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Experiences and consequences of phasing out substances of concern in a multinational healthcare company

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Abstract

Background: In 2015, one of the largest healthcare companies in the world committed to phasing out from all its products and processes worldwide any substances declared by the European Chemicals Agency to be of very high concern. Since then, extended practical experience was gained in the phasing out of substances of concern.

Results: We report in detail on a company-wide programme to phase out substances of concern, the challenges of and the approaches to the phase-out. The paper provides concrete ideas of how to address the legitimate urge to remove substances of concern from economic activities in a holistic way, taking into account the broad diversity of aspects of sustainability. The present paper also reviews the regulatory and societal environment in which substances of concern are being phased out. The paper attempts to contribute to the ongoing discussion of how to improve the chemicals policy in Europe and beyond.

Conclusions: Phasing out substances of concern, substance selection for new products and processes, and the avoidance of regrettable substitutions while maintaining the pace of genuine innovation will stay a major challenge for our industry in the years ahead whereby not only toxicological and ecotoxicological hazards have to be considered in the selection and deselection of substances, but also other sustainability criteria characterising the entire life cycle will play an increasingly important role. Legislators and industry need to pay more attention to how this is implemented while avoiding slowing down innovation, making essential products unnecessarily more expensive, and further pushing material production out of highly regulated countries.

Keywords: Substances of concern, Substitution, SVHC, Phase-out, Green chemistry, REACH, R&D, Innovation, Chemicals policy, Chemical footprint

Introduction

Lay people think they intuitively know what a substance of concern is. However, what is of concern depends very much on the perspective and the context. Illegal drugs, explosives, chemical weapons, food additives with dubious benefits, pesticides, or antibiotic residues in food, highly flammable insulation materials in construction: all these substances can be a cause for concern.[1] In our paper, we discuss "industrial chemicals" that are of concern because they can cause long-lasting adverse effects on human health and the environment. The definition of "high concern" closely follows the one used in the context of "industrial chemicals". "Industrial chemicals" are those chemicals which are not in scope of specialised legislation regulating food, medicinal products or pesticides.

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[1] The term "substance of concern" (SoC) is used by (among others) by the Chemical Footprint Project (CFP) as "chemical of high concern" and in a not very well defined sense also by ECHA in https://echa.europa.eu/irs-infographic. We are using SoC in this paper for SVHC and other substances which also have long-term adverse effects on humans and the environment, but have not (yet) been declared SVHCs.

"Industrial chemicals" are in many countries governed by chemical legislation like the European chemical regulation REACH,[2] which is in many countries considered as the model of such legislation ("REACH-likes").

Therefore, it does not come as a surprise that the entry into force of the European REACH regulation [1] triggered the creation of the currently most powerful list of undesirable industrial-chemical substances in the world: the so-called "Candidate List[3] of substances of very high concern for Authorisation" of the European Chemicals Agency (ECHA) [2]. Substances of very high concern (SVHCs) have serious and often irreversible effects on human health and the environment and are defined by the following hazard properties:

- meeting the criteria for classification as carcinogenic, mutagenic or toxic for reproduction (CMR) category 1A or 1B in accordance with the CLP[4] regulation [3][5];
- being persistent, bioaccumulative and toxic (PBT) according to Annex XIII of the REACH regulation [1];
- very persistent and very bioaccumulative (vPvB) according to REACH Annex XIII;
- causing an equivalent level of concern as CMR or PBT/vPvB substances as per Art. 57 REACH [4].

Substances meeting the SVHC criteria can be added to the Candidate List [2] maintained by ECHA for eventual inclusion in the Authorisation List (Annex XIV of REACH) [5] and/or the Restriction List (Annex XVII of REACH) [6]. Figure 1 provides an overview of the overall regulatory process related to the Candidate List and to the Annexes XIV and XVII.

As of 17 January 2022, 223 substances or groups of substances had been published on the Candidate List and further 59 substances placed on the Authorisation List which is growing from year to year [2, 5].

Once a substance is added to the SVHC Candidate List, the REACH regulation imposes immediate obligations on manufacturers and importers to declare the substances if they are present in an article. Suppliers of articles[6] (products, which are not chemicals or mixtures thereof, but objects like cell phones or T-shirts) are required to immediately notify the professional recipients of the presence of an SVHC in their products exceeding 0.1% weight by weight (w/w) and provide instructions on the safe use of the product. On request by a consumer, any supplier of an article containing an SVHC must provide the consumer with sufficient information to allow safe use of the article including, as a minimum, the name of that substance [1].

Once a substance is added to the Authorisation List (REACH Annex XIV), the use of that substance in the European Economic Area (EEA)[7] is prohibited after the defined sunset date, unless the particular use is authorised for a limited period or the use is exempted, as for example according to REACH article 56.6 (a) the SVHC is present in a concentration limit below 0.1% (w/w) [1, 5]. Manufacturers, importers and downstream users need to apply for an authorisation for their use if they want to continue to use the substance listed in the Authorisation List after the sunset date for a limited time period [8]. This application for authorisation is specific for the use applied for and is bound to high expenses. The preparation of the authorisation dossiers submitted by the Roche Group to date has resulted in costs (internal and external) of several hundred thousand to over one million euros per dossier. Fees are added to these costs: The fees for the application for authorisation for one use currently costs 54,100 euros [9]. Dossier preparation is a lengthy process, as it takes up to two years to prepare an application for authorisation. Additional costs can be caused by measures stipulated in the authorisation decision (e.g. for risk mitigation measures or monitoring obligations).

The inclusion of any substance in the Restriction List (REACH Annex XVII) triggers conditions for the use of this substance. The restriction may apply to the substance on its own, in a mixture or in an article. Some substances might be included in both Annexes XIV and XVII (Restriction List and Authorisation List, respectively).

One example are the nonylphenol ethoxylates (NPEs), which have been widely used as surfactants in the diagnostic industry. This SVHC has been restricted in textile articles from 3 February 2021 with a maximum concentration allowed of 0,01% by weight [10]. NPEs were also included in the Authorisation List (entry 43 of the Annex XIV) [5]. Further, the use of this substance will be described in the study case 3.

In addition to the Candidate List, the Restriction List and the Authorisation List by ECHA, there are other

[2] Registration, Evaluation, Authorisation and Restriction of Chemicals

[3] The term "candidate list" is somewhat confusing to outsiders. This does not mean that the substance is a candidate to be designated as an SVHC, but is a candidate to be banned under REACH or subject to authorisation under REACH terminology. Fact is that any substance on the "Candidate List" is definitely a substance of very high concern.

[4] Regulation on Classification, Labelling and Packaging (Regulation (EC) No 1272/2008).

[5] The CLP regulation is the European Union's implementation of the Globally Harmonised System of Classification and Labelling of Chemicals of the United Nations.

[6] Article: According to the REACH regulations, "article" means an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition (REACH Art.3 (3)).

[7] The geographical scope of the REACH regulation is the EEA, which includes not only the EU Member States, but also Norway, Iceland and Liechtenstein.

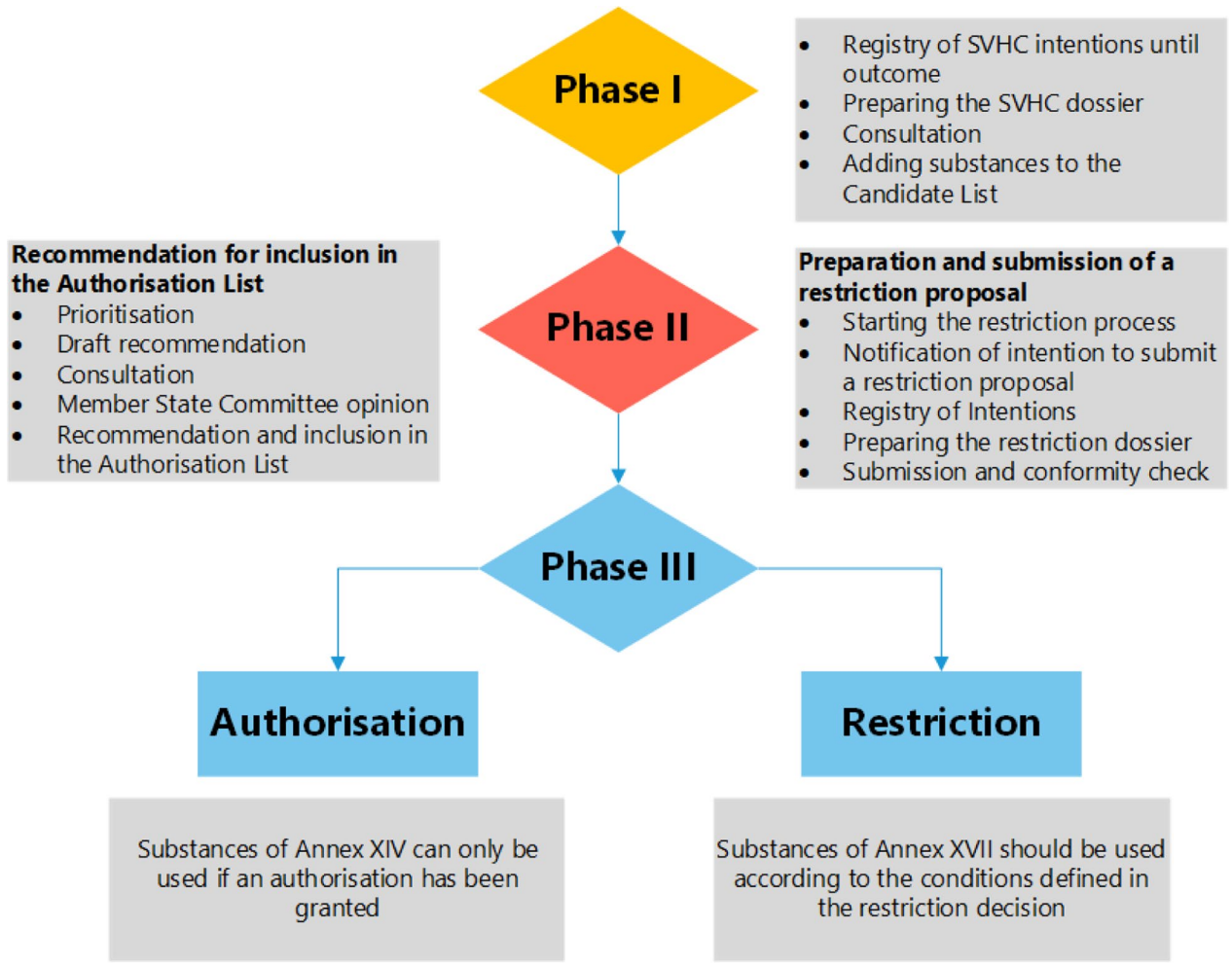

Fig. 1 The current regulatory process related to SVHCs under the REACH regulation, which may ultimately lead to a substance becoming subject to authorisation and/or falling under a restriction [7]

indices with substances of concern published by other regulatory bodies, organisations and agencies. The most important of these lists are discussed in this paper. Further, some company initiatives to identify, list and track chemicals of concern are also reviewed.

Taking an outlook to the fast and continuously changing regulatory development in the European Union, the European Green Deal needs to be highlighted, as it will probably have an appreciable impact on the further phase-out of SVHCs. The Green Deal, an action programme released in December 2019, aims to transform the EU's economy into a climate-neutral, resource-efficient, and competitive economy by 2050 [11]. In particular, the Chemical Strategy for Sustainability (CSS) [12] and the Sustainable Products Initiative (SPI) [13] are two significant policy initiatives, part of the Green Deal, with the declared ambition to reduce substances of concern faster while driving innovation for more sustainable products. The CSS was adopted on 14 October 2020. The strategy is part of the EU's zero pollution ambition—a key commitment of the European Green Deal—and aimed to phase out the most harmful substances and simplify the risk management process [12]. It remains to be seen to what extent the CSS will then really succeed in combining the former with the latter without compromising the manufacturing location in Europe.

The CSS aims to "green up" the chemicals industry in two ways: regulatory measures by banning or minimising the use of certain harmful chemicals and non-regulatory incentives by promoting industrial innovation.

The healthcare sector is a major consumer of chemicals, therefore, it is a key actor to phase out harmful chemicals and reduce negative impacts on environment and health. Hereinafter, the scope of the present study

does not include all facets of the healthcare sector, but only those in which the Roche Group is involved, that is the development and manufacturing of patented medicinal products and in vitro diagnostic devices and assays.

The healthcare industry in general and the above-mentioned subsectors in particular belong to the most regulated economic activities due to the fact that medicines and in vitro diagnostic instruments and their related reagents must be approved by health authorities. In addition, the industry faces large societal demands for performance and pressure to justify its costs to public health systems.

All companies which phase out SVHCs must cope with considerable additional burdens for R&D and their safety, health and environmental protection (SHE) departments. Moreover, healthcare companies have additional challenges to prove that modified manufacturing processes and redesigned products are at least as safe and effective as their predecessors and fulfil the corresponding regulatory requirements. This takes a considerable amount of time—in some cases years—and generates substantial costs.

The development of new products is very often limited by the number of the R&D experts and financial resources available. Correspondingly, an important challenge related to the phase-out programme is prioritisation, which means considering whether to phase out the product or (with higher costs and efforts) to proactively substitute an SVHC before the end of the product life cycle. The decision is made based on whether the substance is only on the Candidate List; on the Candidate List with a high likelihood[8] of being added to the Annex XIV (which is the Authorisation List) and facing authorisation; or the substance is already on the Authorisation List with a fixed sunset date implying that an application for authorisation has to be submitted. Last but not least, business considerations play an important role. The market life expectancy of the existing product and the costs of the substitution must be assessed, as well as the importance of the corresponding product for the business's economic success and whether customers will accept the reformulated product because they are used to the old product and/or doubt the same performance.

These major developments set the scene for our present study, which offers a view into a real company that actively works to eliminate substances of concern in its products and processes and has publicly announced a goal to phase out SVHCs.[9] In order to gain an insight into the drivers for phasing out, the barriers faced by stakeholders, and the duration and cost of overcoming them, a survey of relevant stakeholders was conducted. In addition, interviews were conducted with product managers. We also analysed applications for exemption from the phase-out goal and conducted case studies in order to develop generalised concepts based on our experience in phasing out substances of concern.

Results

The SVHCs phase-out goal of Roche

In 2015, F. Hoffmann-La Roche Ltd[10] decided to phase out SVHCs from all products and manufacturing processes worldwide within 10 years of inclusion in the Candidate List, whenever technically possible. This phase-out goal was approved by the Corporate Executive Committee, was publicly announced and applies to the entire Roche Group. On the one hand, this was a reaction to the growing number of entries on the SVHC list (connected with regulatory pressure on these substances) and, on the other hand, it was born out of the desire to set meaningful and easily measurable Group targets in the area of chemical-related sustainability. The adoption of this very ambitious goal can be justified by the fact that several positive effects could be achieved, namely to

- protect the health of customers and employees, as well as the environment;
- ensure supply chain continuity of raw materials, because discredited substances can become economically unattractive for suppliers;
- allow manufacturing processes to be more easily moved to another site globally, including to the European Union;
- make products more attractive to customers, giving the company a competitive advantage in the marketplace;
- ensure stable compliance; and
- maintain a high sustainability rating, which attracts sustainability-oriented shareholders.

The fact that the family of the company's founder, which holds the majority of the company's ordinary shares, expressly attaches importance to the sustainable management of the Roche Group, had a favourable effect.

After the formal decision to implement the SVHCs phase-out, a document was prepared to define the scope, the processes and the definition of what is "technically impossible" to be phased out and thus defining the applicability of exemptions.

[8] The nomination on the Authorisation List is a stepwise process which is preceded by a recommendation for inclusion on Annex XIV.

[9] Roche also phases out substances that do not belong to the SVHCs, such as mercury and its compounds, EDTA or certain biocides, although these activities are not actively publicised.

[10] F. Hoffmann-La Roche Ltd (often just only called "Roche") is a Swiss multinational healthcare company currently active in the pharmaceutical, diagnostic and diabetes care fields. The company employs over 90,000 people across more than 100 countries. For more detailed information see [14].

All substances as such, mixtures, and articles used in manufacturing processes and/or being part of final products are in scope of the phase-out. No *de minimis* amount or concentration applies as long as the SVHC has been consciously added to the product or used in a process. Traces of impurities below 0.1% (w/w) are exempted. Excluded from the scope are all research and quality assurance activities, whereby researchers are actively advised that they may use SVHCs within their research, but in doing so should not develop manufacturing processes or products in which SVHCs are present. Furthermore, laboratory employees are specifically advised that the use of and the exposure to SVHCs in research and quality control should be kept to a minimum to protect the health of our R&D personnel and the environment of the R&D site.

Also excluded from the scope of the SVHC goal are construction materials, infrastructure, office equipment, furniture, and fuels. These materials should be dealt with within other projects.

For the reader who is not familiar with the regulatory situation within the healthcare industry or the structure of the Roche Group, which manufactures both medicinal products (pharmaceuticals) and medical devices (in vitro diagnostics), it is important to understand that the SVHCs phase-out goal applies in different ways to the two divisions. Whereas the SVHCs phase-out goal applies to both processes and products in the Diagnostics Division of Roche, it only applies to the manufacturing processes, but not to products of the Pharmaceuticals Division. On the one hand, SVHCs are unlikely to be used in medicinal products, on the other hand, according to REACH regulation (Article 2.5(a)), substances which are only used as ingredients of medicinal products cannot be designated as SVHCs.

This goal applies to all companies of the Roche group, regardless of their geographical location. The contract manufacturing organisations of Roche are not in the scope of the goal.

The tool of temporary exemption from the SVHCs phase-out goal

Because the goal includes the clause that phase-out should be executed "whenever technically possible", it was key to define clear conditions to avoid loopholes which would erode the goal and undermine credibility. Therefore written guidance on how to deal with applications for exemptions was developed by the environmental and health protection department.[11] Figure 2 provides an overview of the internal decision-making process for an exemption request of the SVHC phase-out goal at Roche.

The clearest case of a justified exemption is if the substance is essential on a molecular level. For instance, an essential micronutrient or a co-factor of certain enzymes cannot be substituted in a fermentation process with a microorganism or cells which need this substance to function normally, e.g. certain soluble cobalt compounds, which are essential micronutrients. In specific cases, when it can thus be assumed that it is technically not feasible to substitute this substance, an application for exemption can be submitted. In the event that users come to the conclusion that a substance cannot be substituted by the target date (10 years after SVHC listing), they must—in due time before that date—compile a technical documentation which proves the case and submit it to an internal decision board which is not part of the corresponding business (and reporting line) for approval. In case an exemption is then conceded, the documentation (application and approval decision) must be filed for an audit. An open-ended exemption is granted until the change of technology.

Moreover, uses for which the company has successfully applied for an authorisation under the REACH regulation are also exempted from the phase-out goal. Obviously, if the sunset date (from the Annex XIV of REACH—"Authorisation List") is reached before the 10-year term of the phase-out goal has elapsed, the sunset date (as a legal requirement) prevails and the use of the substance must be discontinued (if no application for authorisation was submitted to the ECHA).

Exemptions from authorisation under REACH, e.g. for in vitro diagnostics if the substance is listed on Annex XIV for human health issues only (according to Article 60.2 and 62.6(c) of REACH), do not lead to an exemption from the SVHCs phase-out goal.

In addition to the officially announced goal to phase out SVHCs, the Roche Group has called its R&D staff to reduce the use of other substances of concern which can be subject to other legislation (other than chemical legislation)[12] or have been identified internally for gradual phase-out as there are more sustainable alternatives to them. Sometimes, memos to R&D and procurement on specific substance or substance groups will trigger these phase-outs. In other cases, the phase-out could be driven by means of internal substance selection guides for substance groups such as solvents, chelators, surfactants, buffers, or chaotropic agents.

When the goal was being implemented within the company, situations soon arose where a timely exit would

[11] The environmental and health protection department at the Roche Group's headquarters, which reports to the General Counsel (head Legal and Sustainability). Thus the SVHC phase-out programme is governed by an organisation which has another reporting line than the business to guarantee independent decision making.

[12] Such as: the Directive on the restriction of the use of certain hazardous substances in electrical and electronic equipment and the Medical Device Regulation.

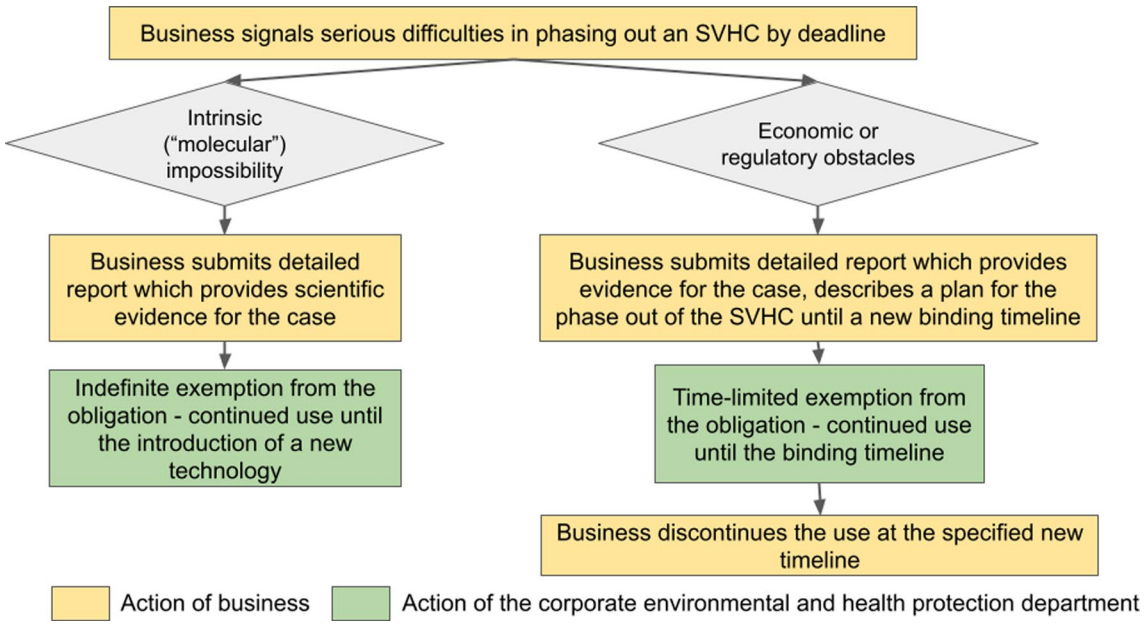

Fig. 2 Internal decision-making process for an exemption request of the SVHC phase-out goal at Roche

have led to very serious disruptions in the supply of essential healthcare products or excessive economic burdens. A situation of this type can occur for instance if a new business that uses SVHCs is acquired, or processes involving SVHCs are insourced, or the SVHC is purchased as a part of a mixture and its presence is not obvious. Also if products are reformulated, which requires a worldwide regulatory approval, and only one production line is available so that the manufacturing of the new product can only start once the approval is obtained in all markets. In some cases there is an additional burden because not only the new formulation needs to be approved but also one specific production line was previously approved by the health authorities, and that production line, including the formulation change, needs to be approved too.

The occurrence of such situations required the creation of an additional tool within the programme, namely that of a temporary exemption. In this way, a failure to meet the target is not just passively tolerated but requires an active application which needs to deliver convincing evidence that the goal cannot be achieved within 10 years after the listing of the SVHC including a plan to phase out the SVHC with a fixed termination date. The approval of temporary exemption (as in the exemption mentioned previously) has to be obtained by an instance which is not in the corresponding business division. Both the formal application and the approval decision are then filed to be available for independent review.

The case of excessive economic burden is obviously a particularly difficult one, as it is hard to define and check the fulfilment of the criterion. A typical acceptable case is when the end date of the phase-out goal is not long before the end of the life cycle of a product or process where the use of the SVHC in question would be discontinued anyway. Then it is completely justified not to dedicate financial and human R&D resources, which could otherwise be used better in real innovation.

Anyway, such "economic" cases would never lead to an open-end exemption. The tool of the temporary exemption helped to establish a broad acceptance of the SVHCs phase-out goal within the business. It offers a little more leeway without fundamentally deviating from the obligation to phase out.

The numbers show that overall, this tool was used with a sense of proportion: As of January 2022, F. Hoffmann-La Roche Ltd granted 22 exemptions for 11 different SVHCs. On top, Roche Group companies applied for an authorisation under the REACH regulation for 5 uses of 3 substances.

Survey among participants of the phase-out

In order to assess the challenges associated with this goal, a survey was conducted among the stakeholders involved in the phase-out of SVHCs in a multinational healthcare company. The survey questions focused on the completeness of the phase-out, whether it was technically possible (see in suppl. mat.). Participants responded to 12 questions listed in the Appendix. In addition, personal

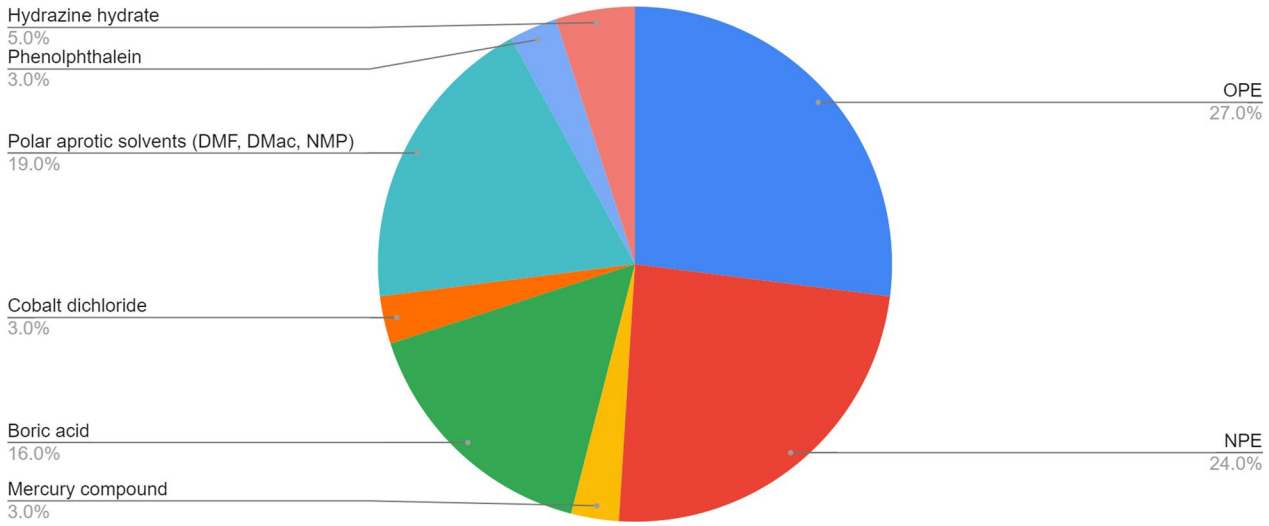

Fig. 3 Occurrence of the identified substances in the survey. NPE: nonylphenol ethoxylates; OPE: octylphenol ethoxylates; polar aprotic solvents: DMF: *N,N*-dimethylformamide; DMac: *N,N*-dimethylacetamide; NMP: *N*-methyl-2-pyrrolidone

experiences, analysis of exemption requests, case studies and interviews with product managers are included in this paper to develop generalised concepts.

In total, 22 stakeholders were contacted and 16 answered the survey. Of the 16 respondents, 69% (11) indicated that phase-out was technically possible but not yet completed, while in 31% of the cases (5) phase-out was technically not possible.

The respondents had the possibility to include several substances and/or uses at the same time, which resulted in a total of 37 substances reported in the survey. Figure 3 shows the occurrence of the identified substances in the survey.

Based on the survey, three groups of substances could be distinguished:

1. Substances on the Authorisation List: OPE (octylphenol ethoxylates; 10–27%), NPE (nonylphenol ethoxylates; 9–24%);
2. Substances in the Candidate List: boric acid / sodium borates (6–16%), polar aprotic solvents (DMF: *N,N*-dimethylformamide, DMac: *N,N*-dimethylacetamide, NMP: *N*-methyl-2-pyrrolidone) (7–19%), hydrazine hydrate (2–5%), cobalt dichloride (1–3%), phenolphthalein (1–3%);
3. Substances concerned by a restriction: mercury compound (1–3%) and NMP.

Substances can occur on both Candidate and Authorisation List on one hand and on the Restriction List on the other.

The timelines for replacements were different for each individual project but the respondents indicated a maximum of up to 10 years considering the three following stages: feasibility test, stability test and regulatory update.

Based on the survey results, the main obstacles to the phasing out of an SVHC can be grouped as: technical, market, economic and regulatory barriers (Table 1).

Interviews were also conducted with two international product managers (IPM) whose portfolios were impacted by the presence of the alkylphenol ethoxylates. The main trigger for the substitution of these SVHCs was the legal status (the alkylphenol ethoxylates are banned in the EEA).

Both IPMs did not communicate the Roche phase-out goal to customers (laboratories, hospitals) as they considered them not to be interested in the details ("The customers only want to have reliable diagnostic instruments and assays."). The communication done was related to the authorisation requirements with marketing notifications.

The presence of SVHCs might pose an issue during tendering, in particular in Asia (Korea, Vietnam, Singapore, Malaysia, China). Both IPMs support the phase-out goal, but suggest that the awareness and the communication about it should be improved.

Lists of substances of concern

In addition to the Candidate List and the Annexes XIV and XVII (substances subject to authorisation and restriction correspondingly) issued by ECHA, there are

Table 1 Main obstacles to the phasing out of SVHCs

Technical barriers	Market barriers
• Lack of capacity (time slots) to produce the batches for the validation • Lack of available alternatives • Technical complexity • Effort to demonstrate that the change does not impact safety and function of the product	• Contractual obligations to keep the existing formulation until the contract ends • Contractual necessity giving advanced notification of changes • Market acceptance of the products manufactured with the alternative
Economic barriers	Regulatory barriers
• Costs to revise an existing product in comparison with the potential income which can be generated • Lack of capacity, essentially human resources, in R&D • Time consumed to find an alternative and to validate it as compared to the remaining life cycle	• Time span to generate additional data to support change registration • Time span to achieve regulatory approval • Costs for testing, dossier generation and authority fees

other indices including lists of substances of concern published by other regulatory bodies, organisations and agencies such as the Chemical Management Plan (CMP) from Canada [15], the Stockholm County Council's phase-out list [16], the ChemSec's SIN list [17], the European Trade Union Confederation (ETUC) list [18] and the Community Rolling Action Plan (CoRAP) by ECHA [19]. The enumeration of such lists can be found in Table 1 in suppl. Mat., but is obviously not exhaustive.

The SIN list aims at encouraging industry to move away from substances which Chemsec, a non-governmental organisation, considers as fulfilling the criteria for SVHC [17]. The ETUC list prioritises chemicals for authorisation under REACH [18]. The CoRAP is a mechanism to evaluate substances between member states of the EU that works on the basis of a list of chemical substances already evaluated or being planned to be evaluated by an EU member state over a period of three years [19]. Furthermore, ECHA is using these external sources, e.g. the SIN list, to support the integrated regulatory strategy and the identification of substances that matter most in terms of protection of human health and the environment [20]. These lists also generate pressure on suppliers of these companies to phase out the listed substances.

Further company initiatives to identify, list, and track current and upcoming chemicals of concern can be seen in Table 2 in suppl. mat.

In addition, there are some other lists of undesirable substances, which are not in the scope of the present paper such as undesirable substances in animal nutrition by EC [21] and the lists of undesirable substances and limited uses of feed ingredients [22].

Appropriate lists should be implemented in the company's enterprise resource planning software (in the material management modules thereof; ideally this is connected to the purchasing software of the company) and should be used to identify concerned raw materials, processes or products containing listed substances. The list should also be used to flag substances in the catalogue used by R&D staff to order materials for their work. These lists are also used as a basis to obtain information from suppliers by requesting from them a declaration of the presence or absence of the listed substances. Ideally, companies have the full composition of the products, mixtures of articles (objects) in their enterprise resource planning software so that the system can flag any product containing any substances of concern. The process can also be automated, so that even as the lists get updated or supplemented by the issuing organisation, the resource planning software automatically shows new inclusions.

Regrettable substitutions

A regrettable substitution is defined as the replacement of a known hazardous substance with another substance that is as harmful or even worse than the replaced one. A regrettable substitution can happen because the substitute has not been sufficiently tested and the hazardous properties have not been revealed yet.

Maertens et al. [23] listed some examples of regrettable substitutions. The most famous one is the substitution of

Table 2 Type of uses and the number of products or processes impacted by APE substitution

Use type	Number of products or processes affected	Type of function of the alkylphenol ethoxylates
Use as an emulsifier in the siliconisation of glass containers used as primary packaging for medicinal products	2 medicinal products	Emulsifier in the silicone oil emulsion
Formulation, filling and use of in vitro diagnostic assays	23 products	Increasing the solubilisation of reagents, cell lysis, protein stabilisation and wetting agent
Use in the production of proteins and the conjugation of latex beads (use in the production of in vitro diagnostic assays)	19 processes*	Increasing solubilisation of reagents, cell lysis, protein extraction and protein stabilisation or dialysis

*These processes impact a larger number of final products

bisphenol A (BPA, CAS no 80-05-7) by bisphenol S (BPS, CAS no 80-09-1) or bisphenol F (BPF, CAS no 620-92-8) [23, 24]. Bisphenol A is considered toxic to reproduction, skin sensitising and an endocrine disruptor [25], while bisphenol S is under assessment as an endocrine disruptor [26] and bisphenol F is a skin sensitiser [27].

A regrettable substitution leads to reputation damage and also an economic burden as the replacement of a substance of concern needs to be performed a second time. There are also some examples in the textile industry, automotive industry, food industry, cosmetics, etc. [28, 29].

Process for substitutions

In a highly regulated industry such as ours, the general steps for substitution are described below. This description is for the in vitro diagnostics business, but the effort required for the pharma business is equally laborious [30].

During this feasibility phase, an alternative substance easily available on the market has to be identified. The corresponding supplier has to be qualified. Then the first batches of the new formulation have to be produced and the performance of the in vitro diagnostic (IVD) assays are tested and compared to the established specifications.

The validation of the IVD assays consist in verifying the shelf-life and the stability of the new reagents. All related manufacturing procedures are updated. Further production of pilot lots are performed for detailed assay performance verification and for the validation of the production process.

The request for regulatory approval and/or updated market health authorisation, if necessary: the IVD assays must have a market authorisation (regulatory approval). Any change in the composition of the assays needs either a notification to the corresponding health authority and, in some cases, an application for a new market authorisation might be needed.

Finally, introduction to the market: the new assay is introduced to the market with a new material number.

The whole process takes several years and some steps might have to be repeated in case of failure (for example feasibility and/or validation has to be repeated with a new substance, or a modified production procedure).

In the pharmaceutical area, the process is similar and comparably demanding in terms of the required time and resources. This can be seen from the list of steps below which roughly outline the process change in the manufacturing of a synthetic molecule.

First there is an identification of an alternative process. The research and development (R&D) needs to be conducted to substitute a substance in a given process step or to find an alternative way of producing the target or intermediate product. This includes confirmation that the quality of the product of the new process fulfils the acceptance criteria and is usable in the downstream chemistry. The supply chain for the alternative process needs to be established. New manufacturing documentation needs to be prepared.

Then the process qualification is done. Stability studies for the product of the new process need to be performed. Acceptable ranges for conditions and parameters need to be defined in a process characterisation study and fate of impurities studies might be required. The robustness and reproducibility of the new manufacturing process has to be demonstrated in process performance qualification before it can be used for commercial manufacturing.

Concerning the regulatory requirements, the registration dossier has to be updated with the information for the new manufacturing process. Depending on the level of change to the process, new stability studies on later intermediates of the process, the final drug substance and drug product might be required. A regulatory complication is the different timelines for change implementation in different countries. Often the old and the new process have to be run in parallel until all countries accept the process change. This can take several years.

The new process can be used to manufacture material for market supply under a new material number.

Ideally, process and product development should be focused on proactively identifying sustainable processes and products in a right-first-time concept. This is well aligned with the principles of green chemistry, which advocate for green by design instead of substitution approaches [31, 32].

As an accompanying measure to support researchers, a specific guidance "Substance Selection and Substitution Guide—how to avoid bad choices and regrettable substitutions" for the R&D population of the Roche Group was developed. This guidance draws upon a set of substance selection guides covering key substance groups used in the Roche Group. Other useful substance selection guides were developed such as the "Guidance on Key Considerations for the Identification and Selection of Safer Chemical Alternatives" by OECD [33] and the "Business Guide to Safer Chemicals" special report [34]. An additional tool is the chemical alternatives assessment (CAA) that provides industry and other stakeholders with the information they need to choose safer chemicals and minimise the potential for regrettable substitutes [35].

Substance selection guides and the phase-out of substances of concern

In order to avoid regrettable substitution, substance selection guides for different types of chemicals were

Table 3 Ways to eliminate substances of concern

Way	Definition
Omission	The substance is removed without replacement from the product or process, which continues to fulfil the same function
Substitution	The substance is replaced by another substance without affecting the product or process
Termination of use	The use of the product or process is permanently stopped
End of life cycle	The substance was contained or used in a durable product that has reached the end of its service life and is therefore being decommissioned
Change of technology	The substance is not used any longer because a more advanced technology is introduced

developed. These guide are essentially based on the evaluation of toxicological and environmental hazards of the substances and should help researchers and developers or even the purchase organisation to choose the right substances for the development of new reagents or choose the right substance for a chemical synthesis. For the usefulness and reliability of these internal guides, it is very important that the internal guides are regularly reviewed and, if necessary, revised to take into consideration new scientific results, latest regulatory developments and updated external guidelines.

Awareness of the phase-out goal

In order to raise the awareness of the Roche phase-out goal and to easily involve the R&D community, an e-learning program was developed. This tool explains the concept of SVHCs, the legal situation and the voluntary phase-out goal, and it lists all available supports (selection guides, exemption documents, etc.).

Case studies: experiences and challenges in the manufacturing of pharmaceuticals and in vitro diagnostic assays

During the development of active pharmaceutical ingredients, certain transformations represent notorious challenges to phase out associated SVHCs. One typical reason for this is that there are established conditions for the synthesis of certain chemical moieties (e.g. use of DMF as solvent in peptide synthesis) without generally established substitution alternatives. For other types of structures (e.g. heterocyclic compounds with N-N bonds), significant synthetic detours are required (if possible at all) to substitute concerning reagents. In those cases, specific attention is required to the environmental impact of the replacement as alternative pathways do not only use other potentially concerning chemicals but also might result in higher general material consumption which could offset advantages from the substitution in a negative way.

Generally, shifting to favourable alternatives is evaluated as early as possible during drug development as the associated efforts increase with the projects progressing through the clinic and into commercial use. Solvents are specifically in focus because it has been shown in a number of cases that alternative synthesis conditions can often be used. Investigations are performed on a project by project basis and are dependent on the expected commercial manufacturing volumes, as the environmental impact is different for high tonnage production (e.g. antibiotics) compared to small kg quantities (e.g. rare diseases). Furthermore, it should be mentioned that in the framework of manufacturing pharmaceuticals, the focus is mostly on substitution of a substance of concern as other options like omission are not applicable or because change of technology (see Table 3) would not necessarily obviate the use of the substance.

Case study 1: hydrazine

In 2011, hydrazine was registered on the SVHC Candidate List due to its carcinogenic properties [2]. To comply with the Roche internal goal, efforts began to phase out the use of this substance within 10 years of its listing as an SVHC candidate. Hydrazine is used in a variety of chemical processes as the simplest building block containing an N–N bond [36]. As such, it has found widespread use especially in the manufacture of heterocyclic rings. At the time of the phase-out decision for hydrazine, this chemical was used in a multitude of processes at Roche. One of these processes is described here to exemplify the implications and problems associated with the phase-out.

In the synthesis of balovaptan (see the structural formula in suppl. mat. Figure 1), a drug used for the treatment of autism, hydrazine was used to establish a 1,2,4-triazole moiety [37]. The process performance qualification of the respective step had already been completed at the time of the phase-out decision. Accordingly, changing the process would have required validation of the potential alternative process and establishing the use of the new material quality in the downstream process. Consequently, significant time and resources would need

to be spent. Nonetheless, the substitution was evaluated with open outcome.

The following alternatives were assessed in order to determine if a substitution was possible:

- Sourcing of a starting material containing the 1,2,4-triazole moiety: this option would have required major changes in the synthetic route with all the respective implications. Even more critical: this would only have shifted the use of the concerning substance hydrazine to an earlier stage of the process as practically all commercial 1,2,4-triazole compounds are manufactured using hydrazine. Essentially, this represents a shift of the substance use from scope 1 to scope 3 and with that potentially to less regulated countries. This is certainly not desirable and does not solve the problem of substance use in the long run.
- Alternative synthetic pathways to instal the 1,2,4-triazole moiety: two routes were conceived and evaluated as potential alternatives. However, the first option would have required the use of hydroxylamine, which is suspected to be carcinogenic as well as to pose significant safety hazards (e.g. explosion hazard) in large-scale manufacturing. The second alternative would have included a copper-mediated cyclisation and consequently generated significant amounts of metal waste. Accordingly, both options would represent regrettable substitutions.

As a consequence of these investigations and considering that hydrazine was used only in the manufacturing of an intermediate which would exempt its use from being banned under Swiss and European Chemical Legislation, it was decided that it was not feasible to substitute hydrazine in the balovaptan process and this specific use received an exemption from the internal phase-out goal.

The manufacturing process was further optimised to minimise the hydrazine stoichiometry in order to reduce the amount of residual hydrazine in the reacted and worked up reaction mixture. Adherence to the required exposure limits is controlled strictly by high pharmaceutical manufacturing standards.

Case study 2: DMA, DMF, NMP

The dipolar aprotic solvents DMA, DMF and NMP were listed on the SVHC Candidate List in 2011, 2012 and 2011, respectively. Nonetheless, these solvents are still being routinely used for a range of synthetic transformations, particularly in peptide chemistry. There has been significant progress in identifying alternative solvent systems in recent years but often DMA, DMF and NMP are still the gold standard and their use is required [38] due to the lack of feasible alternatives.

Sustainable solvent selection is a key pillar in the implementation of green chemistry throughout the chemical industry [39]. At Roche, solvent selection is practised based on an internal selection guide and anchored in the department goals. Accordingly, there are a number of examples where these solvents were substituted by other chemicals or replaced by using different synthesis pathways.

For example, DMF was successfully replaced by more desirable alternatives in the manufacturing processes of taselisib [40], ipatasertib [41] and fenebrutinib [42] (see structural formulas in suppl. mat. Figure 1).

Case study 3: substitution of alkylphenol ethoxylates (APE)

In 2012, the ECHA identified the alkylphenol ethoxylates as an SVHC due to the endocrine-disrupting properties of their degradation products. This triggered within the Roche Group after the establishment of the phase-out goal, the identification of uses of these substances, the analysis of their functions and their substitution.

Due to the complexity of the Roche portfolio and in particular the Diagnostics Division's portfolio, it took several months to identify the presence of the alkylphenol ethoxylates in final products or processes and start the corresponding substitution activities. After the inclusion of the alkylphenol phenolethoxylates on REACH Annex XIV in 2017, the pressure on the substitution projects increased because their use would then officially be forbidden in the EEA after the sunset date of 4 January 2021.

In Table 2, the type of uses and the number of products or processes impacted at Roche are summarised.

The products sold by a healthcare company are submitted to stringent regulations which implicate that the launch of those products is subject to market authorisation. Changes in the composition and/or production process must be notified and eventually approved by the health authorities. This approval might take several months in some countries.

In addition to the different phases needed for such a substitution (see description in section "Regrettable substitution"), we would like to mention that this has a big impact on the R&D budget and on the human resources (limited personal resources).

As in some of the uses the APE could not be replaced before the sunset dates, Roche had to apply for authorisation for 23 products on the specific use covering the formulation, filling and use of in vitro diagnostic assays in 2019 in the EEA. Due to Brexit, a similar application will be submitted in 2022 but only for 11 products as the replacement of the alkylphenol ethoxylates has already been done for the 12 remaining products.

Material declaration and the phase-out of substances of concern

A seemingly trivial fact is that the use of substances of concern must first be identified in a company-wide programme. It is not the case that substances in individual processes or products are unknown, at least as long as they are substances as such or part of mixtures. However, depending on the filing system and the complexity of the corporate structure, this knowledge is not always centrally and easily accessible. To collect the necessary information in the supply chain and to manage the corresponding collected data within the company, appropriate electronic tools must be in place [43]. In the case of the Roche Group, there is an additional problem that certainly also applies to many other companies in the industry: many products are not substances or mixtures, but articles (objects).Two leading trade associations in the European healthcare sector (MedTech Europe and EFPIA) have expressed the opinion that it is expedient that full chemical compositions not only of mixtures, but also of articles (objects) are provided by the suppliers [44, 45].

Discussion

Replacing substances of concern with safer alternatives and greener technologies is strongly driven by legislation in the European Union, in particular by the authorisation and restriction chapters of the European REACH regulation [46]. The declared goal of the Chemical Strategy for Sustainability and the Sustainable Products Initiative under the EU's "Green Deal" is to further enhance the regulatory pressure. Obviously, there are also internal impulses for companies, such as self-motivated sustainability ambitions and goals to better protect the health of customers and employees as well as the environment, or the striving to improve the reputation and to make products more attractive to customers therefore giving the company a competitive advantage in the marketplace. Following such an impulse, seven years ago, F. Hoffmann-La Roche Ltd, one of the world's largest healthcare companies, has committed to phasing out substances which were declared by ECHA to be of very high concern from all its products and processes worldwide. During this time, extensive practical experience was gained with phasing out substances. While preparing the survey presented in this paper to collect this experience, we understood how large the circle of stakeholders (staff involved) actually was within a multinational healthcare company. From the survey and interviews with product managers, from our own personal experience, and from the analysis of exemption requests we were able to gain a variety of insights into the barriers to phasing out SVHCs.

The main obstacles identified within the survey were grouped into technical, market, economic, and regulatory barriers (see Table 1). Several technical barriers were reported such as the lack of capacity (time slots) to produce the batches for the validation, the lack of available alternatives, the technical complexity, and the efforts put into demonstrating that the change does not impact safety and function of the in vitro diagnostic product. Based on a survey conducted by ECHA in 2020 [46], companies faced similar technical barriers in substitution activities and took more than 7 years to complete them. Some of the barriers reported were for instance:

- difficulty to identify potential alternatives;
- a lack of available alternatives;
- technical difficulty to test the performance of the identified alternatives (lack of pilot testing capability, R&D and available technology);
- non-availability of technically feasible alternatives that meet customers' requirements (after testing);
- concerns related to market adoption/approval of the products manufactured with the alternative.

According to this study [46], companies attempted to overcome the technical barriers by involving external experts such as research units; organising R&D projects to find cost competitive processes to meet customers' requirements; process improvement and extensive testing; and partnering with suppliers and customers for the development of safer substitutes and cooperative testing.

Those companies—where substitution is taking more than 7 years—have the highest cost of substitution, which may go as high as 50 million euros [46]. The key cost drivers in the pharmaceutical and diagnostic industry are the industry standards and regulatory requirements [46]. Companies reported that they need four to six years to complete the substitution process due to the high requirements and strict regulations for processes and products in the medical device and pharmaceutical industry. We also identified regulatory barriers such as time span to generate additional data to support change registration; time span to achieve regulatory approval; and costs for testing, dossier generation and authority fees.

In regard to the time required for substitution of an SVHC or other SoC, realistically, the phase-out is in general possible within 10 years in our industry, if the work on this target is started immediately after the substance has been designated an SVHC or has been otherwise recognised as being undesirable. But even with a timely start to the project, it remains a challenge in terms of financial and human resources taking into consideration the

various steps required including feasibility tests, stability, safety and functionality testing and the necessary regulatory approval.

The overall framework in the Roche Group can be assessed as generally very favourable for long-term sustainability programmes, based primarily on the stable ownership structure. The founding family, which is interested in long-term development, holds the majority of voting shares. Despite the generally favourable conditions, the problem remains that the resources for the individual projects have to be raised by the individual departments, which are already heavily burdened by their usual tasks.

The number of company-internal exemption requests asking for prolongation (27 received since the phase-out programme started within Roche) is an indicator for the various challenges of the phase-out. In particular, it is very difficult to substitute within the same technology and prove that the product has the same performance in the regulatory approval process. In a few cases, an open-ended exemption until change of technology was conceded because the substitution was technically not feasible (see "The tool of temporary exemption from the SVHCs phase-out goal" section).

What is the best way to eliminate substances of concern?

Although frequently the term "substitution" is used in the context of ceasing the use of substances of concern, substitution is not necessarily the most appropriate approach, even if technically viable at all. While being involved in a multitude of phase-out projects, we saw that there are five types of approaches as shown in Table 3, where substitution is just one of them.

Omission

In this case, the substance is just removed from the otherwise unchanged product or process. We observed in our practice that sometimes a substance was used "just in case" because the component had been used in similar products or processes in the past or because the formulation had been transferred without the function of the individual components being fully known and thus without a clearly established need for its use. One example was the use of a defoamer to avoid the formation of bubbles in a technological process. When tests were conducted with a formulation which did not contain the defoamer, the quality of the final product was not compromised. Although the omission as a way of phase-out sounds like an easy and obvious approach, it can be complicated and costly in particular in the healthcare industry where there are very high requirements to product stability and safety. Therefore, omission involves extensive testing and in many cases regulatory approval.

Omission can also involve a gradual change in the technology used to obtain a certain result, e.g. sterilisation or safe containment by physical means to replace preservatives.

Substitution

Substitution means that a substance is replaced by an equivalent without changing the product or process. Substitutions can be successful (product and process have afterwards more or less the same function or use) if other substances with a very similar function and/or structure are available. Because of the very similar function and/or structure, specific care needs to be taken to avoid regrettable substitutions [47, 48]. The "simple" substitution of one substance in a product or process is costly and very often just not possible or very complex. Furthermore, in highly regulated industries such as the healthcare sector, there is never such a thing like a simple substitution because there are high performance, quality and stability requirements, the fulfilment of which requires complex and lengthy testing as well as a subsequent regulatory approval.

This is why we see an important issue concerning substitution: when an existing product is reformulated to substitute a substance of concern, time and resources (financial and human) are used which could be better used to create a new product and process on a new technological level which would be to greater benefit to society. This could take longer and would require a transition period but offers greater advantage.

Termination of use

In this case, the use of the product or process is discontinued. Certain uses may be dangerous and/or have little benefit and must be discontinued. With increasing technological progress and ever higher requirements for product safety, these cases are becoming rarer and rarer. It can be assumed that in the product (IVD) and process (IVD and pharmaceuticals) portfolios of reputable companies of the healthcare sector hardly any product or process is outright unacceptably harmful and useless. If only because these products and processes have received regulatory approval of one kind or another.

End of life cycle

There are cases in which a substance that has recently been identified as substance of concern but was used in the past to produce durable high-quality devices that have a high utility value. It may be more economically and environmentally sustainable to operate these

high-quality installations, equipment or instruments until they need to be replaced, if this does not cause any harm to the user or the environment.

Change of technology

A substance is no longer used because, as a result of a disruptive innovation, products or processes are introduced that achieve better results using other natural phenomena and substances. A good example is the introduction of fluorescent markers which made radioactive markers and the corresponding detection devices needless. In terms of gain for the society, this way of phasing out substances of concern is the most beneficial one, although it might take more time and resources to be completed. In our opinion, the legislator should create boundary conditions which support this way of getting rid of substances of concern. In short, we think that the best way is the disruptive change of technology. We therefore believe that instead of pushing for substitution it is more productive to promote a faster technological development. One possibility to facilitate adoption of new sustainable technologies could be the preferred review processes by authorities for submissions fulfilling criteria like complete abandonment of certain substances of concern.

Phase-out of substances of concern in the broader context of product development

As we have been involved in various projects to phase out substances of concern we saw that significant resources in R&D are needed in any of the ways to eliminate substances of concern. This can be seen in a larger context, namely that the productivity of R&D, i.e. the ratio of output to invested resources, generally decreases over time [49]. Although of course scientific productivity is a complex issue, it is clear that greater complexity can lead to lower productivity. Sustainability and product safety considerations have become one of the elements of the observed increasing complexity. Whereby these requirements are also becoming increasingly complex in themselves: avoidance of harmful substances is competing with quite a number of other sustainability goals, such as the reduction of greenhouse gases, recyclability, minimisation of water consumption, product longevity, and defossilisation. These processes impact a larger number of final products.[13] As we described in the previous paragraph, it is very costly to improve a parameter in an existing product or process. When more than one parameter needs to be optimised, then the limits of the available human and financial resources are very quickly reached.

[13] For instance, avoiding SoC in consumer products is a precondition for material recycling. Recycling is often hampered by SoC.

In our view it is imperative, firstly, to train researchers and developers in sustainability issues from the outset and to involve sustainability and product safety experts in the development processes at a very early stage. Society and companies should always keep in mind that any technology is only ever a transitional technology; however, it still has to meet the latest sustainability requirements when it is created, so that it does not have to be replaced before its time.

How does the phase-out of substances of concern fit into the greater context of sustainable chemistry?

The phase-out of substances of concern is closely related to the principles of green chemistry as defined by the American Chemical Society (ACS) (developed by P. Anastas and J. Warner in 1998) [32]. Although in this complex matrix of 12 principles the substitution of substances of concern is a vector which is not necessarily parallel to the directions of the other principles (see Table 4) [50]. Practical experience with green-chemistry projects show that specific attention is needed to avoid regrettable substitution or that substances of concern enter new processes "through the back door".

The diversity of principles of green chemistry also shows that there are many other important goals of a chemicals policy that, in our view, currently focuses too strongly on substances of concern; in other words, it is too hazard-approach driven. We think that chemicals policy should be much more holistic. In particular, it should not only be strictly driven by chemical-hazard considerations, but should also include the energetic budget, aspects of circularity, atom economy, CO_2 goals, mass intensity and the need to defossilise chemistry. Sustainable industrial chemistry is only conceivable if sufficient low-cost and sustainably generated (electrical) energy is available [51]. A society that simultaneously wants to benefit from a prospering chemical–pharmaceutical industry and to minimise the harmful effects of it should use—in addition to chemical-regulatory means—economic policy control elements to generate abundant sustainable energy [52].

As we, the authors of the present paper, have been very much involved in the phase-out of substances of concern, we experienced that this goal is embedded in a complicated trade-off in the force field of several important sustainability needs, the vectors of which are not necessarily parallel. We find that the focus of some stakeholders, in particular from outside the industry, is too much focused on hazardous substances. Over the past two decades, groundbreaking successes have been achieved in the field of hazardous substances containment and control. Further progress means ever greater efforts with asymptotically decreasing benefits. We would welcome

Table 4 The relation of the phase-out of substances of concern with the 12 principles of green chemistry as defined by the ACS

Principle	Relevance for substances of concern phase-out
Prevention	No direct impact
Atom economy	Substitution can have an impact on the atom economy, as alternatives could result in longer and less efficient routes
Less hazardous chemical syntheses	As outlined in the introduction, categorisation of substances as SVHCs occurs due to their hazard properties (e.g. carcinogenicity, mutagenicity). Therefore, phasing out substances of concern is directly correlated with using less hazardous reagents. Some examples are chromium-mediated oxidations, which have been completely removed from modern pharmaceutical chemistry
Designing safer chemicals	No direct impact (design of safer drug substances in terms of their environmental degradability and toxicological profile is an important topic in modern medicinal chemistry but is only linked by way of structural motifs which need to be incorporated during their synthesis into substances of concern)
Safer solvents and auxiliaries	This in principle is directly related to the phase-out of substances of concern and at the same time a tremendous technical challenge, because key aprotic polar solvents have been identified by ECHA as SVHCs: DMAC, DMF, NMP, 2-methoxyethyl ether (DIGLYME) Toxicological safety is only one aspect. Alternatives to the solvents mentioned are often less stable and result in more dangerous (in the sense of physical safety) processes
Design for energy efficiency	No direct impact
Use of renewable feedstocks	No direct impact
Reduce derivatives	No direct impact
Catalysis	No direct impact
Design for degradation	Particularly in the area of surfactants, it may be possible to find good substitutes, as shown by the replacement of alkylphenol ethoxylates We are also aware that there is a broad choice of readily degradable chelators A special case is the replacement of inorganic process aids by readily biodegradable organic substances (ideally without heteroatoms). An example is the replacement of boric acid and borates as buffer substances
Real-time analysis for pollution prevention	No direct impact
Inherently safer chemistry for accident prevention	Process safety is of utmost importance in research, development and manufacturing. When introducing a less hazardous (in terms of toxicology or ecotoxicology) substance, the process safety might deteriorate

a de-ideologisation of the societal discussion on the premises of chemicals policy by all involved stakeholders inside and outside the industry.[14]

It is important that academic research in this area strives for closer connection with regulatory and commercial practice in order to provide more relevant contributions to chemical safety advances. For example, the number of substances in governmental inventories can hardly serve as a measure of the burden of chemical pollution on the earth, as presented in [53]. Especially since the authors do not take into account the marketing quantities of the substances, which can vary by more than nine orders of magnitude. In addition, many inventories contain to a large extent non-active entries (like many pre-registered substances of REACH) or substances with very small quantities, like in the C&L Inventory of ECHA. Other works show a very inadequate understanding of industrial innovation [54]. The number of synthetic materials considered in research, which are displayed in the various databases, can hardly be correlated in relation to the chemical load on planet Earth, but are primarily a measure of the knowledge gained by mankind. These novel chemical entities often exist only in minute quantities in substance libraries and have no impact on the Earth's ecosystem. This becomes understandable if one considers, for example, the relations in pharmaceutical research: to develop a drug, 5,000–20,000 compounds have to be considered in a selection process [55]. Only about five compounds in this process will ever be available in amounts above 1 kg and will be handled in very controlled conditions not presenting any risks to humans or the environment.

A society should also consider that the most ambitious chemical regulation will not benefit the planet unless the goods consumed in that community are actually produced under those rules, rather than production taking place under different, less strict conditions elsewhere.

[14] De-ideologisation means in this context that one strives not to assume dishonourable motives of the other side from the outset, to want to understand the legitimate interests and intentions of the other side, and to seek pragmatic solutions that take the interests of the different sides into account as best as possible.

What are the concepts discussed during the present overhaul of the European chemical policy and how do they relate to the phase-out of substances of concern?

While we are writing the present paper, a major overhaul of the European chemical legislation is being considered. In 2020, the CSS [12] was developed as part of the Green Deal [11]. The CSS has the overarching goal to achieve a toxic-free environment by 2050. While toxic-free sounds attractive, it has to be understood in the right way. It implies elimination of substances of very high concern as much as possible, minimising their use, and controlling emissions where elimination is not possible. The ultimate goal, the European Commission declared, is to drive innovation that will bring safe and sustainable-by-design substances and products onto the market. It is crucial to understand that not only elimination of SVHCs will bring the biggest benefit to society but also getting their use under control in order to avoid exposure to humans and the environment. Both elements (and further requirements as mentioned above) need to be considered in the development of policies. One critical aspect is designing policy and legislation that sets feasible goals for industries and keeps Europe an attractive region for production and innovation.

Revision of the REACH regulation and of its authorisation and restriction processes

Part of the CSS is the revision of the REACH legislation which has the main elements for regulating SVHCs. In this paper we mainly focus on the aspects of the CSS which have major influence on the phase-out of SVHCs. So far, the REACH restriction and authorisation are the main drivers for substitution and it has a high effect on the market [4]. For instance, ECHA has not received applications for almost half of the substances currently on the Authorisation List, which shows that firms seek to substitute SVHCs before their use becomes subject to authorisation [4]. In Sweden, firms have reduced their annual use of SVHCs requiring authorisation by about 40%, which suggests that the inclusion of a substance in the Authorisation List has a sizeable substitution effect [46]. However, these numbers need to be looked at in a broader context. The authorisation process is a very burdensome, cost- and labour-intensive process. In many cases this affects industries with a sectoral legislation[15] that have no choice than applying for an authorisation because of the long and complex regulatory validation and approval process of the sector legislation. In order to drive a phase-out in alignment with the development cycle of a product, applying for an authorisation is the only solution to avoid supply disruption.

[15] Means the legislative acts which lay down the rules for individual sectors, such as pharmaceutical or automotive industries.

By definition, an authorisation dossier includes a socio-economic part, a chemical safety report and an assessment of alternatives, and an authorisation is granted for a defined period of time. It is requested that the applicant uses this time for the substitution of the banned substances. Consequently, at the end of the review period, the substance is effectively phased out unless an application for extension is submitted. The restriction process, on the other hand, has the potential to restrict the use of certain applications or define an exposure threshold value for uses where the risks are adequately controlled. Certain restriction dossiers, e.g. restriction on microplastics, foresee a requirement for an annual reporting on the volumes released to the environment, for uses that are exempted.

Among the respondents of a survey carried out by ECHA, some stated that the substitution of hazardous chemicals in their activities is part of their sustainability policy. These companies claimed that they aim to phase out all substances identified as SVHCs [4].

Both processes, authorisation and restriction, have their advantages and disadvantages. A further development of this system should aim at eliminating the deficits of the present system while preventing a further proliferation of bureaucracy, securing productive jobs and promoting genuine innovation.

Grouping of substances and the introduction of further hazard classes

Further elements within the CSS, which play a major role in controlling SVHCs, are the grouping of substances and the introduction of further hazard classes. The aim of these regulating categories is to increase the amount of SVHCs and to increase the speed of elimination. While this aims to speed up the substitution of SVHCs, the resulting increase in substitution activites can in the short term reduce the capacity for new process and product development and thus hinder fundamental innovation.

Hazard-based versus risk-based approach

The terms "risk" and "hazard" have very specific meanings with respect to chemistry, although they seem similar. "Hazard" refers to a potential harm or danger, e.g. an inherent property of a chemical substance that makes it capable of causing harm to a person or the environment [56]. "Risk" refers to the possibility that harm or injury might occur when exposed to a hazard [56].

The question of whether hazard or risk should be the primary consideration has been at the centre of the discussion on regulatory measures to control substances of concern for the last 25 years. Industrial stakeholders traditionally preferred and advocated the risk-based

approach. This is also understandable from an industrial point of view because, depending on the state of technology, certain hazardous substances cannot be dispensed with, especially if the desired benefit of a substance is tightly connected with its hazardous properties. Most of the advanced chemical legislation in the world combines both hazard- and risk-based approaches. The creation of the category of SVHCs in the REACH regulation is clearly one of the most prominent embodiments of the hazard-based approach. The hazard-based approach has some advantages as it is a seemingly simple, unbureaucratic and fast regulatory tool. On the other hand, the use of the risk-based approach is time-consuming and labour-intensive, as it requires the collection of exposure data and the stipulation of adequate exposure control. The data required are diverse and potentially difficult to describe or to collect.

The voluntary phase-out programme of Roche described in this paper is dominantly hazard driven and sometimes reaches its limits when a hazardous property is intrinsically connected to the performance required. To address this issue and to add the necessary flexibility, we introduced the tool of exemption to the Roche phase-out programme.

Safe and sustainable-by-design chemicals

As part of the CSS, the task was set to develop safe and sustainable by design (SSbD) criteria for chemical substances [57]. The SSbD concept aims at a holistic approach that encompasses environmental and health protection as well as full life cycle and socio-economic analysis. We expressly welcome this approach, although we are aware that an optimum of all parameters is of course difficult to achieve simultaneously and that the practical result achieved will always be a compromise and subject to the discretion of the actors involved. This approach should be combined with primary innovation (change of technology) because to apply this very comprehensive methodology to substitution will make it even more time-consuming and lead to disproportionate costs. Which brings us back to our argument that the best policy and business strategy is one that promotes a shortening of innovation cycles and does not exhaust itself in laborious substitution and as a result a waste of resources. Of course, it is important that this innovation is then closely supported by the necessary experts who ensure that all aspects of the SSbD are taken into account as far as possible. A major challenge for the regulator will be to create powerful vectors for companies to fundamentally innovate their processes and products more quickly, taking SSbD into account, without leading to further over-regulation and bureaucracy. The challenge for businesses is that with the use of SSbD and the necessary increase in complexity, the length of the innovation cycle should not increase excessively, nor should the costs.

What are the challenges of the CSS for the healthcare sector?

The healthcare sector is heavily regulated. This brings the following challenges in the context of removing substances from the manufacturing processes of pharmaceuticals [58–60] and diagnostic products [61]:

- Complex development: R&D of a new pharmaceutical or IVD product takes time, followed by generating the evidence and guiding the product through the certification or approval process. Ten years of development for a new product is quite common.
- Design changes of existing products: Changing the design of already existing products does not vastly shorten the process. Any design change is subject to time-consuming feasibility testing, validation, documentation and approval phases, which would typically amount to at least five and up to twelve years per product.
- Desired characteristics of SVHCs: In many cases, a specific hazardous property of a substance is required for its efficacy in a diagnostic product. For example, when analysing human cell samples to identify a disease, reactive/hazardous chemicals are required to, e.g. stabilise the blood sample, get access to the DNA, inactivate a virus, generate a signal for detection, stabilise the reagent, etc. When moving from an SVHC to another substance the product still needs to deliver the required result, this should be sufficiently tested. Additionally it should not turn into a regrettable substitution.

In order to best fulfil our commitment both to patients and to the environment, we suggest a dedicated transition pathway for the healthcare sector. Changing existing product technologies to exclude newly identified SVHCs is highly challenging. It would mean having to redesign entire systems and associated products, followed by feasibility studies, validation, documentation and the regulatory approval process in the different countries. This occupies resources for several years trying to reform an old product portfolio and prevents us from coming up with true innovations. For existing product technologies, it would be very useful to implement a time-limited, transitionary exemption that allows for phasing them out gradually in line with development cycles of new product generations. It would need to be tied to conditions that prevent, as much as possible, the release of concerning substances to the environment, e.g. by implementing further risk

management measures and controlling release to the environment.

For new products and technologies, disruptive innovation should be considered, taking new concepts into account for avoidance of SVHCs. Working towards a more sustainable environment is our shared responsibility as a society. It is crucial to find pragmatic solutions to effectively protect our environment without leaving patients behind.

What are our suggestions based on the experiences obtained during our phase-out activities?

The EU's regulatory means in this area to date have indeed led to a reduction in the use of substances of concern in Europe but have hardly achieved their goals in terms of promoting innovation and competitiveness and improving the situation globally. The simplistic focus on substitution alone as a means of phasing out the use of substances of concern does not do justice to the complex objectives of chemicals policy. The best way to phase out substances of concern is to promote fundamental innovation leading to a truly new technology.

In our view, this requires a pact between legislators and industry. On the one hand, the legislator must set clear targets for phasing out substances of concern with a realistic (and not populist) timeframe. On the other hand, the companies concerned must make determined use of the timeframe set for them in such a scheme, i.e. start working on an alternative technology as early as possible. For this to happen, both sides must give up hardened ideological positions.

The promotion of new technologies such as the German National Hydrogen Strategy [62] can in principle be seen as a programme to phase out substances of particular concern, if at the same time researchers and developers are given targeted advice not only on the type of chemical substances used but also on how to consider the entire life cycle of the technology. We think that one of the biggest challenges for the current revision of the European chemicals legislation is to introduce elements of life cycle assessment and to maintain the risk-based approach while following the rules of good governance and without triggering further bureaucratisation and increasing the cost of the chemicals control system. Parts of the system, such as the National Competent Authorities involved in the implementation of the Biocides Regulation, are already overburdened with tasks and do not meet the deadlines they have set themselves. Presently, there are discussions in the European Union whether the REACH authorisation system should be changed and if so in which way. We see a certain value in keeping the system stable. On the one hand the present system seems to work in removing SVHCs from the European market, on the other hand it provides legal certainty for companies which have not yet found alternative substances or technologies.

Thus we see quite significant economic incentives within the REACH authorisation system to phase out substances of concern, such as avoiding costs of applying for an authorisation, maintaining business continuity, and using opportunities from a proactive approach to phase-out.

If an innovation-oriented phase-out is aimed at, the number of SVHC nominations cannot be increased at will. Legal certainty and plannability are of great importance for this approach.

Conclusion

F. Hoffmann-La Roche Ltd has set an ambitious goal with the phase-out of SVHCs in its whole portfolio. However, it must be noted that the authorisation requirement of EU's REACH regulation has been, until now, the most powerful driver for the SVHC phase-out in existing products and processes. It has, of course, also been the key driver and motivation behind our voluntary programme. Nevertheless, we see that the voluntary phase-out goal has and will give our internal chemical policy a special dynamic and help improve future products and processes within the Roche Group as R&D personnel's awareness of regulatory and public pressures has been significantly heightened.

After more than seven years of experience in purposeful SoC phase-out, we clearly see that in terms of holistic sustainability (ecological, economic and social) it would make sense if lawmakers would be willing to compromise on the speed of regulatory-enforced phase-out while still setting clear but less ambitious timelines. Phase-out is possible, except for some essential uses or lack of alternatives, but it is a challenging process for industry and in particular in the highly regulated sectors such as healthcare where R&D is facing a complex matrix of requirements, expectations and pressures. The regulatory pressure to get rid of substances of concern should be directed and dosed finely to promote meaningful, genuine innovation.

As far as we can judge it, the Roche goal has not brought any marketing advantage until now. For the time being, most customers are essentially only interested in having reliable diagnostics or safe drugs. The phasing out of SoC has not had any perceptible effect on sales, although there is a lot of talk about green procurement everywhere. We therefore do not see our efforts from the perspective of short-term competitive advantages, but rather as hopefully positioning ourselves more favourably against the competition in the medium-term future.

We also have to take note that very specific uses of SVHCs will not be avoidable within the framework of

today's technology. These include, for example, intermediates used in chemical syntheses of pharmaceuticals. It was therefore far-sighted of the legislator in the European Union to exempt intermediates from authorisation under REACH.

In general, we think that substitution is not necessarily the best way to get rid of substances of concern. This fact should be taken into account both terminologically (use another term instead of substitution) and in practical implementation (promoting also other ways of getting rid of SoC). An economically, ecologically and socially sensible phase-out should be aimed for, which is characterised on the one hand by realistic (not overly ambitious) deadlines set by the legislator (or—in the case of voluntary projects—by the management) and on the other hand by a timely (not wait-and-see) long-term planning, resolute approach in business.

Although it was not the primary intention of our study to provide recommendations for policy development, e.g. to the European legislature, as practitioners we would like to offer some ideas for further legislative development:

- Industry needs legal certainty with staggered regulatory timelines promoting innovation leading to more sustainable products where sustainability goes beyond the avoidance of hazardous chemicals.
- The ability of companies to adapt to a changing environment, which includes the regulatory framework, is limited and competes with their ability to innovate. A publicly desired increase in the "stroke rate" by increasing the number of substances to be declared undesirable within a certain period of time could hinder fundamental innovations instead of promoting them.
- When discussing and evaluating legislative proposals, both legislators and industry advocates should pay closer attention to whether they provide an impetus for fundamental societally beneficial innovation or contribute to unnecessary bureaucratisation. In doing so, lawmakers should be willing to compromise over speed, and industry should be willing to compromise over its insistence on a risk-based approach. The two sides of such a trade-off could be mutually reinforcing, resulting in long-term benefits to society.
- Regulatory bodies responsible for approvals in the healthcare sector (medicinal products and medical devices) could also contribute to the phase-out of SVHC if they installed a preferred (e.g. accelerated) review process for variations or other concessions for more sustainable (non-SVHC) manufacturing processes.
- In the greater context of sustainable chemistry as defined by the American Chemical Society, the phase-out of substances due to their hazard profile is only one parameter and other aspects like defossilisaton or the energetic budget must be given greater consideration.

These are the key learnings gathered during our programme to phase out SoC:

- It is important to launch awareness programmes and tools, such as general and substance-class-specific guidance, that support this goal.
- A phase-out programme in a large company needs a competence centre within the company to support the R&D staff when phasing out SoC or designing new products which should be safe and sustainable by design. This competence centre should include technology and chemical legislation specialists. One important task of this centre should be to funnel all the information from various lists into a digestible format for R&D.
- Primary (fundamental) innovation is the best way to eliminate SoC—in the sense of both higher competitiveness of a company and societal benefit, e.g. direct substitution with another substance is often not the best way of eliminating SoC. The socially and economically best way is fundamentally innovating the product or process.
- The R&D and marketing organisations should have robust channels of two-way communication to prioritise urgent SoC phase-out projects. In this way, R&D personnel should be sensitised to the "green" expectations of customers and society.
- It takes time to out-phase SoC in a process or product. This should be considered when setting deadlines. However, 10 years should usually be sufficient, even for challenging projects. But this time should be well planned and actively used to find solutions that should be part of innovation cycles.
- Particularly in the case of long innovation cycles and long-lived products, it is important when developing new products and processes not only to exclude undesirable substances that are already known, but also possibly to avoid substances that are the subject of discussion in the scientific community and the interested public. This can be achieved by including appropriate experts in the development teams and/or by providing suitable substance selection guides for the developers.

Supplementary Information

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Additional file 1: Table S1. Lists of substances (of concern) issued by states and international organisations. **Table S2.** Company initiatives to identify, list and track current and upcoming chemicals of concern. **Figure S1.** Molecular formulas of balovaptan, taselisib, ipatasertib and fenebrutinib

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References

1. Regulation (EC) No. 1907/2006 of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals. Available via EUR-LEX. https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32006R1907. Accessed 17 Jan 2022.
2. Candidate List of substances of very high concern for Authorisation. Available via ECHA. https://echa.europa.eu/candidate-list-table. Accessed 18 Nov 2021.
3. Regulation (EC) No. 1272/2008 of 16 December 2008 on Classification, Labelling, and Packaging of substances and mixtures. Available via EUR-LEX. https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32008R1272. Accessed 17 Jan 2022.
4. European Chemicals Agency (2021) Causal impacts of the REACH Authorisation process on the use of substances of very high concern in the EU. DOI: https://doi.org/10.2823/415727. Available via ECHA. https://echa.europa.eu/documents/10162/17231/causal_analysis_reach_authorisation_en.pdf/. Accessed 18 Nov 2021.
5. Authorisation List. Available via ECHA. https://echa.europa.eu/authorisation-list. Accessed 18 Nov 2021.
6. Substances restricted under REACH. Available via ECHA. https://echa.europa.eu/substances-restricted-under-reach. Accessed 17 Jan 2022.
7. The authorisation process. Available via ECHA. https://echa.europa.eu/authorisation-process. Accessed 27 Jan 2022.
8. Guidance for downstream users (2014). Available via ECHA. https://echa.europa.eu/documents/10162/2324906/du_en.pdf/9ac65ab5-e86c-405f-a44a-190ff4c36489. Accessed 18 Nov 2021.
9. Commission implementing regulation (EU) 2018/895 of 22 June 2018. Available via EUR-LEX. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0895&from=EN. Accessed 21 Feb 2022.
10. Entry 46a. ANNEX XVII TO REACH – Conditions of restriction. Available via ECHA. https://echa.europa.eu/documents/10162/7dcd73a4-e80d-47c5-ba0a-a5f4361bf4b1. Accessed 27 Jan 2022.
11. European Green Deal. Available via EC. https://ec.europa.eu/clima/eu-action/european-green-deal_en. Accessed 24 Jan 2022.
12. Chemicals Strategy for Sustainability. Available via ECHA. https://echa.europa.eu/en/hot-topics/chemicals-strategy-for-sustainability. Accessed 24 Jan 2022.
13. Sustainable products initiative. Available via EC. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12567-Sustainable-products-initiative_en. Accessed 20 May 2022.
14. Roche Annual Report 2020. Available via Roche. https://www.roche.com/investors/annualreport20.htm#pharma. Accessed 21 Feb 2022.
15. Chemicals Management Plan. Available via Government of Canada. https://www.canada.ca/en/health-canada/services/chemical-substances/chemicals-management-plan.html. Accessed 24 Nov 2021.
16. Phase-out list for chemicals hazardous to the environment and human health. Available via Stockholm County Council. https://www.regionstockholm.se/globalassets/6.-om-landstinget/hallbarhet/miljo/utfasningslista-kemikalier/phaseout_list_chemicals_web_eng.pdf. Accessed 24 Nov 2021.
17. Substitute It Now. Available via the International Chemical Secretariat. https://sinlist.chemsec.org/. Accessed 24 Nov 2021.
18. Trade Union Priority List. Available via European Trade Union Confederation. https://www.etuc.org/en/trade-union-priority-list. Accessed 24 Nov 2021.
19. Community Rolling Action Plan (CoRAP). Available via ECHA. https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table. Accessed 24 Nov 2021.
20. Analysis of the SIN LIST (2017). Available via ECHA. https://echa.europa.eu/documents/10162/19126370/sin-list_analysis_en.pdf/6248cac0-ffa8-5a14-ae55-93ace7ee9017. Accessed 24 Nov 2021.
21. Undesirable substances. Available via EC. https://ec.europa.eu/food/safety/animal-feed/undesirable-substances_en. Accessed 21 Feb 2022.
22. Lists of Undesirable Substances and Limited Uses of Feed Ingredients. https://apps.fas.usda.gov/newgainapi/api/report/downloadreportbyfilename?filename=Lists%20of%20Undesirable%20Substances%20and%20Limited%20Uses%20of%20Feed%20Ingredients_Rabat_Morocco_8-6-2018.pdf. Accessed 21 Feb 2022.
23. Maertens A, Golden E, Hartung T (2021) Avoiding regrettable substitutions: green toxicology for sustainable chemistry. ACS Sustain Chem Eng 9:7749–7758. https://doi.org/10.1021/acssuschemeng.0c09435
24. Trasande L (2017) Exploring regrettable substitution: replacements for bisphenol A. Lancet Planet Health 1(3):88–89. https://doi.org/10.1016/S2542-5196(17)30046-3
25. Substance Infocard of 4,4′-isopropylidenediphenol. Available via ECHA. https://echa.europa.eu/substance-information/-/substanceinfo/100.001.133. Accessed on 2 March 2022.
26. Substance Infocard of 4,4′-sulphonyldiphenol. Available via ECHA. https://echa.europa.eu/substance-information/-/substanceinfo/100.001.137. Accessed on 2 Mar 2022.
27. Substance Infocard of 4,4′-methylenediphenol. Available via ECHA. https://echa.europa.eu/substance-information/-/substanceinfo/100.009.691. Accessed 2 Mar 2022.
28. Blum A (2016) Tackling toxics. Science 351(6278):1117. https://doi.org/10.1126/science.aaf5468
29. Geyer R (2016) The industrial ecology of the automobile. In: Clift R, Druckman A (eds) Taking stock of industrial ecology. Springer, Cham (**10.1007/978-3-319-20571-7_18**)

30. Analysis of alternatives. Available via ECHA. https://echa.europa.eu/documents/10162/b97edaf7-7405-5992-63b9-42798b3c2e3e. Accessed 2 Mar 2022.
31. Zimmerman JB, Anastas PT (2015) Chemistry. Toward substitution with no regrets. Science 347(6227):1198–1199. https://doi.org/10.1126/science.aaa0812
32. Anastas PT, Warner JC (1998) Green chemistry, theory and practice. Oxford University Press, New York
33. Guidance on Key Considerations for the Identification and Selection of Safer Chemical Alternatives. Available via OECD website. https://www.oecd.org/chemicalsafety/risk-management/guidance-on-key-considerations-for-the-identification-and-selection-of-safer-chemical-alternatives.pdf. Accessed 20 May 2022.
34. Business Guide to Safer Chemicals. CW Research Ltd, Talbot House, Market Street, Shrewsbury SY1 1LG.
35. Lavoie ET, Heine LG, Holder H, Rossi MS, Lee RE, Connor EA, Vrabel MA, DiFiore DM, Davies CL (2010) Chemical alternatives assessment: enabling substitution to safer chemicals. Environ Sci Technol 44(24):9244–9249. https://doi.org/10.1021/es1015789
36. Byrkit GD, Michalek GA (1950) Hydrazine in organic chemistry. Ind Eng Chem 42(9):1862–1875. https://doi.org/10.1021/ie50489a046
37. Schnider P, Bissantz C, Bruns A, Dolente C, Goetschi E, Jakob-Roetne R, Künnecke B, Mueggler T, Muster W, Parrott N, Pinard E, Ratni H, Risterucci C, Rogers-Evans M, von Kienlin M, Grundschober C (2020) Discovery of balovaptan, a vasopressin 1a receptor antagonist for the treatment of autism spectrum disorder. J Med Chem 63(4):1511–1525. https://doi.org/10.1021/acs.jmedchem.9b01478
38. Isidro-Llobet A, Kenworthy MN, Mukherjee S, Kopach ME, Wegner K, Gallou F, Smith AG, Roschangar F (2019) Sustainability challenges in peptide synthesis and purification: from R&D to production. J Org Chem 84(8):4615–4628. https://doi.org/10.1021/acs.joc.8b03001
39. Clarke CJ, Tu W-C, Levers O, Bröhl A, Hallett JP (2018) Green and sustainable solvents in chemical processes. Chem Rev 118(2):747–800. https://doi.org/10.1021/acs.chemrev.7b00571
40. St-Jean F, Remarchuk T, Angelaud R, Carrera DE, Beaudry D, Malhotra S, McClory A, Kumar A, Ohlenbusch G, Schuster AM, Gosselin F (2019) Manufacture of the PI3K β-sparing inhibitor taselisib. Part 2: development of a highly efficient and regioselective late-stage process. Org Process Res Dev 23(5):783–793. https://doi.org/10.1021/acs.oprd.9b00050
41. Bachmann S, Iding H, Lautz C, Thomé-Pfeiffer I, Maierhofer C, Mondière R, Schmidt P, Strasser C, Bär T, Aebi A, Schuster A (2021) Development of the commercial manufacturing process for ipatasertib. Chimia 75:605. https://doi.org/10.2533/chimia.2021.605
42. Lebl R, Bachmann S, Tosatti P, Sedelmeier J, Püntener K, Williams JD, Oliver Kappe C (2021) Catalytic static mixer-enabled hydrogenation of a key fenebrutinib intermediate: real-time analysis for a stable and scalable process. Org Process Res Dev 25(8):1988–1995. https://doi.org/10.1021/acs.oprd.1c00258
43. Rolke A, Rath HK, Backmann J (2019) Digital tools and the right to know. ICRL 2(4):171–178. https://doi.org/10.21552/icrl/2019/4/8
44. Guidance on Material Declaration in the in vitro diagnostic medical device and medical device industry. Available via MedTech Europe. https://www.medtecheurope.org/resource-library/guidance-on-material-declaration-in-the-in-vitro-diagnostic-medical-device-and-medical-device-industry/. Accessed on 2 Mar 2022.
45. EFPIA EHSEG paper on material declaration. Available via EFPIA. https://www.efpia.eu/media/554871/efpia-ehseg-paper-on-material-declaration.pdf. Accessed 2 Mar 2022.
46. European Chemicals Agency (2020) Impacts of REACH restriction and authorisation on substitution in the EU. Available via ECHA. https://echa.europa.eu/documents/10162/24152346/impact_rest_auth_on_substitution_en.pdf/7c95222f-5f84-57f7-4cba-65b8463c79d4. Accessed 20 May 2022.
47. How to substitute? Available via ECHA. https://echa.europa.eu/know-your-substances-and-needs-substitution. Accessed 20 May 2022.
48. Substitution of hazardous substances. Available via Swedish Chemical Agency (KEMI). https://www.kemi.se/en/guidance-for-companies/substitution-of-hazardous-substances. Accessed 20 May 2022.
49. Oxford Economics, The state of scientific research productivity, November 2021; Christian Ehrensberger, Unternehmen—Wege in die Zukunft, Nachrichten aus der Chemie/70/March 2022, 31–33.
50. Tickner JA, Simon RV, Jacobs M, Pollard LD, van Gerben SK (2020) The nexus between alternatives assessment and green chemistry: supporting the development and adoption of safer chemicals. Green Chem Lett Rev 14(1):23–44. https://doi.org/10.1080/17518253.2020.1856427
51. Wollensack L, Budzinski K, Backmann J (2022) Defossilization of pharmaceutical manufacturing. Current Opinion in Green and Sustainable Chemistry 2022(33):100586
52. R. Geres, A. Kohn, S. Lenz, F. Ausfelder, A. M. Bazzanella, A. Möller. Roadmap Chemie 2050. Auf dem Weg zu einer treibhausgasneutralen chemischen Industrie in Deutschland. https://www.vci.de/vci/downloads-vci/publikation/2019-10-09-studie-roadmap-chemie-2050-treibhausgasneutralitaet.pdf. Accessed 2 Mar 2022.
53. Wang Z, Walker GW, Muir DCG, Nagatani-Yoshida K (2020) Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. Environ Sci Technol 54(5):2575–2584. https://doi.org/10.1021/acs.est.9b06379
54. Persson L, Carney Almroth BM, Collins CD, Cornell S, de Wit CA, Diamond ML, Fantke P, Hassellöv M, MacLeod M, Ryberg MW, Søgaard Jørgensen P, Villarrubia-Gómez P, Zhanyun Wang M, Hauschild Z (2022) Outside the safe operating space of the planetary boundary for novel entities. Environ Sci Technol 56(3):1510–1521. https://doi.org/10.1021/acs.est.1c04158
55. Innovation process. Available via Roche. https://www.roche.com/innovation/process/. Accessed 7 Jun 2022.
56. Understanding risk and hazard when it comes to chemicals. Available via ChemicalSafetyFacts.org. https://www.chemicalsafetyfacts.org/chemistry-context/understanding-risk/. Accessed 7 Jun 2022.
57. Publications Office of the European Union, Safe and Sustainable by Design chemicals and materials Review of safety and sustainability dimensions, aspects, methods, indicators, and tools. ISBN 978-92-76-47560-6 (online), 978-92-76-47609-2 (print). https://publications.jrc.ec.europa.eu/repository/handle/JRC127109. Accessed 20 May 2022.
58. J. W. Dailey. Drug regulation and approval. https://www.britannica.com/technology/pharmaceutical-industry/Drug-regulation-and-approval. Accessed 20 May 2022.
59. I. Hägglöf, Å. Holmgren (2013) Chapter 20 – Regulatory affairs. Pharmaceuticals regulation. Drug discovery and development (Second Edition), 285–301. https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pharmaceuticals-regulation. Accessed 20 May 2022.
60. R. I. Field (2008) Why is health care regulation so complex? P. T. 33, 10, 607–608. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2730786/pdf/ptj33_10p607.pdf/. Accessed 20 May 2022.
61. Questions and Answers on the progressive roll-out of the new in vitro diagnostic medical devices regulation. Available via EC. https://ec.europa.eu/commission/presscorner/detail/en/qanda_21_5210. Accessed 20 May 2022.
62. The National Hydrogen Strategy. Available bz Federal Ministry for Economic Affairs and Energy. https://www.bmwk.de/Redaktion/EN/Publikationen/Energie/the-national-hydrogen-strategy.pdf?__blob=publicationFile&v=6. Accessed 20 May 2022.

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