



Preventing occupational exposure to cytotoxic and other hazardous drugs

European Policy Recommendations



European Parliament

Dear readers,

There is no denying that health and safety at the workplace, which is and has been at the forefront of the European policy agenda, has seen positive trends over recent years and can be considered one of the successes of the European Union. However, much remains to be done with regard to the protection of workers against exposure to carcinogens, mutagens and substances that are toxic to reproduction.

This is clearly imperative in the healthcare sector, where, as recognised by the European Parliament in November 2015 in its Own Initiative Report on the EU strategic framework on health and safety at work 2014-2020, many healthcare workers are exposed to hazardous chemicals in their workplace. Aware of the need to protect healthcare workers from chemical risks, the European Parliament further called on the Commission to take action on chemical risk factors in the healthcare sector and to include specific provisions on healthcare workers' exposure to hazardous drugs in the OSH strategic framework.

As policy makers we are committed to ensuring healthcare workers' health and safety at the workplace across the EU and to take practical steps to protect them from the most dangerous chemical risk factors in healthcare, cytotoxic drugs.

This is of uppermost importance in light of the health hazard posed by these drugs with potential carcinogenic, mutagenic and reproduction toxic effects. But we are also convinced that good safety and health performance is an important contributor to the sustainability of European's healthcare sector by increasing morale and preventing absenteeism and early retirement of healthcare staff.

This is a critical time for European healthcare, when our ageing population combined with the rising incidence of diseases, such as cancer, places unprecedented pressure on healthcare systems and is leading to a surge in the demands placed on healthcare workers.

The information, expertise and policy recommendations contained within this paper need to be acted upon by policy makers at European Union and national level. We urge the Commission and all member states to work together to rapidly and effectively implement these recommendations so that healthcare workers receive the protection that they deserve.

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Active in the pharmaceutical press, he is an associate editor of the Journal of Oncology Pharmacy Practice and formerly editor in chief and founding editor of the Journal of Hospital Pharmacy Science, an official journal of European Association of Hospital Pharmacists.

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Mr. Vandenbroucke participated in the elaboration of the ISOPP Standards of Practice for the Safe Handling of Cytotoxics (2007) and is the author of numerous publications on the protection of healthcare workers.

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I. Recommendations

- **Recommendation 1:** In order to face an increasing occupational challenge, the EU and Member States should pay greater policy attention to the risk posed by the exposure of healthcare workers to chemical risks during activities such as the preparation and administration of cytotoxic drugs, given their consequences to healthcare workers' health.
- **Recommendation 2:** The EU should consider the prevention of the potential risks associated with working with cytotoxic drugs as part of a long term strategy for the sustainability and resilience of the healthcare systems.
- **Recommendation 3:** Policies at the European and national level should be consistent with the reality of the serious health hazard posed by cytotoxic drugs for medical personnel not properly protected. Specific policy measures, which take into account the wide range of professionals concerned as well as the different routes of exposure, are required to ensure prevention of healthcare workers' exposure to cytotoxic drugs.
- **Recommendation 4:** The prevention of occupational diseases due to exposure to cytotoxic drugs should be specifically addressed in the European legislation. European recommendations for the promotion of successful prevention should be issued by the European Commission.
- **Recommendation 5:** The EU should promote the establishment and adoption of common minimum standards across Member States for the safe handling of cytotoxic drugs. In this harmonisation exercise, the 'International Society of Oncology Pharmacy Practitioners (ISOPP) Standards of Practice Safe Handling of Cytotoxics' should be taken into consideration as a minimum standard.
- **Recommendation 6:** Appropriate personal protective equipment (PPE) should be made available to all healthcare workers who may come in contact with cytotoxic drugs. However, the use of personal protective equipment need to be preceded by other protecting measures.
- **Recommendation 7:** European legislation should establish a common definition for Closed-System Drug Transfer Devices (CSTDs), which details the technical specifications to be met by a medication transfer system to be considered as a closed system, using the definitions established by the National Institute of Occupational Safety and Health (NIOSH) and ISOPP as a basis and taking the system of the American Food and Drug Administration (FDA) with the ONB classification as an example. Harmonised protocols for testing CSTD should be established.
- **Recommendation 8:** In order to improve healthcare workers safety, policies at the EU and national level should promote the use of effective CSTD, which have the potential to protect healthcare professionals from being exposed to cytotoxic drugs.
- **Recommendation 9:** The EU and Member States should promote that all the healthcare professionals involved in the handling of cytotoxic drugs are provided with suitable, sufficient and regular information and education relevant to their work.
- **Recommendation 10:** The European Commission should ensure the provision of suitable decontamination, cleaning and disinfection guidelines based on surface contamination levels and types of drugs. The Commission and Member States should ensure that these guidelines are effectively implemented.
- **Recommendation 11:** The Commission should develop basic guidelines on the regular monitoring of healthcare workers' exposure to cytotoxic drugs. The Commission and Member States should ensure that these guidelines are effectively implemented.

II. Background

“The EU needs to address more effectively the impact of the interaction of Occupational Health and Safety (OHS) with the environment and chemicals”, highlighted the European Commission in the results of the evaluation of the 2007-12 OHS strategy.¹

This recommendation is particularly imperative in the healthcare sector. While the majority of occupational hazards have been successfully addressed by legislation at the European and national level, much remains to be done when it comes to the exposure of healthcare workers to chemical risks during activities such as the preparation and administration of cytotoxic drugs used to treat patients with cancer. These drugs represent the most dangerous chemical risk factors in healthcare² and some of the most hazardous chemicals ever developed.³

The workplace exposure to dangerous drugs and the resulting health risks for healthcare personnel have been well known and documented for over four decades, since it first became a recognised safety risk in the United States in the 1970s.⁴ Nowadays, the challenge of protecting workers persists and is expanding, for a number of reasons. Firstly, the incident rate of cancer is steadily increasing and, in turn, the use of cytotoxic drugs used to treat cancers is growing, amplifying the exposure to healthcare professionals.

Secondly, the number and variety of healthcare workers potentially exposed to cytotoxic drugs is on the rise (e.g., professionals in immunology, rheumatology, nephrology and dermatology) because of the rapidly expanding use of these agents in non-oncology practices for treating non-malignant diseases.

Thirdly, recent studies have demonstrated a persistence of drug contamination on surfaces even though guidelines and recommendations for the safe handling of cytotoxic drugs have been issued and implemented by Member States to minimise the risk of occupational exposure. Moreover, contamination has been detected on work surfaces after recognised cleaning procedures are concluded.

Last but not least, cytotoxic drugs use is on the rise as the population ages and new technology allows people a wider range of medical treatment.

While the risk posed by cytotoxic drugs is recognised by the European Agency for Safety and Health at Work⁵ and publications from the Directorate-General for Employment, Social Affairs⁶ as well as through national guidelines in Member States, there is currently no harmonised approach to the prevention of this chemical risk in the healthcare sector properly reflected in European legislation.

Recommendation 1

- In order to face an increasing occupational challenge, the EU and Member States should pay greater policy attention to the risk posed by the exposure of healthcare workers to chemical risks during activities such as the preparation and administration of cytotoxic drugs, given their consequences to healthcare workers' health.

The above, in spite of the fact that providing safer and healthier conditions in the workplace for healthcare workers is key to improve job quality and working conditions across Member States and to allow them to work for longer. Reflecting a clear Commission initiative, it would contribute to addressing the long-term effects of demographic ageing, in line with the Europe 2020 strategy's objectives for smart, sustainable and inclusive growth.⁷ This would eventually help to ensure a better retention of the healthcare workforce in a context where most EU countries report difficulties in retaining and recruiting health staff with increasing shortages predicted in the longer term.^{8 9 10 11 12} It is also noteworthy that the healthcare sector constitutes one of the most significant sectors in the EU economy, whose demand will increase dramatically with Europe's ageing population.^{13 14}

Recommendation 2

- The EU should consider the prevention of the potential risks associated with working with cytotoxic drugs as part of a long term strategy for the sustainability and resilience of the healthcare systems.

In light of these considerations, it is imperative to appreciate the dangers of these hazardous medications, to adhere to the safety mechanisms, and to use the available safety resources in order to avoid the potential risks associated with working with these agents. Continuous education of healthcare providers is fundamental to ensuring safety and positive outcomes. Safe handling procedures can be implemented by adhering to appropriate standards and consistently integrating them into policies.

The EU must commit to a new era of safe hazardous medicine handling by specifically addressing in its legislation the issue of healthcare workers' exposure to hazardous drugs and chemicals, in particular during the preparation and administration of cytotoxic drugs. This must be addressed by harmonising national provisions relating to the protection of workers by measures to prevent exposure or to keep exposure at a level as low as possible.

III. Cytotoxic drugs: definition, use and risks

Cytotoxic drugs (also referred to as cytostatic or antineoplastic drugs) describe a group of medicines designed to destroy cells that grow in a rapid and uncontrolled manner, preventing their replication or growth.

Worldwide, these medicines are increasingly being used in a variety of healthcare settings, prominently in the treatment of cancer.^{15 16} They also play an important role in haematology and rheumatology and are used to treat non-cancerous diseases such as multiple sclerosis, psoriasis and systemic lupus erythematosus¹⁷, leading to a growing use of these drugs.

The cytotoxic drugs available for current use are generally non-selective, meaning that they do not differentiate between malignant cells and normal healthy tissue and are therefore likely to damage normal (non-tumour) cells, resulting in adverse health effects.^{18 19 20}

By virtue of this, cytotoxic drugs, which have been described as some of the most hazardous chemicals ever developed²¹, are included within the definition of 'hazardous drugs', i.e., those that are known or suspected to cause adverse health effects from exposures in the workplace.^{22 23}

The number of preparations and administrations of cytotoxic and other hazardous drugs in Europe is continuously growing because of the demographic development (as the population ages, many diseases that predominantly affect older individuals, such as cancer, will become more prevalent) and expanded therapeutic possibilities.²⁴

CYTOTOXIC



**HANDLE
WITH
CARE**

IV. Healthcare workers' exposure to cytotoxic drugs

Sold in powder or as a concentrated solution, a form where a drug is more stable, cytotoxic drugs require individual manipulation for each patient prior to being administered as infusions or bolus injections.^{25 26} This may lead to errors, spillages, needle stick injuries and (spread of) contamination, which pose clear health risks to healthcare workers.²⁷ Moreover, cytotoxic drugs may evaporate and form a gas during normal handling which may result in inhalation of the drugs.²⁸

It has been well documented that healthcare workers who handle cytotoxic drugs are at potential risk from exposure when control measures are inadequate. Scientific studies have shown that the risk of exposure to them in the working environment is commonplace despite safety policy improvements and even with recommended precautions in place.^{29 30 31 32 33 34 35 36} This is due to, amongst other reasons, the increasing utilisation of with cytotoxic drugs in treating patients with malignancy, which has led to the potential for widespread exposure of healthcare workers who come into contact these agents in the work place.³⁷ Moreover, with the use of cytotoxic drug expanding into other specialties, the number of workers who are not properly trained in their safe handling has seen an increase.³⁸

Another important consideration is that, while patients receive concentrated doses of a limited number of cytotoxic drugs for a defined period of time, healthcare workers may be exposed to small doses of a broad range of with cytotoxic drugs over decades, with some workers being exposed every workday, year after year.³⁹

In particular, nurses, pharmacists and pharmacy technicians have the highest risk of being potentially exposed.^{40 41 42 43 44 45} Besides these professionals, other healthcare, para-professional healthcare and non healthcare workers, involved in cleaning, transport, laundry and waste disposal of hazardous drugs or contaminated material, are also concerned.^{46 47 48 49}

Scientific data has confirmed that sporadic exposure affects nurses more than pharmacists and pharmacy technicians.⁵⁰ However, it needs to be noted that, because pharmacists handle pure drugs during the preparation phase, they are exposed to much more concentrated drugs. Amongst the nurses, who commonly handle many different cytotoxic drugs and in most cases in combination^{51 52 53}, auxiliary nurses appear to be more contaminated.⁵⁴

Workers may be exposed to these hazardous drugs by inhalation of contaminated air or by skin contact with contaminated surfaces, clothing and medical equipment^{55 56 57 58 59}, throughout the life cycle of the drug (e.g., from manufacturing to transportation and distribution, unpacking and storage, during the preparation of infusions, the in-house transport of inadequately packaged infusions and infusion syringes, the application of cytotoxic drugs on the wards, cleaning activities, waste disposal...etc.).⁶⁰

The more common routes of exposure are,⁶¹

- Skin or mucous membranes contact and absorption;^{62 63}
- Inhalation of aerosols, vapours, dusts and drug particles in the air;^{64 65 66}
- Ingestion (e.g., through eating, drinking or smoking in contaminated areas or from poor hygiene),^{67 68 69}
- Sharps/injections.⁷⁰

Whereas inhalation and ingestion represent a small possibility of exposure, skin contact is the most problematic route, which can occur even in the top or most modern healthcare centres.

The extent of exposure and the likelihood that a worker will experience adverse effects from cytotoxic drugs are influenced by a number of different factors, including the following:^{71 72 73 74 75}

- Drug handling circumstances (preparation, administration, or disposal);
- Amount of drug prepared;

- Laboratory throughput;
- Frequency and duration of drug handling;
- Personnel expertise and training (i.e., participation of professionals with academic education in drug admixture activities);
- Potential for absorption;
- Use of ventilated cabinets, personal protective equipment and/or special devices during preparation and/or administration;
- Patient care.

Job titles that may involve exposure to cytotoxic drugs:

- 1. Pharmacists and pharmacy technicians;
- 2. Nurses;
- 3. Physicians and physician assistants;
- 4. Operating room personnel;
- 5. Home healthcare workers;
- 6. Veterinarians and veterinary technicians;
- 7. Environmental service workers (housekeeping, laundry, maintenance workers);
- 8. Workers who ship, transport or receive hazardous drugs;⁷⁶
- 9. Other professional healthcare workers.⁷⁷



V. Hazardous effects of cytotoxic drugs on healthcare workers

Although the potential therapeutic benefits of cytotoxic drugs outweigh the risks of side effects for ill patients, exposed healthcare workers may face adverse side effects with no therapeutic benefit.

The health hazard for medical personnel handling these drugs is a major concern as they are not only classified as potentially carcinogenic, but also mutagenic or toxic to reproduction.^{78 79 80 81 82 83 84} Since cytotoxic drugs are highly effective active substances, exposures to even very small amounts of certain drugs may be hazardous for workers who handle them or work near them, especially if this happens continuously, day by day over many years.^{85 86}

The European Commission has recognised that, while there are no scientifically documented dose-response relationships with respect to the carcinogenic, mutagenic and reproduction-toxic potential of cytotoxic drugs for quantities taken far below a therapeutic dose.⁸⁷

As mentioned below, the health risk is influenced by the level and frequency of exposure, the toxicity of the drug, the existence of proper work practices and amongst other factors.^{88 89 90 91 92}



Surveys, done primarily with nurses, have associated workplace exposures to cytotoxic drugs with acute health effects and/or chronic effects.^{93 94 95} Indeed, increased genetic damage has been demonstrated in nurses^{96 97 98 99 100 101 102 103 105 106 107 108 109 110 111}, particularly in day hospital nurses^{112 113 114}, the group handling the highest amount of drugs during the administration process.

Importantly, the effects of exposure may be subclinical and not be evident for years or generations of continuous exposure.¹¹⁵ For example, as cancer often takes decades to emerge, a case of leukaemia diagnosed in a nurse or in a pharmacist today might be the product of workplace exposures in the 1970s or the 1980s. Unfortunately, in many instances, the connection between work and disease is never made.¹¹⁶

1. Acute effects

Acute effects can last for weeks or months.

Many cytotoxic drugs are extremely irritant and have harmful local effects after direct contact with skin or eyes as observed in patients. Acute effects reported include dizziness, nausea, headache, dermatitis and menstrual problems.^{117 118 119 120 121 122 123 124}

The number of symptoms present is significantly associated with the number of doses handled and the extent of protection.^{125 126}

Acute events are under-reported, which demonstrates the need for physician awareness regarding their management.¹²⁷

The special vulnerability of female workers

- *As recognised by the EU Strategic Framework on Health and Safety at Work 2014-2020, women can face specific risks, such as specific types of cancer, as a result of the nature of some jobs where they are over-represented.*
- *This is the case of nurses, who are traditionally and predominantly female, and many other female healthcare workers dealing with hazardous drugs.*

The special vulnerability of female workers

- *As a result of this, they may suffer not only from some types of cancer, but also from other effects that include infertility (temporary and permanent) or effects on reproduction and the developing fetus in pregnant women.*
- *In this regard, the changing composition of the increasingly female workforce cannot be disregarded. Women represent over 76% of the overall health professional workforce, and this proportion is growing.^{128 129} This needs to be taken into account as, in female-dominated work areas, taking a ‘gender-neutral’ approach to risk assessment and prevention can result in risks to female workers being underestimated or even ignored altogether.¹²⁹*

2. Chronic effects

Acute effects may last for years and include liver and kidney damage, damage to the bone marrow, damage to the lungs and heart, infertility (temporary and permanent), effects on reproduction and the developing foetus in pregnant women (e.g., smaller babies, malformations and abortions), hearing impairment and cancer.^{130 131 132 133}

a. Cancer

Although the extent of the risk of cancer is difficult to quantify¹³⁴, the International Agency for Research on Cancer (IARC) of the World Health Organisation (WHO)^{135 136 137 138 139 140} and scientific reports^{141 142} have identified a number of cytotoxic drugs as having an association with various forms of cancer.

However, the fact that a cytotoxic drug has not been classified as carcinogenic does not imply that it does not have this effect, often recognised by scientific bodies in different countries, as the Agency has not assessed all of them.¹⁴³

b. Reproductive effects

Adverse reproductive effects have been reported in healthcare workers with long-term, low-level occupational exposure to cytotoxic drugs.¹⁴⁴

The most common reproductive effects found are increased foetal loss^{145 146 147 148 149 150 151}, congenital malformations, low birth weight and congenital abnormalities and infertility.^{152 153 154 155 156 157 158 159 160} Learning disabilities in the children of nurses who had handled cytotoxic drugs have also been documented.¹⁶¹

“The frequency of spontaneous abortion was 26% for the exposed pregnancies and 15% in the unexposed ones.”¹⁶²

Recommendation 3

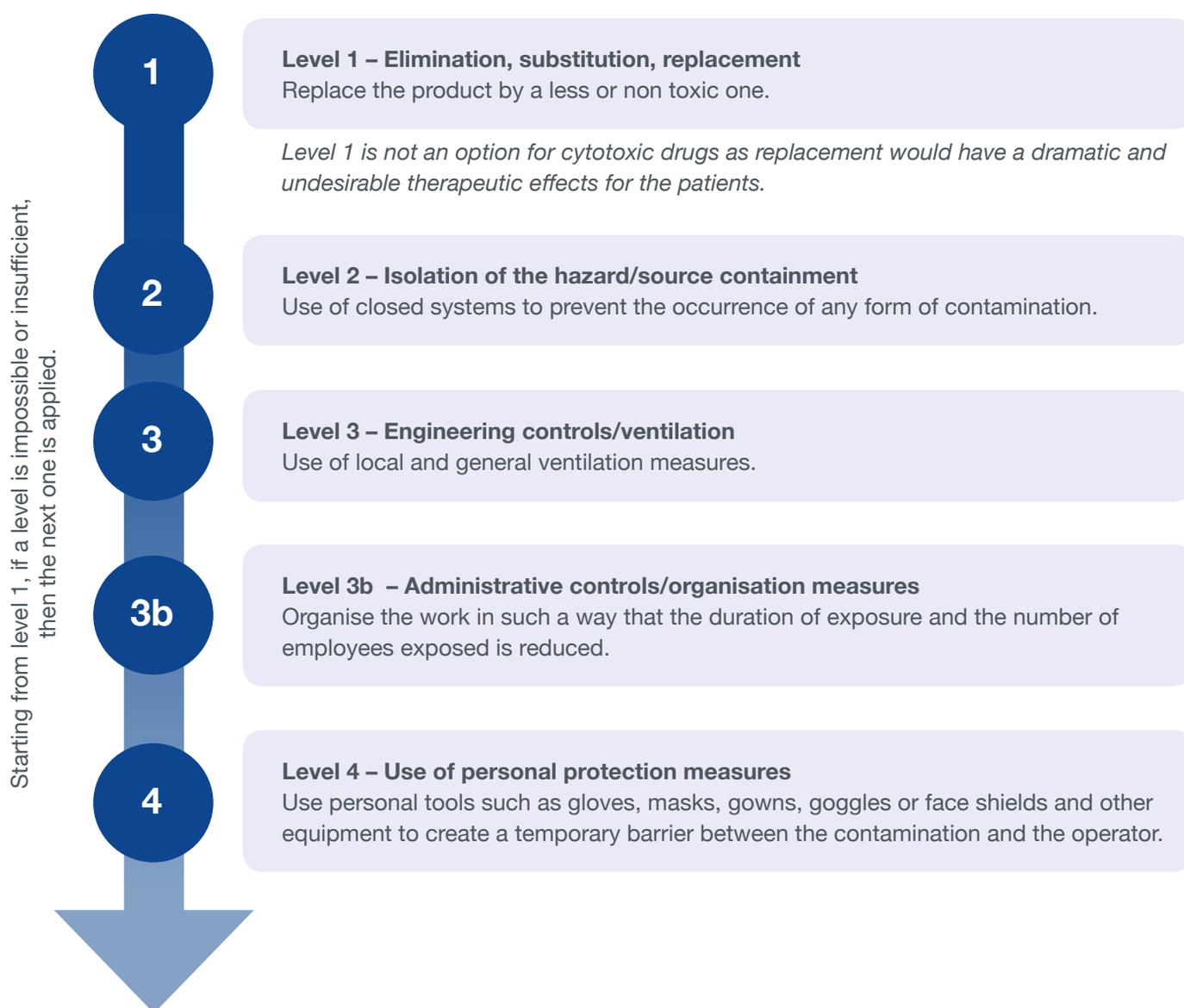
- Policies at the European and national level should be consistent with the reality of the serious health hazard posed by cytotoxic drugs for medical personnel not properly protected. Specific policy measures, which take into account the wide range of professionals concerned as well as the different routes of exposure, are required to ensure prevention of healthcare workers’ exposure to cytotoxic drugs.

VI. Standards for the safe handling of cytotoxic drugs

Since it was first recognised that occupational exposure to cytotoxic drugs posed a potential health risk to exposed workers, various groups, institutions and agencies around the world have developed and published different guidelines or recommendations for the safe handling of these agents.

On the basis of the existing regulations, guidelines, standards and recommendations, the International Society of Oncology Pharmacy Practitioners (ISOPP) produced in 2007 international guidelines under the title '*ISOPP Standards of Practice Safe Handling of Cytotoxics*'¹⁶³, covering all possible items related to the safe handling of cytotoxic medicines.

The ISOPP standard recommends that actions are taken in a hierarchical order of prevention (similarly to the *Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work*¹⁶⁴), as follows,



In Europe, levels 3 and 4 predominantly apply, with some hospitals applying level 2.

VII. Policy landscape in Europe

Not only has the European Commission recognised the clear role for the Union in helping Member States to address occupational risks more efficiently and in ensuring a level playing-field throughout the EU, but it has also emphasised the need to address more effectively the interaction of occupational safety and health with the environment and chemicals and the effective prevention of occupational and work-related diseases.¹⁶⁵

However, much remains to be done in the field of healthcare workers exposure to chemicals, which has not been specifically addressed in the European legislation.

European and national regulations, in the case of carcinogens, mutagens or substances toxic to reproduction, stipulate the identification of the exposure of workers and the regular check of the effectiveness of the technical protective measures taken by the employer.^{166 167 168} For both tasks, either workplace measurements or other methods to identify the exposure of workers are mentioned. In addition, the *'Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work'*¹⁶⁹ stipulates the measurement of carcinogenic substances for early detection of abnormal exposures resulting from unforeseeable events or accidents.

Recommendation 4

- The prevention of occupational diseases due to exposure to cytotoxic drugs should be specifically addressed in the European legislation. The European Commission should issue European guidelines for the promotion of successful prevention strategies.

However, while the above mentioned Directive sets occupational exposure limits (OEL), only a few are available nowadays. Besides, these OELs are only applicable for environmental air concentrations and not for surface contamination or skin contact. Recalling, as noted above, that there is more contamination from cytotoxic drugs on surfaces than in the air and that measurement of surface contamination is currently the only indication of the amount of environmental contamination in areas where hazardous drugs are prepared, administered to patients or handled¹⁷⁰, it can be concluded that OEL's are therefore not suitable for monitoring current working conditions in the healthcare sector.

At the national level, guidelines and recommendations for the safe handling of cytotoxic drugs have been issued and implemented by some Member States to minimise the risk of occupational exposure. However, because there are no harmonised standards of practice or guidelines, significant differences persist with regard to handling of cytotoxic drugs.

The European picture shows that, while some Member States have adopted the standards of the ISOPP (such as Belgium and Spain) or higher, standards in other countries do not reach the same level of protection or are non-existent. In some countries, such as Germany or the Netherlands, guidelines have been provided by scientists or national associations but not necessarily supported by the respective Governments.

Studies have demonstrated that despite the significant improvements in the safe handling of cytotoxic drugs that have taken place over the last twenty years and even though various guidelines and recommendations have been issued and implemented, contamination of the working environment and exposure of healthcare workers continues, which leads to the conclusion that additional steps must be taken at the national level to ensure the protection of healthcare workers.

Recommendation 5

- The EU should promote the establishment and adoption of common minimum standards across Member States for the safe handling of cytotoxic drugs. In this harmonisation exercise, the *'ISOPP Standards of Practice Safe Handling of Cytotoxics'* should be taken into consideration as a minimum standard.

VIII. How to prevent occupational exposure to cytotoxic drugs

It has been demonstrated that currently implemented safe handling practices of cytotoxic drugs are not sufficient to prevent occupational exposure¹⁷¹, in view of which the proper use of protective equipment and implementation of work-practices to avoid health hazards are paramount for the protection of healthcare professionals.

In order to provide workers with the highest protection, Member States must implement necessary administrative and engineering controls and ensure that workers use appropriate and validated procedures for handling hazardous drugs and proper protective equipment. Indeed, the use of safe handling practices and specialised drug handling equipment has proven to greatly reduce the potential exposure of healthcare workers to these drugs.¹⁷²

1. Engineering mechanisms

Engineering controls, used to remove the hazard or to place a barrier between the worker and the hazard, have been demonstrated to reduce environmental contamination and workers exposure.^{173 174} However, because these engineering controls have not been designed for chemical contamination but for prevention of microbiological contamination, contamination may still occur.

Examples of engineering controls include the use of biosafety cabinets, isolators and safety-engineered medical devices.

a. Personal protective equipment

Appropriate personal protective equipment (PPE) (which occupies the fourth place in the hierarchy of protection measures of the ISOPP standards) -protective gloves, gowns, eye protection, facial protection, respiratory protection apparatus, cap, shoe covers, etc. – should be made available to all healthcare workers who may come in contact with cytotoxic agents. Moreover, it is critical that healthcare workers be educated in the appropriate selection and use of PPE for protection against exposure to cytotoxic drugs.

The use of PPE should not be restricted to compounding and administering cytotoxic drugs in the pharmacy and patient treatment areas. Other places where PPE may be required include the loading dock where the drugs are received, inside vehicles that transport drugs to and from the pharmacy, storage areas, oncology patients' rooms, laundry services and waste disposal areas.

Nevertheless, while the use of personal protective equipment represent an important protection tool, they need to be preceded by other measures such as engineering controls and administrative controls as their protective capacity is only temporary and partial.

Recommendation 6

- Appropriate personal protective equipment (PPE) should be made available to all healthcare workers who may come in contact with cytotoxic drugs. However, the use of personal protective equipment must be preceded by other protecting measures.

b. Closed-System Drug Transfer Devices



Closed-system drug transfer device. European Commission Directorate-General for Employment, Social Affairs. 2011. "Occupational health and safety risks in the healthcare sector - Guide to prevention and good practice".

The basic tools and products used in standard drug compounding (e.g., needles, syringes, spikes, vials, bags, etc) are not designed to isolate the medications they manipulate; rather, they are intended to enable the activities of medication transfer, regardless of what substances are being manipulated. Thus, the level of safety provided by these tools becomes insufficient when manipulating and compounding cytotoxic products.¹⁷⁵

Closed-system drug transfer devices (CSTDs) (second place in the hierarchy of protection measures of the ISOPP standards), i.e., those devices which mechanically prohibit the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour concentrations outside the system, are the only devices that have been specifically designed to protect healthcare workers from occupational exposure to hazardous substances.¹⁷⁶

The use of CSTD has been widely recommended by different existing guidelines, standards or recommendations, such as the National Institute for Occupational Safety and Health (NIOSH) alert on Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings¹⁷⁷. In its guide for safe handling of cytotoxic drugs, the International Society of Oncology Pharmacy Practitioners (ISOPP) states that CSTDs are the best, most effective, preventive measure to avoid exposure to contamination during cytotoxics preparation and administration.

“Increased CSTD use signals a new age of hazardous drug safety at the most critical points of the medication use process.”¹⁷⁸

Definition

Some equipment suppliers claim that their devices are closed even if they produce aerosols, vapours and dripping. At the same time, different international organisations have defined what is meant by CSTD, leading to the coexistence of different definitions.

In the light of the above, the establishment of a clear definition for the term “closed system” is pivotal to healthcare workers’ protection.

a) The National Institute of Occupational Safety and Health (NIOSH) and International Society of Oncology Pharmacy Practitioners (ISOPP) definitions

The National Institute of Occupational Safety and Health (NIOSH) defines CSTD as *“a device which mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour concentrations outside the system”*.¹⁷⁹

For its part, the ISOPP splits its guidance on the definition of a closed system into two different categories, making a clear distinction between a closed system in terms of microbiological contamination and a closed system in terms of chemical contamination and occupational exposure.¹⁸⁰ It agreed that the NIOSH definition is the most comprehensive and complete as it includes both microbiological contamination and hazardous drug containment and it is the only definition that includes drug vapours.¹⁸¹

In order to ensure that only closed-system drug transfer devices that meet the definition of the NIOSH are recognised as such, the American Food and Drug Administration (FDA), established in 2013 a product code, the ONB (Closed Antineoplastic And Hazardous Drug Reconstitution And Transfer System)¹⁸², for CSTD's indicated to reduce exposure to hazardous drugs. The FDA rule for ONB classification defines a CSTD as a device that demonstrates no escape of hazardous drug or vapour concentration, no transfer of environmental contaminants and prevention of microbial ingress.

b) European Union

The EU lacks a common harmonised definition for CSTDs.

Under article 5 of the *Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work*¹⁸³, employers must ensure that the carcinogen or mutagen is manufactured and used in a closed system and, if this is not technically possible, that the level of exposure is as low as is technically possible. However, the Directive does not define what is meant by a closed system.

Article 5 | Prevention and reduction of exposure

“1. Where the results of the assessment referred to in Article 3(2) reveal a risk to workers' health or safety, workers' exposure must be prevented.

2. Where it is not technically possible to replace the carcinogen or mutagen by a substance, mixture or process which, under its conditions of use, is not dangerous or is less dangerous to health or safety, the employer shall ensure that the carcinogen or mutagen is, in so far as is technically possible, manufactured and used in a closed system.

3. Where a closed system is not technically possible, the employer shall ensure that the level of exposure of workers is reduced to as low a level as is technically possible.”

In order to ensure that CSTD provide the highest level of safety they should be tested against a range of cytotoxic drugs by a certified independent body. To conduct these robust assessments, harmonised protocols for testing CSTD should be established.

In this regard, the EU could follow the example provided by the NIOSH in its CSTD vapor containment performance protocol¹⁸⁴, whose purpose is to test a CSTD's capability to perform as a closed system. The protocol can be used to provide baseline containment comparisons between different makes and models of CSTDs.

Recommendation 7

- European legislation should establish a common definition for 'Closed-System Drug Transfer Devices', which details the technical specifications to be met by a medication transfer system to be considered as a closed system, using the definitions established by NIOSH and ISOPP as a basis and taking the system of the FDA in the United States with the ONB classification as an example. Furthermore, harmonised protocols for testing CSTD should be established.

Increased safety

In conjunction with standard cytotoxic drugs preparation techniques, CSTDs have been successful in significantly reducing surface contamination and/or the amount of these agents in the urine of exposed Healthcare workers^{185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207}, as compared to traditional techniques alone.

This is especially true with administration tasks, where use of a CSTD is shown to reduce leakage of cytotoxic drugs during normal drug preparation and administration activities, compared with the use of needles and syringes.²⁰⁸

Indeed, whereas using the conventional needle/syringe technique during preparation of a hazardous drug may lead to release of the agent into the work environment, with an effective CSTD there is no relevant leakage observed during any phase of the manipulations^{209 210}, preventing the aforementioned forms of contamination. To emphasise this point, different experiments have proven the increased safety of CSTD in comparison to spikes.^{211 212 213}

With regard to pharmaceutical isolators, used in many countries to contain cytotoxic residues during preparation of cytotoxic drugs, they are heavily contaminated and are difficult to clean, leading to concerns that cytotoxic contamination from the work area could be transferred to surfaces of products leaving the isolator.²¹⁴ It is therefore critical to minimise cytotoxic contamination in these systems, which can be reduced by using CSTDs.²¹⁵ As for robotics, because they do not completely prevent contact, they only provide a partial answer in terms of healthcare workers' safety.

Regarding vented filters, their utilisation is the subject of discussion in relation to their capacity for truly effective filtration of the aerosol contained in the air sent outside the system. For this reason, they are not considered CSTD.²¹⁶

In the light of this, and in view of the number of patients requiring treatment with cytotoxic drugs which is predicted to increase, further efforts to reduce occupational exposure are widely recommended by the scientific community.²¹⁷ This includes the refinement and wider use of CSTDs, which should be considered additions to, and not substitutes for, other safe handling precautions and protective measures.^{218 219}

The benefits of CSTDs in terms of patient safety are also noteworthy. Because CSTDs provide a barrier to the entry of contaminants from the atmosphere into sterile solutions, they contribute to the sterility of the product through manipulation, transport and administration and ensuring the purity of the drug. Furthermore, CSTDs can create shorter waiting time for patients, as they can in some cases save time in the elaboration process.²²⁰

Cost-effectiveness

In this regard, the benefits of using effective CSTD have been largely proven.

As well as preventing the escape of dangerous substances into the atmosphere^{221 222}, effective CSTDs provide a barrier to the entry of contaminants from the atmosphere into the solutions, which can therefore remain sterile.²²³ This means that using an effective CSTD for unpreserved drugs may extend the beyond-use date of single-use vials of cytotoxic medications, providing a way to avoid discarding viable drug product because of sterility concerns and reducing drug wastage.²²⁴ This represents a substantial and measurable cost-saving and resource organisation.²²⁵

^{226 227 228 229}

As a result of the above, CSTD offer significant cost-benefits that outweigh the higher cost of this kind of devices.²³⁰ That is why the World Health Organisation (WHO) has recommended the use of CSTD also in limited-resource settings.²³¹ There is also the opportunity to save time in the elaboration process which leads to savings of resources, organisation advantages for hospital pharmacy services and a shorter waiting time for patients.²³²

Recommendation 8

- In order to improve healthcare workers' safety, policies at the EU and national level should promote the use of effective CSTD, which have the potential to protect healthcare professionals from being exposed to cytotoxic drugs.

2. Administrative mechanisms

Administrative controls include policies and procedures and staff education and training.

a. Information and training of workers

Healthcare workers are not always aware of the risks of working with cytotoxic and the necessary precautions.²³³ In order to understand the risks involved and to ensure the safe handling of these agents, all staff who will be involved in the handling of cytotoxic drugs must be provided with suitable, sufficient and regular information and education. This requires, firstly, that all personnel involved in the preparation and administration of cytotoxic drugs possess a recognised qualification or have received certified training relevant to their work. In other words, cytotoxic drugs should be handled and stored within the pharmacy by trained employees, the preparation of parenteral cytotoxic drugs should be undertaken only by pharmacy personnel and the administration of chemotherapy should be performed only by certified/qualified healthcare personnel.

Furthermore, the personnel involved or likely to be involved in the handling of these drugs, including not only pharmacy staff, nursing and medical staff, but also other support staff such as porters and cleaners, need to be trained and educated, prior to potential exposure, on the hazards associated with each cytotoxic drug, effective methods for reducing or eliminating exposure, appropriate PPE use, decontamination and sanitation, and safe work practices. The need for proper and regular information is strongly supported by the existing European legislation.²³⁴

Last but not least, an assessment of practice should be undertaken on a regular basis for all personnel preparing and administering chemotherapy, in order to verify compliance with procedures.

Recommendation 9

- The EU and Member States should promote that all the healthcare professionals involved in the handling of cytotoxic drugs are provided with suitable, sufficient and regular information and education relevant to their work.

b. Better cleaning procedures

In order to minimize the risk of chronic occupational exposure of cytotoxic drugs, decontamination, cleaning and disinfection of work surfaces where cytotoxic drugs are handled or potentially contaminated is critical in reducing the spread of contamination. Unfortunately, no single chemical can completely clean, disinfect and decontaminate surfaces contaminated with cytotoxic drugs²³⁴ and even with techniques employed to clean contaminated surfaces is still difficult to reduce the residual concentration of cytotoxic drugs found on work surfaces below the limit of detection.²³⁵ Different studies have underlined the importance of combining cleaning techniques successively in order to reduce the residual concentration of hazardous drugs to the maximum extent.

Recommendation 10

- The European Commission should develop suitable decontamination, cleaning and disinfection guidelines based on surface contamination levels and types of drugs.

c. Monitoring exposure

Despite all the previous efforts, contamination of the workplace (safety cabinets and isolators, work tops, floors, vials, equipment etc.) with cytotoxic drugs still occurs^{236 237 238 239 240 241 242 243 244}, and workers exposure is still observed. Hence, it is crucial to investigate how the drugs are released and spread of and thus help to identify possible sources and routes of exposure, as well as to control and improve the effectiveness of protective measures and equipment.

This can be done through an effective monitoring programme for the collection of reliable exposure data.^{245 246} However, as occurs with the handling practices of cytotoxic drugs, chemical contamination monitoring varies across Member States, with some Member States having poor or non-existent monitoring programmes or guidelines. It is important to stress that, under the current EU legislation, employers are obliged to offer employees a monitoring programme for carcinogenic compound which includes most of the cytotoxic drugs.

Monitoring should become a standard in all the Member States and should be performed on a regular basis. A regular repetition of monitoring has proven to have a stronger effect on the reduction of contamination levels and workers' exposure than incidental monitoring.²⁴⁷

Recommendation 11

- The Commission should develop basic guidelines on the regular monitoring of healthcare workers' exposure to cytotoxic drugs. The Commission and Member States should ensure that these guidelines are effectively implemented.

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