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**Forum**

# Towards a more effective REACH legislation in protecting human health

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## Abstract

There is growing evidence indicating the substantial contribution of man-made products to an increase in the risk of diseases of civilization. In this article, the Belgian Scientific Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Committee gives a critical view on the working of REACH. The current regulatory framework needs to further evolve taking into account data generated using modern science and technology. There is a need for improved assessment process not only before but also after entering the market. Objectivity, transparency, and the follow-up after market access can be optimized. Additionally, no guidance documents exist for regulation of mixture effects. Further, the lengthiness before regulatory action is a big concern. Decision-making often takes several years leading to uncertainties for both producers and end users. A first proposed improvement is the implementation of independent toxicity testing, to assure objectivity, transparency, and check and improve compliance. A "no data, no market" principle could prevent access of hazardous chemicals to the market. Additionally, the introduction of novel testing could improve information on endpoints such as endocrine disrupting abilities, neurotoxicity, and immunotoxicity. An adapted regulatory framework that integrates data from different sources and comparing the outputs with estimates of exposure is required. Fast toxicology battery testing and toxicokinetic testing could improve speed of decision-making. Hereby, several improvements have been proposed that could improve the current REACH legislation.

**Keywords:** REACH; ECHA; chemical testing; chemical regulation; chemical legislation; toxicology.

This article is an advice by the Belgian Scientific Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Committee (WCSR), which is a group of experts that offers advice on the dangers and risks of chemical substances to public health and the environment, in particular within the context of the implementation of REACH. This article presents the expert opinion of the committee on the current functioning of REACH, as well as why and how REACH could improve in the future.

## Why should the REACH procedure be improved

### "Diseases of civilization" have a high and often increasing incidence or prevalence

Availability of many food items, socioeconomic conditions, and the medical standard of care have improved markedly in Western countries, allowing a decreased impact of diseases on severe morbidity and mortality (Superior Health Council

Belgium, 2019). Even though a rise in life expectancy is seen, many diseases of civilization show increased incidence and prevalence after correction for ageing (Superior Health Council Belgium, 2019).

Globally, an increase in cancer incidence is observed (Sasco, 2008; Superior Health Council Belgium, 2019). Until recently (2004 for men, 2014 for women), in Flanders (region of Belgium), the incidence of cancer has risen as well (Superior Health Council Belgium, 2019). For men, a clear decrease is noted starting from 2008 (National Belgian Cancer Registry, 2023). Excluding non-melanoma skin cancer, cumulative cancer incidence in 2020 was 32.20% in men and 27.10% in women for ages 0–74 (National Belgian Cancer Registry, 2023; Superior Health Council Belgium, 2019). In the United Kingdom, between 1993 and 2015, an increase in incidence rates of all cancers combined was seen in all broad age groups for both men and women (Cancer Research UK, 2018; Superior Health Council Belgium, 2019). Cancer incidence increased by 24% in ages 0–24, by 20% in ages 25–49, by 13% in ages 50–59, by 15% in ages 60–69, by 11% in ages 70–79, and by 9% in ages 80+ (Cancer Research UK, 2018; Superior Health Council Belgium, 2019).

Increases have been shown in incidence and prevalence of cancer, cardiovascular disease, diabetes, metabolic syndrome, allergies, fertility problems, and obesity whereas the percentage of people free of chronic diseases that can be related to chemicals has, at least until recently, not risen (Aguilar *et al.*, 2015; Balakumar *et al.*, 2016; Comhaire *et al.*, 2007; Eder *et al.*, 2006; Ginter and Simko, 2012; Gorus *et al.*, 2004; Gupta *et al.*, 2007; Pawankar *et al.*, 2008; Sengupta *et al.*, 2017; Superior Health Council Belgium, 2019; The Lancet, 2018). Also, the prevalence of neurodegenerative diseases (Akushevich *et al.*, 2018; The Lancet, 2018) and neurodevelopmental disorders (Bellanger *et al.*, 2015) has increased during the past decades and whereas increases in cognitive capacities were noted over previous decades, there now are indications of them decreasing for more than a decade in some Western countries (Dutton and Lynn, 2013; Superior Health Council Belgium, 2019; Teasdale and Owen, 2005). However, encouraging is that during the last years, a decrease in the incidence of dementia has been observed in Denmark (Taudorf *et al.*, 2019) and also in the United States (Akushevich *et al.*, 2021).

### Substantial contribution of man-made products to the risk of "diseases of civilization"

Growing evidence from epidemiological and molecular-epidemiological studies, which also consider environmental contributions and differences in genetic background, indicates the substantial contribution of man-made products and pollutants to the risk of diseases of civilization (Superior Health Council Belgium, 2019). This has been substantiated for cancer, cardiovascular diseases, reproductive disorders such as early puberty, male and female infertility, diabetes, obesity, neurodegenerative diseases, neurodevelopment and cognition disorders, and immune system-related diseases (Bahna, 2023; Clatici *et al.*, 2018; Elliott, 2006; Emokpae and Brown, 2021; Kones and Rumana, 2017; Lee *et al.*, 2014; Popa-Wagner *et al.*, 2020; Superior Health Council Belgium, 2019; Turner *et al.*, 2020). According to Global Burden of Disease study (Benziger *et al.*, 2016; Cohen *et al.*, 2017; GBD 2015 Risk Factors Collaborators, 2016; Landrigan *et al.*, 2018), in 2015, pollution (all forms combined) were responsible for 26% of deaths due to ischemic heart disease, 23% of deaths due to stroke, 51% of deaths due to chronic obstructive pulmonary disease, 21% of all deaths from cardiovascular disease, and 43% of deaths due to lung cancer (GBD 2019 Stroke Collaborators, 2021; GBD 2019 Risk Factors Collaborators, 2020; Landrigan *et al.*, 2019; Takala *et al.*, 2024).

In contrast to U.S. EPA, who have published reports disclosing guidelines and methodology to perform weight of evidence approaches (eg, United States Environmental Protection Agency [USEPA], 2016), modern science and technology, and the use of "next-generation" weight-of-evidence assessment approaches, are not sufficiently embedded in the regulation of chemicals in Europe. Over the past decades, many new technologies and methods have become available that allow to collect data on different toxicological endpoints in a faster way by using less or even no animals. However, the current regulatory framework is not compatible with the use of data generated via these methodologies as it is focused on collecting data for specific endpoints, mainly via traditional (*in vivo*) testing and depending on tonnage level (European Commission, 2021). In order to better integrate these modern science and technologies, adapted regulatory frameworks are needed. Within this context, as suggested by Cronin *et al.* (2021) and Fentem *et al.* (2021), regulatory frameworks that integrate biological activity and kinetics from different sources and comparing the outputs with estimates of exposure could be of interest.

## How should the REACH procedure be improved

### Independent toxicity testing

In the current regulatory framework for REACH, the type and number of toxicological tests that needs to be performed is driven by the tonnage level (European Commission, 2021). Although the tonnage level is an indirect indication of exposure, the limitation of this approach is that it can lead to the generation of data that is not appropriate or insufficient to evaluate the hazards/risks most relevant for the proposed use. There are limitations on the number of toxicological tests performed on chemicals. Previous reviews of submitted registration dossiers showed insufficient characterization/description of the uncertainties associated with the hazard and risk assessments, and also issues with what data was chosen to report (Armstrong *et al.*, 2021). The EU Regulation (EC) No. 1907/2006 on REACH made the industry in charge of commissioning the tests to testing laboratories. However, due to conflicts of interest, this approach is highly susceptible to bias (Ingre-Khans *et al.*, 2019). There is a lack of control with third parties who only have limited access to the data and a lack of control by authorities with limited resources to check compliance to the REACH regulation (Ingre-Khans *et al.*, 2019).

Each decision a scientist makes throughout the testing process could influence the final result of the test (Armstrong *et al.*, 2021). Funding bias happens when scientists make choices to maximize the chance of an output that is wished for by the party funding the test or research (Richardson and Polyakova, 2012; van Dongen and Sikorski, 2021). Ideological and religious considerations and personal ambitions can be important factors leading to bias. In our societies, embracing economic growth, commercial, industrial, and financial interests are certainly important factors leading to bias, as for instance suggested by Hardell *et al.* (2007), Infante *et al.* (2018), and McHenry (2018). However, publication bias should not be underestimated, resulting in important bias on the scientific side as well (Howland, 2011; Sugita *et al.*, 1994). Several behind-the-scenes practices influence the final result, whereas they are hard to detect (van Dongen and Sikorski, 2021). However, precautions against such problems can be easily

checked in audits (van Dongen and Sikorski, 2021). An example of conflicts of interest has been described assessing the research of bisphenol A (BPA). Studies funded by industry did not report significant effects when assessing low doses of BPA while more than 90% of the research studies funded by governmental agencies did find significant effects for exposure to low doses of BPA (vom Saal and Hughes, 2005). These studies reflect the desired outcomes rather than representing robust scientific research. Within this context, a positive publication bias (ie, the bias that might occur due to the fact that authors are more likely to submit, or editors are more likely to accept, positive results than negative or inconclusive results), should on the other hand also be taken into account.

Currently, the industry only has to deliver a study summary, which must contain sufficient and accurate information on the complete study (Ingre-Khans *et al.*, 2019). Ingre-Khans *et al.* (2019) recently investigated study summaries and found several kinds of errors: from typing errors, to unclear and incomplete reporting, to omission of information that was considered relevant for the assessment of the chemical. The latter is highly concerning for the accuracy of these summaries, which are used for decision-making (Ingre-Khans *et al.*, 2019). As a result, the reliability and quality of the data that are delivered by the industry can be questioned. Therefore and to allow repeatability, we consider it desirable to make toxicological data publicly available in a transparent and unbiased manner. This was also previously suggested by Standard for Exchange of Nonclinical Data (Choudhary *et al.*, 2018). Many of the dossiers submitted to the European Chemicals Agency (ECHA) are non-compliant, with the majority lacking information needed to assess the risks and hazards (European Chemicals Agency, 2020, 2021; European Commission, 2018; Santos *et al.*, 2019). ECHA considers compliance a priority with a focus on long-term effects on human health and on the environment and aims to improve compliance and quality of dossiers in a gradual and planned way (European Chemicals Agency, 2020, 2021; European Commission, 2018; Santos *et al.*, 2019). To improve transparency of data, a potential solution could be to make full study reports available or to allow independent assessment of the data. Also for the risk assessment, all available data should be accessible. However, the majority of the data received from those studies is considered confidential (Ingre-Khans *et al.*, 2019).

To minimize bias and to avoid conflict of interest, it is worthwhile to consider performing the testing and registering of the chemicals by an independent third party (Ingre-Khans *et al.*, 2019). This could help to ensure that studies are performed in a qualitative way with adherence to good laboratory practices (GLP) and include tests that are able to detect low dose effects (Armstrong *et al.*, 2021). GLP criteria are not necessarily sufficient to guarantee results that are really relevant to public health, as was shown for BPA (Myers *et al.*, 2009). Quality of a study should always be considered in its entirety, including GLP, but also experimental setup, conceptualization, … In the case of BPA, FDA and EFSA considered 2 industry-funded GLP studies as superior to hundreds of other studies, whereas later, the 2 GLP studies were determined to have both conceptual and methodological shortcomings (Myers *et al.*, 2009). As mentioned above, GLP compliance is not the only necessity to come to relevant results. The most sensitive experimental approaches available, consistent with the most advanced mechanistic insights should be used. The independent laboratories would have to be subject to more audits to confirm conformity to GLP and to check the quality of their data. Ideally, the laboratories performing the testing should closely collaborate with REACH regulators to identify needs for testing and to perform checking of data. It is noteworthy to mention that currently limited organizations would have the facilities to be able to perform tests in accordance to these requirements. Therefore, at the moment, implementation of this proposal could result in an increase in time to complete these tests.

## Follow-up of substances after putting on the market

Currently, under REACH, substances are only tested for certain endpoints, depending on tonnage manufactured or imported per year (European Commission, 2021). Once allowed on the market, no mechanism is in place to monitor how the risks associated with these substances evolve. Registrants are required to keep their registrations up to date, however, in 55% of the audited companies, systematic approaches to update the registrations were absent and 18% had registration dossiers that had not undergone an obligatory update (European Chemicals Agency, 2021). Further, there is no follow-up on epidemiological, long-term effects of these substances after being put on the market. Scheepers and Godderis (2019) described the importance of post-market evaluation mechanisms that are still lacking in REACH. A molecular-epidemiological approach, in which classical epidemiological data are supplemented by data concerning biological parameters such as genotoxicological, endocrinological, and epigenetic data and data concerning gene expression, could be more sensitive than classical epidemiology (Vineis and Perera, 2007) and is essential in the post-market evaluation. Substances are also mainly evaluated for their intended use separately, whereas new applications for products can arise over time (Scheepers and Godderis, 2019). These new applications of the substances go hand in hand with exposure to new unidentified populations and by new exposure routes, which were not considered at the pre-market assessment (Scheepers and Godderis, 2019). Despite the obligation in REACH to update the chemical safety report when a new, noncovered use arises, it is clear that the update is not always done. This causes uncertainties about the long-term effects of substances on human health and the environment. Like ECHA mentioned in its report on the operation of REACH and CLP (European Chemicals Agency, 2021), REACH only demands restricted information regarding environmental risks. However, between 2016 and 2020, an acceleration was seen in the restriction of substances with risks to the environment and since 2020, persistent organic pollutants are integrated in the portfolio of ECHA (European Chemicals Agency, 2020, 2021).

REACH also includes the regulation of mixture effects, but no guidance documents for their assessment exist, whereas various stakeholders have highlighted their importance (Galert and Hassold, 2021). The absence of information on mixture effects pressures the testing strategy for chemicals (Schoeters, 2010). It has been shown that certain mixtures show more toxicity than the active ingredient, whereas REACH requirements only focus on pure chemicals (Scheepers and Godderis, 2019; Schoeters, 2010). Compared with the United States, the European Union does not have a regulatory framework for assessment of mixture effects (Sarigiannis and Hansen, 2012). Although international guidelines are limited to effects on human health, the European Commission together with the relevant scientific and industrial public would go for guidelines concerning both human health and the environment (Sarigiannis and Hansen, 2012). The European Commission also stated the need for the industry to develop exposure scenarios for mixtures (European Commission, 2021). Martin *et al.* (2021) showed that risk assessments for

mixtures of chemicals in published mixture studies usually can be predicted using the addition concept, however, the potential synergistic or antagonistic action of chemicals should be considered.

Synergism has been observed epidemiologically in the causation of cancer (Kvåle *et al.*, 1986; Pastorino *et al.*, 1984) and has been proven in animal experiments (Kaldor and L'Abbé, 1990; Warshawsky *et al.*, 1993). In particular, agents with different points of action may exhibit a multiplicative effect, rather than additive effect (Kaldor and L'Abbé, 1990). More recently, it has been shown through mechanistic *in vitro* studies that ligands of a receptor and ligands of a partner receptor can act synergistically to activate receptor heterodimers (Germain *et al.*, 2002). Synergistic activation was shown on the Pregnane X Receptor (PXR) where pharmaceutical estrogen (contraceptive 17α-ethinylestradiol [EE2]) and persistent organochlorine pesticide (trans-nonachlor [TNC]) separately exhibit low efficacy, but cooperatively lead to synergism (Delfosse *et al.*, 2015; Superior Health Council Belgium, 2019). It was shown biophysically and in cell-based analyses that EE2 and TNC enhance each other's binding affinity with 100-fold increased avidity compared with each ligand on its own. Therefore, at doses at which TNC and EE2 individually are inactive, a substantial biological response can be induced (Balaguer *et al.*, 2017; Superior Health Council Belgium, 2019). Several *in vitro* cell culture systems permit the assessment of synergistic interactions between different chemicals, including synergistic interactions between cadmium and microplastics on liver fibrosis (Sun *et al.*, 2023), between organic and inorganic pollutants on adipogenesis (Bérubé *et al.*, 2023), triclocarban and triclosan and high fat diet on lipid accumulation in liver cells (Li *et al.*, 2023), between chlorpyrifos and its metabolite 3,5,6-trichloro—2-pyridinol on the paracrine function of Sertoli cells (Gao *et al.*, 2021), and between particulate matter (PM2.5) and sulfur dioxide on neurodegeneration (Ku *et al.*, 2017).

## Increase amount and types of testing

By now, it is evident that classical toxicological tests do not provide sufficient protection against adverse health effects. More sophisticated tests, designed to detect low dose effects (Vandenberg *et al.*, 2012; Vandenberg and Pelch, 2022), mixture and synergistic effects (see above), epigenetic effects (Neven *et al.*, 2018), and ligand-specific effects (Guyot *et al.*, 2013) are needed. Also, the more recent discovery of the existence of ligand-specific effects of exogenous substances binding to nuclear receptors is of concern. It can be expected that differences can occur between binding of chemical to receptors with transcription factor functions compared with binding of hormones and other physiological ligands. However, these effects are more difficult to predict and therefore, might lead to adverse health effects (Superior Health Council Belgium, 2019).

REACH requires certain tests based on what tonnage level the chemical is manufactured/imported in with more extensive testing for chemicals that are manufactured/imported in a higher tonnage level (European Commission, 2021). Although this approach has proven reasonable for marketed substances, it might lead to issues with new substances of lower tonnages that can require market access with less comprehensive testing (European Commission, 2021). Testing of chemicals currently takes a long time, whereas many substances are not yet properly tested with data lacking on their hazards or risks. Moreover, there are indications that certain chemicals can exert nonmonotonic effects, and thus can lead to more effects when exposed to low doses than in higher doses (Park *et al.*, 2021). Required testing to gain market access does not directly address endpoints regarding endocrine disrupting abilities, neurotoxicity or immunotoxicity, which can be important consequences of exposure. Due to long latency periods, most toxicity tests and thus also the required testing under REACH is not predictive for long-term effects of exposure to chemicals. Thereby, there is a lack of studies and investigation into and many uncertainties about toxicological endpoints.

Risk assessment and containment are important concepts in preventing diseases. A proper risk assessment can only be made when all information is available on hazardous properties of the chemical substance taking into account the current state-of-the-art in toxicology. However, due to the limitations in the current testing requirements under REACH and the lack of continuous surveillance and updating, not all available toxicological information on substances is considered. Further, the available information that is required comes mostly from only *in vitro*, or when obliged, *in vivo* experiments, whereas the animals differ physiologically from humans. However, despite the fact that human data are key, they are often missing due to the difficulty of collecting and obtaining this information certainly in the early phase of an application (Palmen *et al.*, 2018). In order to obtain more insights in the toxicological profile of chemicals and to integrate modern science and technologies, we would need an adapted regulatory framework.

Fentem *et al.* (2021) stated that if the obligated testing remains based on tonnage levels, protection from the chemical substances to environment and consumers would fail and registrants would have to generate large volumes of data. Therefore, defining several surrogates for chemical exposure other than tonnage levels is important in the further improvement of protection from chemicals (Fentem *et al.*, 2021).

In 2010, it was already noted that REACH requirements are strictly endpoint-related and that endpoints such as obesity, respiratory toxicity, neurodevelopment, and neurodegeneration are not investigated, with highly relevant and incident diseases such as metabolic syndrome, endocrine and reproductive disorders, neuropsychiatric disease, and pulmonary diseases as potential consequences (Schoeters, 2010). ECHA suggests that this may be the result of the generous use of read-across data (Santos *et al.*, 2019). Since 2019, authorities have been using a grouping approach for similar substances where possible, to increase efficiency and effectiveness of regulatory action (European Chemicals Agency, 2021). Based on structural similarity, substances can exhibit similar physicochemical, toxicological, and ecotoxicological effects and therefore can be considered as members of a group. Within these groups, data regarding health endpoints can be predicted by the data of another member of the group, also known as read-across data (Armstrong *et al.*, 2021). In 2018, the European Commission also suggested to use a grouping approach next to improving the noncompliance present in the registration files (European Commission, 2018).

The strictly defined endpoints allow for an easy evaluation of compliance, but bring doubts whether those tests can be used to predict all health hazards those chemicals give rise to (Schoeters, 2010). ECHA recognizes the relevance of endpoints that are currently not included in column 1 of the information requirements such as immunotoxicity (European Chemicals Agency, 2017a). Tests on endpoints such as developmental neurotoxicity and immunotoxicity should be performed in REACH when available data have shown concern for these endpoints (European Chemicals Agency, 2021). However, subjectivity hits in on how the concern should be established (European Chemicals Agency,

2021). Substances that receive a mutagenic or carcinogenic classification are scarce, which is reflective of the focus within REACH, but the conditions to include testing for mutagenicity and carcinogenicity could be reviewed (European Chemicals Agency, 2021). The past 8 years none of the endocrine-disrupting chemicals (EDC) that were discussed by the EDC Expert Group resulted in restriction or inclusion in the Authorization list (European Environmental Bureau, 2022).

Although Article 25 of REACH states that testing on vertebrate animals only should be undertaken as a last resort and recital 37 states that it should be approached by using other alternative testing strategies whenever possible, ECHA has rejected read-across or nonanimal tests proposed by industry when they were not considered to fulfill the standard information requirements (for instance when the read-across justification by industry was lacking or insufficient). In 2018, the European Court of Justice ruled against ECHA, after it had demanded a developmental toxicity study in animals to Esso Raffinage to eliminate data gaps, whereas Esso Raffinage stated to be able to demonstrate safety with information from other sources (Fentem *et al.*, 2021). This leads to the perception that there is a lack of willingness of ECHA to consider alternative testing strategies, however, ECHA is concerned about the robustness of the alternative approaches to replace standard animal tests (European Chemicals Agency [ECHA], 2017b; Taylor, 2018). Several studies have also been performed on *in silico* profiling, *in vitro* profiling, toxicokinetic modelling, and read-across methods in order to promote their use to their full potential as a transparent and consistent methodology (Berggren *et al.*, 2015; Hasselgren *et al.*, 2019; Pizzo *et al.*, 2016). ECHA published a document describing the read-across assessment framework (European Chemicals Agency, 2017a), and launched a Quantitative Structure-Activity Relationship Toolbox, allowing to extract each other's results (European Chemicals Agency, 2020). According to some researchers, this document does seem to be very demanding to make an acceptable read-across (Taylor, 2018). Due to the adaptation of the requirements for safety information for REACH in 2016, an increase in alternative testing strategies is seen, with more adaptations such as read-across and a more widely use of *in vitro* testing (European Chemicals Agency, 2020). However, in 2018, it was noted that *in vitro* tests were only used at a low level as complete replacements, whereas much effort was put into their validation (Taylor, 2018). For example, between 2008 and 2016, for only 11% for the skin irritation, and 7% for eye irritation only *in vitro* results were submitted (European Chemicals Agency [ECHA], 2017b; Taylor, 2018). There are also delays regarding updating the Test Method Regulation (TMR) (EC) No. 440/2008, which should be updated when ECHA regards a method "appropriate," suggesting like Taylor (Taylor, 2018) mentioned an overly cautious approach of ECHA to consider them as complete replacements.

An important point of criticism on REACH is the need for more chemical control before entry to the market is allowed, especially on long-term effects to human health and the environment (European Chemicals Agency, 2018, 2021; Sachana *et al.*, 2019). A no data, no market principle is proposed and acknowledged by ECHA by a more extensive completeness check since July 2016 (European Chemicals Agency, 2021; European Environmental Bureau, 2022; Santos *et al.*, 2019).

## Need for faster decision-making under the current REACH process

Another point of criticism on REACH is the lengthiness before regulatory action is taken and the low output of substance evaluations (European Chemicals Agency, 2018; Santos *et al.*, 2019). This results in the piling up of substances that need regulatory action and meanwhile consumers and workers stay exposed. Due to the large amounts of substances to be tested and the slow process of doing so under REACH, very little action is taken up until now. Until 2018, only 94 substances had completed the substance evaluation (Santos *et al.*, 2019). Only a quarter of the chemicals identified with a very high concern, have been added to the Authorization list, with half of the uses of such chemicals still allowed awaiting a decision by ECHA (European Environmental Bureau, 2022). Therefore, there is need for more ambitious goals to ensure a safer environment and health. This includes more stringent obligations for industry to provide information and to proof the absence of risks before the substance can be allowed on the market.

When risks emerge for a substance, the authorities have to decide whether the chemical can remain on the market with restrictions for the uses that resulted in risks or should be banned from the market (Scheepers and Godderis, 2019). The report of Late Lessons From Early Warnings of the European Environment Agency concludes there is a lack of mechanisms to respond to early warning signals, with the recommendation to reduce the delay between early warning and taken actions (Palmen *et al.*, 2018). One of the reasons for the slow evaluation process is also the lack of environmental and human data and proposals have been made to set in place (inter)national expert groups with a centralized expert group at EU level to ensure collaboration to evaluate new and emerging risks (Palmen *et al.*, 2018; Santos *et al.*, 2019). With chemical substances evaluated based on priority, some substances will not get evaluated, and thus remain on the market without restrictions (Armstrong *et al.*, 2021). In 13 years, only 27 substances were restricted by REACH (European Environmental Bureau, 2022).

In a nonpaper, the European Environmental Bureau wrote that in the best case scenario, it takes 3 and a half years for identification and classification of a hazardous substance (European Environmental Bureau, 2022). When legal timeframes are respected and depending on the duration of additional testing, a substance evaluation is completed after 7–9 years, which in many cases finds even more postponement throughout the process (Santos *et al.*, 2019). For example, triphenyl phosphate was flagged with concerns about endocrine effects. The evaluation in the Community rolling action plan was postponed 4 years in a row. After 7–9 years to clarify a suspected concern, the implementation of regulatory actions may take 5–7 years, leading to 12–16 years before chemicals of concern are regulated (Santos *et al.*, 2019). However, listing substances of very high concern in the candidate list only takes 6 months (European Environmental Bureau, 2022). Compliance checks of the safety data can take more than 5 years (European Environmental Bureau, 2022).

## Remediation of shortcomings

For the classification of chemicals (no restriction, restriction, ban), no discrimination is made between hazards to human health or to the environment. To guarantee objectivity and completeness of test results, testing should ideally be performed by independent laboratories. However, as mentioned above, currently few facilities have capacity to perform tests according to the requirements. In order to ensure that studies are performed in a qualitative way with adherence to GLP, these independent laboratories would have to be subject to more audits. Ideally, financing of the tests should run via a test fund that is managed by REACH policy-makers and fed by the industry. However,

implementing this fund would pose several challenges at the level of managing it and require additional improvements/expansions of the current laboratory testing facilities.

Once a chemical has been allowed to be put on the market, there should be a follow-up for example by an independent organization. In case substances of concern have been identified, there is a need for epidemiological studies but also a molecular-epidemiological approach should be followed in addition to epidemiology. Indeed, the molecular-epidemiological approach is much more sensitive than classical epidemiology, and can lead to the detection of effects at a point in time where no irreversible health damage has occurred, permitting preventive measures and constant follow-up. Santos *et al.* (2019) showed that for many chemicals for which concerns were demonstrated, regulatory action to confine the risks remains absent. According to the European Commission (2018), improvement is needed with the notification of substances of very high concern in articles, initiatives like digital products passports could help in this regard. Several articles propose mechanisms as pharmacovigilance and the "disease first" method as "early warning systems" as post-market surveillance systems (Palmen *et al.*, 2018; Scheepers and Godderis, 2019). In addition, when potential risks are shown, prospective studies could be set up to be able to monitor those potential effects and risks. However, another promising manner of follow-up are sentinel approaches, where environmental vigilance, similar to pharmacovigilance, results in quicker actions. This envirovigilance could be described as the science and activities relating to the occupational and environmental agent relating problems. The sentinel approach requires well-trained health care professionals that ask and report certain data during a certain period regarding certain potential environmental or occupational issues. By the faster reporting of cases, that then can be confirmed much quicker, this approach could speed up the process until regulatory action. In the PROBE study (Pauwels *et al.*, 2020), it has been shown that chemical occupational exposures can be mapped using a sentinel approach. Currently, this approach is being further developed within EIRENE project (EIRENE, 2022; EU Cordis EIRENE, 2022), implemented in the European surveillance network in the Partnership for the Assessment of Risks from Chemicals (EU Cordis PARC, 2022; PARC, 2022), and extended in the international context within BIONET, a European African partnership (BIONET, 2023; Erasmus+ BIONET, 2023). By the quicker identification of warning signals, actions can be taken faster. Important is the awareness of health professionals to the potential risks that chemicals might have even with the regulations in place (Palmen *et al.*, 2018). Due to the probable rareness of these diseases and their long latency times, Palmen *et al.* (2018) suggest the need for international surveillance systems. These forms of secondary prevention have the potential to prevent new cases in an early phase and to fill knowledge gaps (Palmen *et al.*, 2018).

In order to faster obtain more insights in the toxicological profiles of a larger number of chemicals while at the same time relying less on animals, adapted regulatory frameworks are needed. As highlighted by Cronin *et al.* (2021), such frameworks should integrate data on biological activity and kinetics from different sources and compare the outputs with estimates of exposure. To increase the speed and scope of testing, we propose to include fast battery testing as well as toxicokinetic testing. Further, alternative methods should be considered such as new *in silico* and *in vitro* testing methods to expand the knowledge of the chemical substances before they enter the market. We also think it is necessary to include testing with endpoints such as endocrine disrupting features, neurotoxicity, immunotoxicity, and others as obligation under REACH to cover these effects before market access. It would be in everyone's interest to make all testing data publicly available. In the ECHA strategic plan 2019–2023 final, they describe their desire to have robust data about all chemicals in Europe and to have all registrations dossiers updated with appropriate and complete data about hazards of substances (European Chemicals Agency, 2018). In 2022, the European Environmental Bureau published a nonpaper in which they again stated the need for this kind of policy, suggesting it has not been implemented yet (European Environmental Bureau, 2022).

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