

Unlocking the impact of chemicals on the health and safety of pharmaceutical workers: A concise review

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ABSTRACT

The global pharmaceutical industry has greatly improved healthcare worldwide. Still, it is one of the riskiest due to problems like direct or indirect exposure to dangerous chemicals and active pharmaceutical agents. Therefore, this paper seeks to present an overview of the various developments and issues in the pharmaceutical industry. This text provides a historical perspective on chemical exposure in pharmaceuticals and discusses health risk studies, industry classes, industrial mishaps, legal consequences, future outlook, and recommendations. The paper notes that the health risks of pharmaceutical/chemical exposure are significant and suggests a multifaceted approach, including a comprehensive examination, stricter laws, employee education, and implementation of safety standards such as the threshold limit values (TLVs), biological exposure indices (BEIs), and Hazard Communication Standard (HCS) to mitigate potential hazards. Green chemistry and sustainable methods will curb or reduce the use of hazardous chemicals and waste generation. Moreover, there is a need to promote sustainable and safe work cultures through safer behaviours, increased public awareness, and community interaction. Pharmaceutical companies must commit to continuous enhancement of their operations, decrease the risks associated with chemical exposure, and put worker and environmental health first. This strategy contributes to a safer and more sustainable pharmaceutical future by being in line with the industry's commitment to innovation and safety.

Keywords: Chemicals, Occupational Health, Pharmaceuticals, Sustainability, Workers Safety

Introduction

The use of plant-based herbs to treat diseases and promote good health and wellness in humans dates back many centuries. This practice has given rise to pharmacognosy, which examines the prevention and treatment of human diseases using medicinal plants.¹ Recently, biochemical or radiological-based medicines, microbial, toxins, and plasma-related treatments have replaced herbal remedies for treating human health problems.² Consequently, pharmaceutical manufacturing has become an enormous industry valued at US\$1.27 trillion in the year 2020.³ The global pharmaceutical industry has significantly

improved human health, well-being, and living standards by providing medicines, supplements, and vaccines. Pharmaceutical Industries manufacture synthesized substances used for humans or animals to treat, prevent, or lessen disease symptoms.⁴ Globally, this sector has seen emerging growth in recent times.⁵ However, this growth has brought about enormous challenges, such as ensuring its products and workers' health and safety.⁶

Despite its global importance, the industrial-scale production of pharmaceuticals exposes workers and the general public to hazardous and toxic

chemicals, intermediates, and by-products, which could severely impact human health, safety, and the environment.⁷ The industry is considered one of the most hazardous worldwide due to the various processes, chemicals, intermediates, and toxic waste pollutants.¹ The exposure of pharmaceutical workers to chemical processes/products has the potential to cause severe problems in human health, occupational safety, and environmental balance.⁷ Moreover, with the increasing prevalence of chronic diseases, the growth of this sector is expected to increase significantly. Given that employees are essential to the long-term success of any firm, this growth is predicted to strain pharmaceutical operations and expose workers to a wide range of health risks. Therefore, it becomes vital to take all steps to identify and address problems that could endanger their health and safety.

Over the years, numerous studies have examined the short- and long-term impacts of pharmaceuticals, their intermediates, and waste streams. Gizaw and Yifred⁸ reported that these chemicals could also exert severe and long-lasting effects, such as acute and chronic cardiovascular, respiratory, or obstructive pulmonary illnesses in humans.⁸ The study by Binks corroborated this viewpoint by stating that research, development, and production workers in the pharmaceutical industry are particularly prone to the harmful effects of related chemicals.⁹ It has been widely reported that pharmaceuticals and their intermediates can negatively impact human health due to their non-degradable nature and widespread use.^{10,11} In addition, they can act as physiological modulators, exert potential sudden or long-term toxicity, and negatively impact the environment.¹² Given those above, the health, safety, and environmental risks associated with exposure to pharmaceutical chemicals, processes, and waste streams to industry workers, as well as public health, need to be critically reviewed. Therefore, the primary objective of this paper is to identify, examine, and highlight the potential health effects and safety risks associated with the worker's exposure to pharmaceuticals.

Historical Perspective of Chemical Exposure in Pharmaceuticals

Despite the substantial contributions of the pharmaceutical industry to humanity,¹³ there have been obstacles to scientific advancement and medical advancement. This viewpoint is particularly evident when it comes to the historical view of chemical exposure in pharmaceutical settings. The use of chemicals in pharmaceuticals extends back centuries, with ancient civilizations like the Egyptians and Greeks using various natural substances for therapeutic purposes.¹⁴ The extraction of active ingredients from plants and minerals was a common procedure in early pharmacological practices and thus exposed practitioners to many chemicals, some of which were hazardous. On the other hand, the beginning of the Industrial Revolution and the subsequent Chemical Innovation, which occurred between the 18th and 19th centuries, represented a crucial turning point in the history of pharmaceuticals.^{15,16} The development of chemical synthesis during this time made it possible to produce medications in large quantities. Pharmaceutical personnel were now exposed to a wider variety of synthetic substances, but this also brought many chemical dangers. The risks were heightened by the absence of safety laws and standards in these early pharmaceutical facilities.

As a result, regulations and occupational safety awareness measures were introduced in the pharmaceutical industry.¹⁷ Typically, when incidents of illnesses among workers caused by chemicals began to surface, it became clear that the pharmaceutical sector needed to be regulated. To guarantee the efficacy and safety of pharmaceutical products, regulatory organisations like the United States Food and Drug Administration (FDA) were first established. Hence, many regulatory groups started to establish standards for pharmaceutical production and safety procedures, creating safer working conditions. With the furtherance of these measures, the pharmaceutical sector began to acknowledge the significance of worker safety throughout the 20th century.¹⁸ Through the use of

personal protective equipment (PPE),¹⁹ improvements were made to ventilation systems,²⁰ and safety awareness training measures were put in place to reduce chemical exposure. Additionally, pharmaceutical companies started investing in research to identify the health risks associated with specific chemicals used in drug manufacturing. Despite the progress, problems still exist. For instance, workers in the industry were still at risk from the high toxicity levels of several pharmaceutical compounds, such as solvents and reagents.^{20,21} Many tragic events like chemical explosions and worker fatalities have starkly underscored the significance of chemical safety within the industry.¹⁹ The pharmaceutical industry and regulatory organisations stepped up their efforts in response to these difficulties. The development of safer chemical substitutes and more productive manufacturing techniques have gained wide traction. Worker education regarding the hazards of substances they encounter has become a routine procedure because of hazard communication techniques like Material Safety Data Sheets (MSDS).

This era also marked the introduction of modern pharmaceutical practices. Apropos, the pharmaceutical industry's attitude to worker safety and chemical exposure has drastically changed in the modern era. The risks connected with handling chemicals have decreased thanks to cutting-edge technology, automation, and strict safety procedures. Pharmaceutical businesses make significant investments in employee education and training to make sure that staff members are knowledgeable of potential risks and prepared to protect themselves. The historical viewpoint of chemical exposure in pharmaceuticals shows a path that was both characterised by advancement and difficulty. From the early use of natural chemicals to the industrialisation of medicine production, the pharmaceutical industry has come a long way in addressing the health and safety of its workers.

Because of stricter regulations, higher safety requirements, and a commitment to research, the risks associated with chemical exposure have greatly decreased. Notwithstanding persistent challenges, the pharmaceutical industry's pledge to safeguard employees demonstrates its commitment to safety and innovation in the pursuit of globally enhanced health.

Prior Studies on Health Risk in the Pharmaceutical Industry

The health effects and safety risks posed by workers' exposure to pharmaceutical chemicals is a critical area of research that has gained scientific interest over the years. As reported by Binks the lack of proper control or safety measures in the manufacturing process can exacerbate the occupational or permissible exposure levels of chemicals.⁹ Ultimately, this situation could result in undesirable pharmacological effects on the health and safety of workers. Similarly, the study by Heron and Pickering reported that the absence of suitable preventive measures exposes pharmaceutical industry workers to various chemicals such as organic solvents, particulate dust, or aerosols of manufacturing chemicals.²² Other materials such as steroids, cyclic anti-cancer, and antibiotics compounds also pose dangers to humans on exposure.²³ The difficulty of dealing with these substances lies in their inherent properties, such as the absence of smell and colour, which prevent detection by the human senses if or when present in the atmosphere.²³ Over time, these substances penetrate the worker's bodies through inhalation, ingestion, or penetration through the skin, which ultimately damages cells, tissues, and organs in the human body.²⁴ Other notable effects of pharmaceutical chemical exposure include physical and hormonal disorders in humans.²⁵ Figure 1 shows the major pathways, namely inhalation, skin absorption, ingestion, and injection, through which toxic pharmaceutical chemicals can enter the human body.

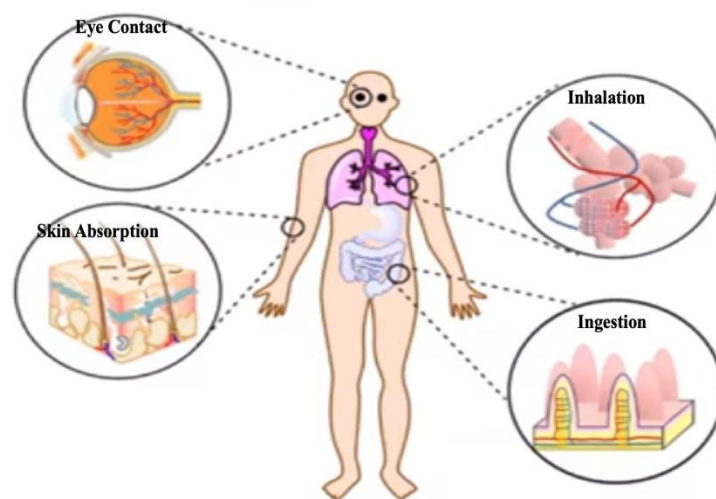


Figure 1: Major pathways for pharmaceutical chemicals entry into human bodies.²⁵

Typically, some symptoms appear immediately after exposure, whereas others appear gradually over time, leaving severe damage that could morph into chronic diseases.²⁶ According to Bhusnure and Dongare,²⁴ the acute health effects of exposure to pharmaceutical chemicals typically include nausea, headaches, vomiting, and skin corrosion. On the other hand, the chronic health effects include asthma, nerve damage, dermatitis, or cancer. Chemicals can also destroy living tissue, scorch skin, and tracheal irritation. Some studies have reported the extent of the health symptoms and harmful effects of pharmaceutical chemicals exposure based on gender.²⁷ The study reported that the common symptoms and severity of exposure observed among employees of a large pharmaceutical company are gender specific. For example, the rates of colon cancers, central nervous system, and kidneys were observably higher in male respondents compared to females.^{28,29} However, the cases of breast cancer are more prevalent in female employees. Taskinen and Lindbohm³⁰ reported that continuous miscarriages and spontaneous abortions are commonplace among women employed in the pharmaceutical industry. The study by Sharma and Kamboj showed that many physiological effects appear in males working in the industry.³¹ Such metabolic effects are long-term, sperm formation failure, and testicular cancer. Teichman and Fallon reported that constant exposure to carcinogens (such as methylene chloride and

benzene) was responsible for the health effects observed in respondents.³²

In recent times, there have also been reports of chronic respiratory diseases arising from exposure to pharmaceutical chemicals. For example, chronic versions of phlegm, cough, shortness of breath and wheezing have been reported among pharmaceutical workers.⁸ The most prevalent diseases among workers in the pharmaceutical industry are respiratory-based illnesses.^{33,34} The list includes chronic obstructive pulmonary illness (covering bronchitis and emphysema), asthma, pneumoconiosis, and chronic rhino sinusitis. Oddone and Negri demonstrated that the exposure of pharmaceutical workers to active pharmaceutical ingredients (APIs) is a significant causative risk factor for health and safety problems.³⁵ The APIs are designed and developed to interact or modify functions within the host organism. However, some carcinogenic compounds, sensitising intermediates or endocrine disruptors could also endanger the host organism.

Nassiri Koopaei and Abdollahi reported that pharmaceuticals and their chemical derivatives detected in water and wastewater streams could cause toxic, teratogenic, and carcinogenic effects on humans and animals in the environment.³⁶ Therefore, the authors called for strict profile analysis, monitoring, and control strategies, as well as framework policies to safeguard public

health and occupational safety. Similarly, the growing menace of pharmaceuticals polluting water bodies and sources such as rivers has been reported worldwide.³⁷ Zhan and Ma examined the profiles and emissions of by-products from the pharmaceutical industry.³⁸ The study showed that pharmaceutical processes could unintentionally generate and emit toxic/carcinogenic compounds and intermediates into the atmosphere. The polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs) were unintentionally formed and released in flue gases from regenerative thermal oxidisers (RTOs) in pharmaceutical companies. Similarly, Vishwakarma reported that the exposure of pharmaceutical workers to the disposal of products such as active pharmaceutical intermediates (API) can gravely affect their health and safety in the workplace.³⁹ In addition, the physical nanosized state of drug formulations, active ingredients, and products has a direct link to the air quality and, by extension, the health and safety of workers. The next Section presents a selection of various classes of pharmaceuticals produced in the industry across the globe.

Classes of Pharmaceuticals in the Industry

There are numerous classes of pharmaceuticals produced annually by the industry across the globe. According to global pharmaceuticals data, the top 10 most common pharmaceuticals produced annually worldwide are Antibiotics, Antidepressants, Anti-hypertensives, Analgesics, Antidiabetic Agents, Anticoagulants, Antivirals, Immunosuppressants, Bronchodilators, and Cholesterol-Lowering Agents.⁴⁰ An overview of a selection of these is highlighted, along with related activities.

Antibiotics: This is a class of pharmaceuticals used to treat bacterial infections. These pharmaceuticals function by preventing the growth and reproduction of bacteria using various modes or mechanisms of action. Examples include amoxicillin, penicillin, and ciprofloxacin.

Antidepressants: This class of medications works by altering brain neurotransmitters to treat mood disorders such as anxiety, depression, and among

other illnesses. The notable examples include Prozac (fluoxetine), Zoloft (sertraline), and Lexapro (escitalopram).

Anti-hypertensives: The class of medicines aim to lower fluid volume or relax blood vessels in order to lower high blood pressure or hypertension. The most common examples of anti-hypertensives include metoprolol, amlodipine, and lisinopril.

Analgesics: This family of drugs, sometimes referred to as “pain relievers”, are designed to reduce discomfort and agony. They fall into two general categories: non-opioid (like acetaminophen) and opioid-based (like oxycodone).

Antidiabetic Agents: This class of medications is intended to manage or stabilise blood sugar levels in individuals with diabetes. This includes insulin for those with type 1 diabetes and oral drugs like metformin for people with type 2 diabetes.

Anticoagulants: Blood thinners, or anticoagulants, are a class of medications that aid in preventing blood clots from forming. Warfarin, Heparin, and Rivaroxaban are among the most widely used across the globe.

Antivirals: The goal of antivirals is to treat infections caused by viruses. Notable examples include medications such as Sofosbuvir (for hepatitis), Oseltamivir (for influenza), and Tenofovir (Human Immunodeficiency Virus, HIV).

Immunosuppressants: These medications are used to suppress the immune system, particularly after an organ transplantation procedure has been administered to a patient. Medicines that are commonly used as examples include Tacrolimus, Cyclosporine, and Mycophenolate mofetil.

Bronchodilators: These medications are frequently used to open up airways in patients with chronic obstructive pulmonary disease (COPD) and asthma. Salmeterol and albuterol are two of the most prevalent examples.

Cholesterol-Lowering Agents: This class of drugs, sometimes known as statins, is intended to lower cholesterol and eventually prevent cardiovascular illnesses. Examples that are frequently prescribed

throughout the world are rosuvastatin, simvastatin, and atorvastatin.

Classic examples of mishaps in the global pharmaceuticals industry and consequences

The rising utilisation of pharmaceuticals has been matched by equally growing rates of production across the globe.⁴¹ These developments have not been without mishaps, ranging from chemical exposure, leaks, and toxic emissions, among others, which have occurred despite the industry's widely reported high safety standards. Table 1 presents ten examples of the most notable industrial mishaps recorded by the global

pharmaceutical industry over the years. As observed, various pharmaceutical companies have been embroiled in multiple legal issues emanating from various mishaps, including exposing individuals to the chemicals and or active agents of pharmaceuticals. Such actions have resulted in dire consequences ranging from heart attacks, strokes, HIV/AIDs and deaths. To stem this tide, judicial authorities across the globe have brought charges upon and fined big pharmaceutical companies various sums ranging from a few to hundreds of millions of dollars over the years.

Table 1: Most notable industrial/chemical mishaps recorded by the global pharmaceuticals industry

Incident/ Mishap	Date(s)	Pharma/ Company	Location	Details of Occurrence	Impacts/ Legal issues	Reference
Tryptophan Contamination	1989	Showa Denko	United States	During production, a batch of the dietary supplement L-tryptophan became tainted.	This accident sparked an eosinophilia-myalgia syndrome (EMS) outbreak that killed many people and sickened countless more.	Simat et al. ⁴²
Vioxx Recall	2004	Merck	Global	Merck voluntarily removed the opioid Vioxx from distribution.	This accident was caused by worries about the higher risk of heart attacks and strokes linked to long-term use, which prompted a regulatory investigation and court settlements.	Gust et al. ⁴³
Heparin Contamination	2007-2008	Scientific Protein Laboratories/ Changzhou SPL Company	China	Batches of the tainted blood thinner heparin were imported.	The contamination caused people to experience severe allergic reactions and pass away, which prompted extensive recalls and inquiries into pharmaceutical supply networks.	Greene meier. ⁴⁴
Trovan (trovafloxacin) Trial	1996	Pfizer	Nigeria	Unethical clinical drug trials.	It was reported that Pfizer did not get participants' informed consent, which sparked legal disputes and debate about what constitutes	Ahmad. ⁴⁵

					appropriate consent in clinical research.	
Contaminated Factor VIII	1980	Bayer	Global	This is due to blood clotting factor VIII, which was contaminated and manufactured by Bayer and others.	The incident caused the infection of hepatitis C and HIV in hundreds of haemophiliacs. Numerous lawsuits and requests for better blood safety procedures followed this.	McHenry and Khoshnood. ⁴⁶
Avandia Controversy	2007	GlaxoSmith Kline	United Kingdom	This case was due to issues with the medication Avandia, commonly used for diabetes.	Due to elevated cardiovascular risks, the occurrence resulted in litigation, regulatory warnings, and a major drop in the drug's use.	Lofstedt. ⁴⁷
Tylenol Recall	1982	Johnson & Johnson	United States	After ingesting tampered-with, cyanide-laced Tylenol capsules, seven persons in the Chicago area perished.	The event resulted in the introduction of tamper-resistant packaging and extensive product recalls. It costs the firm over US\$100 million.	Benson ⁴⁸
Neurontin Off-label Marketing	2004	Pfizer	Global	Neurontin, an epileptic medication, was marketed and pushed for off-label uses that the FDA had not approved.	Legal action against Pfizer led to a sizable payment and heightened scrutiny of the company's pharmaceutical marketing strategies.	Vedula et al. ⁴⁹
Plavix (Clopidogrel) Off-label Marketing	2012	Bristol-Myers Squibb	United States	The company was accused of inflating the effectiveness of its blood thinner Plavix and pushed it for off-label usage.	Due to the occurrence, there was a large cash fine and compliance oversight. The lawsuit resulted in fines of over US\$ 800 million.	Feeley. ⁵⁰
Paroxetine Study Controversy	2004	GlaxoSmith Kline	Global	GSK faced criticism for allegedly suppressing data suggesting that its antidepressant Paxil (paroxetine) was ineffective	The controversy led to harmful effects on adolescents, so regulatory investigations and lawsuits were brought against the company.	Doshi. ⁵¹

Future outlook and recommendations

The overwhelming evidence shows that the release of or contact between humans and drug formulations, active ingredients, reactive intermediates, runaway emissions, and waste by-products from pharmaceutical companies pose grave risks to human health, occupational safety, and environmental sustainability. However, despite the awareness of the issue and publications on the topic, detailed studies on the relationship between chemical exposure and its effects on pharmaceutical workers worldwide remain limited. Given the urgent worries about how the pharmaceutical industry affects both human health and the environment, it is critical to think ahead and explore suggestions and viable solutions to deal with these issues.

Chemical exposure dangers associated with the pharmaceutical sector are a serious threat to worker safety, public health, and the sustainability of the environment.⁵² Comprehensive research on the connection between chemical exposure and its effects on pharmaceutical workers is still scarce, even though the evidence already in place highlights how serious this issue is. It takes a multifaceted strategy to solve these urgent issues. First and foremost, comprehensive study and data gathering are required to comprehend the entire scope of chemical exposure and its long-term health effects. It is essential to implement regulatory changes to enforce more stringent safety and environmental regulations. Pharmaceutical businesses also need to spend more money on employee education and training to raise knowledge of potential hazards and safety precautions.

Green chemistry ideas and sustainable practices can be included in drug manufacturing innovations to lessen the need for dangerous chemicals and the production of trash.⁵³ To gain the trust of stakeholders, the use of chemicals and their related waste emitted streams must be reported openly and transparently. According to the American Conference of Governmental Industrial Hygienists (ACGIH), companies, such

as pharmaceutical firms that utilise chemicals, must adhere to the set threshold limit values (TLVs) and biological exposure indices (BEIs).⁵⁴ The guidelines stipulate that companies must pre-determine safe levels of exposure to chemical substances and physical agents to ensure a safe working environment. Similarly, the Occupational Safety and Health Administration (OSHA) of the United States Department of Labour (US-DoL) established the Hazard Communication Standard (HCS) (Standard Number: 1910.1200) to safeguard workers against chemical exposure. As mandated by OSHA, the HCS guides the development and dissemination of chemical safety information, such as labels, safety data sheets, and training in an understandable form for workers to prevent exposure to hazardous chemicals in the workplace.

To exchange best practices and knowledge, cooperation is required between academic institutions, government agencies, pharmaceutical businesses, and environmental organisations. A culture of sustainability and safety can be developed by interacting with local communities, raising public awareness, and pushing for safer behaviours.⁵⁵ Global standards and international cooperation are necessary to guarantee the industry's sustainability and safety on a worldwide basis. The pharmaceutical sector may work toward a future where chemical exposure hazards are avoided, protecting human health and the environment by consistently improving operations and committing to lowering their environmental impact.

Conclusions

In this paper, a concise review of the impacts of pharmaceutical chemicals on the health and safety of workers in the industry was examined. This review paper focused on the health and safety risks that employees confront while presenting the historical background and contemporary issues of chemical exposure in the pharmaceutical sector. Over the years, the use of natural remedies has given way to large-scale manufacturing in the pharmaceutical industry, which has significantly improved healthcare but also raised concerns

about chemical exposure, particularly in the past when safety laws were weak. The use of improved ventilation systems, new regulations, and personal protective equipment has improved worker safety. However, there are still significant obstacles to overcome, most notably the toxicity of certain medicinal ingredients. The article outlines several short- and long-term health consequences for employees, such as hormone abnormalities, respiratory problems, and cancer risks. Hence, proactive actions are essential to address these issues properly. The proposals include increased worker education and training, more stringent restrictions, increased research and data collecting, sustainable methods, and open reporting of chemical consumption. Companies must also strictly adhere to the guidelines such as the threshold limit values (TLVs), biological exposure indices (BEIs), and Hazard Communication Standard (HCS) set by various global agencies such as OSHA, ACGIH, and US-DoL. The American Conference of Governmental Industrial Hygienists (ACGIH) and the Occupational Safety and Health Administration (OSHA) both emphasize the importance of chemical exposure in the workplace. ACGIH mandates companies to adhere to threshold limit values and biological

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