Inclusion of Hazardous Medicinal Products within the scope of the Carcinogens and Mutagens Directive

The aim of this Brief is to highlight the importance of including Hazardous Medicinal Products (HMP) and in particular cytotoxic, cytostatic and antineoplastic drugs in the fourth revision of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (CMD).

Cancer is a leading cause of work-related deaths in the European Union, accounting for more than 100,000 deaths each year (Musu & Vogel, 2018). In the healthcare sector alone, 12.7 million workers in Europe (of which 7.3 million nurses), are exposed to deadly HMP at work.

HMP are however vital in the battle against cancer and other non-cancerous diseases, so the elimination/substitution obligation defined in the CMD would not apply to HMP. This brief will argue that HMP should be recognised as harmful substances and included in Annex I of the CMD. The inclusion of HMP in Annex I would allow for the implementation of binding legislation, including prevention of exposure through closed technological systems as defined by the CMD, that protects all workers that come into contact both directly and indirectly with such substances.

Hazardous Medicinal Products and their effect on workers' health

HMP include includes medicinal products associated with genotoxicity, carcinogenicity, teratogenicity, fertility impairment or reproductive toxicity, and/or serious organ toxicity at low doses in humans. The ETUI has released another brief that focuses on the effects of reprotoxic substances on workers in the European Union.

In particular, cytotoxic, cytostatic or antineoplastic drugs are a group of medicines that contain chemicals that are toxic to cells and inhibit cell growth and multiplication. These medicinal products are used predominantly for cancer treatment but also in non-oncology practices for treating non-cancerous diseases such as multiple sclerosis, psoriasis and systemic lupus erythematosus.

The hazardous 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, highly likely to damage normal (non-tumour) cells. HMP thus affect workers that handle both, directly and indirectly, such agents.

Hazardous drugs are usually sold in powder form or as a concentrated solution that allows the drug to remain stable. Such drugs require individual manipulation for each patient prior to being administered as infusions or bolus injections. This may lead to errors, spillages, needle stick injuries and (spread of) contamination, which pose clear health risks to workers that are affected by the drug through dermal absorption. Moreover, hazardous drugs may evaporate and form a gas during normal handling, which may result in inhalation of the drugs.

In many instances, the effects of exposure may be subclinical and not be evident for years or generations of continuous exposure. For example, as cancer often takes decades to emerge, a case of leukaemia diagnosed in a nurse or a pharmacist today might be the product of workplace exposures in the 1970s or the 1980s. While patients receive concentrated doses of a limited number of cytotoxic drugs for a defined period of time, workers may be exposed to small doses of a broad range of hazardous drugs over decades, with some workers being exposed every workday, year after year.

In addition to posing a severe threat to healthcare professionals, exposure of patients, visitors and family members can occur just by entering into contact with contaminated work surfaces, clothing items, medical equipment, patient excreta and other surfaces (Viegas et al., 2017). Since an increasing number of patients is now treated at home, HMP can present a threat also to those that are working at home such as cleaners, housekeepers and (unpaid) caregivers.

The health hazard for handling these drugs is thus a major concern. There is broad and conclusive scientific evidence that HMP are potentially carcinogenic (can cause cancer), but also mutagenic (that changes genetic material) and reprotoxic (can affect male and female reproductive health and can affect the health of the next generation) substances (see for example Musu & Vogel, 2018).

Along with the increasing number of cancer patients, a higher number of workers are needed to handle these drugs during production, preparation and administration tasks. Exposure to HMP thus causes thousands of additional deaths from cancer and tens of thousands more miscarriages, fertility problems and congenital disabilities each year in healthcare workers, patients and their carers (Nyman *et al.*, 2007; Ratner *et al.*, 2010; US Department of Health and Services, 2019). Studies show that hospital workers who handle cytotoxic drugs are three times more likely to develop malignancy (Petralia et al., 1999; Polovich & Gieseker, 2011; Skov et al., 1992) and that nurses exposed to cytotoxic drugs are twice as likely to miscarry (Lawson et al., 2012). It is important to stress that workers in the healthcare sector have already been severely overstretched and neglected during the COVID-19 crisis due to a systematic disregard of OSH standards. Workers experience a layering of threats and risks at the workplace: the EU

institutions must take a firm stance in the protection of *all* workers, including those in the healthcare sector.

Workers deserve to be protected by *binding* legislation through the use of the best technology available and with proper education and training programmes to avoid the risks arising from exposure to cytotoxic drugs and other hazardous drugs.

How to ensure the safe handling of HMP

It is clear that HMP are vital for patients' health, and thus (in almost all cases) cannot be substituted. However, clear preventive measures must be put in place in order to allow workers to perform their duties in the safest way possible.

The handling of HMP should include mandatory protocols and minimum requirements on surveillance, training, cleaning, and effective surface decontamination. Appropriate preventative and risk management measures should be introduced in the entirety of the handling cycle from the preparation to waste management. In order to safely handle HMP, they must be manufactured, used and disposed of in a 'closed technological system'. We dispose of ample evidence that the use of closed technological systems and surface decontamination are effective in ensuring the protection of workers (see for example European Biosafety Network, 2015; Harrison *et al.*, 2006; Siderov *et al.*, 2010; Yoshida *et al.*, 2009).

Currently, only a small minority of workers are adequately protected from exposure to HMP, while the vast majority of healthcare workers in all areas – even those in high risk occupational groups such as oncology nurses, pharmacists and pharmacy technicians who both regularly prepare and administer the HMP - are not protected by closed systems and are thus potentially exposed. HMP often arrive contaminated from external compounding units and are transported internally and ultimately, in most cases, disposed of without the protection of a closed system protection. The chain of contamination and exposure therefore exists from the very arrival of HMP at a healthcare facility.

Studies have shown that surface contamination is particularly widespread in the preparation and administration of HMPs in clinical and back office areas. Presence of HMP can also be found on elevator buttons and non-clinical areas within healthcare facilities. The problem is real and widespread, and it affects everyone in the healthcare setting, including patients and visitors as well as workers. In order to guarantee a safe working space, in addition to the requirement of handling HMP in closed technological systems, constant and effective

monitoring of environmental contamination in workplaces (Korczowska *et al.*, 2020), should be undertaken and standardised.

European guidelines that include mandatory protocols and minimum requirements on surveillance, training, cleaning, decontamination and monitoring should also be agreed and underpinned by the inclusion of hazardous, including cytotoxic drugs, in the CMD. This should be part of the upcoming OSH strategic framework which must be adopted by the Commission before the end of 2020.

EU legislation for the protection of workers

A unified legislative framework is the *sine qua non* for the protection of all workers in the EU. Since the adoption of the first Carcinogens directive in 1990 and more forcefully since 2016, National Member States, the Trade Unions and the European Parliament have vocally demanded the expansion of the CMD to a broader range of carcinogens and mutagens. Also, employers found themselves in a difficult position due to the legislative void. The lack of action at the EU level ended up with action being taken elsewhere. National legislation attempted to fill the gaps left at EU level, and the business world soon found itself potentially confronted with 28 (and more if we consider the regional level) distinct national regulations. A prime example are the two initiatives in the Spanish context, one in Castilla-La Mancha (SESCAM, 2018) and in Madrid (Comunidad de Madrid, 2018) that introduced new pieces of regulation and legislation that guarantee a wide protection of all workers that handle or enter into contact with hazardous drugs. Unfortunately, in a majority of EU countries, there is a lack of systematic and consistent binding rules. The level of workers' protection can vary a lot from country to country and, sometimes, from hospital to hospital. There is a need for EU minimal harmonization in such an important field.

Why is the CMD the best framework?

Since 1990, when the EC and the Council adopted the first Carcinogens Directive (extended to mutagens in 1999) there have been significant steps forward in the protection workers' health through the reduction of occupational exposure to chemical agents that may cause cancer or mutations. The CMD of 2004 was a consolidation of the 1990 directive with amendments adopted in 1997 and 1999. The 2004 CMD was then revised in three "batches" adopted from 2017 to 2019 is the starting point of a continuous process for improving the EU legal framework in order to eliminate work related cancers.

Article 1.1 of the third revision of the CMD (Directive 2019/983 of 5 June 2019) introduced a legal binding obligation: "No later than 30 June 2020, the Commission shall, taking into

account the latest developments in scientific knowledge, and after appropriate consultation with relevant stakeholders, in particular health practitioners and health professionals, assess the option of amending this Directive in order to include hazardous drugs, including cytotoxic drugs, or to propose a more appropriate instrument for the purpose of ensuring the occupational safety of workers exposed to such drugs. On that basis, the Commission shall present, if appropriate, and after consulting management and labour, a legislative proposal.'

With some delay, the Commission has organized a consultation process but has not yet released an official proposal for the time being.

The CMD provides a solid basis for harmonized EU wide minimum requirements for the protection of workers from exposure to the most dangerous substances and work processes. Such a directive could strengthen the current system, bring legal coherence and better alignment of chemical legislation at the EU level. The rationale of the CMD's more stringent preventative measures is based on two criteria: potential severe harm due to exposure (that can result in death, severe diseases or impairment) and the long latency period between the exposure and the harm which result in a low visibility of the risk.

It has been questioned whether the CMD is the appropriate piece of EU legislation to address the protection of workers exposed to HMP because of the elimination/substitution obligations and the erroneous suggestion that essential HMP are to be removed from the market and might not be available to treat cancer patients. The objective is, however, to protect workers from exposure to hazardous HMP without jeopardizing the availability of cancer treatments. The CMD is perfectly suited to those objectives because the hierarchy of mandatory preventive and protection measures defined in the legal text allows to implement other measures when elimination/substitution is not possible.

It is obvious that the elimination/substitution obligation defined in the CMD does not apply to HMP because these medicinal products are needed and essential to treat patients. All the other provisions in the hierarchy (such as the use of a closed system and the reduction of exposure) are therefore the added value of the CMD to better protect exposed workers.

Action required on behalf of the European Parliament – inclusion of HMP in Annex I of the CMD

In order to ensure the protection of all workers that may come into contact with HMP the ETUI requests that the EU Parliament commits to protecting all worker from HMP including those with cytotoxic effects in the Annex I of the CMD and tables the following amendment:

> *"Work involving exposure to carcinogenic or mutagenic substances resulting from the preparation, administration or disposal of hazardous drugs, including cytotoxic drugs, and work involving exposure to carcinogenic or mutagenic substances in cleaning, transport, laundry and waste disposal of hazardous drugs or materials contaminated by hazardous drugs and in personal care for patients under treatment of hazardous drugs".*

The reason why the ETUI is arguing for the inclusion of HMP in Annex I and not in Annex III, that sets a limit to occupational exposure levels (OELs), lies in the fact that even minimal exposure to HMP may severely harm the health and safety of workers. Health based threshold levels of exposure to hazardous drugs cannot be derived and therefore contact with HMP should be avoided at all levels. Although OELs might be suited for the production sites of HMP it will be difficult, if not impossible, to set a maximum exposure limit for hospitals and home care workers. Determining an occupational exposure limit value (OEL) and thus including a limited list of cytotoxic substances in Annex III would not provide an adequate protection from the risk of toxic and genetic damage and deadly diseases for several reasons: the rapid development of new drugs. Moreover, as the most common exposure to HMP is through dermal absorption and not airborne transmission. OELs thus cannot be the adequate tool to protect workers from the exposure to HMP.

For all the above-mentioned reasons the legislative amendments to the scope of the CMD to include HMP would only effectively protect workers in the European Union if such substances are included in Annex I of the revised directive (CMD4).

References & Further Readings

Comunidad de Madrid. 2018. Resolution From the Regional Deputy Minister for Health Which Dictates Instructions for Safe Manipulation Of Hazardous Medicines n 51/2018 - General Directorate of Health Care Coordination and General Directorate of Human Resources and Industrial Relationships.

European Biosafety Network. 2015. Preventing occupational exposure to cytotoxic and other hazardous drugs. https://www.europeanbiosafetynetwork.eu/wp-content/uploads/2016/05/Exposure-to-Cytotoxic-Drugs_Recommendation_DINA4_10-03-16.pdf.

Harrison, B.R., Peters, B.G. & Bing, M.R. 2006. Comparison of surface contamination with cyclophosphamide and fluorouracil using a closed-system drug transfer device versus standard preparation techniques. American Journal of Health-System Pharmacy. 63(18):1736–1744.

Korczowska, E., Crul, M., Tuerk, J. & Meier, K. 2020. Environmental contamination with cytotoxic drugs in 15 hospitals from 11 European countries—results of the MASHA project: European Journal of Oncology Pharmacy. 3(2):e24.

Lawson, C.C., Rocheleau, C.M., Whelan, E.A., Lividoti Hibert, E.N., Grajewski, B., … Rich-Edwards, J.W. (in press). Occupational exposures among nurses and risk of spontaneous abortion. American Journal of Obstetrics and Gynecology. 4:327.e1–8.

Musu, T. & Vogel, L. 2018. Cancer and work: understanding occupational cancers and taking action to eliminate them. ETUI. https://www.etui.org/sites/default/files/cancer-EN-WEB.pdf Date of access: 03 Aug. 2020.

Nyman, H., Jorgenson, J. & Slawson, M. 2007. Workplace Contamination with Antineoplastic Agents in a New Cancer Hospital Using a Closed-System Drug Transfer Device. Hospital Pharmacy. 42(3):219–225.

Petralia, S.A., Dosemeci, M., Adams, E.E. & Zahm, S.H. 1999. Cancer mortality among women employed in health care occupations in 24 U.S. States, 1984-1993. Journal of Industrial Medicine. (36:159–165):7.

Polovich, M. & Gieseker, K.E. 2011. Occupational Hazardous Drug Exposure Among Non-Oncology Nurses. 20(2):9.

Ratner, P.A., Spinelli, J.J., Beking, K., Lorenzi, M., Chow, Y., … Dimich-Ward, H. 2010. Cancer incidence and adverse pregnancy outcome in registered nurses potentially exposed to antineoplastic drugs. BMC Nursing. 9(1):15.

SESCAM. 2018. Guidelines for Action on the Risk of Exposure to Hazardous Drugs For Health Service Workers in Castile-La Mancha - SESCAM Occupational Risks Prevention Service. https://www.europeanbiosafetynetwork.eu/wp-content/uploads/2019/03/Hazardous-drugs-Castilla-La-Mancha.pdf.

Siderov, J., Kirsa, S. & McLauchlan, R. 2010. Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device. Journal of Oncology Pharmacy Practice. 16(1):19–25.

Skov, T., Maarup, B., Olsen, J., Rorth, M., Winthereik, H. & Lynge, E. 1992. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. Occupational and Environmental Medicine. 49(12):855–861.

US Department of Health and Services. 2019. Occupational Exposure to Cancer Chemotherapy Agents and Adverse Health Outcomes. https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/completed/chemo/occupational/index.html Date of access: 20 Aug. 2020.

Viegas, S., Ladeira, C., Costa-Veiga, A., Perelman, J. & Gajski, G. 2017. Forgotten public health impacts of cancer – an overview. Archives of Industrial Hygiene and Toxicology. 68(4):287–297.

Yoshida, J., Tei, G., Mochizuki, C., Mazu, Y., Koda, S. & Kumanda, S. 2009. Use of a Closed System Device to Reduce Occupational Contamination and Exposure to Antineoplastic Drugs in the Hospital Work Environment. The Annals of Occupational Hygiene.