European Federation of Pharmaceutical Industries and Associations

EFPIA Survey on Active Pharmaceutical Ingredients: Report on current and proposed CLP[1] hazard classes

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Introduction

In 2020 European Commission (COM) published the 'Chemicals Strategy for Sustainability Towards a Toxic-free Environment' (CSS), setting the scene for the greatest overhaul of the EU chemicals management regulation since the creation of REACH[2] almost 20 years ago. The CSS outlines over 80 actions, including but not limited to introduction of new hazard classes into CLP Regulation (endocrine disruptors, PBT/vPvB and PMT/vPvM[3]), extending the Generic Approach to Risk Management (GRA) under REACH, and introducing 'one substance, one assessment' approach (OSOA).

Whilst EFPIA strongly supports the overarching objectives of the CSS, we are concerned that COM is looking at each of the actions in isolation and without detailed consideration of regulatory interlinks between horizontal and sectoral pieces of EU chemicals regulation.

Active Pharmaceutical Ingredients (APIs) represent a group of chemicals at an intersection between REACH, CLP, and sectoral (medicinal products) legislation. Whilst currently not being subjected to harmonised classification and REACH registration/authorisation, **APIs are at the same time not being exempted from REACH restriction process**. Extending the GRA approach to professional uses (REACH revision process) coupled with potentially expanding the scope of CLP Regulation to medicinal products (CLP revision process) could therefore result in removal of certain medicines from the EU market, irrespectively of the provisions of the Medicinal Products Directive[4] and Regulation for Medicinal Products Authorisation[5].

In order to illustrate the potential impact of ongoing CLP and REACH revision on medicinal products in the EU, EFPIA conducted a survey amongst the member companies in August 2022. The survey aims to identify which APIs would fall under both existing and new hazard classes and serve as input to COM's assessment. Whilst all-encompassing impact assessment of the entire pharma sector was not possible within the compressed timeframe of CLP and REACH revision, the results may provide valuable additional information for specific CSS actions. This document summarises the preliminary results of the EFPIA survey on current and future CLP hazard classes.

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[1] 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

[2] 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)

[3] PBT – Persistent, Bioaccumulative and Toxic; vPvB – very Persistent and very Bioaccumulative; PMT – Persistent, Mobile and Toxic; vPvM – very Persistent and very Mobile

[4] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

[5] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use

Methodology

Each participating company filled in the spreadsheet provided by EFPIA, listing hazard classes conclusions for each API. Following the completion of the survey, received anonymised input was aggregated for the data analysis.

As some of the criteria for the new hazard classes are yet to be defined in the CLP Regulation, at this point it was only possible to apply professional judgement to the best available information on proposed classification criteria. In order to ensure consistency, EFPIA provided guidance for specific hazard classes as specified below.

General API information

For each APIs member companies were asked to specify the molecule type, patent status, and Anatomical Therapeutic Code (ATC Level 2). In addition, member companies were asked to specify would the molecule fulfil the OECD PFAS (per and polyfluoroalkyl substances) definition[6] in order to obtain information on the fluorinated APIs in companies product portfolio.

Human Health: Existing Hazard Classes

The survey contains information on the following existing hazard categories: Carcinogenicity, Mutagenicity, Reproductive toxicity, STOT (single and repeated exposure), and Respiratory sensitisation. The assessment was conducted in line with the criteria currently in place under CLP Regulation.

Human Health: Endocrine Disruption

It was recommended that survey participants use the new criteria referenced in REACH Annex II legal text [BPR - Regulation (EU) 2017/2100 or PPP Regulation (EU) 2018/605]. If this was not possible, reprotoxic classification criteria were applied as follows:

- "Pending the adoption of these criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties"
- "In addition, substances such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties."

Human Health: Immunotoxic & Neurotoxic Substances

In-depth evaluation of the supporting toxicological studies for the STOT RE was not possible in the timeframe available for this exercise. However, as COM intends to propose the introduction of the respective hazard classes into Globally Harmonized System of Classification and Labelling of Chemicals (GHS) in the future, we provided the relevant information where available.

[6] OECD: "PFAS are defined as fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), i.e. with a few noted exceptions, any chemical with at least a perfluorinated methyl group (-CF3) or a perfluorinated methylene group (-CF2-) is a PFAS."

Environment: Endocrine Disruption

At this point it is not yet known how ENV ED properties will be assessed under CLP, but in the absence of other guidance the assessment was based on joint ECHA/EFSA guidance for the identification of endocrine disruptors[7]. As the data requirements outlined in the current Guideline on the environmental risk assessment of medicinal products for human use[8] as well as the available revised draft text of that guidance do not provide a basis to conclude on ED properties in line with ECHA/EFSA guidance document, it was only possible to indicate the potential ENV ED status in case relevant studies were available.

Environment: PBT and vPvB Substances

The CLP guidance document for PBT assessment is yet to be drafted. Following the expert meetings with COM, ECHA, and EU Member States Competent Authorities (MSCAs), the current expectation is that the assessment will be based on ECHA GD Chapter R.11: PBT/vPvB assessment[9]. It is important to note that the current information requirements for medicinal products are not fully compatible with the provisions of ECHA PBT guidance, as specified below for each of the criteria.

Persistence. In cases where the persistence criterion (vP or P) was fulfilled based on Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (OECD 308), the API was concluded to be (very) persistent. If this study was not available, the conclusion was based on ready biodegradability study (OECD 301): API was considered to potentially fulfil the (v)P criterion if not readily biodegradable, and not to fulfil the criterion if readily biodegradable.

Bioaccumulation. In cases where the bioaccumulation (vB or B) criterion was fulfilled based on the study of bioaccumulation in fish (OECD 305), the API was concluded to be bioaccumulative. If this study was not available, the conclusion was based on the octanol-water partitioning coefficient (Kow): API was considered to potentially fulfil the (v)B criterion if Log Kow > 4.5, and not to fulfil the criterion if Log Kow ≤ 4.5.

Toxicity. APIs fulfilling relevant human health classification criteria (Carcinogenicity and Mutagenicity Category 1, Reprotoxicity Categories 1 or 2, STOT RE Categories 1 or 2) were concluded to be toxic. APIs for which chronic endpoints for aquatic organisms (NOEC or EC10) were below 0.01 mg/l were concluded to be toxic.

Environment: PMT and vPvM Substances

The CLP guidance document for PMT assessment is yet to be drafted. Whilst the assessments of P and T criteria could be based on ECHA GD for PBT/vPvB assessment, it is important to note that criteria for mobility in the context of PMT assessment have never been agreed nor implemented in any regulatory framework. Thresholds for the M criterion were discussed in 2021-2022 in several ECHA PBT Expert Group meetings as well as the CARACAL meetings (meetings of competent authorities for REACH and CLP), and the delegated act introducing the new hazard classes is still to be presented by COM.

For the purpose of this exercise, P and T criteria were assessed in the same way as in PBT assessment, as outlined above.

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[7] ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority). 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018; 16(6): 5311, 135 pp.

[8] EMA (European Medicines Agency). 2006. Guidance on the environmental risk assessment of medicinal products for human use. Doc. Ref. EMEA/CHMP/SWP/4447/00 corr 2, 12 pp.

[9] ECHA (European Chemicals Agency). 2017. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB Assessment. ECHA-17-G-12-EN, 158 pp.

Mobility. As all discussions up to date indicate that COM will base the mobility assessment on organic carbon to water partition coefficient (Koc) and the Log Koc values of 2 and 3, this is the approach taken for the purpose of this exercise:

- API was considered to fulfil the vM criterion if Log Koc < 2;
- API was considered to fulfil the M criterion if Log Koc < 3.

The Koc value used was the lowest obtained value from the adsorption - desorption batch equilibrium study (OECD 106) where available, or alternatively the value obtained from the High-Performance Liquid Chromatography (HPLC) study (OECD 121).

Results

Survey responses were collected from 17 member companies, amounting to 520 APIs in total out of 1304 APIs currently approved in the EU by EMA[10]. We acknowledge that there may have been some duplication amongst generic APIs due to anonymisation process.

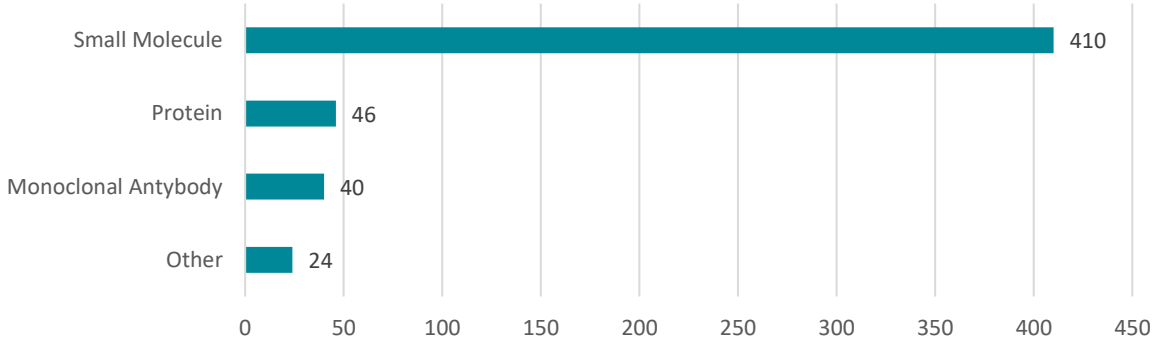


Figure 1. Breakdown of surveyed APIs per molecule type.

Small molecules accounted for most of surveyed APIs (Figure 1). The most represented therapeutical class consisted of medications used to treat cancer (Figure 2). A summary of ATC categories impacted is presented in the Appendix I to this document.

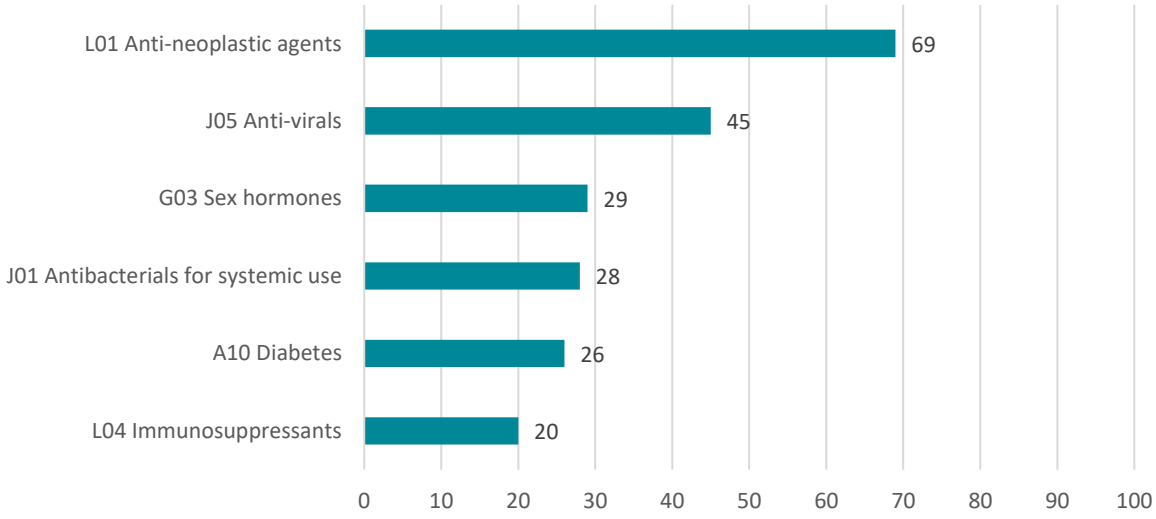


Figure 2. Breakdown of surveyed APIs per ATC code, shown for ATC code counts ≥ 20.

[10] European Medicines Agency (EMA) Table of EPARs (European public assessment reports) accessed online, August 25th 2022

Human Health: Carcinogenicity, Mutagenicity and Reproductive Toxicity (CMR)

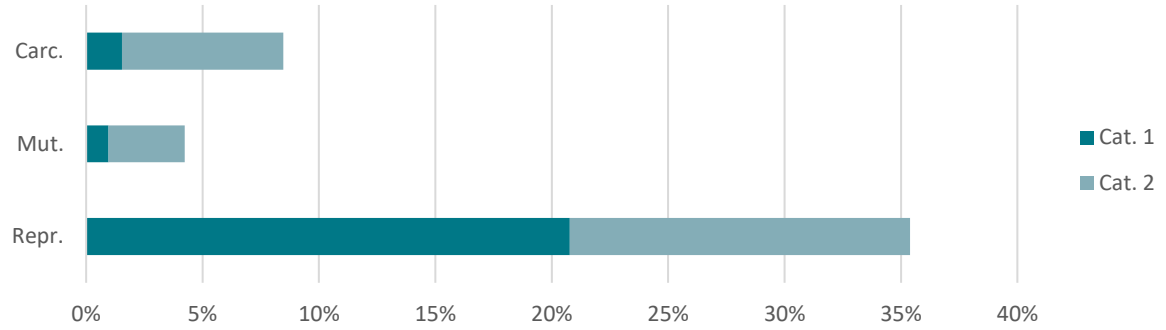


Figure 3. Surveyed APIs meeting CMR criteria.

The most significant impact is seen in reproductive toxicity hazard class, with 108 APIs assigned to Category 1 and 76 APIs assigned to Category 2 – in total approximately 36% of surveyed substances (Figure 3). This is not unexpected, as the therapeutic area of the APIs is predominantly from antineoplastic agents and sex hormone therapies. 22 APIs are classified for mutagenicity, category 1 and category 2 (approx. 4%). Available mutagenicity data for 427 APIs did not warrant hazard classification. 44 APIs are classified for carcinogenicity, category 1 and category 2 (approx. 8%).

Therapeutic area of drug substance is taken into consideration when deriving workplace exposure limits (airborne) for APIs. These in-house OELs enable the collection of exposure monitoring data to evaluate the effectiveness of control measures. The revised CMR directive (Directive EU 2022/431) contains specific provisions for workers handling hazardous medicinal products.

Human Health: Specific Target Organ Toxicity (STOT)

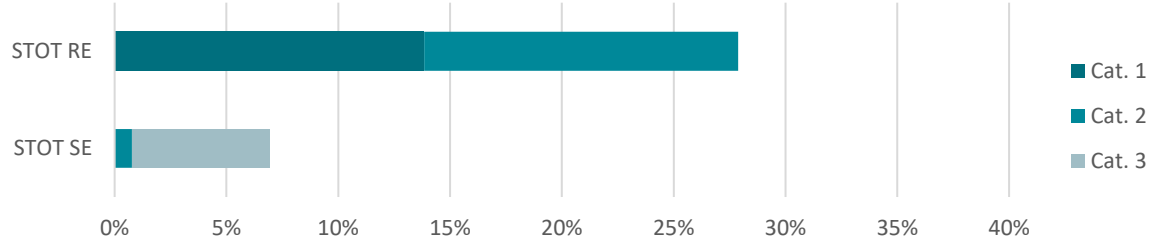


Figure 4. Surveyed APIs meeting STOT criteria.

145 APIs are classified for specific organ toxicity from repeated exposure, category 1 and category 2 (approx. 28% in total, Figure 4). The APIs are from a wide variety of therapeutic classes. The most predominant type of APIs assigned to this hazard class are antineoplastic agents and anti-viral medications.

For the STOT-SE and STOT-RE endpoints, the responses for the significant portion of the data set noted “inconclusive data set / no data available”. 99 APIs were assigned to this group in the STOT SE hazard class. Whilst 57 APIs were assigned to this group in the STOT RE hazard class. It is most likely that the reason for no classification is an inconclusive data set rather than no data available. Since these are APIs from human medicinal products, acute and chronic toxicity data is generated during clinical trials.

Human Health: Immunotoxicity and Neurotoxicity

Classification criteria for immunotoxins and neurotoxins have yet to be defined under GHS and CLP Regulation, so it is not surprising that these endpoints were not evaluated for over 140 APIs. Survey respondents applied professional judgement to classify APIs based on pharmacology of the drug substance. There are 53 immunotoxic substances (approx. 10%). APIs assigned to this hazard class are antineoplastic agents, anti-viral medications, immunostimulants and immunosuppressants. 56 APIs could be classified as neurotoxic substances. These are drug substances intended for the treatment of neurodegeneration and pain.

Human Health: Endocrine Disruption

Based on pharmacology of the drug substance 35 APIs (approx. 7%) are expected to have having endocrine disrupting properties (Figure 5). An additional 64 APIs (approx. 12%) are suspected of having endocrine disrupting properties. Impact in this new proposed hazard category is foreseen across a variety of drug classes, particularly for antineoplastic agents and sex hormone therapies.

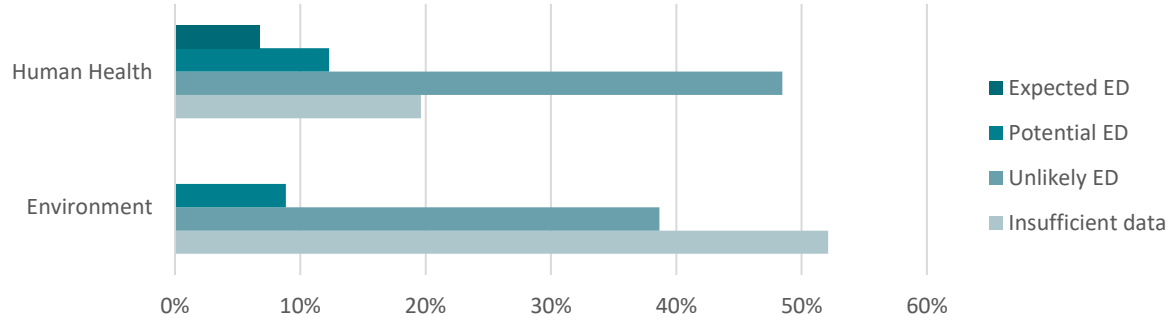


Figure 5. ED properties of surveyed APIs: Human health and environment

Environment: Endocrine Disruption

46 APIs have been identified as potentially exhibiting ENV ED properties, and for 201 it was indicated that ED properties are unlikely. As previously noted, in most cases it is currently not possible to perform ENV ED assessment due to lack of sufficient data. This has been confirmed by survey participants noting that this is currently the case for 271 APIs – over 50% of APIs surveyed (Figure 5).

Environment: PBT and vPvB Substances

Three APIs have been identified as vPvB, and six as PBT substances. For seven APIs it has been indicated they have potential to meet vPvB criteria, and another 8 were identified as suspected PBT substances (Figure 6). For 19% of all surveyed APIs the available data set was not deemed sufficient to conduct a PBT assessment in line with ECHA PBT guidance.

Whilst for over 78% of surveyed APIs it has been indicated that they would not meet PBT/vPvB criteria, this corresponds solely to the parent compound. If ECHA guidance document is to be applied under CLP, the data on transformation and degradation product would be needed to conclude the assessment. As this kind of data is currently not available (nor required) for APIs under relevant sectoral legislation, it is worth noting that the results provided likely present an underestimation and that actual numbers of PBT and vPvB substances could be higher.

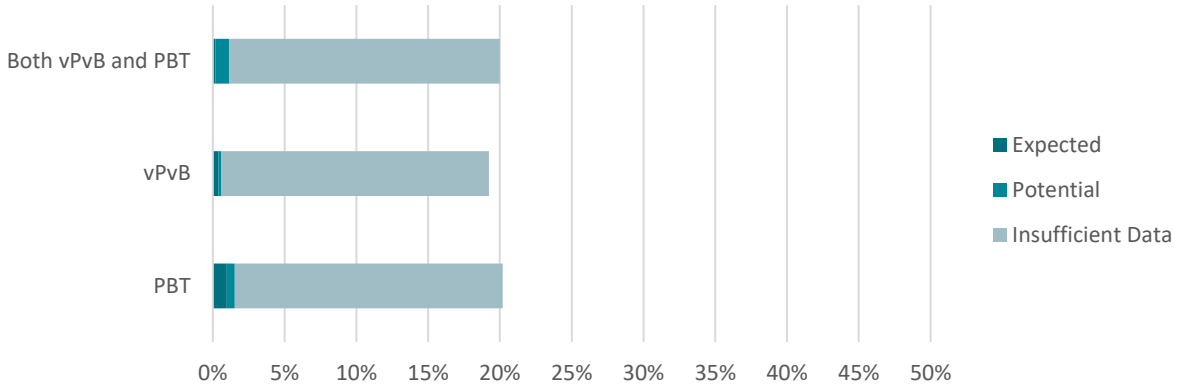


Figure 6. PBT/vPvB properties of surveyed APIs

Environment: PMT and vPvM Substances

10 APIs have been identified as vPvM, and 12 as PMT substances using the selected criteria. For 29 APIs it has been indicated they have potential to meet vPvM criteria, and another 29 were identified as suspected PMT substances (Figure 7). For 38% of all surveyed APIs the available data set was not deemed sufficient to conduct a PMT assessment. Where more data would be available to conclude it is expected that a significant number of these APIs could meet the PMT or vPvM criteria.

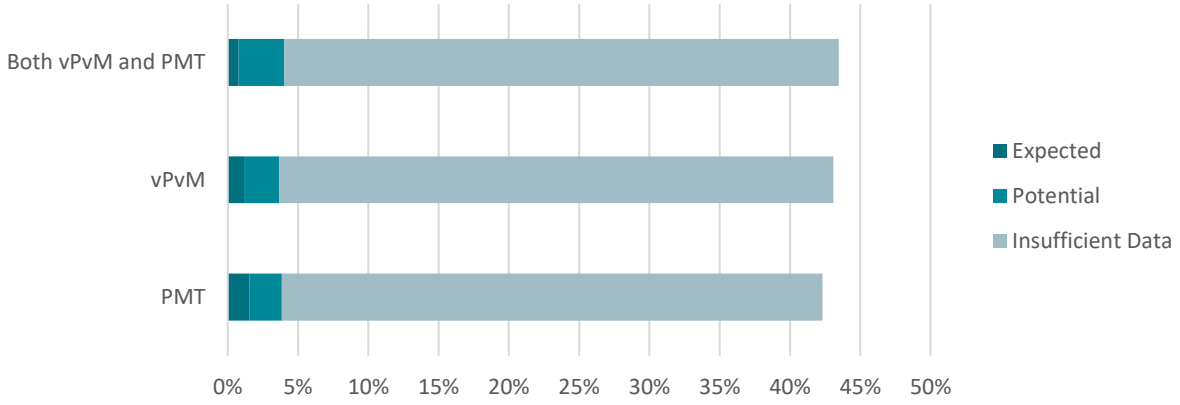
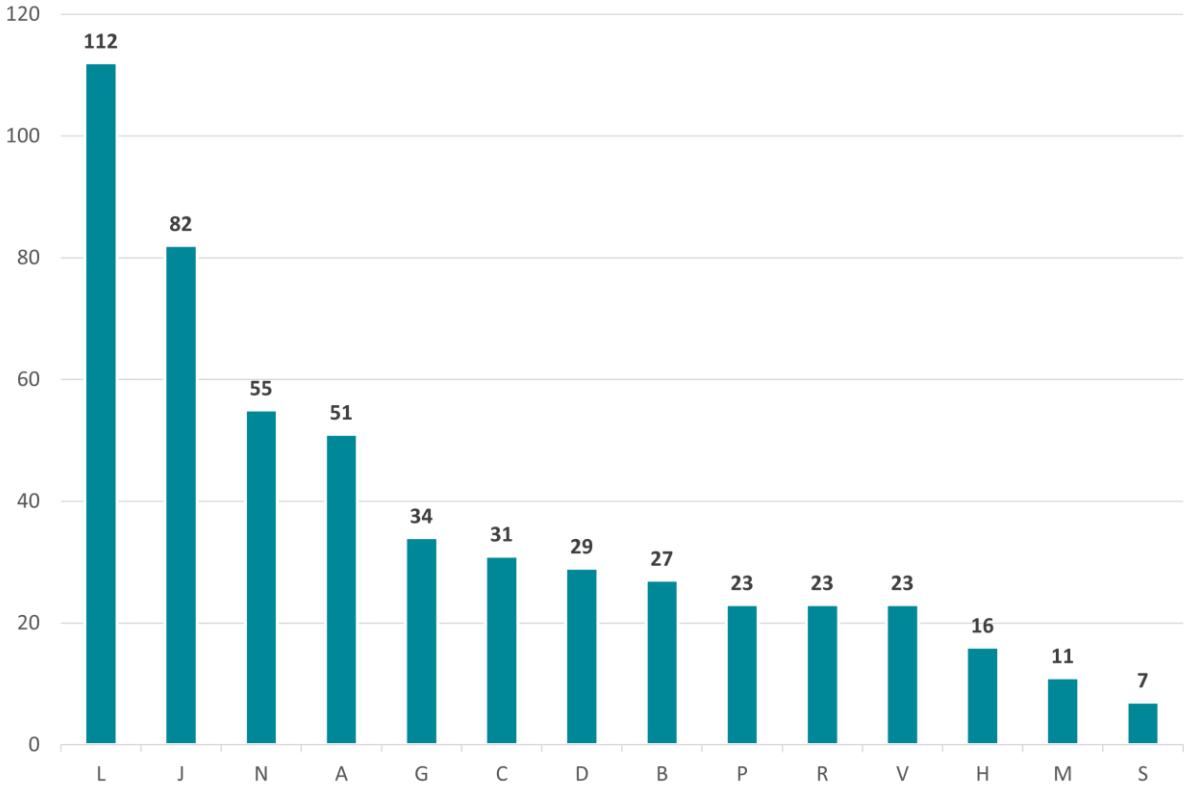


Figure 7. PMT/vPvM properties of surveyed APIs

For 52% of APIs it has been indicated that they would not meet vPvM/PMT criteria. As noted above for the PBT assessment, these numbers are based on the parent compound. In case PMT guidance is based on current ECHA PBT guidance, further data generation and consideration of transformation and degradation products would likely result in more substances being considered PMT and/or vPvM.

For both PBT/vPvB and PMT/vPvM assessment, there was no predominant therapeutic class within APIs being considered confirmed or suspected PBT/vPvB/PMT/vPvM substances.

Appendix I: Summary of surveyed APIs by ATC category



Key:

L	Antineoplastic & Immunomodulating Agents:	Cancer treatments; immunosuppressants etc.
J	Anti-infectives for Systemic use:	Anti-bacterials; Anti-virals; vaccines etc.
N	Nervous system:	Analgesics, anti-Parkinson drugs, psycholeptics, psychoanaleptics etc.
A	Alimentary Tract & Metabolism:	Drugs for acid related disorders, antiemetics, drugs used in diabetes, vitamins etc.
G	Genito Urinary System & Sex Hormones:	Sex hormones, urologicals
C	Cardiovascular System:	Cardiac therapy, antihypertensives, calcium channel blockers, agents acting on the renin-angiotensin system
D	Dermatologicals:	Antifungals, Corticosteroids, Antiseptics & Disinfectants, Anti-acne preparations
B	Blood & Blood Forming Organs:	Antithrombotic Agents, Antihemorrhagics, Antianemic Preparations
P	Antiparasitic Products, insecticides & repellents:	Antiprotozoals, Anthelminitics, Ectoparasiticides
R	Respiratory System:	Nasal preparations, Drugs for Obstructive Airway Diseases, Antihistamines for Systemic Use
V	Various:	Contrast media, all other therapeutic products
H	Systemic Hormonal Preparations, excluding Sex hormones and Insulins:	Pituitary and Hypothalamic hormones & Analogues, Corticosteroids for Systemic Use, Thyroid Therapy, Calcium Homeostasis
M	Musclo-Skeletal System:	Anti-inflammatory & Antirheumatic products, Muscle Relaxants, Drugs for Treatment of bone diseases
S	Sensory Organs:	Ophthalmologicals

Appendix II: Results summary per hazard class

STOT - Single Exposure	# of APIs
STOT SE 1 – H370 Causes damage to organs	10
STOT SE 2 – H371 May cause damage to organs	4
STOT SE 3 – H335 May cause respiratory irritation	14
STOT SE 3 – H336 May cause drowsiness or dizziness	18
No, CLP classification criteria not met	349
Classification not possible, inconclusive data set / no data available	99
No information provided	26
STOT – Repeated Exposure	# of APIs
STOT RE 1 – H372 Causes damage to organs through prolonged/repeated exposure	72
STOT RE 2 – H373 May cause damage to organs through prolonged/repeated exposure	73
No, CLP classification criteria not met	301
Classification not possible, inconclusive data set / no data available	57
No information provided	17
Immunotoxic Substance	# of APIs
No, substance unlikely to be an immunotoxin	315
Yes, based on pharmacology of drug substance	36
Yes, STOT classification lists immune system as affected organ	17
Don't know, no evaluation undertaken	148
No information provided	4
Neurotoxic Substance	# of APIs
No, unlikely to be a neurotoxic substance	319
Yes, based on pharmacology of drug substance	35
Yes, STOT classification lists nervous system as affected organ	21
Don't know, no evaluation undertaken	141
No information provided	4
Respiratory Sensitiser	# of APIs
Resp. Sens. 1, 1A or 1B	13
Based on available data classification criteria are not met	3
Due to lack of data classification is not possible	477
No information provided	27
Carcinogen	# of APIs
Carc. 1A – H350 May cause cancer	2
Carc. 1B – H350 May cause cancer	6
Carc. 2 – H351 Suspected of causing cancer	36
Based on available data classification criteria are not met	332
Due to lack of data classification is not possible	140
No information provided	4
Mutagen	# of APIs
Muta. 1A – H340 May cause genetic defects	1
Muta. 1B – H340 May cause genetic defects	4
Muta. 2 – H341 Suspected of causing genetic defects	17
Based on available data classification criteria are not met	427
Due to lack of data classification is not possible	67
No information provided	4

Reprotoxin	# of APIs
Repr. 1A – H360 May damage fertility or the unborn child	39
Repr. 1B - H360 May damage fertility or the unborn child	69
Repr. 2 – H361 Suspected of damaging fertility or the unborn child	76
Based on available data classification criteria are not met	295
Due to lack of data classification is not possible	37
No information provided	4
Endocrine Disruptor – Human Health	# of APIs
No, substance unlikely to have ED properties	252
Yes, substance has ED properties	35
Potential ED – basis of evaluation criteria set out in BPR/PPP	2
Potential ED – basis of evaluation Repro Cat 2 and/or having effects on endocrine organs	62
Categorisation not possible, inconclusive data set / no data available	102
No information provided	67
Endocrine Disruptor – Environment	# of APIs
Substance unlikely to have ED properties	201
Substance potentially has ED properties	46
Categorisation not possible, inconclusive data set / no data available	271
No information provided	2
PBT	# of APIs
No, substance is not PBT	409
Yes, substance is PBT	6
Substance is potentially PBT	8
Categorisation not possible, inconclusive data set / no data available	97
vPvB	# of APIs
No, substance is not vPvB	412
Yes, substance is vPvB	3
Substance is potentially vPvB	7
Categorisation not possible, inconclusive data set / no data available	98
PMT	# of APIs
No, substance is not PMT	273
Yes, substance is PMT	12
Substance is potentially PMT	29
Categorisation not possible, inconclusive data set / no data available	200
No information provided	6
vPvM	# of APIs
No, substance is not vPvM	271
Yes, substance is vPvM	10
Substance is potentially vPvM	29
Categorisation not possible, inconclusive data set / no data available	205
No information provided	5