New EU legislation on Hazardous Medicinal Products (HMPs) and ETUI list for HMPs identification

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Summit: Preventing occupational exposure to HMPs

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Uses of Hazardous Medicinal Products (HMPs)

- ✓ cancer treatment
  - cytotoxic / cytostatic
  - antineoplastic
- ✓ antivirals
- ✓ vaccines
- ✓ immunosuppressants
- ✓ multiple sclerosis
- ✓ psoriasis
- ✓ lupus erythematosus
- ✓ organ transplantation
- ✓ …

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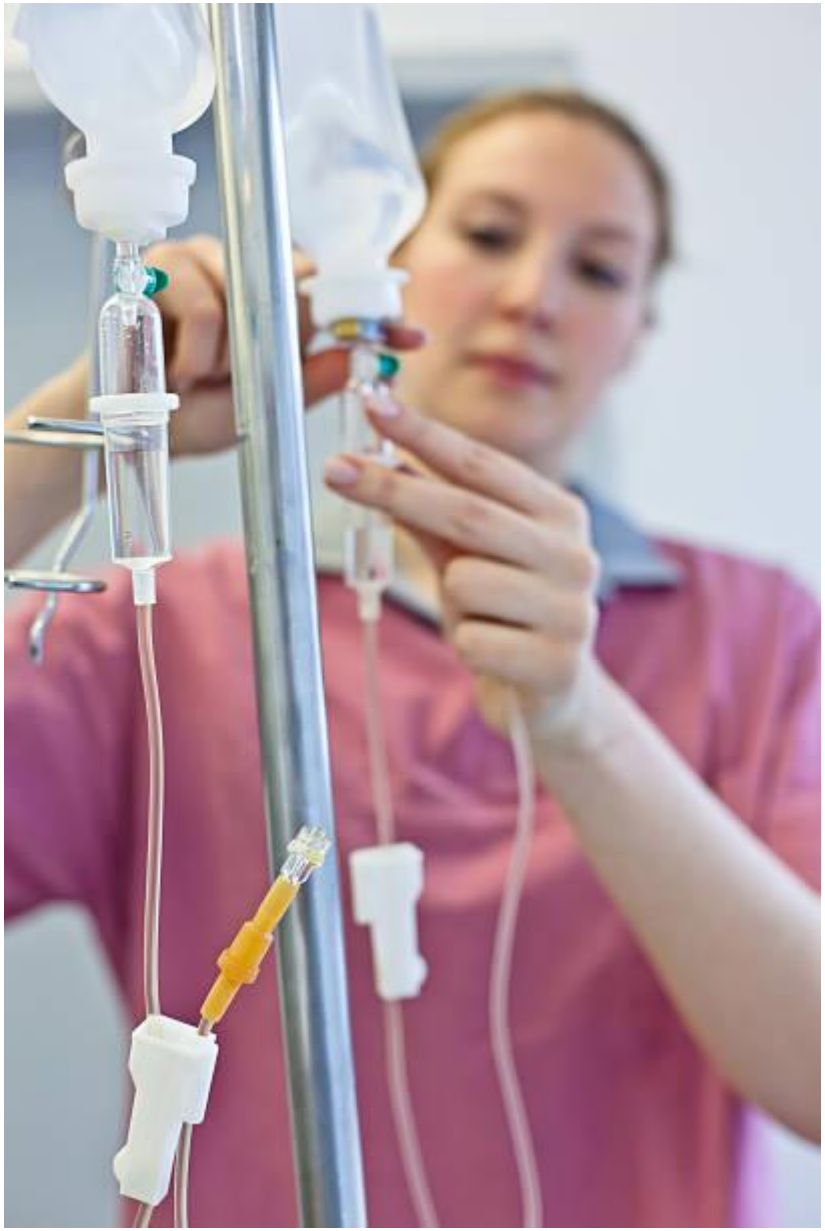
What are the risks for healthcare professionals?



- ✓ hair loss
- ✓ taste disturbance
- ✓ headaches
- ✓ infections
- ✓ respiratory diseases
- ✓ **cancers**
- ✓ **reproductive disorders for male & female workers**

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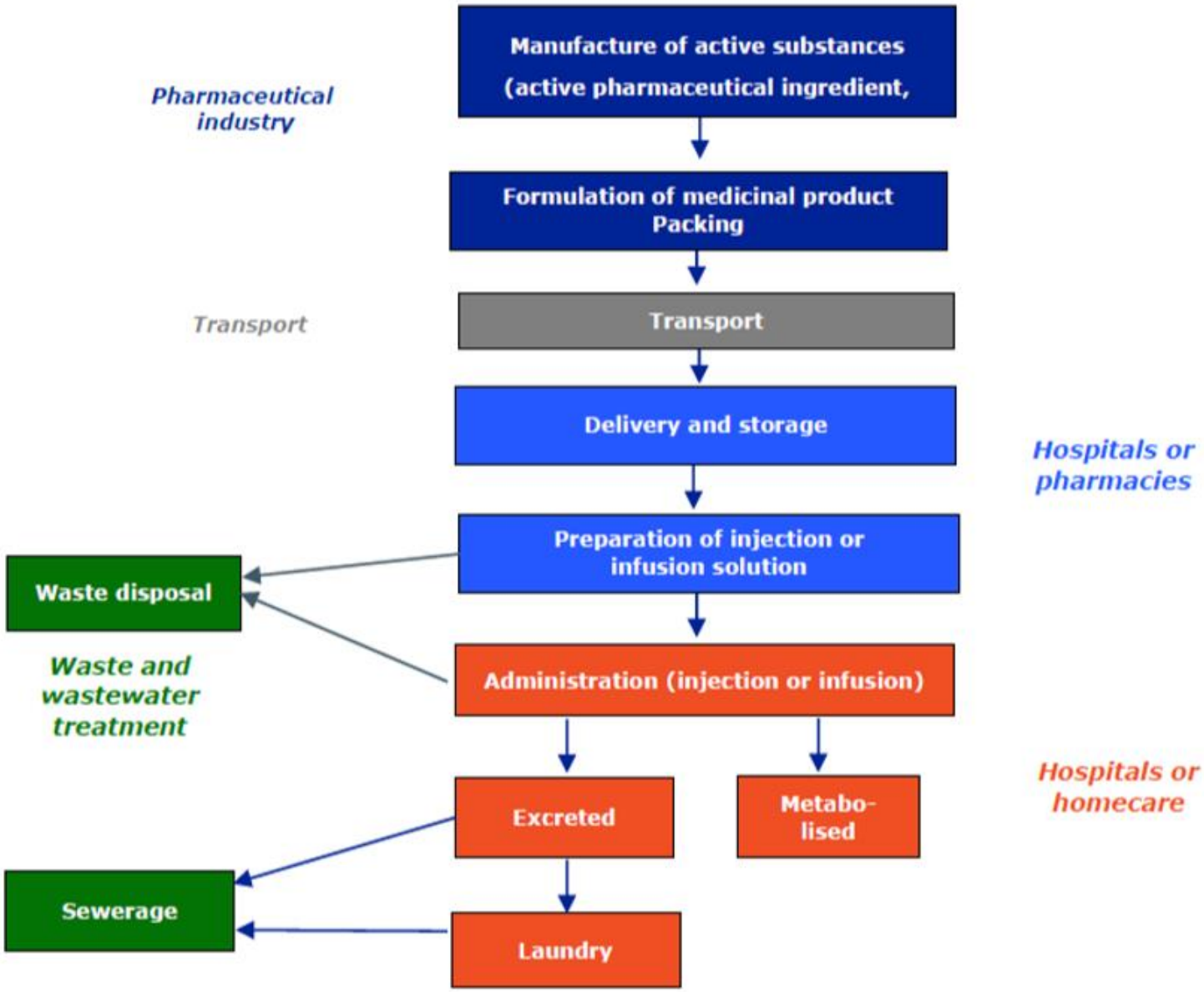
Who and where are the workers at risk?



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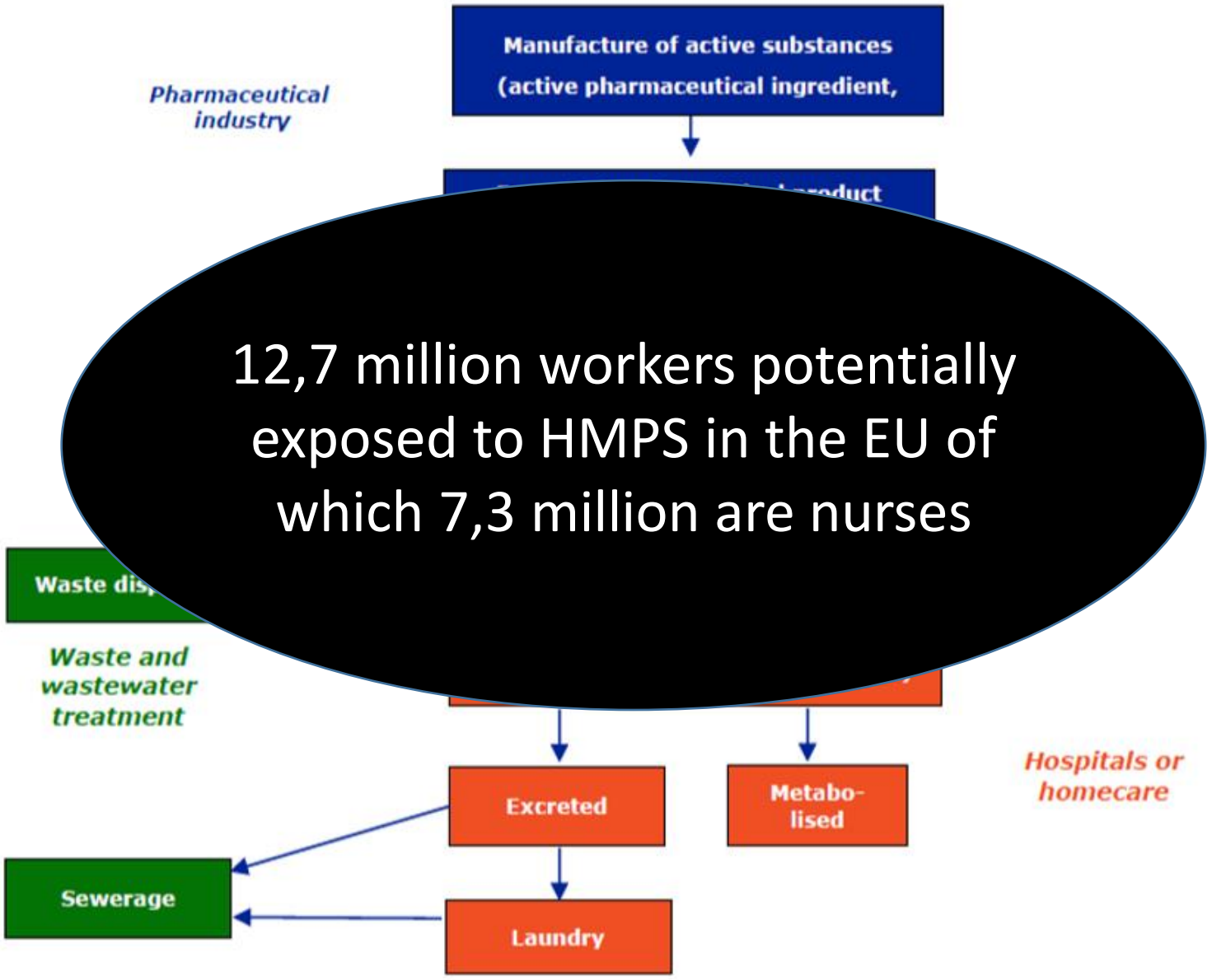

What does the new EU OSH legislation say on HMPs ? 1/2

Directive 2004/37/EC on the protection of workers from the health and safety risks related to exposure to carcinogens, mutagens or substances toxic to reproduction (CMR) at work (revised in Dir 2022/431 to include HMPs, March 2022)

- in Article 11: **mandatory training** for workers exposed to CMRs contained in HMPs

- recital + joint statement acknowledging that **HMPs** that are CMRs (cat 1A/1B) **are in the scope** of CMR Directive

*"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*." – 16 March 2022

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What does the new EU OSH legislation say on HMPs ? 2/2

- In Article 18a, **obligations** put on the Commission:

  - ✓ to prepare updated **EU guidelines** for the preparation, administration and disposal of HMPs at the workplace **no later than 31 Dec 2022**

    Published on EU-OSHA website in April 2023

  - ✓ to develop a **definition for HMPs** and establish an **indicative a list of HMPs** that are CMRs cat 1A/1B **no later than 5 April 2025**

    ongoing work

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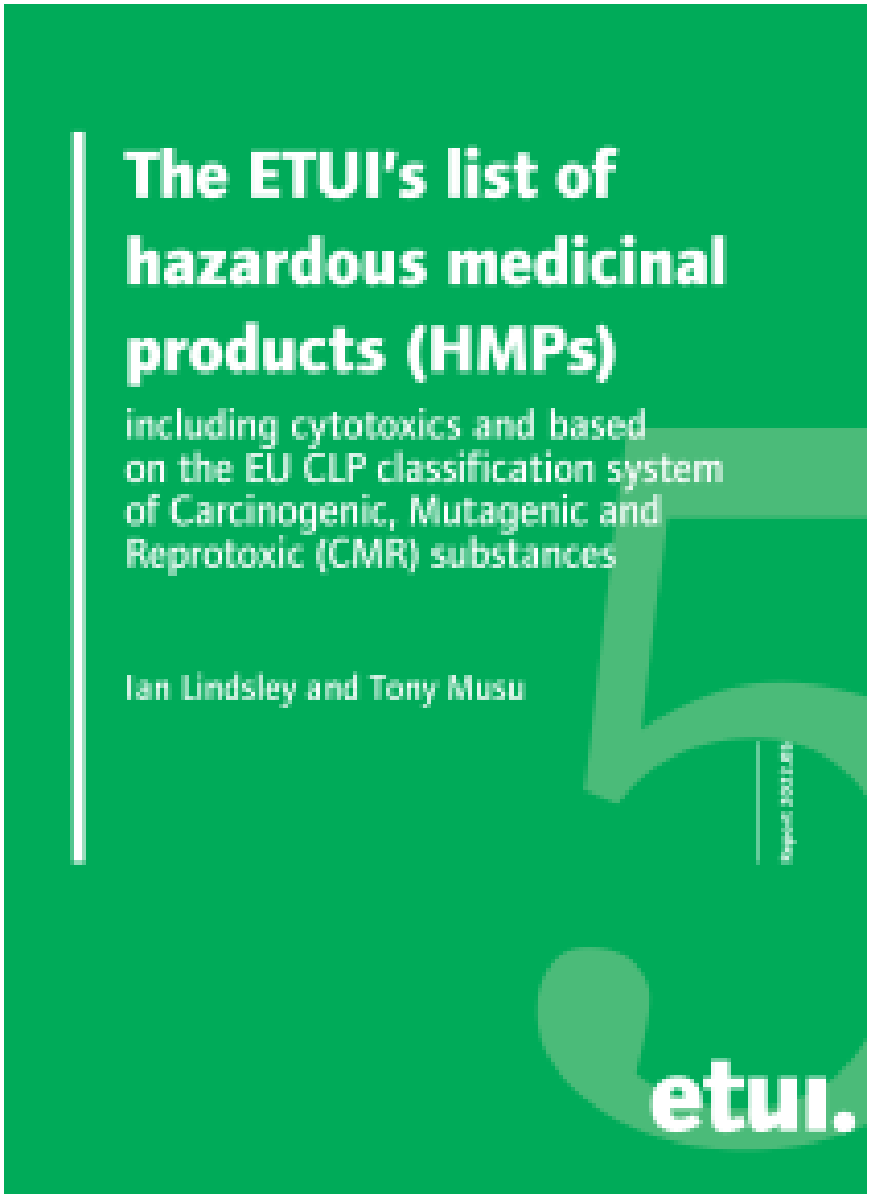
Objectives of the ETUI's list of HMPs ?



1. Identify which HMPs fall under the scope of new EU legislation
2. Help users of the EU 2023 guidelines know which specific HMPs the guidelines apply to, well ahead of 2025
3. Raise awareness of the risks of HMPs in healthcare workers

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Working definition of HMPs used in the 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.

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Definition of Carcinogens, Mutagens, Reprotoxics (CMRs)

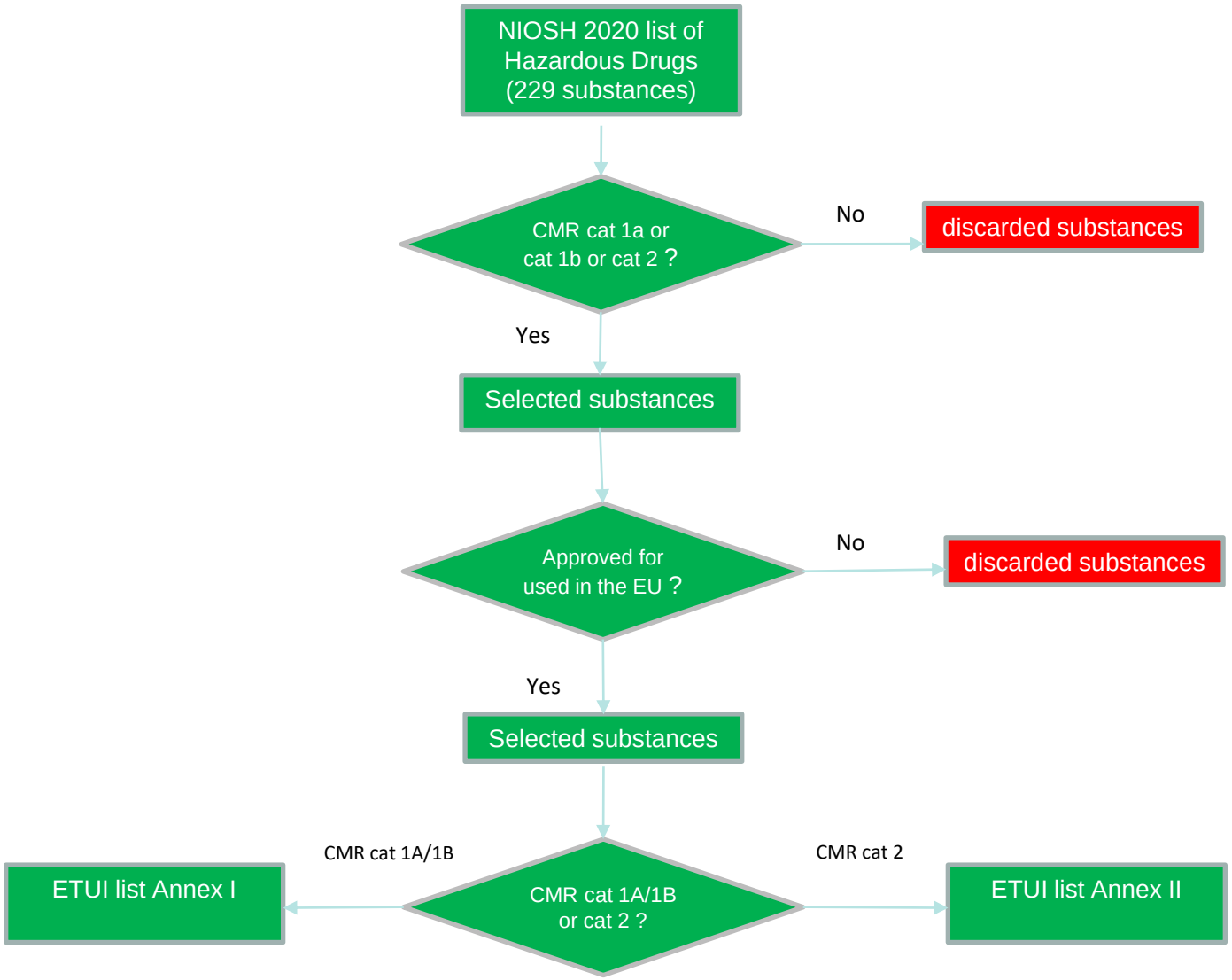
The EU legislation regarding Classification Labelling and Packaging of substances – the CLP Regulation or Reg (EC) No 1272/2008

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

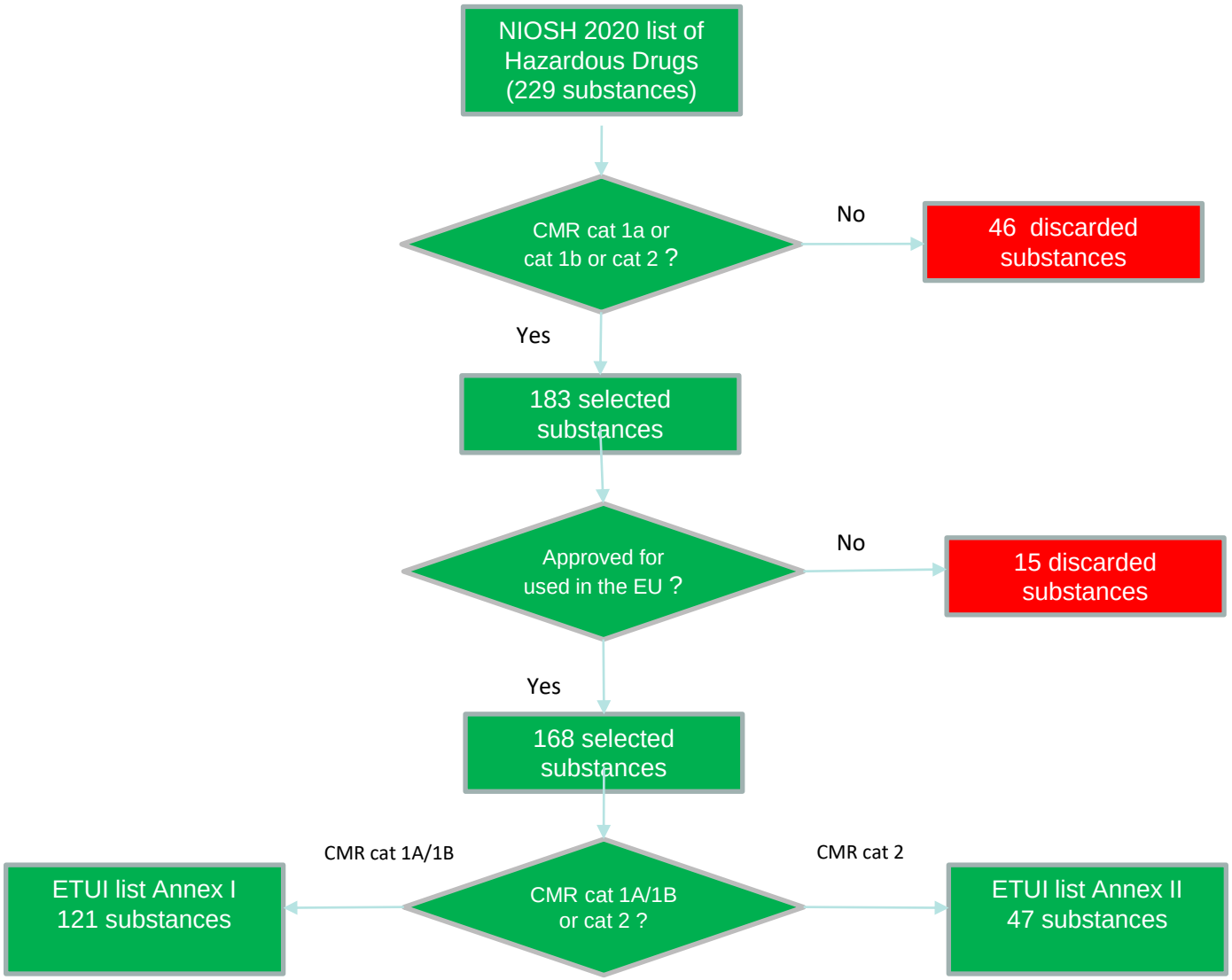
The European Chemicals Agency (ECHA)'s Classification & Labelling Inventory lists all CMR substances on the EU market with:

- EU harmonized classification or
- Self-classification from suppliers

Methodology used in the ETUI's list of HMPs



Results of the identification of HMPs in the ETUI's list



Annex I of ETUI's list = 121 HMPs strictly falling under CMRD scope

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*

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Annex II = 47 HMPs to be treated as Annex I (precautionary approach)

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	

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What are the limitations of ETUI's list of HMPs?

- HMPs are identified principally by their CAS number rather than by their brand names
- Some HMPs approved for use in the EU but not yet in the US may not be identified
- HMPs erroneously discarded from the ETUI list (even if this is unlikely)
- The ETUI's list of HMPs will need to be updated on a regular basis

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How does the ETUI's list compare with other lists of HMPs?

Other existing lists of HMPs & publication year	Country	Hazards covered	% of HMPs in ETUI's list included in other lists
RiFaS 2007	The Netherlands	CMRs + many others (sensitisers…)	100 %
INSHT 2016	Spain	IARC CMRs, FDA reprotoxics	100%
SIFO/AIIAO 2017	Italy	IARC CMRs + reprotoxics	100%
SIFO 2021	Italy	IARC + CLP CMRs	100 %
ANSES 2021	France	18 HMPs	100 %

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How does the ETUI's list compare with other lists of HMPs?

- The ETUI list (Annex I) only selects HMPs that are strictly included within the scope of the CMRD as defined above in the joint statement by the European Parliament and Council

- Other published lists and databases use their own criteria for selecting hazardous drugs and rely on a range of different definitions of HMPs

- When comparing the ETUI list with other existing lists of HMPs there is a very good match for CMR substances

- However, most of the existing lists use a broader classification system than category 1A or 1B CMRs under the CLP Regulation which is the classification system and definition used in the ETUI list

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Conclusions

- Annex I of the ETUI list of HMPs is the **first and only list** of HMPs publicly available identifying hazardous drugs used in the EU that strictly fall within the scope of the EU legislation (CMRD)
- Annex II contains hazardous drugs used in the EU which are not in the scope of the CMRD but which **should be treated as those in Annex I** to avoid exposure of workers **in a precautionary approach**
- The application of the European 2023 guidelines on the safe management of HMPs at work to the drugs identified in the ETUI list should **help prevent future occupational exposure in millions of workers across the EU**, such as cancers and reproductive disorders related to manufacture and use of HMPs
- The ETUI list is **used by the European Commission** to help meet its legal obligation **to establish by April 2025 an indicative list of HMPs that are CMRs**

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Thank you for your attention !

The ETUI's list of HMPs is available for free at

https://www.etui.org/publications/etuis-list-hazardous-medicinal-products-hmps

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