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ORIGINAL PAPER

EXPOSURE ASSESSMENT OF PHARMACEUTICAL POWDERS BASED ON AN ENVIRONMENTAL MONITORING METHOD: A PILOT STUDY

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Abstract

Background: About 8 million healthcare workers in the USA are potentially exposed to hazardous drugs or their toxic metabolites over a long period of time despite the fact that both the Occupational Safety and Health Administration and the European Parliament recommend the monitoring of exposure among workers dealing with substances which have carcinogenic, mutagenic or toxic effects on the reproductive system. The objective of this study is to determine exposure to active pharmaceutical ingredients (APIs) among pharmaceutical industry workers, and to develop a methodology which promotes the accurate monitoring, evaluation and control of exposure to active pharmaceutical ingredients, also in compliance with good manufacturing practice. **Material and Methods:** The pilot study was designed in accordance with "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice," issued by the U.S. Food and Drug Administration. The samples were collected with the swab technique which was recommended in the "Validation of Cleaning Processes (7/93)" guideline. The minimum numbers of locations ($N_L = 9$) and sampling points ($N_L(T) = 63$) were determined according to ISO 14644-1:2015 "Cleanrooms and Associated Controlled Environments" issued by the International Organization for Standardization. The samples were analyzed using an ultra performance liquid chromatography system, with an analytical method which was developed and validated according to "Q7A, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" issued by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. The low limit of quantification of the employed method (17 ng/ml) enables the determination of exposure at low concentrations. **Results:** While contamination was detected in 43 (68.3%) of the 63 samples collected, 20 (31.7%) could not be detected. The environmental monitoring results ranged 0–15 000 ng/cm^2 and the potential risk of exposure to API was considered to be >2 g. **Conclusions:** The results clearly prove and reveal the magnitude of the hazard, both objectively and scientifically, when compared to the research which suggests that 10 ng/cm^2 should be considered the prohibitory risk level in quantitative terms. Med Pr. 2020;71(6):649–63

Key words: environmental monitoring, occupational safety in the pharmaceutical industry, risk assessment, working environment measurement, exposure to API, determination of surface contamination

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INTRODUCTION

The effects of active pharmaceutical ingredients (APIs) on pharmaceutical production workers have been studied since Watrous [1] proposed raw herbal drugs and its extracts as sources of hazard, just like chemical substances used in synthesis studies, in 1946. Research comparing the causes and mortality rates of workers in the production and marketing departments of a pharmaceutical company in the USA revealed that the workers employed in the production department had higher mortality rates and incidence rates of various diseases [2].

Even though some research has suggested a correlation between reproductive system disorders, congenital anomalies and low fetus weight with workers exposed to dangerous drugs [3], no clear result has been obtained about the exact cause of such correlation due to lack of data about the workers' genetic dispositions, histories of illnesses and habits. However, the degree of absorption that takes place at the workplace and the significance of secondary early biological effects for each individual are difficult to assess and may vary depending on the hazardous drug in question [4].

As a result of numerous studies focused on mortality and morbidity in the pharmaceutical industry, the common belief that exposure to APIs affects workers' health in a negative way has led researchers to investigate various controlling methods and acceptable limits of exposure. Nevertheless, studies on API exposure in pharmaceutical drugs production are very limited, particularly

for new-generation cancer drugs. The antineoplastic and other hazardous drugs (AHDs) which are mostly investigated in hospitals, also as regards workers' exposure, are methotrexate, 5-fluorouracil, cyclophosphamide and cisplatin. These were all approved by the U.S. Food and Drug Administration (FDA) in 1999, 2000, 1999 and 2000, respectively.

In this study, the potential risk of exposure to pharmaceutical drugs in the production process was investigated, and the risk management of API exposure was presented in a pilot study for a new-generation AHD.

Occupational exposure to APIs

About 8 million healthcare workers in the USA are potentially exposed to hazardous drugs, including pharmacy and nursing personnel, physicians, environmental services workers, workers in research laboratories, veterinary care workers, and shipping and receiving personnel [5], despite the fact that both the Occupational Safety and Health Administration (OSHA) [4] and the European Parliament (EP) [6] recommend the monitoring of exposure among workers dealing with substances which have carcinogenic, mutagenic or toxic effects on the reproductive system. Even in the healthcare services where standards and regulations are more pronounced than in the pharmaceutical industry, the National Institute for Occupational Safety and Health (NIOSH) survey results indicate that the regulatory guidelines for the safe handling of chemotherapy drugs are not being universally followed [7].

Among the European Union countries, legally permissible levels of occupational exposure in the air of the working environment have been determined for some cytostatics [8], and once sufficient quantitative data are obtained, regulatory institutions will likely determine the quantitative limit values for more APIs [9], especially for potent drugs. Since the limit values are determined only for some cytotoxics and there is no generally accepted method, exposure to these materials still continues in the USA and Europe [10]. So, pharmaceutical drug manufacturers carry out these studies in accordance with the methods, standards, criteria and limits determined by themselves. The band system, which is the most commonly applied exposure control and prevention system, is based on the principle of the classification of APIs according to their general pharmacokinetic, pharmacological, chemical and physical properties, since there are insufficient data about any impacts of exposure.

Preventive policies of the companies applying these studies are based on risk assessments which involve evaluating the relevant hazards. Risk assessments are completed by monitoring and controlling exposure using appropriate methods and equipment.

Monitoring of occupational exposure to APIs

Research studies focusing on the exposure levels of AHDs began with biological monitoring of workers exposed to these drugs. Then, guidelines and regulations were issued according to the results obtained from these studies, and it was seen that exposure decreased in the body fluids. However, these methods began to be less preferable after it was observed that some AHDs could not be detected in the body fluids because of low selectivity and precision [11]. Therefore, environmental monitoring methods which are in line with the EP's proactive approach to the early detection of exposure have become the preferable alternative methods. These are more precise and selective methods in which only APIs or their metabolites are investigated in the body fluids.

Axitinib

Chemical structure and production processes

This article investigates the potential risk of API exposure among workers during the production of a highly potent AHD named Axitinib, with the brand name Inlyta, manufactured by Pfizer Inc. Axitinib, or more specifically N-methyl-2-[[3-[(E)-2-pyridin-2-ylethenyl]-1H-indazol-6-yl] sulfanyl] benzamide (CAS No. 319460-85-0), belongs to indazoles, pyridines, aryl sulfide and benzamides (Figure 1) [12] with vapor pressure of 0.0±2.0 mm Hg at 25°C [13].

Axitinib was approved for renal cell carcinoma by FDA in 2012. Additionally, FDA approved axitinib combinations with avelumab and pembrolizumab (different APIs) in 2019.

The Axitinib 5 mg film-coated tablet was produced using a direct compression method. The substances in the formulation are mixed as dry powder after being processed, and the powder is compressed to become a tablet. The formulation to prepare 50 000 tablets includes axitinib (250 g), microcrystalline cellulose, anhydrous lactose, magnesium stearate and opadry II. The exact amount of these chemicals in the formulation and the production processes applied were not explained in detail to avoid patent infringement.

Hazard statements and adverse effects on workers

Axitinib belongs to category 2 in terms of germ cell mutagenicity, reproductive toxicity and specific target

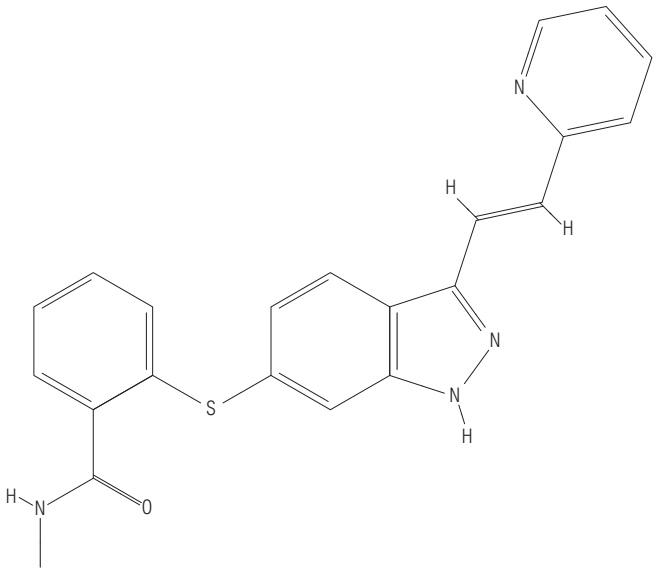


Figure 1. Chemical structure of Axitinib

organ systemic toxicity (repeated exposure) according to the Globally Harmonized System of Classification and Labeling of Chemicals. Hazard statements were determined as H302, H400, H341, H361, H373, H410 [14–16].

In 2016, Axitinib was included in the List of Antineoplastic and Other Hazardous Drugs by NIOSH due to its characteristic properties which are "Carcinogenicity, teratogenicity or other developmental toxicity, reproductive toxicity, organ toxicity at low doses, genotoxicity and mimicking existing drugs" [17].

This definition of hazardous drugs like Axitinib, as used in the NIOSH Alert, is based on the American Society of Health-System Pharmacists definition that was originally developed in 1990. Thus, the definition may not accurately reflect the toxicity criteria associated with the newer generation of pharmaceuticals entering the healthcare setting [18]. In fact, NIOSH and other organizations are still gathering data on the potential toxicity and health effects related to highly potent drugs and bioengineered drugs. Therefore, while working with any hazardous drug, workers should follow a standard precautions approach along with any recommendations included in the manufacturer's material safety data sheet.

The combination of high potency of APIs, along with the anticipated increase in the frequency of their use, poses a growing exposure threat to pharmaceutical workers. This worrying increase should be monitored with urgency.

MATERIAL AND METHODS

Surface contamination and environmental monitoring

Environmental monitoring is an important risk assessment approach for current Good Manufacturing Practices (GMP), which evaluates the cleanliness of the working environment and the effectiveness of cleaning and disinfection programs and controls [19]. Its purpose is not to determine the quality of the final product, but to assess the condition of the facility regarding occupational health and safety (OHS). Environmental monitoring of surface contamination is based on collecting samples directly from surfaces by using the swabsticks which FDA prefers [20].

The surface contamination method is defined as a more reliable and hazard preventing method, as a result of the recently increased scientific interest to prove biological exposure proactively. Current research suggests that pharmaceutical powders cannot be detected sufficiently on the high-efficiency particulate-arresting filters by using air monitoring [10], and the concentration of pharmaceuticals in the atmosphere of the preparation areas is many times lower than their actual concentration [21]. In addition, as the pharmaceutical formulation changes, the dustiness, particle size and weight of the powder is also subject to change, so the air suspension time of the powder changes too. Since air sampling methods cannot be standardized for these reasons, surface monitoring has been preferred.

Study design

Even though designing the method and collecting samples from predetermined locations may lead workers to focus on these locations and may manipulate the results, the potential risks of chemical substances, equipment and processes should be assessed while designing the study. Determining the locations using scientific approaches promotes more accurate and precise results [22]. However, the professional judgment of most industrial hygienists is currently calibrated to visual cues related to particle mass concentrations that may not be reliable for infrequently used aerosol concentration metrics, such as the number and surface area, which may be critical. Thus, the creation of exposure zones should be a combination of a subjective professional judgment and objective measurements.

The study design was based on monitoring time, frequency and duration, specific equipment and processes, while the sampling locations and monitoring methods

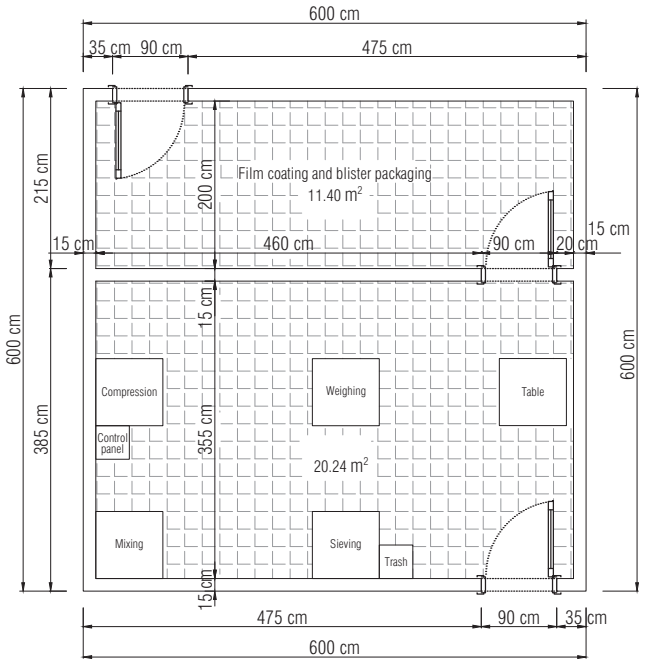


Figure 2. Layout of the cleanroom

were described below in detail to obtain repeatable and objective results as recommended by FDA [23]. More than 1 location was determined, and the sampling locations and the number of samples were meant to represent the entire cleanroom, from high risk to low risk. An API concentration map was drawn up at all processes by collecting samples from the areas surrounding the equipment and its different parts in order to meet these criteria.

Time, frequency and duration of monitoring

Pharmaceutical drug production is a dynamic process and its duration depends on the production method, batch size and the results of quality controls, and it may range from a few hours to a few days, which is specific for each drug. Although it is planned to be completed within a few hours, the process may be extended due to any unexpected events occurring during production. Therefore, it is clear that documenting the potential exposure weekly, monthly or yearly would not meet the requirements. Monitoring and sampling should be performed during production or after it is completed. The samples should be collected at the end of the workday or right before the shift of workers. Otherwise, the risk of personal exposure cannot be evaluated.

Specific equipment and processes

During pharmaceutical production, most of the equipment and processes such as mixing, concentrating, centrifugation or transfer may cause spillages and generation of aerosol. However, since pharmaceutical drug production consists of specific processes, it is not possible to change the production method or the substances used. So, utmost attention has to be given to substances, their amounts and production methods like granulation, sieving and micronization. Otherwise, patent infringements may occur.

In the pilot study, the Axitinib 5 mg film-coated tablet production method consisted of weighing, sieving, mixing, compression, film coating and blister packaging, and equipment in which these processes were conducted. Film coating and blister packaging machines were located in another part of the cleanroom for use when core tablet results met the specifications. The layout of the cleanroom is shown in Figure 2. The equipment and its vicinity are the most risky zones when it comes to workers' exposure.

Sampling locations and the number of samples

There is no regulatory guideline determining sampling locations to evaluate API exposure among workers. So, an approach to determining the number of sampling locations, as the one recommended by the International Organization for Standardization, i.e., ISO 14644:2015 "Cleanrooms and associated controlled environments," would be convenient to address in a similar manner [22]. This standard classifies cleanrooms by the number of particles using a standard method which involves determining the minimum number of sampling locations, the location and time, etc., according to the actual risk. The minimum number of sampling locations (N_L) is determined according to the area (A) of the cleanroom in m^2 per unit, as stated in ISO 14644-1:2015, Annex B: Table A.1 [24].

The minimum number of sampling locations (N_L) determined according to the area of a cleanroom ($A = 36\ m^2$) is $N_L = 9$. As many as 6 of the 9 sampling locations were determined as equipment and its vicinity since API is processed in ($N_{L1} = 6$).

Instead of collecting 1 sample from each determined location, samples were collected from the area within reach of workers. This space is referred to as "reachable workspace" or "risk circle." The centre of the risk circle, O, is the input of each piece of equipment from which API/powder/tablet is fed into. The worker is standing in front of the equipment, and at the centre of the risk circle, during the process. The radius of the risk circle was determined in accordance with the functional lengths of the human body parts. According to the static

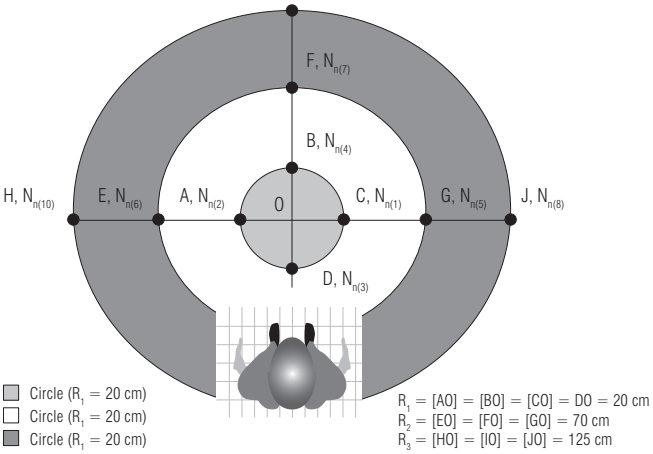
anthropometry, the average arm length is approx. 70 cm for women and 75 cm for men, and the distance that can be reached by changing the posture is 125 cm on average [25]. Therefore, the radius of the risk circle is r = [HO] = 125 cm.

The distances of other sampling points to the centre are as follows: [AO] = [BO] = [CO] = [DO] = 20 cm; [EO] = [FO] = [GO] = 70 cm; and r = [HO] = [IO] = [JO] = 125 cm. This risk circle was designed separately for all pieces of equipment, and 10 samples were collected from each ($N_{L1(n)}$ = 60). In this way, the total potential exposure and its distribution can be evaluated objectively. The risk circle was divided into areas as 1 circle and 2 rings in accordance with the sampling points to evaluate distribution. The amount of API in each area was calculated separately. The risk circle, the areas and the sampling points are shown in Figure 3.

Other locations were determined relative to the most frequently used locations. These were: a 50-cm-wide inner side of the door used for the entrance and exit of the materials, equipment and personnel; the control panel of the tablet compression machine and the surface of the table in the cleanroom (N_{L2} = 3). Three samples were collected from these 3 locations ($N_{L2(n)}$ = 3). As a result, the samples were collected from 63 different points and 9 locations (N_L = 9, $N_{L(T)}$ = 63).

The production proceeded as planned and 3 workers, i.e., a pharmacist, an engineer and an operator, participated. The operator performed all the operations specified in the prescription while the pharmacist and the engineer were in the cleanroom to guide the operator and intervene where necessary. The chemical substances, equipment and materials specified in the prescription were placed in the cleanroom before the production.

The research was made more comprehensive by evaluating the API concentration in the samples collected from different surfaces. The first surface upon which the samples were collected was the workers' personal protective equipment (PPE) to compare the environmental monitoring results and API concentrations on various parts of PPE. The samples were collected from gloves, gowns and masks. A total of 9 samples were collected from 3 different pieces of PPE of 3 different workers. The second surface that the samples were collected from was the corridor next to which the cleanroom was located. Exposure distribution outside the cleanroom, which may be a consequence of the lack of an anteroom or a dressing room integrated into the cleanroom, was investigated.



A, $N_{n(x1)}$ to J, $N_{n(y)}$ are sampling points in the reachable workspace of worker.

Figure 3. Risk zone and sampling points

Analytical method

When the standards and regulations related to the pharmaceutical industry are examined, it is seen that there is neither any regulation related to API exposure nor any validation of analytical methods to monitor such exposure. Because of the similarity of the procedures, the validation of the analytical method was performed in compliance with the parameters and criteria of the validation of cleaning procedures. The only difference is that while the validation of cleaning procedures proves that the working environment and equipment are clean and safe for the product, the monitoring of the risk of exposure proves that the these are clean and safe for the worker. The environmental monitoring method is used to measure the amount of residues in the working environment, while other one determines whether there are any residues and if so, their amount after cleaning procedures.

The samples were analyzed using the ultra performance liquid chromatography (UPLC) system (Waters Corporation, Milford, USA) using the analytical method which was developed and validated in accordance with the parameters and criteria stated in the "Q7A, Good Manufacturing Practice guide for active pharmaceutical ingredients" issued by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use [26]. The Empower software (version 3, Waters Corporation, USA) was used to evaluate the chromatograms.

The analytes used in this study were prepared as stated in the guidelines with the swab samples collected from the stainless steel plates placed on various surfaces and equipment [22,27]. However, the placement

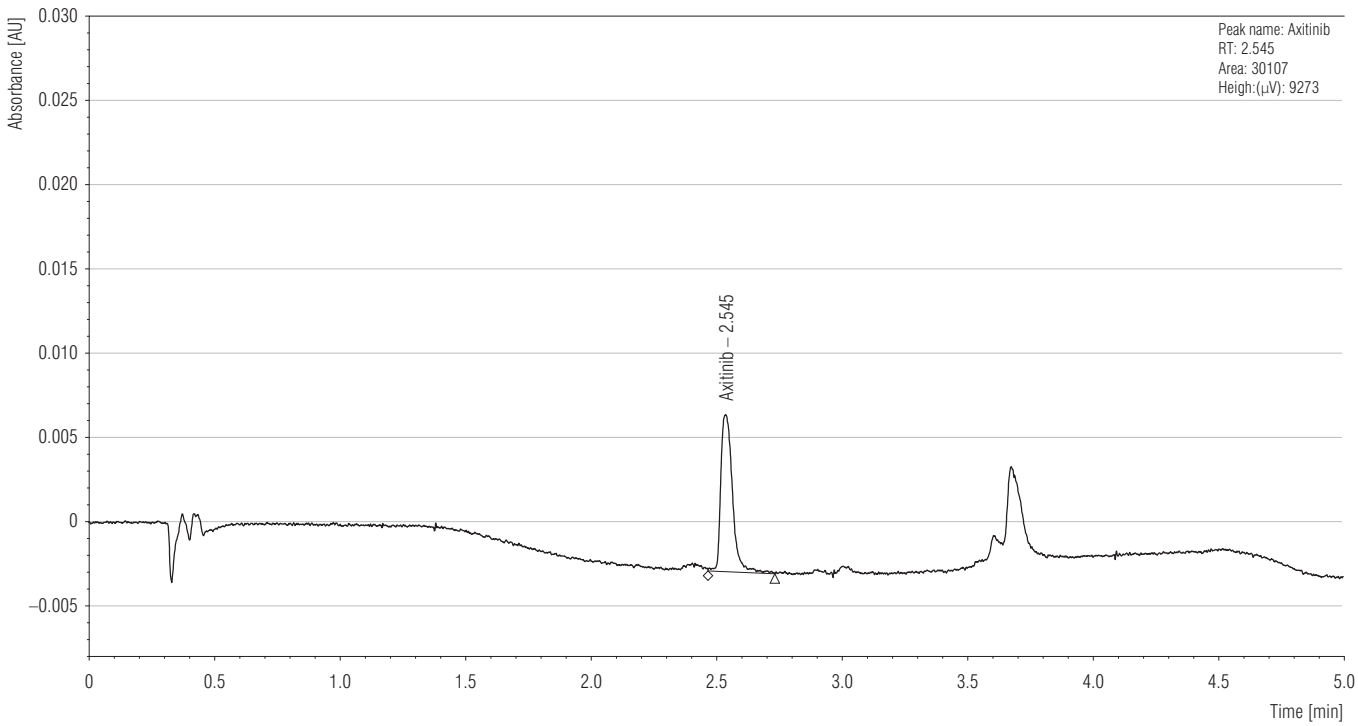


Figure 4. Standard solution chromatogram

of stainless steel plates in sampling locations provides specificity to the measurements.

Axitinib and all other chemicals were supplied by Sigma-Aldrich. The grade of the water used for preparing the solutions was determined as an UPLC grade. The buffer solution, UPLC-grade methanol and acetonitrile were filtered through a 0.45 µm filter.

Chromatographic separation was achieved on a UPLC system using ethylene bridged hybrid (BEH) C18; 50×2.1 mm, 1.7 µm column. The mobile phase consisted of a combination of mobile phase A (a buffer solution of 4 mM ammonium formate, with pH adjusted to 3.2 with ortophosphoric acid) and mobile phase B (a buffer solution of Acetonitrile [90:10 (v:v)]) [28]. The initial conditions of the gradient program were 95% for mobile phase A and 5% for mobile phase B for 0.15 min. Mobile phase B increased linearly to 30% until 0.8 min, and then to 90% until 3 min, and continued at this condition until 3.5 min, and then decreased linearly to 5% until 4 min and continued at this conditions until 5 min. The run-time was 5 min, the wavelength was 254 nm, and the injection volume was 5 µl. Both the standard and sample solutions were prepared with methanol. Polyester swabs (Texwipe Large Alpha swab; TX714A) were wetted with methanol.

The calibration curve was found to be linear (r^2 = 1.000) between the concentration range limit of quantification (LOQ) and 20 000 ng/ml. A linearity study was performed in a wide range of concentrations to provide for detection at low and high contamination levels. The LOQ level was 17.4 ng/ml. The retention time of Axitinib was 2.5 min. No interference was observed for any other substances and the solutions were stable for 48 h. The accuracy of the results ranged 90–110%. The relative standard deviations (RSDs) of the precision studies were <10%. The method was found to be robust when minor changes were made to some parameters.

Preparation of the standard solution

The stock standard solutions were prepared by dissolving the accurately weighed Axitinib in methanol to yield a concentration of 1 mg/ml. These solutions were then diluted with methanol to yield a concentration of 0.001 mg/ml (1000 ng/ml), and then injected into the chromatographic system. The standard solution chromatogram is shown in Figure 4.

Preparation of sample solutions

At first, 100 cm^2 of the sampling surface was cleaned vertically with one side of a swabstick wetted with methanol, and then horizontally with the other side. This procedure was repeated with another swabstick. Finally, the surface was cleaned with a dry swabstick. After collecting the swab samples, the sticks of the swabsticks were cut and the swabs were put into a beaker, and then 20 ml of methanol was added. The samples were

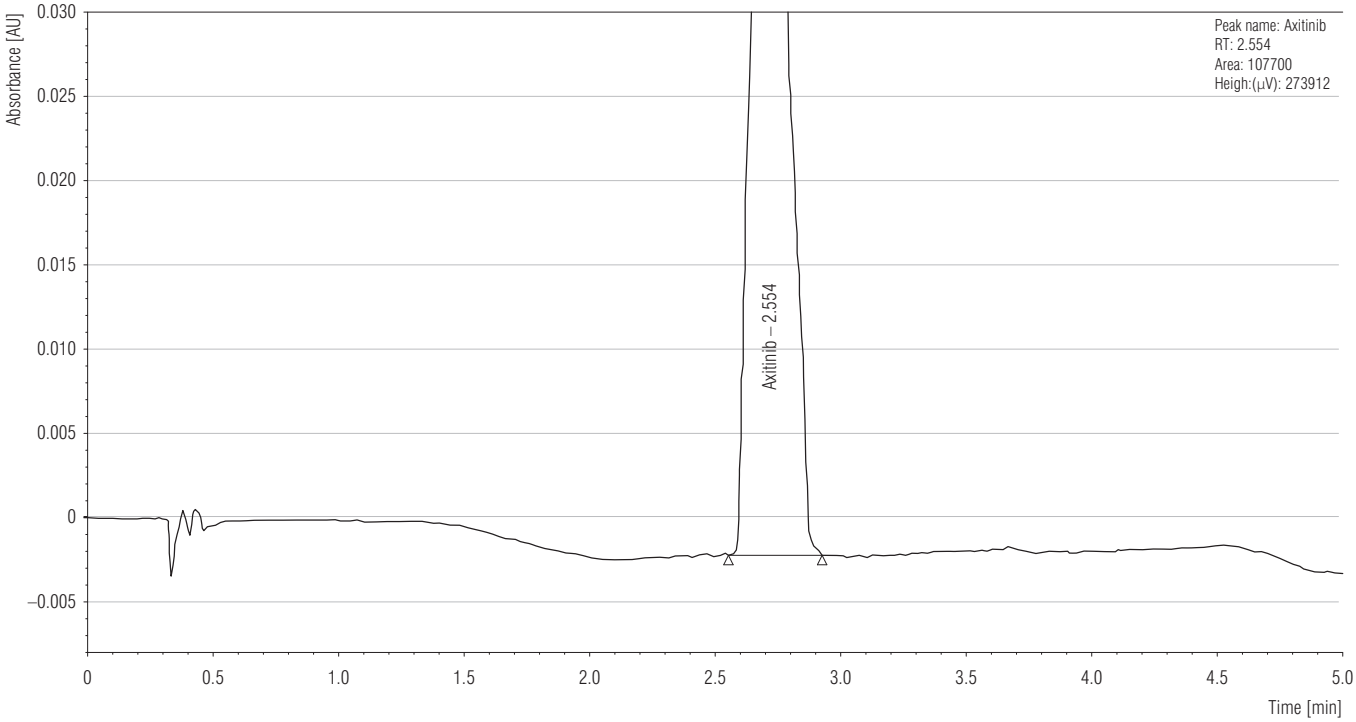


Figure 5. Sample solution chromatogram ($N_{(1)1}$)

mixed at a magnetic stirrer for 10 min. This solution was filtered through a 0.45 μm PTFE filter and put into a vial, and then injected to the chromatographic system. This procedure was applied to all samples collected from the determined surfaces. A sample solution chromatogram ($N_{(1)1}$) is shown in Figure 5.

RESULTS

The standard and sample solutions were prepared and injected into the chromatographic system. The API concentration on the surfaces was calculated by direct proportion, comparing the known concentration and the absorbance of the standard solution with the absorbance obtained from the sample solutions.

Among the 63 samples collected from the surfaces, contamination was detected in 43 (68.3%), while no contamination was found in the remaining 20 samples (31.7%). The potential risk of exposure was detected in all processes, from weighing to coating. The sieving and mixing processes were considered the most risky because of generating powder. In contrast, no surface contamination was detected in the coating and blister packaging processes.

The risk of exposure was found to decrease by moving away from the equipment. The spilling of API or powder in any of the processes changed the contamination results (Table 1). Based on the obtained results, the loss on production, and thus the API amount on the surfaces that might cause exposure, was estimated to be >2 g (Table 2). This means that at least 1% of 250 g of Axitinib used in the production remained on the surfaces as a residue. Contamination was detected also in the other 3 most frequently used locations (Table 3). Table 4 summarizes the environmental monitoring results of all the locations sampled. The average result of environmental monitoring is 1324 ng/cm^2 and RSD is 167.7 (Table 4).

Although the contamination levels were different in each PPE, contamination was detected on all parts of PPE of all workers participating in the production processes. The operator, working with chemical substances and conducting the processes, was found to bear the highest risk of exposure (Table 5).

The contamination level was 23 ng/cm^2 in the samples collected from the surface of the corridor next to which the cleanroom was located and where the workers took off their PPE.

DISCUSSION

Depending on the equipment, process and distance, certain variations were determined in the results obtained from the samples collected from different locations and points in the risk circle. These variations show that the sampling locations should be determined objectively

Table 1. Environmental monitoring results of selected points in N_{L1} in the study of exposure to active pharmaceutical ingredients (APIs), 2018, Duzce, Turkey

Sampling point	Axitinib residue [ng/cm²]					
	weighing device ($N_{L1(1)}$)	sieve ($N_{L1(2)}$)	mixer ($N_{L1(3)}$)	tablet compression machine ($N_{L1(4)}$)	film coating machine ($N_{L1(5)}$)	blister packaging machine ($N_{L1(6)}$)
$N_{Ln(1)}$ – 20 cm right	7 136	6 008	11 854	81	0	0
$N_{Ln(2)}$ – 20 cm left	1 998	5 777	13 285	155	0	0
$N_{Ln(3)}$ – 20 cm front	3 202	5 824	13 732	101	0	0
$N_{Ln(4)}$ – 20 cm back	2 203	6 005	12 967	118	0	0
$N_{Ln(5)}$ – 70 cm right	2 244	2 077	5 304	75	0	0
$N_{Ln(6)}$ – 70 cm left	1 329	2 304	4 992	97	0	0
$N_{Ln(7)}$ – 70 cm back	1 055	2 236	5 386	82	0	0
$N_{Ln(8)}$ – 125 cm right	525	1 030	1 628	23	0	0
$N_{Ln(9)}$ – 125 cm left	85	1 055	1 165	29	0	0
$N_{Ln(10)}$ – 125 cm back	67	1 024	918	10	0	0

Table 2. Estimation of active pharmaceutical ingredients (APIs) amount on the surfaces that may cause exposure in the study of exposure to API, 2018, Duzce, Turkey

Sampling location (N_L)	Axitinib residue [ng/cm²]		API*		
	sampling point ($N_{L(n)}$)	M	area (A) [cm²]	M×A	
				ng	mg
Weighing (N_1)					
circle		3 635	1 256	4 565 246	46
A	7 136				
B	1 998				
C	3 202				
D	2 203				
first ring		1 543	14 130	21 797 880	218
E	2 244				
F	1 329				
G	1 055				
second ring		226	33 677	7 599 664	76
H	525				
I	85				
J	67				
Sieve (N_2)					
circle		5 904	1 256	7 414 796	74
A	6 008				
B	5 777				
C	5 824				
D	6 005				

Table 2. Estimation of active pharmaceutical ingredients (APIs) amount on the surfaces that may cause exposure in the study of exposure to API, 2018, Duzce, Turkey – cont.

Sampling location (N_L)	Axitinib residue [ng/cm^2]		API*		
	sampling point ($N_{L(n)}$)	M	area (A) [cm^2]	M×A	
				ng	mg
Sieve (N_2) – cont.					
first ring		2 206	14 130	31 166 070	312
E	2 077				
F	2 304				
G	2 236				
second ring		1 036	33 677	34 900 080	349
H	1 030				
I	1 055				
J	1 024				
Mixer (N_3)					
circle		12 960	1 256	16 277 132	163
A	11 854				
B	13 285				
C	13 732				
D	12 967				
first ring		5 227	14 130	73 862 220	739
E	5 304				
F	4 992				
G	5 386				
second ring		1 237	33 677	41 657 831	417
H	1 628				
I	1 165				
J	918				
Tablet compression machine (N_4)					
circle		114	1 256	142 870	1
A	81				
B	155				
C	101				
D	118				
first ring		85	14 130	1 196 340	12
E	75				
F	97				
G	82				
second ring		21	33 677	695 981	7
H	23				
I	29				
J	10				

Table 2. Estimation of API amount on the surfaces that may cause exposure in the study of exposure to active pharmaceutical ingredients (APIs), 2018, Duzce, Turkey – cont.

Sampling location (N_L)	Axitinib residue [ng/cm^2]		API*		
	sampling point ($N_{L(n)}$)	M	area (A) [cm^2]	M×A	
				ng	mg
Film coating machine (N_5)					
circle (A–D)		0	1 256	0	0
first ring (E–G)		0	14 130	0	0
second ring (H–J)		0	33677	0	0
Blister packaging machine (N_6)					
circle		0	1 256	0	0
first ring		0	14 130	0	0
second ring		0	33 677	0	0

* Total API on the surfaces that may pose exposure 2413 mg.

Table 3. Environmental monitoring results in selected sampling locations (N_{L2}) in the study of exposure to active pharmaceutical ingredients (APIs), 2018, Duzce, Turkey

Sampling location (N_{L2})	Axitinib residue [ng/cm^2]
Interior of the cleanroom – 50 cm from the door (N_7)	62
Dashboard of the compression machine (N_8)	110
Surface of the desk (N_9)	332

Table 4. Summary of environmental monitoring results in selected sampling locations (N_L) in the study of exposure to active pharmaceutical ingredients (APIs), 2018, Duzce, Turkey

Sampling location (N_L)	Axitinib residue [ng/cm^2]
Weighing device (N_1)	1 801
Sieve (N_2)	3 049
Mixer (N_3)	6 475
Tablet press machine (N_4)	73
Film coating machine (N_5)	0
Blister machine (N_6)	0
Interior of the cleanroom – 50 cm from the door (N_7)	62
Dashboard of the compression machine (N_8)	110
Surface of the desk (N_9)	332

* M±SD = 1322±2203.9 ng/cm^2, % RSD = 166.7.

using scientific and statistical methods, instead of personal observations and judgments. Additionally, collecting much more samples from different locations/points, instead of samples collected from 1 location/point, would make monitoring valid and consistent. The evaluation of the total potential exposure would decrease such variations.

A substance with a high vapor pressure at normal temperatures is often referred to as volatile, and the substance volatility is closely linked to its vapor pressure. It is seen that the ventilation system is not capable of removing the API or drug powder in the air of the cleanroom, and these substances accumulate on the surfaces after a while, as a consequence of low but non-negligible vapor pressure of pharmaceuticals [21]. The research reveals that the air monitoring method is not suitable for monitoring exposure to APIs. There are also studies proving dermal exposure to AHDs in various working environments, and the risk of API exposure being investigated with the surface contamination method allows the assessment of dermal exposure.

Instead of a pre-determined time for sampling, collecting samples at the end of the production processes, when API accumulates on the surfaces, will make the results more reliable and objective. In this way, more rational and objective results can be achieved by removing the subjectivity that may occur from knowing the sampling times and points while the variations decrease.

The risk of exposure to API begins with weighing and continues until compression in tablets. The risk of exposure was found to reach the maximum level during mixing. In contrast, no contamination was detected during film coating and blister packaging, as these processes were carried out in other sections, separate from the processes that generate dust in the cleanroom, while

Table 5. Surface contamination results of the samples collected from personnel protective equipment (PPE) in the study of exposure to active pharmaceutical ingredients (APIs), 2018, Duzce, Turkey

Sampling point	Axitinib residue [ng/cm^2]		
	operator	engineer	pharmacist
Gloves	5 845	4 784	1 285
Gown (chest)	5 323	3 031	1 095
Mask (filter)	4 296	1 473	834

API was only present in tablets in a compressed form. The isolation of equipment or processes that result in exposure eliminates the risks to a large extent. The barrier isolation solution systems like glove boxes, glove bags, fume hoods, separate sections, etc. can be useful for these processes and equipment that generate aerosol. It should be noted that the use of PPE is the last option according to the hierarchy of hazard control in OHS.

The loss in production is about 2 g and this value is acceptable according to the release limits specified in the European Pharmacopoeia. The amount of API on the surfaces that may cause exposure in the cleanroom is considered to be >2 g while the total daily intake of Axitinib for patients is established at 10 mg [29]. The price of 1 box of Inlyta (Axitinib) is approx. USD 16 000 per 60 tablets in the USA. The loss in production corresponds to USD 150 000 per 400 tablets with other operating expenses, approximately. On the other hand, Pfizer reported revenues of USD 298 million in 2018, USD 339 million in 2017, USD 401 million in 2016, and USD 430 million in 2015, for Inlyta (Axitinib). This loss may seem extremely high when evaluated on its own, but when compared with revenues, it comes to represent a small amount of money. This marked difference may be one of the reasons why legal regulations regarding OHS in the pharmaceutical industry have not been made until today. In addition, since the negative effects of API exposure emerge after many years, and the retrospective data used in the diagnosis and treatment of occupational diseases are not sufficient and reliable, OHS regulations may be ignored by regulatory institutions.

High contamination results determined on PPE show that the risk of exposure does not stick and remain on the surfaces. Utmost attention should be given to the disposal of PPE. Cleaning staff should be trained about API exposure, as should all other workers.

The contamination detected in the cleanroom reveals that engineering controls are not effective, and API or drug powder could not be isolated in the cleanroom in which negative pressurizing is applied. The lack of a dressing room or an anteroom between the cleanroom and the corridor, or the fact that GMP procedures are not integrated with OHS requirements, may cause this contamination in the corridor. There should be a dressing room or an anteroom integrated to the cleanroom, and standard operational procedures (SOPs) should be prepared regarding the use and disposal of PPE.

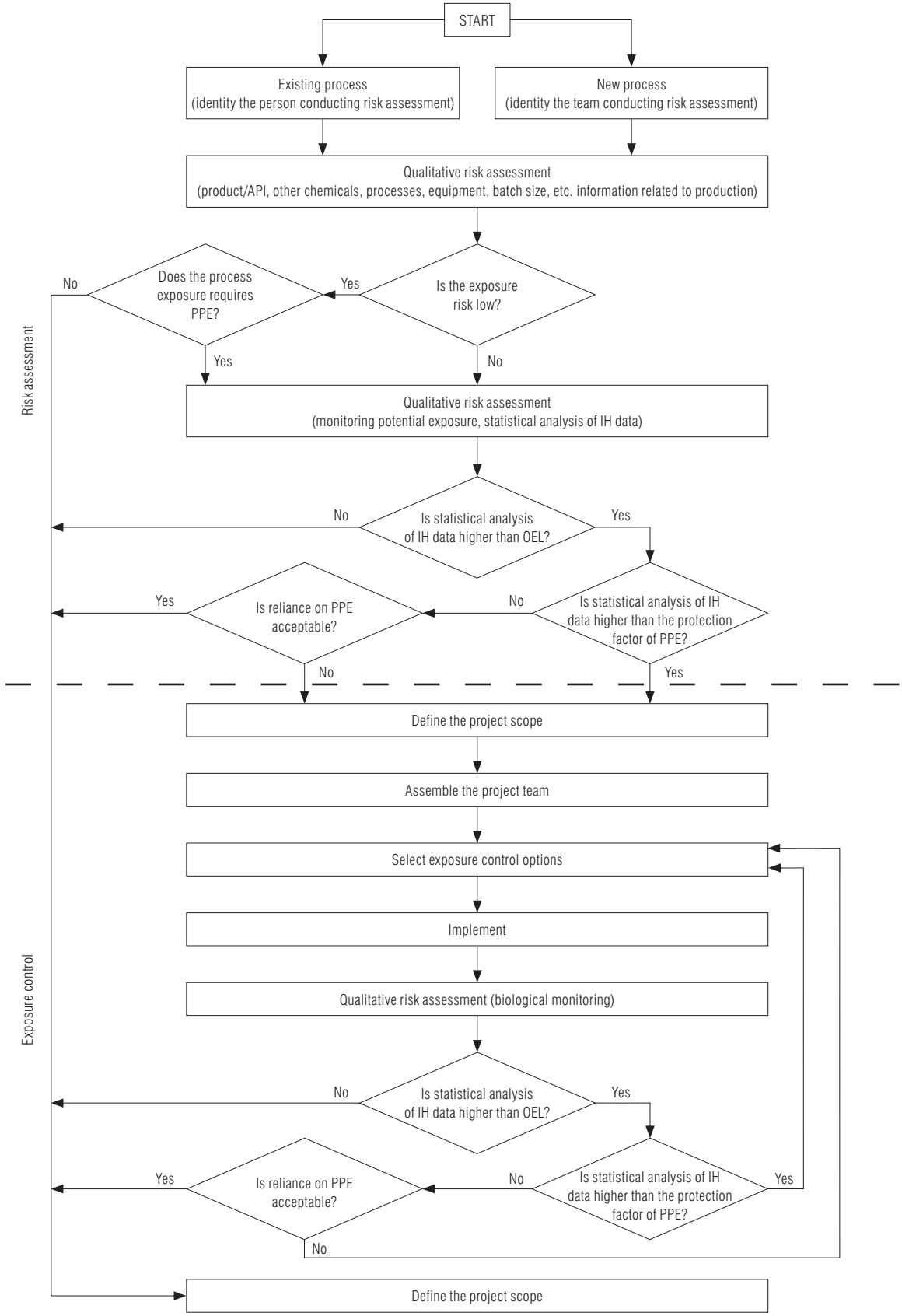
Workers should be trained and informed about OHS, properties and hazards related to APIs, production methods and processes, equipment and PPE. Before starting production, workers must confirm in writing that they have the knowledge about every production aspect.

Since there are insufficient retrospective or cumulative data obtained from the exposed pharmaceutical production workers, the results were compared with the research conducted in hospitals and pharmacies involving healthcare workers, nurses, pharmacists, etc. When the average level of contamination determined as 1322 ng/cm^2 is compared with the research suggesting the reference values of 0.1 ng/cm^2 (safe) and 10 ng/cm^2 (not acceptable) [11], the magnitude of risk is revealed.

The contamination level of 0.1 ng/cm^2 was determined as safe because the urine samples from healthcare professionals who worked in facilities with contamination levels <0.1 ng/cm^2 were negative for one of the most widely used and carcinogenic hazardous drugs, i.e., cyclophosphamide [11]. In 2019, the European Biosafety Network published a brochure on recent amendments to the Carcinogens and Mutagens Directive, and their implications for the healthcare sector, and most of the studies performed on the surface monitoring of hazardous drugs in Europe (e.g., in Germany and Spain) suggest 0.1 ng/cm^2 as the threshold level [30].

Although these working environments, dosage and duration of exposure, as well as efficacy and safety levels of PPE, are different from the pharmaceutical industry, it is obvious that precautions should be taken immediately. Otherwise, pharmaceutical production workers would be risking exposure to overdoses of different APIs on a daily basis. As a result of exposure in high doses, workers will have to work with the risk of contracting both long-term and short-term occupational diseases.

In order to prevent occupational diseases, environmental monitoring should be performed to assess and control the risk of exposure. While it is not difficult to control exposure with environmental monitoring, it can



IH – industrial hygiene, OEL – occupational exposure limit, PPE – personal protective equipment.

Figure 6. Flow sheet for risk management

be routinely implemented as a part of the validation of cleaning procedures that must be performed in pharmaceutical manufacturing facilities that meet GMP requirements. Specific SOPs should be established to prevent exposure, and qualitative and quantitative risk assessments should be performed for each API or similar API groups, and limit values should be determined scientifically. The simultaneous evaluation of environmental monitoring and the validation of cleaning procedures must be performed by collecting samples before and after the cleanroom is made ready for another production. The same analytical methods and chromatographic systems can be used while analyzing the samples. In this way, the loss of labor, time and costs will be cut to the minimum. Environmental monitoring results should be evaluated after each production, and precautions should be improved if necessary. If the risk of exposure is still high despite the precautions, samples from the body fluids must be collected and the actual equivalent exposure among workers must be determined. All monitoring results should be well documented and archived. Workers should be properly informed, and API exposure control and risk assessment methods should be applied as SOPs.

The flow sheet for risk management is shown in Figure 6.

CONCLUSIONS

The lack of determined occupational exposure limits and uncertainty regarding the categorization of APIs obstruct the prevention of API exposure among workers. Contamination has been detected which does not comply with the OHS requirements even in a pharmaceutical manufacturing facility that meets the requirements of GMP. The risk of exposure can be minimized to acceptable levels by defining OHS precautions in detail and by incorporating them to GMP regulations.

While evaluating exposure, OHS professionals should not fully rely on personal judgments. Risk assessments and personal judgments should be supported with environmental monitoring results obtained scientifically.

Measurements related to the risk of API exposure in the pharmaceutical industry should be applied as a legal obligation. Otherwise, companies do not carry out studies on monitoring exposure and refrain from supporting research, in order not to encounter any other situation as a result of obtaining unfavorable results.

In order to control the risks, API exposure should be defined in all processes. Risk assessments should be performed for each API and process, precautions should be taken in accordance with the hierarchy of hazard control, all employees should be trained, and emergency action plans should be created. Exposure controls should be evaluated separately for each production process, and employees' health should be monitored with periodic medical examinations at regular intervals. Finally, all results regarding API exposure should be well documented and archived.

This article presents a beneficial guideline which characterizes workplaces and monitors the potential risk of exposure to API. It also reveals the magnitude of the risk for OHS professionals, industrial hygienists, researchers, regulatory authorities, company executives, etc., and suggests a systematic approach which they could use for assessing and managing the risk of exposure. Strategies and suggestions mentioned in this study represent an effective and efficient exposure management system for many cases and workplace environments.

Recommendations for future research

Research investigating the potential API exposure among pharmaceutical industry workers is insufficient. The body of literature should, therefore, be enriched by performing similar studies about the potential API exposure, which is the main hazard to pharmaceutical production workers. There is only a small body of literature investigating the potential occupational exposures to new-generation cancer drugs. In order to evaluate the potential risk of exposure, these studies may be validated with different APIs or API classes.

Results obtained with the air monitoring method may be compared with results obtained with the surface monitoring method.

The potential exposure results obtained with environmental monitoring methods can be compared with the exposure results obtained from the workers' body fluids, and the effectiveness of OHS procedures can be evaluated.

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