National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Progress report on New or Emerging Risks of Chemicals (NERCs)

RIVM Letter report 2014-0040
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J. Bakker et al.

Colophon

Joost Bakker
Yuri Bruinen de Bruin
Elbert Hogendoorn
Myrna Kooi
Nicole Palmen
Joanne Salverda
Theo Traas
Dick Sijm

Contact:
Elbert Hogendoorn
VSP
elbert.hogendoorn@rivm.nl

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P.O. Box 1│3720 BA Bilthoven
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Nationale en internationale wetgeving is erop gericht dat chemische stoffen veilig worden geproduceerd, verwerkt en gebruikt. Zo is in de Europese wetgeving REACH (Registratie, Evaluatie, Autorisatie en restrictie van CHemische stoffen) vastgelegd dat de industrie verantwoordelijk is dat de chemische stoffen die ze op de markt brengen, veilig kunnen worden geproduceerd en gebruikt. Toch kunnen er op korte of lange termijn nieuwe risico's van stoffen voor mens of milieu ontstaan. Van stoffen die al langer worden gebruikt, kunnen ongewenste effecten aan het licht komen als de stof via een andere blootstellingsroute (bijvoorbeeld inhalatie) bij de mens binnenkomt. Ook nieuw op de markt gebrachte stoffen die bijvoorbeeld niet voldoende zijn getest, kunnen de gezondheid van mens en milieu schaden. Voor zowel bestaande als nieuwe stoffen geldt bovendien dat een screening vooraf nooit alle mogelijke schadelijke effecten kan onderkennen.
Sinds 2012 doet het RIVM onderzoek naar methoden om dergelijke nieuwe risico's van stoffen, ook wel *New or Emerging Risks of Chemicals* (NERCs) genoemd op te sporen, zodat tijdig maatregelen kunnen worden genomen. Het gaat hierbij om de blootstelling en nadelige effecten van stoffen voor werkers, consumenten en het milieu. Daarbij kan het gaan om onbekende risico's van bestaande stoffen of risico's van nieuwe stoffen. Dit rapport is een voortgangsrapportage van de onderzoeksresultaten die tot nu toe voor de drie beschermingsgroepen verkregen zijn.
In dit onderzoek zijn methodieken ontwikkeld voor het vinden van potentiële NERCs. Een voorbeeld hiervan is de signalering van diacetyl als nieuw risico voor Werkers. Blootstelling van werkers via de lucht aan smaakstoffen die diacetyl bevatten kan zeer ernstige luchtwegaandoeningen veroorzaken en kan bijvoorbeeld vrijkomen bij de productie van popcorn. Als maatregel hiervoor wordt aanbevolen om een veilig blootstellingsniveau op te stellen, en beschermingsmaatregelen te treffen, zoals het gebruik van luchtfilters, om de gevolgen te beperken.
Een strategie is in ontwikkeling waarbij de methodieken geïntegreerd worden om na te gaan in hoeverre een gesignaleerde NERC ook voor de andere beschermingsgroepen schadelijk kan zijn.

Trefwoorden: Blootstelling, nieuwe risico's, stoffen, werkers, consumenten, milieu,

Abstract

Despite existing legislation to prevent or manage the risks of chemical substances, chemical risks continue to emerge on the short or long term. On the one hand, these risks can be the result of new substances, new applications, technological developments or process innovations. On the other hand adverse effects not recognized before might arise from the long-term use of existing substances. Therefore, a project coordinated by RIVM Bureau REACH and financed by the Dutch Ministry of Infrastructure and the Environment, the Ministry of Social Affairs and Labour and the Ministry of Welfare and Sport was initiated in 2012 advocating the development of a system to identify New or Emerging Risks of Chemicals (NERCs) at an earliest stage. The project aims to link (new) information on chemical stressors to effects for three protection goals - workers, consumers and the environment- with the purpose to better protect man and the environment.
This report summarizes the progress of work and results of the project presenting the methodologies in finding and prioritizing NERCs for each protection goal, and suggesting measures in order to reduce exposure of the selected NERCs in the nearby future.
In addition to similarities in the methodologies for the identification of NERCs, the complexity and route of exposure of NERCs also resulted in differences in approaches for the three protection goals. The common features are using various sources (e.g. scientific literature, news sites, websites, electronic databases, stakeholder networks) for searching information and the evaluation of information involving international networks of experts to assess the causality between the chemical exposure and the effect.
The next and future steps in the identification of NERCs is to develop a stepwise comprehensive strategy including follow-up measures, where needed, to manage, restrict or reduce the exposure of such compounds.

Keywords: Exposure, NERCs, New emerging risks, workers, consumers, environment

Contents

1 Introduction

Under REACH [EC 1907/2006] importers and manufacturers are to register their chemicals and show safe use of that chemical within their individual supply chains. Safe use has to be demonstrated, sometimes involving adequate risk management measures, in the registration dossier of chemicals used at the workplace, in the environment or when consumers are exposed to chemicals in consumer products.

However, there are various circumstances where REACH cannot safeguard safe use. When registrations are involved covering various supply chains, the aggregation of uses may in theory cause exceeding Predicted-No-Effect Concentration (PNECs) or Derived-No-Effect-Levels (DNELs). Also, REACH does not cover every substance as, for example, chemicals below 1 ton per year need not to be registered. Finally, it is not possible to discover all possible hazards and risks in pre-screening tests. Some effects might not be discovered by standard tests used and not all relevant tests and information might be required, especially in the case of low tonnage chemicals (1-10 ton/year).

The objectives of the Dutch government are to protect the environment, consumers and workers. REACH as well as other chemical legislation (e.g., Water Framework Directive [2000/60/EC], Cosmetics Regulation [1223/2009/EC], Chemicals Agents Directive [98/24/EC], etc.) are instrumental in aiming for these objectives.

In 2012 an initiative coordinated by RIVM Bureau REACH and financed by the Dutch Ministry of Infrastructure and the Environment, the Ministry of Health, Welfare and Sport, and the Ministry of Social Affairs and Employment (since 2013) started to trace and, moreover, to link (new) information on chemical stressors to effects in workers, consumers or the environment with the purpose to better protect man and the environment.

The definition of EU-OSHA (EU-OSHA, 2009) is used in this report for New or Emerging Risks of Chemicals (NERCs) involving both new and emerging risks:

New risks:
- the issue is new and caused by new types of substances, new processes, new technologies, new types of workplaces, or social or organizational change; or
- a risk due to a change in social or public perceptions (e.g. stress, bullying); or
- new scientific knowledge allows a longstanding issue to be identified as a risk (e.g. repetitive strain injury (RSI) where cases have existed for decades without being identified as RSI because of a lack of scientific evidence).

Emerging risks:
- number of hazards leading to the risk is growing; or
- likelihood of exposure to the hazard leading to the risk is increasing, (exposure degree and/or the number of people exposed), or
- effect of the hazard on the workers' health is getting worse, or
- More or new information becomes available.

In order to identify NERCs at an early stage, methodologies and/or procedures have been developed or are under construction for the three protection 'goals': Workers, Consumers and the Environment.

This report provides a short comprehensive view of the current state of the results for all three protection goals regarding proposed methodologies, the identification of NERCs and work to be done in the near future.

The next sections present the general approach of the overall methodology followed by a more detailed description of the developed approach and related activities including results for each protection goal. Finally, the proposed methodologies and results are discussed with the perspective to possibly combine information in order to prioritize indicated NERCs preferably valid for all three protection targets.

2 General approach methodology

Figure 1 reflects the proposed general methodology in finding NERCs. The first step is to pick up or search for information on new or emerging chemical risks and possible related effects, using various sources (e.g. scientific literature, news sites, websites, electronic databases, stakeholder networks). In the case of human risks (workers or consumers), epidemiological research and case reports are also valuable sources. If the signal has already been identified before and actions or regulatory measures have already been implemented, the identified signal will be forwarded to enforcement or inspection authorities.

The next step is to evaluate the obtained information and to assess the evidence for the causality between the chemical exposure and the harmful effect. Initial expert assessment is an essential factor in this evaluation process. Specific expert groups discuss the resulting signals for NERCS and make a priority list based on the strengthening of the signals, the severity of the risk and the options in place for risk management measures. This prioritization step will result in a list of potential NERCs requiring a follow-up procedure. Follow-up measures include derivation of a safety limit (e.g. SCOEL), actions taken up by REACH or CLP (e.g. SVHC roadmap, restriction or harmonized classification and labelling) or making use or adaptation of other legislation.

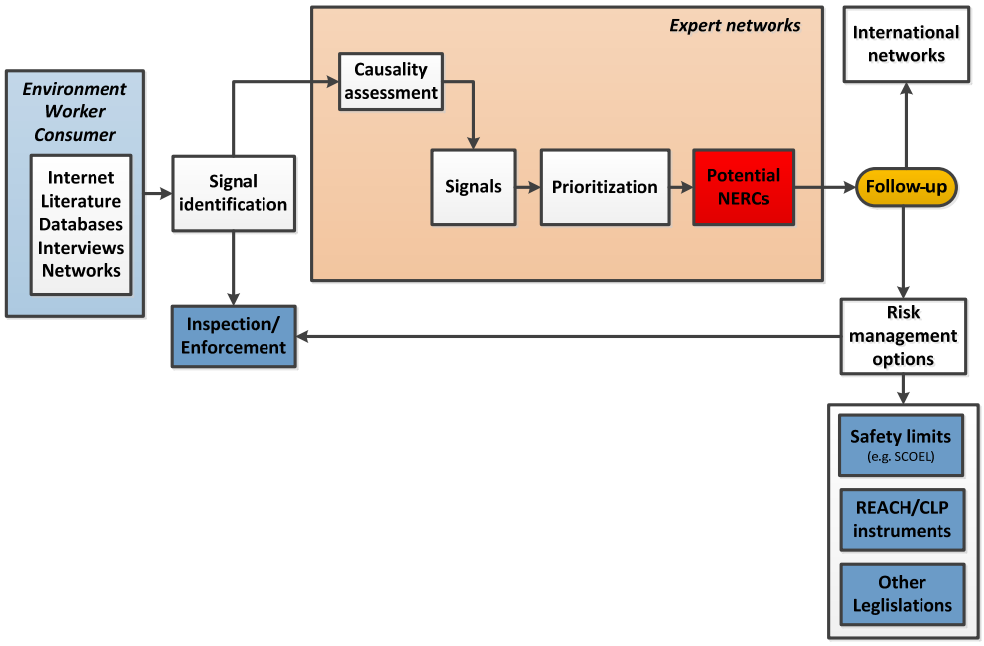

Figure 1. Scheme of general approach in finding NERCs

In the amplifying process of indicated potential NERCs, the gained and shared information on chemical stressors and effects from various sources will be evaluated making use of expert judgment in order to point out the chemicals that cause the harmful effects. Sources of information are the internet, literature, search machines, questionnaires or outcomes or opinions from interviews.

The search for NERCs is performed in parallel by three groups, for each of the protection goals: workers, consumers and the environment. These three groups share their experiences and methodologies and integrate the resulting NERCs.

3 Workers

3.1 Methodology to identify NERCs for Workers

The first report on NERCs at the workplace was recently published (NGM Palmen et al., "Detecting emerging risks for workers and follow-up actions", RIVM report 601353004/2013). Figure 2 shows schematically the set-up of the procedure for Workers.

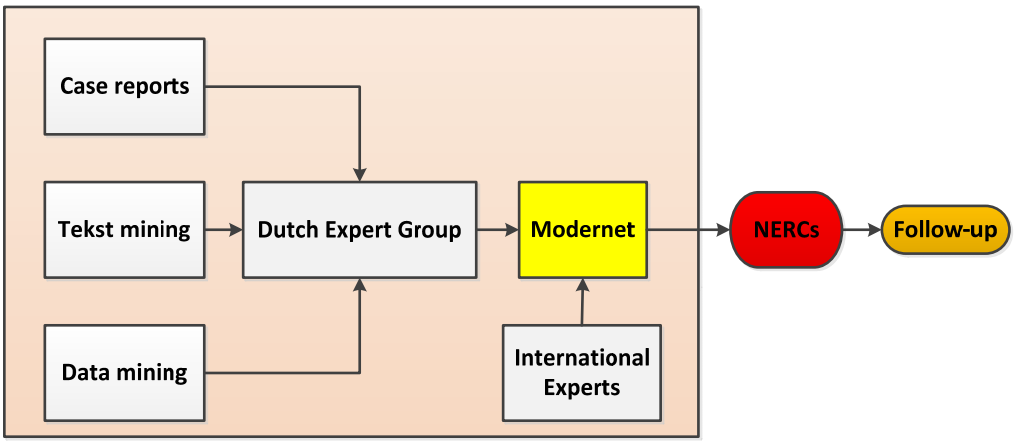

Figure 2. Scheme methodology for Workers

The identification of emerging risks requires several complementary methods. Case reports are an important source of potential NERCs in case of a rare disease with a clear cause – effect relationship. The Netherlands Centre for Occupational Disease launched the online counter SIGNAAL (https://www.signaal.info/) where physicians can report a possible new work related risk.

Text mining techniques reduce the number of publications in the scientific literature and on websites of organizations that generate information on NERCs for workers. In this way all known and unknown linguistic relationships between chemicals, occupational exposure and health effects are identified.

Epidemiological research among large groups of employees is more appropriate in cases of frequently-occurring health effects with a low cause – effect relationship.

These signals must be evaluated by experts. The 'Dutch expert group of new or emerging risks of substances' consisting of (occupational) physicians, toxicologists, industrial hygienists and epidemiologists prioritizes the incoming signals and tries to strengthen and confirm the signals. The evaluations will be discussed within the network on 'Monitoring trends in Occupational Diseases and tracing new or Emerging Risks in a NETwork' (Modernet), an international network of professionals that study new risks and share knowledge with each other with the intention to stimulate taking measures to reduce the risk. The Netherlands was one of the initiators of Modernet, which exists for some years already.

3.2 Results identified NERCs for Workers

As a result of the developed methodology a concise overview of new risks, which cause occupational health problems, is given in Annex 1 showing an overview of a selection of (potential) new occupational health risks, which was taken from the report of Palmen et al. (2013). The reported health effects in the workers, the work they performed and the substance the workers were exposed to, is shown. Information on the reason for the concern (whether it concerns a new technology, a new use, a new risk, health effects caused by historical exposure etc.) and the organization, which reported the new risk are given, as well as the literature source.

For every individual substance, additional information is gathered on the identity of the substance, its classification (self-classification by the notifiers and/or harmonized classification, if available), the use of the substance (which branch or process), the seriousness of the health effect, the height of the exposure to the substance in relation to the health effect reported (if available), and a qualitative calculation of the risk with the aim to prioritize the list of new risks.

The strengthening of a reported potential new risk signal is done in a national expert group on emerging risks that was initialized recently on this behalf. In this national expert group, we search for additional cases, try to get more insight in workers exposure to the suspected substance, and try to find out whether there is a causal relationship between the exposure to the suspected substance and the reported health effect. The national expert group is in tight connection with the international network on 'Monitoring trends in Occupational Diseases and tracing new or Emerging Risks in a NETwork' (Modernet). So, potential new risks can be discussed also in the international network on emerging risks via the national expert group.

3.3 Follow-up actions

In case a substance is identified as a new risk, action has to be taken to prevent further health damage. If a substance is already regulated, the new risk will be reported to the concerned inspection department(s) of the ministries of I&M, SZW and/or VWS, so that measures can be taken. An example is when there is no compliance with a public OEL. Enforcement of the OEL should be enough to prevent further health damage. However, it is possible that health effects are reported below the concentration of the public OEL. In that case, further action has to be taken, for example, a request for re-evaluation of the public OEL.

Professional societies on occupational health and safety are an important first contact to communicate a NERC, for example via an alert. Professionals like industrial hygienists, safety engineers, occupational physicians etc., should be informed as soon as possible on a NERC to check whether the NERC is used in the companies they advise. The ultimate aim is to take measures to reduce the exposure to the NERC at the earliest possible stage to prevent further health damage and/or to start a preventive medical examination among workers to check for first signs of health problems that may be caused by the NERC.

If a substance that causes a new risk is on the ECHA list of substances that have been evaluated already by ECHA or one of the member states in one of the REACH processes, these member states and ECHA will be informed about the information on the new risk. In case a substance is not on the ECHA list, a risk management options analysis (RMOA) may be performed. This analysis will reveal possible actions, such as:

- The need for deriving an Occupational Exposure Limit (OEL) by the Scientific Committee on Occupational Exposure Limits (SCOEL);
- The need to identify the substance as a substance of very high concern (SVHC) and for authorization under REACH;
- The need to generate additional information, which may be provided via the substance evaluation instrument (SEv) within REACH. This additional information on the hazard or the exposure of a substance may lead to:
    - a proposal for a (change in) harmonized classification and labelling of a substance, which may subsequently have an effect on the REACH requirements and/or the requirements coming from worker safety legislation;
    - a proposal for restriction of the use of the substance;
    - a proposal for the identification of the substance as an SVHC and authorization; or
    - take away of the concern over the substance.
- Applying other legislation, to prevent that new cases will occur (for example legislation on medicine, cosmetics, biocides etc…)

The new risks will always be communicated to the ministries of I&M, SZW and VWS. This is essential for taking responsibility over the provision for safe and healthy environmental, consumer and working conditions. Information on new risks at the earliest stage is essential to be able to take actions as soon as possible to prevent further health damage.

Another action might be to inform industry on the new risk. Industry is obliged to use the new information in their chemical safety report (CSR), which may lead to a re-evaluation of the risk management measures that are needed to work safely with the substance under concern. The new information will then be communicated to the downstream users by way of the safety data sheet (SDS) and the ECHA website.

Non-governmental organisations (NGO’s) are independent from authorities and may ask attention for a NERC once they are informed.

4 Consumers

Through the use of various products, such as cosmetics, cleaning products, pharmaceuticals, biocides, detergents or paints, consumers are exposed to a wide range of chemical substances. Also, food products, through contamination or intentional addition, are a potential source of exposure to NERCs.

4.1 Legislation aspects

Chemical legislation, including REACH, the Water Framework Directive [2000/60/EC], the Cosmetics Regulation [1223/2009/EC], Medicinal Products Directives [2001/83/EC], Biocidal Products Regulation [528/2012/EC] or the Food Additives Regulation [1333/2008], aim to protect the consumer from the potential risks of chemical exposures. EU legislation and enforcement notwithstanding, consumers may encounter undesirable reactions after using consumer products. Also new risks continue to emerge. This could be the result of new hazards not identified by conventional test methods or new types of exposure introduced by innovations, technological developments and trends. These signals could be identified by scientific research, medical reports, postmarketing surveillance, monitoring or inspection. It is important to collect and prioritize these signals of emerging risks with the purpose of improving enforcement activities and updating legislation to ensure an optimal level of consumer protection and to safeguard public health.

4.2 Signal collection

In the past years RIVM has gained considerable experience with post marketing surveillance in the CESES (Consumer Exposure, Skin Effects and Surveillance) project (see Figure 3), which was initiated at the request of the Netherlands Food and Consumer Product Safety Authority (NVWA) and the Ministry of Health, Welfare and Sport (VWS). CESES is focused on monitoring adverse effects from cosmetics use. Cosmetic products, such as shower gel, deodorant, toothpaste and make-up, are used by most consumers on a daily basis. In Europe, the safety of cosmetic products is regulated by the Cosmetic Products Directive [76/768/EEC] which was replaced by the Cosmetic Products Regulation (EC No 1223/2009] in July 2013.

Despite EU legislation and enforcement, there are still negative health impacts on consumers, including the induction of sensibilisation and the development of contact allergy, after using cosmetic products. As these undesirable reactions could lead to acute or chronic health impairment, RIVM started the CESES project and initiated a system that offered consumers, general practitioners and dermatologist the possibility to report undesirable reactions attributed to cosmetics use. In addition to the reporting facility, RIVM also supported dermatologists to investigate the cause of the adverse reaction by providing them with product-specific ingredients that are not included in the routine patch test series. To this end, trends in the prevalence of allergic reactions to known cosmetic allergens and new allergens in cosmetic products could be identified. All together, the CESES project has proven to be a valuable tool for the monitoring of known adverse skin reactions from cosmetic products and the identification of new risks. This information has been used to take national or international measures and has contributed to the update of the Cosmetics Regulation with the purpose to better protect consumers.

Figure 3. Website of the CESES project, enabling consumers to report undesirable effects attributed to cosmetics use, see also http://www.cosmeticaklachten.nl (in Dutch).

The NERCs project has a wider scope than the CESES project and aims to identify new or emerging risks from various sources of consumer exposure, including cosmetic products. To this end, the CESES project will be used as one of the sources of information.

4.3 Methodology to identify NERCs for Consumers

The identification of NERCs for consumers requires several steps, essentially as described in Figure 1 in Chapter 2. The first step is to collect data. To this end, several information sources are used among which scientific literature, case reports (e.g. obtained from the CESES project), news sites (screened with dedicated EU text mining techniques), websites, electronic databases, (international) networks and stakeholder reports. An important basis for information is the REACH bulletin, a weekly update of relevant chemical news items based on ~30 sources of information collected by AWChemAdvice at the request of RIVM. All information relevant for the identification of consumer risks is collected in a database, and additional data on type of exposure, cosmetic products involved is included. If the risk has already been identified before and actions or regulatory measures have already been implemented, the identified signal will be forwarded to enforcement or inspection authorities. The next step in the identification of NERCs for consumers is to further assess the collected information in order to come to a list with NERCs with priority in terms of follow-up. To achieve this, expert consultation is essential and therefore RIVM is investigating the options to setup an expert network (work in progress). The third step is to share potential NERCs with an international network. RIVM is currently exploring the options to engage with existing international networks. For instance, RIVM has presented the NERCs project in a specific session on emerging risks at the Society of Risk Analysis (SRA) conference held in Istanbul on 16-18th of June, 2014. The fourth step in the NERCs procedure is to identify risk management options, such as the development of (more stringent) safety limits (e.g. maximum concentration limits) and the use of REACH/CLP instruments (e.g. harmonized classification).

4.4 Results identified NERCs for consumers

Using the methodology as described in the previous section generally results in finding three not yet identified risks of substances for consumers a week. As mentioned, the development of the NERCs project is still in progress and further refinement of the methodology in the context of (international) networks and activities is required. Annex 2 provides an overview of several examples of NERCs for consumers identified within the NERCs project.
The overview includes a number selected potential NERCs with a different observed health effect applied in various types of products and includes information on the reason of concern and the proposed action to reduce the exposure of the NERC.

5 Environment

For the identification of environmentally relevant NERCs several activities and studies have been carried out which are summarized below. In addition to a description of these activities, the overall procedure and related relevant aspect in the selection of environmental NERCs, that is partly based on the results of these studies and experience, will be given with reference to detailed information in Annex 3 and 4.

5.1 The set-up of an informal Network of Experts for the input and output of signals

An interactive group on New or Emerging Risks of Chemicals started on the internet platform Pleio. The aim of this group is to link information on chemical stressors to workers, consumers and environmental effects to the use of (new) chemicals, new applications, technological and social developments and process innovations. The focus is on observed/reported effects and exposure data (monitoring, inspections, etc.), but also on suspected effects.

This group shares information on chemical stressors and effects from various sources. Sources can be the internet, literature, questionnaires, (laboratory) analytical data, or outcomes or opinions from interviews. The philosophy is that by sharing, discussing and communicating signals/information on possible environmental problems with various experts and organizations/groups, a process of understanding is initiated of the environmental effects and possible risks that are potentially related to the use of and exposure to chemicals and products.

In short, NERCs are identified by (i) signal identification: screening scientific literature, news sites, databases, networks and outcomes of stakeholder interviews, (ii) signal strengthening by consultation between experts including the possible causality assessment (linking chemical exposure to identified effect(s)), (iii) signal prioritization: based on the previous step, involved human and environmental risks, (iv) options for risk management, societal and ethical concerns, potential NERCs requiring follow-up will be ranked , and (v) follow/up actions which may include derivation of safety limits, enforcement or inspection, using or modifying existing regulations (e.g. REACH, CLP), etc.

The network forms a discussion group that consists of a small group of Experts with a large scope of relevant disciplines. Such a structure aims to successful tracing and communicating of early signals on effects of hazardous environmental compounds. A major beneficial opportunity is to combine efficiently forces of the disciplines of analytical chemistry, bio-monitoring and risk assessment via an interactive platform gaining time to detect signals.

5.2 Matching REACH and Monitoring data

The study carried out by KWR and RIVM (Kolkman and Laak, 2012) aims to explore whether (*in situ*) environmental monitoring data can be used to support regulatory activities within REACH. For this purpose, GC/MS and LC/MS databases of monitoring data of organic chemicals in Dutch surface waters and ground water were searched for chemicals listed by REACH and other priority lists.

The matching exercise resulted in 178 hits of listed chemicals within the targeted monitoring data. Subsequently, 46 of the 178 observed chemicals in databases were selected for further research. Chemicals were selected when they were found in all searched datasets, the percentage of measurements above the detection limit was at least 20% and/or when the maximum concentration of a chemical was higher than 2 µg/L[1] and/or if the chemical was detected at more than 10 locations. Additionally chemicals were also selected based on their occurrence on priority lists such as the PBT list or CMR list.

Subsequently, observed measured environmental concentrations (MEC) were compared to predicted no-effect concentrations (PNEC), which were estimated using QSARs (Rorije et al. 2011). Chemicals with the highest MEC/PNEC ratios were prioritized for further evaluation, see Appendix 3, Table A3.1.

Table A3.1 shows the twelve chemicals with MEC/PNEC ratios exceeding 0.5. The table also lists the fraction of positive observation and information on their occurrence

Additionally, a much wider screening was done on all registered high production volume chemicals (2010 registration) for which single chemical structures are available. These non-targeted screening data obtained with liquid chromatography coupled to high-resolution accurate mass spectrometry (LC-HRMS) were matched with listed REACH and other priority chemicals (Kolkman and Laak, 2012). This resulted in a list of 32 unique elemental compositions for all the samples (see Appendix 3, Table A3.2).
The LC-HRMS approach, does not allow a full verification of the identity of matching masses, as there are currently no libraries of LC/MS mass spectra. The non-targeted approach is therefore not (yet) suitable to support or guide evaluation and regulation of chemicals. However, when identification of matching chemicals can be confirmed, this approach can become a valuable evaluation tool to support regulation of chemicals.
Since in GC/MS atomic spectra of many compounds have been collected, these spectra allow identifying numerous (~30,000) chemicals that can be analysed by GC-MS (http://www.nist.gov/pml/data/asd.cfm). A disadvantage is that this analysis does not enable reliable quantification of concentrations since standards are not included in the analysis. The obtained data are therefore qualitative.

A way forward would be to first identify the chemicals with the highest concern based on several criteria that relate to potential exposure and toxicity. The next step would be to concentrate the effort of the quantification of the concentrations on these prioritised/selected chemicals

5.3 Early warning systems scouting internet news

Two search systems collecting information on occurrence and effects of hazardous compounds are installed in tracing NERCs. At RIVM, looking for early warnings is done employing a list of key words combining hazardous compounds and environmental effects on a two-weekly basis. Another worldwide internet screening is performed by the European Media Monitor developed by the EC-JRC with a focus on generic hazardous compounds and environmental effects and with a focus on specific endocrine disrupting compounds and their effects. This

[1] According to the PBT criteria that have been defined in Annex XIII of the REACH regulation, the criterion for a substance to be toxic is that the chronic NOEC should be < 1 µg/L. As a clear initial exceedance cut-off value 2 µg/L has been chosen

internet screening takes place every 10 minutes and hits can be seen immediately. Also for this screening a list of key words has been developed in close collaboration with an experienced scientific newsreporter/journalist. From both systems, hits are gathered and the relevance to identify them as signals on the Pleio website is discussed.

5.4 Desk top study on the occurrence and environmental effects of endocrine disrupting compounds (EDs) in Dutch open surface waters

A desktop study was commissioned by RIVM and carried out by IVM [Lamoree 2014] as a follow-up of the extended LOES (Landelijk Onderzoek Estrogene Stoffen) project finalized in 2002. This study was carried in order to obtain current information about the occurrence of EDs and observed ecological effects in Dutch large surface waters. After LOES, endocrine disruption studies now cover various other endpoints, such as androgenicity and thyroidogenicity, however, no large scale studies on these novel manifestations have been done in the Dutch aquatic environment. A few pilot studies on thyroidogenicity with a limited scope were carried out as well as studies focused on the combined use of chemical analysis and *in vitro* and *in vivo* bioassays, considering not only estrogenic but also androgenic effects. Despite observed androgenic effects in these studies, the overall conclusion was that there is still a lack of information whether endocrine disruption in its various manifestations occurs in organism in the Dutch aquatic ecosystems, and whether these potential effects would lead to adverse effects at population and community level. Obviously, this type of studies is comprehensive, time consuming and very costly, requiring the integration of chemical analysis and biological/toxicological test methods. However, to properly evaluate the risks of the occurrence of endocrine disrupting compounds, studies providing filed data for e.g. anti-androgenicity and thyroidogenicity are of major importance.

5.5 Methodology to identify NERCs for the Environment

The proposed procedure involves three steps: (i) initial selection of potential NERCs, (ii) refining selection of potential NERC, and (iii) identifying a measure of control. These steps which will be discussed below.

5.5.1 Initial selection of NERCs

As shown in Figure 1, the initial selection of signals about potential NERCs starts with the collection of information, which can be obtained from several routes as, discussed above. A relevant signal should address at least one of the following aspects:

1. a relation between occurrence and effect
2. new identified risk, effect or newly identified hazardous property of a substances
3. new substance on the market, which might be a potential alternative for existing substances subject to risk management measures or a substance of concern, which is already known to exist but recently, seems to be commercially used at larger scale then in the past
4. new type of use of an already know substance with the potential to be released into the environment

There are no limitations with regard to a specific kind of EU legislation, the type of substances and the types of uses, applications or products in, which a substance occurs.

News items and literature are collected and reported on a weekly basis and discussed. Items are then selected based on the above criteria and gathered in a table of potential NERCs. Annex 5 gives an overview of potential NERCs identified for the environment involving various types of chemicals related to various issues of concern. In our methodology, further information collection is necessary to strengthen the first signals of a potential NERC.
The strengthening of the signals and further substantiation is based on readily available information from databases that can be easily checked on updates and, preferably with automated selection procedure, further processed.

The refining procedure is applied to all substances from the pre-selection stage. There will be no limitation based on type of use for instance on intermediates or chemicals falling under a specific EU legislation (medicines, pesticides or biocides, feed and foodstuffs etc.). The final stage takes information on the EU legislation into account that is applicable to the substance of concern.

The selection criteria and information used will be indicative for covering hazard, exposure, and risk. Therefore different types of information on exposure, hazard and risk of a substance varying in degree of soundness will be used in order to be as complete as possible for each criterion, see section 5.5.2 for further elaboration. The highest weight of evidence will be assigned to the most solid data for instance production volume data or data on tonnage band from the REACH registrations or measured environmental concentrations. When there are no data available the gaps will be filled by applying QSARs or expert judgement.

5.5.2 Prioritizing NERCs

A number of important aspects regarding *Exposure, Occurrence*, *Hazard*, and *Risk potential*, have to be considered in order to determine the strength of a signal and to decide on the urgency for further evaluation.

Information on volume and use can be used as exposure indicators. Some type of risk quotient can be derived from measured data and environmental quality limits or predicted no effect concentrations. The information on the hazard (toxicity, persistence, endocrine disrupting properties etc.), exposure (monitoring data, use and market volume) could be taken from the literature, risk assessment dossiers or various databases to make a priority list of chemicals. Additionally, estimations can be calculated, e.g. based on QSARS, when little or no information is available on specific aspects considered in the process of signal strengthening and determining the urgency for further evaluation.

A further elaboration of the prioritization procedure, giving more detailed considerations and description of the information and data that are used, is provided in Appendix B. The process of determining the urgency for further evaluation is still under developmentand other exposure routes as well as data sources might be included in future. For a selection of substances, the data for further prioritization have been collected and also presented in Appendix B.

The next step is to build a prioritization scheme or selection process from experiences that were gainedduring the expert consultations and discussions on the information gathered. One of the suggested further refinements is to include drinking water monitoring data.

5.5.3 Identifying potential measures for control

After prioritising the chemicals, the next step is to build a dossier to address and describe the concerns and identify and work out potential risk management options for the selected chemicals. Further elimination on the follow-up is provided in the next chapter in section 6.3 (step 6) on the overall approach.

6 Aspects set-up overall approach

6.1 General considerations

The developed procedures, tools and results in finding NERCs and subsequent follow-up actions for the protection goals (Workers, Consumers and the Enviroment) are, at this stage of research, not completely similar, although they have some similarities. The differences in approach are caused by the differences in the routing and triggers for the three protection goals. Here, the word 'trigger' is used to indicate that it starts a follow-up process to pinpoint and further identify the concern.

Ideally, these triggers are effect based because this directly motivates why we want to identify the chemical that causes effects that we consider as detrimental to health or the environment.

For workers, this effect based signalling is called the 'disease first' method. Triggers can be reported by (occupational) physicians via the e-tool SIGNAAL, where information on the health effect, work and exposure is gathered. Analysis for causality of these triggers is done in both national and international expert groups.

For consumers, several types of effects believed to be caused by chemicals in (cosmetic) products, and e.g. foodstuffs are recorded by governmental bodies.

For the environment, effects of chemicals are also monitored, e.g. for river water or drinking water quality. Because of the complexity of ecosystems, chronic or subtle effects are not so easily attributed to specific chemicals. In many cases, environmental exposure concentrations are routinely monitored by measuring concentrations of chemicals as a proxy for risk or effects of known chemicals.
For the workplace, in general no routine monitoring measurements take place. Based on the potential exposure of workers to a substance, every employer has to assess the chemical risk. However, this risk-assessment is based on known hazards/risks of the substances used. The risks of yet unknown effects by substances will thus not be assessed in this way.

In addition, concentration based monitoring can be a way to identify chemicals relevant for human or environmental exposure that may not yet be linked to effects considered adverse, seen as some kind of early warning system.
In conclusion, two different types of triggers start a process of further identifying a substance of concern:

(i) effect based, without necessarily knowing the causative relationship between the effect and one or more chemicals and
(ii) concentration based, without necessarily knowing whether these concentrations will cause adverse effects.

6.2 Identifying risks of new chemicals or unknown risks of known chemicals

Both effects based and concentration based monitoring can lead to the final identification of chemicals of concern. In both cases, chemical analyses need to be available that identify relevant chemicals that can either be linked to the effects (effects based) or are a trigger to think about unknown risks or effects due to potential for exposure (concentration based).

Different types of chemicals can be found in such assessments, picked up by chance in a broad non-specific assessment , or by intention by comparing known lists of chemicals to what has been analysed either routinely (e.g. at standard monitoring sites in the environment or in consumer products or the workplace) or incidentally.

The range of chemicals is co-dependent on the goal of the monitoring exercises where many different approaches are possible:

- Substances identified as a consequence of the causality analysis of the effect based approach;
- Routine comparison of known lists, e.g. registered chemicals (industrial chemicals, biocides, cosmetics, pharmaceuticals, etc.) with chemicals that are *routinely* monitored in the environment or in products to identify potential risks due to relevant exposure concentrations. Routine monitoring usually focusses on chemicals of known concern.
- Specific comparison of known lists in a broad analytical non-target screening to pick up chemicals in relevant media *without prior knowledge* to identify whether they are important or not.
- Specific monitoring of known high priority chemicals, e.g. (potential) CMR chemicals, (potential) PBT chemicals, SVHCs under REACH, to identify whether chemicals regulation is effective or not.
- Broad non-target screening to pick up unknown or poorly-known chemicals, e.g. those recently introduced to the market.

6.3 Proposed step-wise overall approach

A stepwise approach is advocated where triggers that identify a chemical of concern need to be further analysed, in order to clarify

a) whether there is a risk,
b) and if so, which policy framework, regulatory body or actor is most suitable to address the risk and
c) what kinds of actions are needed to ensure risks are controlled.

<u>Step 1 - Identifying a concern</u>

1.1. Effects based. When effects are found and some suspicion is raised that these are due to substances, a causative agent (the substance responsible) should be identified. This can be handled by various organizations, depending on the nature of the target populations and locale. For workers, different complementary methods are necessary to identify a concern (e.g. case reports, literature screening, data mining, etc). These signals are evaluated for causality within an (international) expert group. For environmental effects other than acute toxic events due to e.g. spills, it is often difficult to establish such links to single chemicals. In this scheme, we do not intend to address the difficulties of establishing causal links.

1.2. Concentration based. Depending on the goal of the measurement campaign, known chemicals, unknown chemicals or priority chemicals (e.g. SVHCs under REACH) can be picked up. This does not necessarily mean that the chemicals identified are problematic or cause effects. This will need to be established.

<u>Step 2 – Identifying already regulated chemicals</u>

It is assumed that a chemical that is regulated, is already linked to suspected effects or may be causing effects.

In all these cases, chemicals that are already regulated[2] need to be taken up first. This is because the mere presence of regulated chemicals already indicates a situation that is *a priori* considered undesirable. However, it is possible that a substance which is regulated by setting an occupational exposure limit (OEL) is still a trigger because of the fact that health effects are detected under the level of the current OEL. Especially when hazard based criteria are dominant as for CMR and PBT, there is not much merit in further ranking of urgency based on risk quotient (exposure/ hazard) calculations.

Because CMRs and PBTs are regulated, their presence may trigger a reconsideration of the control mechanisms that are installed

- Are the controls enforced by the regulation(s) effective?
- The exposure may be incidental not needing additional controls
- If the chemical is a (registered) intermediate, it should be established if other non-registered uses exist. If not, e.g. emission controls during production could be ineffective

Many of these practical issues need action by national or regional enforcement agencies to further clarify the issue before further (regulatory) action is considered.

Step 3 – Identifying chemicals that are under scrutiny by other parties
In some regulatory frameworks (e.g. REACH), many parties are involved in further clarifying hazard, exposure and risk issues for chemicals or concern. These activities may be kept up to date (as in REACH, but also think of UNEP-POP, Stockholm convention, etc.) and lists are available that can be searched for specific chemicals.

This means that some chemicals are evaluated for the need to generate further CMR or PBT information, some chemicals are evaluated for risk due to high exposure, and others may be proposed to be regulated due to established risks (e.g. in a REACH restriction) or hazards (authorization of SVHC under REACH). In such cases, it is suggested to provide the screening information to the evaluating Member State(s). It may be necessary to consider further follow-up, depending on the outcome of the ongoing evaluation. These substances should therefore be flagged for potential future action.

Step 4 – identifying potential CMRs and potential PBTs
Because the two groups of chemicals are regulated based on intrinsic hazard properties and not primarily on exposure and ensuing risk, it makes sense to identify these substances based on existing lists or available information elsewhere. When a potential PBT would be found in an environmental monitoring campaign, the presence and frequency of occurrence at various sites (both in place and time) would initially be more informative of the risks of wide dispersive use than concentrations per se (setting analytical issues with PBTs aside for the moment).

If a potential hazard is identified, further information could be requested. Exposure of workers to carcinogens and mutagens should be prevented. Carcinogens and mutagens should be replaced by less toxic substances if possible. In case of possible exposure, it should comply with the ALARA principle (as low as reasonably achievable).

[2] Different lists exist for e.g. PBTs, CMRs, SVHCs etc.

Step 5 - Risk estimation and ranking

Depending on the number of chemicals that are found in a specific setting, there may be a need to estimate the urgency of addressing the remaining substances after step 4.

In many screening exercises or priority setting exercises done so far, information on hazard, exposure, use and market volume is used to determine the strength of the trigger for further action.

In many cases, some type of risk quotient was determined together with information on volume and use as an indicator of urgency for further evaluation. Direct information on toxicity, exposure, use and market volume could be taken from the literature or dossiers, and discussed in an expert group to make a priority list of chemicals. Alternatively, estimations or proxies can be calculated, e.g. based on QSARS, exposure modelling and use information stored in various databases.

Step 6 – Identifying the need for further action (the Sherlock Step)

Depending on the outcome of the ranking exercise, each chemical should be scrutinized in more detail. First, all available information from chemicals legislation should be consulted to establish the correctness of estimated or proxy information and to find clues as to why the substance is present and or causes effects. Since many issues may be at play, it is not yet possible to give single most preferential way to proceed. However, the next steps check whether there is sufficient suspicion that risks are likely (top-down ranking).

6.1 Check use information
- Is the registration on an intermediate only or are there also other uses?
    - For intermediates, generally exposure should be controlled or low

6.2 Check hazard information
- in some cases, hazards were estimated for ranking purposes, establish validity
- check for potential hazards not yet established
    - If a potential hazard is identified, further information could be requested to establish concern

6.3 Check exposure information
- Does the available (dossier) information on use and exposure suggest exposure or not?
- Is the substance produced, formulated or sold in a product locally or not?
    - The actual exposure needs to be compared to that predicted or measured in a regulatory framework. Enforcement action may be needed, or further information on use and exposure could be requested as evaluation activity within a framework

6.4 Check risk information
- Does the available (dossier) information suggest risk or not?
    - The actual risk needs to be compared to that predicted in a regulatory framework. Enforcement action may be needed (see 6.3) , or further regulatory action to ensure control of risk (e.g. market restrictions or authorization) could be required.

6.5 Consult on cases that are not resolved in networks etc. to increase evidence of risk.

By going through these steps, issues that could be addressed by enforcement or permits etc. should be taken up by the responsible parties. In some cases, the issue remains unclear and further consultation could be considered.

7 Recommendations future work

Our research for the identification of NERCs comprises in summary the following results:

- A full methodology for Workers, including a list of NERCs with recommendations for further actions.
- A proposed methodology in development for Consumers similar to that for Workers, including a list of potential NERCs which has to be worked out further to find out which substance can be identified as a NERC with subsequent measures to be taken.
- A proposed detailed and worked out methodology for the Environment employing several tools, for the identification of potential NERCs. Likewise Consumers, the cases have to be worked out further to find out which substance can be identified as a NERC with subsequent measures to be taken.
- An overview of all aspects to be considered for the overall approach

Due to different starting times and target-specific issues, the state of play for the identification of NERCs for the three protection goals, the work so far has followed parallel routes.

One of the challenges for future work is to further harmonize the methodology for the identification of NERCs for all the three protection goals. The necessity of such, an overall approach is highly wanted in order to be informed whether a signal of a potential NERC for one protection goal might also be a NERC for one of the other protection goals.

Hence, for the development of a comprehensive methodology future work involves:

- Integrating as far as possible the methodologies for Workers, Consumers and Evironment, employing all relevant sources of information and involving experts of the three disciplines.
- The set-up/development of a database including the information on NERCs on Workers, Consumers and Environment. Such a comprehensive database should facilitate mutual NERCs for all the protection goals
- Further improvement of the selection process, including improvement of selection criteria and causality assessment in order to come to a list of NERCs.
- Establishing further networks and involving experts from other international institutes making use of the various expertise for the identification of NERCs.

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9 List of abbreviations

BRFs	Brominated Flame Retardants
CESES	Consumer Exposure, Skin Effects and Surveillance
CLP	Classification, Labelling and Packaging of substances and mixtures
CMR	Carcinogenic, Mutagenic or Reprotoxic
CSR	Chemical Safety Report
DNEL	Derived-No-Effect-Level
DTPA	Di-ethylene-Triamine Penta-Acetic acid
EC	European Commission
ECHA	European CHemical Agency
ECSA	European Chlorinated Solvent Association
ED	Endocrine Disruptor
EDTA	Ethylene Diamine Tetra Acetic acid
EMPODAT	Emerging Pollutant DATabase
EQS	Environmental Quality Standard
ER	Estrogen Receptor
EU-OSHA	European Agency for Occupational Safety and Health Administration
EU-RAR	European Risk Assessment Report
GC/MS	Gas Chromatography hyphenated to Mass Spectrometry
I&M	Dutch ministry of Infrastructure and the Environment
KWR	Watercycle Research Institute
LC-HRMS	Liquid Chromatography High Resolution Mass Spectrometry
LOES	Landelijk Onderzoek Estrogene Stoffen
MEC	Measured Environmental Concentration
Modernet	Monitoring trends in Occupational Diseases and tracing new or Emerging Risks
MPC	Dutch Maximum Permissible Environmental Concentration
MTR	Maximaal Toelaatbaar Risiconiveau
MW	Molecular Weight
NERCs	New or Emerging Risks of Chemicals
NGO	Non-Governmental Organization
NIOSH	National Institute for Occupational Safety and Health
OECD	Organization for Economic Co-operation and Development
OEL	Occupational Exposure Limit
PBDE	Poly Brominated Diphenyl Ethers
PBT	Persisent, Bioaccumulative and Toxic
PFCs	Perfluorinated Chemicals
PNEC	Predicted-No-Effect Concentration
PVC	PolyVinylChloride
QSAR	Quantitative Structure-Activity Relationship
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals
REWAB	REgistratie WAterkwaliteitsgegevens Bedrijven
RIVM	National Institute of Public Health and Environment
RIWA	Vereniging van RIvierWAterbedrijven
RMOA	Risk Management Options Analysis
RSI	Repetitive Strain Injury
rtER	Rainbow trout estrogen receptor
RWS	RijksWaterStaat
SCCP	Short Chained Chlorinated Paraffins
SCOEL	The Scientific Committee on Occupational Exposure Limits
SDS	Safety Data Sheet
SRA	Society of Risk Analysis

SVHC	Substance of Very High Concern
SZW	Dutch ministry of Social Affairs and Employment
TTBP-TAZ	2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine
USEPA	United States Environmental Protection Agency
VWS	Dutch ministry of Health, Welfare and Sport
WFD	Water Framework Directive

10 Annex 1: Examples of emerging risks for Workers (taken from Palmen et al.,2013).

Substance	Worker population / tasks	Observed health effect	Emerging risk (reason of concern)	Organization	Literature
Indium tin oxide	Manufacture of flat-panel displays (LCD, plasma screen)	Pulmonary fibrosis	New technology	NIOSH (inquiry based on case reports)	Homma et al. (2005), Cummings et al. (2010), NIOSH HHE (2012b)
Crystalline silica (sand)	Sandblasting of textiles	Silicosis	New use, intensified exposure	Atatürk University (Turkey) - investigation based on case reports	Akgun et al. (2005), Akgun et al. (2008)
Synthetic polymeric fibres	Textile workers from a nylon flocking plant	Interstitial lung disease (Flock worker's lung)	New risk	Memorial Hospital of Rhode Island - investigation based on case reports NIOSH	Lougheed et al. (1995), Kern et al. (1998), Eschenbacher et al. (1999), Kern et al. (2000)
Vinyl chloride	Hairdressers and barbers - use of hairspray	Angiosarcoma of the liver	Historical risk	3 universities in US (publication of case reports)	Infante et al. (2009)

Substance	Worker population / tasks	Observed health effect	Emerging risk (reason of concern)	Organization	Literature
Tricresyl phosphate	Pilots and cabin crew	'Aerotoxic syndrome' (neurological symptoms)	New exposure scenario	Universities US (case report), Occupational Health Services (evaluation physicians) Daily mail news item on case	Montgomery et al. (1977), Rayman et al. (1983), Tashkin et al. (1983), Sparks et al. (1990), Abou-Donia et al. (2013), Van Netten (1998), Winder et al. (2002), Winder (2006)
Diacetyl-containing flavourings	Workers in flavouring production facility and workers that apply flavours (microwave popcorn production facility, cookie factory, coffee processing facility)	Bronchiolitis obliterans	New risk	NIOSH alert	Kreiss et al. (2002) Akpinar-Elci et al. (2004) Kanwal et al. (2006) Cavalcanti Zdo et al. (2012) NIOSH Alert (2003) NIOSH HHE (2009a) CDC (2013) CDC (2002) Kreiss (2007) Kullman et al. (2005) Parmet et al. (2002) van Rooy et al. (2007)

Substance	Worker population / tasks	Observed health effect	Emerging risk (reason of concern)	Organization	Literature
Perchloroethylene	Dry cleaning	Oesophageal squamous cell carcinoma	Historical risk	Connolly Hospital, Dublin, Ireland (case report) Parliamentary questions in EU Parliament ECSA (product safety summary and health summary on perchloroethylene)	Babiker et al. (2012) ECSA (2011a) ECSA (2012a)
5-Aminosalicylic acid	Drug manufacturing	Occupational asthma	New risk	Biomedical research network centre on respiratory diseases, Madrid, Spain (case report)	Sastre et al. (2010)

11 Annex 2: Examples of emerging risks for consumer

Substance	Consumer Product	Observed health effect	Issue	Reason of concern	Proposed action	Links
Lead	Childrens' jewellery	Neurological damage at very low levels	Levels above legal limits	Historical risk	Removal from market, more intense market surveillance	http://www.umweltbundesamt.at/aktuell/presse/lastnews/news2014/news_140514/
Nickel	Childrens' jewellery	Allergic reaction	Levels above legal limits	Historical risk	Removal from market, more intense market surveillance	http://www.umweltbundesamt.at/aktuell/presse/lastnews/news2014/news_140514/
Bromide	Fruit and sport drinks	Memory loss and skin and nerve problems.	Found in brominated vegetable oil	Historical risk	Removal from cola drinks	http://www.bbc.com/news/business-27289259
TTBP-TAZ	Plastic consumer products	Yet unknown, no data regarding toxicity	Found as in flame retardant in plastic consumer products and house dust	New risk (substance is replacement for banned PBDEs)	More info needed on this new flame retardant. Also present in other products??	http://pubs.acs.org/doi/abs/10.1021/es4057032, A Novel Brominated Triazine-based Flame Retardant (TTBP-TAZ) in Plastic Consumer Products and Indoor Dust - Environmental Science & Technology (ACS Publications)
Triclosan and triclocarban	Household products,	Endrocrine disrupting,	New limits needed	Increasing knowledge	Measures are already (partly) taken	http://pubs.acs.org/doi/pdf/10.1021/es500495p

	cosmetics	cross-resistance antibiotics		on potential risk for cross-resistance	(cosmetics, REACH), more needed??	
Formaldehyde	In hair straight-ening products	Air concentrations above limits for salon	Limits exist, inspection and more strict limits needed,	Emerging risk (increased exposure due to trends)	EU COM has accepted a ban on the use of formaldehyde (methylene glycol) in hair straigtheners. Formaldehyde now only accepted for use in oral care products (0.1%) and other products (0.2%).	2014 - 03/27/2014 - US Department of Labor's OSHA forms alliance with Concerned Beauty Professionals to reduce chemical hazards in the beauty industry
Isothiazolinone	Various, e.g. cosmetics, detergents, paints etc.	Sensitizer, increased use, potential risks for inhalation	Allergic contact dermatitis	Emerging risk (increased exposure due to trends)	Measures were taken for use cosmetics, also REACH/CLP actions (RMOA, CLH)	http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_145.pdf
PFC's (perfluorinated chemicals)	Swimwear, drinking water, food contact materials, football boots	More toxic than initially thought		New risk	Better labelling, more information on hazards needed	
Endocrine disrupting	Water		fracking may increase health		More information needed	The Guardian

chemicals in water samples from drilling sites			risks through exposure to EDC			
1,4 dioxane	Cosmetics	Carcinogenic	Ban in cosmetics, however still used in US	Historical risk, potential risk due to internet sales	Reinforcement, particular on internet sales	
Emerging and Novel Brominated Flame Retardants (BFRs)	Food		concern for bioaccumulation.			Scientific Opinion on Emerging and Novel Brominated Flame Retardants (BFRs) in Food
Microplastics	Various, e.g. cosmetics		Environmental risk, potential human risk		More information is needed, ban on use in cosmetic scrubs is proposed	http://www.volkskrant.nl/vk/nl/2844/Archief/archief/article/detail/3355880/2012/11/30/Zeepier-vindt-microplastics-onverteerbaar.dhtml

12 Annex 3: Results KWR study (Kolkman and ter Laak, 2012)

Table A3.1: MEC/PNEC ratios and relevant monitoring data and chemical properties for substances with a ratio above 0.5.

CAS NR	Chemical	MEC (µg/L)	PNEC^ (µg/L)	MEC/ PNEC	Selection criterion	% Positive measurements
117-81-7	bis(2-ethylhexyl) phthalate *mainly applied as plasticizer for PVC*	2.7 (b)	0.0079	340.1	PBT list	5% (6/115)
100-97-0	Hexamethylene-tetramine (urotropine) *industrial intermediate, food preservative*	1.3 (b)	0.1299	10	Occ.	89% (16/18)
60-00-4	EDTA *complexing agent*	23 (c)	29.272	7.9	Occ.	71% (17/24)**
128-37-0	2,6-di-tert-butyl-p-cresol *Anti-oxidant in food and other products*	1.455 (a)*	0.3601	4	Occ.	14% (11/77)
84852-15-3	4-nonylphenol *Degradation product of nonlylphenol ethoxilates*	0.91 (b)	0.41	2.2	PBT list	5% (5/92)
1222-05-5	Galaxolide *Fragrance*	0.206 (a)*	0.1184	1.7	PBT list	5% (4/77)
67-43-6	DTPA *complexing agent*	4.4 (**b,c**)	30.814	1.4	Occ.	17% (12/69)
947-04-6	Laurolactam *Monomer for polyamide*	0.123 (a)*	0.1152	1.1	Occ.	25% (19/77)
205-99-2	benz[e]acephenanthrylene *combustion by product*	0.09 (c)	0.1445	0.6	Occ.	1% (2/205)**
85535-84-8	5-chlorodecane (SCCP) *Flame retardant, PVC plasticizer*	0.3 (b)	0.5129	0.6	PBT list	5% (5/92)
62-53-3	Aniline *Industrial Intermediate*	0.18 (a,b,**c**)	0.3163	0.6	Occ.	6% (12/240)**
87-68-3	Hexachlorobuta-1,3-diene *numerous applications*	0.09 (c)	0.1836	0.5	PBT list	0.25% (1/400)**

a = RWS, b = RIWA, c = REWAB raw water: The letter in **bold** indicates in which dataset the MEC value was detected.

* Concentrations of RWS data are indicative values as no quantification was applied with this GC MS broad screening.

** Positive measurements of aggregated data per sampling location that contains between 1-13 individual measurements,

Chemicals which were detected with only a single measurement in the RWS data were excluded from this list.

^ PNEC from QSAR, EPIWin

Table A3.2: The top-list of matching elemental compositions from the 5 STP and 2 surface water samples

Name	CAS NR	Verified identity
1,1',1''-nitrilotripropan-2-ol	122-20-3	
1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol	102-60-3	
Dacarbazine	4342-03-4	
2-nitroanisole	91-23-6	+
Cycloheximide	66-81-9	
Benomyl	17804-35-2	+
1,3-diphenylguanidine	102-06-7	
hexyl D-glucoside	54549-24-5	
dibutyl phthalate/ diisobutyl phthalate	84-74-2	
2-(2-butoxyethoxy)ethyl acetate / 3-hydroxy-2,2-dimethylpropyl 3-hydroxy-2,2-dimethylpropionate	124-17-4	
dicyclohexylamine / dodecanenitrile	101-83-7/ 2437-25-4	+
N-[3-(dimethylamino)propyl] methacrylamide	5205-93-6	
2-(2-(2-butoxyethoxy)ethoxy)ethanol / [2-(2-methoxymethylethoxy)methylethoxy]propanol	143-22-6/ 25498-49-1	
isopentyl acetate / heptanoic acid	123-92-2/ 111-14-8	
2,2'-[oxybis(methylene)]bis[2-ethylpropane-1,3-diol]	23235-61-2	
2-butoxyethyl acetate*	112-07-2	
3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	4098-71-9/ 53880-05-0	
4,4'-bis(dimethylamino)-4''-(methylamino)trityl alcohol	561-41-1	
6,6'-di-tert-butyl-4,4'-thiodi-m-cresol	96-69-5	
climbazole	38083-17-9	
dibutyl fumarate / dibutyl maleate	105-75-9/105-76-0	
5-allyl-1,3-benzodioxole	94-59-7	
dimethyl(tetradecyl)amine	112-75-4	
tris(2-chloro-1-methylethyl) phosphate	13674-84-5	
triphenylphosphine oxide	791-28-6	+
3-(isodecyloxy)propiononitrile	64354-92-3	
exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl methacrylate	7534-94-3	
tris(2-butoxyethyl) phosphate	78-51-3	+
tributyl phosphate	126-73-8	+
2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol/ alpha,2,2,6-tetramethylcyclohexene-1-butyraldehyde	28219-61-6 / 84518-22-9	
tert-butyl perbenzoate[3]	614-45-9	
(Z)-cyclooctene	931-87-3	

13 Annex 4: Information prioritization NERCs for Environment

Exposure
Scale of use. As an indication of the scale of use the production volume of the substance in the European Union is used. The production volume gives no indication of the potential of the substance to be released in the environment. For an assessment of the potential to be released into the environment, substance properties, industrial processes, applications, and uses in different type of products have to be considered. To some level, this information is available in disseminated data of the REACH registration dossiers. Substance properties like water solubility and vapour pressure are provided and information on manufacture, use and exposure is provided by indication of relevant environmental release categories, chemical product categories, the sector of use and process categories. This information provides insight in the different uses of a substance. The main issue is that there is no or too little information on the breakdown of the total volume of the substance over the different uses. This may lead to a completely wrong assessment of the potential release of a substance into the environment. Additional information is needed for a more thorough assessment of the potential release into the environment. This would require too much effort for the purpose of the initial refining procedure. Therefore, at first instance only the production volume is used as a selection criterion in the identification of potential NERCs completed with an indication of the main types of use.

Release potential. The release potential is mainly determined by the type of use of a substance and the type of source. A good impression of the potential to be released into the environment can be obtained from the technical function of a substance as such, in a preparation or in an article. The technical function of a substance can be categorized according to the fate of a substance as either a processing aid, its use resulting in inclusion into or onto a matrix or its use as a monomer and intermediate. Furthermore, an important indicator for the environmental release is the type of source, which can be divided in two main categories either (industrial) point sources or wide dispersive used
The release potential can be characterized qualitatively by the combination of the type of use and type of source

The release potential is considered to be low for substances that are chemically converted into another substance (intermediates or monomers) or chemically bound to a matrix (initiators, vulcanizing agents, curing agents, chain transfer agents, etc.)

The release of substances, that are physically or chemically bound to a matrix, from articles like plasticizers in the in the use (processing) and service life stage are inextricably bound and scored as a whole

	Processing aid	In matrix	Intermediate/ monomer
Point source	Medium	Low	Low
Wide dispersive use	High	Medium	Low
Article/dried preparation			

Occurrence in the environment
Several databases are consulted to get a picture on the presence of chemicals in the aquatic environment including sediment and whether the measured concentrations are of any concern. The most import database is built within Norman project. They initiated a database of environmental quality monitoring data from European Union member states. The monitoring data are collected in the EMPODAT database for various environmental compartments like soil, air and water. Furthermore, several database containing monitoring data for the Netherlands are used. An overview of the databases and other source used is presented in the Table below.

Name database	Instituted/organisation	Geographic coverage
EMPODAT	NORMAN (EC)	European Union (differs per substance)
Waterbase	Rijkswaterstaat	Netherlands
Bestrijdingsmiddelen Atlas	Centrum voor Milieuwetenschappen Leiden	Netherlands
RWZI Watson database	Emissieregistratie	Netherlands
RIWA Rhine, Meuse	Vereniging van rivierwaterbedrijven	Germany, Belgium, Netherlands
FATE	Joint Research Centre, European commission	European Union

At first instance, the focus is on fresh water quality. The water monitoring data are used to derive a 95th percentile value of measured concentrations (MEC). This values is compared to the selected no effect concentration. There is a potential concern for the aquatic environment when the MEC exceeds the PNEC, i.e. the MEC/PNEC quotient is larger than one.

Hazardous properties
To identify the hazardous properties of a substance for the environment the toxicity for aquatic species, persistency, bioaccumulation and endocrine disrupting properties are considered. For completeness and identification of possible concern for consumers or at the workplace human end- points for carcinogenicity, mutagenicity and reprotoxicity are considered.

Toxicity. For an indication of the toxicity of a substance, environmental quality standards from the Water framework directive, Dutch maximum permissible environmental concentrations (MPCs) or predicted no effect levels (PNECs) applied in the risk assessment of chemicals in the EU are used.

Predicted no effect levels (PNECs) are available in the publically available data from REACH registration dossiers and EU risk assessment reports. Only for

intermediates there is no obligation to derived a PNEC within the context of REACH. Furthermore environmental quality standards from the Water Framework Directive and the maximum permissible concentrations that have been derived in the Netherlands are employed. For the latter there are either officially established values or ad hoc values. Ad hoc values are derived through a quick procedure applying assessment factors depending on the amount of readily available information whilst for the official procedure a more in depth assessment is done usually resulting in the application of lower assessment factors not necessarily resulting in higher limit values.

Persistency and bioaccumulation. For the identification of possible PBT properties of substances, the information on the candidate list of substances of very high concern drawn up in the context of the REACH directive is used. In addition to this, the work on deriving PB-scores for 64,000 chemicals by Rorije et al. (2011) will be applied to identify the potential PBT properties of substances. Substances are scored on their persistent and bio-accumulative properties. The highest score for each property has the value one, so the maximum score for PB-properties has the value of two.

Endocrine disrupting properties. To get an impression of the endocrine disrupting potential of chemicals the results of the actions undertaken by the European Commission to address the potential problems posed by endocrine disruptors (EDs) are used. One of the actions was to review chemicals to determine the strength of evidence for endocrine disruption. Chemicals were assigned to one of three categories: Category 1 - evidence of endocrine disrupting activity in at least one species using intact animals; Category 2 - at least some in vitro evidence of biological activity related to endocrine disruption; Category 3a - no evidence of endocrine disrupting activity or Category 3b no data available.

A total of 553 chemicals that had been suggested by various organisations or in published papers or reports as being suspected EDs were assessed in several studies. The results of these studies are compiled in a database, which is available at the website of the European Commission on the EU-strategy for endocrine disruptors (EC, 2014).

In addition to this work 26 chemicals that have been evaluated by the Danish Centre on Endocrine Disrupters to test the proposal of the Danish Environmental Protection Agency for criteria for the identification of substances with endocrine disrupting properties (Hass, 2012). Only one of these 26 chemicals (triclosan) was not included in the database on ED categories that resulted van the actions undertaken by the European Commission. In general the conclusions are very comparable, only for perchloroethylene the conclusions were different. From the methodology applied by the Danish EPA it was concluded that there is no evidence for endocrine disrupting activities as the database from the European Commission reported that there is at least some in vitro evidence of biological activity related to endocrine disruption (Category 2).

For substances that are not (yet) included in the database the potency for endocrine disrupting activity will be indicated by using a QSAR. There are various possibilities for SAR screening of endocrine activity. In literature several QSAR models for predicting “endocrine disruption” exist, although almost all of them focus on the estrogen receptor (binding or expression) disregarding other endocrine pathways such as androgen receptor, steroidogenesis or thyroid receptor. Furthermore, a high possibility of (estrogen) receptor binding is not a

guarantee that a substance will therefore definitely be an "endocrine disruptor", especially since this class of chemicals is not very well defined yet. However, for screening purposes the hypothesis can be used that likely estrogen binding chemicals have a high(er) probability of being endocrine disruptors.

The OECD QSAR Toolbox (free available software; OECD, 2014) gives the possibility to screen substances for their potential endocrine activity through using two different profiles:

(i) Estrogen receptor binding

Estrogen receptor (ER) binding is a molecular initiating event much like protein binding. It is an endpoint where several comprehensive databases exist, which has led to the development of several approaches for using (Q)SARs to predict ER binding and possible subsequent endocrine disruption. The incorporated Toolbox ER binding profiling scheme is based on structural and parametric rules extracted from literature sources and supported by experimental data. The ER-binding profiler classifies chemicals as non-binders or binders depending on molecular weight (MW) and structural characteristics of the chemicals:

a) Very strong binders: Chemicals with MW between 200 and 500 Da and two rings with a hydroxyl group connected to each of them.
b) Strong binders: Chemicals with at least one 5-or 6-members carbon ring with an unhindered hydroxyl or amino group and MW between 200 and 500 Da;
c) Moderate binders: Chemicals with at least one 5-or 6-members carbon ring with an unhindered hydroxyl or amino group and MW between 170 and 200 Da;
d) Weak binders: Chemicals with at least one 5-or 6-members carbon ring with an unhindered hydroxyl or amino group and MW less than 170 Da;

If the target chemical does not meet any of the structural and parametric requirements listed above it is classified as Non binder:

- Non binder with impaired hydroxyl or amino group;
- Non binder, MW more than 500 Da;
- Non binders without hydroxyl or amino group;
- Non-binder, non-cyclic.

(ii)rtER Expert System ver.1 – USEPA

The rtER Expert system as developed by the USA classifies substances according to their structure as possible Estrogen Receptor binding substances, much like the Estrogen receptor binding profile. In addition, there is a possibility to run the (quantitative) rtER Expert system QSAR to predict the relative binding affinity of a substance to the estrogen receptor. Strong binders are more likely to exert an endocrine disrupting effect (through the estrogen receptor pathway.

For practical uses, the Estrogen receptor binding profile will be used to classify substances as either endocrine disrupting vs. non-endocrine disrupting, and the rtER Expert System QSAR can be used to rank the group of estrogen receptor binders.

SVHCs. In the context of the REACH Regulation, substances of very high concern are identified and put on the candidate list. The final goal is to list these substances on annex XIV of the REACH Regulation for the authorization procedure. Substances of very high concern are substances classified as being carcinogenic, mutagenic or, reprotoxic, having PBT or vPvB properties or substances of equivalent concern for instance with endocrine disrupting

properties. PBT or vPvB properties and endocrine disrupting properties are separate hazard criteria next to the CMR-properties.

In addition to the hazardous properties identified for substance on the candidate list of SVHCs, the CMR properties of substances from the harmonized classification of substances as reported in Table 3.1 of annex VI of the CLP Regulation and the self-classification of chemicals as reported in ECHA's classification and labelling inventory are referred to.

Risk potential
The potential of a substance to constitute a risk to the environment depends on the exposure and hazardous properties. The exposure potential is determined by the release potential, which is considered to be mainly determined by the amount and type of use. Hazardous properties are considered as such. The potential risk to the environment is expressed by the quotient of the registered amount of a substance in the European Union and the toxicity of the substance. The degree of toxicity is determined by the value of the environmental quality limit. The limited set of substances for which the potential risk has been determined in this way indicates that low values are smaller than 10 with values even below one. Values in the mid-range reach up to 100 as higher values go beyond and might range up to 1000 or more.

A better indication for the potential risk of a substance to the environment is the quotient of the measured environmental concentration (MEC) and the predicted no effect concentration (PNEC). Preferably, the PNEC is based on toxicological data. If these are not available, QSAR models will be used to provide an estimate. Measured concentrations in the aquatic environment will be used to calculate the 95^{th} percentile, which will be used as the MEC in calculating the risk quotient. As a first simple approach the 95^{th} percentile of the whole available data set will be used, which might cover several years and locations and countries. MEC/PNEC quotients above one might indicate a potential risk to the environment.

Tabel A4.1: Part 1 of table of prioritization, exposure data

Name	Use	Main type of source [A]	Type of registration dossier Full/Intermediate	REACH registration volume (kton)[1]	PNEC water (µg/L)[2]		Measured concentration in water (MEC, µg/L)[3]	MEC/PNEC[4] EQS;QSAR	Tonnage/PNEC (1000 m^3)
					EQS	QSAR***			
Fluoxetine (Prozac)	Medicine, anti-depressant	Wide dispersive	not registered	-	0.6	-	0.0006-0.4	max 0.7	-
Oxazepam	Medicine, tranquiliser	Wide dispersive	not registered	-	2	-	0.001-0.8	max 0.4	-
17-β-estradiol	Intermediate; medicine, contraconceptive	Wide dispersive	intermediate	confidential	0.14*; 0.001	-	0.001-0.01 [d]	± 1	-
2,4,6-tris(2,4,6-tribromophenoxy-1,3,5-triazine	Brominated flame retardant	Industrial physically bound in matrix	Full	1-10	0.01#-0.37#	-	-	-	1000-27
2,2,4,4-tetramethyl-1,3-cyclo butanediol	Monomer for polyester plastic	Industrial, chemically bound in matrix	Full	0.1-1	100#	-	-	-	0.001

Tabel A4.2: Part 2 table of prioritization, hazard data

Name	PBT/CMR/ED[5]								
	PB[a]	P-score	B-score	PBT[b]	ED Humaan[c]	ED Environment[c]	rtER expert system	ER binding	ED potency
Fluoxetine (Prozac)	1.29	0.72	0.57	not listed	not listed	not listed	No alert found	Non binder, without OH or NH2 group	NO
Oxazepam	0.33	0.33	0.00	not listed	not listed	not listed	No alert found	Non binder, impaired OH or NH2 group	NO
17-β-estradiol	0.45	0.45	0.00	not listed	not listed	not listed-	No alert found	Very strong binder, OH group	YES
2,4,6-tris(2,4,6-tribromophenoxy-1,3,5-triazine	1.67	1.00	0.67	not listed	not listed	not listed	No alert found	Non binder, MW>500	NO
2,2,4,4-tetramethyl-1,3-cyclo butanediol	0.09	0.09	0.00	not listed	not listed	not listed	No alert found	Non binder, impaired OH or NH2 group	NO

Notes for Tables A4.1 and A4.2

1) Registration volume: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances
2) PNEC water: *MTR = JG-MKN (KRW) or ad-hoc MTR; ** PNEC EU-RAR or SIDS; # PNEC from public available REACH registration dossier; ***QSAR based on ECOSAR
3) MECwater
a) RIWA database
b) RWS database
c) REWAB database
d) EMPODAT
4) Risk characterisation: 95th percentile/PNEC < 0.5 Low; 0.5-1.0 Medium; > 1.0 and 50th percentile > 1 Possible risk
5) Hazard properties
a) PB-scores, Rorije et al, 2011 (PB-scores have been derived for almost 65,000 substances use this list for a check and categorise, for instance as high > 1.5; medium 1-1.5; low 0.5-1.0; very low < 0.5
b) JRC PBT information System:http://esis.jrc.ec.europa.eu/index.php?PGM=pbt
c) EC EDS Database: http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm
Category 1 - Evidence of endocrine disrupting activity in at least one species using intact animals; Category 2 - at least some in vitro evidence of biological activity related to endocrine disruption; Category 3 - a. Substances with sufficient data for evaluation, which are not considered to be endocrine disrupters; b. Substances with no or insufficient data available.
d) SVHC list - http://echa.europa.eu/nl/candidate-list-table
e) 1-harmonized/2-self classification - http://echa.europa.eu/information-on-chemicals/cl-inventory

14 Annex 5: Examples of emerging risks for environment

Chemical	CAS NR	Function of the substance	Issue/concern	Reference
Fluoxetine (Prozac)	59333-67-4	Medicine, antidepressant	Behavioral effects on fish in the laboratory at environmental relevant concentrations.	http://www.nature.com/news/human-drugs-make-fish-flounder-1.11843
Oxazepam	604-75-1	Medicine, tranquillizer	Behavioral effects on fish in Swedisch Lakes	http://www.trouw.nl/tr/nl/5009/Archief/archief/article/detail/3394313/2013/02/15/Met-pilletje-op-gooit-baars-alle-remmen-los.dhtml
17-β-estradiol	50-28-2	Medicine, contraconception	Behavioral effects on fish in laboratory experiments	http://www.nature.com/news/human-drugs-make-fish-flounder-1.11843
2,4,6-tris(2,4,6-tribromophenoxy-1,3,5-triazine	25713-60-4	Brominated flame retardant	detected in plastic samples > 2012	http://pubs.acs.org/doi/abs/10.1021/es4057032
Bisphenol A	80-05-7	Intermediate and monomer (polycarbonate and epoxyresins)	Measured concentrations in sediment factor 6 above the PNEC	Personal communication Willie Peijnenburg, Norman WG meeting February 2014 http://europepmc.org/abstract/med/24888621
2,2,4,4-tetramethyl-1,3-cyclo butanediol	3010-96-6	Intermediate and monomer (polycarbonate and epoxyresins)	Substitute for bisphenol A	http://www.oeconline.org/our-work/healthier-lives/tinyfootprints/toxic-prevention/safer-alternatives-to-bisphenol-a-bpa
Triclosan	3380-34-5	Anti-bacterial ingredient in cosmetics and personal care products	Exceedance of the predicated no effect concentration	http://www.sciencedaily.com/releases/2008/05/080516100942.htm
Triclocarban	101-20-2	Anti-bacterial ingredient in cosmetics		http://www.ime.fraunhofer.de/content/dam/ime/e

		and personal care products		n/documents/AE/newsletter_norman_3a.pdf
di(2-ethylhexyl) fumarate (DEHF)	141-02-6	Plasticizer for PET	detected significant antiestrogenicity in bottled drinking water, linked to the presence of this substance	http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0072472

RIVM
De zorg voor morgen begint vandaag