

NEMO CENSETUR IGNORARE LEGEM: WHAT RESEARCH CHEMISTS SHOULD KNOW ABOUT THE EU LEGAL FRAMEWORK

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Organic chemistry operates within its own intricate set of rules, governed by the strict principles of matter and physics, while law structures societal order through evolving legal frameworks. Both fields, though inherently distinct, converge. Organic chemistry seeks to solve societal challenges that law must regulate and adapt to fit in a constantly shifting landscape punctuated with geopolitical tensions, economic interests, public health and evolving needs. The subtle balance between academic freedom, fundamental human rights, and bene- or malevolent intentions, drives the interface of synthetic organic chemistry and law. Seemingly innocent and routine actions for synthetic organic chemists, such as ordering reagents, exporting final products, building international collaborations, and disseminating results, are increasingly regulated by (inter)national laws. This Tutorial Review serves as a vade mecum, providing an in-depth overview of international and European laws affecting organic chemistry in research laboratories. It focuses on areas of significant societal impact and direct concern for research chemists: narcotic/psychotropic substances, chemical warfare-related compounds and dual-use items. It is set to ensure better cooperation between the two main actors: public officers and chemists.

Key learning points

1. Essential legal concepts and historical background on narcotics/psychotropics, chemical warfare-related compounds and dual-use substances.
2. Anticipating compliance requirements throughout the research lifecycle.
3. Practical navigation of EU and international rules for restricted substances and precursors.
4. Awareness of hidden triggers: procurement, shipments, collaborations, publications and data sharing.
5. Responsible communication and lab-level compliance through licensing, training, and records.

1. Introduction

Organic chemistry is deeply embedded in human life, shaping both everyday activities and the work of professional chemists. While chemistry and law may seem worlds apart, they intersect in increasingly important ways. In the laboratory, the decisions chemists make, from ordering reagents to sharing research findings, are governed not only by scientific protocols but also by a growing set of legal provisions. In today's research environment, legal compliance is no longer just the concern of institutions or administrators; it has become an integral part of a chemist's daily routine. As the idiom goes, *nemo censeatur ignorare legem* – no one can ignore the law. This principle holds true under the umbrella of scientific research, where even inadvertent violations can carry significant consequences.

Over the past few decades, the European Union (EU) has developed an increasingly complex legal framework to regulate the handling, production, and dissemination of chemical substances, based on broader United Nations (UN) Resolutions and international treaties. From the control of drug precursors to the classification of dual-use chemicals, these laws aim to address evolving risks, including public health crises, environmental concerns, and international security threats, while also preserving the integrity of scientific research. These developments mirror broader societal shifts in which emerging technologies, from the internet back in the days to artificial intelligence today, have required new regulations to protect privacy, safety, and ethical standards.¹⁻³ Just as the General Data Protection Regulation (GDPR) responded to the widespread use of digital technologies,^{4,5} the legal framework for chemical research is adapting to ensure responsible innovation in a rapidly changing world.

The legal implications surrounding the use and misuse of chemistry have, indeed, attracted increasing attention. Since the early 20th century, a progressively stringent legal framework has emerged to address chemical-related concerns. Crises triggered by the recreational misuse of pharmaceuticals, the rise of potent synthetic narcotics, and an increasingly tense geopolitical context have all contributed to the adaptation of these laws, particularly to better regulate specific chemical substances. Two key areas of concern are psychoactive drugs and chemical weapons, each highlighted by recent historical examples. First, reflecting the opioid crisis in North America,⁶ recent data from the European Monitoring Centre for Drugs and Drug Addiction show that synthetic opioids, despite being an essential part of Western pharmacopeia, are also increasingly found on the illegal drug market in Europe.⁷ Second, Russia's invasion of Ukraine has not only escalated geopolitical tensions and prompted economic sanctions, but has also reinforced the EU's recognition of the urgent need to invest in defense.^{8,9} In that regard, chemical weapons have become a real problem as Russia has been accused by the OPCW of using chemical weapons against Ukraine, and the EU has already taken new sanctions in 2025 against it (see Section 4.4 for more details).¹⁰ In light of these challenges, ensuring that legal systems remain aligned with evolving threats is critical to upholding fundamental rights and the security of States.¹¹ While associated with different legal frameworks, drugs and chemical weapons, as well as their precursors, are highly monitored, with strict regulations on their circulation enforced to mitigate threats.

The daily routine of research chemists, whether supervising a research group or actively working at the bench, involves seemingly innocent actions that increasingly require careful attention due to the applicable legal framework. These actions typically concern both tangible elements (*e.g.*, samples, intermediates, products, prototypes) and non-tangible ones (*e.g.*, AI algorithms, SI with protocols, data sharing, plans for 3D-printed parts). Legal considerations can thus potentially affect the entire value chain of chemical research: from drafting proposals and forming international collaborations to synthesizing compounds and disseminating results. The earlier these aspects are considered, the better, ideally already at the stage of developing a research proposal, drafting a scientific publication or preparing a presentation for an international audience.¹² Many funding applications, particularly those involving foreign sponsors, collaborators, or talents, may include the disclosure of new technologies or synthetic methodologies with potentially broad applications. In some cases, these may pertain to controlled substances or unintentionally reveal protocols relevant to the synthesis of chemical warfare agents, psychotropic compounds, or their precursors. With adequate foresight and legal awareness, such risks can be anticipated early on, enabling the implementation of appropriate safeguards before the research is initiated.

Once funding is secured and research is underway, even routine lab activities, such as ordering reagents, can carry additional administrative burden and legal obligations. Filing exemption forms and end-user declarations has become standard practice for acquiring a large array of chemicals from suppliers. The regulated chemicals can be organic (60%) or inorganic compounds (40%) and they include reagents, precursors, solvents and more (see Fig. 1). Even at the final stage of the research value chain, similar concerns arise in the dissemination of results, whether through publications, conferences, or patents.

These challenges can generate anxiety among researchers: fear of compromised academic freedom, of navigating complex legal frameworks without expert support, and of administrative burdens that could hinder research progress (Fig. 2). Such concerns reflect the tension between the legal system's responsibility to address contemporary chemical research risks and the scientific community's need to sustain innovation and productivity.

It is rather difficult to pinpoint which was the first law in the EU that impacted organic chemistry in research labs, since each EU Member State has always had its own legal framework. However, the impulse to create a real legislative framework was due to the promulgation of international treaties and key historical events. For narcotics and psychotropic substances, the key moment was the 1912 Opium Convention, or Hague Convention, the first international treaty addressing these substances.^{13,14} Concerning dual-use, World War I (WWI) marked a turning point with the advent of large-scale chemical weapons.¹⁵

This vade mecum provides a tutorial, educated overview of the EU legal framework, along with relevant international provisions when necessary for clarity, that directly impacts academic research labs. Its purpose is to fill an existing gap in the literature by offering a comprehensive review of a complex topic: the legal framework governing security (national and international) and obligations related to organic chemistry. The document aims to unpack the legal considerations and requirements

for chemical synthesis and the associated handling, export, and control of certain chemicals. Ultimately, it seeks to educate both non-experts and peers about the legal implications of their research and laboratory practices, while enriching the academic literature on this subject. This effort is based on the observation that, despite its importance, this topic is rarely taught to early-career researchers, and even experienced professionals may struggle to find all relevant information in a concise and accessible format. Existing literature often addresses dual-use items or specific aspects of chemical regulation in a fragmented manner. For example, some sources focus on drug-related chemicals and their legislation, while others examine narrow segments of the discipline. These overviews tend to be highly specialized and frequently more theoretical than practical. For instance, some references discuss “designer” or “masked” precursors, a highly relevant issue for chemists, but do not cover the broader and complex framework governing drug precursors. Other references address the dissemination of knowledge and publication concerning dual-use items in general, but without a direct focus on organic chemistry specifically.

With the goal of providing tangible support to organic chemistry researchers, this review offers concrete examples and clear, case-oriented answers to the specific challenges faced in laboratories. Specifically, we identify the steps that require special attention, additional procedures, licenses or specific authorizations. Given the broad scope of organic chemistry, we focus on two main topics of high societal concern within the current context: drug-related chemicals (narcotics, psychotropic compounds and precursors thereof, masked precursors and new psychoactive substances) and dual-use items (explosive-related compounds, chemical warfare agents, and precursors thereof). While regulatory frameworks such as REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) are fundamental in the governance of chemical substances within the EU, this review does not address REACH-related obligations. The REACH legislation is very broad and obliges companies to register chemicals that are produced or imported in the EU in quantities equal to or more than one ton per year.¹⁶ Additionally, at the time of writing (August 2025), the REACH legislation is in change, with the European Commission planning to table a complete revision in the last quarter of 2025 following earlier postponements.¹⁷ Instead, this review focuses on legal instruments that directly affect academic research in organic chemistry, particularly in relation to controlled substances and dual-use concerns at the bench scale.

We have structured this tutorial review according to six main sections. Firstly, we provide essential knowledge about the basic functioning of law (Section 2), before analyzing its impact on chemists. Next, we present a historical digest of both narcotics/ psychotropic substances and dual-use items (Sections 3 and 4). With this theoretical foundation, we then describe what a chemist is (not) legally allowed to do in a laboratory, focusing on both good internal laboratory practices and the external transfer of goods and information of results. The key questions addressed are:

- Inside the laboratory (Section 5):
 - Which substances are restricted, and to what extent?
 - Can I legally prepare these compounds?
 - Why must I disclose certain information to unlock orders, and are these orders monitored?
 - Are there import quotas, and is a license needed?

- What does obtaining a license involve, and is it time-limited?
- Is a product exportable without a license, and what would a license imply?
- Is there assistance available if a chemist is unsure about legal requirements?
- How can a scientist stay informed about changes in the law?
- International collaborations, publications, and dissemination of results (Section 6):
 - Can I ship reaction products abroad for collaboration, and are there any restrictions?
 - What role do customs play?
 - Can disseminating results (*e.g.* through publications, conferences, or patents) be unlawful?
 - Why do some journals require a Dual-Use Research of Concern (DURC) declaration while others do not?
 - Why are there increasing obligations to declare the involvement of dual-use items in EU-funded projects (*e.g.*, Horizon Europe)?
 - Given that publications are accessible worldwide, could they pose a threat, and should they be restricted if they address sensitive chemistry?
 - How does the legal framework impact global collaborations?

In Section 7, we illustrate how legal, regulatory, and ethical issues manifest in real-life research. To do so, we present a series of case studies, including published work from our team and examples involving orders of scheduled compounds.

The ultimate objective of this work is to explore and better delineate the boundaries between academic freedom, legal obligations and gray areas, seeking for a new equilibrium between synthetic organic chemistry and law in the 21st century. All abbreviations used in this review are reported in Table 1 in alphabetical order. A small glossary for the juridical definitions employed can be found in the SI in Table S1.

2. A general overview on the concept of law

Before addressing the relevant legislation itself, it is essential to first outline some fundamental legal concepts. The seemingly simple question, “*What is law?*”, is in fact a deeply complex one as its definition varies across jurisdictions and evolves over time. This question and its broader implications have long been central to the field of legal theory and philosophy, with thinkers such as Aristotle and Plato exploring the nature of law as early as antiquity.¹⁸ In this article, only the core practical concepts relevant to the topic at hand will be introduced.

The focus here will be mainly on European law, but also with frequent reflections on international law, as these frameworks are intricate in these specific areas. Within the EU, Member States have limited competence in this field, which leaves scope for national variations in a few areas, such as penalties and licensing timelines. The European legal system was selected as the primary reference for this article due to its comprehensive coverage of 27 countries and its complex regulatory structure, encompassing areas such as importation, possession, and export of substances. Other legal systems will not be addressed.

2.1. COMMENTS ON INTERNATIONAL LAW

International law and its enforcement are complex and often influenced by external factors such as national politics or economic context.¹⁹ Originally rooted in wartime agreements, peace treaties or diplomacy between nations (*i.e.*, international treaties), it has since expanded to involve states, international organizations, and individuals. Its scope now includes areas such as trade, competition, and human rights. Understanding international law is challenging because it encompasses hard law (legally binding norms), soft law (non-binding norms), and general principles, forming a network of interconnected rules and practices.

States can adhere to an international treaty in three ways: by signature, by signature and ratification, or by accession. Signature, or signature and ratification typically occur during the negotiation phase of a treaty, while accession allows a state to join after the treaty has been finalized and entered into force.²⁰ A key concept is the “entry into force” of a convention, which means it becomes legally effective. If a law or treaty has not entered into force, it has no legal effect.²¹ A clear example of this process is the United Nations (UN) Convention on Psychotropic Substances of 1971, which entered into force on August 16, 1976, the ninetieth day after 40 states had signed or ratified it (Article 26 §1 – “Entry into Force” section).²² Article 25 §1 of that convention specifies that states may adhere by signature, signature and ratification, or accession. Moreover, Article 25 §2 confirms the possibility of accession after the first January of 1972. However, it is important to note that these rules do not apply universally, as EU law has its own particularities, which will be discussed in the next section.

2.2. COMMENTS ON EUROPEAN LAW

The EU has a rich history that shaped its current legal framework and continues to influence areas directly related to the work of chemists, such as customs and export regulations. The EU was formally established as a legal entity by the Treaty of Maastricht, signed in 1992 and entered into force on November 1, 1993. However, the process of European integration began much earlier, shortly after World War II (WWII), with the primary aim of maintaining peace, particularly between France and Germany.

In 1951, the European Coal and Steel Community (ECSC) was created, bringing together Belgium, West Germany, France, Italy, Luxembourg, and the Netherlands.²³ The ECSC aimed to ensure the free movement and establish a common market for coal and steel among its Member States. It was already clear at the time that the main goal was to create an area of free circulation, a principle that remains central to the EU today, as reflected in Article 3(3) of the Treaty on European Union (TEU). The ECSC is considered the first step toward European integration, eventually leading to the Treaty of Maastricht.²⁴

The next significant milestone occurred in 1957 with the Treaty of Rome, which established the European Economic Community (EEC) and the European Atomic Energy Community (Euratom).²⁵ These treaties expanded economic cooperation beyond coal and steel among the same group of founding countries. The primary goal was to create a common market and to enhance cooperation between the Member States, with the long-term objective of forming a more integrated organization. As a result,

the Treaty of Rome introduced common policies on agriculture, trade, and transport, and it also established the Court of Justice of the European Union, which plays a crucial role in upholding treaties and ensuring compliance with EU law. Another key aim at the time was to abolish customs duties between Member States. It is important to note that this process did not occur overnight.

Among the significant changes brought by the Treaty of Rome and Maastricht, it is worth mentioning the creation of the Economic and Monetary Union, of the European single market and of the four freedoms (free movement of persons, services, goods and capital).²⁶ While the EU is much more than just an economic union, this brief overview highlights the importance of the free movement of people, goods, and ideas within its Member States. These principles are directly relevant to chemists and their work. At the same time, the legal framework, particularly regarding drugs and dual-use items, can impose significant restrictions on that free circulation.

To better understand decisions and legislation related to organic chemistry, some procedural background is necessary. Two primary treaties form the foundation of the EU: the TEU and the Treaty on the Functioning of the European Union (TFEU).²⁷ Alongside these, the Charter of Fundamental Rights of the European Union (referenced in Article 6 TEU) is also relevant.²⁸ TEU, TFEU and the Charter of Fundamental Rights constitute primary law (see Fig. 3).

Primary law is considered the highest source of law within the EU and covers fundamental aspects such as the Union's creation, competences, accession, and overall functioning. Secondary law, by contrast, focuses on the practical implementation of the EU's objectives, such as the establishment of the single internal market.²⁹ In terms of secondary legislation, there are three main types of legislative acts: Regulations, Directives, and Decisions. Regulations and Directives are the most significant. Additionally, there are non-legally binding acts such as Recommendations and Opinions. The legal basis for these categories is outlined in Article 288 of the TFEU.

A Regulation is directly applicable in all Member States; it does not require transposition into national law and applies in its entirety.³⁰ A Decision functions similarly but is addressed to specific individuals, companies, or Member States. A Directive, however, differs fundamentally.³¹ It establishes a legally binding objective that Member States must achieve, but it is not directly applicable. Instead, Member States are required to transpose the Directive into national legislation, typically within two years, allowing them some flexibility in how the objective is met. In practice, this means that individuals must consult national law to understand the legal effects of a Directive.

When examining key legislation relevant to synthetic organic chemistry and its wide range of applications, it becomes clear that drug-related and dual-use frameworks are governed by Regulations.³²⁻³⁴ This means they are directly applicable in all EU Member States without requiring national transposition. However, while the explanations provided above apply to the 27 EU Member States, it is important to recognize that the actual legal landscape can be more complex than it might first appear.

Along with described legislative acts, there are also non-legislative ones. Non-legislative acts are legal tools that do not follow the full legislative process. Instead, they are used to modify or update existing laws more efficiently. The European Commission (EC) can adopt non-legislative acts under certain

conditions, but only when the EU's legislators have already allowed it in a parent law. These acts usually deal with technical details or non-essential parts of a law.

Delegated acts are a kind of non-legislative act that, according to the EU, “are used, typically, when legislative acts—including their Annexes—have to be (regularly) adapted to take account of technical and scientific progress”.³⁵ As a result, their adoption is quicker, involves fewer institutions, and eventually streamlines the legislative process.³⁶

As explained in the introduction, legislation must remain aligned with current developments so European law can, and must, be updated when necessary, through a process known in the EU legal system as the “consolidation of the law” (see Fig. 4). Consolidation refers to the combination of an initial legal act with all its subsequent amendments and corrections into a single, updated document. This consolidated version shows the legal rules that are applicable at a specific point in time. Amendments may involve inserting, deleting, replacing, or adding text to the original act.³⁷

In the context of synthetic organic chemistry, this process is especially critical, because many relevant Regulations include Annexes that list specific chemical substances. These annexes are not static: they are regularly updated to reflect scientific, technical, or security-related developments. Importantly, it is the EC that has been granted the power to update these Annexes using delegated acts. For example, article 3(8) of Regulation 273/ 2004 empowers the Commission to amend the annexes to address new trends in the diversification of drug precursors.³³

The Annexes are, indeed, where chemists must look to find the up-to-date list of controlled or regulated chemical substances. However, accessing this information is not always straightforward. In some cases, the Commission publishes the entire amended Annex within a delegated act, making the updated list clear and self-contained (see gray square in Fig. 4, e.g. “*Commission Delegated Regulation (EU) 2024/2547 of 5 September 2024 amending Regulation (EU) 2021/821 of the European Parliament and of the Council as regards the list of dual-use items*”).³⁸ In other cases, only the amendment itself is published, without republishing the full annexes. This occurs, for example, with Regulation (EC) No 273/2004 on drug precursors, which has been amended by eight different delegated acts (e.g., see ref. 33). In these situations, to obtain a complete and updated list of substances, chemists must consult the non-legally binding “consolidated text” (see pink squares in Fig. 4, e.g. “*Consolidated text: Regulation (EC) No 273/2004 of the European Parliament and of the Council of 11 February 2004 on drug precursors*”). The consolidated version integrates all changes into one readable document, including the full list of substances in the annexes. Once a consolidated version has undergone the full legislative process, it becomes a “codified text,” which is then legally binding.³⁹

That said, it is essential to understand that the Annexes themselves, containing the chemical lists, are legally binding at all times, regardless of whether the main text has been codified. What matters for chemists is that the most recent consolidated version will always provide the clearest and most practical overview of the substances currently regulated.

2.3. THIRD COUNTRIES AND THEIR PARTICULARITIES

This subsection concerns countries that are not part of the EU but maintain close ties with it. A third country is defined in Art. 2(6) of Regulation (EU) 2016/399 (Schengen Borders Code) as *“a country that is not a member of the European Union as well as a country or territory whose citizens do not enjoy the European Union right of free movement as defined in Art. 2(5)”*.^{40–42}

A relevant example of a third country is the United Kingdom (UK). Although the UK formally exited the EU in 2020 (Brexit), its relationship with the Union remains significant. The EU–UK Trade and Cooperation Agreement, which entered into force in May 2021, preserves several aspects of prior collaboration. While the level of economic integration no longer matches that of full EU membership, the agreement goes beyond traditional free trade deals and establishes a framework for continued cooperation and mutual commitments, including in environmental matters and trade. A key component of this agreement is the Free Trade Agreement, which can directly affect the movement of chemicals between the UK and the EU.⁴³ For example, Article 765 of the Trade and Cooperation Agreement focuses on countering the proliferation of weapons of mass destruction. It requires both parties to establish effective national export control systems that regulate not only the export but also the transit of goods related to such technologies. This includes end-use controls on dual-use items and mandates appropriate penalties in the event of violations. These provisions are implemented through the EU dual-use Regulation. According to Annex II of that Regulation, the UK benefits from simplified export procedures compared to regular third countries.

In addition to the UK, there are several countries that, while not EU members, are geographically located within Europe and maintain particularly close relationships with the EU (Fig. 5). These relationships are possible under Article 217 of the TFEU, which allows the EU to conclude agreements with non-member countries. Norway, Iceland, and Liechtenstein are notable examples, as they participate in the European Economic Area (EEA). The EEA Agreement, signed in 1992 and effective since 1994, aims to extend the EU’s internal market to European Free Trade Association (EFTA) countries. Although these countries do not intend to join the EU, they incorporate EU legislation related to the internal market once agreed upon. This includes the four freedoms (free movement of goods, persons, services, and capital) as well as related policies such as competition, transport, energy, and economic cooperation. Switzerland presents a unique case. Although it is not a member of the EU or the EEA, it has entered into numerous bilateral agreements with the EU that aim to strengthen economic cooperation and facilitate movement within the Schengen Area.⁴² These agreements are especially relevant when trading or exporting chemical substances, as Switzerland’s relationship with the EU differs in structure from that of EEA countries. Notably, all four of the cited countries (Norway, Iceland, Liechtenstein, and Switzerland) are part of the Schengen Area, unlike Cyprus and Ireland.⁴⁴ This distinction has practical consequences for the free movement of goods, particularly those related to drugs and dual-use chemicals. It is important to note that, like the UK, Norway, Iceland, Liechtenstein, and Switzerland are listed in Annex II of the EU dual-use Regulation, and therefore benefit from simplified export procedures (see Section 5.6).

When trading or exporting chemicals to countries outside the EU, it is essential to consider any relevant bilateral or multilateral agreements, particularly those involving the Schengen Area or specific arrangements with countries like Switzerland. Export control frameworks play a significant role in shaping the EU's relationships with third countries regarding sensitive items (see Section 4.5), and should not be overlooked in import or export operations.

Now that the fundamentals of the EU legal framework have been outlined, the following section will delve into the juridical notion of drugs. These include natural substances, synthetic drugs, new psychoactive substances, and chemical precursors. These classifications have evolved over time and reflect broader legal and social developments related to drug use. Before exploring current legislation, we will provide an overview of how this legal framework has historically developed.

3. From opium to synthetic drugs

3.1. MEDICINE – DRUGS – PRECURSORS: A CHRONOLOGICAL LEGISLATIVE OVERVIEW

Medicine has been regulated by law for a very long time. For instance, the Code of Hammurabi (1755–1750 B.C.) already included provisions (§215–225) that addressed the penal responsibility of medical professionals in cases of surgical error.^{45,46} From the early stages of medicine, the availability of a broad pharmacopeia was essential. Already in antiquity, herbs, plants, and certain minerals were used as medicinal substances.⁴⁷ One early example is the *Ebers Papyrus* (c. 2900 B.C.), an Egyptian pharmaceutical record that documents over 700 plant-based drugs, including gargles, pills, infusions, and ointments.⁴⁸ However, the lack of knowledge about the Egyptian vegetal world makes it hard to connect Egyptian names to actual plants and it is not always easy to determine the exact nature of these drugs or how they were consumed.^{49,50} Historical sources indicate that psychoactive substances, including narcotics, such as opium and plants containing psychotropic compounds, such as cannabis, were commonly used. For example, their use is referenced in Homer's *Odyssey*, written in the mid-8th century B.C.^{51,52}

Until the 20th century, both the development of pharmacopoeias and the legal frameworks governing them evolved at a relatively slow pace. One notable example can be found in the history of opium, a naturally occurring alkaloid derived from the opium poppy (*Papaver somniferum*). While opium had clear therapeutic uses, particularly as an analgesic, it was also widely used recreationally, especially in regions such as India.⁵³ A significant turning point came in early 17th-century China, where opium began to be smoked rather than ingested.^{49,54} This change in route of administration significantly increased the potential for addiction since smoking delivers active compounds more rapidly to the bloodstream.⁵⁵ In response, China banned the import and sale of opium in 1729, and further reinforced this ban in 1796 and 1800. Other Southeast Asian countries (e.g., Myanmar and Thailand) soon followed,⁵³ marking some of the earliest documented legal efforts to regulate psychoactive substances. The issue of opium dependence intensified in the 19th century, with the so called “Opium Wars”

between China and European powers, primarily the UK and France, highlighting the geopolitical stakes of the drug trade.⁵⁶ At the same time, the isolation of morphine from opium in the early 19th century exacerbated the global opiate crisis, prompting initial calls for international cooperation in drug regulation.⁵⁷

A major milestone came in 1909 with the International Opium Commission held in Shanghai.^{58,59} Initiated by the United States (US) under President Roosevelt, the meeting gathered representatives from 13 countries, including Austria-Hungary, China, France, Germany, the UK, Japan, and Russia.⁵⁹ Although the resolutions adopted were non-binding, they laid the foundations for a legally binding international agreement: the Hague Opium Convention of 1912. This Convention addressed the regulation of morphine, cocaine, heroin, and opium, (see structures in Fig. 6) and represented a key step toward global drug control.¹⁴

Following WWI, the Treaty of Versailles and other peace agreements required signatory states to ratify the 1912 Hague Convention, eventually securing adherence from over 60 nations, including all major opium-producing and -consuming countries.⁵³ In the 1920s, the supervision of the application of this treaty shifted from individual states (such as the Netherlands) to an international body under the League of Nations. This marked a decisive moment in the evolution of international drug law. During the interwar period, global efforts remained focused on regulating drugs of natural origin. A key legal development occurred in 1931 with the adoption of the *“Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs”*.⁶⁰ This Convention introduced the principle of “scheduling”: the classification of substances into different regulatory groups based on their potential for harm and legitimate medical use. Two distinct schedules were established, reflecting the perceived risk-benefit balance of each substance. However, as WWII approached, the effectiveness of the League of Nations diminished, and international coordination on drug regulation weakened significantly.⁵³

Before continuing the historical overview, it is important to consider the emergence of synthetic drugs. While previously discussed substances are either natural or semi-synthetic (for example, heroin, also known as diacetylmorphine, is a semisynthetic opioid derived from morphine-rich opium poppy latex), the advent of fully synthetic drugs significantly changed both the drug landscape and the regulatory challenges associated with it (see Fig. 6).^{61,62} Unlike natural substances, synthetic drugs are not dependent on environmental factors such as climate or harvest cycles and they can be produced at scale in virtually any location, pending starting materials availability.

Initially, chemical innovation focused on reproducing natural active compounds through synthetic means (so-called “synthetic natural drugs”). The goal was to reduce production costs and improve accessibility for therapeutic use. This drive to enhance medical treatment encouraged a wave of pharmaceutical discoveries throughout the 19th and 20th centuries.⁶² The first fully synthetic drug, chloral hydrate, was synthesized by Justus von Liebig in 1832 (see Fig. 6).⁶³ However, this wave of innovation was largely unregulated in its early stages. The potential health risks and side effects of these newly synthesized compounds were often underestimated or overlooked. While many of these drugs were initially available without significant restriction, the rise in misuse and recreational consumption eventually led to tighter regulations. These restrictions, in turn, contributed to the

development of illicit production and trafficking routes, issues that continue to complicate global drug control today.⁶⁴ For instance, despite the rise of synthetics, natural and semi-synthetic drugs remained prevalent with most of Europe's supply coming from Afghan opium. However, after the Taliban's 2022 cultivation ban, production dropped sharply, raising concerns that fully synthetic opioids could fill the gap.^{61,65}

After WWII, the UN initiated a new era of international drug regulation. The Commission on Narcotic Drugs (CND) was established in 1946 to oversee the implementation of international drug treaties (Table 2). It now serves as the governing body of the United Nations Office on Drugs and Crime (UNODC), which was created in 1997.⁶⁶ The UNODC's mandate extends beyond drug issues, encompassing organized crime, corruption, terrorism, and broader drug-related concerns (Table 2). One of its primary missions is *"tackling the world drug problem through balanced, evidence-based responses to address drug abuse and drug use disorders, as well as the production and trafficking of illicit drugs."*⁶⁷

While the UNODC handles crime and drugs, the health dimension of drug use brings the World Health Organization (WHO) into play. Founded in 1948, the WHO addresses global public health and can recommend the scheduling of new substances under UN Conventions (Table 2).^{68,69} Another key body in this system is the International Narcotics Control Board (INCB), an independent, quasi-judicial entity established in 1968.⁷⁰ The INCB monitors the implementation of the drug control treaties (Table 2). Despite the UNODC's broad mandate, the CND remains central to drug-specific policymaking. In 1961, the CND drafted the Single Convention on Narcotic Drugs, aimed at unifying earlier treaties and regulating narcotic substances.⁷¹ This was followed by the 1971 Convention on Psychotropic Substances (Table 3).²² While both treaties share the goal of limiting misuse, they apply to different categories of substances.

Psychotropic substances form a broad class of compounds that alter mental processes such as perception, mood, cognition, or consciousness. This category includes stimulants, hallucinogens, sedatives, tranquilizers, and hypnotics. Within this framework, the term "narcotic" refers specifically to substances with sedative and analgesic effects on the central nervous system, typically opioids.⁷² In strict pharmacological terms, all narcotics are opioids. However, in legal and colloquial usage, narcotic is sometimes applied more broadly to any controlled or illicit drug. For example, the 1961 Single Convention classifies cocaine, a stimulant, as a "narcotic drug", despite its nonopioid pharmacology.

According to these treaties, both conventions were adopted *"to limit the diversion and abuse of certain psychotropic substances, such as central nervous stimulants, sedative-hypnotics, and hallucinogens, which had resulted in public health and social problems in some countries"*.⁷³ Additionally, both treaties emphasize that controlled substances may be used for medical and scientific purposes, while preventing their illicit use due to negative health effects.⁷⁴ Substances listed in these conventions are referred to as scheduled, while those not included are termed non-scheduled. One of the key functions of the CND is to vote on whether to include, remove, or reschedule substances (Table 2).⁶⁶

The CND's regulatory role expanded with the 1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, which addressed the entire illicit drug production chain,

from precursor chemicals to money laundering (Table 3).⁷⁵ This Convention acknowledged that *“measures are necessary to monitor certain substances, including precursors, chemicals and solvents, which are used in the manufacture of narcotic drugs and psychotropic substances, the ready availability of which has led to an increase in clandestine manufacture”*.⁷⁵

This marked a pivotal shift in international control: from a focus solely on end-products to the upstream regulation of precursors (Fig. 7). Whether synthesizing semi-synthetic drugs from natural sources or producing fully synthetic analogues, all pathways require starting materials. The 1988 convention introduced clear obligations to monitor and regulate these substances, classifying them into licit and illicit precursors. However, as regulations tightened, clandestine chemists began exploiting legal loopholes, giving rise to designer precursors or hidden precursors.

Designer precursors are chemically altered versions of scheduled precursors, modified to evade detection and regulation while remaining easily convertible into controlled drugs via minimal synthesis. Unlike licit precursors, which often have legitimate uses in pharmaceuticals, cosmetics, or industrial processes, designer precursors typically lack any commercial application and are synthesized solely to circumvent legal controls.

As authorities identify and schedule these substances, illicit chemists quickly respond by modifying structures: an adaptive process that regulators struggle to keep pace with. As noted in official reports, *“each time a new substance is scheduled, criminals will be able to ‘tweak some molecules’ and come up with a new designer precursor. The time needed for this can be short, and in any case, is often shorter than the period needed to schedule a new substance”*.⁷⁶ Designer precursors, pre-precursors or masked precursors are upstream chemicals that are not listed in any international schedules, but are imported legally and subsequently converted, often in a single step, into regulated precursors.⁷⁷ The UN recognizes this as a major vulnerability in the international control system. For example, in the EU, 3,4-methylenedioxymethamphetamine (MDMA), amphetamine, and methamphetamine are listed as highly problematic illicit drugs, following this pattern of *designer precursor drugs*.⁷⁷

It is important to distinguish between designer precursors and pre-precursors. As previously mentioned, a designer precursor is intentionally designed or selected to evade legal control while remaining functionally viable for the synthesis of illicit drugs. In contrast, pre-precursors are substances not controlled by legislation and not directly used in drug synthesis but can be converted into a controlled precursor.

The sequence involving benzyl chloride, benzyl cyanide, phenylacetic acid, and its esters (methyl or ethyl phenylacetate) provides a representative pathway illustrating challenges in both precursor regulation and evasion strategies (see Fig. 8). Benzyl chloride is considered a pre-precursor: it is unscheduled but can be converted into benzyl cyanide, which can then be hydrolyzed to phenylacetic acid (Fig. 8). Phenylacetic acid is a Category 1 scheduled precursor under the 1988 UN Convention due to its central role in synthesizing amphetamine-type stimulants.⁷⁸

To circumvent restrictions on phenylacetic acid, illicit operators often resort to methyl or ethyl phenylacetate, known designer precursors. These esters are not scheduled and can be easily hydrolyzed under mild conditions to form phenylacetic acid (Fig. 8).⁷⁹ Importantly, although methyl

and ethyl phenylacetate are unregulated and widely used in legitimate applications, such as fragrance chemistry and pharmaceutical synthesis, their structural similarity to phenylacetic acid and ease of conversion make them susceptible to misuse.

This example shows the ongoing challenge of balancing security concerns with the need to maintain access to essential reagents for research and industry, highlighting regulation as the key instrument to achieve that balance. The fact that a compound can be misused as a designer precursor does not render it illegitimate or banned. Methyl and ethyl phenylacetate remain important and lawful chemicals in many laboratories and industrial settings. Their double nature warrants monitoring and awareness but does not automatically justify restriction.

A parallel trend can be observed with New Psychoactive Substances (NPS, Fig. 7). A NPS is a substance of abuse that is not controlled under the Conventions of 1961 or 1971, but may nonetheless pose a public health threat.⁸⁰ In this framework, the term “new” does not necessarily imply novel chemical invention: it refers to substances that have only recently appeared on the market or in drug use patterns. Even substances that have been placed under international control since 2015 may still be referred to as NPS, to facilitate continuity in monitoring and data analysis.⁸¹ Since their emergence, NPS have been marketed under names such as “designer drugs,” “legal highs,” “herbal highs,” or “bath salts”. While the term “designer drugs” had been traditionally used to identify synthetic NPS, its meaning has been recently broadened to include all psychoactive substances that mimic the effects of illicit and prescription drugs (*e.g.* stimulation, sedation, hallucination).⁷⁷ These compounds are typically produced by making small chemical modifications to known controlled substances in order to evade legal classification, mirroring the strategy seen with designer precursors. Some examples of designer drugs are reported in Fig. 9.

The rapid proliferation of NPS in the global drug market presents a major challenge for public health and regulatory authorities. These substances are often poorly characterized, with limited toxicological data available, making it difficult to predict their pharmacological effects or risks. Their chemical diversity further complicates detection and identification efforts, particularly when many structurally unrelated compounds appear on the market simultaneously. This situation emphasizes the need for robust monitoring systems, timely information sharing, and the establishment of early warning mechanisms to support rapid risk assessment and appropriate public health responses.

Whether through designer precursors, designer drugs, or NPS, the intent remains the same: to bypass legal controls through structural innovation. However, this momentum also has implications for legitimate science. Standard reagents, intermediates, or compounds synthesized in the course of legitimate organic chemistry research may increasingly fall under control lists, complicating procurement, handling, and publication. As a result, evolving drug regulations are likely to have a growing impact on laboratory workflows, particularly in synthetic and medicinal chemistry.⁸²

3.2. THE PARTICULAR CASE OF THE UNITED STATES OF AMERICA

In the post–WWII international context, the US stood out by adopting an assertive and highly punitive strategy in response to the growing drug crisis. This approach, later labelled the “War on Drugs,” was

formally initiated in 1971 when President Nixon declared drug abuse to be “*public enemy number one*” during a press conference on June 17 of that year.⁸³ In 1973, the federal government merged several existing agencies to form the Drug Enforcement Administration (DEA), whose mandate was to enforce drug-related legislation and control both domestic and international narcotics trafficking.⁸⁴ A significant policy shift occurred in 1981 under President Reagan, who placed a stronger emphasis on criminalization and enforcement. This culminated in the Anti-Drug Abuse Act of 1986, which introduced mandatory minimum sentences for a broad range of drug offenses, including non-violent possession.⁸⁵ The legislation was widely criticized for its severe penalties and for reinforcing systemic racial disparities, particularly due to the blunt sentencing gap between crack cocaine, more prevalent in low-income communities, and powder cocaine, more commonly associated with wealthier users. Although initially met with public approval, the increasingly coercive nature of these laws began to generate widespread criticism.

This case study of US drug policy is instructive in demonstrating how legislative frameworks can be used, sometimes counterproductively, as tools in the management of drug-related issues. The US War on Drugs exemplifies a punitive paradigm that ultimately proved ineffective. As one analysis notes: “*policymakers believed that harsh law enforcement action against those involved in drug production, distribution and use would lead to an ever-diminishing market in controlled drugs (...) In practice, the global scale of illegal drug markets – largely controlled by organized crime – has grown dramatically over this period*”.⁸⁶

3.3. THE EUROPEAN UNION DRUG LEGISLATIVE FRAMEWORK

The current state of drug policy and illicit trafficking in the EU is also complex and evolving. According to EU estimates, “*the illicit drugs market is one of the major sources of income for organised crime groups in the European Union, and represents an estimated yearly retail value of at least €30 billion*”.⁸⁷ Europe has now overtaken the US as the world’s largest market for cocaine, underscoring the magnitude of the challenge.⁸⁸

In response to the escalating threat, the EC introduced a new EU Roadmap of priority measures to fight organized crime and drug trafficking in October 2023.⁸⁹ These actions build on the EU Drugs Strategy and Action Plan for 2021–2025, which address both public health and criminal dimensions of drug policy.⁷⁷ Among the key initiatives is the creation of a European Ports Alliance, aimed at strengthening control over entry points for illicit substances, as nearly 70% of drug seizures by customs authorities occur in EU ports.^{65,90} The 2021–2025 EU Drugs Strategy provides a political framework and sets priorities that complement national drug policies. Its main objectives include ensuring a high level of public health protection, promoting social stability and security, and increasing public awareness.⁹¹

One of its strategic priorities, Strategic Priority 2, is to “*increase the detection of illicit wholesale trafficking of drugs and drug precursors at EU points of entry and exit*”.⁹¹

While the EU lacks exclusive competence over national health policy, it exercises authority in drug-related matters through several provisions of the TFEU.⁹² These include Article 207 on common commercial policy (an exclusive competence), Article 168 on public health, and Article 114 on the

internal market.²⁷ Together, these articles support a shared legal framework for the regulation of both medications and controlled substances. Key EU pharmaceutical laws include Directive 2001/83/EC and Regulation (EC) No 726/2004, which define procedures for marketing authorization of medicinal products.^{93,94}

When it comes to EU legislation on the illicit manufacture and trafficking of drugs, the cornerstone legal instrument remains Council Framework Decision 2004/757/JHA of 25 October 2004.⁹⁵ This framework sets out minimum provisions for defining drug-related criminal offenses and penalties, and still serves as the legal foundation for national sanctions concerning the unlawful production and distribution of narcotic and psychotropic substances. Although framework decisions were phased out following the entry into force of the Lisbon Treaty in 2009, those not superseded remain legally binding.⁹⁶ In addition to this, two now-repealed but still highly influential regulations (Regulations (EU) 2017/2101 and 1920/2006) continue to be frequently cited in the literature.^{97–101} The Regulation from 2006 was central in strengthening institutional and data-monitoring frameworks, most notably through the continuation and improvement of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), which was created in 1993. The Regulation from 2017 was also fundamental as it was handling the exchange of information and early warning system for new psychoactive substances. While formally repealed, their legacy persists in shaping current EU approaches to drug policy, surveillance systems, and the control of precursor chemicals. The EMCDDA, originally established in 1993, was officially transformed into the European Union Drugs Agency (EUDA) in July 2024.¹⁰² The EMCDDA's primary mission was to provide EU institutions and Member States with objective, reliable, and comparable data on drugs, drug use, and their consequences, serving as a knowledge base to inform policy decisions. The new EUDA has a broader mandate. While maintaining its evidence based health focus, it now integrates additional objectives such as prevention, treatment, harm reduction, rehabilitation, social reintegration, and recovery, as well as more comprehensive analysis of drug markets, supply chains, and trafficking dynamics.¹⁰³ Though the EUDA is not a legislative body, it plays a crucial role by conducting risk assessments, issuing technical guidance, coordinating information exchange, and shaping national and EU-wide action plans. Among its regular activities, it publishes annual drug reports and provides detailed scientific assessments of specific substances, including emerging synthetic compounds.¹⁰⁴

As previously stated, a critical element of the 2021–2025 EU Drugs Strategy, is Strategic Priority 2, which aims to improve detection and control of both illicit drugs and drug precursors. Precursor chemicals are of particular importance to chemists, as they are often legally produced and widely used in legitimate industries and research laboratories, but also diverted for illegal drug manufacturing. To address this, two key legal instruments are in force: regulation (EC) 273/2004, and Regulation (EC) 111/2005, which implement the 1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.^{33,34} These regulations establish a monitoring system for the possession of precursors within the EU, and for the trade of drug precursors between the EU and third countries.⁷⁷ By tightening controls on these substances, authorities aim to disrupt the supply chains of synthetic drug production. However, such measures also pose significant challenges for chemists and chemical suppliers, as many of the controlled precursors are common reagents in synthetic organic chemistry

and pharmaceutical development. Compliance with licensing, record-keeping, and reporting requirements can therefore add administrative and operational burdens to legitimate scientific work. Starting from August 2025, Regulations 273/2004 and 111/2005 are amended by Commission Delegated Regulation 2025/1475 that introduces new compounds in the list of scheduled precursors.¹⁰⁵

The regulation of NPS adds a further layer of complexity. The most recent legislation concerning NPS is Directive (EU) 2017/ 2103 of the European Parliament and of the Council of 15 November 2017.¹⁰⁶ This Directive amended the 2004 Framework Decision to explicitly include NPS within the legal definition of “drugs”. This move was intended to accelerate the regulatory response to emerging synthetic compounds that pose serious public health and social risks. Complementing this, Regulation (EU) 2017/2101 established a streamlined system for the exchange of information and risk assessment of new psychoactive substances.⁹⁷ The mechanism involves preparing an initial report, followed by a formal scientific evaluation to determine whether a given substance warrants EU-wide control measures. By integrating NPS into the drug classification system, this framework has improved cooperation between Member States, allowing for faster identification, tracking, and disruption of trafficking routes for novel compounds. Table 4 presents the relevant EU regulations on drugs, organized by their primary focus: precursors, controlled substances, and NPS.

In addition to substances controlled under narcotics and psychotropics legislation, chemists operating in the EU must be aware of a broader group of regulated compounds that are still subject to specific legal requirements due to their pharmacological activity, therapeutic application, or potential for misuse. This category includes medicinal substances used in both human and veterinary medicine, such as hormonally active agents (*e.g.*, estrogens, corticosteroids, dimethyl sulfoxide, iodine), beta-adrenergic agonists (*e.g.*, clenbuterol), antiparasitics (*e.g.*, ivermectin), antihormonal drugs (*e.g.*, anti-androgens), anti-infectives (*e.g.*, antibiotics), anti-inflammatories (*e.g.*, nonsteroidal anti-inflammatory drugs), and anabolic agents (Fig. 10).

Two key EU legal instruments govern the handling of these substances: Directive 2001/83/EC, which regulates medicinal products for human use, and Regulation (EU) 2019/6, which addresses veterinary medicinal products.^{93,107} While these frameworks do not include annexes listing specific substances, they establish stringent requirements for the authorization, manufacture, import, export, and use of medicinal compounds, particularly those with potential for misuse or significant public health implications. Regulation 2019/6 specifically introduces tighter controls on veterinary medicinal products, addressing issues such as antimicrobial resistance and the illegal use of performance-enhancing agents in livestock. In addition, compounds such as anabolic steroids, beta-agonists, and hormonal growth promoters fall under Council Directive 96/22/EC, which restricts or prohibits their use in food-producing animals.¹⁰⁸

Chemists involved in the synthesis, formulation, or handling of these substances must comply with regulatory procedures such as Good Manufacturing Practice, registration with national competent authorities, and, where necessary, manufacturing authorization. For research or export purposes,

additional obligations may include end-use declarations, clinical trial approvals (under Regulation (EU) 536/2014), and traceable documentation throughout the supply chain.¹⁰⁹

Moreover, regulation (EC) no 726/2004 established the European Medicines Agency (EMA) and defined the centralized procedure for the authorization and supervision of medicinal products across the EU.⁹⁴ Since its founding in 1995, the EMA has played a central role in ensuring that all medicines available in EU and EEA Member States are safe, effective, and of high quality.

Although these pharmacologically active substances are legally marketed and widely used in legitimate pharmaceutical and veterinary contexts, their double potential, therapeutic potency, or misuse in unregulated settings (*e.g.*, doping, illicit supplements, or black-market veterinary products) make them a subject of regulatory concern. Chemists must therefore stay informed not only about scheduled substances but also about these equally sensitive but less-visible regulatory frameworks, especially when working in synthesis, formulation, or analytical contexts involving such compounds.

4. From chemical warfare agents to the concept of dual-use items

In an organic chemistry laboratory, chemists are not solely concerned with issues related to drugs. They are also frequently confronted with challenges arising from chemical weapon-related legislation. Before addressing the complex regulatory frameworks in this area, it is essential to clarify several key legal and conceptual terms, namely, chemical weapons, chemical warfare agents (CWAs), and weapons of mass destruction (WMDs), all of which carry specific meanings in international law.

According to the UN, WMDs are defined as *“atomic explosive weapons, radioactive material weapons, lethal chemical and biological weapons, and any weapons developed in the future which might have characteristics comparable in destructive effect to those of the atomic bomb or other weapons mentioned above”*.¹¹⁰ Within this category, chemical weapons and CWAs represent a significant class of concern. By contrast, conventional weapons are defined as *“weapons other than weapons of mass destruction. They are the most commonly known and widely used armaments in conflict and crime settings and encompass a wide range of equipment”*.¹¹¹

Although the terms chemical weapons and CWAs are often used interchangeably in UN and OPCW (Organisation for the Prohibition of Chemical Weapons) documents, they bear slightly different connotations depending on the context.^{112,113} CWAs typically refer to the specific toxic chemicals designed for use in chemical weapons. These include nerve agents, blister agents, choking agents, and blood agents.¹¹⁴ On the other hand, chemical weapons is a broader category that includes the toxic substances themselves, their precursors, and the means of delivery.¹¹³

This distinction is especially relevant in legal contexts and regulatory compliance, where both the chemical substances and their potential uses must be considered. These definitions and distinctions have evolved significantly over recent decades, reflecting heightened international attention and

increasingly sophisticated control measures intended to prevent proliferation and misuse, particularly in contexts where chemicals may serve both legitimate scientific purposes and potential hostile applications.

4.1. CHEMICAL WARFARE AGENTS

CWAs have a long and complex history, with instances of their use dating back to antiquity. Homer's *Iliad* recounts the use of poisoned arrows during the Trojan War, and the Byzantine Empire employed incendiary weapons such as Greek fire as early as the 7th century.^{15,115} However, it was during WWI that chemical warfare reached an unprecedented, industrial scale.

The Industrial Revolution of the 19th century transformed the nature of warfare by enabling the large-scale production of both conventional and chemical weapons.¹¹⁶ Parallel advancements in chemistry, beginning with the seminal work of Lavoisier at the end of the 18th century, led to the discovery and synthesis of numerous compounds with toxicological potential. By the outbreak of WWI in 1914, the static nature of trench warfare and the close proximity of troops created conditions that made chemical agents particularly devastating. During WWI, more than 50 different CWAs were employed, among which chlorine, phosgene, and sulfur mustard (also commonly known as *yperite*) were responsible for the majority of casualties (see Fig. 11). Chemical weapons inflicted over one million injuries and caused nearly 100 000 deaths, with phosgene alone accounting for the highest number of fatalities.¹⁵ Notably, the first use of CWAs in WWI was by the French army, which deployed grenades filled with ethyl bromoacetate, originally used by the Paris police in 1912 for riot control, against German forces in 1914. The deployment of CWAs quickly escalated, supported by eminent scientists of the time, including Nobel laureates such as Planck, Haber, Nernst, Franck, Hertz, and Hahn.¹⁵

The use of weaponized chemicals in warfare was already prohibited under international law. Efforts to regulate warfare had intensified in the late 19th century, driven by the rise of nation-states and the increasing destructiveness of modern weapons. The Brussels Declaration of 1874 (called the Project of an International Declaration concerning the Laws and Customs of War), though never ratified, laid important groundwork for future agreements.^{15,117} Around the same time, the International Committee of the Red Cross began its codification of humanitarian law, starting with the Geneva Convention of 1864, which addressed the treatment of wounded soldiers.¹¹⁸ These initiatives culminated in the Hague Conventions of 1899 and 1907, which included early prohibitions relevant to chemical warfare (not to be confused with the 1912 Hague Convention on opium). For example, Article 23 of the 1899 Convention prohibited: “(a) *To employ poison or poisoned weapons; [...] (e) To employ arms, projectiles, or material calculated to cause unnecessary suffering*”.¹¹⁹

Despite the ratification of these conventions by major powers, including Germany and France, chemical weapons were used extensively during WWI, in clear violation of Article 23. The failure of these provisions prompted renewed international efforts, leading to the 1925 Geneva Protocol, formally titled the “Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare”.¹²⁰ This agreement, which entered into force in 1928, prohibited the use of chemical and biological weapons in armed conflict. However, it notably did

not prohibit the development, production, or stockpiling of such weapons, nor did it include enforcement mechanisms. As a result, many states continued to produce and accumulate chemical weapons. Although chemical weapons were not widely used on the battlefield during WWII, Zyklon B, a hydrogen cyanide-based agent, was used extensively in Nazi extermination camps, highlighting the horrific consequences of non-battlefield use.

A more comprehensive regulatory regime was introduced with the Chemical Weapons Convention (CWC), signed in 1993 and entered into force in 1997.¹²¹ The CWC represents a fundamental shift in international disarmament efforts by completely prohibiting the development, production, acquisition, stockpiling, retention, transfer, or use of chemical weapons (see Section 4.3 on CWC for more details).^{15,121} The CWC also established the OPCW, tasked with overseeing implementation of the treaty, verifying compliance, and coordinating the destruction of existing stockpiles.¹²²

4.2. EMERGENCE OF THE CONCEPT OF DUAL-USE ITEMS

Beyond humanitarian law, WMDs are defined as items explicitly designed for military use, with no civilian application such as nuclear, chemical, and biological weapons. While their construction may require specific materials, chemicals, or technologies, WMDs themselves are not considered “dual-use” items, as they are purpose-built for warfare. What does fall under the concept of dual-use are materials or technologies that can contribute to the development of such weapons. These materials (including chemicals), equipment, or know-how, have legitimate civilian applications but may also be repurposed for military or terrorist use. It is this potential for misuse that places them under international control regimes.

The concept of dual-use emerged after WWII and gained prominence during the Cold War, when technology transfer between military and civilian sectors became increasingly common.^{123,124} As noted: *“The reduction in defense budgets, the continuing growth in the costs of new weapons systems, coupled with the higher innovation rates of the high-tech commercial sector relative to the defense sector, have led to a growing reliance of the military on commercially-developed technologies, especially information and communication technologies”*.¹²⁵

Although the term “dual-use” is relatively recent, concerns about the misuse of scientific research predate it. In 1939, physicists Fermi and Szilard debated whether to publish their work on uranium fission, fearing it might assist Nazi efforts to build an atomic bomb. Their study was eventually published, as similar findings had already been released by other scientists.¹²⁶

The current EU legal definition of dual-use items is as follows: *“Dual-use items means items, including software and technology, which can be used for both civil and military purposes, and includes items which can be used for the design, development, production or use of nuclear, chemical or biological weapons or their means of delivery [...]”* (Fig. 12).³² It is worth underlining that the term “items” encompasses both tangible and intangible assets, such as technology. Moreover, the term “technology” is defined as *“the specific information required for the development, production, or use of a product, including software or technical data”*.¹²⁷

Chemical examples of dual-use items can include substances such as ammonium nitrate, which can be used both as a fertilizer and in explosives, but also materials like quantum dots, used in biomedicine and optoelectronics but also in military-grade sensing technologies.¹²⁸ Concerning intangible items, examples can be found in software algorithms that optimize chemical syntheses and could lower barriers to producing controlled substances.

Despite attempts at legal clarity, the concept of dual-use remains ambiguous and contested and definitions vary across contexts, leading to ongoing debates.¹²⁴ For clarity in this article, we distinguish three main interpretative frameworks for dual-use items:

- Civilian vs. military use: rooted in Cold War logic, where technologies had potential applications in both sectors.
- Peaceful vs. non-peaceful use: acknowledging the possibility that an item whose designated end use is peaceful may be diverted or “misused” for non-peaceful purposes, especially those linked to the production or use of WMD.^{124,127}
- Intent-based criteria: highlighting that dual-use items may be used for benevolent or malevolent purposes depending on the user’s intention. By avoiding explicit references to “military” or “civil,” this criterion also captures the risks posed by non-state actors.

This last criterion has become especially important since September 11, 2001 attacks, which prompted a significant shift in how international trade control regimes address the threat of terrorism.¹²⁷ Export control frameworks now routinely include the risk of diversion for terrorist purposes, as mandated by UN Security Council Resolution 1540 (2004): “*All States shall refrain from providing any form of support to non-State actors that attempt to develop, acquire, manufacture, possess, transport, transfer or use nuclear, chemical or biological weapons and their means of delivery*”.¹²⁹ A monitoring committee was established to oversee implementation of this resolution, with a mandate extended until 2032 as declared by the Resolution 2663 from 2022.¹³⁰ It is to be noted that not all legislations or export controls regimes related to dual-use items explicitly employ the word “dual-use”, but they use the different definitions given above to tackle the issue (see Section 4.5).¹²⁴

However, the scope of what qualifies as a dual-use item has gradually expanded beyond materials linked to WMDs. Increasingly, items are being identified as “dual-use” not because of a direct link to WMDs, but because of their potential to threaten legally protected values such as public security or human rights. One prominent example is cyber-surveillance software, which has been added to the Wassenaar control list and subsequently included in the EU’s regulation on dual-use items (see Section 4.4). This inclusion by the EU was justified on the basis of potential human rights violations, indicating a shift in the legal rationale behind export controls.¹³¹ Such legal broadening raises concerns for chemists and other scientists: items may be added to dual-use control lists not because they can directly be used to create WMDs, but because of broader security or ethical considerations.

This development raises important questions:

- Where is the boundary between dual-use items and items intended for conventional weapons?

- Which materials used in conventional weapons manufacturing might eventually be subject to export restrictions?
- How can legal frameworks remain consistent and predictable without unduly burdening legitimate scientific and industrial activity?

That said, these expansions are likely to be tempered by economic and competitiveness considerations, especially within the EU, which must balance non-proliferation goals with its role in global trade.¹²⁴

Thus, to summarize WMDs are not considered as dual-use items. They are inherently military and designed solely for hostile purposes. However, this may evolve in the future with emerging anticancer applications for sulfur and nitrogen mustards.¹³² Dual-use items are materials, technologies, or know-how with legitimate civilian applications that may also be repurposed to contribute to WMD development or other hostile uses. The law typically refers to three main criteria to assess dual-use status (a) civilian vs. military application, (b) peaceful vs. non-peaceful use and (c) intent-based duality (benevolent vs. malevolent purposes). WMDs and dual-use items are thus conceptually and legally distinct. While WMDs are subject to direct regulation under arms control treaties (e.g. EU Military List,¹³³ Council Common Position 2008/944/CFSP),¹³⁴ dual-use items fall under specific trade control regimes due to their potential misuse.

4.3. CHEMICAL WEAPONS CONVENTION

Although the term “dual-use” does not explicitly appear in the CWC, the Convention nonetheless regulates numerous dual-use weaponizable chemicals. These are substances with legitimate civilian applications that may also be employed in the development of chemical weapons. The CWC, currently in force in 193 countries and covering approximately 98% of the global population, requires signatories to declare and destroy chemical weapons stockpiles.¹³⁵

However, several states remain outside the Convention: Israel has signed but not ratified it, while Egypt, North Korea, and South Sudan have neither signed nor acceded. While all declared chemical weapon stockpiles have been verified as destroyed, concerns persist. The destruction accounts only for declared arsenals, leaving the possibility that undeclared stockpiles may still exist. Additionally, numerous maritime dump sites containing remnants from WWI and II remain untouched and pose long-term environmental and safety risks due to potential leakage over time.^{136,137} This “do-not-touch” policy toward marine dump sites is one reason chemists continue to explore safer and more efficient neutralization methods for CWAs.^{138–141} This area of research, despite aiming at a peaceful final application, is inherently sensitive since it requires the access to CWAs (or at least simulants mimicking CWAs without their acute toxicity) to validate the neutralization. Experimental protocols for these simulants may be disclosed, which raises security concerns: given their chemical proximity to the parent CWAs, the procedures could be adapted for misuse.

Another concern is the legal grey area that persists as long as some states remain outside the Convention. Even with full destruction of declared weapons, individuals, organizations, or states could potentially produce chemical weapons, either using existing knowledge or by developing new-

generation CWAs. This risk arises from the continued availability of chemical precursors, many of which have legitimate industrial or pharmaceutical uses, a situation reminiscent of illicit drug production.

Article I of the Convention states: *“Each State Party to this Convention undertakes never under any circumstances: (a) to develop, produce, otherwise acquire, stockpile or retain chemical weapons, or transfer, directly or indirectly, chemical weapons to anyone; (b) to use chemical weapons; (c) to engage in any military preparations to use chemical weapons; (d) to assist, encourage or induce, in any way, anyone to engage in any activity prohibited to a State Party under this Convention”*.¹²¹

A broad and inclusive definitions for chemical weapons is given in Article 2 as: *“Toxic chemicals and their precursors, except where intended for purposes not prohibited under this Convention, as long as the types and quantities are consistent with such purposes”*. Toxic chemicals are defined, always in Article 2, as: *“Any chemical which, through its chemical action on life processes, can cause death, temporary incapacitation, or permanent harm to humans or animals. This includes all such chemicals, regardless of their origin or method of production, and regardless of whether they are produced in facilities, munitions, or elsewhere”*. Thus, any illegitimate use of chemicals falling under this definition is strictly prohibited, while legitimate applications, as described in Article 2.9, are allowed under specific conditions (industrial, agricultural, research, medical, pharmaceutical or other peaceful purposes).

Despite ratification, state-level violations remain possible. In a recent example, Russia was accused by the US of using chemical weapons against Ukrainian forces, triggering international sanctions.¹¹ The matter is currently under investigation by the OPCW. Under Article 9 of the CWC, any State Party that suspects non-compliance has the right to request a “challenge inspection”, enabling the OPCW to conduct an on-site investigation. However, no such inspection has been conducted to date.

The European Union has since taken actions in May 2025 regarding this matter, by sanctioning 3 Russian entities (Radiological Chemical and Biological Defense Troops, the 27th Scientific Centre and the 33rd Central Scientific Research and Testing Institute of the Ministry of Defense of the Russian Federation, all belonging to the Russian Armed Forces), following reports from the OPCW in 2024 and 2025, as riot control agent CS (2-chlorobenzalmalononitrile) and related compounds were used. The OPCW has still not given its final word on this matter and the EU is pressing them to give a clear answer.¹⁰

The threat also extends to non-state actors, a growing area of concern. For example, the UN Investigative Team to Promote Accountability for Crimes Committed by Da’esh/ISIL (UNITAD; ISIL = Islamic State of Iraq and the Levant) spent five years investigating chemical weapons used by ISIL in Iraq between 2014 and 2017. The team concluded that ISIL developed at least eight chemical warfare agents, including sulfur mustard, which is explicitly prohibited by the CWC.¹⁴² In 2024, UNITAD confirmed that sulfur mustard was used in a 2015 chemical attack in Marea, Syria.¹⁴³

These findings underscore that the threat posed by chemical weapons is not confined to the past or to state actors alone. Despite international agreements like the CWC, the risk of misuse, by both state and non-state actors, remains a pressing concern. This highlights the need for continuous vigilance, effective enforcement mechanisms, and robust national implementation measures. In this context, the

EU has taken significant steps to reinforce its own legal and regulatory framework, aiming to align with international obligations while addressing region-specific challenges. The following section explores how the EU currently approaches this complex landscape.

4.4. THE CURRENT SITUATION IN THE EUROPEAN UNION

The primary legal framework currently governing dual-use items within the EU is Regulation (EU) 2021/821, adopted by the European Parliament and Council on May 20, 2021.³² This regulation establishes a Union-wide control system for the export, brokering, technical assistance, transit, and intra-EU transfer of dual-use items. Regulation 2021/821 replaces and repeals the earlier Regulation (EC) No 428/2009, updating the EU's export control regime to better align with international obligations, including UN Security Council Resolution 1540, the CWC, and also multilateral export control regimes. Its legal foundation lies in Article 207 of the TFEU, which governs the EU's common commercial policy, including exportation and trade protection measures.³²

Dual-use items are formally defined in Article 2, as already explained above. Article 3 gives the basic rule that an authorization is required for the export of any items in annex 1 of the Regulation. Next to that basic rule, other possibilities exist. Article 9 introduces the possibility for Member States to impose additional controls on non-listed items and to render those items scheduled in their own legislation. It means a Member State can have a slightly different annex than the European one, with more controlled items.

Specifically, a Member State may require authorization for the export of items not included in Annex I for reasons related to public security, including the prevention of terrorism, or to uphold human rights. Importantly, the scope of dual-use controls has expanded beyond traditional concerns related to WMDs. Since 2021, the regulation incorporates a human rights criterion, emphasizing the potential use of exported technologies in surveillance, repression, or other violations (Art. 5).¹²⁷ This shift has significant implications for the chemical sector, especially in synthetic organic chemistry, where chemicals or technologies not previously considered sensitive may now fall under stricter scrutiny. Of particular relevance is Article 4, often referred to as the "catch-all clause". It enables Member States to require an export authorization for items not listed in the annexes if there is a known or suspected risk that they may contribute to WMD programs, military end-use in embargoed destinations, or human rights and public security violations under Article 9. Article 3.2 explicitly states that authorizations may be required even for non-listed items, provided certain risk-based conditions are met (see Articles 4, 5, 9, and 10).

These regulatory provisions are critical for addressing gaps in existing controls, ensuring that chemicals and technologies with potential misuse are appropriately regulated, even when not explicitly listed.¹²⁷ Chemists involved in the synthesis, handling, or export of dual-use substances should remain vigilant, as regulatory focus increasingly incorporates intent, end-use, and potential human rights impacts alongside traditional security concerns.

In early 2024, the EC published a white paper assessing the effectiveness of the dual-use Regulation 2021/821. The analysis highlights that the evolving geopolitical climate, particularly the war in Ukraine,

has introduced significant challenges to the implementation of this export control framework. As noted in the report: *“Since the entry into force of the Dual-Use Regulation, the global context for export controls has fundamentally changed. Russia’s war of aggression against Ukraine has been met with unprecedented and rapid deployment of sanctions. This includes swift imposition of export restrictions on Dual-Use and sensitive items critical for curbing the long-term war efforts of Russia”*.¹⁴⁴ However, a major obstacle arises from Russia’s continued participation in the Wassenaar Arrangement, a multilateral export control regime for conventional arms and dual-use goods (see Section 4.5), where it holds veto power. Russia has used this position to block the introduction of new export controls, thereby creating gaps in the multilateral control framework.

In parallel, EU Regulation 2021/821 provides Member States with the authority to adopt unilateral export controls under Articles 9 and 10.³² This flexibility has been used by several Member States, including the Netherlands, Spain, Lithuania, and Finland, which implemented national-level control measures in 2023. In 2024, other Member States used that possibility as well, for example France.¹⁴⁵ These unilateral measures are compiled and published annually by the EC, but their adoption by other Member States remains optional.

As multilateral export control mechanisms stall, largely due to Russia’s obstruction, some EU countries have taken independent action. While these unilateral regimes serve as a rapid response to global security risks, they also raise concerns about regulatory fragmentation within the EU. Such fragmentation can directly impact chemists and other scientific professionals involved in the trade or development of dual-use items. For example, a chemist in Member State A may be bound by stricter export restrictions than a colleague in Member State B, even if both are engaged in the same research project. This disparity opens the door to “forum shopping”: goods restricted in one country may be exported from a less-restrictive Member State, and from there, legally exported outside the EU (Fig. 13).

This situation is particularly problematic because intra-EU transfers of dual-use items are generally not subject to export controls, with the exception of those listed in Annex IV of the Regulation. As a result, exporters could circumvent stricter controls in one Member State by routing goods through another with more permissive regulations. While Article 10 outlines conditions under which a Member State may impose control on such transfers, this mechanism is not always sufficient to prevent such circumvention.¹⁴⁴ Ultimately, while unilateral actions may enhance national security, they also risk undermining the cohesiveness of the EU’s export control regime, potentially placing stricter Member States at an economic disadvantage and creating compliance uncertainty for chemists operating across borders.

In parallel with Regulation 2021/821 on the control of dual-use items, Regulation 2019/1148 was adopted to address a more targeted but equally urgent threat: the misuse of certain chemicals for the illicit manufacture of homemade explosives.¹⁴⁶

Its introduction followed a series of terrorist attacks in Europe in which perpetrators exploited the easy availability of consumer-grade substances (*e.g.*, hydrogen peroxide or ammonium nitrate) that were not uniformly regulated across the EU. The regulation’s core objective is to prevent the diversion of

explosive precursors by strengthening control mechanisms, improving reporting obligations, and imposing restrictions on sales to the general public.

Importantly, the regulation also reflects the EU's growing awareness of forum shopping. Indeed, Regulation 2019/1148 seeks to harmonize rules and enforcement practices across all Member States, closing loopholes that had previously undermined the effectiveness of precursor control regimes. While enhancing public safety is its primary goal, the regulation also carefully balances this with the need to preserve access to these substances for legitimate professional and industrial use through licensing, registration, and traceability systems.¹⁴⁶

4.5. MULTILATERAL EXPORT CONTROL REGIMES

The export procedure governs the movement of Union goods out of the EU customs territory. Upon export, goods lose their status as "Union goods" and are reclassified as "non-Union goods." This process involves all applicable exit formalities, including, when necessary, the presentation of export licenses and payment of export refunds.¹⁴⁷

As the EU is primarily an economic union, exports outside its borders are subject to regulatory controls, particularly through the export licensing system. This is especially relevant for dual-use goods that are tightly regulated under EU law and enforced by national customs authorities. The EU considers export controls on dual-use items a vital mechanism for international security and the protection of human rights.¹⁴⁴

To coordinate such controls, the EU or its Member States are taking part in several multilateral export control regimes (see Fig. 14), including:

- The Australia Group: focused on chemical and biological weapons;
- The Wassenaar Arrangement: covering dual-use items and conventional arms;
- The Nuclear Suppliers Group (irrelevant for organic chemistry, and therefore not further discussed);
- The Missile Technology Control Regime (irrelevant for organic chemistry, and therefore not further discussed).

Although these arrangements are not legally binding (they constitute soft law), they are central to EU export policy. In fact, Annex I of the dual-use Regulation, is essentially a compilation of the control lists from these regimes.¹⁴⁸

The Australia Group, formed in 1985, is an informal consortium comprising 42 participating states and the EC. It convenes annually to assess the effectiveness of export controls related to the non-proliferation of chemical and biological weapons, including precursor chemicals and associated technologies.¹⁴⁹

The Wassenaar Arrangement, established in 1995 and operational since 1996, aims to prevent the destabilizing accumulation of sensitive technologies and arms. It obliges participating states to implement export controls on all items listed in its dual-use and munitions lists, in order to prevent

unauthorized end-uses or transfers: “Participating States apply export controls to all items set forth in the List of Dual-Use Goods and Technologies and the Munitions List, with the objective of preventing unauthorized transfers or re-transfers of those items”.¹⁵⁰ All EU Member States, with the exception of Cyprus, are participants in the Wassenaar Arrangement (Fig. 14).

These multilateral regimes are vital because they extend export control efforts beyond EU borders, ensuring a wider international reach in preventing the proliferation of WMDs. They also operate more flexibly than formal international treaties. In practice, many substances are first introduced into export controls via these regimes before being integrated into binding legal instruments. As a result, the EU can respond more swiftly to emerging threats by updating its control lists annually, a process that would be significantly slower under treaty law.¹⁴⁴

5. Inside the laboratory

Having reviewed the broader legal landscape, covering narcotic and psychotropic substances, as well as dual-use and chemical weapon-related controls, we now turn to the practical realities chemists face in the laboratory. Understanding legislation is one thing; applying it correctly in day-to-day research and chemical handling is another. This section aims to bridge that gap, translating legal requirements into clear, actionable guidance for professionals working in chemistry. We present here the scope of regulatory obligations that a chemist must follow while actively working in the lab, such as obtaining licenses, following orders, and complying with specific authorizations.

To do so, we revisit the key questions posed in the introduction that reflect real concerns from within the scientific community:

- Which substances are restricted, and to what extent?
- Can I legally prepare these compounds?
- Why must I disclose certain information to unlock orders, and are these orders monitored?
- Are there import quotas, and is a license needed?
- What does obtaining a license involve, and is it time-limited?
- Is a product exportable without a license, and what would a license imply?
- Is there assistance available if a chemist is unsure about legal requirements?
- How can a scientist stay informed about changes in the law?

Before answering these, it is necessary to make the distinction between a license and an authorization: two crucial tools for legal compliance. A license allows an institution or individual to perform certain regulated activities, such as possessing or handling narcotic or psychotropic substances, and is typically issued by national authorities based on qualifications and safety standards. An authorization, on the other hand, is required for specific actions involving sensitive materials, such as the export of dual-use chemicals or the acquisition of controlled precursors, and is granted on a case-by-case basis. While a license enables ongoing activity, an authorization is usually transaction- or substance-specific, and subject to strict oversight. The two terms may sometimes be used interchangeably in some contexts

(for example, export controls). However, in the context of chemistry, these are usually treated as separate concepts, as illustrated in Regulation 111/2005 (see Section 5.4 and Fig. 18b).

To help answer the broader set of compliance questions, each of the following sections is dedicated to a specific piece of legislation, such as the Conventions on narcotics and psychotropics, the CWC, the EU dual-use Regulation and so on. By closely examining the annexes, schedules, and associated procedures, we will clarify what these laws mean in practice, and how chemists can ensure they remain in full compliance, without compromising their research or workflow. At the end of each subsection, an explanatory figure with a Q&A box helps chemists navigate the legislation. In addition, Section 5.9 compiles practical tools to support compliance and deepen understanding of the regulations, while Table 5 provides a summary of the discussed legislations with brief descriptions and hyperlinks to the full legal texts.

5.1. THE SINGLE CONVENTION ON NARCOTIC DRUGS OF 1961 AND THE CONVENTION ON PSYCHOTROPIC SUBSTANCES OF 1971

When it comes to EU law, some types of legislations are enforceable before national and European Courts. “Direct effect” means individuals can use a European Law before a national Court.¹⁵¹ Regulation carries direct effect if its rules are sufficiently clear, precise and relevant to the situation of the individual litigant. This principle is recognized in Article 288 TFEU and reinforced by the famous case law from the European Court of Justice “Van Gend and Loos judgment”.¹⁵²

Unlike EU regulations, the Single Convention on Narcotic Drugs of 1961 is not directly applicable within national jurisdictions. As an international treaty, it imposes obligations on States, not individuals or institutions. This means that the relevant legal authority for chemists lies in national legislation or, where applicable, in EU law, both of which implement the Convention’s requirements. This principle is stated in Article 4, which obliges Parties to adopt the necessary legal and administrative measures at the national level.⁷¹ Nevertheless, these United Nations Conventions are important, as they apply in almost every country (186 states for the Narcotic Drugs Convention and 184 for the Psychotropic Substances Convention), and they shape the entire legislative framework that States are required to implement.

Importantly, the Convention does not prohibit the substances it lists. As noted in its preamble, narcotic drugs are considered indispensable for medical use, particularly in pain relief and surgical sedation. Accordingly, Article 4, paragraph C, specifies that production, manufacture, import, export, distribution, and possession of these substances must be limited exclusively to medical and scientific purposes. In addition, Article 2.9 provides an important exemption: “*Parties are not required to apply the provisions of this Convention to drugs which are commonly used in industry for other than medical or scientific purposes*”. This clause acknowledges that certain substances, while chemically similar to narcotics, may have legitimate industrial uses beyond the scope of the Convention.

According to the INCB, substances are primarily placed under control based on their pharmacological properties as narcotic drugs – namely, their ability to induce numbness, sedation, sleep, or pain relief.

However, the scope of the Convention also includes certain natural substances, such as the cannabis plant, whose effects are more stimulatory than strictly narcotic.¹⁵³ This highlights a long-standing terminological inconsistency: the term “narcotic” in this context reflects historical usage rather than strict chemical accuracy. The original naming of the Convention mirrors the early days of drug control treaties, when only natural drugs were known and regulated.

The Convention establishes four schedules of controlled substances (Fig. 15a and b), organized based on therapeutic value and potential for abuse:

- Schedule IV: most strictly regulated substances, considered to have high abuse potential and minimal therapeutic use (*e.g.*, heroin). Schedule IV are already part of Schedule I, with additional constraints.
- Schedule I: substances with significant abuse potential but also recognized medical uses (*e.g.* cannabis, cocaine, and opium). Schedule II: substances with a lower risk of abuse (*e.g.* methadone).
- Schedule III: pharmaceutical preparations containing narcotic drugs that present a lower abuse risk, such as certain codeine-based medications.

Overall, scheduling decisions are based on a risk-benefit assessment that weighs the danger of misuse against the real and recognized therapeutic value of each substance.

As with the 1961 Convention, the 1971 Convention on Psychotropic Substances does not have direct effect: its provisions must be transposed into national legislation by each State party. The 1971 Convention focuses on synthetic psychotropic substances, organizing them into four schedules based on their potential for abuse and recognized medical use (Fig. 15c and d):

- Schedule I: most strictly controlled substances, considered to have high abuse potential and no accepted therapeutic use, such as LSD or MDMA.
- Schedule II: substances with limited therapeutic applications, like amphetamines, but still associated with a significant risk of misuse.
- Schedule III: compounds with established medical value and moderate risk of abuse, such as pentobarbital.
- Schedule IV: substances that are widely used in medicine and present a lower potential for dependence, such as alprazolam.²²

It is worth noting that the classification of substances may evolve. For example, LSD and MDMA, traditionally placed in Schedule I, are now being re-evaluated in light of emerging therapeutic research, especially for the treatment of psychiatric disorders and treatment-resistant depression.^{154–156}

Fig. 15e reports a “Q&A” box to help researchers comply with the Conventions of 1961 and 1971.

5.2. UNITED NATIONS CONVENTION AGAINST ILLICIT TRAFFIC IN NARCOTIC DRUGS AND PSYCHOTROPIC SUBSTANCES OF 1988

The 1988 Convention addresses the criminal dimension of drug control, specifically focusing on the illicit production and trafficking of narcotic and psychotropic substances.⁷⁵ It complements the 1961 and 1971 Conventions by closing legal gaps related to the clandestine supply chain.

Under Article 3, Parties are required to criminalize a wide range of activities when carried out without proper authorization, including the production, manufacture, extraction, preparation, transport, import, and export of substances covered by the earlier Conventions as well as by the 1988 Convention's own Annex. This Annex contains two Tables, listing chemical precursors and hardware commonly used in the illicit synthesis of controlled substances. For example, acetic anhydride (used in heroin production) and piperidine (used in synthetic drug synthesis) are listed in Table I. Both are very common reagents in synthetic organic chemistry and peptide synthesis.^{157–159} Article 3 explicitly targets not only these substances but also the knowledge-based intent of misuse: *“The manufacture, transport or distribution of equipment, materials, or substances listed in Tables I and II, knowing that they are to be used in or for the illicit cultivation, production, or manufacture of narcotic drugs or psychotropic substances”*.

As with the previous Conventions, the annexed tables are dynamic and require frequent updates. This task is carried out by the CND. Importantly, the texts of the original Conventions often remain outdated: the annexes in the official UN documents may show updates only up to the early 1990s (*e.g.*, 1990 for the 1961 Convention). To access the most current schedules and tables, chemists must consult the CND's official website, specifically the page titled “International Drug Control Conventions”, under the section “Scheduling decision”.¹⁶⁰ This webpage is updated several times per year to reflect the inclusion of new precursors and controlled chemicals. The INCB also publish usually once a year a full list of the scheduled substances: the Yellow list for the 1961 Convention,¹⁶¹ the Green list for the 1971 Convention,¹⁶² and the Red list for the 1988 Convention.¹⁶³

To assist chemists in understanding and complying with the 1988 Convention, a Q&A box is provided in Fig. 16.

5.3. REGULATION 273/2004: EU REGULATION ON DRUG PRECURSORS

This Regulation, which was formerly a Directive, governs the intra-EU control of chemical substances frequently used in the illicit manufacture of narcotic drugs and psychotropic substances.³³ The transition from Directive to Regulation reflects a key need: speed. Under a Directive, each EU Member State had to transpose the rules into national law, often resulting in delays. There is a need for harmonized, EU-wide controls on intra-Union trade in drug precursors (*i.e.*, replacing a directive with a directly applicable regulation so uniform rules apply simultaneously across all Member States). Recitals 3 and 4 (check the definition for “Recitals” in Table S1 in the SI) stress intra-EU monitoring and the switch to a regulation for consistent application, and the 2020 Commission evaluation reiterates

the EU-level “added value”, including symmetrical regulation of intra-EU and external trade with common definitions and approaches.^{33,76}

The Regulation’s objective, stated in Article 1, is to harmonize rules for controlling the movement and availability of drug precursor chemicals within the EU only; exports and imports outside the EU are handled separately under regulation (EC) no 111/2005 (see Section 5.4). Article 3 lays down the general rules for the placing scheduled substances on the market. In Annex I, substances are divided into three categories (Fig. 17a and b):

- Category 1 substances (*e.g.*, 1-phenyl-2-propanone) are subject to the strictest controls: a special authorization is required even for possession in lab inventory, and a Public Officer must be appointed to oversee compliance. For instance in Belgium, this task is superintended by the Federal Agency for Medicines and Health Products. Special licenses are granted to pharmacies, armed forces, and certain types of public authorities. This also concerns academic research laboratories that are eligible under very strict conditions for such licenses, many of these compounds being common building blocks for broad applications in synthetic organic chemistry.
- Category 2 substances (*e.g.*, piperidine and acetic anhydride) require registration for possession, but the process is simpler and more easily obtained than for Category 1 substances. An example of the requested Custom Declaration for acetic anhydride is reported in the SI (Fig. S10).
- Category 3 substances, which are widely used in industry, are not subject to licensing or registration, though operators must still report any suspicious transactions.³³

Identifying the proper channel to access such authorizations falls to the chemist, for which legal affairs offices can provide some support. For both licenses and registrations, officials have the final say, and these can be revoked if conditions are not met or if the holder has acted inappropriately (*e.g.*, failure to comply with the requested annual inventory or failure to renew licenses or registrations in due time). Member States may impose a fee for applying for a license or a registration.

Article 4 mandates that when Category 1 or 2 substances are supplied, the operator must obtain a customer declaration detailing the intended end-use. Without proper filing, the order is not processed and the chemicals will not be delivered. Templates for these documents are provided in Annex III of the Regulation (see Fig. S1 and S2). Article 6 outlines specific exemptions for Category 2 substances, for example when used in small quantities or by designated institutions. Under Article 8, if any unusual or suspicious activity is noticed, operators (*i.e.*, chemical suppliers) are obliged to inform the relevant national authorities.

The Regulation also recognizes non-scheduled substances, defined in Article 2(b), as: “*Any substance which, although not listed in Annex I, is identified as having been used for the illicit manufacture of narcotic drugs or psychotropic substances*”. This clause offers flexibility for addressing emerging synthetic routes and designer chemicals not yet formally scheduled. The Regulation empowers the EC (Article 9) to maintain a list of nonscheduled substances suspected of being used in illicit manufacture.

While Member States are not obliged to act on this list, they may choose to monitor such substances. Finally, Article 10 allows Member States to monitor suspicious transactions.

Starting from August 14th 2025, Regulation 273/2005 has been amended by Commission Delegated Regulation 2025/1475 that included 4-piperidone and 1-Boc-4-piperidone in Category 1 precursors.¹⁰⁵ These compounds have indeed common use as direct fentanyl precursors and, in order to work with them, a license is now required.

To facilitate compliance with regulation 273/2004, Fig. 17c offers a dedicated Q&A box for researchers.

5.4. REGULATION 111/2005: REGULATION ON PRECURSORS INVOLVING THIRD COUNTRIES

Regulation 111/2005 complements Regulation 273/2004, but instead of covering the intra-EU circulation of drug precursors, it focuses on their export to third countries.³⁴ It lays down rules for the supervision of trade in drug precursors between the EU and non-EU countries and is essential for addressing international trafficking.

According to Article 3, any export, import, or intermediary activities involving a scheduled substance (apart from Category 4) must be documented by the operator. Documents include summary declarations, customs declarations, invoices, cargo manifests, transport and other shipping documents. These records must be retained for three years following the transaction (Article 4). Maintaining a trace of all activities involving these substances is mandatory.

As stated in Article 6, a license is required for any operator dealing with Category 1 substances (*e.g.*, phenylacetone), except for transporters who only provide cargo services. Category 2 substances, such as acetic anhydride, require registration for import, export and intermediary operations, while Category 3 substances (*e.g.*, acetone) require registration for transportation according to Article 7. As for the previous regulation, licenses and registrations can be revoked. Any suspect activity must be notified, and the EC is required to publish guidelines (Articles 9 and 10). As per Article 12, an export declaration for any scheduled substance requires a custom declaration. To summarize (Fig. 18a), depending on the category where the substance is listed, different documents need to be filed:

- Category 1 substances: license for import, export or intermediary activities (Art 6);
- Category 2 substances: registration for import, export or intermediary activities (Art 7). An example of the requested Custom Declaration for acetic anhydride is reported in the SI (Fig. S10);
- Category 3 substances: registration for export (Art 7);
- Categories 1 to 4 substances: export authorization with exception for category 3 under certain conditions (Art 12).

There are two Regulations that complete Regulation 273/2004 and 111/2005, namely the Commission delegated Regulation 2015/1011 and the Commission Implementing Regulation 2015/1013.^{164,165} Regulation (EU) 2015/1011 introduces important clarifications regarding Category 3 substances under Regulation 111/2005. Specifically, Article 6(b) provides an exemption from the registration

requirement for operators exporting small quantities of these substances. It states that operators exporting Category 3 scheduled substances are exempt from registration if the total amount exported during the previous calendar year (January 1 – December 31) does not exceed the thresholds specified in Annex I of Regulation 2015/1011. However, if these quantities are exceeded at any point during the current year, the operator must immediately comply with the registration requirement.

Both Regulation 2015/1011 and Regulation 2015/1013 elaborate on the technical procedures related to licensing, registration, exemptions, and the required documentation:

- Article 3 of Regulation 2015/1011 outlines the steps operators must follow to obtain a license, including the information and documentation to be submitted.
- Article 3 of Regulation 2015/1013, on the other hand, details the procedure national authorities should follow to evaluate and decide whether to grant the requested license.

Both Regulations are accompanied by annexes that include standard models for various documents and licenses. While the format of these models is not legally binding, the content (the specific information required) is mandatory. These annexes serve as a practical reference to help operators ensure that their submissions contain all the necessary elements required by the authorities. To assist researchers in understanding and complying with these regulations, a Q&A box is provided in Fig. 18b.

5.5. DIRECTIVE 2001/83/EC AND REGULATION 2019/6 ON MEDICINAL PRODUCTS FOR HUMAN AND VETERINARY USE

Two cornerstone pieces of EU legislation governing the handling of pharmacologically active substances are Directive 2001/83/EC, relating to medicinal products for human use, and Regulation 2019/6, concerning veterinary medicinal products.^{93,107} Both legal instruments are structured around a harmonized regulatory framework for the authorization, manufacture, import, distribution, and labelling of medicinal substances. While they do not contain annexes listing individual controlled substances in the manner of drug precursor or psychotropic substances, they refer to classes of compounds and establish detailed procedural and technical requirements in the annexed modules of the Common Technical Document format, which is mandatory for marketing authorization dossiers. These modules cover aspects such as chemical and pharmaceutical quality, pharmacology, toxicology, clinical data, and manufacturing processes.

Examples of compounds regulated under these frameworks include clenbuterol (a beta-agonist with both therapeutic and performance-enhancing uses), dexamethasone (a corticosteroid with strict veterinary restrictions under food safety laws), and trenbolone acetate (an anabolic steroid prohibited for use in food-producing animals under Directive). Although not illegal *per se*, these substances are subject to stringent control regarding their use, formulation, and movement within the EU.

For a chemist intending to synthesize or work with such substances, several compliance steps may apply. First, an authorization for manufacturing is required if the work is not limited to research or analytical purposes. This includes registration with the national competent authority (*e.g.*, AIFA in Italy, BfArM in Germany, MHRA in the United Kingdom and FAMHP in Belgium) and compliance with Good

Manufacturing Practice.¹⁶⁶ In cases involving export or import, particularly for investigational or compounded substances, additional documentation such as end-use certificates and customs declarations may be required.

Ultimately, while these legal instruments do not prohibit research or synthesis *per se*, they impose a regulatory environment focused on traceability, risk assessment, and public health protection, requiring chemists to adopt a compliance-oriented mindset when handling medicinal substances.

Fig. 19 includes a Q&A section intended to support researchers in finding the tools to comply with legislation.

5.6. CHEMICAL WEAPONS CONVENTION

The CWC classifies chemicals into three schedules to control their production, use, and trade. While the synthesis of CWAs is unequivocally banned, certain listed compounds, including some CWAs and their precursors, may still be legally produced under controlled circumstances due to recognized civilian applications.¹²¹ For example, phosgene and some sulfur or nitrogen mustards have legitimate industrial or medical uses, including as intermediates or in anticancer therapies.

Schedule 1 chemicals are subject to the most stringent controls, as they generally lack any substantial commercial use beyond military applications (*e.g.*, sarin, VX). Their production, acquisition, and use require prior licensing from the national authority, in accordance with the Convention's Annex (Part VI, Schedule 1 Regime). Schedule 2 substances pose a significant risk to the Convention's objectives but have limited, legitimate small-scale uses (*e.g.*, in specialty synthesis). Schedule 3 chemicals are more widely used in industry but are still regulated due to their potential application in CWA production (Fig. 20a and b).

Each schedule is subdivided into Part A (toxic chemicals) and Part B (precursors), as depicted in relevant regulatory diagrams and tables. An interesting example is given by methylphosphonic acid, its esters, and methylphosphonic dichloride (Fig. 20a and b). These are not CWAs themselves but can serve as essential building blocks in the synthesis of schedule I agents such as Sarin and VX, and are therefore regulated under Schedule 2B of the CWC. While the term "*pre-precursor*" is not officially used in the CWC framework (unlike in drug control legislation), such compounds function analogously: they are several steps upstream in synthetic pathways but are still controlled due to their strategic importance. Including these early-stage chemicals in the regulatory structure highlights the Convention's emphasis on preventive control rather than focusing solely on end-products.

Beyond scheduled chemicals, the Convention also addresses Discrete Organic Chemicals (DOCs), defined in the Verification Annex as any carbon-containing compounds (excluding oxides, sulfides, and metal carbonates) that can be distinctly identified by name, structure, or CAS number. Unscheduled DOCs (UDOCs) must be reported if production exceeds 200 metric tons per facility per year. Additional reporting is required for UDOCs from PSF-plants (those involving phosphorus, sulfur, or fluorine) if the production threshold of 30 metric tons is exceeded. These compounds are considered dual-use:

though often integral to legitimate chemical manufacturing, they may also serve as pre-intermediates for CWAs.¹²¹

The regulatory requirements, including licensing, notification, and reporting thresholds, are detailed across several annexes of the CWC. Compliance is monitored both nationally and by the OPCW. A Q&A box is shown in Fig. 20c to aid researchers in meeting the requirements of the CWC.

5.7. EU REGULATION 2021/821: REGULATION ON DUAL-USE ITEMS

EU Regulation 2021/821, while relatively concise in its main body, derives most of its operative detail from its four Annexes.³² A notable introduction in this Regulation is the inclusion of technical assistance within its scope. Article 2(9) defines technical assistance as “*any technical support related to repairs, development, manufacture, assembly, testing, maintenance, or any other technical service,*” including forms such as instruction, advice, training, or consultancy, even when delivered remotely, such as by phone or email. This has direct implications for chemists: for example, if a chemist travels to a non-EU country to assist with reactor operations, and the reactor includes dual-use components, that assistance may legally require an export license; seemingly, teaching, collaborating or working on research involving dual-use items in a third country or even in an EU-based laboratory with a colleague/researcher from a third country may be deemed to constitute the provision of technical assistance.

Another key update is the broadened definition of “exporter.” Article 2(3)(c) states that an exporter includes “*any natural person carrying the dual-use items to be exported where these dual-use items are contained in the person’s personal baggage*”. Thus, if a researcher travels abroad with a laptop containing dual-use software or technical data (such as manuscripts or their SI), that act may constitute an export and require prior license.¹⁶⁷ Furthermore, it is important to recall that under the definition of “export”, even storing specific information in a cloud service or sending it by email to a researcher in a third country may be considered an export, as it falls under the notion of “making available” (Art. 2.2.d).

Under Article 3, all items listed in Annex I require an export license. These include a wide range of dual-use goods, from certain chemicals (*e.g.*, diethylamine) to cyber-surveillance tools. In addition, catch-all clauses (see Section 4.4) allow Member States to impose controls even on non-listed items if there is a risk of diversion to weapons programs or embargoed destinations. Article 7 gives Member States the power to prohibit the transit of items for specific reasons outlined in Article 4(1). Article 11 mandates licensing even for intra-EU transfers of sensitive items listed in Annex IV. Though intra-EU transfers typically do not require a license, exceptions exist for particularly sensitive goods. Furthermore, it is essential to monitor the final destination of any dual-use item, as exports to embargoed countries or those under restrictive measures are subject to additional scrutiny.

While extensive, the structure of the Annexes is clearly organized (Fig. 21a). Annex I contains the full list of dual-use items subject to export authorization and is aligned with international control regimes (Section 4.5). Each dual-use item is assigned a classification code, combining numbers and letters to indicate the item’s category, subcategory, and specific control entry (Fig. 21b). These classification

codes are essential for the authorization and export documentation processes, referring to both the nature of the item and the control regime that governs it (Fig. 21b). Annex II introduces Union General Export Authorizations (UGEAs): simplified procedures that replace individual licenses with a one-time notification letter. These apply only under strict conditions to designated items and countries. UGEAs are divided in eight sections: for instance, UGEA EU006, specific to chemical items, facilitates the export of substances such as potassium cyanide and arsenic trichloride to countries like Argentina, South Korea, Turkey, and Ukraine, all participants in the Australia Group.

The broader UGEA EU001 allows exports of all Annex I items to countries with a special regulatory relationship to the EU, including the USA, UK, Japan, and others. Annex III provides a model authorization form to simplify application procedures (see Fig. S3–S6), while Annex IV details dual-use technologies that require licensing even for transfers within the EU (especially sensitive categories see Article 11).

Article 12 distinguishes between four types of export authorizations:

- Individual (one exporter, one or more dual-use items, one end-user or consignee in a third country); it may cover multiple dual-use items, provided they form part of a single transaction between the same two parties;
- Global (one exporter, multiple items, multiple end-users or destinations);
- National General (specific dual-use items, certain countries of destination as defined by individual Member States under Article 12(6), and applicable only to exporters based in the relevant EU Member State);
- EU General (one or more dual-use items to certain destination and conditions, as outlined in Annex II).³²

Fig. 21c features a Q&A box offering practical guidance for researchers navigating Regulation 2021/821.

5.8. REGULATION 2019/1148 – PRECURSORS OF EXPLOSIVES

Among the various chemical threats to public safety, such as dual-use items and drug precursors, explosive precursors have gained increasing regulatory attention due to their involvement in terrorist attacks. These substances, many of which are common organic compounds, can be misused to manufacture home-made explosives (HMEs). Regulation 2019/1148 was introduced to harmonize rules across Member States and reduce the risk of diversion for illicit purposes.¹⁴⁶

The Regulation divides explosive precursors into two categories related to some obligations (Fig. 22a and b):

- Annex I (Article 5, restricted precursors): chemicals such as nitric acid, which pose a high risk, are not available to the general public unless a license is obtained under strict conditions. National authorities differ in how this is implemented (some issue licenses under Article 6, while others restrict access entirely) Chemists working in academia or industry are considered professional users (Article 3(10)) and do not require a license, but must provide an end-use

declaration to suppliers. An example of the requested declaration for nitric acid is reported in the SI (Fig. S11 and S12);

- Annex II (reportable precursors): substances like acetone are not prohibited for public use, but suspicious transactions, thefts, or disappearances must be reported to authorities under Article 9.

These categories aim to safeguard legitimate use in professional environments, while restricting non-professional access. A template of the form that must be filled in order to get a license is reported in Annex III (see Fig. S7 and S8) and the one for the Customer's Statement in Annex IV (see Fig. 9). Several attacks in the EU (*e.g.*, Paris, Brussels, Lyon) have involved HMEs made from easily accessible chemicals, sometimes purchased from hardware or convenience stores. As highlighted in Recitals 4 and 15 (definition in Table S1), the simplicity of illegal manufacture highlights the need for vigilance at every point in the supply chain.¹⁶⁸ Provisions under regulation 2019/ 1148 create a layered regulatory framework that ensures the availability of key substances for legitimate research and industrial activity, while limiting their misuse. To facilitate compliance with regulation 2019/1148, Fig. 22c offers a dedicated Q&A box for chemists.

5.9. WHAT ARE THE SUPPORTS AVAILABLE TO CHEMISTS?

Despite the concise and instructional nature of the present document, the legislative framework remains complex and can pose a significant administrative burden for researchers in the chemical sciences. Fortunately, several tools and resources exist to support compliance and facilitate understanding.

5.9.1 CHEMICAL SUBSTANCES.

For chemists, a critical reference is the Export Control Handbook for Chemicals, published by the Joint Research Centre of the European Commission and authored by Arnés-Novau and Sevini.¹⁶⁹ This comprehensive handbook, available both in print and online, lists chemical substances of concern by CAS number and links them to the relevant international legal frameworks. The most recent edition (2023) includes analyses of both the EU dual-use Regulation and the Chemical Weapons Convention (see pp. 10 and 34). It also includes analyses of the Regulation 111/2005 (export of drug precursors) and Regulation 2019/1148 (explosive precursors). This handbook serves as a reference tool for assessing chemical export controls.

5.9.2 CONTROLLED DRUGS AND PRECURSORS.

On the topic of controlled substances, detailed legal commentaries have been issued for each of the UN Conventions, offering precise definitions, such as those for "cannabis" and "drugs" (see pp. 2 and 9 of the Commentary on the Single Convention on Narcotic Drugs of 1961).¹⁷⁰ At the EU level, EUDA has also produced a glossary of terms, further aiding in the consistent interpretation of terminology across regulatory contexts.⁷² It is strongly recommended to seek advice from the relevant national contact points (either national medicines agencies or customs).

5.9.3 DUAL-USE ITEMS

In 2021, the European Commission issued Recommendation 2021/1700 on internal compliance programs for research involving dual-use items, under the scope of EU Regulation 2021/821.¹⁷¹ While this Recommendation is not legally binding, it represents a valuable and reliable reference published by the Commission itself. It includes guidance specifically tailored to researchers, with a glossary providing technical definitions; Appendix 1 (SI), which outlines research domains likely to be impacted by dual-use regulations (including chemistry, artificial intelligence, and automation); Appendix 2 (SI), which presents real-world scenarios that may trigger export control requirements; and Section 2.2, which contains practical examples and clarifying commentary. These are only some of the key elements contained in the Recommendation, which also cover additional content relevant to compliance and best practices. Fig. 23 of this article reproduces content from Appendix 7 (SI) of the Recommendation, which chemists may find particularly illustrative.

In addition to EU-level guidance, Member States often provide national guidelines to help researchers navigate this complex field. For example, Belgium has issued detailed national guidance and Germany has published the “Export Control and Academia Manual”.^{172,173} These documents offer tailored advice for researchers and institutions engaging in activities potentially subject to export control.

5.9.4 EXPLOSIVES PRECURSORS.

The EC’s guidelines on Regulation 2019/1148 (“Commission Notice Guidelines for the Implementation of Regulation (EU) 2019/1148 on the Marketing and Use of Explosives Precursors 2020/C 210/01”) provide further clarity, especially relevant to chemists working with precursor substances.¹⁷⁴ For example, the guidelines specify that students cannot submit customer declarations on behalf of their University unless formally authorized. Such provisions clarify roles and responsibilities regarding the handling and procurement of explosives precursors.

5.9.5 LOCAL TOOLS AND INSTITUTIONAL RESOURCES.

Researchers are encouraged to consult tools developed at the institutional level to support early-stage compliance, including during the preparation of project proposals. A notable example is the Dual-Use Assistance App developed by the University of Liège. This tool enables users to assess whether their activities may fall under the scope of dual-use regulation. It can be accessed by visiting the University’s website and navigating to the section “dual-use” - “Dual-Use Assistance App”.¹⁷⁵

Other leading Universities in Belgium provide support to researchers with similar tools. For instance, KU Leuven offers a dedicated Knowledge Security Helpdesk and an Ethics Committee on Dual-Use, Military Use & Misuse (EC DMM) to assist researchers with project screening and export control considerations.¹⁷⁶ Similarly, Ghent University provides institutional guidelines and ethical review procedures for dual-use research.¹⁷⁷

Comparable support mechanisms exist at several other institutions across Europe. In the United Kingdom, the Export Control Joint Unit (ECJU) has published guidance specifically tailored to academic research, including a structured self-assessment decision tree.¹⁷⁸ Moreover, Imperial College London

provides a Research Security Self-Assessment Record that faculty must complete if their work involves potentially controlled items or overseas collaborators. Researchers receive tailored guidance from the Research Office on export licensing and compliance.¹⁷⁹

Germany's BAFA (Federal Office for Economic Affairs and Export Control) offers an online portal for dual-use licensing and comprehensive documentation tools.¹⁸⁰ In addition, Freie Universität Berlin's Joint Committee for Ethics in Security-Relevant Research collaborates with the university's export control coordination unit to advise researchers on dual-use or security-sensitive research activities, especially those involving international partnerships.¹⁸¹ They offer case-specific guidance to ensure compliance with export control regulations.

These institutional and national-level resources aim to reduce administrative uncertainty, raise awareness, and promote proactive compliance, especially in disciplines, such as chemistry and engineering, where dual-use risks may arise even at early stages of research planning.

Fig. 24 includes a Q&A section intended to support researchers in finding the tools to comply with legislation.

6. International collaborations, publications, and dissemination of results

Having explored the legal requirements that govern chemical work within the laboratory, we now shift our attention to the obligations and potential risks that arise outside the lab: in the dissemination of results, international collaboration, and cross-border movement of materials and knowledge. Research does not end at the benchtop, and the growing interconnectedness of science brings legal challenges that extend well beyond chemical handling. In this section, we explore how dissemination, communication, and collaboration intersect with regulatory frameworks, particularly when research involves sensitive materials, potential dual-use items, or international partners.

To guide this analysis, we revisit a new set of practical questions raised in the introduction, questions that reflect the evolving responsibilities of chemists as communicators and global actors:

- Can I ship reaction products abroad for collaboration, and are there any restrictions?
- What role do customs play?
- Can disseminating results (e.g. through publications, conferences, or patents) be unlawful?
- Why do some journals require a Dual-Use Research of Concern (DURC) declaration while others do not?
- Why are there increasing obligations to declare the involvement of dual-use items in EU-funded projects (e.g., Horizon Europe)?
- Given that publications are accessible worldwide, could they pose a threat, and should they be restricted if they address sensitive chemistry?
- How does the legal framework impact global collaborations?

By addressing these questions, the following sections aim to clarify how research activities, ranging from sending a compound to publishing a paper, can carry legal implications. We will outline the key scenarios and frameworks involved, and offer practical strategies to help chemists stay compliant while continuing to engage with the global scientific community. At the end of each section an explanatory box with questions and answers is always reported.

6.1. SANCTIONS AND EXPORT

As discussed earlier, sanctions are tools used against countries, entities, or individuals that violate international conventions or national laws. Sanctions against States are typically economic or diplomatic, as one definition puts it, “*economic sanctions are an attempt by states to coerce a change in the policy of another state by restricting their economic relationship with the latter*”.¹⁸²

The EU, international bodies (like the UN) and individual comes to international bodies, some of them can conduct verification and impose sanctions if infractions are committed. For example, under the CWC, a State Party can initiate a *challenge inspection* if it suspects non-compliance by another State. Such mechanisms are part of the broader international framework to ensure global chemical safety.

In the EU, a range of legal instruments exist to impose and enforce sanctions against individuals. For example, Regulation 2018/1542 imposes restrictive measures in relation to the proliferation and use of chemical weapons.¹⁸³ Recital 1 states that “*the use of chemical weapons [...] is completely unacceptable,*” and Article 2 mandates the freezing of all funds and economic resources belonging to listed individuals or entities (Annex I) (check the definition for “Recitals” in Table S1 in the SI).

To navigate this landscape, the EU Sanctions Map offers a public, searchable tool where chemists can verify which countries, companies, or individuals are under restrictive measures.¹⁸⁴ The EU Sanctions Map is an online tool managed by the EC that provides up-to-date, searchable information on all active EU restrictive measures, including those related to specific countries, sectors, and individuals. It covers financial sanctions, travel bans, and restrictions on the transfer of goods, technology, and know-how, including in areas such as chemicals, biotechnology, and energy.

According to the EU, sanctions aim to “*prevent conflict or respond to emerging or current crises, and to promote peace, democracy, respect for the rule of law, human rights and international law*”.¹⁸⁵ Article 215 of the TFEU enables the EU to impose sanctions not only on governments of third countries, but also on non-state actors, including companies or individuals involved in terrorism or human rights violations. These sanctions may include arms embargoes, travel bans, freezing of assets, restrictions on financing and exports, diplomatic measures, and economic sanctions. Of special relevance to chemists are the economic sanctions, which can directly affect the shipment and export of chemicals, equipment, or research data. These sanctions may cover sectors such as trade, defense, technology, finance, transport, and energy.¹⁸⁶ Importantly, Article 7 of the TEU allows the EU to sanction its own Member States by suspending certain rights, such as voting, if a country is found to be violating the values listed in Article 2 TEU, including human dignity, democracy, and the rule of law.¹⁸⁷ At the international level, the UN Security Council can also impose sanctions under Article 41 of the UN

Charter, including arms embargoes, travel bans, and economic restrictions.¹⁸⁸ In some instances, these sanctions prohibit the export of dual-use items or cyber surveillance equipment to specific countries.

This is closely related to the EU dual-use Regulation (2021/ 821). Recital 16 emphasizes that Member States may block the transit of dual-use items if there is reason to believe they might be diverted for military use in an embargoed country or for WMDs.

Recital 2 and Article 15 from that same Regulation emphasize the role of Common Position 2008/944/CFSP, (definition for “Recitals” in Table S1) in that regard.^{134,189} Article 2 of the Common Position outlines eight criteria for denying a license, including:

- Violation of international obligations and sanctions (arms embargoes);
- Respect for human rights in the country of final destination;
- Civil war or armed conflicts in the country of final destination;
- Preservation of regional peace, security and stability;
- National security of a Member State;
- Behavior from the country of final destination towards terrorism and international law;
- Risk for the military equipment to be diverted in the country of final destination;
- Technical and economic capacity of the country of final destination compared to the military technologies involved.

Illicit drug trafficking is also a domain where EU sanctions apply. For example, Council Decision 2022/2319 (now amended by Council Decision 2024/1968) targets individuals involved in organized crime in or through Haiti, specifically citing drug production and trafficking as sanctionable offenses.¹⁹⁰ On the other hand, the illicit drug trafficking can be criminalized under national laws, as mandated by the EU. However, it is inherently different as it constitutes an obligation the EU imposes on its Member States, rather than an international sanction. Council Framework Decision 2004/757/JHA focuses specifically on penalties Member States should impose on individuals committing those offenses.⁹⁵ Article 2 of this decision obliges each Member State to implement national measures to punish any legal persons involved in the manufacture, trafficking, or cultivation of drugs or their precursors.

A Q&A box summarizing key points related to this section is presented in Fig. 25.

6.2. TALENTS FROM ABROAD

Sometimes, the issue is not with the research itself, but rather with the researcher, institution, or country intending to carry it out. This concern is directly connected to Section 6.1 of this article, as the UN Security Council or the EU may prohibit any form of collaboration with specific countries, individuals, or entities. In such cases, the restriction does not concern the export of a physical product or technology, but rather the act of conducting research or sharing knowledge on sensitive areas. For example, engaging in joint work with a researcher from a sanctioned country on topics related to chemical weapons or dual-use substances may constitute a violation of international or EU sanctions, even if no materials or equipment are transferred.

These prohibitions often derive from EU regulations or international treaties designed to prevent the spread of sensitive technologies. Before hiring staff, inviting visiting researchers, or entering into a collaborative project, it is crucial to verify whether the partner is subject to such restrictions.¹²⁶ A notable case is Council Regulation 36/2012, which forbids the transfer of equipment and technology for the oil and gas sector to a sanctioned third country. In this context, not only the export of such technology, but also research and knowledge exchange on related topics may be forbidden.¹²⁶

To help assess potential risks, chemists and research managers are strongly advised to consult the EU Sanctions Map and the EU consolidated list of sanctioned individuals and entities.¹⁹¹ For researchers, the EU Sanctions Map is particularly valuable because it allows you to check whether a proposed collaborator, funder, or institution is subject to sanctions, and whether specific sectors (*e.g.*, chemical processing, petrochemicals, or dual-use research) are restricted.¹⁸⁴ Unlike general policy documents, the map is organized by country and type of sanction, making it highly navigable for non-legal experts. Using this resource during the early planning stages of a project or hiring process can help avoid serious legal risks and delays due to export control issues or institutional restrictions.

Additional guidance is provided by national security agencies such as the UK's National Protective Security Authority, which has published the *Trusted Research* framework to help academics identify and mitigate risks associated with international collaboration.¹⁹² This resource provides practical advice on safeguarding sensitive research, understanding institutional affiliations, and managing export control responsibilities. Though focused on UK academia, its principles are broadly applicable and can support researchers in assessing whether potential partners may pose security, reputational, or legal risks in high-stakes areas.

In addition to these resources, researchers can consult tools developed by independent policy organizations to assess institutional affiliations. For example, the China Defence Universities Tracker, created by the Australian Strategic Policy Institute, provides a searchable database mapping the connections between universities and government or military-linked entities in China.¹⁹³ This resource is useful when evaluating the background of prospective collaborators or visiting scholars, particularly in research areas involving sensitive technologies or dual-use applications. While primarily focused on China, it serves as a useful model for assessing the broader context in which an institution operates, particularly relevant for projects involving sensitive research areas or international consortia.

Consulting such databases can support responsible research management and help ensure compliance with applicable security and export control regulations. For a concise overview of the main issues raised in this section, see the Q&A box in Fig. 26.

6.3. DISSEMINATION OF RESULTS

The dissemination of research results through publication, conferences or patents, raises critical concerns in the context of dual-use items or drugs, as it may inadvertently disclose sensitive or potentially dangerous information. While such disclosure is rarely intentional, it often stems from the academic drive to publish novel findings. However, publications may contain knowledge that could

facilitate illicit drug production (e.g., new hidden precursors or synthetic routes for NPS), or aid in developing materials with dual-use potential (e.g., synthetic pathways toward CWAs).

This raises the complex question of whether scientific publications themselves could be considered controlled exports, given that intangible transfers (e.g., via email, online journals, or oral presentations) fall under EU export control law. According to Article 2(d) of the EU dual-use Regulation, “export” includes not only the physical transfer of items but also the transmission of software or technology by electronic or oral means to recipients outside the EU.³² Importantly, Recital 13 of the same Regulation specifically addresses academia, highlighting the need for researchers to be aware of the security implications of their work, particularly when it involves sensitive items or technologies (definition for “Recitals” in Table S1).

Therefore, academic publications may also be subject to dual-use export control. EU Recommendation 2021/1700, particularly Appendix 2 (SI) and Section 2.3.12, states that if a publication contains controlled technology, a license may be required before disseminating it.¹⁷¹ If the publisher is located outside the EU, it is assumed that the last person within the EU involved in the transmission is considered the exporter and bears legal responsibility. This view aligns with Section 2.2 of the Recommendation, which emphasizes that export control laws do not aim to censor science but to prevent sensitive knowledge from being misused for security-related threats. While academic freedom is a protected right under the EU Charter of Fundamental Rights, researchers are not exempt from compliance with export control laws.¹⁷¹ The lack of clear guidelines in these matters strongly suggest to seek advice with the publishing body.

This entire framework is part of what is referred to in EU documents as “research involving dual-use items”: a legally recognized concept that encompasses any scientific work dealing with controlled dual-use materials or technologies. This must be distinguished from Dual-Use Research of Concern (DURC), which is not a legal category, but an ethical framework focused on research that could be intentionally misapplied to cause harm. While DURC originally emerged in the life sciences, it now applies broadly, including to chemistry, engineering, and data science.¹⁹⁴ For example, DURC would cover research that could result in environmental or security threats, such as work on drug precursors, explosives, or toxin synthesis, even if those items are not explicitly listed in dual-use control lists. It asks: *What if this research, though beneficial, was weaponized?*

Scientific publishers have begun responding to this risk. Leading names like Wiley, Springer Nature, Thieme, and the Royal Society of Chemistry include DURC clauses in their editorial policies. These typically place the responsibility on the author to assess whether their submission could pose a threat and to flag any relevant content. For instance, Springer Nature advises editors to escalate DURC-related concerns to the publisher if they suspect that a manuscript could present a misuse risk.¹⁹⁵ Usually, DURC is part of a code of conduct from that publisher that the author should respect. These codes can take several names, such as “author responsibilities”, “editors code of conduct”, etc.^{195–197} In addition to DURC policies, authors increasingly face questions about how to handle sensitive experimental details in SI. Although not legally mandated, journals generally allow researchers to include voluntary security or safety notes in their SI files when dealing with classified or sensitive

substances. Such notes can alert readers to legal restrictions, licensing requirements, or specific compliance obligations associated with reproducing the described chemistry. This practice, while optional, represents an important educational tool for both specialists and non-experts and helps contextualize the legal implications of publishing methods involving controlled materials.

In the US, the National Science Advisory Board for Biosecurity has developed codes of conduct around DURC and responsible research dissemination.¹⁹⁸ Within the EU, the European Code of Conduct for Research Integrity, supported by the Commission, encourages researchers to “*recognise and weigh potential harms and risks relating to their research and its applications,*” including dual-use concerns.¹⁹⁹ While the code focuses mainly on issues like falsification and plagiarism, it extends to safety, security, and public impact.

As research involving dual-use items in fields like organic synthesis, quantum technologies, and advanced materials increasingly blurs the line between civil and military applications, the EU has strengthened its oversight of dual-use technologies in publicly funded research. This shift is particularly visible in Horizon Europe, where researchers now face growing obligations to declare any involvement of dual-use items.^{200,201}

While Horizon Europe program forms mention dual-use only once, stating that projects involving these items must comply with the relevant legal framework,^{190,191} this reflects the EU’s broader effort to reinforce compliance requirements across publicly funded research. There is a shift in the legal expertise, and an idea to go with an approach of “dual-use by design”, as suggested by recent reports from the Commissions.^{202,203} While it is not the official view of the European Union at the moment, it is worth looking at the implications of such an approach. It recognizes that many emerging technologies may serve both civilian and defense purposes. “*Under such a “dual-use-by-design” model, a project or a company could pursue—where appropriate and cost-effective in the long term—a simultaneous alignment with both civil and defence requirements, or unified requirements. This would ensure that only minimal modifications would be needed to adapt a given technology to civil or defence standards when targeting the respective market.*”²⁰² For example, one of the ideas which has been circulating within the expert community is to focus on setting up “universal standards for dual-use AI in the military context”, which, perhaps, could be integrated with the standard setting process of the civil sector.²⁰² Recent policy initiatives, including expert reports and a White Paper on European defense, call for greater transparency, risk assessment, and compliance with export controls in EU-funded research and innovation projects.

Patents represent another critical area where dual-use concerns intersect with public disclosure. Once a patent application is filed and published, the technical details, methods, and plans become publicly accessible worldwide, typically through platforms such as Espacenet. Patents represent another critical area where export control concerns intersect with public disclosure. When national security is at stake, restrictions may be imposed on patents and, in some cases, secrecy orders may be issued (see for example the German legislation regarding patent “Patentgesetz”, article 50).²⁰⁴ If secrecy is ordered, the European Patent Convention states the application is not possible, under its article 77.²⁰⁵ Within the EU framework, and in particular regarding dual-use technologies, the regulation provides an

exemption allowing the disclosure of the minimum information necessary to apply for a patent. However, this exemption does not extend to highly sensitive fields. Procedures may also vary across countries, with some requiring specific licenses in particular cases. This legal landscape means that researchers and institutions must carefully evaluate patent filings to ensure compliance with export controls and avoid unintentionally facilitating proliferation.²⁰⁵ This legal landscape means that researchers and institutions must carefully evaluate patent filings to ensure compliance with export controls and avoid unintentionally facilitating proliferation.

The EU's increasing obligations to declare dual-use involvement in research can sometimes conflict with the broader policy goals of open science, including open access publications and the use of public repositories such as GitHub. While open access promotes transparency, collaboration, and accelerated innovation by freely sharing technical details, protocols, and designs, it also raises concerns regarding the uncontrolled dissemination of potentially sensitive dual-use information. Under the dual-use Regulation, the transfer of controlled technology, including intangible transfers such as online publication, may require authorization to prevent misuse. Researchers and their institutions must therefore balance openness with compliance, often relying on internal review and risk assessment processes to ensure that dissemination does not violate export control regulations while respecting open science mandates.

A related and growing threat is data theft or espionage. Even before a publication is submitted, sensitive findings might be compromised through inadequate cybersecurity, poorly managed collaborations, or intentional data breaches. This risk is particularly high in areas such as chemical weapons, synthetic drugs, or explosives. Malicious actors may attempt to intercept research data during project planning, grant applications, or manuscript exchanges. Chemists working with such material should ensure robust data governance, internal access controls, and cybersecurity practices to prevent misuse. As emphasized in EU guidance: *“Ensuring the secure handling, storage and dissemination of chemical research is paramount to prevent the misuse or release of materials that could potentially cause harm”*.¹²

Fig. 27 provides a Q&A box addressing common concerns and practical considerations discussed in this section.

7. Case studies: legal and ethical challenges in contemporary chemical research

To bridge theory and practice, this section illustrates how various legal, regulatory, and ethical issues manifest in real research. We draw mostly on publications of our own research lab to demonstrate how specific compounds or processes may raise concerns under international treaties, national regulations, or dual-use provisions. Table 6 shows an overview of the selected case studies with relative type of risk, related regulations and some legal and ethical considerations.

In Section 7.3 we describe a practical test of purchasing controlled chemicals from various vendors and the insights we gained into their compliance and monitoring practices.

7.1. DRUGS PRECURSORS

A multikilogram-scale synthesis of *threo*-methylphenidate hydrochloride (Ritalin), a Schedule II substance under the 1971 Convention on psychotropic substances, was developed through continuous-flow strategies involving both inter- and intramolecular C–H carbene insertions (Fig. 28a).¹⁵⁹ The work required special authorization from the Federal Agency for Medicines and Health Products due to the controlled nature of the target phenidate ester compounds.

In addition to the end product's legal status, the synthesis employed piperidine, a precursor listed in Category 1 of EU Regulations 273/2004 and 111/2005, and in Table I of the 1988 UN Convention against illicit traffic in narcotic drugs and psychotropic substances. This case illustrates how even early-stage synthetic development, when involving scheduled reagents or intermediates, can trigger significant administrative and legal oversight, potentially complicating research timelines and scalability assessments.

In another example from Monbaliu and coworkers, a threestep continuous-flow process for synthesizing ketamine was developed (Fig. 28b).²⁰⁶ Ketamine itself, although not internationally scheduled under the 1961 or 1971 UN Conventions, is nationally controlled in several countries (*e.g.*, Belgium, France, Germany, the UK, and the USA) and an authorization was needed in order to be able to work on it. Moreover, the synthetic pathway involves methylamine. Methylamine is scheduled in Table I of the 1988 UN Convention since it can be used to produce methamphetamine and MDMA. In addition, it is included in Category 2 of Regulation 273/2004 and 111/2005 as a substance frequently used in the illicit manufacture of drugs but with broader industrial applications. However, the starting ketone (2-chlorophenyl)cyclopentyl ketone is not unrestricted and easily accessible. While not scheduled, this precursor is in the so-called “grey zone” and it can be treated by national authorities as a *non-scheduled precursor of interest* (*i.e.*, part of the EU Voluntary monitoring list of non-scheduled substances).²¹⁶ The disconnection between the regulation of starting materials and final products reveals inconsistencies in precursor legislation across jurisdictions. These disparities pose challenges for international collaboration and can lead to inadvertent regulatory breaches when sourcing or shipping intermediates.

Further, the development of a scalable α -aminohydroxylation process for enolizable ketones, using highly reactive α -chloronitroso derivatives, demonstrated how seemingly innocuous chemical transformations can inadvertently position a laboratory within the scope of international drug control treaties (Fig. 28c).²⁰⁷ Some products obtained can be easily used as precursors for the preparation of scheduled compounds such as cathinone, mephedrone and norephedrine. Cathinone and mephedrone are stimulant drugs that are listed in Schedule I of the 1971 UN Convention on psychotropic substances.²¹⁷ Norephedrine, on the other hand, is a common precursor for amphetamines and it is, indeed, scheduled in the 1988 Convention. This highlights the need for

rigorous internal review when publishing general-purpose synthetic methodologies, as even enabling transformations can carry risk under evolving legal interpretations.

7.2. CWAS, DUAL-USE ITEMS AND EXPLOSIVES

Several works by Legros and Monbaliu focused on the neutralization of CWAs and involved the use of simulants such as ethyl chloroethyl sulfide, a non-scheduled analogue of sulfur mustard, as well as various phosphonate compounds that mimic the structural features of VX nerve agents (Fig. 29a and b).^{208–211} Although these analogues fall outside the schedules of the CWC, their clear structural and functional resemblance to controlled agents may trigger scrutiny under dual-use frameworks, including Regulation (EU) 2021/821 and the CWC itself. This work exemplifies how purely military or academic research can still fall under DURC classifications or involving dual-use items, particularly when transparency, end-use documentation, or communication with regulatory authorities is lacking.

The importance of proactively evaluating DURC risks and/or the involvement of dual-use items, even in seemingly benign contexts, has been highlighted in other studies from our team. An example is the publication about the continuous flow production of cyclic phosphate for pharmaceutical and cosmetic application (Fig. 29c).²¹² The starting material is phosphorus trichloride (CAS 7719-12-2), a compound concerned by Regulation (EU) 2021/821 as dual-use item.

One of the cyclic intermediates in the synthetic pathway, namely, 2-chloro-1,3,2-dioxaphospholane (CAS 822-39-9) has been reported as a probable intermediate to access Novichok nerve agents.²¹⁸ While cyclic chlorophosphite are not scheduled by CWC, Novichok nerve agents are Schedule I compounds. While the intermediates for cyclic phosphates are not directly scheduled, they fall again in the “gray zone” and chemical structure-based risk assessment becomes essential. Such cases again underline the importance of anticipatory security and legal obligations review and internal risk audits when operating near the edge of legislatively defined boundaries.

Further regulatory considerations arise in the context of nanomaterials. In a 2024 work, a detailed continuous flow multistep and scalable synthesis of cadmium-based quantum dots was reported.²¹³ Also if the paper aimed at a greener production with less risk for the operator, it nonetheless could raise concerns about potential dual-use applications of semiconductor nanomaterials.

According to EU Regulation 2021/821, materials of this type may be subject to export control depending on composition, purity, and end-user declarations, despite not being explicitly scheduled.¹²⁸ The quantum dot case illustrates how even sustainability-driven research may intersect with security legislation when advanced functional materials are involved.

Another study focused on continuous flow nitration for the synthesis of nitrofurans-class pharmaceuticals, involved the *in situ* generation of acetyl nitrate from nitric acid and acetic anhydride.²¹⁴ Both reagents fall under Regulation 2019/1148 on explosives precursors and required end-use declarations and heightened vigilance for unauthorized diversion. This highlights how routine synthetic operations, particularly those involving energetic transformations or sensitive reagents, can

unexpectedly fall under stringent chemical security frameworks depending on scale, access control, and intended application.

Finally, digital tools have added a new dimension to the dual-use landscape. In a recent study by Urbina et al., generative AI models originally trained for therapeutic discovery were repurposed to design toxic compounds.²¹⁵ This finding has sparked significant concern across both scientific and policy domains, as it illustrates how computational pipelines can bypass traditional physical barriers to access and modify potentially hazardous chemical information. With little legal infrastructure currently in place to regulate AI-based synthesis planning, this emerging intersection between machine learning and chemical space exploration demands urgent attention from regulators, ethicists, and scientists alike.

These examples demonstrate that even routine or benevolent research may trigger regulatory scrutiny depending on the final product, precursors used, structural similarity to controlled agents, or technological platforms involved. Chemists should proactively assess the legal and ethical landscape of their work, ideally in collaboration with compliance officers or legal advisors. Transparent documentation and early risk assessment are essential for navigating the complex terrain of chemical regulation today.

7.3. VENDOR COMPLIANCE AND MONITORING PRACTICES FOR CONTROLLED CHEMICALS

To assess the practical enforcement of chemical control legislation, we conducted a controlled procurement exercise with a selection of chemicals listed under various regulatory frameworks (Fig. 30). We considered compounds scheduled under CWC (**CW-1-6**), explosive precursors under Regulation 2019/1148 (**EX-1-3**) and several drugs precursors (**DP-1-7**). Sixteen different compounds were ordered, with some chemicals purchased from up to five different vendors (see Fig. 30 and Table 7) to assess the consistency of compliance procedures, in particular, whether end-user declarations or other checks were required. The vendors or their subsidiaries were located in the EU (A–D), the USA (E), and China (F) (Table 7).

Of the CWC-listed compounds ordered (**CW-1-6**, only methylphosphonyl dichloride (**CW-1**, CAS 676-97-1) could not be obtained; as a dual-use item, its import into the EU requires a license under Council Regulation (EU) 2021/821. All EU suppliers we approached refused the sale; one vendor suggested alternative compounds such as dimethyl methylphosphonate (**CW-2**, CAS 756-79-6) or the corresponding phosphonic acid (methylphosphonic acid, CAS 993-13-5), for which no further documentation was requested. This illustrates a limitation of the legal framework: both methylphosphonic acid and its dimethyl ester **CW-2** have legitimate uses in synthesis and as flame retardants, yet they can be readily converted into methylphosphonyl dichloride using procedures widely described in the primary scientific and patent literature. For explosive precursors, we considered compounds **EX-1-3**, for which no license or prior authorization is generally required under EU law when acquired in small quantities for legitimate research purposes, provided concentration thresholds and end-use restrictions are respected.

For drug precursors, we considered substances listed in EU Regulation 273/2004 (**DP-1,2**), as well as compounds listed on EU voluntary monitoring list of non-scheduled substances (**DP-3–5**). The latter are not directly scheduled but are listed as unscheduled precursors (see also Fig. 8) or with structural similarities to listed substances and potentially usable to manufacture designer drugs (*e.g.*, 4-methoxyphenylacetone **DP-5**, CAS 122-849). Some of these compounds were also regulated in the US under the Drug Enforcement Administration (DEA) framework. The DEA regulates certain chemicals under the Controlled Substances Act, categorizing them into List I (key starting materials, such as **DP-1,3**) and List II (important reagents for drug manufacture, such as **DP-2,4,6,7**). Handling, distribution, and international trade of these substances require DEA registration, detailed record-keeping, and, in many cases, prior notification or reporting to the agency. For the remaining substances (**DP-6,7**), no license or prior authorization is generally required under EU. This difference in stringency of control between substances **DP3** and **DP-6,7** is somewhat surprising, given that both **DP-6** and **DP-7** can be readily converted into phenylacetic acid in much the same way as **DP-3** (see also Fig. 8).

European vendors sometimes requested an end-user declaration (entries 7–13 and 16 Table 7), including in some cases for drug precursors that are scheduled only under US DEA regulations (entries 12, 13 and 16 Table 7). Table 7 shows minimal variability in vendor-level compliance (*e.g.*, entry 16). By contrast, neither the US vendor nor the Chinese vendor requested any documentation.

For the Chinese order, direct contact with the seller ceased immediately after purchase confirmation; all subsequent communication was handled by staff in California, USA, and the shipment originated from there rather than China. We assumed this originates from the existence of a formal EU-US agreement on the monitoring of precursor chemicals frequently used in illicit drug manufacture (Council Decision 97/389/EC of 21 May 1997).²¹⁹ Under this agreement, the EU and US exchange pre-shipment notifications for listed chemicals, allowing each side to verify the legitimacy of transactions before export. The arrangement also includes a joint follow-up mechanism to update the list of monitored substances and coordinate enforcement actions. The absence of any vendor-level checks or documentation requests from US-based shipments indicates a gap in how this agreement is applied at the commercial transaction level.

In some EU deliveries, the accompanying paperwork included a warning stating that “export from the EU for this item is permitted under dual-use regulations (*e.g.*, entry 6 Table 7); re-export outside the EU requires a Community export license (Council Regulation (EU) No. 2021/821).” The US vendor included only a dangerous goods declaration (hazmat) warning that non-compliance may be punishable under applicable law, along with a “for laboratory use only” disclaimer. All shipments originating from outside the EU were received without customs intervention or licensing. This outcome is not necessarily indicative of regulatory failure, as most substances in the experiment do not legally require a license under the tested conditions. However, it does illustrate variability in vendor-level compliance and the limited role of customs in routine low-volume transactions.

Chemical vendors and distributors play a critical role in promoting legal compliance and security. Greater transparency about the regulatory status of substances, especially those requiring specific authorizations, can significantly support safer procurement practices and informed decision-making

by researchers. For example, only the US chemical supplier clearly indicates on product pages whether a substance is scheduled under specific regulations (in this case, DEA). This makes it immediately clear to customers that special authorization is needed. This model of proactive disclosure, if more widely adopted, could reduce accidental noncompliance and improve traceability across supply chains. Vendors are thus encouraged to implement clear labeling, provide access to relevant safety and legal information, and collaborate with research institutions in managing regulated substances responsibly. In Fig. 31, we imagined how a chemical vendor's website page could be integrated with legal information.

To gain insight into how chemicals are monitored, we first examined publicly available regulatory information from the European Chemicals Agency (ECHA). On the ECHA "Search for Chemicals" portal, each compound has a "substance infocard" displaying its characteristics, common uses, and the regulatory framework governing it.²²⁰ For all the compounds ordered in our case study, however, the "regulatory framework" section only referenced REACH, CLP, and certain other regulations (*e.g.*, Active Implantable Medical Devices Directive, Inland Transport of Dangerous Goods Directive, Cosmetic Products Regulation). Notably, there was no mention of key instruments such as Regulation on drug precursors, Regulation on explosive precursors, CWC, or the dual-use Regulation. This shows that public databases, while useful for hazard and safety information, do not provide a complete picture of legal controls.

To obtain additional perspectives, we contacted several chemical suppliers with a list of targeted questions on the internal protocols to navigate monitored chemicals. Only one supplier accepted to answer. They confirmed that ECHA is indeed one of the official sources they use to monitor compounds, alongside helpdesks and third-party services. Their internal system tracks both regulated and many non-regulated substances with potential for illicit use, and is continuously updated to reflect emerging compounds. Each order is evaluated individually rather than based on quotas, though larger orders of regulated items naturally receive closer scrutiny. Suspicious orders often come from new or previously unknown customers and are flagged for review. If an order is deemed potentially illicit, it is blocked, and authorities are notified when sufficient evidence exists. While the vendor cannot share its full monitoring list, it draws on a wide range of regulations and practical experience. By combining various sources with their own internal monitoring, the vendor can compensate for gaps in publicly available regulatory information, ensuring a more comprehensive assessment of potential legal and safety risks. The company's Technical Department, which includes scientists, oversees this process. They use a combination of a general statement for new customers, acknowledging the vendor's guidelines, and specific End-User declarations for particular compounds. The latter are the principal way they monitor orders. Certain compounds are also subject to REACH-related restrictions, even in small quantities ordered by academic labs, and are therefore strictly monitored to ensure authorized use. Overall, their approach reflects proactive oversight, careful risk assessment, and strict compliance with international and European regulations.

8. Conclusions and perspectives

Law and chemistry may seem like distant disciplines, but in the modern research landscape, they are increasingly linked. This *vade mecum* is designed to help chemists, especially those working with drug-related substances, explosives, or dual-use items, navigate the complex legal frameworks and emerging ethical challenges that shape chemical research and dissemination. In the 20th century, legal intervention became necessary to limit the devastating impacts of synthetic drugs and chemical weapons. Today, new technological breakthroughs and geopolitical tensions demand a renewed legal and ethical response.

Chemists must now contend not only with complex licenses and export rules, but also with new threats involving emerging technologies. Technologies like AI, robotics, 3D printing, and micro- and mesofluidics are becoming deeply integrated into chemical protocols, offering powerful tools for innovation but also introducing serious security risks. For example, drones could potentially deliver chemical weapons, while 3D-printed microreactors might facilitate the mobile and less detectable production of controlled chemicals. AI-based retrosynthetic planning algorithms such as SYNTHIA™, now integrated into databases like SciFinder, can provide endless inspiration for circumventing listed precursors or discovering new ones. Although safeguards exist to prevent generating protocols for established CWAs, these can be circumvented or manipulated, as seen with AI tools like ChatGPT, which may inadvertently provide protocols for unlisted analogs. Alarming, such safeguards seem less effective when queried about psychotropic drugs. This challenge is not new; as early as 2012, in an article by Grzybowski and coworkers, it was demonstrated how algorithms could identify routes to nerve agents and highlighted the limitations of existing legal barriers.²²¹ Similar concerns arise in recent work on fentanyl.²²² The dark web further sustains these risks by enabling illicit chemical trade, including to terrorist groups.²²³ Legislative frameworks are struggling to keep pace. Regulation (EU) 2024/1689 addresses artificial intelligence, focusing primarily on harmonizing the internal market and protecting fundamental rights, but its economic emphasis means it is unlikely to serve as a robust barrier against the misuse of AI in chemical synthesis.

The legal regulation of chemistry, drugs, explosives, and dual-use items is complex but essential for public health and security. Chemists must understand that licenses and/or special authorizations apply not only to final products but also to precursors and intermediates. Misconduct or failure to comply can lead to license revocation and severe administrative or criminal sanctions. It is incumbent on chemists to recognize that drugs, explosives, and chemical weapons form part of global security frameworks, and compliance requires ongoing cooperation between chemists, legal experts, and regulators. Platforms fostering best practices and dialogue on dual-use and controlled substances, such as the European Export Control Association for Research Organisations (EECARO), a network uniting EU research organizations and compliance officers, are critical.²²⁴ Although there is no similar platform dedicated exclusively to controlled chemicals, the approaches used by EECARO are broadly applicable, including within industrial research environments. Ethical committees within academic institutions should address dual-use proliferation seriously, and internal compliance programs (IPCs)

are recommended to manage inventories and legal obligations, particularly as responsibilities shift over time.¹⁷¹

For example, substances ordered a decade ago may now be controlled or require special handling, raising questions about record-keeping and destruction protocols. Despite these efforts, many questions remain open, and emerging technologies introduce new challenges that demand ongoing collaboration between legal and chemical communities to safeguard both security and the healthy advancement of chemistry. The diagram reported in Fig. 32 helps chemists assess whether a substance is subject to legal restrictions under the regulatory frameworks discussed in this review. It guides users through key questions and highlight important tools to answer them.

To conclude, the evolving interface between law, chemistry, and emerging technologies demands heightened awareness and interdisciplinary cooperation. Chemists must remain vigilant and informed to uphold scientific integrity, comply with legal obligations, and navigate the delicate balance between regulation and academic freedom, ensuring their contributions strengthen both global security and the pursuit of innovation.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. Sophie Bianchi: conceptualization, writing – original draft; Carlotta Campalani: conceptualization, writing – review & editing; Veronica Vella: writing – review & editing; Quentin Michel: conceptualization, funding acquisition, writing – review & editing; Jean-Christophe M. Monbaliu: conceptualization, project administration, supervision, funding acquisition, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Supplementary information (SI) containing a legal glossary and definitions, legal authorizations, licence forms and practical examples of custom/end-user declarations. See DOI: <https://doi.org/10.1039/d5cs01021g>.

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Tables

Table 1 Abbreviations used in this review with relative definition

Abbreviation	Definition
CND	Commission on Narcotic Drugs
CWA	Chemical Warfare Agents
CWC	Chemical Weapons Convention
DEA	Drug Enforcement Administration
DURC	Dual-Use Research of Concern
EC	European Commission
ECSC	European Coal and Steel Community
EEA	European Economic Area
EEC	European Economic Community
EECARO	European Export Control Association for Research Organisations
EFTA	European Free Trade Association
EU	European Union
EUDA	European Union Drugs Agency
HMEs	Home-made Explosives
INCB	International Narcotic Control Board
NPS	New Psychoactive Substances
OPCW	Organisation for the Prohibition of Chemical Weapons
TEU	Treaty on the European Union
TFEU	Treaty on the Functioning of the European Union
UN	United Nations
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization
WMD	Weapons of Mass Destruction
WWI	World War I
WWII	World War II

Table 2 Roles of key international bodies in drug control

Body	Established in	Primary role	Main functions related to drug control
CND	1946	Governing body of UNODC & policymaking body	<ul style="list-style-type: none"> - Principal decision-making body on drug-related matters; - Oversees implementation of international drug control treaties; - Adopts scheduling decisions for substances under UN conventions.
UNODC	1997	Implementation and coordination	<ul style="list-style-type: none"> - Technical assistance and capacity building; - Collects and disseminates global data on drug trends; - Supports Member States in treaty implementation.
WHO	1948	Health-based scientific assessment	<ul style="list-style-type: none"> - Evaluates the medical use, abuse potential, and public health risks of substances; - Issues scientific recommendations for scheduling (under UN Conventions); - Advises on essential medicines.
INCB	1968	Independent monitoring body	<ul style="list-style-type: none"> - Monitors compliance with drug control treaties; - Oversees licit production and trade of narcotics and psychotropics; - Issues annual reports and alerts on treaty violations.

Table 3 Key international drug control conventions

Year	Name	Main role/significance
1909	Shanghai Opium Commission	First international meeting to address opium trade; laid the groundwork for future treaties.
1912	International Opium Convention	First international treaty on narcotic drugs; targeted trade in opium, morphine, and cocaine.
1931	Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs	Introduced production quotas and reporting obligations.
1961	Single Convention on Narcotic Drugs	Merged previous treaties; created a unified control system and scheduling.
1971	Convention on Psychotropic Substances	Brought synthetic drugs (e.g., LSD, amphetamines) under control.
1988	United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances	Criminalized drug trafficking; introduced precursor control and extradition measures.

Table 4. Overview of key EU regulations on drug control

Entry	Legislation focus	Legislation
1	Scheduled precursors	Regulations 273/2004 and 111/2005 (intra EU or with third countries – amended by Delegated Regulation 2025/1475)
2	Non-scheduled precursors	Not controlled
3	Designer precursors	Not controlled
4	Illicit drugs	Council Framework Decision 2004/757/JHA
5	NPS	Directive 2017/2103 (now included as “illicit drugs”)
6	Designer Drugs	Not controlled

Table 5 Legislations described in this section with short description and hyperlink to the body of the law

Legislation	Content of the law	Section	Hyperlink
Single Convention on Narcotic Drugs of 1961	Establishes a global system to control production and distribution of narcotic drugs, limiting their use to medical and scientific.	5.1	https://www.unodc.org/pdf/convention_1961_en.pdf
Convention on Psychotropic Substances of 1971	Regulates the manufacture and distribution of synthetic psychotropic substances to prevent abuse while ensuring availability for medical use.	5.1	https://www.unodc.org/pdf/convention_1971_en.pdf
UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988	Targets drug trafficking by requiring states to criminalize illicit drug production, distribution, and precursor diversion.	5.2	https://www.unodc.org/pdf/convention_1988_en.pdf
Regulation (EU) 273/2004 on drug precursors	Rules for the control of drug precursors to prevent their misuse in illicit drug manufacture.	5.3	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R0273
Regulation (EU) 111/2005 on precursors involving third countries	Regulates the international trade of drug precursors between the EU and non-EU countries to combat illegal drug production.	5.4	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005R0111
Directive 2001/83/EC and regulation (EU) 2019/6 on medicinal products for human and veterinary use	Establish a harmonized framework for the authorization, manufacture, and distribution of medicinal products for human and veterinary use.	5.5	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083
Chemical Weapons Convention	Prohibits the development, production, stockpiling, and use of chemical weapons and promotes their destruction.	5.6	https://www.opcw.org/chemical-weapons-convention
Regulation (EU) 2021/821 on dual-use items	Controls the export, brokering, and transit of dual-use items to prevent their misuse in weapons or surveillance systems.	5.7	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32021R0821
Regulation (EU) 2019/1148 on explosive precursors	Restricts access to explosive precursors to prevent their misuse in the illicit manufacture of homemade explosives.	5.8	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R1148

Table 6 Case studies with relative type of risk, applicable regulations and comments

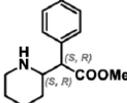
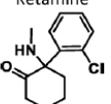
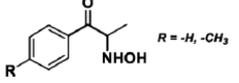
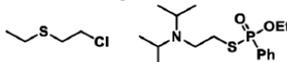
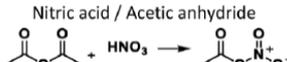
Entry	Article/compound	Type of risk	Applicable regulation(s)	Authorization/comment	Ref.
1	Methylphenidate (Ritalin) 	Scheduled substance (Schedule II, 1971 Convention); regulated precursors (e.g. piperidine)	- 1971 Convention - 1988 UN Convention (Table I) - EU Reg. 273/2004, 111/2005	Authorization from Federal Agency for Medicines and Health Products	159
2	Ketamine 	Controlled substance (national level); some regulated intermediates (e.g. MeNH ₂)	- National legislation (e.g. France, UK, US) - EU precursor control (273/2004)	National authorization required; intermediates not always listed	206
3	α -Amino hydroxylation products 	Precursor to scheduled cathinone, mephedrone and norephedrine	- 1971 Convention (Schedule I-III) - National controls depending on derivative - 1988 Convention	No authorization required for research, but highlights precursor transformation risk	207
4	CW Agent Simulants 	Potential DURC and CWC-related analogues	- Chemical Weapons Convention (CWC) - EU Reg. 2021/821 (dual-use)	Simulants not scheduled; risk due to structural similarity	208-211
5	Cyclic phosphate monomers 	Potential Novichok precursor-like intermediates (DURC & dual-use items-related concerns)	- Not currently listed - CWC (if classified as toxic precursor)	No authorization required, but high DURC sensitivity	212
6	Quantum dots (CdTe, CdSe, CdS)	Potential dual-use application (electronics, imaging)	- EU Reg. 2021/821 (dual-use) - Export control possible depending on composition	Not listed, but monitoring recommended	213
7	Nitric acid / Acetic anhydride 	Explosive precursor chemicals	- EU Reg. 2019/1148	End-use declarations filed for both reagents	214
8	AI-designed toxins (Urbina <i>et al.</i>)	AI misuse for toxic compound generation	- No specific regulation yet	Illustrative DURC case; not yet regulated	215

Table 7 Overview of ordered regulated compounds, vendors by country, and required documentation or warnings

Entry	Scheduled in	Compound	Vendors					
			Europe				USA	China
			A	B	C	D	E	F
1	CWC schedule II	CW-1	—	—	Dual-use	Dual-use	—	—
2		CW-2	No forms	—	—	—	No forms	—
3		CW-3	No forms	No forms	No forms	—	Hazmat	No forms
4		CW-4	No forms	—	—	—	—	—
5	CWC schedule III	CW-5	No forms	—	—	—	—	No forms
6		CW-6	Warning	—	—	—	—	—
7	Regulation 2019/1148 on explosive prec.	EX-1	—	End user	—	—	—	—
8		EX-2	End user	—	—	—	—	—
9		EX-3	—	End user	End user	End user	Hazmat	No forms
10	Drugs precursors-related legislations (see also Fig. 30)	DP-1	—	—	—	End user	—	—
11		DP-2	—	End user	—	—	—	—
12		DP-3	End user	—	—	—	—	—
13		DP-4	—	—	—	End user	—	—
14		DP-5	—	—	No forms	—	No forms	No forms
15		DP-6	—	No forms	—	—	—	No forms
16		DP7	No forms	No forms	End user	—	—	—

(—): not ordered from this vendor; (dual-use): dual-use items with restrictions for import to EU; (No forms): no further documentation was requested upon ordering; (Hazmat): additional charges for shipping hazardous materials; (Warning): the delivery note included a warning statement; (End user): a signed, compound-specific end user declaration was requested to unlock the order.

Figures

Fig. 1 Breakdown of regulated chemicals by lab function. The percentages are estimated using a representative subset of substances from the Annexes of the legislations discussed in this review.

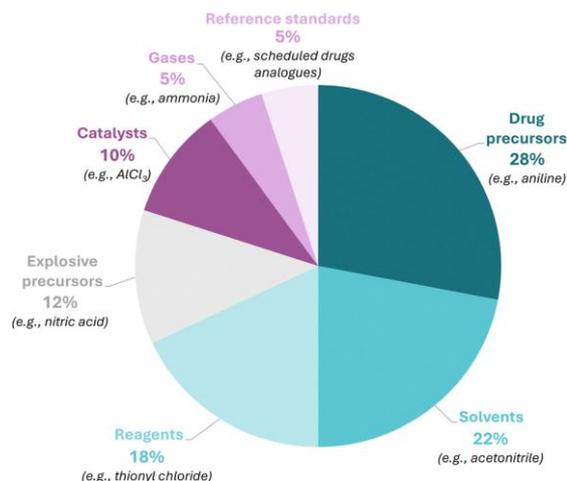


Fig. 2 Legal aspects that a chemist should consider during the whole research pipeline and that are addressed in this review.

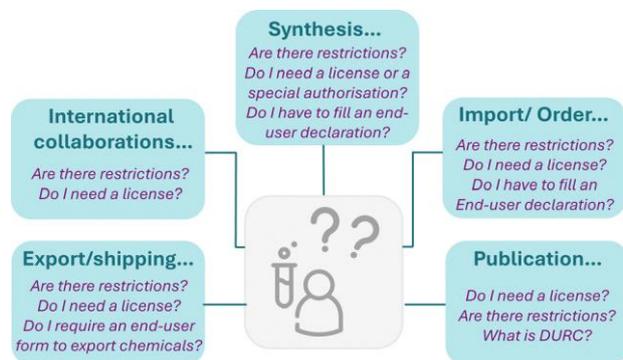


Fig. 3 European Union law system. TEU = Treaty of the European Union; TFEU = Treaty on the Functioning of the European Union.

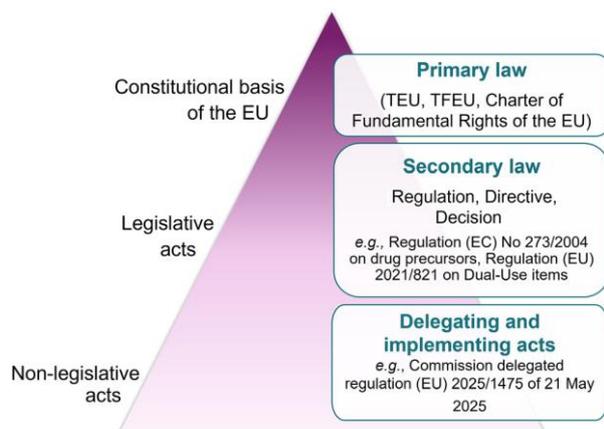


Fig. 4 The “consolidation of the law” process. The microscope icons show where chemists must look in order to have an exhaustive list of regulated substances depending on the stage of the process.

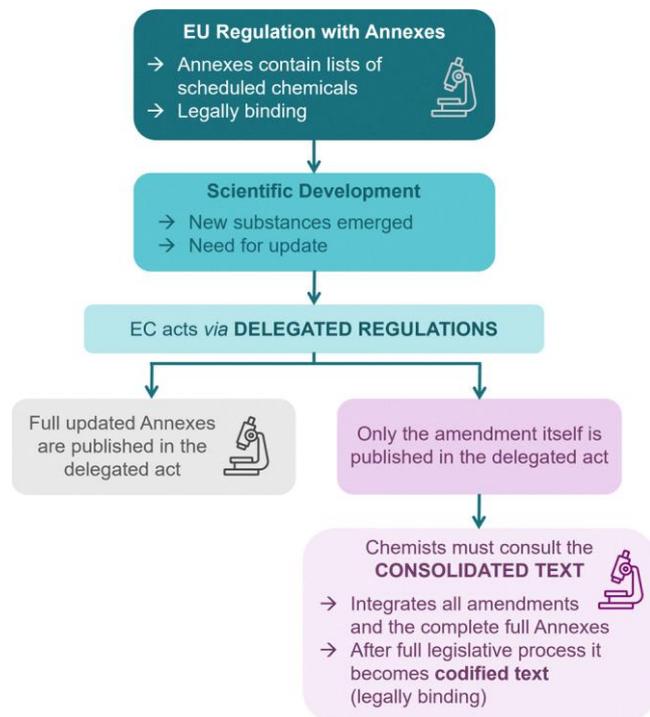


Fig. 5 The Schengen Area and the EU in 2025 (created with mapchart.net).

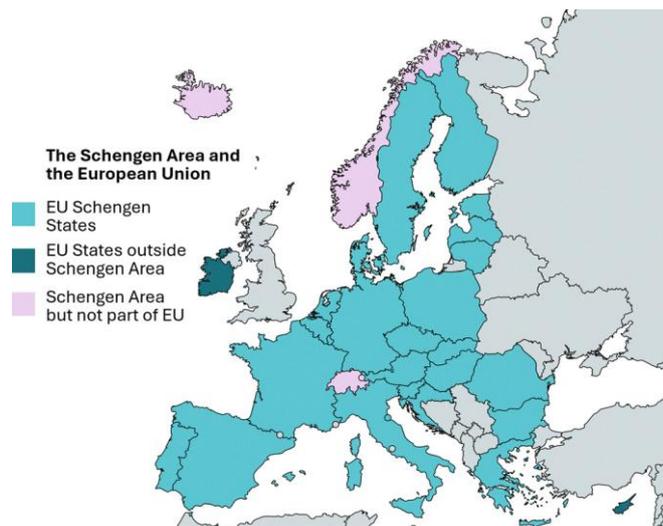


Fig. 6 Drugs classification into natural, semi-synthetic and synthetic with examples for each category.

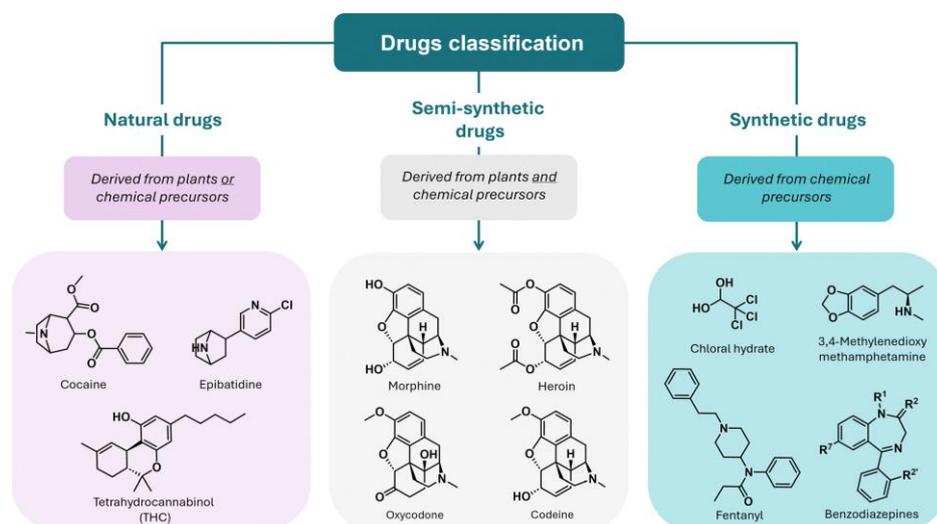


Fig. 7 Overview of UN legislations about drugs with examples for each category. For designer precursors and designer drugs the year in bracket represents the year where the drug/precursor was added in the Annex of the respective Convention. For scheduled precursors in brackets there is the corresponding illicit drug.

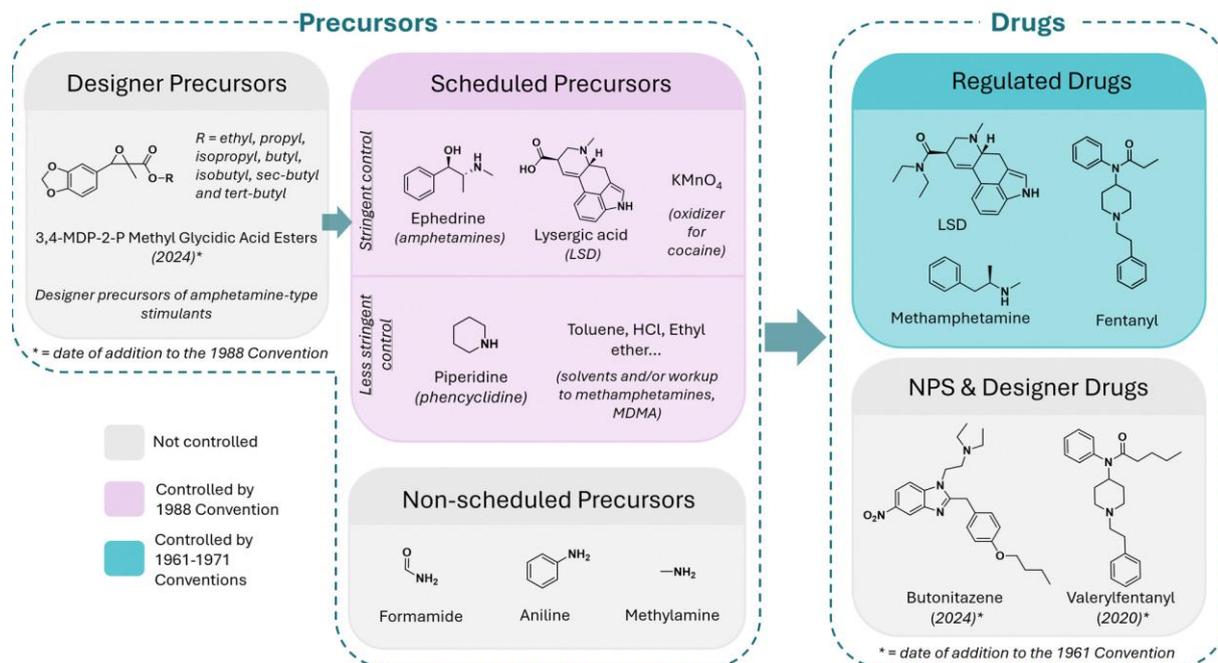


Fig. 8 The pathway to obtain amphetamines involving benzyl chloride as a pre-precursor or methyl/ethyl phenylacetate as designer precursor.

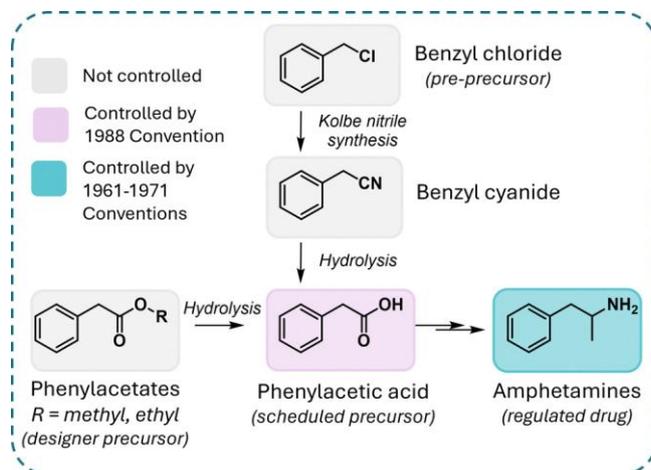


Fig. 9 Examples of designer drugs.

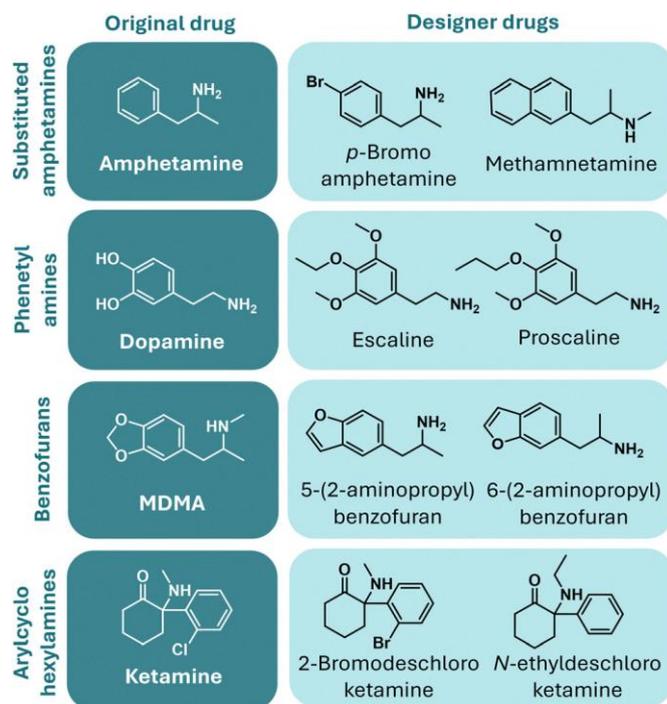


Fig. 10 Examples of compounds controlled by Directive 2001/83/EC (human use) and by Regulation 2019/6 (veterinary use).

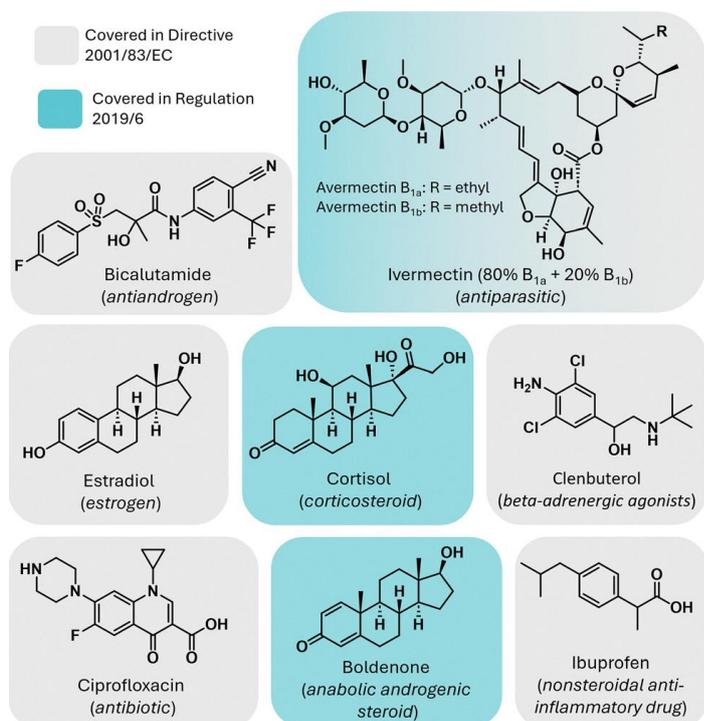


Fig. 11 Main chemical warfare agents used during WWI.

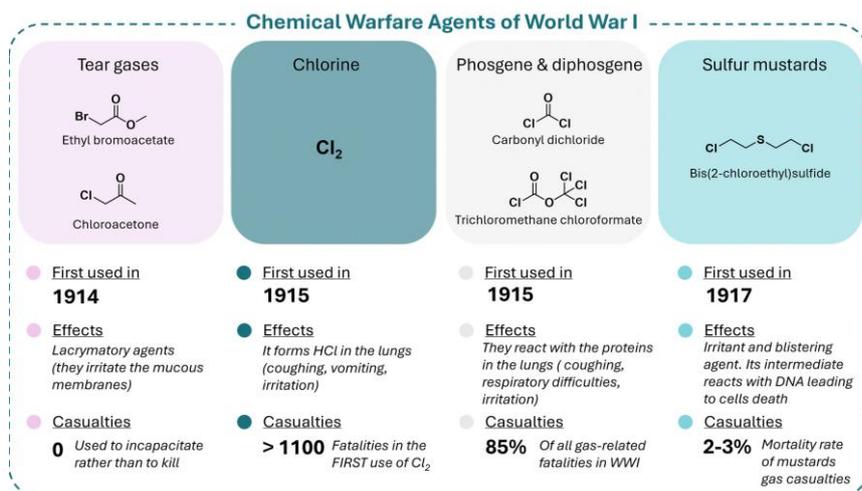


Fig. 12 Definition of dual-use items and timeline of key dual-use technologies and their shifting applications over the 20th and 21st centuries.

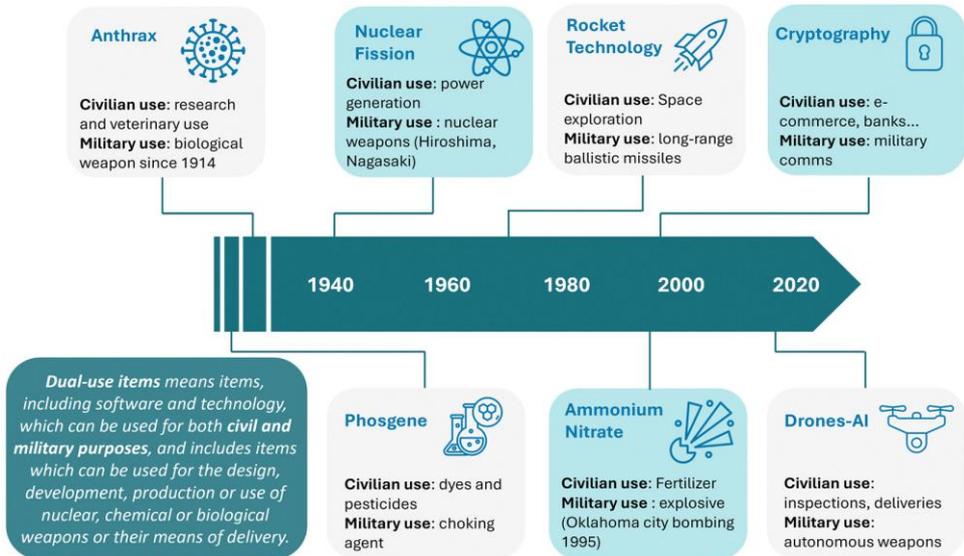


Fig. 13 Forum shopping mechanism (MS = Member State).

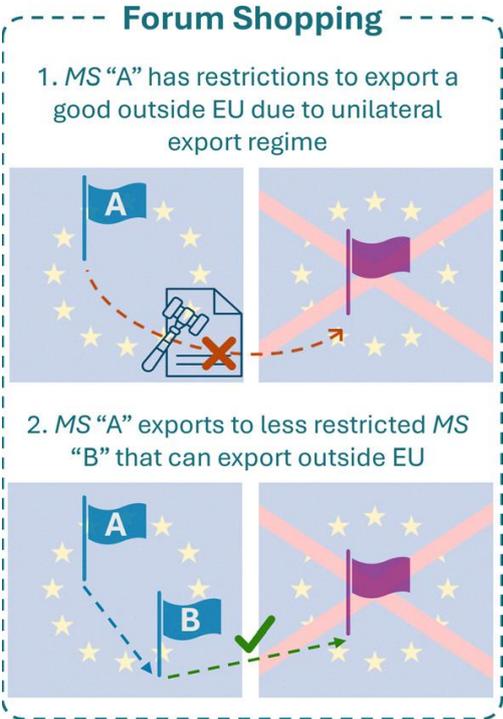


Fig. 14 Overview of the different multilateral export control regimes relevant to organic chemistry. AG = Australia group, WA = Wassenaar Arrangement. (created with mapchart.net).

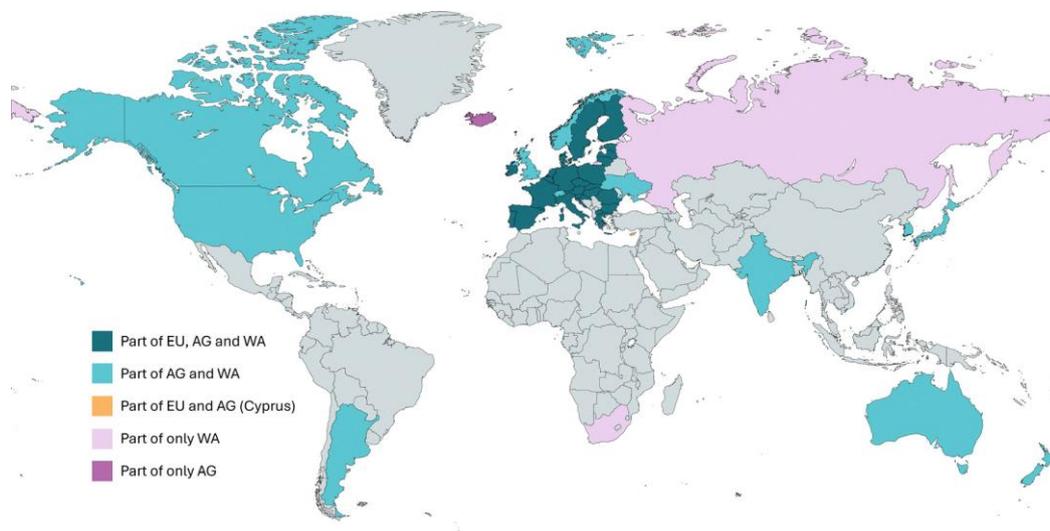


Fig. 15 Overview of the Schedules in 1961 Convention on Narcotic Drugs and respective examples (a. and b. respectively). Overview of the Schedules in 1971 Convention on Psychotropic Substances and respective examples (c. and d. respectively); e. Questions and answers.

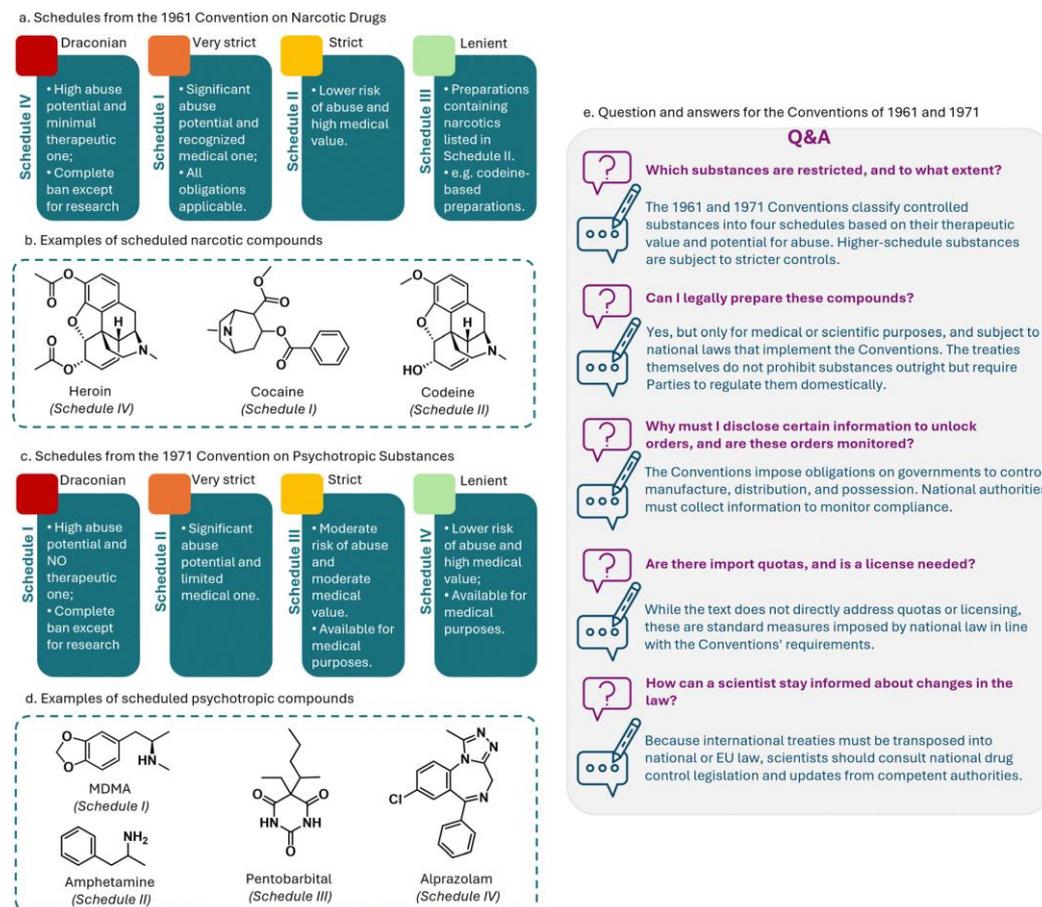


Fig. 16 Questions and answers for Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

Q&A

Which substances are restricted, and to what extent?
 Restricted substances are listed in Table I and Table II of its Annex, focusing on precursors used in the illicit manufacture of narcotic and psychotropic substances.

Can I legally prepare these compounds?
 Yes, only with proper authorization. Article 3 requires Parties to criminalize the unlicensed preparation, production, or handling of listed substances.

Why must I disclose certain information to unlock orders, and are these orders monitored?
 The Convention mandates criminalization of unauthorized activities and misuse of listed substances, transactions involving these chemicals are subject to strict monitoring, and disclosure obligations may apply to prevent diversion.

Are there import quotas, and is a license needed?
 While specific quotas are not detailed in this text, licensing and authorizations are required under national law in line with the Convention's criminalization framework.

How can a scientist stay informed about changes in the law?
 Because international treaties must be transposed into national or EU law, scientists should consult annexes from EU Regulation 273/2004 and EU Regulation 111/2005.

Fig. 17 (a) Overview of Annex I of Regulation 273/2004 and its categories; (b) examples of compounds present in each category; (c) questions and answers.

a. Overview of Annex I of Regulation 273/2004

Very strict	Strict	Lenient
Category 1 • License needed for possession; • Declaration if suspect transaction.	Category 2 • Registration needed for possession; • Declaration if suspect transaction; • Exemptions are possible under Art 6.	Category 3 • Declaration if suspect transaction.

b. Examples of scheduled precursors

<chem>CC1=CNC2=C1C(=O)N(C)C2</chem> Lysergic acid (Category 1)	<chem>C1CCNCC1</chem> Piperidine (Category 2)	<chem>Cc1ccccc1</chem> Toluene (Category 3)
<chem>CC(=O)Cc1ccccc1</chem> Phenylacetone (Category 1)	<chem>CC(=O)OC(=O)C</chem> Acetic anhydride (Category 2)	<chem>CCOC</chem> Diethyl ether (Category 3)
	<chem>CC(=O)C</chem> Acetone (Category 3)	

c. Question and answers for Regulation 273/2004

Q&A

Which substances are restricted, and to what extent?
 Substances are classified in three categories (Annex I), with Category 1 subject to the strictest controls, including licensing for possession.

Can I legally prepare these compounds?
 Yes, but only if you hold the appropriate license or registration depending on the category of the substance.

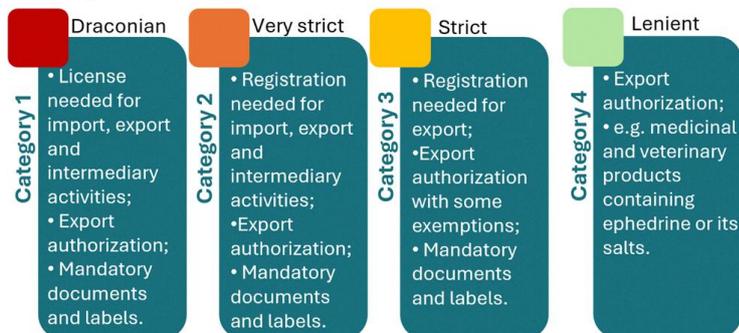
Why must I disclose certain information to unlock orders, and are these orders monitored?
 Operators must provide customer declarations for certain transactions and notify authorities of any suspicious activity (Articles 4 and 8).

What does obtaining a license involve, and is it time-limited?
 Licenses require official application and compliance with strict conditions; they can be revoked or expire if not renewed.

How can a scientist stay informed about changes in the law?
 Updates are made directly in the Regulation, which is publicly accessible and amended regularly by the European Commission.

Fig. 18 (a) Overview of Annex I of Regulation 111/2005. (b) Questions and answers.

a. Categories from Regulation 111/2005



b. Question and answers for regulation 111/2005

Q&A

Which substances are restricted, and to what extent?
 Substances listed in Annex I, categorized by level of risk and subject to export conditions based on that classification.

Can I legally prepare these compounds?
 Yes, but if intended for export, licenses or registrations are required depending on the category, and shipment is only legal with proper authorization.

Why must I disclose certain information to unlock orders, and are these orders monitored?
 Exporting controlled substances requires pre-export notifications and, in some cases, import certificates to prevent diversion.

Are there import quotas, and is a license needed?
 There are no fixed import quotas, but quantity thresholds apply (Regulation 2015/1011, Category 3 exports require registration only if thresholds are exceeded). No quotas, but licenses (Category 1) and registrations (Category 2) are required for export.

What does obtaining a license involve, and is it time-limited?
 Yes, licenses and authorizations are specific to operators and time-limited; revocable if requirements are not met.

Fig. 19 Questions and answers for Directive 2001/83/EC and Regulation 2019/6.

Q&A

Which substances are restricted, and to what extent?
 Many pharmacologically active substances are regulated based on their use, risk of misuse, or public health impact. EU law sets strict conditions for their manufacture, handling, and distribution.

Can I legally prepare these compounds?
 Yes, but only under specific conditions: chemists must comply with manufacturing authorization rules unless the activity is strictly limited to research or analytical purposes.

What does obtaining a license involve, and is it time-limited?
 Licensing involves registration with national competent authorities and compliance with Good Manufacturing Practice; validity and renewal depend on the specific national system.

Is there assistance available if a chemist is unsure about legal requirements?
 Yes, national agencies like AIFA (Italy) or BfArM (Germany) provide regulatory guidance and can advise on compliance pathways.

Fig. 20 (a) Overview of the schedules in the Chemical Weapons Convention; (b) examples of compounds present in each schedule; (c) questions and answers.

a. Overview of the Schedules in CWC

Schedule	Regulation
Schedule 1A-B	Draconian
Schedule 2A-B	Strict
Schedule 3A-B	Lenient

- Schedule 1A-B (Draconian):** High risk, little commercial use; "Protective testing" allowed for researcher under strict conditions.
- Schedule 2A-B (Strict):** High risk, legitimate small-scale commercial use; Can be used to produce substances in Schedule 1.
- Schedule 3A-B (Lenient):** Moderate risk, legitimate large commercial use; Can be used to create substances in Schedule 1-2B.

All chemical weapons are banned

b. Examples of scheduled compounds

A - Toxic chemicals	B - Precursors
<chem>CC(=O)N(C)C(F)(F)F</chem> Sarin (Schedule 1)	<chem>OP(=O)(R)R</chem> Methylphosphonic acid and derivatives (Schedule 2) <i>R = -OMe, -Cl</i>
<chem>ClCCSCC</chem> Bis(2-chloroethyl)sulfide (Schedule 1)	<chem>ClP(=O)(Cl)Cl</chem> Arsenic trichloride (Schedule 2)
<chem>CC(C)N(C)COP(=O)(OC)OC</chem> VX (Schedule 1)	<chem>CCOP(=O)(OC)OC</chem> Triethyl phosphite (Schedule 3)
<chem>CC(C)N(C)COP(=O)(OC)OC</chem> Amiton (Schedule 2)	<chem>ClC(=S)Cl</chem> Thionyl chloride (Schedule 3)
<chem>ClC(=O)Cl</chem> Phosgene (Schedule 3)	

c. Questions and answers for CWC

Q&A

Which substances are restricted, and to what extent?
 Schedule 1 substances are highly restricted; Schedules 2 and 3 have legitimate uses but are monitored and subject to reporting.

Can I legally prepare these compounds?
 Yes, if thresholds, intended uses, and license requirements are met. Schedule 1 requires advance authorization; Schedules 2 and 3 may require declarations.

Why must I disclose certain information to unlock orders, and are these orders monitored?
 Disclosures ensure compliance with national and OPCW reporting obligations. Orders involving scheduled substances may be subject to notification, licensing, and inspection.

Are there import quotas, and is a license needed?
 This falls outside the scope of the CWC and is governed at EU level by the EU Dual-Use Regulation 2021/821 (see section 5.7).

What does obtaining a license involve, and is it time-limited?
 Licenses are operator-specific and typically time-bound. They may involve documentation of end use, site inspections, and periodic renewal.

Is there assistance available if a chemist is unsure about legal requirements?
 Yes. National Authorities provide guidance, and institutional compliance offices are a key resource for support.

How can a scientist stay informed about changes in the law?
 Monitor updates from your National Authority or the OPCW and consult internal compliance teams regularly.

Fig. 21 (a) Overview of dual-use Regulation Annexes with relative examples; (b) explication of the classification codes of Annex I with relative examples; (c) questions and answers. (D-U = dual-use, WA = Wassenaar Arrangement, AG = Australia Group, CWC = Chemical Weapons Convention).

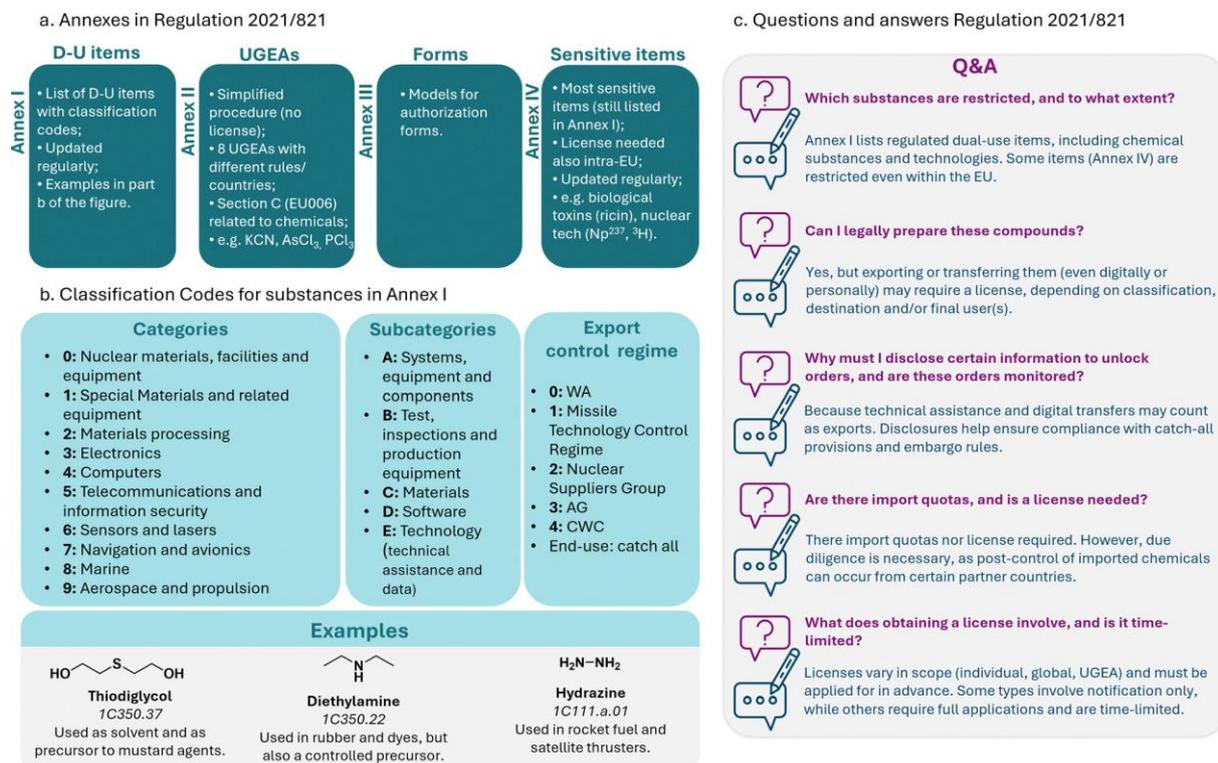
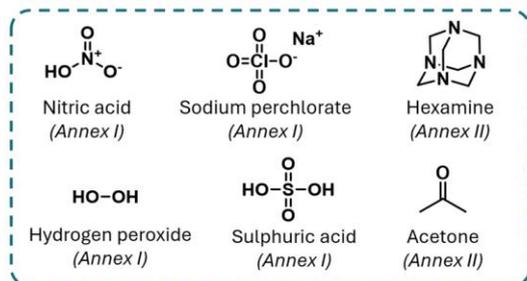


Fig. 22 (a) Overview of the Annexes in Regulation 2019/1148; (b) examples of compounds present in each Annex; (c) questions and answers.

a. Overview of the Annexes in Regulation 2019/1148



b. Examples of scheduled precursors



c. Questions and answers for Regulation 2019/1148

Q&A



Which substances are restricted, and to what extent?



Annex I and II define levels of restriction and reporting requirements based on potential for misuse.



Can I legally prepare these compounds?



Yes, professional users can legally handle these substances with an end-use declaration; public access is more restricted.



Why must I disclose certain information to unlock orders, and are these orders monitored?



Any person or entity involved in the supply chain has to assess and report suspicious transactions, which are monitored by authorities.



Are there import quotas, and is a license needed?



No quotas apply, but a license is needed for general public access to Annex I substances; professional users are exempt with conditions.



What does obtaining a license involve, and is it time-limited?



Licenses are issued by Member States and may vary in duration and scope; national rules determine specifics.

Fig. 23 Summary of license requirements for dual-use items, from Recommendation 2021/1700, Appendix 7 (SI).171

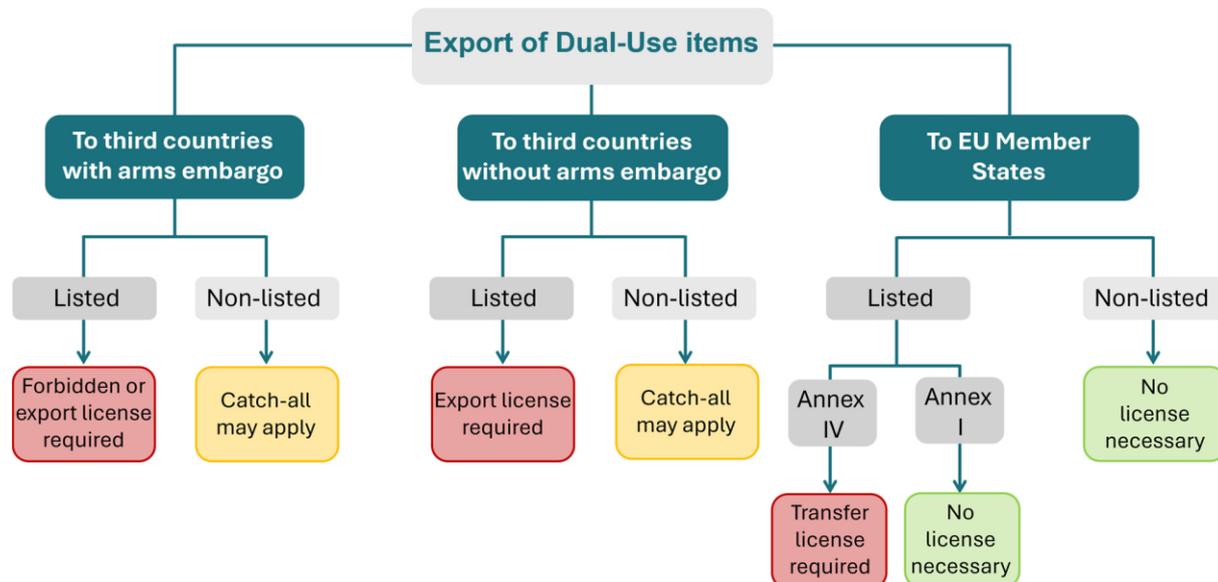


Fig. 24 Questions and answers about supports available for chemists.

Q&A

Which substances are restricted, and to what extent?
 The **Export Control Handbook for Chemicals** lists controlled substances by CAS number under key international regulations, including the Dual-Use Regulation and the CWC.

Is there assistance available if a chemist is unsure about legal requirements?
 Yes, tools such as the EU Recommendations, national guidelines (e.g. Belgium's) and University of Liège's Dual-Use Assistance App provide tailored support.

How can a scientist stay informed about changes in the law?
 By consulting regularly updated resources like **Export Control Handbook for Chemicals** (dated 2023), national guidance documents, and institutional compliance tools. Referring to the EC's official website or the official websites of individual national authorities is always recommended.

Fig. 25 Questions and answers about sanctions and export.

Q&A

 **Can I ship reaction products abroad for collaboration, and are there any restrictions?**

 Yes, but depending on the product and destination, export may be subject to sanctions or embargoes, especially when Dual-Use goods or restricted countries are involved, so a license may be required.

 **Is a product exportable without a license, and what would a license imply?**

 Some products can be exported freely, but if they fall under control lists or are headed to sanctioned regions, a license is mandatory and may involve case-by-case risk assessments, compliance checks, and end-use declarations.

 **What role do customs play?**

 Customs authorities are responsible for enforcing sanctions and export regulations at borders; they may inspect or block shipments that violate legal or licensing requirements.

 **How does the legal framework impact global collaborations?**

 Sanctions, export controls, and embargoes can limit who chemists are allowed to collaborate with, where materials can be sent, and what technologies or data can be shared, often requiring due diligence and formal authorization.

Fig. 26 Questions and answers about talents from abroad.

Q&A

 **How does the legal framework impact global collaborations?**

 Collaborations may be restricted or prohibited if the partner is linked to a sanctioned country, entity, or individual, especially in sensitive research areas like dual-use chemistry or chemical weapons. The EU Sanctions Map provides an accessible tool to verify these restrictions.

 **Can disseminating results (e.g., through publications, conferences, or patents) be unlawful?**

 Yes, if the research involves restricted technologies, even the act of sharing knowledge can constitute a violation.

 **Is a product exportable without a license, and what would a license imply?**

 In some cases, licenses are required not for the product itself but for the act of engaging in research with a sanctioned partner; failure to comply may result in legal penalties. The EU Sanctions Map and lists can help in assessing the need for a license requirement, while an authority can clarify when an activity is prohibited outright.

Fig. 27 Questions and answers about the dissemination of results.

Q&A

 **Can disseminating results (e.g., through publications, conferences, or patents) be unlawful?**

 Yes. Publications that include controlled dual-use technology may be considered exports and require a license. The regulation applies also to intangible transfers (emails, conference talks, or cloud access).

 **Why do some journals require a Dual-Use Research of Concern (DURC) declaration while others do not?**

 DURC is an ethical, not legal, framework that asks researchers to consider whether their work could be misused to cause harm. Publishers implement DURC declarations as part of editorial policies to promote responsible science, especially in sensitive fields.

 **Why are there increasing obligations to declare the involvement of dual-use items in EU-funded projects (e.g., Horizon Europe)?**

 Because the EU is promoting a “dual-use by design” approach to ensure the responsible development of sensitive technologies with both civilian and military potential.

 **Given that publications are accessible worldwide, could they pose a threat, and should they be restricted if they address sensitive chemistry?**

 Yes. Publications in areas such as chemical weapons precursors, explosives, or advanced synthesis tools may be misused by malicious actors. Both legal frameworks and ethical frameworks aim to prevent such misuse through licensing, review, and institutional responsibility.

Fig. 28 Legislative implications for (a) synthesis of Ritalin from ref. 159; (b) synthesis of ketamine from ref. 206; (c) α -aminohydroxylation process for enolizable ketones from ref. 207.

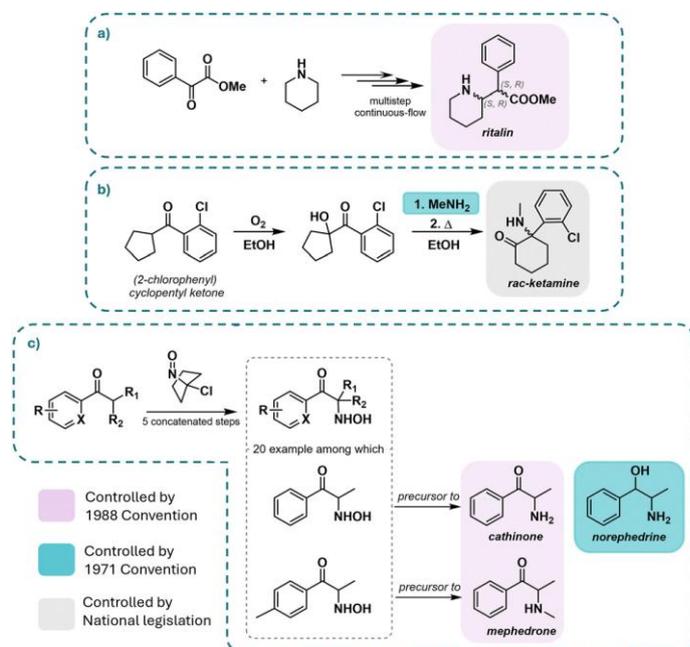


Fig. 29 Legislative implications for the neutralization of chemical warfare agents (a) mustard gas, 208–210 (b) VX211) and for the synthesis of cyclic phosphonates (c). 212

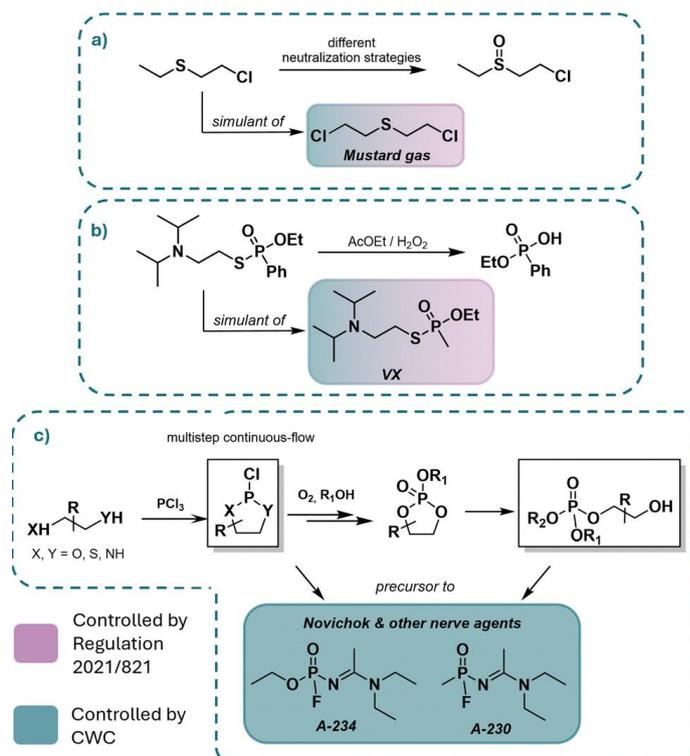


Fig. 30 Overview of the controlled procurement exercise with the selection of chemicals listed under various regulatory frameworks: (a) chemical weapons convention; (b) Regulation 2019/1148 on explosive precursors; (c) Regulations 273/2004 and 2005 on drug precursors and EU voluntary monitoring list.

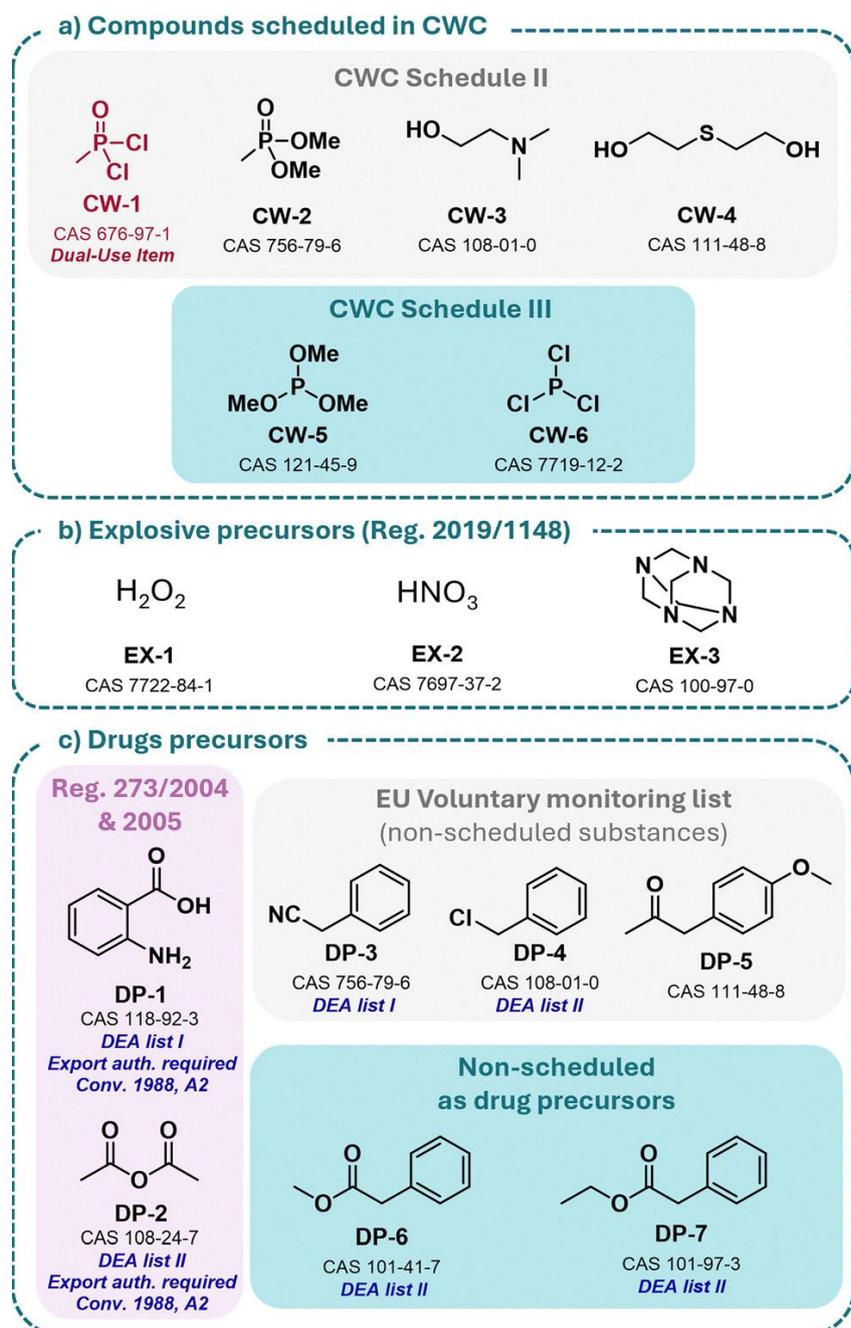


Fig. 31 Illustration of a chemical vendor's product page showing how legal and regulatory information could be integrated.

The illustration shows a product page for Thiodiethanol. At the top, the chemical structure is shown with the name "Thiodiethanol" below it. To the right, the CAS number (111-48-8), catalog number (000), and molecular weight (122.19) are listed. A "VIEW PRICING" button is located below the molecular weight. Below the product information, a warning icon is followed by the text "Regulated under Chemical Weapons Convention".

The page is divided into two main sections: "ABOUT CHEMICAL WEAPONS CONVENTION" and "HOW TO PURCHASE".

ABOUT CHEMICAL WEAPONS CONVENTION

- Overview +
- List of scheduled compounds +
- List of scheduled compounds in our catalog +

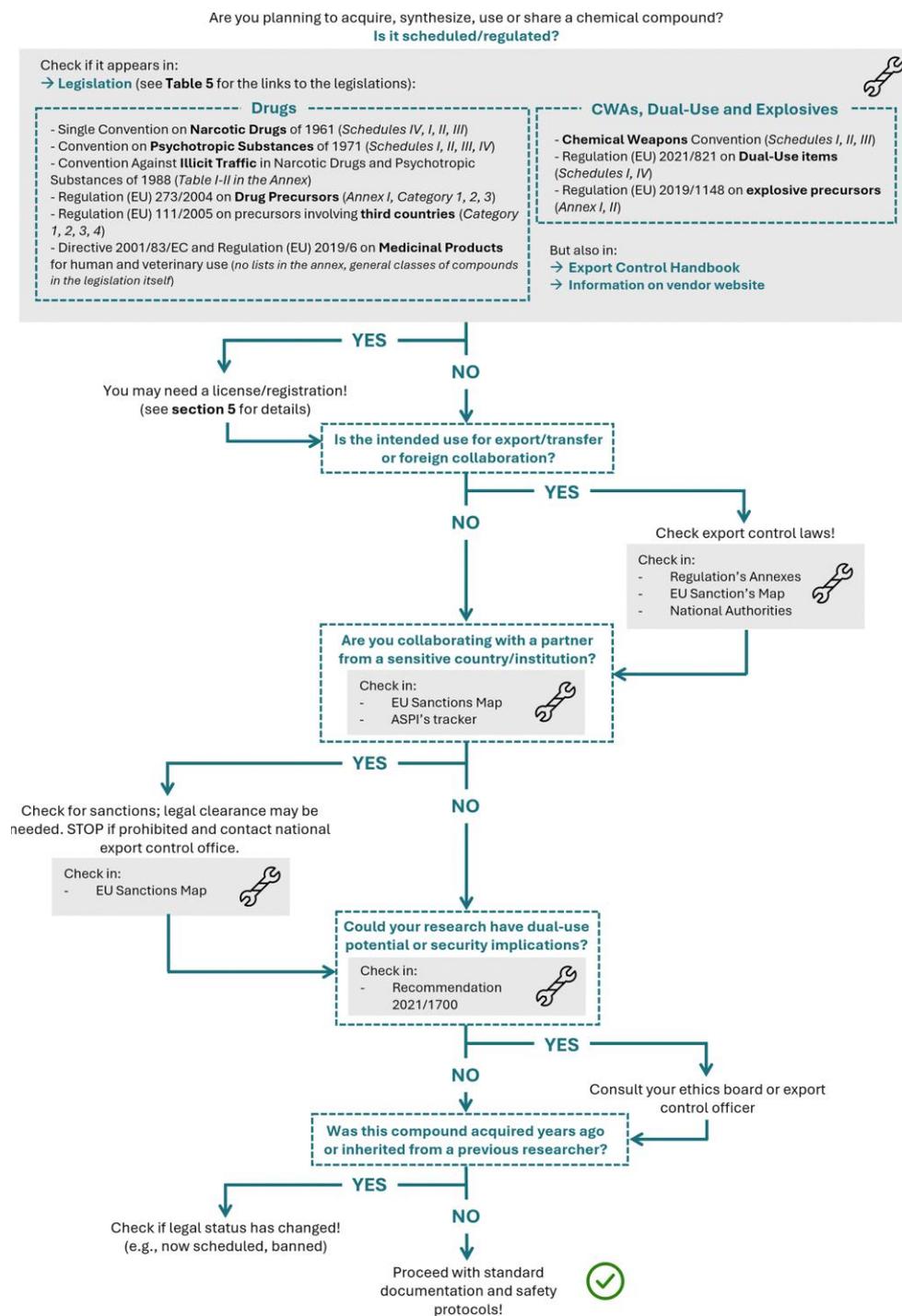
HOW TO PURCHASE

- Fill out End-User Declaration +
- Obtain an import-export licence +
- Who cannot purchase? +

Annotations with arrows point to specific elements:

- An arrow points from the text "Clearly stated if the compound is **regulated** and in which legislation" to the "Regulated under Chemical Weapons Convention" warning.
- An arrow points from the text "Explanation of the **legislation and link** to the original text" to the "Overview" item in the "ABOUT CHEMICAL WEAPONS CONVENTION" section.
- An arrow points from the text "**List** of the scheduled compounds in the legislation and in the vendor's catalog" to the "List of scheduled compounds" and "List of scheduled compounds in our catalog" items.
- An arrow points from the text "Clear explanation on how to **obtain a license** with contact of the Authorities in charge" to the "Obtain an import-export licence" item.
- An arrow points from the text "Additional list of customers that are **not authorized** to purchase regulated compounds" to the "Who cannot purchase?" item.

Fig. 32 Decision tree for chemical compliance: a quick guide to help chemists identify regulatory obligations when handling sensitive substances. Grey boxes highlight tools and resources to support legal compliance.



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