measures both in the world and in Ukraine up to date.

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Kuzminov B.P. – conceptualization, methodology, writing – review & editing;

Zazulyak T.S. – data curation, writing – original draft.

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