The ETUI's list of hazardous medicinal products (HMPs)

including cytotoxics and based on the EU CLP classification system of Carcinogenic, Mutagenic and Reprotoxic (CMR) substances

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Executive Summary

Workers exposed to hazardous medicinal products (HMPs), or hazardous drugs, which are carcinogenic, mutagenic or reprotoxic substances (CMRs), within the meaning of the recently adopted Carcinogens, Mutagens and Reprotoxic Substances Directive (CMRD – Directive (EU) 2022/431), must be given specific training by their employers to prevent risks of adverse effects on their health.

In order to help employers meet their obligations, the European Commission has to publish European guidelines for the safe management of HMPs at work, including cytotoxics, by the end of 2022, and must draw up a definition and establish an indicative list of HMPs that are CMRs, no later than 5 April 2025.

The objective of this ETUI report and the list included is to identify which HMPs fall under the legislative scope of the CMRD in Europe, so that users of the European 2022 guidelines know which specific HMPs the guidelines now apply to, well ahead of the Commission's indicative list, to be published by 2025.

The ETUI list of HMPs is based on the working definition of HMPs used in the development of the European 2022 guidelines, and therefore on the HMPs that meet the criteria for classification as category 1A or 1B CMRs set out in Annex VI to the EU Classification, Labelling and Packaging (CLP) Regulation (Regulation (EC) No 1272/2008). These are HMPs containing one or more substances with a harmonised classification or a self-classification as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B) or toxic for reproduction (category 1A or 1B), all available in the Classification & Labelling Inventory of the European Chemical Agency (ECHA).

Starting from the 2020 list proposed by the National Institute for Occupational Safety and Health (NIOSH) of 229 hazardous drugs in healthcare settings, and utilising the regularly updated national registers of authorised medicines compiled by the European Medicines Agency (EMA), our analysis results in the selection of 121 HMPs in Annex I of the ETUI list that fall under the scope of the CMRD, namely that meet the criteria for classification as category 1A or 1B CMRs as defined in the CLP Regulation.

Moreover, we have identified another 47 HMPs in Annex II of the ETUI list that meet the criteria for classification as category 2 CMRs, as defined in the CLP Regulation, or that have Manufacturer's Special Handling Information provided by their suppliers, or are monoclonal antibodies (mAbs), which now and in future will be used in therapy much more frequently than traditional HMPs. These

HMPs in Annex II do not fall strictly under the scope of the CMRD, but we believe they should be treated in the same way as HMPs listed in Annex I to prevent occupational exposure of workers. Also, the European 2022 guidelines on the safe management of HMPs at work, including cytotoxics, should apply to them as a precautionary approach.

All the HMPs listed in both Annex I and Annex II of the ETUI list are authorised medicines in at least one Member State of the EU, according to the EMA national registers of authorised medicines, accessed on 22 July 2022.

Application and implementation of the preventive measures of the European 2022 guidelines to the drugs identified in the ETUI list of HMPs should help prevent future occupational cancers and reproductive disorders in millions of workers exposed to these HMPs across the EU.

1. Introduction

1.1 Background

Hazardous medicinal products (HMPs) are hazardous substances used predominantly for cancer treatment as cytotoxic/cytostatic or antineoplastic drugs, but also in non-oncology practices, as antivirals, vaccines and immunosuppressants, for treating non-cancerous diseases such as multiple sclerosis, psoriasis and systemic lupus erythematosus and in organ transplantation.

Such HMPs usually require individual manipulation for each patient prior to being administered as infusions or bolus injections but others can be administered orally and some are ready-to-use. This may lead to errors, spillages, needle stick injuries, aerosolisation and contamination of the workplace environment, which pose clear health risks to workers, who could be affected by the medicine through dermal, mucosal, oral absorption and airborne transmission. While patients receive concentrated doses of a limited number of hazardous medicinal products for a defined period of time, workers may be exposed to small doses of a broad range of hazardous medicinal products over decades, with some workers being exposed every workday, year after year (Leso et al. 2022). Some of the acute effects of exposure to HMPs include hair loss, taste disturbances, headaches, reproductive disorders, infection and respiratory disease for both female and male workers and cancers. Often, the effects of exposure may be subclinical and long term and not be evident for years or generations of continuous exposure. To illustrate, as cancer often takes decades to emerge, a case of leukaemia diagnosed in a nurse or in a pharmacist today might be the result of workplace exposure to HMPs in the 1980s. (Vencovsky et al. 2017; Musu and Vogel 2018)

Along with the increasing number of cancer patients, a higher number of workers are needed to handle these parenteral and oral drugs during production, preparation, administration and disposal tasks. Exposure to HMPs could thus cause 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; National Toxicology Programme 2019) if workers are exposed without the proper protection. Studies show that hospital workers who handle cytotoxic drugs are three times more likely to develop malignancy (Petralia et al. 1999; Polovich and Gieseker 2011; Skov et al. 1992) and that nurses exposed to cytotoxic drugs are twice as likely to miscarry (Lawson et al. 2012).

In addition to posing a threat to healthcare professionals and other healthcare workers, exposure of patients, visitors and family members (Yuki et al. 2013) 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 are now treated at home, HMPs can present a threat also to those who are working in the home such as cleaners, housekeepers and caregivers.

According to a recent European Commission study on HMPs published in March 2021, there are almost 1.8 million workers exposed to relevant HMPs in the EU (European Commission, 2021). When taking into account all those potentially exposed in the healthcare sector, that number may be as high as 12.7 million exposed workers in the EU, of which 7.3 million are nurses (ETUI, 2020).

1.2 EU legislation for the protection of workers

Workers' protection against exposure to HMPs is provided for in the EU legislation through the general principles of the Framework Directive on the introduction of measures to encourage improvements in the safety and health of workers at work (Directive 89/391/EC[1]) and normally through its daughter directives covering hazardous substances: the Chemical Agents Directive (Directive 98/24/EC[2]) and the Carcinogens and Mutagens Directive (Directive 2004/37/EC[3]). Other relevant occupational safety and health directives include the Personal Protective Equipment Directive (Directive 89/656/EEC[4]), the Pregnant Workers Directive (Directive 92/85/EEC[5]) and the Young Workers Directive (Directive 94/33/EC[6])

However, HMPs were not mentioned in these daughter directives and it was previously unclear to Member States, employers and enforcers whether the directives' provisions apply to them. In March 2022, the Carcinogens and Mutagens Directive was revised, with an extension of its scope to both substances toxic for reproduction and to HMPs that are category 1A or category 1B CMRs according to the CLP Regulation (CMRD Directive (EU) 2022/431[7]).

More specifically, a new recital and a joint statement of the European Parliament and Council were included in the revised CMRD in March 2022, to clarify that HMPs which are CMRs within the meaning of the CLP Regulation are covered by

1. Directive 89/391/EEC - OSH 'Framework Directive' https://eur-lex.europa.eu/eli/dir/1989/391
2. Directive 98/24/EC - Risks related to chemical agents at work, https://eur-lex.europa.eu/eli/dir/1998/24/
3. Directive 2004/37/EC - Carcinogens, mutagens or reprotoxic substances at work, https://eurlex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405
4. Directive 89/656/EEC - Personal protective equipment directive, https://eur-lex.europa.eu/legalcontent/EN/AUTO/?uri=CELEX:01989L0656-20191120
5. Directive 92/85/EEC - Pregnant workers' directive, https://eur-lex.europa.eu/eli/dir/1992/85
6. Directive 94/33/EC - Young workers' directive, https://eur-lex.europa.eu/eli/dir/1994/33
7. Directive (EU) 2022/431 amending Directive 2004/37/EC - Carcinogens, mutagens or reprotoxic substances at work, https://eur-lex.europa.eu/eli/dir/2022/431

the Directive and fall within its scope, while Article 11 explicitly mentions HMPs by providing that specific training must be given to those handling them. Moreover, the Commission is required to publish and update European guidelines on the preparation, administration and disposal of HMPs in the workplace by the end of 2022, and to draw up a definition and establish an indicative list of hazardous medicinal products that are CMRs no later than 5 April 2025 (see box 1).

It continues to be the case that, for all substances within the scope of the CMRD, employers are legally obliged to perform a risk assessment and respect the hierarchy of prevention and protection measures defined in the text of the Directive. The first measure is to eliminate a CMR substance or to substitute it with a non- or less hazardous substance. Where this is not possible, the substance is to be manufactured and used in a closed system. HMPs falling under the scope of CMRD have to be compounded, prepared, administered and disposed of in a closed system, including the use of biological safety cabinets, containment isolators and closed system transfer devices (CSTDs). Where no closed system is possible, an employer must keep worker exposure as low as technically possible, including by the use of engineering techniques such as ventilation and personal protective measures.

HMPs are however vital in the treatment of cancer and other non-cancerous diseases, and therefore the substitution obligation defined in the CMRD does not apply in reality to HMPs (see recital 12 in box 1). All other measures to reduce workers' exposure apply, from the prevention of exposure through the use of closed technological systems to the other controls lower down the hierarchy.

Box 1 **Legal text of the Carcinogens, Mutagens and Reprotoxic Substances Directive (CMRD) referring to HMPs**

Recital 10
There is a need for workers to receive sufficient and appropriate training when they are exposed or are likely to be exposed to carcinogens, mutagens or reprotoxic substances, including those contained in certain hazardous medicinal products. The training that the employer is required to provide pursuant to Article 11 of Directive 2004/37/EC should be adapted to take account of a new or changed risk, in particular when workers are exposed to new carcinogens, mutagens or reprotoxic substances or to a number of different carcinogens, mutagens or reprotoxic substances, including in hazardous medicinal products, or in the case of changing circumstances related to work.

Recital 11
Certain hazardous medicinal products contain one or more substances which meet the criteria for classification as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B) or toxic for reproduction (category 1A or 1B) in accordance with Regulation (EC) No 1272/2008 of the European Parliament and of the Council and therefore fall within the scope of Directive 2004/37/EC. However, clear and

updated information concerning whether a medicinal product meets those criteria is not easily accessible to workers, employers or enforcement authorities. In order to ensure the proper implementation of Directive 2004/37/EC and to provide clarity with regard to the use of and risks relating to the handling of those hazardous medicinal products, it is necessary to take steps to help employers to identify them. The Commission, in line with the Commission communication of 28 June 2021 on an EU strategic framework on health and safety at work 2021-2027, is to provide guidelines, including on training, protocols, surveillance and monitoring, for protecting workers against exposure to hazardous medicinal products.

Recital 12
With regard to the risk assessment provided in Article 3 of Directive 2004/37/EC, when assessing exposure to hazardous medicinal products falling within the scope of that Directive, employers should pay specific attention to ensure that the requirement to replace such products would not be to the detriment of patients' health.

'Article 11 is amended as follows:
(a) in paragraph 1, the second subparagraph is replaced by the following:
"The training shall be:
— adapted to take account of new or changed risk, in particular when workers are or are likely to be exposed to new carcinogens, mutagens or reprotoxic substances or to a number of different carcinogens, mutagens or reprotoxic substances, including those contained in hazardous medicinal products, or in case of changing circumstances related to work,
— provided periodically in healthcare settings to all workers who are exposed to carcinogens, mutagens or reprotoxic substances, in particular where new hazardous medicinal products containing those substances are used, and
— repeated periodically in other settings if necessary."'

'Article 18a is replaced by the following:
Where appropriate and no later than 5 April 2025, taking into account the latest developments in scientific knowledge and after appropriate consultation of relevant stakeholders, the Commission shall develop a definition and establish an indicative list of hazardous medicinal products or the substances contained therein, which meet the criteria for classification as a category 1A or 1B carcinogen set out in Annex I to Regulation (EC) No 1272/2008, a mutagen or a reprotoxic substance. No later than 31 December 2022, the Commission shall, after appropriate consultation of relevant stakeholders, prepare Union guidelines for the preparation, administration, and disposal of hazardous medicinal products at the place of work. Those guidelines shall be published on the website of EU-OSHA and shall be disseminated in all Member States by the relevant competent authorities.'

In addition, the OJ dated 16 March 2022 includes a Joint statement of the European Parliament and the Council on the scope of Directive 2004/37/EC published as follows:

'Joint statement of the European Parliament and the Council on the scope of Directive 2004/37/EC

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.'

Source: The Official Journal of the European Union L 88/2, published on 16 March 2022, at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L:2022:088:TOC

2. Objectives

In March 2022, a consortium led by the consultancy RPA started its work for the European Commission to develop the guidance for the safe management of HMPs at work, including cytotoxics, required by the amendment to and the new Article 18a of the CMRD, which is due to be completed and published by the end of December 2022.

While the European 2022 guidelines will be available for users starting in 2023, the European Commission's indicative list of HMPs to which they apply is unlikely to be ready before 2025. This is likely to hinder the proper and effective use of the guidance document and reduce its usefulness.

The objective of this report and its list is therefore to help users of the guidelines to identify the HMPs that fall under the scope of the new CMRD, and which are present at their workplace, so that they know which drugs apply well ahead of the Commission's indicative list, to be published by 2025. Further, HMPs that are suspected CMRs are also identified, to encourage users of the guidelines to adopt a precautionary approach towards prevention of exposure.

3. Method – Definition and Classification, Labelling and Packaging Regulation (CLP)

This list of HMPs is based on the working definition of HMPs used in the Working Party on Chemicals' Steering group[8], which includes ETUI, and which has been developing the 2022 European guidelines on HMPs with the consortium led by RPA and the European Commission (see box 2). It covers medicinal products (MPs) for both human and veterinary use.

Box 2 **Agreed working definition of HMPs in the 2022 EU guidelines:**

'"Hazardous Medicinal Products (HMPs)" are medicinal products that contain one or more substances that meet the criteria for classification as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B) or toxic for reproduction (category 1A or 1B) in accordance with Regulation (EC) No 1272/2008 of the European Parliament and of the Council and therefore fall within the scope of Directive 2004/37/EC.'

Regulation (EC) No 1272/2008 or CLP (see box 3) is a European Union regulation from 2008[9] which aligns the European Union system of classification, labelling and packaging of chemical substances and mixture with the Globally Harmonised System (GHS).

Box 3 **Regulation (EC) No 1272/2008, also known as the Classification, Labelling and Packaging Regulation (CLP)**

This regulation requires manufacturers, importers or downstream users of substances and mixtures to classify, label and package their substances and mixtures appropriately before placing them on the market. It aims to protect workers, consumers and the environment as well as the free movement of substances, mixtures and articles across the EU.
CLP is legally binding across the Member States and directly applicable to all industrial sectors except the pharmaceutical sector, which has its own rules for the

8. This is a working group within the EU tripartite Advisory Committee on Health & Safety, a body advising the European Commission on Occupational Safety and Health issues.
9. Regulation (EC) No 1272/2008 - Classification, labelling and packaging of substances and mixtures (CLP) https://eur-lex.europa.eu/eli/reg/2008/1272

authorisation and the marketing of medicines (Regulation (EC) No 726/2004[10]). This means that CLP does not apply to MPs for human or veterinary use which are in the finished state intended for the final user. However, CLP applies to substances, including active pharmaceutical ingredients, for use in MPs in a form which is not the final MP.
Under the CLP regulation, suppliers are required to determine whether a substance or a mixture displays properties that lead to a hazardous classification (i.e. physical, health, environmental and additional hazards). Once a substance or mixture is classified, the identified hazards must be communicated to other actors in the supply chain to alert them to the presence of hazards and the need to manage the associated risks. This is done through specific labelling elements made up of pictograms, signal words and standard statements for every hazard and category. For hazards of highest concern, in particular carcinogenicity, mutagenicity or reproductive toxicity (CMR), the classification and labelling is harmonised to ensure an adequate risk management throughout the EU. In practice, this means that suppliers have to classify and label those substances according to the harmonised classification and labelling (CLH) decided at EU level. Substances having CLH are listed in Annex VI to the CLP Regulation.

For substances without CLH, suppliers have to gather and collect all available information, compare them with the CLP criteria, self-classify those substances and mixtures, and label them accordingly. Self-classifications performed by suppliers have to be notified to the European Chemicals Agency (ECHA) which make them publicly available in its C&L inventory[11].The ECHA's C&L inventory lists both substances with a harmonised classification and substances with self-classification.

The starting point of the ETUI list of HMPs (see figure 1) is the National Institute for Occupational Safety and Health (NIOSH) list of hazardous drugs in healthcare settings (see box 4). The NIOSH list includes 229 drugs identified by NIOSH as hazardous to workers in healthcare settings. NIOSH published updated Lists in 2010, 2012, 2014, 2016, and the latest list proposed and published in 2020 has been used in this work and report. The same HMPs are used for both humans and animals, although there are fewer used in animal health than human health, and the 2022 guidelines apply equally to those employed in the healthcare and veterinary sectors.

The working definition of HMPs used in the 2022 European guidelines has then been applied to the 2020 NIOSH list to select the HMPs identified by their CAS number[12] falling under the scope of the CMRD (category 1A or 1B CMRs) or meeting the criteria for classification as category 2 CMRs under the CLP Regulation.

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10. Regulation (EC) No 726/2004 - Community procedures for the authorisation and supervision of MPs for human and veterinary use and establishing the EMA https://eur-lex.europa.eu/eli/reg/2004/726/oj
11. https://echa.europa.eu/information-on-chemicals/cl-inventory-database
12. The Chemical Abstracts Service (CAS) number is a unique numerical identifier assigned by the Chemical Abstracts Service, US to every chemical substance described in the open scientific literature. https://www.cas.org/

For each of these drugs, it has been verified whether they are approved for use in humans under the EU legislation[13] and whether they are being used in at least one EU Member State; this was done by consulting the national medicine registers[14] in France, Ireland, Italy, the Netherlands and Spain. Drugs approved in the US but not in the EU were discarded.

Finally, the remaining HMPs with a harmonised classification or a self-classification as category 1A CMR or category 1B CMR under the CLP Regulation and therefore clearly falling under the scope of the CMRD were listed in Annex I. Those HMPs with a harmonised classification or a self-classification as category 2 CMR are listed in Annex II. All the CLP classifications for the substances included in Annex I and Annex II are derived from the ECHA's C&L inventory. The CLP Regulation defines the hazard categories for mutagens, carcinogens and reproductive toxic agents in tables 3.5.1, 3.6.1 and 3.7.1(a) respectively.

Category 1A: includes chemical substances for which there is scientific evidence based on humans that the substance is **known** to be carcinogenic, mutagenic or reprotoxic for humans; classification in this category is primarily based on human data.

Category 1B: includes chemical substances for which there is scientific evidence based on animals that the substance is **presumed** to be carcinogenic, mutagenic or reprotoxic for humans; classification in this category is primarily based on animal data.

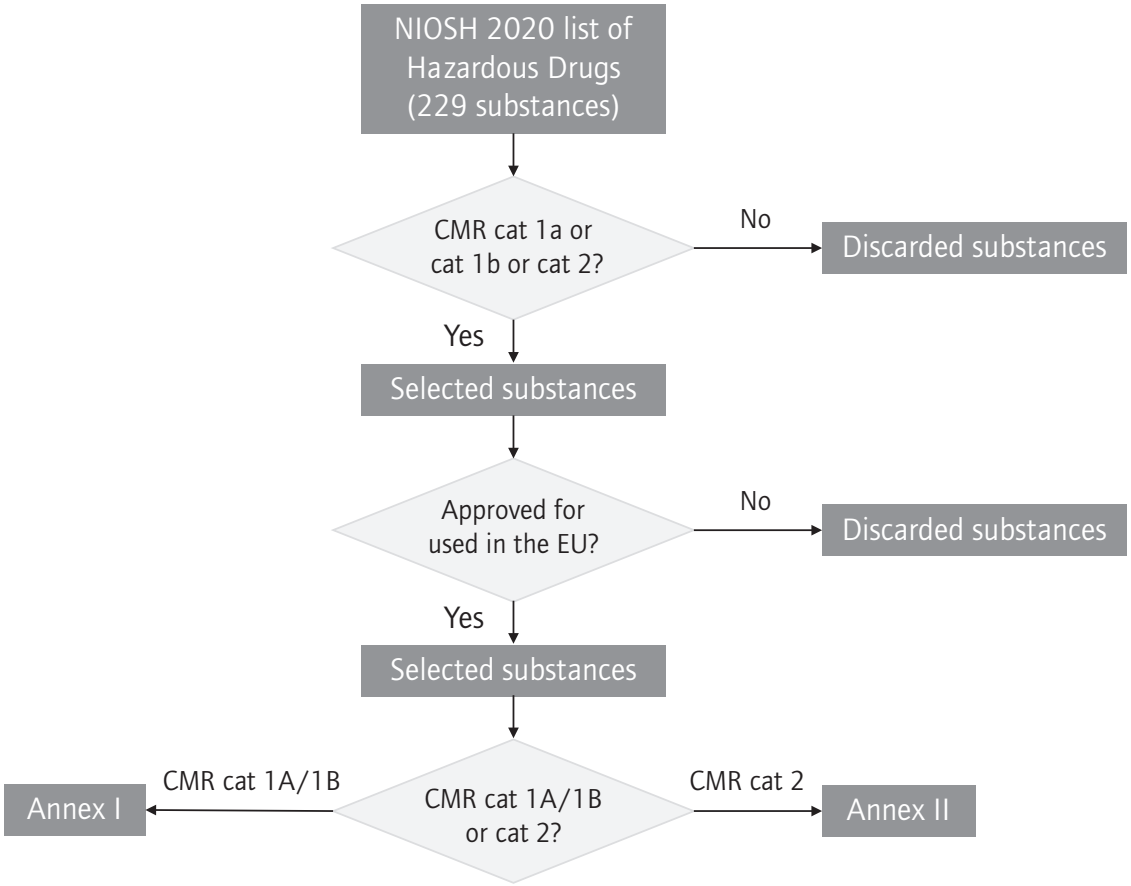
For the CLP classification, notifications from suppliers (self-classification) have been used as the determinant of CLP category. If there was a majority in favour of a 1A or 1B category, it is listed as in a normal text. If there were several self-classifications in a 1A and/or 1B category, but not the majority, asterisks are recorded on the classification, and the notes section shows how many reports considered the HMP to be in that higher CLP category (e.g. 59 of 134).

Category 2: includes chemical substances **suspected** of being carcinogenic, mutagenic or reprotoxic for humans. This classification is done on the basis of evidence obtained from human and/or animal studies not sufficiently convincing to place the substance in category 1A or 1B.

Category 2 substances are not included in Annex I of the list of HMPs as they fall outside the above definition of HMPs. However, they are included in Annex II of the list of HMPs, together with those which contain Manufacturer's Special Handling Information (MSHI) in the package insert.

13. Ibid. 10
14. https://www.ema.europa.eu/en/medicines/national-registers-authorised-medicines

Figure 1 **Methodology ETUI list of HMPs**



Box 4 **NIOSH list of hazardous drugs in healthcare settings**

The NIOSH List of hazardous drugs in healthcare settings assists employers in providing safe and healthy workplaces by identifying drugs approved by the FDA Center for Drug Evaluation and Research (CDER) which have intrinsic properties that meet the NIOSH definition of a hazardous drug.

NIOSH defines a hazardous drug as a drug that is:

1. Approved for use in humans by the FDA-CDER;
2. Not otherwise regulated by the U.S. Nuclear Regulatory Commission;
3. Either: a. Is accompanied by prescribing information in the 'package insert' that specifies special handling information (Manufacturer's Special Handling Information-MSHI) to protect workers handling the drug; or

b. Is identified as a carcinogenic hazard, developmental hazard, reproductive hazard, genotoxic hazard, or other health hazard by exhibiting one or more of the following toxicity criteria in humans, animal models, or in vitro systems:

- carcinogenicity;
- developmental toxicity (including teratogenicity);
- reproductive toxicity;
- genotoxicity;
- organ toxicity at low doses; or
- structure and toxicity profile that mimics existing drugs determined hazardous by exhibiting any one of the previous five toxicity types;

unless the drug also exhibits a molecular property that may limit the potential for adverse health effects in healthcare workers from exposure to the drug.

The NIOSH list creates no legal obligation for employers; it is advisory in nature and informational in content. The latest available version of the list proposed in 2020 contains 229 entries.

Table 1 of the NIOSH 2020 list includes drugs that meet the NIOSH definition of a hazardous drug and contain manufacturer's special handling instructions (MSHI) in the package insert; and/or are classified by the NTP as 'known to be a human carcinogen', or classified by IARC as 'carcinogenic' or 'probably carcinogenic'. In the 2016 List this table identified antineoplastic drugs; however, in this update not all of the drugs in Table 1 are antineoplastic drugs.

Table 2 of the NIOSH 2020 list contains drugs that meet one or more of the NIOSH definitions of a hazardous drug but are not drugs which have MSHI or are classified by the NTP as 'known to be a human carcinogen', or classified by the IARC as 'carcinogenic' or 'probably carcinogenic', some of which also have adverse reproductive effects for populations at risk. This table now also includes drugs that only meet the NIOSH criteria as a developmental (including teratogenicity) and/or reproductive hazard. In the 2016 update of the List this table did not include drugs that only posed a developmental and/or reproductive hazard.

4. Results and Discussion

The working definition of HMPs used in the European Guidance document has been applied to the 2020 NIOSH list to select the 183 HMPs identified by their CAS number[15] falling under the scope of the CMRD (category 1A or 1B CMRs) or meeting the criteria for classification as category 2 CMR under the CLP Regulation. 46 out of the 229 drugs in the proposed 2020 NIOSH list were deselected because they are considered hazardous for other reasons (e.g. organ toxicity at low doses).

For each of these 183 drugs, it has been verified whether they are approved for use in humans under the EU legislation and whether they are being used in at least one EU Member State. 15 out of the 183 substances were deselected as they are not authorised in the EMA national registers of authorised medicines in France, Ireland, Italy, the Netherlands or Spain.

Of the 168 remaining substances, 121 HMPs listed in Annex I fall under the scope of CMRD as CMRs as they have a harmonised classification or a self-classification as category 1A or category 1B CMR under the CLP regulation. 47 HMPs listed in Annex II are suspected of being CMRs as they are classified as category 2 CMRs under the CLP Regulation. These 47 substances do not strictly fall under the scope of the CMRD.

Annex II of the ETUI list also includes 23 HMPs which contain Manufacturer's Special Handling Information (MSHI) in the package insert, of which seven are monoclonal antibodies (mAbs). The physical structure of a drug as a monoclonal antibody does not alone define it as being hazardous. However, while mAbs conjugated with a cytotoxin are to be considered as cytotoxic, it is still unclear whether unconjugated forms are hazardous and whether they can present risks for patients (Bauters and Vandenbroucke 2019). As a precautionary approach, drugs included in Annex II of the ETUI list should be treated in the same way as HMPs listed in Annex I, to prevent the occupational exposure of workers.

The vast majority of HMPs in the ETUI list are self-classified, based on the information provided by manufacturers, suppliers or users who self-classify and label hazardous substances according to the CLP regulation criteria before placing them on the market.

15. Ibid. 12

As the same HMPs are used for both humans and animals (although fewer are used in animal health than in human health), the HMPs identified in the ETUI list are therefore relevant to those employed in both the healthcare and veterinary sectors.

4.1 Further Information provided in Annex I and Annex II of the ETUI list of HMPs

In addition to the CLP classification system, the list also includes the CAS number, the EC number for each compound, the pharmacotherapeutic group for the HMPs (based on the Anatomical Therapeutic Chemical (ATC) classification for the therapeutic category) and then includes the International Agency for Research on Cancer (IARC) categories, National Toxicology Program (NTP) categories (if any), whether the package includes MSHI, and whether, and if so in which table (Table 1 or Table 2) it is included in the NIOSH 2020 proposed list in the US. The therapeutic group included in the ETUI list of HMPs is the main pharmacotherapeutic group, but some HMPs are also used for other off-label indications, and not just the primary indication.

The CAS number of the salt version that is in the medicinal product has also been used where appropriate. In some instances, it is difficult to determine the best CAS number to use so, when in doubt, the number with most notifiers/CLP classification responses has been used.

Drugs that were moved from NIOSH Table 1 to NIOSH Table 2 from the 2016 NIOSH list to the 2020 NIOSH list have been displayed in bold in the list of HMPs.

4.2 Comparison of the ETUI list with other existing lists of medicinal products with hazardous properties

Several lists or databases of medical products with hazardous properties have been developed in different countries. Each of these lists has its own criteria for selecting hazardous drugs.

4.2.1 The Netherlands

In April 2007, the Pharmacy Business Foundation (SBA) and the Royal Dutch Pharmacists Association (KNMP) published the Pharmaceutical Substances Risk Instrument (RiFaS)[16] in the Netherlands. This is a web application that provides insight into the risk assessment regarding the handling of hazardous substances

16. https://rifas.nl/

in pharmacies. It provides advice on how to minimise any health risks during the HMP preparation process. The classification system utilised in this Dutch web application is much broader than the classification system for CMRs used in the ETUI list, in that it does not just include CMRs falling under the CLP regulation but also CMRs classified by the Dutch Health Council and substances with other hazards (such as sensitisers). 100% of the HMPs in the ETUI list are found in the Dutch web application.

4.2.2 Spain

In September 2016, the Spanish National Institute of Safety and Hygiene at Work (INSHT) published a technical document 'Hazardous Drugs, prevention measures for their preparation and administration'[17].

This included, in Table 2, a list of more than 300 hazardous drugs used in Spain and handling and protection recommendations. The HMPs listed were selected on the basis of the classification system used by IARC[18] and included Group 1, a proven carcinogen, Group 2A, a likely carcinogen, Group 2B, a possible carcinogen, or the FDA risk categories for a foetus or pregnant woman, including categories B, C, D or X[19]. The classification system utilised in this Spanish list is much broader than the classification system for CMRs under the CLP Regulation and thus the classification system used in the ETUI list, in that it does not just include proven or likely carcinogens but also possible carcinogens, as well as the FDA categories for reprotoxic risk. Almost 90% of the HMPs in the ETUI list are included in the 2016 Spanish list.

4.2.3 Italy

In April 2017, the Italian Society of Hospital Pharmacists (SIFO) and the Italian Association of Oncology Nurses (AIIAO) published a consensus paper on 'Management of the risk of exposure of healthcare staff in the handling of injectable antineoplastic drugs: prevention aspects and characterisation of safety measures'[20]. This paper included a section on the toxicity of injectable antineoplastic drugs and a list of 20 antineoplastic drugs classified as known carcinogens (Group 1 IARC table), probable carcinogens (Group 2A IARC table) and possible carcinogens (Group 2B IARC table), with their related FDA pregnancy category and pharmaceutical form in use. Like the Spanish list, this Italian list includes a broader classification system than that used for CMRs under the CLP Regulation but restricts it to just injectable antineoplastic drugs that are

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17. https://www.insst.es/documentacion/catalogo-de-publicaciones/medicamentos-peligrosos.-medidas-de-prevencion-para-su-preparacion-y-administracion

18. http://monographs.iarc.fr/ENG/Classification/

19. Content and Format of Labelling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labelling, Federal Register, 73 (104), 29 May 2008.

20. https://www.sifoweb.it/images/pdf/attivita/attivita-scientifica/aree_scientifiche/area_oncologica/CONSENSUS_DOCUMENT_FINALE.pdf

carcinogenic. 100% of the injectable antineoplastic drugs in the 2017 Italian list are included in the ETUI list of HMPs, and 19 of them are in Annex I, with one in Annex II of the ETUI list.

In April 2021, SIFO published a document called 'Hazardous drugs and occupational risk: the unknown siblings of antineoplastic drugs'[21], which includes a list of 116 hazardous non-antineoplastic drugs. This further Italian list was obtained by cross-referencing several international databases, although mainly derived from the NIOSH 2020 list, and thus uses a much broader definition for HMPs than those covered by the CMRD and without any further restriction, by applying either the IARC or CLP classification systems. For each active substance, reported in alphabetical order, the following is specified: pharmaceutical category, formulations currently available on the market, toxicity properties and the relevant bibliographical references. The list also includes drugs that may expose users to biological risk. This further 2021 Italian list includes 55 HMPs included in the ETUI list out of a total of 116 hazardous non-antineoplastic drugs.

4.2.4 France

In July 2021, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) published online the summary and conclusions of a study on exposure to cytostatic agents based on the work of an expert committee and working group[22]. This included a total of 18 cytostatic agents which are currently proposed for inclusion in French national legislation, or Ministerial Order. The ANSES working group primarily selected the cytostatic agents classified as Category 1A and 1B carcinogens according to the CLP Regulation, and agents classified in Groups 1 and 2A by IARC, whose classification criteria are deemed equivalent to those of the CLP. When IARC and EU classifications did not agree, the working group undertook a case-by-case evaluation of CLP and IARC assessments in order to decide whether or not to include the substances in the Ministerial Order. The experts in the working group did not consider the proposed equivalence between IARC's Group 2B and the CLP Regulation's Category 1B to be relevant, or that the classification categories 'likely' (US EPA), 'reasonably anticipated to be a human carcinogen' (NTP) and 'A2' (ACGIH®) were equivalent to categories 1A or 1B of the CLP Regulation. Thus, the classification system utilised in this French list is narrower than the classification system used in the ETUI list of HMPs; also ANSES only considered cytostatic agents with known or suspected carcinogenic properties, rather than the much broader definition of carcinogenic, mutagenic and reprotoxic HMPs under the CLP, included in the scope of the CMRD. 100% of the HMPs in the French 2021 list proposed by ANSES are included in the ETUI list.

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21. http://documentodiconsensofarmacipericolosi.edizioniedra.it/materiali/pdf-farmacipericolosi-eng.pdf

22. https://www.anses.fr/en/content/anses-collective-expert-appraisal-summary-and-conclusions-work-involving-exposure-cytostatic

When comparing the ETUI list (Annex I and Annex II) with other existing lists of HMPs, there is a very good match for CMR substances. However, most of the existing lists include hazards other than CMRs (e.g. sensitisers) and these HMPs are therefore not covered by the provisions of the CMRD. The ETUI list Annex I is the first one that selects only HMPs that strictly fall within the scope of the CMRD.

4.3 Limitations of the ETUI list of HMPs

The starting point of the ETUI list of HMPs is the NIOSH list, which is considered the gold standard at the global level for identifying hazardous drugs to which healthcare workers may be exposed. All hazardous drugs in the NIOSH list are approved for use in the US and it cannot be excluded that some HMPs in the CMRD scope are not identified in the ETUI list because they are approved for use in the EU but not yet in the US.

In 2022, NIOSH made the broad decision to only list drugs on their hazardous drug list that are approved by the FDA subcommittee CDER (Center for Drugs Evaluation and Research), and to remove and not consider drugs approved as biologicals by the FDA Subcommittee CBER (Center for Biologics Evaluation and Research). This further filtering of hazardous drugs by NIOSH now pushes the onerous review and assessment task onto individual healthcare facilities and countries. The biological products approved by CBER are one of the more prolific flows of new drugs, thus relegating the NIOSH from an extremely useful list to one of several outdated lists limited to small molecule drugs. In future, this may hamper the usefulness of the NIOSH list in carrying out a broad and meaningful identification of HMPs used in healthcare settings.

Also, the ETUI list has deselected 15 CMR HMPs (category 1A, 1B or 2) from the NIOSH list because they were not authorised in the national registers of authorised medicines in five EU countries. As the other national registers were not scrutinised, it cannot be excluded, although it is unlikely, that some of these HMPs were erroneously discarded from the ETUI list.

The HMPs in the ETUI list are identified by the names of their active substances and their CAS number, rather than by their brand names, which might have made the list easier to use for healthcare professionals. However, there are many brand names, which also differ from one HMP formulation and from one country and language to another: it would therefore have been very difficult to provide a comprehensive list.

The ETUI list reflects the state of knowledge at the time it was assembled. New HMPs are constantly being brought to market[23], removed from the market or have their authorisation withdrawn. When new toxicological data become available, this list will need to be updated.

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23. For example, one emerging field of new HMPs includes carriers and substrates for drugs such as nanoparticles and viral-vector based encapsulated drugs.

5. Conclusion

Annex I of the ETUI list of HMPs is the first and only publicly available list of HMPs identifying hazardous drugs used in the EU that fall strictly within the scope of the CMRD.

Annex II contains hazardous drugs used in the EU which are not in the scope of the CMRD but which should be treated in the same way as those in Annex I, to avoid exposure of workers, as a precautionary approach.

The ETUI list reflects the state of knowledge at the time it was published. As new HMPs are constantly brought to market, or removed from the market or have their authorisation withdrawn, this list will need to be updated on a regular basis.

Application of the European 2022 guidelines on the safe management of HMPs at work, including cytotoxics, to the drugs identified in the ETUI list should help prevent future occupational exposure for millions of workers across the EU and prevent them from adverse events, such as cancers and reproductive disorders related to the manufacture and use of HMPs.

The ETUI list can also be used by the European Commission to help meet its legal obligation to establish, by April 2025, an indicative list of HMPs which are CMRs.

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All links were checked on 14.09.2022.

Glossary

Term	Definition
Acute effect	An adverse effect on a human or animal body, with severe symptoms developing rapidly during short-term exposure to toxic substances
AIIAO	Italian Association of Oncology Nurses
ANSES	French Agency for Food, Environmental and Occupational Health
Antineoplastic drug	A drug used to treat cancer by inhibiting or preventing the growth and spread of tumours
Antiviral drug	A class of medication used for treating viral infections
Biological safety cabinet (BSC)	An enclosed, ventilated workspace used to protect personnel against biohazardous or infectious agents and maintain quality control of the material being worked with. BSCs are classified into classes I, II, and III depending on the level of protection provided
Bolus injection	The injection of drug in a single large volume
CAD	Chemical Agents Directive (89/391/EEC) Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC)
Carcinogens	Substances and preparations that may cause cancer or increase its incidence
Carers	Patient's family members/friends/volunteers providing care and support for the patient.
CAS number	Chemical Abstract Number, a unique identifier for every substance described in the open scientific literature
CBER	Center for Biologics Evaluation and Research, US
CDER	Center for Drugs Evaluation and Research in the Food and Drug Administration, US
Closed system transfer device (CSTD)	A medicine transfer device that mechanically prevents the transfer of environmental contaminants into the system and the escape of the HMP or vapour concentrations outside the system.
CLP	Classification, Packaging and Labelling Regulation (1272/2008/EC) Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006
CMR	Carcinogenic, Mutagenic or Reprotoxic
CMRD	Carcinogens, Mutagens and Reprotoxins Directive (2004/37/EC) Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC)
Cytostatic	The property of inhibiting cell multiplication or development.
Cytotoxic	The property that a chemical possesses that produces a toxic effect on the cell
Dermal absorption	A route of exposure – taking in HMP or related waste through the skin.
ECHA	European Chemicals Agency
EC number	A unique identification number assigned to chemicals that are commercially available in the EU
EMA	European Medicines Agency
Employer	Any natural or legal person who has an employment relationship with the worker and has responsibility for the undertaking and/ or establishment
EU	European Union
EU-OSHA	European Agency for Safety and Health at Work

Term	Definition
Exposed	A person is exposed to a hazardous chemical if they are in a situation where they absorb or are likely to absorb the substance by ingestion, inhalation or through the skin or mucous membrane. Exposure may also occur as a result of percutaneous injuries.
Exposure (to an HMP)	Exposure to an HMP in the workplace that involves contact between the HMP and the worker, usually by inhalation or through the skin.
FDA	Food and Drug Administration, US
GHS	Globally Harmonised System for Classification and Labelling of Chemicals
Hazard	A hazard is the potential for a substance to adversely affect the health and safety of people in the workplace
Hazardous substance	A substance or mixture with hazardous properties including physical hazards, health hazards or environmental hazards.
HMP	Hazardous medicinal product
IARC	International Agency for Research on Cancer, an intergovernmental agency forming part of the World Health Organization of the United Nations.
Immunosuppressant	A substance or procedure that lessens or prevents adequate response of the immune system
Injection	A sterile fluid preparation of a medicament to be used parenterally (such as by injection, subcutaneously, intramuscularly, intravenously or intrathecally).
INSHT	Spanish National Institute of Safety and Hygiene at Work
Isolator	Provides a perfectly hermetic and secure containment area. It is a piece of equipment for the protection of aseptic preparations.
mAb	Monoclonal antibody
MP	Medicinal Product
MSHI	Manufacturer's Special Handling Information
Mutagens	Substances and preparations that may cause hereditary genetic effects or increase their incidence.
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program in the US
Occupational cancer	Cancer contracted as a result of work performed as a worker during their employment.
Occupational exposure	Exposure to HMPs during a work activity
Oncology	Relating to cancer
Oral	A method of administration – usually in the form of tablets or capsules
OSH	Occupational Safety and Health
OSH FD	Occupational safety and health framework directive (89/391/EEC) Council Directive of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work (89/391/EEC)
Parenteral	Administration of HMP by methods other than through the alimentary canal, such as intravenous, subcutaneous, intramuscular, intrapleural, intraperitoneal, intravesical
Personal protective equipment (PPE)	Any equipment intended to be carried or held by the worker to protect him or her from one or more risks likely to threaten his or her safety or health, and any attachment or accessory intended for that purpose. Personal protective equipment includes gloves, gowns, respiratory protective equipment, and eye protection equipment.
Preparation of HMPs	Handling of HMPs up to the stage of administration to a patient
Prevention	All the steps or measures taken or planned at all stages of work in the undertaking to prevent or reduce occupational risks
Pregnant worker	A pregnant worker who informs her employer of her condition, in accordance with national legislation and/or national practice

Term	Definition
PWD	Pregnant workers' directive (92/85/EEC) Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breast-feeding
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (Regulation (EC) No 1907/2006) Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC
Reprotoxins	Substances and preparations that may produce negative effects on progeny, or increase their frequency, or affect male or female reproductive ability.
RiFaS	Pharmaceutical Substances Risk Assessment (Risico instrument Farmaceutische Stoffen RiFaS) developed by the Royal Dutch Pharmacists Association (KNMP)
Risk	The likelihood that an HMP hazard will cause illness or injury in the conditions of its use.
Risk assessment	Evaluation of the probability that an adverse health effect may occur under the conditions that are likely to develop. Risk assessment of an HMP will take account of its toxicity, the frequency and duration of exposure, control measures in use (engineering, administrative, or personal protective equipment), its effectiveness, and conditions of use.
Risk management	Analysis and judgment that uses the results of risk assessments to produce decisions about actions to be initiated to avert risks.
RPA Ltd	Risk &Policy Analysts Ltd
Sharp	Article capable of piercing skin, such as a used needle or fragment of broken glass that has been in a healthcare setting
SIFO	Italian Society of Hospital Pharmacists
Spill	An unintended release of an HMP from a system such as a primary package of HMP, a syringe, an infusion-set or waste
Substitution	Control measure that substitutes an HMP for a less hazardous one.
Systemic lupus erythematosus	Autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs.
Teratogen	Agent capable of causing harm to an embryo or foetus to produce birth defects.
WHO	World Health Organization
Worker	Any person employed by an employer, including trainees and apprentices
YWD	Young Workers' Directive (Council Directive 94/33/EC) Council Directive 94/33/EC of 22 June 1994 on the protection of young people at work

Annexes

Annex I **Drugs which contain one or more substances which meet the criteria for classification as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B) or toxic for reproduction (category 1A or 1B) in accordance with Regulation (EC) No 1272/2008 of the European Parliament and of the Council**

Bold denotes medicinal products that moved from Table 1 to Table 2 in NIOSH 2020 list

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
abacavir	1B*	-	2	188062-50-2	620-488-4	antiviral	-	-	no	2	"3 of 45 consider carc 1B, Malignant tumors observed in male and female mice and rats; Genotoxic in vivo micronucleus test."
acitretin	-	-	1A*	55079-83-9	259-474-4	antipsoriatics	-	-	no	2	"9 of 47 consider repro 1A (otherwise 1B), Only met the NIOSH criteria as a developmental and/or reproductive hazard"
alitretinoin	-	-	1B	5300-03-8	610-929-9	antineoplastic agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
arsenic trioxide (diarsenic trioxide)	1A	-	-	1327-53-3	215-481-4	antineoplastic agent	1	Known to be human carcinogen	yes	1	"Harmonised CLP classification NTP Classification for 7440-38-2 (arsenic)"
azacitidine	1B	-	-	320-67-2	206-280-2	antineoplastic agent	2A	Reasonably anticipated to be a human carcinogen	yes	1	
azathioprine	1A	1A	1A	446-86-6	207-175-4	immunosuppressant	1	Known to be human carcinogen	yes	1	
bendamustine	2	-	1B	3543-75-7	631-540-0	antineoplastic agent	-	-	yes	1	Cytotoxic; Developmental toxicity
bicalutamide	2*	-	1B*	90357-06-5	618-534-3	antineoplastic agent	-	-	no	2	12 of 196 consider carc 2, repro 1A/B
bleomycin	2	1B	2	9041-93-4	232-925-2	antineoplastic agent	2B	-	yes	1	
bosentan	-	-	1B*	147536-97-8	643-099-1	antihypertensives	-	-	no	2	"1 of 4 consider repro 1B (otherwise 2), Only met the NIOSH criteria as a developmental and/or reproductive hazard"

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
busulfan	1B	-	-	55-98-1	200-250-2	antineoplastic agent	1	-	yes	1	
cabazitaxel	-	2	1A	183133-96-2	680-632-7	antineoplastic agent	-	-	yes	1	
cabozan-tinib	-	-	1B	1140909-48-3	691-711-0	antineoplastic agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard; Embryo lethal in rats at exposures below the recommended human dose"
capecitabine	1B	2	1B	154361-50-9	604-948-1	antineoplastic agent	-	-	yes	1	Metabolized to 5-fluorouracil
carboplatin	-	1B	1B	41575-94-4	255-446-0	antineoplastic agent	-	-	yes	1	
carmustine	1B	-	1B	154-93-8	205-838-2	antineoplastic agent	2A	-	yes	1	
cetrorelix	-	-	1B	145672-81-7	685-963-0	hormonal agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
chlorambucil (leukeran)	1B	-	-	305-03-3	206-162-0	antineoplastic agent	1	Known to be human carcinogen	yes	1	
cisplatin	1B	-	-	15663-27-1	239-733-8	antineoplastic agent	2A	Reasonably anticipated to be a human carcinogen	yes	1	
clofarabine	-	-	1B*	123318-82-1	631-422-9	antineoplastic agent	-	-	yes	1	5 of 46 consider repro 1B
colchicine	-	1B	-	64-86-8	200-598-5	antigout agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
cyclophos-phamide	1B	1B	1A	50-18-0	200-015-4	antineoplastic agent	1	Known to be human carcinogen	yes	1	
cyclosporine	1B	-	1B	59865-13-3	611-907-1	immunosup-pressant	1	Known to be human carcinogen		1	
cytarabine	-	1B*	1B*	147-94-4	205-705-9	antineoplastic agent	-	-	yes	1	30 of 73 consider repro 1B and muta 1B

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
dacarbazine	1B	1B	-	4342-03-4	224-396-1	antineoplastic agent	2B	Reasonably anticipated to be a human carcinogen	yes	1	
dactinomycin	1A	1A	-	50-76-0	200-063-6	antineoplastic agent	-	-	yes	1	
dasatinib	-	-	1B	863127-77-9	638-874-6	antineoplastic agent	-	-	yes	1	
daunorubicin (daunomycin)	2	-	1B*	23541-50-6	245-723-4	antineoplastic agent	2B	-	yes	1	34 of 138 consider repro 1B
decitabine	-	2	1B	2353-33-5	219-089-4	antineoplastic agent	-	-	yes	1	
diethyl-stilbestrol (distilbene)	1B	-	1B	56-53-1	200-278-5	hormonal agent	1	Known to be human carcinogen		1	
dinoprostone	-	-	1B	363-24-6	206-656-6	uterotonics	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
divalproex (depakote)	-	-	1A	76584-70-8	630-325-9	antiepileptic	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard; Black box warning on embryo-fetal death or severe birth defects; Recommend effective contraception for females during therapy and for seven months after treat-ment; Present in semen; No sperm donation during and three months post-treat-ment"
docetaxel	-	-	1B*	114977-28-5	601-339-2	antineoplastic agent	-	-	yes	1	4 of 11 consider repro 1B
doxorubicin	1B	1B*	1B*	25316-40-9	246-818-3	antineoplastic agent	2A	-	yes	1	49 of 155 cosnider muta 1B and repro 1B
dutasteride	-	-	1B	164656-23-9	638-758-5	urologicals	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
entecavir	2	-	1B*	209216-23-9	606-668-5	antiviral	-	-	no	2	1 of 7 consider repro 1B (otherwise 2)

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
enzaluta-mide	-	-	1B*	915087-33-1	805-022-1	antineoplastic agent	-	-	no	2	"4 of 9 consider repro 1B, Only met the NIOSH criteria as a developmental and/or reproductive hazard; Embryo-fetal toxic-ity in mice at exposures that were lower than in patients receiving the recommended dose"
epirubicin	1B*	1B*	1B*	56390-09-1	260-145-2	antineoplastic agent	-	-	yes	1	37 of 128 consider muta 1B and repro 1; 35 of 128 consider carc 1B
ergonovine/ ergometrine/ methyler-gonovine/ methylergo-metrine	-	-	1B*	57432-61-8	260-734-4	uterotonics	-	-	no	2	"4 of 44 consider repro 1B (otherwise 2), Only met the NIOSH criteria as a developmental and/or reproductive hazard; Developmental toxicity – third trimester"
erlotinib	2	-	1A*	183319-69-9	620-491-0	antineoplastic agent	-	-	no	2	"2 of 9 consider repro 1A, Only met the NIOSH criteria as a developmental and/or reproductive hazard"
estramustine	2	-	1B	4891-15-0	225-512-3	antineoplastic agent	-	-	yes	1	
estrogen/ progesterone combinations	1B		1B			hormonal agent	1	Known to be human carcinogen		1	IARC Group 1 carcinogen
estrogens, conjugated	1B	-	1B	12126-59-9	235-199-5	hormonal agent	-	Known to be human carcinogen		1	Black Box warning for endometrial cancer and cardiovascular risks; Long-term use in women and laboratory studies increases frequency of several cancers
estrogens, esterified	1A*	-	1A	50-28-2	200-023-8	hormonal agent	-	Known to be human carcinogen		1	" 57 of 155 consider carc 1A Black Box warning for endometrial cancer and cardiovascular risks"
etoposide	1B	-	-	33419-42-0	251-509-1	antineoplastic agent	1	-	yes	1	
exemestane (aromasid)	-	-	1B	107868-30-4	643-090-2	antineoplastic agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
finasteride	-	-	1B	98319-26-7	620-534-3	urologicals	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
fluconazole/ fluconazol (diflucan)	-	-	1B	86386-73-4	627-806-0	antimycotic agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
fludarabine	1B*	2	1B*	75607-67-9	616-242-0	antineoplastic agent	-	-	yes	1	24 of 81 consider carc 1B and repro 1B (other-wise 2)
fluorouracil	-	1B	1B	51-21-8	200-085-6	antineoplastic agent	-	-	yes	1	
flutamide	-	-	1B*	13311-84-7	236-341-9	antineoplastic agent	-	-	no	2	"12 of 155 consider repro 1B, Indicated only for men"
fulvestrant	-	-	1B	129453-61-8	642-998-6	antineoplastic agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
ganciclovir	2	1B	1B	82410-32-0	627-054-3	antiviral agent	-	-	yes	1	
ganirelix	-	-	1B	124904-93-4	689-234-8	hormonal agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
gemcitabine	-	1B*	1B	122111-03-9	601-823-3	antineoplastic agent	-	-	yes	1	14 of 60 consider muta 1B
goserelin	-	-	1B*	65807-02-5	686-281-6	antineoplastic agent	-	-	no	2	"1 of 18 consider repro 1B, Only met the NIOSH criteria as a developmental and/or reproductive hazard"
histrelin (vantas)	1	1	1B	76712-82-8	636-025-4	antineoplastic agent	1	1	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard; Can cause fetal harm when administered to a pregnant patient with the possibility of spontaneous abortion"
hydroxyurea	-	1B	2	127-07-1	204-821-7	antineoplastic agent	-	-	yes	1	Special warning on handling bottles and capsules
idarubicin	2	-	1B	57852-57-0	260-990-7	antineoplastic agent	-	-	yes	1	
ifosfamide	1A*	1A*	1A*	3778-73-2	223-237-3	antineoplastic agent	-	-	yes	1	1 of 93 considers carc 1A, muta 1A, and repro 1A
imatinib	2*	-	1B*	220127-57-1	606-892-3	antineoplastic agent	-		yes	1	12 of 115 consider repro 1B, 17 of 115 considers carc 2
irinotecan	-	-	1B	136572-09-3	603-967-2	antineoplastic agent	-	-	yes	1	

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
isotretinoin	-	-	1B	4759-48-2	225-296-0	anti-acne agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard; Developmental toxicity
ivabradine	-	-	1B*	148849-67-6	638-798-3	cardiac agent	-	-	no	2	"5 of 47 consider repro 1B, Only met the NIOSH criteria as a developmental and/or reproductive hazard; Developmental toxicity"
ixazomib	-	-	1B	1239908-20-3	813-102-2	antineoplastic agent	-	-	yes	1	Male and female patients of childbearing potential must use effective contraceptive measures during and for 3 months following treatment
lenalidomide	-	-	1B	191732-72-6	691-297-1	immunosup-pressant	-	-	yes	1	Analog of thalidomide; FDA Black box warnings for limb abnormalities; in laboratory studies, caused thalidomide-type limb defects in monkey offspring
letrozole	2*	-	1A*	112809-51-5	675-034-8	antineoplastic agent	-	-	no	2	"7 of 198 consider carc 2, Only met the NIOSH criteria as a developmental and/or reproductive hazard"
leuprolide/ leuprorelin	-	-	1B	53714-56-0	633-395-9	antineoplastic agent	-	1	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
lomitapide	2	-	1B	202914-84-9	692-734-9	lipid modify-ing agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
lomustine	1B	-	-	13010-47-4	235-859-2	antineoplastic agent	2A	-	yes	1	
mechlore-thamine (chlorme-thine/methyl chloride)	1B	1B	1B	55-86-7	200-246-0	antineoplastic agent	-	-	yes	1	
medroxypro-gesterone acetate (provera)	2	-	1B*	71-58-9	200-757-9	hormonal agent	-	-	no	2	"92 of 226 consider repro 1A/1B (otherwise 2), Only met the NIOSH criteria as a developmental and/or reproductive hazard; IARC Group 2B"
megestrol	1B*	-	1A	595-33-5	209-864-5	antineoplastic agent	-	-	no	2	"29 of 124 consider carc 1B (otherwise 2), Nursing should be discontinued if megestrol is required; Women at risk of pregnancy should avoid exposure"

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
melphalan (alkeran)	1A	1B	2	3223-07-2	643-091-8	antineoplastic agent	1	Known to be human carcinogen	yes	1	
methotrexate (jylamvo)	-	1B*	1B	59-05-2	200-413-8	antineoplastic agent	-	-	yes	1	41 of 189 consider muta 1B
mifepristone (mifegyne)	-	-	1B	84371-65-3	617-559-7	other sex hormone	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
misoprostol	-	-	1B	59122-46-2	664-288-5	uterotonics	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
mitoxantrone	-	1B	1B	70476-82-3	274-619-1	antineoplastic agent	2B	-	yes	1	
mycopheno-late mofetil	-	-	1B*	128794-94-5	627-027-6	immunosup-pressant	-	-	yes	2	"11 of 52 consider repro 1B. Black Box warning for embryo fetal toxicity, malignancies and serious infections; Increased risk of first- trimester pregnancy loss and increased risk of congenital malformations; Special warning: tablets should not be crushed and capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in capsules and oral suspension (before or after constitution). If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water."
mycophe-nolic acid (myfortic)	-	2	1B	24280-93-1	246-119-3	immunosup-pressant	-	-	no	2	"Black Box warning for embryo fetal toxicity, malignancies and serious infections; Increased risk of first- trimester pregnancy loss and increased risk of congenital malformations; Black Box warning for lymphomas and other malignancies; genotoxic in vitro and in vivo"
nelarabine	2	2	1B*	121032-29-9	642-916-9	antineoplastic agent	-	-	yes	1	1 of 5 considers repro 1B (otherwise 2)
nilotinib	-	-	1A*	641571-10-0	700-544-5	antineoplastic agent	-	-	no	2	"1 of 5 consider repro 1A (2 of 5 consider repro 2), Only met the NIOSH criteria as a developmental and/or reproductive hazard"

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
olaparib	-	-	1B	763113-22-0	642-941-5	antineoplastic agent	-	-	no	2	Genotoxicity; Developmental toxicity
oxaliplatin	2	1B*	1B*	61825-94-3	621-248-1	antineoplastic agent	-	-	yes	1	13 of 112 consider muta 1B, 15 of 112 cosnider repro 1B
paclitaxel	2	1B*	1B*	33069-62-4	608-826-9	antineoplastic agent	-	-	yes	1	52 of 227 consider repro 1B (otherwise 2), 31 of 227 consider muta 1B
panobinostat	-	-	1B	404950-80-7	803-814-1	antineoplastic agent	-	-	yes	1	Special warnings on contraception for females while taking and one month post- treatment
pasireotide	-	-	1B*	396091-73-9	686-178-6	hormonal agent	-	-	no	2	"1 of 5 consider carc 2, repro 1B (otherwise 2) Only met the NIOSH criteria as a developmental and/or reproductive hazard"
pazopanib	2*	-	1B*	635702-64-6	619-728-0	antineoplastic agent	-	-	no	2	"1 of 5 consider carc 2, repro 1B (otherwise 2). Only met the NIOSH criteria as a developmental and/or reproductive hazard"
pemetrexed	2	-	1B	137281-23-3	680-625-9	antineoplastic agent	-	-	yes	1	
pomalido-mide	-	-	1B*	19171-19-8	805-902-5	immunosup-pressant	-	-	yes	1	"3 of 7 consider repro 1B (otherwise 2) Analog of thalidomide; Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping treatment"
prednimus-tine	1B	-	-	29069-24-7	249-410-3	antineoplastic agent	-	-	-	NA	
procarbazine	1B	-	1A	366-70-1	206-678-6	antineoplastic agent	2A	Reasonably anticipated to be a human carcinogen	yes	1	
progesterone (crinone)	-	-	1A	57-83-0	200-350-6	hormonal agent	2B	-	no	2	
raloxifene	2	-	1A	82640-04-8	639-789-7	hormonal agent	-	-	no	2	"Abortion and developmental abnormalities seen at low doses in laboratory studies; Evidence of tumors at low doses in laboratory studies"

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
regorafenib	-	-	1B	755037-03-7	815-051-1	antineoplastic agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard; Black box warning on severe and sometimes fatal hepatotoxicity; Total loss of pregnancy at doses lower that recommended human dose"
ribavirin	-	-	1B*	36791-04-5	636-825-3	antiviral	-	-	no	2	"55 of 113 consider repro 1B. Only met the NIOSH criteria as a developmental and/or reproductive hazard"
sorafenib	-	-	1B	475207-59-1	641-758-8	antineoplastic agent	-	-	no	2	" Only met the NIOSH criteria as a developmental and/or reproductive hazard"
spirono-lactone (aldactone)	-	-	1B	52-01-7	200-133-6	diuertic agent	-	-	no	2	"Black box warning for tumorogenicity in labora-tory studies"
streptozocin	1B	-	-	18883-66-4	242-646-8	antineoplastic agent	2B	Reasonably anticipated to be a human carcinogen	yes	1	
sunitinib	2	-	1B	341031-54-7	638-825-9	antineoplastic agent	-	-	no	2	
tamoxifen	1A	-	1A	10540-29-1	234-118-0	antineoplastic agent	1	Known to be human carcinogen		1	
temozolo-mide	1B	1B	1B	85622-93-1	630-358-9	antineoplastic agent	-	-	yes	1	
temsirolimus	-	-	1B	162635-04-3	686-177-0	antineoplastic agent	-	-	yes	1	
teniposide	1B	-	-	29767-20-2	249-831-2	antineoplastic agent	2A	-	yes	1	
testosterone (androgel)	2	-	1A	58-22-0	200-370-5	hormonal agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
thalidomide	-	-	1A	50-35-1	200-031-1	immunosup-pressant	-	-	yes	1	

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
thiotepa	1B	1B*	1B*	52-24-4	200-135-7	antineoplastic agent	1	Known to be human carcinogen	yes	1	11 of 52 consider muta 1B and repro 1B
tofacitinib	-	-	1B	540737-29-9	638-826-4	antineoplastic agent	-	-	no	2	Black box warning for lymphoma and other malignancies
topotecan	-	1B*	-	123948-87-8	687-471-1	antineoplastic agent	-	-	yes	1	9 o7 condider muta 1B (otherwise 2)
treosulfan	1A	-	-	299-75-2	206-081-0	antineoplastic agent	-	-	no	NA	
tretinoin	-	-	1B	302-79-4	206-129-0	antineoplastic agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
triptorelin	-	-	1A	124508-66-3	689-181-0	antineoplastic agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
ulipristal	-	-	1B*	126784-99-4	682-170-1	hormonal agent	-	-	no	2	"2 of 7 considers repro 1B, Only met the NIOSH criteria as a developmental and/or reproductive hazard"
urofollitropin	-	-	1B	146479-72-3	686-287-9	hormonal agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard; Developmental toxicity"
valganciclovir	1A	1A	1A	175865-59-5	641-360-4	antiviral	-	-	yes	1	
valproate/ valproic acid (epilim/de-paken)	-	-	1A	99-66-1	202-777-3	antiepileptic	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
vandetanib (calpresa)	-	-	1B	443913-73-3	669-841-4	antineoplastic agent	-	-	yes	1	
vinorelbine	-	2	1B	125317-39-7	639-264-2	antineoplastic agent	-		yes	1	
voriconazole	-	-	1B*	137234-62-9	629-701-5	antimycotic agent	-	-	no	2	"36 of 176 considers repro 1B, Only met the NIOSH criteria as a developmental and/or reproductive hazard"
warfarin/ warfarin sodium	-	-	1A	129-06-6	204-929-4	antithrom-botic agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
zidovudine	1B	2	2	30516-87-1	623-849-4	antiviral	2B	-	no	2	

Annex II **Drugs that contain one or more substances which meet the criteria for classification as carcinogenic (category 2), mutagenic (category 2), or toxic for reproduction (category 2) in accordance with Regulation (EC) No 1272/2008 of the European Parliament and the Council and/or which contain drugs that contain Manufacturer' s Special Handling Information (MSHI) in the package insert**

Bold denotes medicinal products that moved from Table 1 to Table 2 in NIOSH 2020 list

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
abiraterone	-	-	2	154229-18-2	620-314-7	antineoplastic agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard; Women who are pregnant or women who may be pregnant should not handle without protection (e.g., gloves)"
altretamine (hexastat)	-	-	-	645-05-6	211-428-4	antineoplastic agent	-	-	yes	1	
ambrisentan	-	-	2	177036-94-1	658-059-9	antihyperten-sives	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
amsacrine	-	-	-	54301-15-4	637-255-8	antineoplastic agent	2B	-	yes	1	
axitinib	-	2*	2*	319460-85-0	638-771-6	antineoplastic agent	-	-	no	2	"32 of 71 consider repro 2, 31 of 72 consider muta 2 Teratogenic, embryotoxic and fetotoxic in mice at exposures lower than human exposures"
bexarotene (targretin)	-	-	2	153559-49-0	681-650-8	antineoplastic agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
bortezomib	-	-	2	179324-69-7	605-854-3	antineoplastic agent	-	-	yes	1	
brentuximab vedotin	-	-	-	914088-09-8	-	antineoplastic agent	-	-	yes	1	Monoclonal antibody conjugated to vedotin
carfilzomib	-	-	2	868540-17-4	692-054-2	antineoplastic agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard; Special warnings on contraception while taking and two weeks post-treatment"
chloram-phenicol	2	-	2	56-75-7	200-287-4	antibacterial agent	2A	Known to be human carcinogen		1	
cidofovir	2	2	2	113852-37-2	638-807-0	antiviral	-	-	yes	1	
cladribine	-	-	-	4291-63-8	636-978-6	antineoplastic agent	-	-	yes	1	

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
clomiphene (clomid)	-	-	2	50-41-9	200-035-3	hormonal agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard
crizotinib	-	2	-	877399-52-5	638-814-9	antineoplastic agent	-	-	no	2	
dabrafenib	-	-	2	1195765-45-7	689-166-9	antineoplastic agent	-	-	no	2	"Special warnings on contraception for females while taking and two weeks post-treatment"
dexrazoxane (savene)	-	-	-	24584-09-6	635-584-1	Detoxifying agent	-	-	yes	1	Secondary malignancies observed in patients treated long term with Razoxane (a racemic mixture containing dexrazoxane); Genotoxic in vitro and in vivo; in labora-tory studies, Testicular atrophy observed at or below the human dose
dronedarone (multaq)	-	-	2*	141625-93-6	630-355-2	Antiarrhyth-mic agent	-	-	no	2	"4 of 13 consider repro 2, Only met the NIOSH criteria as a developmental and/or reproductive hazard"
enfortum-ab vedotin	-	-	-	1346452-25-2	-	antineoplastic agent	-	-	yes	1	Monoclonal antibody conjugated to vedotin; Cytotoxic; Developmental toxicity
eribulin	2	2	2	253128-41-5	803-583-7	antineoplastic agent	-	-	no	2	
everolimus	-	-	-	159351-69-6	621-003-9	antineoplastic agent	-	-	yes	1	
exenatide	2	-	2	141758-74-9	686-356-3	diabetic agent	-	-	no	2	Carcinogenicity; Developmental toxicity
gemtuzumab ozogamicin	-	-	-	220578-59-6	-	antineoplastic agent	-	-	yes	1	Monoclonal antibody conjugated to ozogamicin; Cyto-toxic; Developmental toxicity
gonadotro-pin, chorionic	-	-	2	165174-59-4	634-095-0	hormonal agent	-	-	no	2	"Only met the NIOSH criteria as a developmental and/or reproductive hazard"
inotuzumab ozogamicin	-	-	-	635715-01-4	-	antineoplastic agent	-	-	yes	1	Monoclonal antibody conjugated to ozogamicin; Cyto-toxic; Developmental toxicity
lenvatinib	-	-	2	857890-39-2	812-398-0	antineoplastic agent	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard; Developmental toxicity
liraglutide recombinant	2	-	2	204656-20-2	810-818-7	diabetic agent	-	-	no	2	"Black Box warning for thyroid C-cell tumors, with sup-porting evidence in laboratory studies; In laboratory studies, teratogenic at or below the MRHD"
mercaptopu-rine	-	-	-	50-44-2	200-037-4	antineoplastic agent	-	-	yes	1	

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
methimazole (thiamazole)	-	-	2	60-56-0	200-482-4	antithyroid agent	-	-	no	2	Appears in human breast milk
mitomycin	2	-	-	50-07-7	200-008-6	antineoplastic agent	2B	-	yes	1	
mitotane (lysodren)	2	-	-	53-19-0	200-166-6	antineoplastic agent	-	-	yes	1	
ospemifene (senshio)	2*	-	2*	128607-22-7	664-452-6	hormonal agent	-	-	no	2	"29 of 68 consider carc 2, repro 2, Black box warning on increased risk of endometrial cancer in certain populations; Risk of adverse outcomes during pregnancy and labor"
pentostatin (nipent)	-	-	-	53910-25-1	637-271-5	antineoplastic agent	-	-	yes	1	
phenytoin (epanutin)	2	-	2	630-93-3	211-148-2	antiepileptic	2B	-	no	2	
polatuzumab vedotin	-	-	-	1313206-42-6	-	antineoplastic agent	-	-	yes	1	Monoclonal antibody conjugated to vedotin; Cytotoxic; Developmental toxicity
ponatinib	2	-	2	1114544-31-8	696-530-0	antineoplastic agent	-	-	no	2	
propylthi-ouracil	2	-	-	51-52-5	200-103-2	antithyroid agent	2B	-	no	2	IARC Group 2B
sirolimus	2	-	2	53123-88-9	610-965-5	immunosup-pressant	-	-	no	2	"AKA rapamycin; Increased risk of lymphomas and other malignancies; Embryotoxic and fetotoxic at 0.2 HD"
tacrolimus	-	-	2	104987-11-3	658-056-2	immunosup-pressant	-	-	no	2	Increased risk of lymphomas and other malignancies; Reproductive effects seen in laboratory studies below the MRHD; Excreted in breast milk
thioguanine (lanvis)	-	-	-	154-42-7	205-827-2	antineoplastic agent	-	-	yes	1	
trabectedin	-	2	2	114899-77-3	695-026-8	antineoplastic agent	-	-	yes	1	Cytotoxic; Genotoxic
trametinib	-	-	2	1187431-43-1	629-898-8	antineoplastic agent	-	-	no	2	Embryotoxic and abortifacient at doses less than recom-mended human dose
trastuzumab deruxtecan	-	-	-	-	-	antineoplastic agent	-	-	yes	1	Monoclonal antibody conjugated to deruxtecan; Cytotoxic

Drug	CLP Carc. Group	CLP Muta Group	CLP Repro Group	CAS Number	EC / List Number	Therapeutic Group	IARC Group	NTP Cate-tory	MSHI	NIOSH 2020 Table	Supplemental Information
trastuzumab emtansine	-	-	-	1018448-65-1	-	antineoplastic agent	-	-	yes	1	Monoclonal antibody conjugated to mertansine (emta-sine)
trifluridine	2	-	-	70-00-8	200-722-8	antineoplastic agent	-	-	yes	1	Embryo-fetal lethality and embryo-fetal toxicity at doses lower than or similar to exposures at the recommended human dose
vinblastine	-	-	-	143-67-9	205-606-0	antineoplastic agent	-	-	yes	1	
vincristine	-	2	2	2068-78-2	218-190-0	antineoplastic agent	-	-	yes	1	
zonisamide	-	-	2	68291-97-4	614-395-8	antiepileptic	-	-	no	2	Only met the NIOSH criteria as a developmental and/or reproductive hazard

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