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Pharmaceutical illness related...



INTEGRATIVE REVIEW OF THE LITERATURE

Adoecimento pelo trabalho de farmacêuticos-bioquímicos: revisão integrativa da literatura

Pharmaceutical illness related to work: integrative literature review

Enfermedades relacionadas al trabajo en los farmacéuticos: revisión integradora de la literatura

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ABSTRACT

Objetive: investigate in the literature ways of developing occupational diseases in the professional category of pharmaceuticals-biochemical and the strategies used for prevention occupational injuries and illnesses among these health professionals. Method: it is an integrative literature review, which search strategies was by consultation in Lilacs, Pubmed (Medline), ISI Web of Knowledge and Scopus databases, during the period of 1986 to 2010 and the following key-words were selected: accidents, occupational; chemical contamination; occupational health; control and prevention; accident prevention; disease prevention; health personnel; pharmaceutics and biochemical. Results: a total of eight articles were selected and classified according their level of evidence. The mutagenic risk, caused by the handling of chemotherapeutic agents, was the most frequently risk reported. Conclusion: some reports of occupational cancer and cytogenetic alterations were have been reported, but further investigations are necessary to prove the real cause. Descriptors: pharmacists, occupational risks, occupational accidents, occupational health.

RESUMO

Objetivo: investigar na literatura as formas de adoecimento pelo trabalho na categoria profissional dos farmacêuticos e bioquímicos causados pela exposição a agentes químicos e as estratégias utilizadas para prevenção de adoecimentos e acidentes de trabalho entre esses profissionais. Método: trata-se de uma revisão integrativa da literatura, realizada nas bases de dados eletrônicas Lilacs, Pubmed (Medline), ISI Web of Knowledge e Scopus, no período de 1986 a 2010, utilizando os descritores e palavras-chave: acidentes de trabalho; contaminação química; saúde do trabalhador; prevenção e controle; prevenção de acidentes; prevenção de doenças; pessoal da saúde; farmacêuticos e bioquímicos. Resultados: um total de oito artigos foram selecionados e classificados segundo o nível de evidência. O risco mutagênico, ocasionado pela manipulação de quimioterápicos, foi relatado com maior frequência. Conclusão: alguns casos de câncer ocupacional e alterações citogenéticas foram descritos, porém sugere-se maior investigação para comprovação da causa. Descritores: farmacêuticos, riscos ocupacionais, acidentes de trabalho, saúde do trabalhador.

RESUMEN

Objetivo: investigar, en la literatura, las formas de enfermedades causadas por el trabajo en la categoría profesional de los farmacéuticos y bioquímicos y las estrategias utilizadas para la prevención de lesiones y accidentes do trabajo relacionados a estos profesionales. Método: el estudio se trata de una revisión integradora de la literatura, cuya estrategia de búsqueda fue por consulta a las bases de datos electrónicas, en el período de 1986 hasta 2010 en las bases de datos Lilacs, Pubmed (Medline), ISI Web of Knowledge y Scopus. Los seguintes descriptores fuerón utilizados: accidentes de trabajo; contaminación química; salud laboral; prevención de accidentes; prevención de enfermidades; personal de salud; farmacéuticos e bioquímicos. Resultados: un total de ocho artículos fueron seleccionados y clasificados según el nivel de evidencia. El riesgo mutagénico, causado por la manipulación de agentes quimioterápicos, fue relatado con la mayor frecuencia. Conclusión: algunos casos de cáncer profesional y alteraciones citogenéticas han sido descritos, pero se sugiere más investigaciones para probar la causa. Descriptores: farmacéuticos, riesgos laborales, accidentes de trabajo, salud laboral.

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INTRODUCTION

he theoretical framework of Worker Health has as its object of study the health-disease processes of human groups in their relationship to the job, seeking the understanding of how and why these processes occur. As well as the development of alternative forms of intervention, that will lead to their transformation. Actuation in health promotion has as its fundamental objective the appreciation of the human being in its totality, contributing to the reduction of accidents and diseases related to labor. ²

The occupational risks originate from unhealthy or dangerous situations, defined as all conditions or factors existing in the work environment that may generate damage to workers' health and are classified into: physical, chemical, biological, ergonomic and psycosocial.³

The regulatory Standard No. 09 (NR 9) considers as chemical agent substances, compounds or products that can penetrate the organism by the respiratory route (dust, smoke, haze, fog, gasses or vapors) or that may have contact or may be absorbed by the body through the skin or by ingestion.⁴

The physical damage related to chemical exposure include irritation from skin and eyes, minor burns, up to poisoning and toxicity. In a general way, chemical substances are introduced in the area of health in its various states, such as gasses, vapors and liquids for use in sterilization, disinfection of materials, anesthetics and drug treatments for patients like, for instance, chemotherapy.⁵

In the hospital, when exposure to antineoplastic agents occurs without the proper follow-up of appropriate safety recommendations, workers may be exposed to the risk of contact and/or absorption of chemical agents whilst carrying out activities. This includes manipulation of antineoplastic agents, preparation of doses to be administered, administration of the medication to the patient and contact with excretions of the patient in treatment interruption.

Scientific evidence shows that professionals in the hospital area with greater involvement in such activities are the area of nursing and pharmacy. In addition, other groups are also exposed, even that is not acting in a hospital environment, as for example, the individuals who work in pharmaceutical industries, the cleaning staff and the researchers.⁶

In relation to professional pharmacists-biochemists, with the growth of the profession and the great diversity of tasks performed, these professionals are subject to risk factors of physical, chemical, biological and ergonomic nature when performing their of its activities, in addition to the risks of organizational and psychosocial nature.⁷

A bibliographic study⁸ revealed that great attention should be given to the sector of pharmacy and radio-pharmacy, due to excessive workload, failures in the use of Personal

Protection Equipment (PPE), budgetary constraints and professional burnout identified by surveys carried out with professionals of this area.

Research carried out with the objective to verify the occurrence of work-related accidents in the biennium 2002-2003 through the assessment of 570 health professionals practicing in public hospitals in the Federal District, showed an index of 17.6% of accidents with biological material in the category of pharmacists-biochemists. However, there is little scientific evidence suggesting work-related accidents and illness within this occupational category through contamination by chemical agents.

With this in mind, this study was conceived to answer the following research questions:

- What are the causes of work-related accidents and illnesses of pharmaceutics and biochemists, caused by exposure to chemical risk?
- What are the proposed interventions for prevention of illnesses by working with this professional category?

Thus, the present study has to investigate in national and international literature the accidents and illnesses caused by exposure to chemicals in pharmacists and biochemists and the strategies used to prevent them.

METHOD

TYPE OF STUDY

The methodology adopted was the integrative review of literature that together with the systematic review composes the method of Practice Based on Evidence.¹⁰

The integrative review enables the understanding of a given phenomenon by means of knowledge on it, which leads to the identification of gaps yet to be investigated.¹¹

DEVELOPMENT OF THE RESEARCH STRATEGY

The following stages were observed, as recommended by the literature: 1 - establishment of the research question; 2 - search strategies (establishments of inclusion and exclusion criteria, data base and selection of studies); 3 - categorization of studies (extraction, organization and summarization of data); 4 - assessment of studies included in the review; 5 - interpretation of results and 6 - synthesis of knowledge. 10

The following descriptors and key words in Health Science (DeCS) were selected: accidents at work, chemical contamination, worker health, prevention and control, accident prevention, prevention of diseases, personal health, pharmacists and biochemists. Two authors of this research have worked independently in order to identify those descriptors and key words and cross them separately and in combination in the following databases: *Lilacs, Medline Pubmed* (), *ISI Web of Knowledge* and Scopus.

DEFINITION OF INCLUSION AND EXCLUSION CRITERIA

Articles on quantitative or qualitative methodology, on work-related accidents and diseases caused by exposure to chemical hazards among pharmaceutical and biochemical workers and the strategies for prevention of same; published in Portuguese, English and Spanish languages from 1986 thru 2010, available in the selected databases. The exclusion criteria was the unavailability of articles in their entirety.

With respect to the classification of the selected articles, classification of evidence level¹² was followed in order to compose a sample of studies. This classification is shown in Figure 1.

Evidence Level	Description		
1	Systematic Review (RS) or meta-analysis of all Randomized Controlled Trials (RCT) or relevant clinical guidelines based on RS of RCT		
2	2 At least one RCT well delineated		
3	Well-designed clinical Trials without randomization		
4	Case-control Studies and cohort well delineated		
5	RS of descriptive studies or qualitative		
6	6 Single study descriptive and qualitative		
7	Opinion of authorities and/or report of committees of experts		

Figure 1 - System of evidence classification, as to hierarchical levels of quality¹².

RESULTS AND DISCUSSION

The search in the databases delivered the following number of studies: Lilacs (1097); Medline (601); Scopus (965) and Isi Web of knowledge (536), totaling 3199 studies to be reviewed. After the exclusion of duplicates, 675 articles remained to be analyzed.

Many studies were excluded after reading the summaries, seeing that they would not meet the criteria for inclusion. Some studies that showed relevant summaries were, however, excluded after complete reading by the authors of the research for not addressing the exposure to chemical hazards or for relating to other professional categories. Other studies were excluded because they were not in accordance with the methodological criteria of classification level of clarity. After rigorous analysis of the studies, the final sample subsisted of eight articles.

The presentation and discussion of the results and conclusions were performed in a descriptive way, seeking answers to the questions raised initially. Among the studies included in the sample, three (37.5%) were of descriptive methodology, three studies (37.5%)

%) were experimental and one (12.5 %) retrospective cohort study. The type of methodology and the level of evidence of the studies are described in Figure 2.

N	Authors	The Study Design	Evidence Level
1	Gregoire, Segal, Hale ¹³	Descriptive-analytical study	6
2	Arrington ¹⁴	Descriptive study	6
3	McDevitt, Lees, McDiarmid ¹⁵	Descriptive-anal <mark>ytical study</mark>	6
4	Edling, Mr Friis, Mikoczy, Hagmar, Lindfors ¹⁶	Retrospective cohort study,	4
5	Welch, Deffenbaugh ¹⁷	Opinion of auth <mark>orities and reports of committee of experts</mark>	7
6	Hessel, Radon, Pethran, Maisch, Gröbmair, Sautter ¹⁸	Experimental study, non- randomized	3
7	Schreiber, Radon, Pethran, Schierl, Hauff, Grimm et al.	Experimental study, randomized	4
8	Tanimura, Yamada, Sugiura, Mori, Nagatta, Tadokoro et al.	Experimental study, non- randomized	3

Figure 2 - Presentation of the synthesis of articles included in the integrative review, according to the design of the study and classification of the level of clarity¹².

The studies brought the topic of factors of chemical risks through exposure to agents present in neoplastic and antineoplastic chemotherapy drugs, and its main findings are represented in Figure 3.

Authors	Periodical Publication	Topics Covered	Main findings
Gregoire, Segal, Hale ¹³	American Journal of Hospital Pharmacy	Exposure to chemotherapeutic agents and preventive strategies	Approximately 94% of the institutions used the Cab of Biological Safety and workers considered the need to join the majority of EPI. Some preventive strategies were cited.
Arrington ¹⁴	American Journal of Hospital Pharmacy	Exposure to chemotherapeutic agents and preventive strategies	Implementation of strategies for reducing exposure to chemotherapeutic agents, as to the multidisciplinary, training and continuing education.
McDevitt, Lees, McDiar mid ¹⁵	Journal of Occupational and Environmental Medicine	Exposure to chemotherapeutic agents	The analysis of samples of air and surfaces in a pharmacy and an oncology clinic indicated contamination by cyclophosphamide.
Edling, Mr Friis, Mikoczy, Hagmar, Lindfors ¹⁶	Scandinavian Journal of Work, Environment & Health	Exposure to chemotherapeutic agents	Identification of cases of cancer among the workers that have been manipulating chemotherapeutic agents, but the causality was not proven.
Welch, Deffenbaugh	American Journal of Health System	Exposure to chemotherapeutic agents and	The authors' opinions converge to the need for the constant presence of a pharmacist responsible during

Figure 3 - Presentation of the synthesis of articles included in the integrative review, according the approached risk and the main results.

The sample of studies confirms the occurrence of work-related accidents with exposure to chemotherapeutic agents, but it is not conclusive as to the causation of occupational diseases and diseases related to such exposure. Some studies have confirmed the presence of biological changes in workers due to exposure to chemical hazards, such as the presence of the excretion of the drug in the urine in excess quantities, thus showing the urgent need for interventions of corrective and preventive character.

Although the findings are not conclusively indicating causality of diseases generated by occupational contamination through the manipulation of various chemotherapeutic agents, the results suggest that the implementation of security measures directed to all workers, in a multi-disciplinary character, may reduce exposure and possible contamination of workers.

The articles selected for the sample composition treat chemical risks, in particular the carcinogenic, teratogenic and mutagenic risks originating from exposure to chemotherapy drugs.

The literature reveals that among the various types of occupational hazards to which workers in the area of health care are exposed, chemical risks represent exposure to agents and chemical substances common in work processes, among them: dust, smoke, haze, fog, gasses, vapors, substances, compounds or chemical products in geral.³ Among the activities of handling these substances, is the preparation and administration of medications that, if not carried out correctly, can cause from allergic reactions up to neoplasias.²

The adverse effects of exposure to chemotherapeutic agents were in 1993 still proposed as a potential problem for occupationally exposed populations.¹⁵ The authors evaluated exposure to antineoplastic agents through analysis of samples of cyclophosphamide (an alkylating compound classified as a carcinogenic, mutagenic and teratogenic human and animal), present in the air and on the surface of objects in a

pharmacy and oncology clinic of a university hospital, where the safety standards of the Occupational Safety and Health Administration (OSHA) were implemented.²

The results of the study mentioned above, included in this sample, 15 found rare air samples with detection of drugs, but several samples of surfaces showed measurable concentrations of cyclophosphamide, indicating that the staff of the pharmacy can be exposed even with the use of the Cab of Biosafety (CSB). These results bring implications for healthcare professionals who handle antineoplastic and, according to the authors, show several situations that allow the occurrence of exposure by digestive and epidermal ways.

Chemotherapy drugs are used in the treatment of some diseases, one of which is cancer. In this case, they destroy the tumor cells, and so are classified as oncogenic. For this reason, the handling of this type of medication, without strict observation of appropriate standards and security procedures recommended, can lead to numerous toxic effects to the worker that handles them.

One of the studies analyzed 16 verified exposures to antineoplastic agents by means of the evaluation of the cancer cases in workers of a pharmaceutical company in Sweden. The findings identified 72 cases of incidence of cancer in this population. This number is lower than the rates of incidence of cancer expected, 74 cases, for the Swedish population in general. This study identified four cases of acute leukemia and eight cases of urogenital cancer by the workers of the company. These indices were considered significant, but it was reported that this finding cannot be related to any specific chemical exposure, due to other causal factors intrinsic to the development of a cancer.

Literature findings indicate that a study of bibliographic review conducted with nursing workers, showed that these workers had chronic damage possibly originated from exposure to antineoplastic agents (liver damage and nasopharyngeal carcinoma). In that study it was highlighted that intravenous drugs, including chemotherapy, in past decades were prepared without the proper adherence of workers to the standard precautions. It was however concluded that in none of the cases reported, the causal relationship managed to be firmly established, there is the possibility that, in the majority of cases, the causal relationship is only speculation.²³

Due to the risk of accidents and occupational diseases originating from exposure to antineoplastic agents, the adverse effects of exposure to chemotherapeutic agents have been studied and the risk of exposure and contamination among health workers is a reality. Among these workers, pharmacists, responsible for preparation of drugs, present a higher risk to exposure to chemotherapeutic agents than nurses, who handle and administer the same.²⁴ According to the author of this study, the effect of chemotherapy is considered desirable in patients in treatment, but are not acceptable when they occur as a result of an occupational exposure.

The risks of chemotherapeutic agents for the long-term health are less well known, but some authors^{16,24} reported occurrences of chronic effects, such as: reproductive problems, abnormalities of chromosomes and cancer development in pharmacists, but the specific causality towards the manipulation of antineoplastic and loop diuretic still needs further study.²³

Some authors $^{23-4}$ reported that the chemical exposure to antineoplastic agents is a problem for the health, and even in small quantities can cause damage to the exposed

worker. The excretion of cyclophosphamide was found in technical professionals (pharmacists, nursing technicians and nurses) who manipulated chemotherapeutic agents and in some cases, the detection of drugs was also present in the urine of those who do not directly manipulate.²³ These workers reported symptoms, such as skin irritation, sore throat, cough, malaise, headache, allergic reactions, diarrhea, nausea and vomiting.²⁴

Contamination of the environment can result in contamination of workers not involved in handling. This fact was observed in an experimental study present in the studied sample¹⁹, carried out with samples of urine 24 hours earlier harvested from 87 technicians of pharmacy and pharmacists from 14 hospitals in Germany to investigate the presence of antineoplastic agents, aiming to verify the influence of different working conditions observed during the preparation of cytostatic drugs. The results showed at least one positive result of urine for cytostatic agents in 56 (64 %) participants in the sample, while 32 (37 %) workers presented more than one cytostatic agent in their urine.

The authors of the study concluded that both the workers who act as assistants during the preparation of antineoplastic agents as those who work directly in the preparation of them, did not show differences in relation to the frequency of exposure to cytostatic drugs. The same was observed with the workers who alternate the two functions and it was suggested that both were included for review and implementation of protective measures and disposal of the recommended safety precautions.

The work conditions were also verified in this study, defining them as: tasks performed and the different forms of execution; conditions of cleaning up the environment; disposal of cytostatic agents; number of preparations; quantity of substances handled and the use of gloves (considering the type of material, thickness and interval). The conclusion was that the absorption of antineoplastic agents happens during work routine and that the increase in the number of preparations carried out can lead to an increased exposure to workers who work in preparation and administration of chemotherapeutic agents. ^{7, 19}

A study conducted in Japan and selected to compose the sample²⁰, evaluated the level of cyclophosphamide present in 24-hour urine of pharmacists who prepare chemotherapeutic agents. The drug was detected in urine samples of pharmacists, even with the use of security measures and protection to the worker. However, after further review and implementation of the measures of safety precautions related to the manipulation of chemotherapeutic agents, a decrease of the presence of the drug was observed, although the authors report that this difference is not statistically significant.

Findings in the literature are convergent with the reduction of exposure of workers after the implementation of the measures of occupational safety. It was concluded that there was a reduction of cytogenetic alterations in health care workers after the imposition of specific measures of security, such as the use of protective equipment for workers' safety and compliance with the recommendations of *guidelines*.²³

An experimental study, included in the sample¹⁸, aimed at examining the frequency of genotoxicity induced by chemotherapeutic agents in a sample of 247 workers of pharmacy and nursing by means of blood collection and used a control group with 60 workers in offices, who had no exposure to such medicines. Among the results, the authors identified that there were no significant differences in the analysis of the frequency of toxicity caused by exposure to cytostatic agents in exposed individuals and that the

comparison of the frequency of genotoxicity by time of occupational exposure not suggested an time-dependent accumulation for mutagenic effects.

Another study included to compose this review aimed to assess the practices of manipulation of chemotherapeutic agents in cancer treatment centers and check the attitudes of workers involved in the handling of these drugs. Thus, a survey was carried out involving four categories: use of PPE and Collective Protection Equipment (EPC); practice of workers; policies and institutional procedures for security and observation of possible spills and disposal of the medicines.¹³

Among the results of this study, the researchers found that more than 94% of the institutions used cab of biosafety (CSB). The majority of workers considered the use of gloves and disposable static jackets of great importance, as with raincoats with closed sleeves, but denied the importance of using footwear and balaclavas. In addition, it was found that the absence of specific tests for the assessment of the concentration of exposure of workers during the preparation of chemotherapeutic agents, as well as the limits of exposure, and the rest periods were defined for only 6% of workers.

Available literature shows that some chemicals can cause side effects to health professionals that handle them. For this reason, they must be handled in CSB, used as primary containment in working with agents of biological and/or chemical risk. The CSB are able to minimize the exposure of the operator, the product and the environment and should be used in conjunction with the EPI.²⁵

In a study carried out in Brazil with 30 nurses who manipulated and administrated chemotherapeutic agents in a university hospital, it was found that 40% had no information on the purpose and use of a laminar flow; 56,70% claimed to have knowledge, and 3.30% did not respond. The study found, by means of workers reports, the occurrence of work-related accidents with dermal exposure to antineoplastic agents in 16.7% of the professionals, which occurred during the dilution of these agents²⁶. In this study, the professionals who participated did not follow the recommendations of the Brazilian Ministry of Health ²⁷⁻⁸ and OSHA.²⁹

The standards recommended by OSHA, concerning the handling of antineoplastic agents, determine the required PPE for handling of chemotherapeutic agents: the use of gloves (long, disposable, not pinched, manufactured with latex or polypropylene, with a thickness between 1.8 to 2.3 mm or the use of two pairs of these); aprons with closed front, long sleeves, cuffs with elastic bands and disposable; masks with protection of activated charcoal; goggles, caps and footwear. As collective protection equipment (EPC), it establishes the use of chapel of vertical laminar flow class II, type B. 20.29

In relation to the strategies used for the prevention of illness and accidents at work, the studies presented some methods to control exposure, such as biological and environmental monitoring and the awareness and training of work teams in order to improve compliance with the recommendations of existing security.

Among the strategies of prevention mentioned in the analyzed studies the transfer of pregnant women or mothers in breastfeeding for sectors with less exposure to various risks was presented as a follow-up of standard precautions and development of policies for legal counseling to workers in some cancer treatment centers. Regarding the method of

chemotherapy waste disposal, was cited the incineration of the same as the method most used by the majority of treatment studied centers.¹³

Another included study¹⁴ developed in a university institution, taking as a reference the first *guideline*²² for safe handling of antineoplastic agents, showed the importance of the implementation of strategies aimed at the reduction of exposure to chemotherapeutic agents, highlighting the development of a multidisciplinary program for safety in the handling of chemotherapeutic agents. The communication with the team of pharmacists, considering the adoption of implementations of the program and the need for awareness of workers with respect to adherence to safety recommendations, contributed significantly to the realization of the project. Among other actions, the above study has deployed a training program for workers who deal with antineoplastic every two years and the maintenance of a process of continuing education with all workers.

The literature refers to the recommendations of occupational safety published in guidelines not being followed properly, although the fulfilment of standards has progressed since the release of the guidelines by OSHA^{22, 29} when the health institutions have established policies for the follow-up to the precepts of security. The awareness of the potential risks of exposure is not universal and the implementation of the recommendations of these guidelines is not complete and should be exploited. Due to the risk of contamination by aerosols, the masks with filter N-95 respiratory protection must be used, in particular, during the exchange of gloves used in the preparation of medications. Devices with closed systems in locations where there is preparation of chemotherapy must be implemented.²³

In Brazil, researchers analyze the problems related to the exposure of workers to chemical agents, stating that the implementation of the activities of workers still occurs in precarious conditions, without regard to the safety and hygiene of the work, and without guarantees of a decent work. For these authors these problems are not recent, but are growing, due to the availability of new substances and the growth in their use, only continues.³⁰

Study on the views of authorities, chosen to compose the present sample regarding the issue of exposure to chemical hazards resulting from chemotherapy, points out that their manipulation can bring serious and fatal consequences to patients, health care teams and the community. A preventive strategy to the occurrence of accidents at work would be the constant presence of a pharmacist during the manipulation of these drugs, conducting the assessment, the coordination, preparation, administration and the correct disposal thereof.¹⁷

Thus, from the analysis of preventive strategies, aiming to reduce the exposure of pharmacists to antineoplastic agents, it was observed that the planning and implementation of security measures can be effective in reducing contamination of workers. Simple measures like as the standard precautions and planning and implementation of multidisciplinary programs aiming at the prevention of accidents and better communication between the team, have achieved good results. However, it can be inferred, by means of the analysis of the studies included, that the implementation of security measures is an ongoing process based on periodic training, continuing education,

permanent updates and constant evaluations, with views to the prevention and control of diseases present in occupational environment.

CONCLUSION

With regard to the findings of the studies, in a general way, the tests of environmental and biological monitoring cited were not conclusive relating to the illness of workers exposed to antineoplastic agents, but many have found the real contamination by chemotherapeutic agents who directly or indirectly deal with these substances. In this way, it is suggested that further studies be carried out to ensure that the causality of occupational diseases due to exposure to chemotherapeutic agents can be proven.

The results mark the absence of national Brazilian literature in the sample of studies included in this integrative review, which highlights gaps in Brazilian scientific production.

The evidence presented herein are an advancing scientific knowledge in the area of worker health and corroboration of strategies in health that are planned in a preventative character. The results also reported that the follow-up of standard precautions by professionals and the attention directed at the prevention of work-related accidents and illness on the part of health institutions contribute to the reduction of exposure to the risks inherent in the work processes and lead to the promotion of the health of workers.

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