European Biosafety Network

Prevention of exposure to hazardous medicinal products (HMPs) and other substances in Belgium and Europe

Presentation by Ian Lindsley, European Biosafety Network

25 March 2022



About the EBN

European Biosafety Network

- Established in 2009 by the founding partners, the Spanish General Council of Nursing and the British public services union UNISON.

UNISON
the public service union

Spanish General Council of Nursing

- The Network is an inclusive organisation made up of national and European professional institutions, representative associations, unions and other interested parties committed to biological and occupational and patient safety in healthcare throughout the European Union.

The 2nd European Biosafety Summit
1 June 2011, Dublin

European Biosafety Network

Background on Hazardous Drugs

European Biosafety Network

- The European Commission said that in 2012 up to 106,500 cancer deaths were attributed to occupational exposure to carcinogenic substances, making cancer the first cause of work-related deaths in the EU.

- Every year more than 12.7 million health workers, mostly women, in Europe are potentially exposed to carcinogenic, mutagenic and reprotoxic hazardous drugs, including cytotoxic or antineoplastic drugs.

- Studies show that nurses exposed to cytotoxic drugs are twice as likely to miscarry and that hospital workers who handle cytotoxic drugs are three times more likely to develop malignancy.

- Increased genetic damage has been demonstrated in nurses, particularly in day hospital nurses, the group handling the highest amount of drugs during the administration process.

Risk of occupational exposure to Hazardous Drugs

European Biosafety Network

From the NIOSH Alert 2004-165 - www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf

"Several reports have addressed the relationship of cancer occurrence to health care workers' exposures to antineoplastic drugs. A significantly increased risk of leukemia has been reported among oncology nurses identified in the Danish cancer registry for the period 1943–1987 [Skov et al. 1992]. The same group [Skov et al. 1990] found an increased, but not significant, risk of leukemia in physicians employed for at least 6 months in a department where patients were treated with antineoplastic drugs."

Skov T, Maarup B, Olsen J, Rørth M, Winthereik H, Lynge E [1992]. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. Br J Ind Med 49: 855–861.
Skov T, Lynge E, Maarup B, Olsen J, Rørth M, Winthereik H [1990]. Risk for physicians handling antineoplastic drugs [letter to the editor]. The Lancet 336:1446

Risk of occupational exposure to Hazardous Drugs

European Biosafety Network

A Dutch study (Fransman 2014) that shows a model of an increase of 154 deaths from leukemia per million nurses working with the cytotoxic drug cyclophosphamide.

Another study, Ratner 2010 shows increased incidence of breast cancer (RR = 1.83; 95% CI = 1.03 - 3.23, 12 cases) and rectal cancer (RR = 1.87, 95% CI = 1.07 - 3.29, 14 cases) in nurses working in a cancer centre.

Fransman W, Kager H, Meijster T, Heederik D, Kromhout H, Portengen L and Blaauboer BJ. Leukemia from dermal exposure to cyclophosphamide among nurses in the Netherlands: quantitative assessment of the risk. Ann Occup Hyg. 2014; 58:271-282.
Ratner PA, Spinelli JJ, Beking K, Lorenzi M, Chow Y, Teschke K, Le ND, Gallagher RP, Dimich-Ward H. Cancer incidence and adverse pregnancy outcome in registered nurses potentially exposed to antineoplastic drugs. BMC Nurs. 2010; 9:15.

European Commission report on preventing exposure to HMPs March 2021

European Biosafety Network

The European Commission published a report based on consultation with Member States, experts, professionals, patients and employers and workers in healthcare, to include 3 groups of hazardous drugs, or hazardous medicinal products (HMPs), in the CMD in combination with new guidance and a regular review of a list of HMPs based on an agreed definition.
https://ec.europa.eu/social/main.jsp?catId=148&langId=en

The report recommended to add 3 groups of hazardous medicinal products and their active substances in Annex I of the CMD combined with non-legislative guidance. The 3 pharmacotherapeutic groups identified by the report are antineoplastics, immunosuppressants and antivirals.

In addition, the report includes two further non-legislative options which are (a) to produce new EU guidelines and standards of practice on the handling of HMPs and (b) to define HMPs and produce an EU list of HMPs which should be regularly reviewed.

The legislative option of including HMPs in the CMD combined with guidance was supported by the 16 out of 24 of Member States responding to the consultation, including Belgium, and most stakeholders consulted agreed, including the health social partners.

European Commission report on preventing exposure to HMPs March 2021

The Belgian Federal Public Service submitted to the consultation a document detailing a set of recommendations which include amongst others:

- Regular monitoring of surface contamination should be universal, frequent and comprehensive considering that this is currently carried out in none of the hospital pharmacies;
- A European list of hazardous drugs should be formalised and used by the hospital pharmacies: the current list of NIOSH is used but is based on non-European criteria and is insensitive to the particulars of the European Oncology environment;
- An increase of the use of all forms of PPE should be foreseen where appropriate as this is critical to worker safety;
- The use of outdated administration system should be eliminated and the use of systems offering full protection such as CSTDs should be promoted; and
- HMPs should be included in EU 2004/37 or in a specific regulation in Europe as combined with mandatory European guidelines and combined with a European list of hazardous drugs.

ANSES recommendations on cytotoxic/cytostatic agents
July 2021

European Biosafety Network

- The French OSH agency ANSES received a formal request from the Directorate General for Labour on 17 November 2017 to provide an opinion on new carcinogenic processes that could fall within the scope of French national legislation.

- Initially in December 2020, and then in July 2021, it published a document summarising the work of the Expert Committee on "Health reference values" and the Working Group on "Carcinogenic processes".

https://www.anses.fr/fr/system/files/VSR2017SA0237Ra.pdf and ANSES COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS on work involving exposure to cytostatic agents

The working group recommended changing the Ministerial Order. in French national law. to:

- update the list of carcinogenic, mixtures and processes (or even of Annex I of Directive 2004/37/EC);
- Increase the protection and awareness of workers potentially exposed to the carcinogenic cytotoxic/cytostatic active principal ingredients; and
- Improve knowledge of the carcinogenic risk associated with exposure to cytotoxic/cytostatic anti-cancer drugs.

ANSES recommendations on cytotoxic/cytostatic agents December 2020/July 2021

European Biosafety Network

- ANSES recommended adding 18 new cytotoxic/cytostatic substances in relation to work involving exposure to cytotoxic/cytostatic active principle substances used specifically in the context of anti-cancer treatments for human and veterinary use and considered equivalent to Category 1A or 1B carcinogens according to the CLP Regulation.

The circumstances of exposure to be taken into account include specifically the following:

- exposure during the manufacture, packaging, preparation, transport and handling of medicinal products;
- exposure when implementing protocols involving one or more of the substances listed below;
- exposure through contamination of the working environment or via management of waste and excreta.

- The list of active principle substances is as follows: adriamycin or doxorubicin; azacitidine ;azathioprine; busulfan; carmustine; chlorambucil; chloromethine (tri); cisplatin; cyclophosphamide; etoposide; lomustine; melphalan; prednimustine; procarbazine; teniposide; thiotepa; treosulfan; arsenic trioxide.

EU Classificaton of Carcinogenic, Mutagenic or Reprotoxic (CMR) substances

Classification of CMRs in the EU is based on the strength of evidence showing that they present one of the CMR types of hazards to human health.

The EU legislation regarding Classification Labelling and Packaging of substances – the CLP Regulation 1272/2008 – uses the hazard categories below for substances and for mixtures that contain CMRs.

EU classification of CMR substances	
Category	Criteria
Cat. 1 A	known to have CMR potential for humans, based largely on human evidence
Cat. 1 B	presumed to have CMR potential for humans, based largely on experimental animal data
Cat. 2	suspected to have CMR potential for humans

Amendments and joint statement to Carcinogens, Mutagens and Reprotoxic Substances Directive 2004/37/EC

European Biosafety Network

Joint statement of the European Parliament and the Council on the scope of Directive 2004/37/EC – 16 March 2022

The European Parliament and the Council share the common understanding that **hazardous medicinal products which contain substances which meet the criteria for classification as carcinogenic (categories 1A or 1B), mutagenic (categories 1A or 1B) or reprotoxin (categories 1A or 1B)** in accordance with Regulation (EC) No 1272/2008 fall under the scope of Directive 2004/37/EC. All requirements of Directive 2004/37/EC apply to hazardous medicinal products accordingly.

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L:2022:088:TOC

Amendments and joint statement to Carcinogens, Mutagens and Reprotoxic Substances Directive 2004/37/EC

European Biosafety Network

Inclusion of reprotoxic substances in the scope of the new Carcinogens, Mutagens and Reprotoxins Directive (CMRD). For 12 of these substances, a binding occupational maximum exposure level limit value will be introduced in Annex III of the Directive.

Inclusion of hazardous medicinal products (HMPs) in the scope of the new Directive, whereby **t**he European Commission is required to:

> Prepare **guidelines for the preparation, administration, and disposal of HMPs** no later than 31 December 2022; and
>
> Develop a **definition and establish an indicative list of HMPs based on their classification as a category 1A or 1B carcinogen**, no later than one year after the transposition of this Directive.

Workers who deal with HMPs and other CMRs will receive sufficient **training periodically,** in particular for new substances and new risks.

Carcinogens, Mutagens and Reprotoxic Substances Directive 2004/37/EC

European Biosafety Network

Its key provisions continue to include:

- The employer shall assess and manage the risk of exposure to carcinogens, mutagens or reprotoxic substances. Workers' exposure must be prevented.
- The employer shall reduce the use of carcinogens, mutagens or reprotoxic substances by replacing them with a substance that is not dangerous or less dangerous.
- Where it is not technically possible to replace the carcinogen, mutagen or reprotoxic substance 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, mutagen or reprotoxic substance is, in so far as is technically possible, manufactured and used in a closed system.**
- Where a closed system is not technically possible, the employer shall reduce exposure to the minimum.

Existing European Commission Guidelines

Guidance on handling HMPs is already published in many Member States and globally.

- The European Commission already published specific guidance on the handling of cytostatic/cytotoxic drugs in 2011, as part of a comprehensive document called ‘Occupational health and safety risks in the healthcare sector’ as follows:

https://op.europa.eu/en/publication-detail/-/publication/b29abb0a-f41e-4cb4-b787-4538ac5f0238

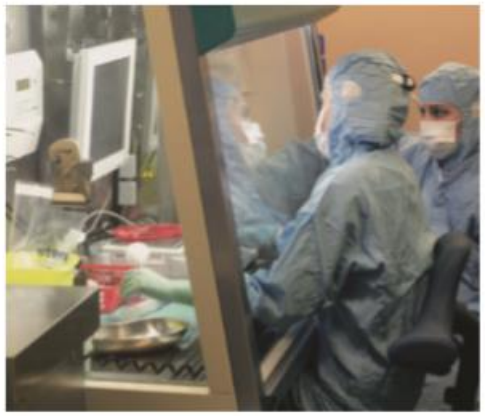
This includes the following pages:

European Commission - Guidance on cytostatic/cytotoxic drugs

European Biosafety Network

6.6.3.1. Preparation of cytostatic drugs

Work areas	With the installation of a centralised facility for the preparation of cytostatic drugs physically separated from other work areas, specially marked and out of bounds to unauthorised persons, it is possible to ensure the efficient use of complex protective measures with a high throughput of preparations.
Work-benches	Preparations are manufactured in particularly safe conditions on so-called cytostatic workbenches (special laminar-flow workbenches).
Transfer systems	Pressure relief systems, transfer systems etc. help to prevent the release of cytostatic drugs in the individual work steps of the preparation process.
Personal protective equipment	The wearing of suitable personal protective equipment also prevents any exposure of the workers. This includes in particular: – suitable protective gloves, where necessary with cuffs; there are special cytostatic protective gloves and sometimes it is recommended that two pairs be worn (double gloving); – a laboratory coat closed right up to the neck with long sleeves and close-fitting cuffs.
Cleaning	It may be necessary to take further protective measures (e.g. wearing respiratory mask P2) when cleaning the workplace/the workbench as well as during maintenance work.



14 15 **Separated working areas, safety work-benches and reliable lead-over systems represent the most important technical protective measures when preparing chemotherapeutic agents.**

T

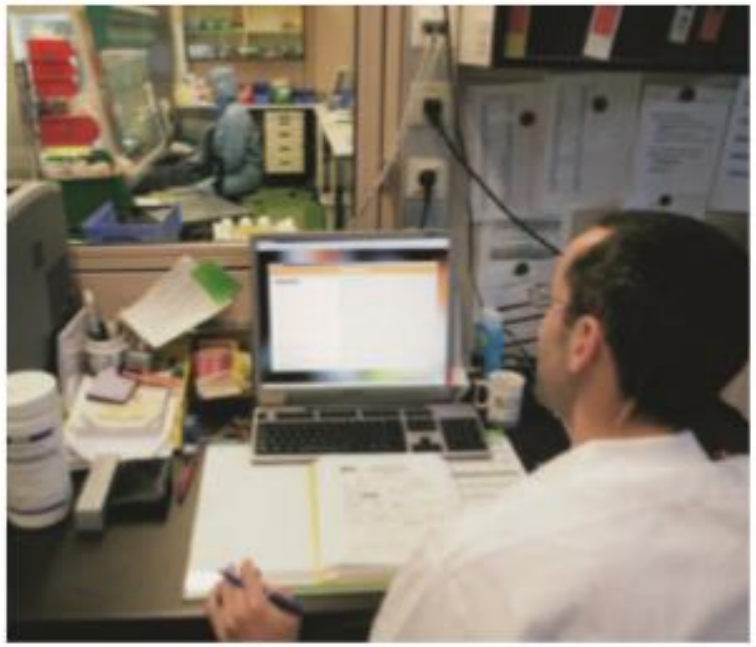
O

P

European Commission - Guidance on cytostatic/cytotoxic drugs

European Biosafety Network

16 **Separated working areas, safety work-benches and reliable lead-over systems represent the most important technical protective measures when preparing chemotherapeutic agents.**



6.6.3.2. Preparatory work and application

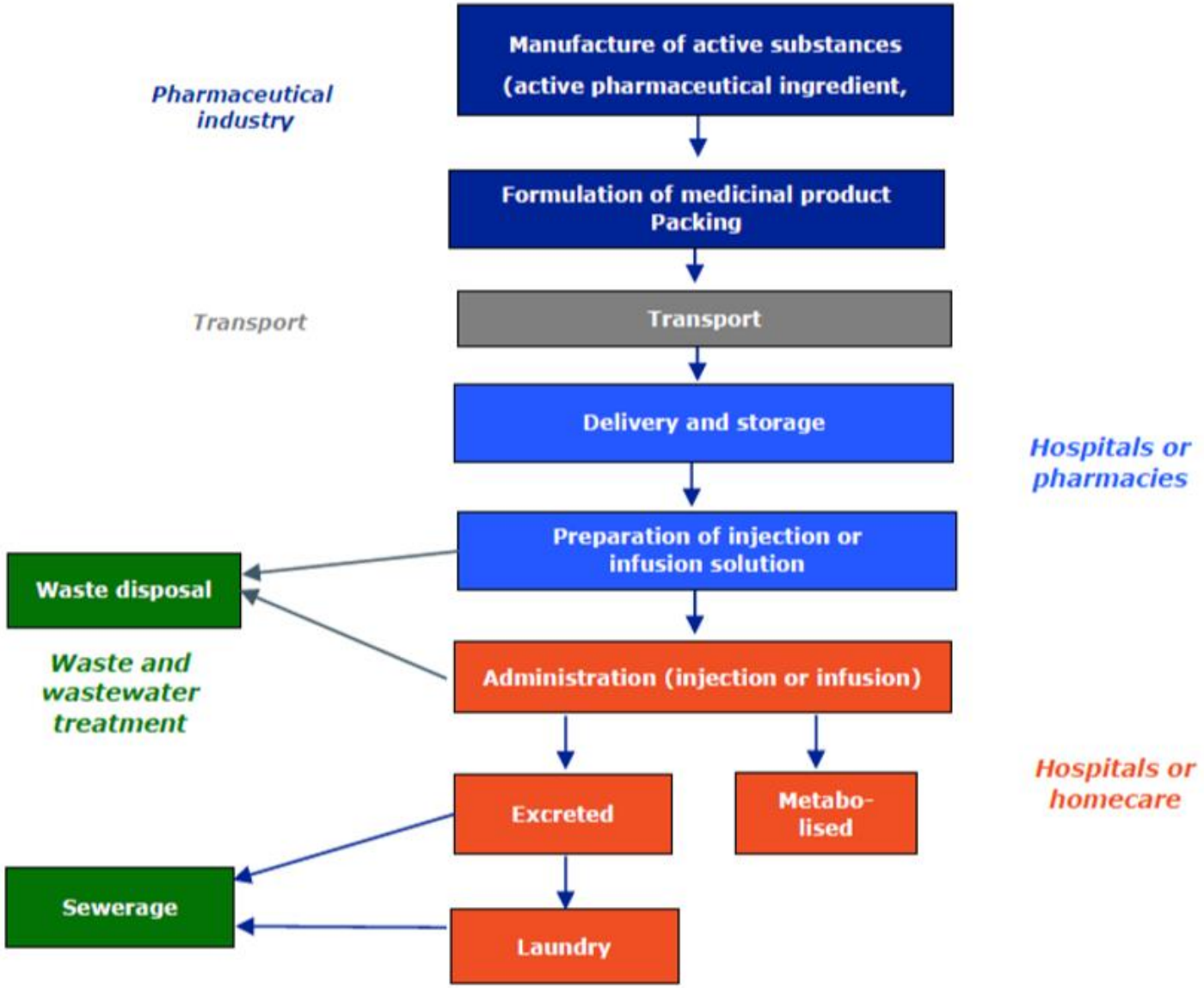
General	All jobs should be performed in a quiet environment and good preparation of the individual work steps helps to work cleanly and avoid emissions. Infusion devices ready for application should be filled with a suspending agent; avoid venting with solutions containing cytostatic drugs.
Work area	Preparatory work steps should, as far as possible, be performed in a central cytostatic preparation facility.
Technical measures	The use of equipment with easy-to-wash surfaces helps when conducting the necessary cleaning. With the application, if possible, use closed infusion and instillation systems with safe connection and transfer units. Administer infusions and injections over an absorbent surface which is impermeable downwards.
Personal protective equipment (PPE)	Once again it may be necessary to wear adequate protective equipment, such as: – protective gloves (cytostatic gloves) – protective coat – where relevant goggles (in the case of emergency measures). If there is any contamination of the protective gloves, these should be changed immediately.
Waste/disposal	Any waste products which arise should be disposed of in an orderly fashion immediately. Do not disconnect infusion bags and bottles after administering but dispose of them completely.

Next Steps – Development and Publication of EU Guidelines

A consortium led by the consultancy RPA has been appointed recently to undertake the development of guidance for the safe management of hazardous medicinal products at work, including cytotoxics, with the following timetable:

- Initial engagement round: inform about the study and timeline, identify and review existing relevant guidance documents **03-04/2022**
- Workshops: discuss the inventory of measures and gap analysis and develop a list of agreed measures to be included in the guidance **05-06/2022**
- Consultation and call for comments: large-scale invitation to comment on the first draft (text only) **07/2022**
- Pilots: gather additional views from specific providers and discuss usability **08-09/2022**
- Second and final draft **10/2022** and project completion **12/2022** – guidelines will be published by EU-OSHA and disseminated in Member States

Next Steps – Development and Publication of EU Guidelines



Next Steps – Development and Publication of EU Guidelines

The guidelines will set out and provide practical guidance for the use of HMPs by the following stakeholders and target groups: employers, workers, occupational health and safety services and experts, personal training managers and others concerned with advice on the safe management of HMPs at work.
Existing studies and guidelines inside and outside the European Union will be taken into account.

- The consultation and involvement of the relevant stakeholders, such as social partners in healthcare, in the development of guidance is key to the acceptance of the final document.
- The draft guidance will be structured in a modular form according to the different stages of the supply chain of HMPs.
- It will be easy to use in particular for SMEs and self-employed workers.
- The guidance will be based on didactic principles so as to facilitate its use by non-specialists.

Next Steps

European Biosafety Network

- Healthcare professionals need to input to the development of EU guidelines and to ensure that the hierarchy of controls in the CMRD is applied to prevent exposure to HMPs
- It is not clear how the new commitment in the CMRD to ensure the delivery of training for those exposed to HMPs will be implemented in practice but ultimately it is for employers to deliver training to workers in the Member States.
- The Commission should move quickly to deliver its commitment to produce a list and definition of HMPs and these should be included in the new EU guidelines and next revision of the CMRD.
- Further amendments will be put forward by the European Parliament to the next revision of the Directive this year: and should include HMPs in Annex I according to the classifications 1A and 1B set out in the CLP regulation and the agreed scope of the CMRD.

Whatever the legal or other circumstances, healthcare systems in Europe and Belgium need to be prepared to transpose and meet the new and existing requirements of the CMRD in relation to how they manage HMPs now and in the future to protect healthcare workers from occupational exposure and its health impacts, including cancer and miscarriages.

European Biosafety Network

www.europeanbiosafetynetwork.eu