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Methods for early identification of **new and emerging risks of chemicals** (risk-first-approach)

RIVM letter report 2025-0133
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Colophon

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Synopsis

Methods for early identification of new and emerging risks of chemicals (risk-first-approach)

Every year, an estimated 3,000 people in the Netherlands die as a result of exposure to hazardous substances at work, despite all the laws and regulations designed to prevent work-related illnesses. One explanation is that there is insufficient information about a hazardous substance or the type of work that can cause illness, resulting in the link to work often being recognised only after someone has fallen ill (disease-first-approach).

A better approach is to identify hazardous substances or work before people fall ill (risk-first-approach). To that end, the RIVM has compiled an overview of methods for predicting whether a hazardous substance or type of work can cause an occupational disease. The overview shows that each method has a different purpose. The amount of work and the information required also differ per method.

The RIVM will further develop the risk-first-approach using two of these methods. One method focuses on prediction (Lexces AI tool), while the other compiles information from various sources (RIVM tool for identifying endocrine disruptors). Both methods use large databases containing information about the chemicals and their uses.

In the future, elements from other methods may be incorporated to further develop risk-first methods.

Keywords: new risks, hazardous chemicals, worker, working conditions, risk-first, disease-first, method

Publiekssamenvatting

Methoden om nieuwe en opkomende risico's van chemicaliën eerder te signaleren (risk-first-benadering)

Elk jaar sterven naar schatting 3000 mensen in Nederland doordat zij op hun werk blootstaan aan gevaarlijke stoffen. Dit gebeurt ondanks alle wet- en regelgeving om te voorkomen dat mensen ziek worden door hun werk. Een verklaring is dat er niet genoeg informatie is over een gevaarlijke stof, of over het soort werk waar mensen ziek van kunnen worden. Daardoor kan er vaak pas een verband met werk worden gelegd nadat iemand ziek is geworden (disease-first-benadering).

Het is dan ook beter om gevaarlijke stoffen of werk te herkennen vóórdat mensen ziek worden (risk-first-benadering). Het RIVM heeft daarom een overzicht gemaakt van methoden die kunnen voorspellen of een gevaarlijke stof of type werk een beroepsziekte kan veroorzaken. Het overzicht laat zien dat elke methode een ander doel heeft. Ook verschilt per methode de hoeveelheid werk en welke informatie nodig is.

Met twee van deze methoden gaat het RIVM de risk-first-benadering verder uitwerken. De ene methode is gericht op voorspellen (Lexces AI-tool), terwijl de andere informatie uit verschillende bronnen bij elkaar brengt (RIVM-tool om hormoonverstorende stoffen te herkennen). Beide methoden gebruiken grote databases met informatie over de stoffen en hoe ze gebruikt worden.

In de toekomst kunnen onderdelen van andere methoden worden gebruikt om de risk-first-methoden verder te ontwikkelen.

Kernwoorden: nieuwe risico’s, gevaarlijke stoffen, werker, arbeidsomstandigheden, risk-first, disease-first, methode

Contents

Summary

Exposure to hazardous chemicals leads to 3,000 deaths among workers every year, despite all (inter)national regulations that try to prevent illness and death from hazardous chemicals. Early detection of new and emerging risks is a way to discover and prevent illness from chemical exposure at work. Vigilant occupational health professionals sometimes discover previously unknown health effects from exposure to hazardous chemicals by observing a link between illness and exposure to a substance or a specific type of work. This is considered a disease-first-approach for early detection of new and emerging risks. However, it is important to identify health risks from chemical exposure before people fall ill; i.e. a risk-first-approach for early detection. This requires predicting which substances and exposures could potentially pose a health risk, based on known information about chemicals and exposure. Currently, there is no overview of methods for early detection that follow a risk-first-approach. This report provides an overview of (inter)national risk-first-methods and evaluates which risk-first-methods are suitable for further development of the identification of potential New and Emerging Risks of Chemicals (NERCs).

Risk-first-methods for early detection of risks have been developed or are under development at several research institutes and regulatory agencies (e.g., European Food Safety Authority (EFSA), European Chemicals Agency (ECHA), European Agency for Safety and Health at Work (EU-OSHA), Organization for Economic Co-operation and Development (OECD), the European Commission, United States Environment Protection Agency (US-EPA), and RIVM. Furthermore, some risk-first-methods have been developed within the framework of collaborations and partnerships, for example within Partnership for the assessment of Risks for Chemicals (PARC), the Dutch national expertise centre for substance-related occupational diseases(Lexces), and Mistra SafeChem. Additionally, a few other methods were identified that can serve as risk-first-methods, including the TICHNER process and several other in silico methods for early detection of chemical toxicity.

The identified risk-first-methods were assessed on a number of criteria to indicate their useability for optimalization of the risk-first approach. The most promising would be high-throughput methods using large databases and combining hazard and exposure data. No single method meets all criteria, and all methods require some expert judgment for prioritization and follow-up.

Two risk-first-methods were selected for further development:
- Lexces in silico prediction tools;
- RIVM Endocrine Disruptor toolbox.

Both methods were chosen because they are high-throughput methods using large databases, they incorporate both hazard and exposure information and they are readily available. In addition to meeting these evaluated criteria, they align with expertise and existing project workflows that are currently present within the Lexces program. The

methods each have a different perspective, with one focusing on prediction, whereas the other brings together information from various sources. Additional elements from other methods may be integrated in the future to further enhance these methods for risk-first screening for work-related diseases.

1 Introduction

Each year, nearly 3000 workers die as a consequence of working with hazardous chemicals at work in the Netherlands (Nederlandse Arbeidsinspectie, 2025). Despite existing laws and regulations in place to limit the risks of hazardous chemicals at work, new risks continue to emerge (Palmen et al., 2013; Palmen and Verbist, 2015). Unknown effects of existing chemicals are regularly discovered, which can lead to new, as yet unknown health risks. It may also be the case that known effects of chemicals are known in one sector but not yet in another, causing people to fall ill there. We have seen this in the past with the sandblasting of jeans in Turkey, where people in the clothing industry developed silicosis, a disease that has long been known in the mining and construction industries. We speak of emerging risks when the number of people exposed to a substance suddenly increases, causing the number of people who fall ill to rise. In order to identify these new and emerging risks of chemicals (NERCs), it is considered increasingly important to have an early warning and action system.
A work-related disease (WRD) can arise as a result of the above situations summarised by EU-OSHA (2009):

1. possible health effects resulting from unknown hazard properties,
2. a known hazard but a different type of exposure or use, or
3. a substantial increase in an "at risk" population (more people are exposed to the hazardous substance).

The current Dutch system for signalling of NERCs includes WRD caused by one or multiple of these scenarios (Palmen, 2016). A signal of potential NERCs can arise from indications found in toxicological studies, case reports, epidemiological research and reviews, or detailed data analyses.

In general, knowledge about the harmful effects and exposures of chemicals at the workplace still contains gaps. This is at least partly due to the fact that the risk assessment of most chemicals is based on oral toxicity tests. Workers, however, are mainly exposed to chemicals via the airways (inhalation) or the skin. In addition, other yet not identified health effects might be overlooked, or exposure information may be lacking and/or underestimated. The result is that it is difficult to make a valid risk assessment (Palmen et al, 2018). Early detection of NERCs can identify substances and/or work for which a risk assessment is required. Namely, unknown health effects and/or exposures may necessitate (the update of) a risk assessment.

The identification of NERCs is also considered important within legislation and regulations. On December 9 2023, the European Commission adopted a legislative proposal to ensure early detection and action on emerging chemical risks (European Commission, 2023; article 19). Prevention plays also a major role in the research programme of the Dutch national expertise centre for substance-related occupational diseases (Lexces). The timely identification of substances and activities that pose an increased risk of occupational diseases can prevent people from falling ill as a result of their work. This research contributes to that

goal. Early detection of chemical-related WRD and signalling of new hazards and risks that may lead to new or more prevalent WRD is one of the core tasks of Lexces.

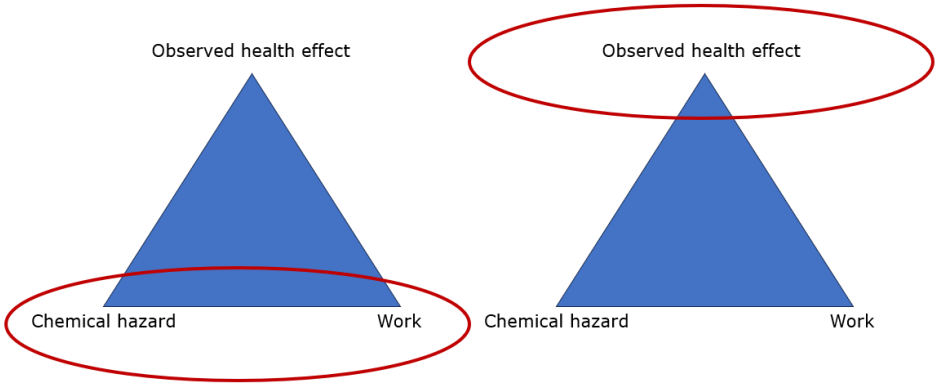
1.1 Risk-first- and disease-first-approach

Early detection of NERCs can be approached in two ways (Palmen et al., 2018):

- Risk-first-approach; NERCs are detected by recognizing the potential hazard of a chemical or its potential exposure.
- Disease-first-approach; NERCs are detected by observing health effects or diseases linked to a specific workplace exposure and/or chemical.

Work-related diseases can be identified using information about the observed health effect and exposure. Exposure may consist of information about the type of work, but may also include specific information about the chemical hazard. To identify a work-related disease, information about all three is needed: the observed health effect, the (type of use at) work, and the chemical hazard.

Figure 1 Left figure: risk-first-approach: signals are detected by identifying potential chemical hazards or work exposures. Right figure: disease-first-approach: signals are detected by observing adverse health effects in workers.



The **risk-first-approach** identifies signals on 'chemicals with an increased risk of health effects' and 'work of concern' based on potential risk/impact predictions. It looks for (causal) relationships between chemicals and hazards to identify chemicals of concern, after which a link with certain types of work can be made. In other words: the risk-first-approach identifies potential hazardous properties of chemicals, after which this can be linked to (types of) work where these chemicals are used. The approach can also be applied to early identify work where certain types of exposure are observed, after which this can be linked to certain chemical hazards. Figure 1a visualizes the approach. The red circle indicates that the chemical hazard and the type of work can both be starting points for the risk-first-approach to identify new and emerging risks.

The **disease-first-approach** is based on the identification of adverse health effects in an individual or population and investigates a potential causal relationship between observed health effects and exposure to

chemicals at the workplace. The health effects are expected to mainly arise from known chemical exposures occurring in new work settings or potential new associations between chemical exposure and observed health effects. In Figure 1b, the starting point of the disease-first-approach is the observed health effect, represented by the red circle.

The scope of these two approaches may differ, depending on the innovation phase of chemicals, materials, or process development.The development of a chemical or material from start to finish is divided into four phases (chemical-material-process developmental phases):

- First phase: Early innovation phase in which the chemical/material is not even technically ready and produced on a small scale in a laboratory (comparable to Technology Readiness Level (TRL) 1,2 and 3)
- Second phase: Innovation phase in which the chemical/material is becoming technically ready and put on the market as a pilot; production is being scaled up (comparable to TRL 4 - 8)
- Third phase: Early market phase; pioneering is successful and hypes are possibly leading to increased use of the chemical/material (comparable to TRL 9)
- Fourth phase: Established and late market phase; the chemical/material is being produced and used.

In principle, NERCs can be detected in all four stages of development using both the risk-first- and disease-first-approaches.

Using a *risk-first*-approach, signals on potential chemical and work related hazards can be retrieved from chemicals or materials that are mainly in innovation phase 1, 2 or 3, by using data on potential hazardous properties and (potential) exposure or use.

A *disease-first*-approach is primarily applied if the chemical is already in production and being used, i.e. phase 3 or 4. However, workers can also develop health problems as a result of exposure to the chemical during the other developmental phases.

1.2 Types of methods to identify NERCs

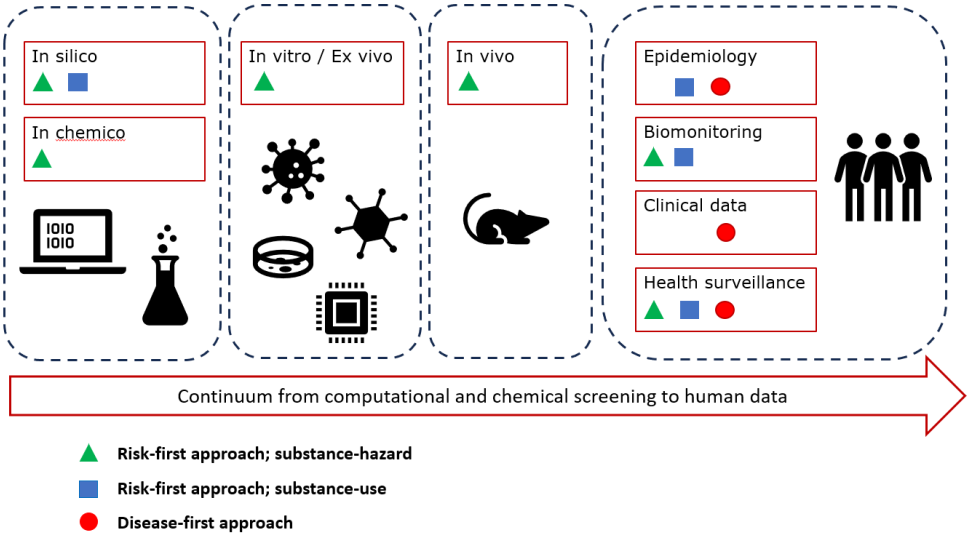
There are several types of methods that can be used to identify NERCs. Figure 2 presents an overview of these types for the risk-first-approach. For comparison, types of methods that can be used for the disease-first-approach are also included in the figure.

In the disease-first-approach workers have already fallen ill due to work. For this approach, only human information is used from clinical data, epidemiology and health surveillance to identify NERCs (indicated with a red dot in Figure 2).

In the risk-first-approach workers have not (yet) fallen ill. A combination of both human and animal data can be used to identify potential hazardous chemicals or potential uses, applications or sectors where exposure to hazardous chemicals may be expected. This may be data about the relation between a chemical and a (potential) hazardous property (indicated with a green triangle), or data about the relation

between the type of work and a (potentially) hazardous chemical (indicated with a blue square). The information on the relation between a chemical and hazardous properties can be based on *in silico-*, *in chemico-*, *in vitro, ex vivo* data, *in vivo*, and health surveillance or biomonitoring data. The information on the relation between work and hazardous chemicals can be based on *in silico* data, health surveillance, biomonitoring or epidemiological data to indicate exposure to certain chemicals.
The application and integration of these methods is supported by information available from (public) databases and supplementary data sources, like ECHA registration dossiers or safety data sheets.

Figure 2 Overview of types of methods that may be used for the identification of NERCs. Disease-first-methods are indicated with a red dot. Risk-first-methods may identify relationships between potential hazardous chemicals and effects (indicated with a green triangle) or relationships between potential uses/applications/sectors and effects (indicated with a blue square).



1.3 Current methods for signaling of NERCs

At the moment, several disease-first-methods are used within the EU for detection of possible work-related NERCs. For an overview of these methods see the report 'Methodologies to identify work-related diseases: Review of sentinel and alert approaches'(EC, 2017). Until 2024, Dutch and Belgian occupational physicians were able to report a possible new work-related health risk at the online contact point SIGNAAL. SIGNAAL was developed by the Dutch Centre of Occupational Diseases (NCvB) in collaboration with KU Leuven (Belgium), and is based on the principle of post marketing surveillance for pharmaceuticals (Van der Laan et al., 2009). Potential signals were collected in the SIGNAAL database. These signals were stored in the New and Emerging Risks DataBase (NERDB), which is a database set up by RIVM in collaboration with NCvB. However, only few new signals were submitted to SIGNAAL, and signals were often provided by occupational physicians without exposure information from the workplace. For this reason, the system of reporting through SIGNAAL is currently being updated.

In addition to reports by occupational physicians, RIVM actively searches for potential signals of WRD from the national and international literature. These signals are also stored in the NERDB.

Potential worker-related NERCs from these disease-first-signals in the NERDB are discussed within the Dutch-Belgian expert group New and Emerging Risks of Chemicals (NERCs) on a regular basis. This group consists of occupational physicians, clinicians, toxicologists, occupational hygienists and others. Potential signals of NERCs are also communicated within MODERNET; an international network of professionals that study new risks of WRD and share knowledge with each other, with the aim of introducing measures to reduce the risk (MODERNET, 2025).
Besides discussing signals among experts, all potential signals in NERDB are added to the RIVM-NERCs database. This database contains NERCs related to workers, consumers and the environment. In the latter database, signals are prioritized and possible regulatory actions are inventoried by RIVM.

The above-mentioned methods for signal identification for workers suffer from several difficulties:

1. the number of reported potential signals in SIGNAAL is small. This is partly due to lack of vigilance among occupational health and safety professionals, problems with the SIGNAAL platform in terms of usability, and the lack of capacity and means to follow up reported signals. Identifying health effects as a result of exposure to hazardous chemicals is difficult as many occupational physicians lack specific knowledge about the role of hazardous substances in development of adverse health effects ;
2. another problem in signalling WRD and NERCs is the lack of communication between the Dutch health care sector and occupational health services concerning possible connections between health effects and the work environment;
3. in the Netherlands, there is no incentive for insurers to investigate the underlying cause of an illness and its possible relationship with work. Several European countries do have such incentives, where new cases are reported and processed in a database potentially leading to more registered cases (Palmen et al., 2013);
4. another, more practical aspect that hampers identification of NERCs, is that the currently used process of manually searching literature is complex and time consuming, and would benefit from improvement.

1.4 Project aim

Lexces is the center of expertise for substance-related occupational diseases. In this network organization, various organizations work together to gather and further develop knowledge and expertise in the field of hazardous substances and health risks for workers, and to promote the dissemination of this knowledge. In this way, Lexces actively contributes to the prevention and assessment of substance-related occupational diseases.

As part of the Lexces research program, project 2.2 aims to make an inventory of available risk-first- and disease-first-methods for early identification of NERCs, optimize these methods and integrate them into an improved framework for signal identification of WRD.

The current report will focus on the inventory of risk-first-methods. The disease-first-method (SIGNAAL) and an outlook for a system to integrate these methods will be described separately.

The research questions addressed in this report are:

1) Which risk-first-methods exist or are being developed for early detection of new and emerging risks of chemicals?
2) Which risk-first-methods are suitable for further development to improve signal identification in the Dutch system?

1.5 Document outline

The methods to answer the above questions are described in Chapter 2. In chapter 3 a non-exhaustive overview of specific existing risk-first-methods for the identification of NERCs is presented. These methods, or collections of methods, are categorized based on the type of organization that has developed the method(s). Lastly, the identified methods are evaluated based on several criteria, to be able to determine their usefulness for signal identification (Chapter 4). The results are discussed in Chapter 5, which includes a conclusion on the most promising risk-first-methods for further development for the identification of potential NERCs for WRD.

2 Methods

To the best of our knowledge, the term 'risk-first' is not a widely used term. Methods that may be used in a risk-first-approach are not usually described as such. The methods are therefore not easy to recognize to be used for this purpose, and are difficult to search for in literature. There are different types of screening methods that could contribute to a risk-based approach.

To answer the first research question, a search for risk-first-methods was performed through a literature search. This included a grey literature search using Google Scholar with keywords: "method*, new emerging risks of chemical*, worker*". Furthermore, websites of international agencies and research institutes were searched for information on risk-first-methodologies.

In addition to the literature search, experts in the field of hazardous chemicals were interviewed, and input from colleagues about existing risk-first-methods was collected during a presentation for colleagues working for the competent authority of REACh in the Netherlands and during a presentation at the MODERNET conference in Prague in 2024.

To be able to determine how the resulting risk-first screening methods can be used to improve signal identification (research question 2), the methods were qualitatively evaluated based on several criteria, including availability, application, labour intensiveness, low or high throughput, and presence of information about hazard and exposure. To this end, the methods were numbered and assessed color coded based on 6 questions:

- Is the method available or is it yet to be developed?
  - Green: method is publicly available
  - Orange: method is under development or can only be used for prioritization of NERCs
  - Red: method is only conceptual
- Has the method already been applied in practice, specifically to workers?
  - Green: method has been applied to workers
  - Orange: method has been applied but not to workers
  - Red: method has not been applied
- Is the method labor intensive? This is determined by the amount of expert assessment needed.
  - Green: no expert assessment needed
  - Orange: method depends partly on expert assessment
  - Red: Method depends only on expert assessment
- Is it a high throughput method?
  - Green: input possible from large databases;
  - Orange: input possible from several sources (e.g. data sources / data collections/ expert consultations)
  - Red: input is single chemical(group) or scenario
- Does the method take into account hazard information?
  - Green: yes
  - Red: no

- Does the method take into account exposure information?
  - Green: yes
  - Red: no

3 Identified risk-first-methods

In practice, several types of methods are usually combined to form a system in which emerging risks can be signalled during all innovation phases (see Chapter 1). Therefore, risk-first- and disease-first-approaches often overlap. This chapter gives a non-exhaustive overview of methods or collections of methods that are used or may be used for a risk-first-approach for NERC identification.

3.1 Research institutes and regulatory agencies

3.1.1 European Food Safety Authority (EFSA)

EFSA has an active method for identification of emerging risks for food and feed safety. This collection of methods combines risk-first- and disease-first-methods, to be able to (i) carry out activities to identify emerging risks; and (ii) develop and improve emerging risk identification methodologies and approaches and iii) communicate on identified issues and risks.

The EFSA method relies on three fundamental steps, namely 1) preliminary identification of priority emerging issues, 2) identification of appropriate data sources and data collection, 3) final evaluation and identification of emerging risks. Priority emerging issues should be identified preferably through expert consultations and *via* exchange of information with qualified organizations (EFSA, 2012a). Various EFSA projects have been conducted for the identification of emerging chemical issues/risks. A wide range of methodologies and tools are used, including risk-first-methods like text and data mining, drivers' analysis, foresight and chemical analysis (suspect screening, non-target analysis) (EFSA, 2024).

In 2010, the Emerging Risks Exchange Network was established to exchange information with EU Member states on possible emerging risks for food and feed safety. The role of this network is to provide a platform for scientific cooperation in the area of emerging risk identification between risk assessors of the EU member states and EFSA and to enhance risk assessment practices in the area of emerging risk identification methodologies (EFSA, 2020). The Emerging Risks Exchange Network and the EFSA Stakeholder Discussion Group on Emerging Risks, have identified several emerging chemical issues/risks (EFSA, 2024).

According to EFSA, emerging risk identification requires a high level of expertise due to major data gaps and uncertainties in the evaluation process. Effective networking has proven to be essential for exchanging methods, data and evaluations of emerging risks (EFSA, 2012b)

3.1.2 European Chemicals Agency (ECHA)

The ECHA CHEM database contains a lot of information about the toxicity and potential exposure of chemicals. This information can be used for research purposes like hazard and risk assessment and prioritization. Research with REACH data is mostly done by ECHA and

ECHA stakeholders and partners, like OECD (paragraph 3.1.4), JRC (paragraph 3.1.5.1) or individual member states. In its Strategy 2024-2028, ECHA has detailed its goals and priorities over the next five years to protect human health and the environment. In this context, ECHA has mapped its key areas of regulatory challenge, translating them into ECHA's needs for further scientific research, under the umbrella of the Partnership for the Assessment of Risks from Chemicals (PARC) (see paragraph 3.2.1) (ECHA, 2024). However, ECHA itself has no active method to identify NERCs.

3.1.3 European Agency for Safety and Health at Work (EU-OSHA)

The European Agency for Safety and Health at Work published a European Risk Observatory Report on emerging chemical risks (EU-OSHA, 2009). The Community strategy on health and safety at work for 2002-2006 called on the Agency to 'set up a risk observatory' and to 'anticipate new and emerging risks' in order to tackle the continuously changing world of work and the new risks and challenges it brings. The Community strategy for 2007-2012 reinforced the European Risk Observatory's (ERO) role and explicitly mentioned the identification of new risks and dangerous chemicals as a research priority. The ERO provides an overview of safety and health at work in Europe, describes the trends and underlying factors, and anticipates changes in work and their likely impact on occupational safety and health. The sources to identify new and emerging risks may cover data from official registers, the research literature, expert forecasts or survey data (e.g. questionnaires sent to (emerging) industries) (Palmen et al, 2013).

Expert forecasts are performed using the Delphi method, in order to reach a broad consensus and to avoid non-scientifically founded opinions. The Delphi method is a labour intensive methodology used widely to create foresight information on topics for which only uncertain or incomplete knowledge is available. There are several variations of the Delphi method, but all of them are based on an iteration process with at least two survey rounds in which the results of the previous rounds are fed back and submitted again to the experts for new evaluation. ERO has described a detailed method for this method when dealing with emerging chemical risks related to occupational safety and health (EU-OSHA, 2009).

The Delphi method was applied to a Foresight of New and Emerging Risks for New Technologies in Green Jobs by 2020. This foresight was performed using a scenario-building approach, resulting in a set of scenarios and their possible impact on workers' health and safety (EU-OSHA, 2011).

3.1.4 Organization for Economic Co-operation and Development (OECD)

In recent years, several activities regarding early detection have been initiated under the auspices of the OECD. The following methods can be used as risk-first-method for early detection of NERCs.

3.1.4.1 OECD (Q)SAR Toolbox

OECD has developed a (Quantitative) Structure-Activity Relationships [(Q)SARs] toolbox to increase regulatory acceptance of (Q)SAR methods (OECD, 2025a). (Q)SARs are methods for estimating properties of a

chemical from its molecular structure. The Toolbox is a free software application, intended to the use of governments, chemical industry and other stakeholders in filling gaps in (eco)toxicity data needed for assessing the hazards of chemicals. It has been developed in close collaboration with the European Chemicals Agency (ECHA). The Toolbox incorporates information and tools from various sources into a logical workflow. The seminal features of the Toolbox are:

1. Identification of relevant structural characteristics and potential mechanism or mode of action of a target chemical.
2. Identification of other chemicals that have the same structural characteristics and/or mechanism or mode of action (read-across).
3. Use of existing experimental data to fill the data gap(s).

3.1.4.2 Early awareness and action system for advanced materials (Early4Adma)

Early4AdMa is a proactive and preventative method that aims to identify and describe potential safety, sustainability and regulatory issues of advanced materials early in their development or use. This tiered method was initially developed by RIVM, BfR, BAuA and UBA (Oomen et al, 2022) and was further developed by the OECD Working Party on Manufactured Nanomaterials in 2023. The Early4AdMa method starts with selection of a certain advanced materials, and a simple screening assessment based on the NESSI score (Novelty, Exposure, Severity, Scope, Immediacy). This is followed by considerations on safety for human health and the environment, the applicability of existing regulations, and sustainability aspects.

Early4Adma is a method that is applied to facilitate regulatory preparedness related to novel or advanced materials. In the context of an OECD project, possible regulatory, sustainability, health and environmental issues of 2D titanium carbide MXenes have been investigated using this method during an expert workshop (OECD, 2025b)

3.1.5 European Commission

3.1.5.1 Joint Research Centre (JRC)

Two publications have been released under the auspices of the European Commission's JRC that describe possible risk-first-methods for the identification of NERCs. Berggren and Worth (2023) propose a method that is centered on a classification matrix in which New Approach Methodologies (NAMs) for toxicodynamics and toxicokinetics are used to classify chemicals according to their level of concern. In a complementary paper, Worth and Berggren (2024) propose three levels of information requirements (basic, common and specific) necessary for classification of chemicals:

- Basic information requirements, applicable to any chemical, would be based on existing toxicity data and computational modeling. High throughput data can be generated here for the purpose of Early Warning;
- Common information requirements, applicable to all chemicals registered/authorized under REACH, would be based on information in the REACH database and other data from legislative frameworks. The aim is to identify chemicals of high

concern so that risk assessment can be performed and measures can be taken if needed;
- Specific information requirements, applicable to chemicals with specific uses, would be based on information requested in specific legislation (e.g. medicines, cosmetics). It aims at identifying chemicals with low concern, for the purpose of safe use.

Worth and Berggren also propose a safety net through post-marketing surveillance (e.g. biomonitoring) to identify new risks. Chemicals that are common and that are a concern can be provided with an alert (Early Warning System Alert).

3.1.5.2 Science for Environment Policy (SfEP)

An overview of general methods to identify emerging environmental risks was published in a Future Brief by the European Commission initiative Science for Environmental Policy (SfEP, 2016). Five tools and methods were presented for identification of early warning signals:

- Foresight methods; the two most commonly used tools for this purpose are horizon scanning and scenario planning;
- Technology; it can strengthen the scientific basis for Early warning signals, by collecting the data used in foresight methods;
- Citizen science; this means community-based monitoring;
- Online media monitoring; this method for early warning is widely used in the health sector, where it is also referred to as 'tele-epidemiology', a novel form of epidemiology. MediSys is an internet monitoring and analysis system that scans information from the *European Media Monitor (EMM)*, software that gathers reports from worldwide news portals, in 60 different languages, to rapidly identify potential threats to public health (MediSys, 2025);
- Rate change theories; it is based on critical slowing down (CSD's) which measures how quickly a situation recovers to the status quo ante following a small perturbation.

3.1.6 U.S. Environmental Protection Agency

3.1.6.1 US-EPA ToxCast

The US EPA Toxicity Forecaster (ToxCast) program provides accessible bioactivity data for toxicology. In vitro medium- and high-throughput screening assay data, covering different biological targets, are publicly available for thousands of chemicals, which may be used for risk assessment. The assay data comes from several different sources, like internal and external research laboratories. The data is stored in a database, where it is computationally processed into a singular resource that supports chemical evaluations. The most recent ToxCast data is available in the online (US-EPA, 2025).

3.1.6.2 US-EPA ExpoCast

Just as Quantitative Structure-Activity Relationships (QSARs) have aided in high-throughput screening of *in vivo* potency for large libraries of molecules by correlating molecular activity with its structure and physicochemical properties, quantitative structure–use relationship (QSURs) should elucidate which features and properties of a chemical give rise to its function and identify chemicals with similar properties and features that could also fulfill that role (Philips et al. 2017).

EPA's ExpoCast program is developing complementary high throughput methods for characterizing the human and ecological *exposures*. These exposure characterizations are necessary to interpret high throughput hazard data (e.g. from the ToxCast program) in a real world risk context. These New Approach Methodologies (NAMs) for exposure include computational and analytical tools for characterizing multiple components of the complex pathways chemicals take from their source to human and ecological receptors. The ExpoCast team has defined a set of NAMs for exposure science, covering high-throughput data, modeling, and measurement methods suitable for addressing the thousands of chemicals in commerce having limited chemical exposure information (Wambaugh et al. 2019).The landscape of traditional and exposure NAM data was examined covering chemical use, emission, environmental fate, toxicokinetics, and ultimately external and internal exposure. It was demonstrated that exposure NAMs drastically improve the coverage of the chemical landscape compared to traditional methods (Isaacs et al. 2022).

3.1.7 National Institute for Public Health and the Environment (RIVM)

RIVM is actively involved in several initiatives for early detection of NERCs, such as projects including KIR-nano, and initiatives under the Dutch national expertise centre for substance-related occupational diseases (Lexces; paragraph 3.2.2). Several additional risk-first-methods are outlined in the following sections.

3.1.7.1 RIVM ED toolbox

There is a concern on the safety of cosmetic ingredients and their endocrine-disrupting (ED) potential. Therefore, RIVM has developed a toolbox to screen lists of compounds to identify and prioritize possible endocrine disrupting chemicals (EDCs) (Bouwmeester et al., 2025). This toolbox was developed to crosscheck available online lists of compounds with information on potential ED properties derived from open-source initiatives (i.e. chemical lists from the European Chemicals Agency, national authorities, and non-governmental organizations). Based on the available information on ED properties in these databases compounds are categorized in the toolbox into three groups:

- Concern for ED
- Indication for ED properties
- No concern for ED properties

Compounds that were present on at least one of the lists were manually evaluated regarding ED concern based on the available information in the databases. The chemicals that were not on the lists, currently do not have an established ED concern in the EU. Together with chemicals that were present on one of the lists for other non-ED concerns, these continued the workflow and were further prioritized based on an aggregate exposure score. For compounds with high potential exposure via cosmetics, a literature search was performed. Based on the available literature the compounds were divided in two additional groups: Limited indication or no/insufficient information for EDC properties.

This final prioritization step of uncategorized compounds could be adjusted depending on the input list of compounds or ingredients. This could be based on expected exposure to or use of a specific product

depending on available information. Additionally, in the near future, the toolbox needs to be expanded to provide more information on the potential ED properties of the compounds, for example by the inclusion of ED related QSARs. RIVM and Leiden University (LACDR) are currently working on the improvement and development of ED in silico models (SPR Pinpoint, 2023-2026).

3.1.7.2 Dutch Chemicals of Very High Concern (ZZS) Similarity tool
The ZZS Similarity Tool compares the chemical structure of a chemical with the structure of chemicals on the Dutch list of Chemicals of Very High Concern (In Dutch: Zeer Zorgwekkende Stoffen, ZZS) (RIVM, 2021). This tool can be used for chemicals for which little is known about potential properties of concern. A similarity in structure to a ZZS may indicate similar hazardous properties. The results of the ZZS Similarity Tool provide a prediction of potential ZZS-properties. Absence of structural similarity to a ZZS does not necessarily mean that there is no ZZS-concern. Conversely, similarity to a ZZS does not necessarily mean that a chemical is ZZS. It is a trigger to further evaluate a chemical.

3.1.7.3 KIR-nano
The RIVM Risks of Nanotechnology Knowledge and Information Centre (KIR-nano) identifies developments and scientific insights about advanced (nano)materials and their potential risks to human health and the environment. Within this initiative, one of the focus points is occupational health risks. Signals of emerging risks are identified and shared publicly. Furthermore, research is conducted to enhance risk assessment of advanced (nano)materials, for example the Early4AdMa method (paragraph 3.1.4.2).

3.1.7.4 New Approach Methodologies (NAMs) and risk assessment
NAMs are potential alternatives to animal testing, including (a combination of) *in vitro*, *in chemico* and *in silico* methods. The use of NAMs in risk assessment have for example been investigated for Botanical Tabernanthe iboga and for hormone containing dermal creams, two data-poor chemicals (De Wit et al, 2024). The cardiotoxic effect of Botanical Tabernanthe iboga and dermal absorption capacity of hormone containing creams were assessed using NAMs. NAMs were considered mostly useful for hazard identification and, to a limited extent, hazard characterization (i.e., derivation of a hazardous dose) *in vitro.* They may play a role as supporting evidence to substantiate human data on health effects caused by hazardous chemicals.

3.2 Methods developed by (inter)national collaborations and partnerships

3.2.1 Partnership for the assessment of Risks for Chemicals (PARC)
PARC is a partnership of a.o. universities, public health organisations, research institutions, national health authorities and health care institutes from 29 countries. The goal is to develop next-generation chemical risk assessment, in order to protect both human health and the environment. In the context of the European Union’s Chemicals Strategy for Sustainability (CSS) announced by the European Commission, an early warning and action system will be set up in PARC task 8.2. An

identification framework will be developed to identify new hazardous chemicals, their sources and transformation products. Therefore, a wide range of methodologies will be applied to prioritize new toxic drivers, delivered through toxicological assessment in PARC, including NAMs. The task involves development and validation of (a) early warning monitoring tools in humans, environment and products combining exposure and hazard data, (b) effect-directed tools based on bioassays using new approach methodologies (NAMs) taking stock of the relevant JRC work, (c) suspect and non-target screening tools, (d) effect-directed analysis (EDA), (e) metabolomics based biomarkers, and (f) machine learning for pattern recognition of potential vectors that would need further scrutiny from big and complex data sources, including system modelling (PARC, 2024; Marx-Stoelting et al, 2023).

3.2.2 National expertise centre for chemical-related occupational diseases (Lexces)

The Dutch Lexces is an expertise centre for prevention and assessment of chemical related occupational diseases. It comprises a collaboration between five Dutch knowledge institutes, that perform scientific research aiming at primary, secondary and tertiary prevention of chemical-related occupational diseases. Some risk-first-methods are developed under the auspices of Lexces.

3.2.2.1 AI chemical prediction models

In the context of Lexces, a project is carried out on the topic of "Hazard and Use Predictions of Chemicals with Artificial Intelligence".

Within this project an *in silico* AI-based screening model is under development by RIVM (Van de Burgwal et al. 2026), which can be used to identify:

- Potential hazardous properties of chemicals. This provides information on potential chemical concerns.
- Potential uses and applications of chemicals. This can provide information on potential sectors of use, processes/activities or products in which chemicals are used.

For both models, predictions are based on molecular fingerprints, structure properties, physico-chemical properties or predictions from other in silico models, like quantitative structure-activity relationship (QSAR) models and quantitative structure-use relationship (QSUR) predictions.

The combination of these models may be used to identify and prioritize potential high-risk chemicals or uses at the workplace.

3.2.2.2 ASReview and INDRA

Another Lexces project concerning AI-models focusses on screening available literature information on specific topics of concern. It focusses on combining various methodologies on 1) identifying relevant literature reporting e.g. specific effects of chemicals, using ASReview or alternative methods, and 2) automatic extraction of relevant information from these literature studies using an Integrated Network and Dynamical Reasoning Assembler (INDRA). These methodologies will be further investigated and developed within this Lexces project, and may

be useful when screening literature in the context of early detection of NERCs.

3.2.3 Mistra SafeChem

Mistra SafeChem is a Swedish research programme for a green and sustainable chemical industry (IVL, 2025). The programme has both research and industry partners that perform research to develop tools and methods within several work packages.

The website shows a toolbox with three subcategories, of which *hazard and exposure screening* is of interest for this report. It contains a collection of publications on chemical screening, *in silico* predictions and *in vitro* predictions for screening of hazard and exposure. The current focus is on defined approaches for mutagenicity, endocrine disruption and skin sensitization endpoints.

- For *chemical screening* a suspect and non-target analytical screening toolbox is available, using GC/MS and LC/HRMS. This has been applied to several areas that may be of interest for workers. This includes an automated high-throughput analytical method for health hazards in textiles (Carlsson et al. 2022; Carlsson et al. 2023), and non targeted sampling of surfaces and air using silicone foam (Papazian et al. 2022).
- *In silico* methods are divided into predictive models using artificial intelligence (AI) and machine learning (ML) based tools. ML methodologies are available for endocrine disruption and CMR hazard screening (Ylipää et al, 2023). Machine learning based tools are available for identification of 23 endocrine receptors and CMR chemicals (Dracheva et al, 2022; Sapounidou et al. 2022). Within Mistra SafeChem, a pool of computational methods for chemical risk and hazard prediction is currently being assimilated and described using existing literature data and methods with the aim to indicate future development of improved models using state-of-the-art machine learning technologies.
- Mistra SafeChem contains an *in vitro* toolbox, containing several tools for the identification of a number of hazards (mutagenicity, skin sensitization, liver toxicity and endocrine disruption). This allows individual chemicals or mixtures to be analyzed for their hazardous properties.

3.3 Other methods

3.3.1 TICHNER

TICHNER (Technique to Identify and CHaracterize NERs) is a qualitative and structured technique that aims to identify and characterize new and emerging risks (NER) arising from manufacturing systems. Manufacturing systems are a combination of everything involved in making a product, such as employees, materials, machines, processes, techniques, etc. The TICHNER process contains several phases: (1) System analysis; (2) Identification of potential NERs present in the system; (3) Characterization of relevant NERs arising from the system (including exposure indicators); and (4) Characterization of the NERs arising from system components (Brocal et al, 2018). It is a tool used to analyze the NERs arising from a system or manufacturing process in a

systematic and structured way. It bases the identification of the NERs on the ISO standard ISO/IEC 31010:2009. The input is based on:

- Evidence based methods, such as literature reviews, and analysis of historical data;
- Empirical methods, including testing and modelling to identify what might happen under particular circumstances;
- Perception surveys, which canvas the views of a wide range of experienced people.

3.3.2 Overview of in silico methods

Various in silico methods are mentioned in the previous sections, in the context of specific methods for NERC identification. Besides these methods, many other in silico methods exist. An overview of *in silico* methods for the prediction of chemical toxicity was presented by Raies and Bajic (2016). Three types of *in silico* methods are described that are relevant for the identification of NERCs:

- Structural Alerts and Rule-based Models:
  - Structural alerts (SAs) (also called toxicophores/ toxic fragments) are chemical structures that indicate or associate to toxicity.

    Formula: *IF (chemical_substructure) IS (present) THEN (skin_sensitizer IS certain)*

    SAs use only binary features (e.g., chemical structures are either present or absent) and only qualitative endpoints (e.g., carcinogenic or non-carcinogenic). SAs do not provide insights into the biological pathways of toxicity and may not be sufficient for predicting toxicity.
  - There are two main types of rule-based models: human-based rules (HBRs) and induction-based rules (IBRs). HBRs are derived from human knowledge of field experts or from literature, but IBRs are derived computationally. It is possible to have hybrid-based rules systems that contain IBRs and HBRs, with new rules being generated computationally.

  The list of SAs and rules may be incomplete, which may cause a large number of false negatives (i.e., toxic chemicals predicted as non-toxic) in predictions. But could also be insufficiently specific, resulting in false positives.
- In silico Chemical Category, Read-Across, and Trend Analysis:
  - A chemical category is a group of chemicals whose properties and toxicity effects are similar or follow a similar pattern. The OECD Guidance On Grouping Of Chemicals lists several methods for grouping, such as chemical identity and composition, physicochemical and ADME properties, mechanism of action (MoA), and chemical/biological interactions.
  - Read-across is a method of predicting unknown toxicity of a chemical using similar chemicals (called chemical analogs) with known toxicity from the same chemical category. There are several advantages of read-across. Read-across is transparent, easy to interpret and implement. Read-across can model quantitative and qualitative toxicity endpoints, and it allows for a wide range of types of descriptors and similarity

measures to be used to express similarity between chemicals. In reality, read-across uses small datasets compared to other methods such as QSAR because there are usually only a few analogs for a given chemical.
    - Trend analysis is a method of predicting toxicity of a chemical by analyzing toxicity trends (increase, decrease, or constant) of tested chemicals.
- Quantitative Structure–Activity Relationship: Quantitative structure–activity relationship (QSAR) is a family of models that uses molecular descriptors to predict chemicals' toxicity. It is assumed that chemicals that fit the same QSAR model may work through the same mechanism. A local QSAR is generated from congeneric chemicals (i.e., similar chemicals); otherwise, the model is a global QSAR if it was made from diverse chemicals. Local QSARs are more accurate as they are customized for specific chemicals. Quantitative Structure Toxicity/Property Relationship (QSTR/QSPR) models are QSAR models that predict toxicity and chemical properties, respectively. Structure activity relationships (SAR) are used for categorical endpoints.

4 Evaluation of identified methods

As explained in Chapter 1, a risk-first-approach can involve a broad range of methods, such as in vivo, in vitro, in silico models, or human data. When comparing the identified methods in this report, it should be considered that the method may be a combination of multiple elements or toolboxes (e.g. Mistra Safechem) or may be a single element (e.g. EPA toxcast). Therefore, in this chapter, the identified methods are evaluated based on several criteria (see Chapter 2), to be able to compare them regardless of the different types of methods, and to determine their usefulness for signal identification via a risk-first-approach.

4.1 Method evaluation

Table 1 Overview of strengths and weaknesses of the identified risk-first-methods. The criteria and colours (green, orange**, red***) are explained in chapter 2.*

Method	Available?	Applied?	Labor intensive?	High throughput?	Hazard information?	Exposure information?
Research institutes and regulatory agencies						
(1) EFSA	*	**	***	**	*	*
(2) ECHA	***	n.a.	n.a	n.a.	n.a.	n.a
(3) EU-OSHA	*	*	***	***	*	*
OECD						
(4) OECD (Q)SAR toolbox	*	**	**	*	*	***
(5) Early4Adma	*	**	***	***	*	*
European Commission						
(6) JRC	***	n.a.	n.a	n.a.	n.a.	n.a.
(7) SfEP	*	**	***	**	*	*
US-EPA						
(8) US-EPA ToxCast	*	**	**	*	*	***
(9) US-EPA ExpoCast	*	**	**	*	***	*
RIVM						
(10) RIVM ED toolbox	*	**	**	*	*	*

Method	Available?	Applied?	Labor intensive?	High throughput?	Hazard information?	Exposure information?
(11) ZZS similarity tool	*	**	**	*	*	***
(12) KIR-nano	*	*	***	***	*	*
(13) NAMs – risk assessment	*	**	**	***	*	***
Collaborations and partnerships						
(14) PARC	***	n.a.	n.a	n.a.	n.a.	
Lexces						
(15) *In silico* prediction models	*	***	**	*	*	*
(16) ASReview and INDRA	*	***	**	**	*	*
Mistra SafeChem						
(17) Chemical screening	*	**	**	*	*	***
(18) *In silico* predictions	*	**	**	*	*	***
(19) *In vitro* predictions	*	**	**	*	*	***
Other methods						
(20) TICHNER	*	**	***	***	*	*
(21) Other *In silico* methods	*	**	**	*	*	***

n.a.: not applicable

4.1.1 Justification for classification

The justification for the classification of the methods is described in this paragraph, based on the assessment using the questions in chapter 2. The methods are numbered according to their order of appearance in chapter 3.

Research institutes and regulatory agencies

(1) EFSA (3.1.1) has a working method for identifying NERCs related to food. It is labor intensive since it relies heavily on the exchange of information between experts, but it makes also use of both hazard and exposure information from appropriate data sources and data collection. It is not based on high throughput identification of NERCs.

(2) ECHA itself has not yet developed a method for the identification of NERCs (3.1.2).

(3) EU-OSHA regularly publishes European Risk Observatory (ERO) Reports that explicitly mention the identification of new risks posed by hazardous chemicals (3.1.3). The ERO uses the Delphi method and is very labor intensive. The method is based on both hazard and exposure information, but it is not possible to search large databases with hazard and exposure information for an increased health risk.

(4) Within the OECD, a (Q)SAR toolbox was developed for hazard identification of large quantities of chemicals (3.1.4.1). However, expert assessment remains necessary for interpretation of the results. It has not been applied to workers.

(5) Early4Adma was developed under the auspices of the OECD (3.1.4.2) Early4Adma is available and is applied to a number of predefined advanced materials. The method is based on expert opinion and labor intensive. Exposure is estimated at a high level and is not classified.

(6) The JRC does not have a working method for the identification and evaluation of NERCs according to risk-first-methods, but does indicate in a number of publications which types of data sources such methods could use (3.1.5.1).

(7) The research in the context of science for environmental policies (SfEP) has yielded five labor intensive signaling tools and methods (3.1.5.2). One of these methods, online media monitoring using MediSys, also contains some information about incidents involving hazardous chemicals, but most information involves the risks of biological agents.

(8) The US-EPA ToxCast program (3.1.6.1) provides a database and associated software for high throughput hazard identification of chemicals. Experts can use this information in a risk assessment.

(9) The US-EPA ExpoCast program (3.1.6.2) has delivered a high throughput method to characterize exposure of chemicals and mixtures from source to human, that can be used for risk assessment of chemicals.

(10) The RIVM ED toolbox (3.1.7.1) is available and applied for consumer products and based both on hazard and exposure. At first, the method is high throughput since large databases can be analyzed. Then, experts need to evaluate the signals.

(11) The ZZS similarity tool (3.1.7.2) is an available and applied high throughput method for hazard identification, but signal evaluation by experts remains necessary.

(12) KIR-nano (3.1.7.3) is a knowledge and information centre that identifies potentials signals of emerging risks of advanced (nano) materials. Identification is mainly based on existing data on single or groups of materials, which is evaluated by experts in the fields of environment, consumers and workers.

(13) Specific NAMS (3.1.7.4) have been applied in risk assessment of predetermined consumer products and can play a role in hazard identification of pre-identified chemicals. However, expert risk evaluation remains necessary.

Collaborations and partnerships

(14) Within the PARC project (3.2.1), the foundation will be laid for an early warning system for the general population based on a high-throughput risk-first-methodology.

(15) In the context of Lexces, in silico AI-based screening tools (3.2.2.1) have been developed for the identification of chemicals, uses and applications with an increased risk of occupational diseases. These tools are available but not yet applied to large databases. Using these tools, large databases can be analyzed with minimal effort. However, expert evaluation of potential signals remains necessary.

(16) Another Lexces project concerns screening of available literature with AI techniques ASReview and INDRA (3.2.2.2). Large amounts of literature may be screened, although the screening itself focuses on a single search term. Expert evaluation of the results remains necessary. The techniques have not been applied specifically to NERCs.

Relevant methods mentioned under Mistra SafeChem (3.2.3) consist of 3 types of techniques that can be used for hazard and exposure detection of potential NERCs, but expert assessment remains necessary:

(17) Chemical screening focuses on suspect or non-targeted analytical screening. High-throughput techniques are used, which can be applied for hazard identification and exposure screening;

(18) Several *in silico* techniques are already being applied for the identification of multiple hazard endpoints, but not specifically for workers. A pool of computational methods for chemical risk and hazard prediction is currently being assimilated;

(19) The *in vitro* toolbox can be used to identify a number of hazards in individual chemicals or mixtures of chemicals.

Other methods

(20) The TICHNER process (3.3.1) can be used to identify and characterize NERCs generated by a manufacturing system. It is a labor intensive method that is based on already known data as well as on models and the views of experts, and is based on hazard and exposure knowledge.

(21) Several other *in silico* methods (3.3.2) are available and used for hazard identification of chemicals in which one is previously interested. These are high-throughput methods not specifically for workers that still require expert judgment.

4.2 Outlook for a risk-based approach

Based on the overview of strengths and weaknesses in Table 1, comprehensive risk-first-methods for identifying NERCs for workers can be selected. The most important criteria are the availability of the methods, the consideration of both hazard and exposure information, and a high-throughput principle. For all identified methods, the input of experts remains important to some extent for the prioritization and further follow-up of possible NERCs.

Several methods meet most of these criteria, but none of them meet all. Ideally, methods should be combined to be able to meet more criteria. For example, NERCs could be identified using a combination of information on toxicity from US-EPA Toxcast and information on exposure from US-EPA Expocast. But other combinations of methods or elements of certain methods are possible as well.

Two methods will be further developed in the next phase of this project: the Lexces in silico prediction models and the RIVM ED toolbox. These methods meet many of the criteria for which they were evaluated; i.e. they are both high throughput and rely on large databases, they can take into account both hazard and exposure information, and they are available. In addition to meeting these criteria, the selection of these methods is pragmatic, as it aligns with the current expertise and established workflows already present within the Lexces program. The methods each have a different perspective, with the Lexces in silico prediction model focusing on prediction, while the RIVM ED toolbox brings together information from various sources.

Alongside these two methods, elements from other methods may be considered in the future to further advance the selected risk-first-methods. This integration of additional elements will help to refine and improve the current methods.

5 Discussion and conclusion

This report provides a non-exhaustive overview of (inter)national methodologies that can be used to detect NERCs according to the risk-first-approach. The most commonly used approach for detection of NERCs currently is the disease-first-approach, which means that workers have already fallen ill as a result of exposure to chemicals at work. The risk-first-approach attempts to detect NERCs at an earlier stage, i.e. before workers fall ill. This approach needs information on both the potential hazards and exposure of a chemical.

The optimal method for a risk-first-approach would be a method that can be used to search large databases for hazard and exposure characteristics that could lead to the development of an occupational disease.

Following the evaluation described in this report, several methods or combinations of methods are promising for implementation as risk-first signalling methods due to their availability and their ability to search large databases containing hazard and/or exposure data. None of the methods meet all criteria for usability in our risk-first approach. Two risk-first-methods for identifying NERCs for workers have been selected for further development as part of the Lexces follow-up project 2.2: the Lexces in silico prediction models and the RIVM ED toolbox. These methods were chosen because they meet many of the criteria evaluated in this report (i.e. they are high-throughput and use large databases incorporate both hazard and exposure information and are available). In addition to meeting these criteria, they are readily available for use within the project's existing workflows. In the future, elements from other methods may be integrated to further improve these methods.

The information collected with these methods will always have to be reviewed by a group of experts. In addition to the risk-first-approach, the disease-first-approach will also continue to play a role in the detection of NERCs, because the output of the risk-first-analyses allows for more targeted searches for potential risky situations that may already exist in practice. These issues were also raised during a meeting that was held between Lexces 2.2 project members and international experts to discuss risk-first- and disease-first-strategies for the early detection of NERCs. The meeting highlighted the importance of broader reporting and international collaboration, and emphasized the need for data sharing despite privacy challenges. All experts expressed their commitment to ongoing cooperation and recognized that structured, joint efforts are essential for strengthening occupational disease surveillance.

Besides methods for identification of NERCs, methods for prioritization have been developed. In the past, RIVM carried out a screening on the ECHA database for carcinogenic and mutagenic properties of chemicals which led to a prioritization tool for consumers for chemicals that are carcinogenic, DNA damaging, harmful to reproduction, or potentially allergenic by skin contact or inhalation (Schuur and Traas, 2011). This

method can prioritize NERCs but not identify them. For risk prioritization, the hazardous properties of the chemicals have been mapped and combined with the extent to which consumers are exposed to the chemicals (Woutersen et al, 2015). The method was then applied to a database with consumer product information (ISA)(Woutersen et al, 2019) and textile products (Nijkamp et al, 2014). These methods may be useful as next steps following NERC identification.

The above mentioned methods will be explored further for their use in a risk-first-approach for NERC identification for WRD in a follow-up project under the auspices of Lexces. The project will also involve making a common plan for assessment, management and communication of signals identified via both risk-first- and disease-first-approaches.

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List of acronyms and terms

ADME	Absorption, distribution, metabolism, and excretion
AI	Artificial Intelligence
BAuA	German Federal Institute for Occupational Safety and Health
BfR	German Federal Institute for Risk Assessment
Biomonitoring	Also known as biological monitoring, is the process of measuring chemicals or their breakdown products in human body fluids and tissues (like blood, urine, breast milk, etc.) to assess exposure to chemicals.
Clinical data	Refers to health-related information collected during patient care or clinical trials.
CMR	Carcinogenic, Mutagenic and Reprotoxic
CSD	Critical slowing down
CSS	Chemicals Strategy for Sustainability
Data mining	The process of discovering patterns, anomalies, and correlations within large datasets to extract valuable information and insights.
Delphi method	A structured communication technique, often used in forecasting and decision-making, that relies on a panel of experts to reach a consensus through iterative rounds of questionnaires and controlled feedback.
Drivers' analysis	A statistical method used to determine which factors (drivers) have the most significant impact on an outcome variable. It involves data collection, statistical analysis and interpretation of results.
Early4Adma	Early awareness and action system for advanced materials
ECHA	European Chemicals Agency
ED	Endocrine-disrupting
EDA	Effect-directed analysis
EDC	Endocrine disrupting chemicals
EFSA	European Food Safety Authority
EMM	European Media Monitor
Epidemiology	The study of the "distribution and determinants" of diseases or disorders within groups of people, and the development of knowledge on how to prevent and control them.
EU	European Union
EU-OSHA	European Agency for Safety and Health at Work
ExpoCast	US EPA Exposure Forecast
Ex vivo	Refers to the study of a chemical's toxicity on tissues or organs that have been removed from a living organism and kept in an artificial environment, but with conditions closely resembling the in vivo (within the living body) state. It bridges the gap between in vitro (purely in a lab dish) and in vivo studies, offering a more physiologically relevant model for toxicity testing.

Foresight analysis	Involves systematic approaches to understand potential future developments and their implications for present-day decisions.
GC/MS	Gas chromatography–mass spectrometry
HBR	Human-based rules
Health Surveillance	The systematic monitoring of an individual's or a population's health status to detect potential health problems early, especially those related to occupational hazards or disease outbreaks.
IBR	Induction-based rules
In silico methods	Refers to the use computer-based methods to predict and assess the potential toxicity of chemicals. This field leverages computational tools and data to model, simulate, and analyze potential adverse health effects, complementing traditional toxicological testing methods. In essence, it's a way to understand and predict toxicity using computer models and simulation.
In chemico methods	Refers to toxicity testing conducted in a test tube or other laboratory apparatus (i.e., not in a living organism). It involves studying the chemical reactions and properties of a chemical to predict its potential toxicity, particularly focusing on how it interacts with biological molecules.
In vitro	Refers to the study of the toxic effects of chemicals on cells or tissues grown outside of a living organism, typically in a laboratory setting.
In vivo	Refers to the study of the harmful effects of chemicals on living organisms, typically using animal models.
ISA	Informatie Systeem Artikelen; database with consumer product information
IVL	Swedish Environmental Research Institute
JRC	Joint Research Centre
LC/HRMS	Liquid chromatography/high resolution mass spectrometry
Lexces	Dutch national expertise centre for substance-related occupational diseases
Mistra SafeChem	Mistra SafeChem is a research programme that aims to create a sustainable chemical industry and reduce exposure to hazardous substances
MoA	Mechanism of action
MODERNET	Monitoring trends in Occupational Diseases and tracing new and Emerging Risks in a NETwork
NAM	New Approach Methodologies; non-animal-based methods used to assess chemical hazards and risks are non-animal-based methods used to assess chemical hazards and risks.
NCvB	Netherlands Center for Occupational Diseases
NERC	New and Emerging Risks of Chemicals
NERDB	New and Emerging Risks DataBase
NESSI	Novelty, Exposure, Severity, Scope, Immediacy
OECD	Organization for Economic Co-operation and Development

PARC	Partnership for the assessment of Risks for Chemicals
(Q)SAR	(Quantitative) Structure-Activity Relationship; a computational method that establishes a mathematical relationship between the structure of a chemical compound and its biological activity.
QSTR/QSPR	Quantitative Structure Toxicity / Property Relationship
QSUR	Quantitative Structure-Use Relationship; a computational method that utilizes chemical structures to predict the function of a chemical within a formulated product or an industrial process.
REACH	Regulation on the registration, evaluation, authorisation and restriction of chemicals
Read across	a method used to predict the toxicological properties of a chemical (the "target chemical") by using data from one or more structurally similar chemicals (the "source chemicals" or "analogues").
RIVM	National Institute for Public Health and the Environment
SA	Structural alert
SfEP	Science for Environment Policy
SIGNAAL	Online portal for concerns about new associations between health and work.
SPR	Strategic Programme RIVM
Text mining	the process of extracting valuable information from large amounts of unstructured text data using computer algorithms and techniques.
TICHNER	Technique to Identify and CHaracterize NERs
Tissue cultures	the process by which cells are grown under controlled conditions in an artificial medium separate from the parent organism.
ToxCast	US EPA Toxicity Forecaster
UBA	Umwelt Bundesamt; German environmental protection agency
WRD	Work Related Diseases
ZZS	Zeer Zorgwekkende Stoffen / Chemicals of Very High Concern

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