



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

Early warning systems to detect new and emerging risks in Europe

RIVM Letter report 2016-0022
N.G.M. Palmen



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Colophon

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Vroege detectie van nieuwe en opkomende, werk gerelateerde gezondheidseffecten, zoals kanker, in Europa

Het ministerie van Sociale Zaken en Werkgelegenheid wil dat mensen op de werkvloer minder aan kankerverwekkende stoffen blootstaan. Hiervoor is het belangrijk dat stoffen en processen die kanker kunnen veroorzaken snel worden opgespoord. Op Europees niveau is ook interesse voor deze zogeheten *early warning systems*, maar landen gebruiken hiervoor verschillende systemen. Het RIVM heeft in 51 Europese landen geïnventariseerd welke dat zijn om nieuwe en toenemende risico's op te sporen.

Zeven landen hebben, soms met een ander land, een 'signaleringssysteem' ontworpen. Hiermee kunnen artsen gezondheidseffecten, waaronder kanker, melden als ze vermoeden dat die effecten worden veroorzaakt door stoffen of arbeidsprocessen waarvan het kankerverwekkende effect nog niet bekend is. Naar aanleiding van een melding onderzoekt vervolgens een expertgroep of er daadwerkelijk sprake is van een oorzakelijk verband tussen de blootstelling en de gemelde gezondheidseffecten. Tien andere landen gebruiken een systeem dat niet speciaal is ontworpen om onbekende risico's te signaleren, maar daar desgewenst wel voor kan worden ingezet.

Naast de signaleringssystemen zijn er een aantal databases beschikbaar die informatie bevatten over de blootstelling aan gevaarlijke stoffen of processen en gezondheidseffecten. Deze databases kunnen worden gebruikt om mogelijk schadelijke stoffen op te sporen. Ook hier vervullen expertgroepen een elementaire rol om de signalen te evalueren.

Experts vinden het essentieel dat elk land expertisecentra heeft waar werknemers terecht kunnen die mogelijk ziek zijn geworden door hun werk en die onderzoeken of er een verband is tussen de blootstelling en het gemelde gezondheidseffect. Deze casussen dienen te worden verzameld en geëvalueerd; volgens de meeste landen die aan dit onderzoek hebben meegedaan bij voorkeur in internationaal verband. Ook hebben zij hiervoor mogelijkheden aangereikt. Onder andere is voorgesteld om het bestaande netwerk van specialisten op het gebied van arbeidsgelateerde gezondheidseffecten (MODERNET) of andere internationale comités die hierover adviseren, te gebruiken.

Als uit de evaluaties blijkt dat er werkelijke sprake is van een nieuw of toenemend risico, is actie nodig om het risico te beperken. Deze studie reikt hiervoor mogelijkheden aan.

Kernwoorden: vroege detectie, werk gerelateerde kanker, kanker door het werk, nieuwe en toenemende risico's, clinical watch systeem, database, biomarker, expertgroep

Synopsis

Early warning systems to detect new and emerging risks, e.g. cancer, in Europe

The Dutch ministry of Social Affairs and Employment aims to reduce worker exposure to carcinogens. So, it is important to identify carcinogens and work processes that may cause cancer as early as possible. Also at the European level there is much interest in so-called *early warning systems*, but countries use different systems. RIVM made an inventory in 51 European countries for identifying new and emerging risks for workers.

Seven countries developed a signaling tool, sometimes in cooperation with another country. Using such a tool, physicians can report health effects, e.g. cancer, when they suspect a hitherto unknown causal relationship between substances or work processes and the reported health effect. Next, a group of experts in occupational disease and exposure will evaluate the possible causal relationship. Ten other countries reported systems which are not specifically designed to identify new and emerging risks of chemicals, but which may be used as such.

Besides signaling tools, databases are available with information on exposure to hazardous substances and processes, and health effects. These databases can be used to identify possible carcinogens. Again, expert groups play a fundamental role in the evaluation.

National centres that investigate work-related health effects of workers play an essential role in the evaluation of a possible causal relationship between exposure and health effect, according to experts in the field. According to most of the countries in this study, cases should be collected and evaluated preferably at an international level. Many suggestions were given; e.g. using an already existing international network of professionals who evaluate and discuss new and emerging risks for workers (MODERNET) or other international advisory committees.

Once a new and emerging health risk has been established, action has to be taken to control the risk. This study gives an overview of possible actions.

Keywords: early warning system, work related cancer, occupational cancer, new and emerging risk, clinical watch system, database, biomarker, expert group

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Summary

All workers are entitled to work in environments where risks to their health and safety are properly controlled. This holds also for exposure to chemicals. Under the Dutch presidency of the European Union during the first half of 2016, The Netherlands aim to take action to reduce work related cancer. The identification of substances and work leading to work related health effects like cancer is therefore important. The way in which these substances and work processes can be identified needs both close cooperation between countries and the use of various methods.

This report presents an overview of different methods used in European countries, which can be used to identify new and emerging risks of chemicals (NERCs). These methods can also be applied to the identification of substances that cause work related health effects like cancer. A questionnaire (see Appendix B) was sent to representatives of all European countries with questions on:

- The presence of clinical watch systems¹.
- The availability of databases for epidemiological research to study a causal relationship between exposure and health effects (e.g. cancer).
- The use of biomarkers for the identification of work related health effects, especially cancer.
- The need for an international expert group on work related health effects.

Twenty three of 51 European countries filled in the questionnaire. Seven countries reported to have clinical watch systems that were specifically designed to detect NERCs (e.g. cancer) and 10 countries have systems that can be used for that purpose. Labour inspectorates, research organizations and insurance funds are the main institutions collecting NERCs. Medical doctors can report NERCs in all systems. In several systems also industrial hygienists, occupational nurses, employers, trade unions and workers can report. Literature search and discussions in an expert group play a key role in the evaluation of a possible causal relationship between the exposure and the reported health effect.

There are several databases, containing information on both exposure or work and health effects, that can be used to study work related health effects. Several of them are directly connected to the clinical watch systems, but there are also other databases that can be used for that purpose. Research on work related health effects takes place for most of these databases and expert groups are usually available.

Both the Czech Republic and Romania reported using biomarkers specifically for occupational cancer. In Romania, detection of NERCs caused by substances using biomarkers is legally established. Most

¹ Clinical watch system: the aim of sentinel surveillance systems in occupational health involve the ongoing and rapid identification of sentinel health events (cases and their corresponding occupational risks) for purposes of follow-up and for developing statistical trends (Samant et al., 2015)

countries applying biomarkers reported that these biomarkers have not been specifically developed for the identification of NERCs. Biomarkers are mostly used in research projects where occupational health services and research organizations play a key role in taking the initiative.

It is the general perception that an *international* group of experts should evaluate the candidate NERCs. Many ideas were generated by the responders on the way in which such an international group of experts should be organized.

It is recommended to discuss among policy makers how the evaluation of possible NERCs can be institutionalized within Europe and how substances that turn out to be a NERC will be effectively regulated.

1 Introduction

The first six months of the year 2016 The Netherlands holds the presidency of the European Union. During that period, the Dutch Ministry of Social Affairs and Employment (SZW) organizes an international conference on how to ban work-related cancer in the EU. The main purpose of this conference is to set policy agenda points for the years to come. RIVM is asked to prepare the scientific substantiation for some of the themes. One of the themes is the availability and use of 'early warning systems' to identify and evaluate new and emerging risks (NERCs) leading to health effects like occupational cancer, so that substances and/or processes will be identified and measures can be taken by policymakers to control or prevent exposure. The preparation of the conference will be done in close cooperation with other EU stakeholders to establish a solid basis and level playing field to arrive at agenda points to be agreed upon at the end of the conference.

Early warning systems are important to detect new or emerging work related health effects. Some examples identified by early warning systems are the occurrence of (1) a rare life threatening lung disease caused by inhalation exposure of diacetyl (butter flavouring) in a diacetyl production facility and during the use of diacetyl in food industries (popcorn, cookie, coffee production facilities), (2) silicosis caused by crystalline silica inhalation exposure in textile industry during sandblasting of jeans, and (3) lung fibrosis caused by inhalation exposure to indium tin oxide during manufacturing of flat panel displays and waste treatment (recycling). Early warning systems are also important in the detection of occupational cancer. This is a difficult endpoint because of the long latency between the exposure and the diagnosis.

The novelty of the use of early warning systems is to use signals from the field, such as cases or clusters of health effects allegedly related to occupational exposure. Obviously, occupational health specialists (occupational physicians, lung specialists, dermatologists, industrial hygienists etc..) need to be on the alert on the occurrence of any possible work related health effects. These health effects may be a consequence of a known hazard(s) or substance(s), or of an unknown hazard of a known substance through a new use of a substance leading to an unknown risk (e.g., via inhalation exposure instead of oral exposure), or even exposure to a completely new health hazard. Since new hazards may be rare or present after long latency periods, European collaboration is of great importance to detect and streamline these signals, as was already recognized by WHO:
http://www.who.int/occupational_health/activities/occupational_work_diseases/en/.

This study is the third in a series of reports issued by the RIVM on NERCs and gives an overview of different methods used in European countries, which can be used to identify NERCs. The first study (Palmen et al, 2013) gives an overview of NERCs detected during the last decades and the need to use complementary methods for their

detection. It also gives good arguments for the need of international expert groups to study the causal relationship between exposure and health effect(s). In the second study (Palmen and Verbist, 2015), a list of 49 NERCs were prioritized to address those substances that deserve the most attention, and an inventory was made showing the extent to which these 49 substances are already being regulated by the European chemicals legislation REACH or other legislation.

It is not the intention to create a harmonized or uniform approach, but to use the existing systems and share the knowledge. This report gives an overview of existing 'early warning systems' in the different European countries. New insights on NERCs can be generated by sharing information of the outcomes of the analyses made by scientists all over Europe. In this way, substances with still unknown properties may be identified. Another possibility is that another way of exposure to a substance (e.g. inhalation compared to oral) leads to other health risks because of altered working methods.

In any case, the identification of emerging risks requires the use of several complementary methods. An overview of methods that may be used is summarized in Palmen et al. (2013). In short, information from case reports, literature, data mining and health surveillance have to be integrated and used to evaluate a possible NERC. Such an evaluation should be performed by a group of experts, in order to discuss the information and make a decision on the work related risk of the substance or process to cause cancer.

In preparation of the conference, RIVM was asked by the Dutch Ministry of Social Affairs and Employment (SZW) to make an inventory of 'early warning systems' already existing in the EU member states. This report gives an overview of:

- Clinical watch systems for the collection of spontaneously reported cases in Europe
- Databases that may be used for epidemiological research on possible relationships between occupation and/or exposure to substances and health effects (e.g. occupational cancer)
- Information on biomarkers that can be used to detect NERCs
- The opinions of the member states regarding the necessity to evaluate NERCs in an international expert group.

2 Methods

Selection of EU countries and their contact persons:

An overview of all European countries² was made and contact persons for every country were delivered by the Dutch Centre of Occupational Disease. At first instance members of the MODERNET Network³ were asked to participate in the enquiry. Countries that are not a member of the network were approached via research institutions and/or occupational health centers in their country using the internet (email addresses). For an overview of countries and their organizations, see Appendix A. In many cases, several research institutions and/or occupational health centers were approached in one country in which case they were asked to fill in the questionnaire together, so that one questionnaire was received for every country. The questionnaire was distributed in June 2015. In November 2015, a reminder was sent to the non-responders to increase the response rate.

Enquiry

All European countries were kindly requested to fill in a questionnaire on 'early warning systems' (see Appendix B). Information was gathered on:

- the existence of one or more 'clinical watch systems'⁴ for the collection of spontaneous reported cases in Europe;
- the existence of databases that may be used for epidemiological research on possible relationships between occupation and/or exposure to substances and health effects (e.g. occupational cancer);
- biomarkers for exposure and/or biomarkers for biological effects that can be used to detect NERCs;
- the opinion of the member states on the necessity to evaluate NERCs in an international expert group.

Analysis:

The completed questionnaires were analyzed qualitatively and quantitatively. The answers were qualitatively organized in an excel spreadsheet and presented in tables (see results). If applicable, frequencies were presented. The first draft of the report was submitted to the respondents and revised if necessary.

² List of European countries: <https://www.countries-of-the-world.com/countries-of-europe.html>

³ MODERNET: Monitoring trends in Occupational Diseases and tracing new and Emerging Risks in a Network

⁴ Clinical watch system: the aim of sentinel surveillance systems in occupational health involve the ongoing and rapid identification of sentinel health events (cases and their corresponding occupational risks) for purposes of follow-up and for developing statistical trends (available <http://occm.ed.oxfordjournals.org/content/65/8/611.full.pdf+html>)

3 Results

All European countries were asked to fill in the questionnaire. This list contained the 28 EU member states, 5 candidate EU member states and 2 potential candidate EU member states⁵. An overview of all European countries is given in Appendix A.

Table 1 shows an overall response of 45%. The response of Current and Candidate EU member states is 64 and 60% respectively. The two countries that filled in the questionnaire without having an EU membership status were Norway and Switzerland.

Table 1: Response to the questionnaire.

Status of country	Number of countries	Number of countries that filled in the questionnaire	Percentage of countries that filled in the questionnaire
Current EU member state	28	18	64%
Candidate EU member state	5	3	60%
Potential Candidate EU member state	2	0	0%
Other EEA countries and Switzerland ⁶	4	2	50%
Others	16	0	0%
Total	51	23	45%

The 23 countries that filled in the questionnaire are listed below: Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Luxemburg, Netherlands, Macedonia, Norway, Poland, Romania, Serbia, Spain, Sweden, Switzerland, Turkey, United Kingdom.

3.1 Questions related to the existence of a clinical watch system:

3.1.1 Existence of a clinical watch system?

The collection of 'spontaneously reported cases' is a very important source of information for the identification of NERCs. It is especially effective in cases of rare, serious health effects with a low incidence rate. The reporter or notifier suspects a relationship between the health effect and exposure to chemicals and/or an occupation. It is an effective, relatively inexpensive method that covers the whole working population. Drawbacks of this method are dependence on the willingness to notify (underreporting) and the need for further research on a

⁵ EU member states: http://europa.eu/about-eu/countries/index_en.htm

⁶ EEA = European Economic Area. The EEA includes EU countries and also Iceland, Liechtenstein and Norway. It allows them to be part of the EU's single market. Switzerland is neither an EU nor EEA member but is part of the single market.

possible causal relationship. The case reports need to be collected in a database and analyzed by experts.

The questions asked in the questionnaire related to the existence of a clinical watch system were:

- Are you aware of any type of clinical watch system to identify possible (new and emerging) work-related health risks in your country? If yes,
- What is the name of the system /registry/instrument aimed at identifying possible (new and emerging) work-related health risks

It was found that there are three categories of clinical watch systems:

1. Clinical watch systems that are designed to detect NERCs;
2. Systems that are not specifically designed to detect NERCs but can be used for that reason;
3. Clinical watch systems in preparation

Several countries reported to have more than one clinical watch system. Below, the different types of clinical watch systems will be discussed separately.

Clinical watch systems that are designed to detect NERCs

An overview of clinical watch systems is provided below. More information on the organizations behind these systems and the way they work is reported in the paragraphs 3.1.2 and 3.1.3.

Five clinical watch systems serving 7 countries were specifically designed to detect NERCs. These are systems which gather information on work related health effects, work processes and exposure, and are based on epidemiological principles.

1. England and Ireland founded the THOR network, which is an abbreviation of "The Health and Occupation Research" network. It is a network composed of several other networks:
 - a. OPRA: Occupational Physicians Reporting Activity
 - b. EPIDERM: occupational skin disease
 - c. SWORD: surveillance of work-related and occupational lung disease
 - d. THOR-GP: reporting scheme for general practitioners with training in occupational medicine
2. France has three clinical watch systems:
 - a. RNV3P: French National Occupational Diseases Surveillance and Prevention Network
 - b. GAST: occupational health warning groups
 - c. OccWatch: occupational diseases sentinel clinical watch system project
3. The Netherlands together with Belgium created the SIGNAAL tool
4. Italy has the MALPROF system, a system for recording and surveillance of work-related diseases
5. Spain: At *regional level* there are many initiatives. Among them, the system of the region Asturias (EVESCAP), which is specifically designed for detecting and registering occupational cancer. It includes an evaluation system (EVESCAP) and a specific register (cancer). The region of Navarre has a sentinel clinical watch system of Occupational Diseases in general, and is considered as

a reference in Spain (García López, 2011). An overview of Spanish systems is shown in appendix D.

Systems that are not specifically designed to detect NERCs but can be used for that reason.

This type of systems is based on claims for recognition and compensation of occupational diseases⁷ and, administered by national social security systems.

However, these systems are constructed in such a way that NERCs can be reported and analyzed. Ten countries reported to have such type of a reporting system:

1. Belgium: Fund occupational diseases
2. Bulgaria: Occupational disease register
3. Denmark: Erhvervs sygdomsregistret; Doctors and dentists must submit a notification if they learn or suspect that a patient's injury is related to his job
4. Finland: Register of occupational safety and health administration
5. Hungary: Mandatory reporting and registration system of occupational diseases
6. Latvia: The National Registry of Occupational diseases of Republic of Latvia
7. Norway: Registry of work-related diseases
8. Spain: At a *national level*: CEPROSS (for occupational diseases of the official list approved by a Royal Decree) and PANOTRASTSS ("annex" to the OD list to register non traumatic health effects that could be consider in the future as OD but are not today)
9. Sweden: Doctor's reporting of illness according to AFS 2005:6, § 11.
10. Switzerland: Statutory Health Surveillance organized by Swiss Accident Insurance Fund (Suva)

System in preparation:

The National Institute of Occupational health of the Czech Republic is preparing a sentinel clinical watch system, which will be launched in the near future. A sentinel clinical watch system is an early warning system where physicians can report cases; i.e. workers that may have fallen ill because of their work.

No system that can be used as such

Seven countries reported to have no early warning system that can be used to detect NERCs; i.e., Germany, Luxemburg, Macedonia, Poland, Romania, Serbia and Turkey.

3.1.2

Organizations collecting possible new and emerging work related risks

The question asked in the questionnaire was: "Which organization collects the possible (new and emerging) work-related health risks?". Table 2 gives an overview of the institutions collecting NERCs. In most countries (n=6) the labor inspectorate is the most common institution to collect possible NERCs, especially in the Northern countries. Both research organizations (n=6) and insurance funds (n=5) are also

⁷ Occupational disease: The term 'occupational disease' has a categorical legal connotation and not just a scientific causal one. This in contrast to the term 'work-related disease' which has a broader scope and thus is more interesting in the detection of NERCs (Samant et. al; 2015).

important institutions in collecting possible NERCs. Especially research organizations are very important since they organize and analyze those clinical watch systems that are designed to detect NERCs.

Table 2: Overview of organizations collecting possible NERCs. Clinical watch systems that are designed to detect NERCs are printed in bold.

Type of institute	Country	Additional information
National Institute of Occupational Health	Czech Republic (under construction)	---
	Hungary	Office of the Chief Medical Officer – Department of Occupational Health
Government	Spain	Most of the existing regional systems are dependent of the REGIONAL GOVERNMENTS
Labor inspectorate	Finland	--
	Norway	--
	Sweden	SWEA
	Denmark	Working Environment Authority
	Latvia	--
	Italy	--
Research organizations	United Kingdom	Centre of Occupational and Environmental Health (COEH), University of Manchester
	Belgium	SIGNAAL, hosted by the University of Leuven: Centre for Environment and Health
	The Netherlands	SIGNAAL, hosted by the Netherlands Center for Occupational Diseases; Part of Coronel Institute on Work and Health, AMC, University of Amsterdam
	Ireland	Physician epidemiological reporting schemes funded by the labour inspectorate HAS (Ireland)
	Latvia	The Center of Occupational and Radiological Medicine of Pauls Stradins University hospital (Center)
	France	RNV3P (ANSES): The French Agency for Food, Environmental and Occupational Health & Safety GAST (InVS): The French Institute for Public Health Surveillance ⁸ OccWatch: MODERNET network (Monitoring Occupational Diseases and Emerging Risks New Network)
Insurance funds	Switzerland	Swiss Accident Insurance Fund (SUVA)
	Belgium	Fund occupational diseases
	Bulgaria	National Social Insurance Institute (Bulgaria)
	Spain	At a NATIONAL level: Ministry of Labour. Secretary of State for Social Security (CEPROSS and PANOTRASTSS)
	Italy	INAIL (National Institute for Insurance against Accidents at Work) – MALPROF system
Others	Denmark	National Board of Industrial Injuries

⁸ InVS will become in 2016 the (French) National Agency for Public Health

3.1.3 *Reporting new and emerging work related risks*

The questions asked in the questionnaire related to the reporting of NERCs are summarized below and will be answered in this paragraph:

1. Who can report possible (new and emerging) work-related health risks?
2. Who evaluates a first report of a possible (new and emerging) work-related health risks?
3. How is a first report of a possible (new and emerging) work-related health risks evaluated?
4. Will the reporter or notifier be informed on the process and the outcome of his report?
5. How does the communication of a (new and emerging) work related health risk between the reporter/notifier and the evaluating body take place?
6. How does the follow up of possible (new and emerging) work-related health risks take place?
7. Are possible (new and emerging) work-related health risks collected in a (national) database?

Germany, Luxemburg, Macedonia, Poland, Romania, Serbia and Turkey, stated in the questionnaire to have no clinical watch system, and thus will not be mentioned in the following.

Who can report possible (new and emerging) work-related health risks?

Occupational physicians, medical specialists and general practitioners can report possible NERCs in almost all the clinical watch systems. Only occupational physicians can report in the Latvian and Belgian 'SIGNAAL' system. In addition, in Denmark also dentists can report. Industrial hygienists can report in the Swiss, the Latvian and the French systems (GAST and OccWatch). Employers and trade union delegates can report in the Danish and French (GAST) systems. Self-reporting of workers is allowed in the Danish, French (GAST), Latvian and Swiss systems.

Who evaluates a first report of a possible (new and emerging) work-related health risks?

The evaluation of possible NERCs is done by a group of experts. The composition of this team of experts depends on the reporting system (see Table 3). Research institutes play an important role in the evaluation of most of the reporting systems, but also the labour inspectorate is often mentioned as the evaluating organization. Bulgaria, has a special commission evaluating NERCs.

Table 3: Organizations and names of evaluating committees that evaluate the possible NERCs

Type of organization	Country / (system)	Name of evaluating committee
Research institutes	United Kingdom (THOR) Ireland (THOR)	Centre of Occupational and Environmental Health (COEH), University of Manchester
	France (RNV3P)	ANSES; physicians of the occupational disease centres, experts in dedicated working group on emerging work related diseases
	France (GAST)	InVS; "Occupational Health Warning Group" composed by epidemiologists of the French Institute for Public Health Surveillance (InVS), an occupational physician and a regional medical officer inspector of labor
	France (OccWatch)	MODERNET ⁹ ; international network of specialists
	The Netherlands (SIGNAAL) Belgium (SIGNAAL)	Researchers/occupational disease experts of SIGNAAL employed at the Netherlands Center for Occupational Diseases (NL), the Catholic University of Leuven. A network of Clinical Occupational Health Specialists (B).
	Finland Hungary Czech Republic (under construction)	National Institute of Occupational Health
	Latvia	Pauls Stradins University hospital; the Commission of occupational physicians of the Center of Occupational and Radiological Medicine
Other institutes	Spain (Regional systems)	Navarre: Institute of Public and Occupational Health of Navarre (ISPLN: Instituto de Salud Pública y Laboral de Navarra)
		Asturian Institute of Prevention of Occupational Risks (IAPRLs: Asturian Institute of Prevention of Occupational Risks)
Ministry (Social affairs / Labour)	Finland	Team of experts within the ministry of social affairs
	Spain (National level: (CEPROSS and PANOTRASTSS)	Team consisting of Medical Doctors/Experts proposed by the Ministry of Labour / Social Security System
Labor inspectorate authority	Norway Sweden France (GAST) Hungary Italy	Medical doctors within the labor inspectorate authority NOTE: the French "Occupational Health Warning Group" of GAST also contains a physician of the labor inspectorate. NOTE: in Italy the labor inspectorate is within the National Health Service
National authority/board	Denmark	The Working Environment Authority and the National Board of Industrial Injuries

⁹ MODERNET: Monitoring trends in Occupational Diseases and tracing new and Emerging Risks in a NETWORK

Type of organization	Country / (system)	Name of evaluating committee
Insurance institution	Switzerland Belgium (fund of occupational diseases)	Medical doctors within or affiliated with the insurance funds. Also physicians and experts (toxicologists, researchers, ...) carrying out reviews upon request of the fund of occupational diseases (B)
Special Commission	Bulgaria	Team consisting of representatives from: <ul style="list-style-type: none"> • National Social Insurance Institute • Occupational medicine specialist • Labor inspectorate • Insurer • Workers

How is a first report of a possible (new and emerging) work-related health risks evaluated?

Cases reported in a clinical watch system have to be evaluated with the aim to check whether the reported case really is a new risk and whether this signal can be strengthened by the finding of additional cases.

Literature search is a common way to investigate whether the reported case was known already in the past. Hence, it often occurs that risks that were known in the past, are not common knowledge among the professionals any longer. Communication between experts is often used to build knowledge on the causal relationship between exposure and the reported health effect, and to find additional cases to strengthen the causal relationship. It depends on the clinical watch system how a first report will be evaluated. Table 4 gives an overview of the countries that stated to have a clinical watch system and the way a new possible risk will be evaluated. It shows that communication between experts is mostly used to evaluate new cases. An expert group is connected with all clinical watch systems, with the exception of the Italian Malprof system. However this system reports to evaluate a patient's working history, which could mean that an industrial hygienist is checking the historical exposure of a case and communicates with the physician.

Literature search is also mentioned as a means to evaluate a case for most clinical watch systems. All systems, with the exception of the Bulgarian, French (GAST) and Latvian system perform a literature search. In the Belgian (Fund Occupational Diseases) system, literature searches are performed on request by the commissions within the fund.

Table 4: This table describes in which way a first report of a possible NERC will be evaluated.

Country	Literature search	Communication between experts	Remarks
Belgium	Yes (SIGNAAL) No/yes (Fund Occupational Diseases)	Yes (SIGNAAL and Fund Occupational Diseases)	
Bulgaria	No	Yes	
Czech Republic	Yes (under construction)	Yes (under construction)	Physical examination by specialist
Denmark	No answer	No answer	
Finland	Yes	Yes	
France	Yes (RNV3P, OccWatch) No (GAST)	Yes (RNV3P, OccWatch, GAST)	
Hungary	Yes	Yes	
Ireland	Yes	Yes	QSAR structural analysis if & as appropriate
Italy	Yes	No	Patient's working history
Latvia	No	Yes	
The Netherlands	Yes	Yes	
Norway	Yes	Yes	
Spain	At a National level: Yes (CEPROSS and PANOTRASTSS) At a Regional level: NAVARRE: Yes	At a National level: Yes (CEPROSS and PANOTRASTSS) At a Regional level: NAVARRE: Yes	
Sweden	Yes	Yes	
Switzerland	Yes	Yes	
United Kingdom	Yes	Yes	

Will the reporter or notifier be informed on the process and the outcome of his report?

Table 5 shows that most clinical watch systems inform the reporter or notifier of the outcome of the evaluation of the case they reported. In the Spanish national system reporters or notifiers are not always informed. No communication is reported by the Belgian Fund of Occupational Diseases on specific cases, Finland and Italy.

How does the communication of a (new and emerging) work related health risk between the reporter/notifier and the evaluating body take place?

The most common way to communicate between reporter or notifier and the evaluating body of the clinical watch system is by e-mail/ website or on paper (see also Table 5). The French RNV3P system has a very elaborate way of reporting, containing several steps leading from the clinicians within the RNV3P network to an international alert.

How does the follow up of possible (new and emerging) work-related health risks take place?

The follow-up of a possible NERC is in most instances provided by a national and/or international expert group. In some instances communication takes place within an expert group of the insurance company (i.e. Switzerland and Denmark). The Labor inspectorate may also play a role in some countries (United Kingdom and Norway). For an overview, see also table 5.

Are possible (new and emerging) work-related health risks collected in a (national) database?

Most clinical watch systems that are designed to detect NERCs report to collect them in a database. It concerns the English and Irish THOR system, The French RNV3P, GAST and OccWatch systems and the Italian MALPROF system. The Dutch and Belgian SIGNAAL tool reports the cases and the outcomes via the website and collects them in a database.

The cases in the Latvian National Registry of occupational diseases are collected in a database containing the occupational disease, occupational health risk factors and exposure data. Also Bulgaria and Denmark have databases of cases, and in Spain there are regional systems with a database of cases (see also table 5).

Table 5: This table describes the communication between reporter or notifier and the clinical watch system, and the collection of cases in a database

Country	Will the reporter/notifier be informed?	Way of communication between reporter and evaluating body	Follow-up of a possible new/emerging risk	Possible NERCs collected in a database?
Belgium	No (Fund Occupational Disease) Yes (SIGNAAL)	email/web (SIGNAAL)	<ul style="list-style-type: none"> • None (Fund Occupational Disease) - see also higher (determined by commissions) • international expert group (SIGNAAL) 	No (Fund Occupational Diseases) Yes: (SIGNAAL)
Bulgaria	Yes	On paper	National expert group	Yes
Czech Republic*	Yes	Email/web	Not certain yet	No
Denmark	No answer	On paper	Expert group at insurance company meetings between ministries***	Yes
Finland	No	--	None	No
France	Yes (RNV3P, OccWatch, GAST)	on paper, oral presentations, email/web (GAST) email/web (OccWatch) different levels (RNV3P)**	<ul style="list-style-type: none"> • National expert group (GAST, OccWatch, RNV3P) • International expert group (OccWatch) 	Yes (RNV3P, OccWatch, GAST)
Hungary	Yes	On paper	National expert group	No
Ireland	Yes	Email/web	Both international and national expert group	Yes
Italy	No	On paper	National expert group	Yes
Latvia	Yes	On paper	National expert group	Yes
The Netherlands	Yes	Email/web	(Inter)national expert group	Yes
Norway	Yes	On paper	Labor inspections	No

Country	Will the reporter/notifier be informed?	Way of communication between reporter and evaluating body	Follow-up of a possible new/emerging risk	Possible NERCs collected in a database?
Spain	Not always (CEPROSS and PANOTRASTSS) Yes in certain regional systems as that of Navarre	Email/web NAVARRE: On paper, oral communication, web, Epidemiological Bulletins, digital Patient's working history	Both National and Regional expert groups	Yes (CEPROSS and PANOTRASTSS) Yes
Sweden	Yes	On paper Email/web	National expert group	No
Switzerland	Yes	On paper Personal communication	Expert group at insurance company	No
United Kingdom	Indirectly	Email or Web	<ul style="list-style-type: none"> • Both national and international expert group • Labor inspections 	Yes

* Under construction

** Different levels:

- Level 1 : Internal alert to clinicians in the rnv3p network,
- Level 2 : Information to rnv3p partners + search for similar cases outside the network
- Level 3 : Widely diffused via Anses agency to authorities in order necessary actions to be taken
- Others : International papers/Oral communications

*** Meetings between ministries of Environment, Health, Food Safety and Working Environment

3.2 Databases

Data mining in databases of case report notification registries, is a valuable tool for generating hypotheses on possible NERCs and for epidemiological research. Relationships between health effects and exposure and/or occupation can effectively (objectively and reproducibly) be studied, especially when exposure data are incorporated in the database. The questions asked in the questionnaire related to such a database are summarized below, and will be answered in this paragraph:

1. Does your country have (a) database(s) *that allow research between work – exposure to substances – health effects*? If so, please give the name(s) and answer the next questions:
2. Which organization(s) manage(s) and maintain(s) the database(s)?
3. Does research on identification of (new and emerging) work-related health risks take place?
4. Is the database available for other research/researchers?
5. Is an expert group on (new and emerging) work-related health risks available, discussing the causality between exposure and health effect?
6. How will research results be disseminated?

Bulgaria, Czech Republic, Denmark, Germany, Italy, Luxemburg, Macedonia, Poland, Romania, Serbia, Sweden and Turkey reported to have no database of case reports.

3.2.1 *Databases and organizations behind them*

The first two questions mentioned above are reported in table 6. An overview of the names of the databases and the organizations behind them is presented. Several of the databases mentioned are based upon the clinical watch systems mentioned in the former paragraph:

- the THOR system of the United Kingdom and Ireland
- the French RNV3P database of ANSES

However, there are other databases that could be used for (epidemiological) research on work related health effects. The organizations behind these databases are divers (i.e. occupational health provider, institute of occupational health, labor inspectorate and insurance funds)

3.2.2 *Characteristics of the databases and dissemination of results*

Questions 3-6 are presented in table 7. It shows that research always takes place using the information in the databases and that expert groups are available to discuss possible NERCs. It also shows that many databases allow other research or other researchers to use them.

As expected, dissemination takes place via international papers and symposia and via reports and websites.

Table 6: An overview of databases and the organizations behind them

Country	Name of database	Organization
Belgium	<ul style="list-style-type: none"> • Precube • Claims of Fund occupational diseases 	Occupational health provider IDEWE Fund occupational diseases
Finland	The Finnish Institute of Occupational Health's register of occupational diseases	Finnish Institute of Occupational Health
France	RNV3P	The French Agency for Food, Environmental and Occupational Health & Safety (ANSES)
Hungary	<ul style="list-style-type: none"> • Register of occupational diseases, • Register of reported infectious diseases, infections and epidemics 	Office of the Chief Medical Officer – Department of Occupational Health (former Hungarian Institute of Occupational Health)
Ireland	The Health and Occupation Research (THOR) network	THOR: Centre of Occupational and Environmental Health (COEH), University of Manchester
Latvia	The National Registry of Occupational diseases of Republic of Latvia	The Center of Occupational and Radiological Medicine of Paula Stradins University hospital
Netherlands	<ul style="list-style-type: none"> • National notification and registration system • Sentinel surveillance system for the notification of ODs • National Cancer Registry 	Netherlands Center for Occupational Diseases, Coronel Institute on Work and Health, AMC, University of Amsterdam Netherlands Comprehensive Cancer Organization (IKNL)
Norway	Registry of work-related diseases	Labor inspectorate
Switzerland	<ul style="list-style-type: none"> • Statistikpool der Sammelstelle für die Statistik der Unfallversicherungen (SSUV), • Future Radar. 	<ul style="list-style-type: none"> • SSUV: Swiss Accident Insurance Fund (Suva) and Sammelstelle für die Statistik der Unfallversicherungen UVG • SUVA: Swiss Accident Insurance Fund
Spain	<p>National level:</p> <ul style="list-style-type: none"> • CEPROSS • PANOTRASTSS • Tumor registry or Cancer registries (Population registries and Hospital registries) <p>Regional level: Database from the Navarre Occupational Health Surveillance Program</p>	<p>National level:</p> <ul style="list-style-type: none"> • PANOTRASTSS & CEPROSS: Secretary of State for social security, Spanish Ministry of labour. • Tumor registry or Cancer registries: Departments of Health of the Local/Regional Governments <p>Regional level: Navarre: Institute of Public and Occupational Health of Navarre (ISPLN). Government of Navarre.</p>

Country	Name of database	Organization
United Kingdom	<ul style="list-style-type: none"> The Health and Occupation Research (THOR) network, Industrial Injuries Disablement Benefit (IIDB) Scheme, The Reporting of Injuries, Diseases, and Dangerous Occurrences Regulations (RIDDOR). Others e.g., HSE's register on pesticides 	<ul style="list-style-type: none"> THOR: Centre of Occupational and Environmental Health (COEH), University of Manchester IIDB: Department of Work and Pensions RIDDOR: The UK health and Safety Executive (HSE)

Table 7: Characteristics of the databases and way of dissemination of results

Country	Does research take place?	Available for other researchers?	Expert group available?	Way of dissemination of results
Belgium	Yes	Yes, upon request	Yes	International papers/symposia Reports
Finland	No	No	Yes	N.A.
France	Yes	Yes*	Yes	International papers/symposia Reports to stakeholders
Hungary	No	Yes	Yes	N.A.
Ireland	Yes	Yes	Yes	International papers/symposia
Latvia	Yes	Yes	Yes	International papers/symposia
Netherlands	Yes	No (NCOD) Yes (IKNL)	Yes	(Inter)national papers/symposia
Norway	Yes	Yes	Yes	International papers/symposia
Switzerland	Yes (SSUV, Suva)	No (Suva) Yes (SSUV)	Yes (SSUV, Suva)	Reports
Spain	Yes from both National (PANOTRASTSS, CEPROSS, tumor registry or cancer registries)** and Regional systems	Yes from both National and Regional systems	Yes from both National and Regional systems	All the systems: reports, being: <ul style="list-style-type: none"> Technical Notes of the National Institute of Hygiene and Security at Work, National and international papers/symposia Reports to stakeholders "Bulletins of Epidemiology" Statistics of the Social Security System" Bulletins of Epidemiology for Medical Doctors that collaborate

Country	Does research take place?	Available for other researchers?	Expert group available?	Way of dissemination of results
				with Regional Occupational Health Surveillance Programs
United Kingdom	Yes (THOR, IIDB, RIDDOR)	No (IIDB, RIDDOR) Yes (THOR)	Yes (IIDB, RIDDOR) Yes (THOR)	International papers/symposia (THOR, IIDB, RIDDOR) Websites: <ul style="list-style-type: none"> • Health and Safety Executive (HSE)(THOR) • Industrial Injuries Advisory Council and of the UK Health and Safety Executive (HSE)(IIDB) • UK Health and Safety Executive (HSE)(RIDDOR)

*upon conditions

** Scientists get data on Spanish workers exposition to carcinogens from CAREX-Esp (computer application system adapted form CAREX) (Kogevinas et al, 2006). In addition, a job-exposure matrix for research and surveillance of occupational health and safety was developed in Spanish workers (called MatEmESp) (García et al, 2013)

N.A. = not available

3.3 Biomarkers

The active detection of health effects via health surveillance of workers is a valuable tool. Biomarkers for exposure can be used to determine total (oral, inhalation, dermal) exposure to substances. Biomarkers for biological effects may be an indication of early health effects leading to occupational disease. This prospective method is useful since a causal relationship between the level of exposure and possible health effects is easier to prove.

The questions asked in the questionnaire related to the use of biomarkers for exposure are summarized below, and will be answered in this paragraph:

1. Are you aware of any type of health surveillance using biomarkers in your country to identify possible (new and emerging) work-related health risks?
2. If so, which biomarkers *for identifying carcinogens or mutagens* are used, and for which (group of) substances?
3. Which organization takes the initiative to measure biomarkers for (new and emerging) work-related health risks?
4. Are the results of the biomarkers collected in a for research available (national) database?
5. How does the follow up of possible (new and emerging) work-related health risks take place?

Ireland, Macedonia, Poland, Serbia, Spain, Sweden and Turkey reported to use no biomarkers to identify possible new and emerging work-related health risks.

The first three questions mentioned above are reported in table 8. Only a few countries that declared using biomarkers for the identification of NERCs on a regular basis, use them specifically for that purpose (i.e., Czech Republic, Romania, Latvia). Several countries only use biomarkers specific for the identification of NERCs in research projects (i.e., Belgium, Denmark, France and Germany). Most countries, however, do not use biomarkers specifically to detect NERCs.

Both the Czech Republic and Romania are using biomarkers specifically to detect exposure to NERCs. Detection of exposure to NERCs using biomarkers is legally established in Romania. Romania uses biomonitoring to detect early biological effects caused by carcinogens and ionizing radiation. The Czech Republic uses inflammation and oxidative stress markers to measure exposure to nanoparticles.

In many countries, occupational health services and research institutions play an important role in taking the initiative to use biomarkers for the identification of NERCs.

Finland, Norway, Latvia and Hungary collect the results of biomonitoring of NERCs in a database. In Norway the EXPO database was developed, which is a database for voluntary reporting of all types of exposures, maintained by the National Institute of Occupational Safety and Health. In Hungary they have a "Register of excessive exposures" to arsenic,

benzene, cadmium, chromium and nickel.. Data within normal values are not collected.

The follow up of possible NERCs is very diverse. It is up to national or local expert groups in Finland, Hungary and Italy. In Latvia, the University of Riga Stradin is responsible. In Luxemburg and The Netherlands, occupational health services have the obligation to follow up occupational risk exposure and health surveillance. The insurance fund Suva is responsible for the follow up in Switzerland, and the labor inspectorate in Norway. No follow up is reported by Bulgaria, Czech Republic and Romania.

Table 9: Biomarkers used to identify NERCs and the organization(s) that collect them.

Country	Biomarkers for NERCs* used in health surveillance?	Which biomarkers?	Which organization?
Belgium	Only in research projects and through the Policy Research Centre of Environment and Health	Genetic and epigenetic markers Markers of mechanisms: e.g. oxidative stress, inflammation, etc. Agents and metabolites in human samples	Research institutes
Bulgaria	Yes, not specifically for NERCs	benzene (trans-muconic acid and S-phenylmercapturic acid), vinylchloride (thiobiglycolic acid), Nickel (Nickel in urine), Chrome (Chromium in urine)	Research institutes
Czech Republic	Yes, specifically for NERCs	markers of inflammation and oxidative stress in workers exposed to nanoparticles (Markers of oxidation of nucleic acids, including 8-hydroxy-2-deoxyguanosine (8-OHdG), 8-hydroxyguanosine (8-OHG), 5-hydroxymethyl uracil (5-OHMeU), and of proteins and lipids)	<ul style="list-style-type: none"> Occupational health services Research institutes
Denmark	Only in research projects	biomarkers in firefighters (BIOBRAND)	The National Research Centre of Working Environment
Finland	Yes, not specifically for NERCs	levels of exposing agents and their metabolites in serum and urine	Occupational health services
France	Only in research projects	No information	InVS together with ANSES and INRS**
Germany	Only in research projects	No information	No information
Hungary	Yes, not specifically for NERCs	Arsenic: Arsenic, Benzene: t,t-muconic acid, Cadmium: Cadmium, Chromium: Chromium, Nickel: Nickel	Occupational health services
Italy	Yes, not specifically for NERCs	Metals	<ul style="list-style-type: none"> Research institutes regional environmental agencies
Latvia	Yes, specifically for NERCs	Not for carcinogens/mutagens: We use biomarkers for confirmation occupational stress	Research institutes

Country	Biomarkers for NERCs* used in health surveillance?	Which biomarkers?	Which organization?
Luxemburg	Yes, not specifically for NERCs	Those which are internationally recommended (1. examinations by the occupational health physician(OHP), 2. if there are exposure biomarkers, the OHP will propose the required surveillance to the worker)	Occupational health services
Netherlands	Yes, not specifically for NERCs	Levels of exposing agents and their metabolites in serum and urine In research projects	Occupational health services Research institutes
Norway	Yes, not specifically for NERCs	Lead in Blood, Mercury in Urine, Benzene in Urine, However, not any other substances at this time	Labor inspectorate
Romania	Yes, specifically for NERCs	sputum cytology (respiratory carcinogens), micronuclei test (ionizing radiations), chromosomal aberrations (ionizing radiations)	The biomarkers measurements are established by specific legal acts
Switzerland	Yes, not specifically for NERCs	aromatic amines (urine cytology), Arsenic (Arsenic), Benzene (S-phenylmercapturic acid; t,t-muconic-acid), Beryllium (Beryllium), Cadmium (Cadmium), Cobalt (Cobalt), Lead (Blood lead), Nickel (Nickel), trichlorethene/trichlorethylen (trichloroacetic acid (TCA)), vinylchloride (liver ultrasound)	<ul style="list-style-type: none"> • Insurance funds (Swiss Accident Insurance Fund (Suva)) • Companies
United Kingdom	Yes, not specifically for NERCs	only for specified hazards where the validity and utility of the biomarkers is well established	---

*NERC: new and emerging risk of chemicals

**InVS: French Institute for Public Health Surveillance, ANSES: French Agency for Food, Environmental and Occupational Health & Safety, INRS: French Institute for Occupational Safety and Health

3.4 How to bring possible work-related NERCs further?

Once a possible (new and emerging) work-related health risk has been identified by the methods mentioned above, we find it of paramount importance that there should be discussion in an expert group on the possibility of a causal relationship between the exposure and the reported health effect, and if (additional) research is needed to provide the necessary evidence.

The questions asked in the questionnaire related to the way possible work-related NERCs could be pursued, are summarized below, and will be answered in this paragraph:

- Do you think that possible (new and emerging) work-related health risks should be discussed in an *international* group of experts
- If yes, please specify how this should be organized according to you
- If no, please specify why not

Of the 23 countries that responded to the questionnaire, only one country did not answer this question (i.e., Denmark). All responders think that possible NERCs should be discussed in an *international* group of experts on work related diseases. An overview of the answers given on the ways this should be organized, is given in appendix C.

Some of the suggestions that were mentioned are:

- The availability of expertise centers in every country, so that patients can consult occupational experts (both on exposure and health effect) to study whether the NERC is work or environmentally associated
- Arrangement of an *international* platform of specialists working on work related health effects and occupational diseases. Such a group already exists in the MODERNET network. Communication between the specialists in het MODERNET network is provided by scientific meetings where cases and research are presented and discussed. In addition, the online tool OccWatch was built by MODERNET, to discuss cases and strengthen the evidence of a causal relationship between exposure/ work and the health effect, by finding additional cases in other countries. Further development of the MODERNET network was mentioned by several responders
- Establishment of a group of experts financed by the EU and working on work related and occupational diseases. They could be organized like the SCOEL (scientific committee on occupational exposure limits). Such a group could also identify the diseases (e.g. cancers) which need further evaluation, consider how such evaluation should be carried out, agree what research is needed to provide the necessary evidence, and develop coordination mechanisms so that research and evaluation is efficiently carried out (EU, 2013)
- Establishment of a European tripartite expert group consisting of government, unions, and employers associations on work related and occupational diseases

- Discussions in existing international advisory committees, (e.g. SCENIHR¹⁰, European Union of Medical Specialists, OCCUSTAT¹¹)
- Regular meetings between (national) institutes for health and safety
- Discussions during international conferences

¹⁰ SCENIHR: Scientific Committee on Emerging and Newly Identified Health Risks

¹¹ OCCUSTAT: expert group on occupational diseases statistics founded by the European Commission and EU-OSHA

4 Conclusions

This report shows that:

- There are several clinical watch systems available in Europe to detect NERCs. It also shows that only a few systems are specifically designed for that purpose.
- Databases containing information that may be used to identify NERCs are available in several European countries and they are often available for other researchers. The usefulness of these databases should be checked since they are mostly not set up for the purpose of detecting NERCs.
- There is general agreement among the responders that possible NERCs should be discussed in an international expert group. Several ways were proposed for the organization for such an expert group.

Once a possible NERC is identified in one of the early warning systems, additional case finding on other early warning systems is important in order to strengthen the signal. Initializing new research may also be one of the actions needed to study the causality of a potential NERC. So, it is important that experts work together at an (inter)national level. Once a possible NERC has become a NERC, actions have to be taken to control the health risk. An overview of possible ways to pursue on a NERC is provided in Palmen and Verbist (2015). In short, it comprises:

- Informing the relevant inspection department(s) in case a substance is already regulated;
- Informing professional societies focused on occupational health and safety;
- Checking whether the NERC is already on any of ECHA's lists of substances and is being evaluated by ECHA or one of the member states in one of the processes under the REACH¹² or CLP¹³ Regulations. If so, they need to be informed on the NERC. In case the substance is not on ECHA's list, a risk management options analysis (RMOA) may be performed to reveal possible actions like:
 - 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;
 - A proposal for a (change in) harmonized classification and labelling of a substance under the CLP Regulation, which may subsequently have an effect on the REACH requirements and/or the requirements coming from worker safety legislation;
 - The need to generate additional information, which may be provided via the substance evaluation instrument (SEv)

¹² REACH is the European Union regulation 1907/2006/EC concerning the Registration, Evaluation, Authorisation & restriction of CHemicals.

¹³ CLP is the European Union regulation 1272/2008/EC for the Classification, Labelling and Packaging of chemicals and mixtures.

within REACH. This additional information on the hazard or the exposure of a substance may lead to:

- a proposal to identify the substance as an SVHC and for authorization; or
 - a proposal to restrict the use of the substance;
 - a proposal for a (change in) harmonized classification and labelling of a substance under the CLP Regulation
 - take away of the concern over the substance.
- Applying other legislation to prevent new cases (for example, legislation on medicine, cosmetics, biocides etc...)

Since international collaboration is essential in the identification, evaluation and handling of NERCs, it is recommended to discuss the way this can be organized an institutionalized in Europe.

5 Acknowledgements

I would like to express my very great appreciation to representatives from European countries who were willing to take time to fill in the questionnaire on early warning systems.

6 Literature

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Appendix A: overview of countries and their organizations

Country¹⁴	Organization approached to fill in the questionnaire
Albania	Inspektorati Shteteror i Punes dhe Sherbimeve Shoqerore
Albania	MODERNET*
Andorra	Ministry of Health and Welfare
Armenia	Ministry of Health
Armenia	Ministry of Nature Protection of the Republic of Armenia
Azerbaijan	THE MINISTRY OF LABOUR AND SOCIAL PROTECTION OF POPULATION OF THE REPUBLIC OF AZERBAIJAN
Azerbaijan	State Labour Inspectorate
Austria	Unfallverhütung und Berufskrankheitenbekämpfung Allgemeine Unfallversicherungsanstalt
Austria	Arbeitsinspektion
Belarus	Ministry of Labour and Social Protection Republic of Belarus
Belgium	KU Leuven
Belgium	Federale Overheidsdienst Werkgelegenheid, Arbeid en Sociaal Overleg
Bosnia and Herzegovina	Ministry of Civil Affairs of Bosnia and Herzegovina
Bosnia and Herzegovina	Ministry of Health and Social Welfare of Republika Srpska
Bosnia and Herzegovina	MODERNET*
Bulgaria	National Center of Public Health and Analyses
Croatia	University of Zagreb, School of Medicine
Cyprus	Department of Labour Inspection, Ministry of Labour, Welfare and Social Insurance
Cyprus	World Health Organisation
Cyprus	Ministry of health
Czech Republic	Charles University, faculty of medicine, Prague
Czech Republic	National institute of public health
Czech Republic	Charles University, faculty of medicine, Prague
Denmark	National Research Centre for the Working Environment
Denmark	National Centre for the working environment
Denmark	Danish working environment authority
Estonia	Department of Public health, faculty of medicine, University of Tartu
Estonia	North Estonia Medical Centre Foundation
Finland	Finnish Institute of Occupational Health
Finland	Local Tapiola General Mutual Insurance Company
Finland	Ministry of social affairs and health
France	ANSES
France	Eurogip

¹⁴ An overview of the status of these European countries: http://europa.eu/about-eu/countries/index_en.htm

Country¹⁴	Organization approached to fill in the questionnaire
Germany	Deutsche Gesetzliche Unfallversicherung (DGUV)
Germany	Gesellschaft für Versicherungswissenschaft und -gestaltung e.V
Georgia	Ministry of Labour, Health and Social Affairs
Greece	Social Insurance Services of the Ministry of Labour and Social Insurance
Greece	Centre Hellenic Institute for occupational health and safety
Hungary	Ministry for National Economy - Department of Labour Inspection
Hungary	Ministry of Human Resources
Hungary	Office of the Chief Medical Officer - OTH, Department of Occupational Health
Iceland	Focal point EU-OSHA
Iceland	MODERNET*
Iceland	Ministry of Welfare
Ireland	MC member Ireland
Ireland	Health and Safety Authority
Italy	Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro (INAIL)
Italy	MODERNET*
Kazakhstan	Centre of Health Management
Kazakhstan	The Center for Healthcare Management
Kosovo	Ministry of Labour and Social Welfare Labour Inspectorate
Latvia	Pauls Stradins Clinical University Hospital
Latvia	Centre of occupational and radiological centre
Liechtenstein	Amt für Volkswirtschaft
Lithuania	Occupational Health Centre, Institute of Hygiene
Luxembourg	Inspection du Travail et des Mines
Luxembourg	Ministry of Health
Luxembourg	Service de santé au travail multisectoriel
Macedonia	MODERNET*
Malta	Director at Department of Health Information & Research
Moldova	Ministry of Health
Monaco	Directorate of Health and Social Work
Montenegro	Administration for Inspection Affairs
Montenegro	Ministry of Health
Netherlands	RIVM; National Institute of Public Health and Environment
Netherlands	NCOD / Coronel institute on Work and Health
Netherlands	ASRI; hogeschool voor sociale zekerheid
Netherlands	Foundation learning and developing occupational health; instituut klinische arbeidsgeneeskunde
Norway	National Institute of Occupational Health (STAMI)
Norway	Arbeidstilsynet
Norway	Stami; statens arbeidsmiljøinstitutt
Poland	NIOM
Portugal	National School of Public Health, Lisboa
Romania	National Institute of public Health Romania
Russia	Ministry of Labour

Country¹⁴	Organization approached to fill in the questionnaire
San Marino	Institute for Health and Social Welfare
Serbia	Ministry of Labour, Employment, Veterans and Social Policy
Serbia	MODERNET*
Slovakia	Comenius University Bratislava; Department of Occupational Medicine and Toxicology in Bratislava
Slovakia	Pavol Jozef Šafárik University in Košice
Slovenia	Institute of Occupational Safety
Slovenia	Department, Occupational Medicine and Clinical Toxicology
Spain	Occupational Medicine Forensic Science and Toxicology, University of Zaragoza
Spain	Parc de Salut, Barcelona
Sweden	Institute of Environmental Medicine (IMM)
Sweden	Arbetsmiljöverket (Swedish Work Environment Authority, SWEA)
Switzerland	Institute of Social and Preventive Medicine, University of Lausanne
Switzerland	SUVA, insurance plus
Turkey	Calisma ve Sosyal Guvenlik Bakanligi
United Kindom	The University of Manchester, Centre for Occupational and Environmental Health
Ukraine	National O. Bohomolets Medical University, Department of industrial hygiene and occupational diseases
Vatican City	Facoltà di Medicina e chirurgia

*MODERNET members are invited on a personal basis. MODERNET: Monitoring trends in Occupational Diseases and tracing new and Emerging Risks in a NETWORK.

Appendix B: Questionnaire 'Early warning systems'

The first six months of the year 2016 the Netherlands will be the chair of the European Union. During that period, the Dutch Ministry of Social Affairs and Employment (SZW) will organize an international conference on how to ban work-related cancer in the EU. The main purpose of this conference is to address policy agenda setting points for the years to come. The RIVM is asked to prepare the scientific substantiation for some of the themes. One of the themes is the availability and use of 'early warning systems' to identify and evaluate NERCs leading to occupational cancer, so that substances and/or processes will be identified and measures can be taken by policymakers to control exposure. The preparation of the conference will be done in close cooperation with other EU stakeholders to establish a solid basis and level playing field to agree on the agenda points to be set at the end of the conference.

Early warning systems are important to detect new or emerging work related health effects, including occupational cancer. The novelty of the use of early warning systems is to use signals from the field, such as cases or clusters of cancers suspicious to be related with occupational exposure. Obviously occupational health specialists (occupational physicians, lung specialists, dermatologists, industrial hygienists etc..) need to be on the alert on the occurrence of any possible work related cancers. These cancers may be a consequence of a known hazard or substance, but also of an unknown hazard of a known substance, through new use of a substance leading to an unknown risk (e.g. inhalation exposure instead of oral exposure), or even a completely new substance. Since new hazards may be rare or present after long latency, European collaboration is of great importance to detect and streamline these signals as was already recognized by WHO:
http://www.who.int/occupational_health/activities/occupational_work_diseases/en/.

It is not the intention to create a harmonized or uniform approach, but to use the existing systems and share the results. So, the aim is to create an overview of existing 'early warning systems' in the different EU countries and share the outcomes of the analyses made by scientists. In any case, the identification of emerging risks requires the use of several complementary methods. In the end, an international group of experts may be needed in order to discuss the information, and make a decision on the work related risk of the substance or process to cause cancer.

In preparation of the conference, RIVM would like to make an inventory of 'early warning systems' already existing in the member states. Underneath you find a description of the systems we are looking for (clinical watch systems, databases for data mining, use of biomarkers in health surveillance etc.). We kindly request you to inform us about any system in your country that can be looked upon as 'early warning

system' by completing the questionnaire. The results will be analyzed and published before the start of the conference.

In addition, we ask you to provide us with names of policy makers that should be invited to the conference according to you.

'Clinical watch systems':

The collection of 'spontaneous reported cases' is a very important source of information for the identification of NERCs. It is especially effective in cases of rare, serious health effects with a low incidence rate. The reporter or notifier suspects a relationship between the health effect and exposure to chemicals and/or an occupation. It is an effective, relatively inexpensive method that covers the whole working population. Drawbacks of this method are dependence on the willingness to notify (underreporting) and the need for further research on a possible causal relationship. The case reports need to be collected in a database and analyzed by experts.

Questions related to the existence of a clinical watch system:

Are you aware of any type of clinical watch system to identify possible (new and emerging) work-related health risks in your country?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, please answer the next questions: <i>In case there are more than one clinical watch systems, please copy this table.</i>	
What is the name of the system /registry/instrument aimed at identifying possible (new and emerging) work-related health risks:	
Which organization collects the possible (new and emerging) work-related health risks?	<input type="checkbox"/> national institute of occupational health <input type="checkbox"/> labor inspectorate <input type="checkbox"/> fund occupational diseases <input type="checkbox"/> occupational health providers <input type="checkbox"/> other, which.....
Who can report possible (new and emerging) work-related health risks?	<input type="checkbox"/> occupational physician <input type="checkbox"/> medical specialist <input type="checkbox"/> general practitioner <input type="checkbox"/> industrial hygienist <input type="checkbox"/> worker <input type="checkbox"/> other; who.....
Who evaluates a first report of a possible (new and emerging) work-related health risks?	<input type="checkbox"/> the national institute of occupational health <input type="checkbox"/> fund occupational diseases <input type="checkbox"/> other; who.....

How is a first report of a possible (new and emerging) work-related health risks evaluated?	<input type="checkbox"/> literature search on historical reporting <input type="checkbox"/> communication between experts <input type="checkbox"/> other, how?
Will the reporter or notifier be informed on the process and the outcome of his report?	<input type="checkbox"/> yes <input type="checkbox"/> no
Are possible (new and emerging) work-related health risks collected in a (national) database?	<input type="checkbox"/> yes <input type="checkbox"/> no If yes, please give the name:.....
How does the communication of a (new and emerging) work related health risk between the reporter/notifier and the evaluating body take place?	<input type="checkbox"/> via the web <input type="checkbox"/> on paper <input type="checkbox"/> other;
How does the follow up of a possible (new and emerging) work-related health risks take place?	<input type="checkbox"/> no follow-up <input type="checkbox"/> national expert group <input type="checkbox"/> international expert group <input type="checkbox"/> if so, which one?

'Databases'

Data mining in databases of case report notification registries, is a valuable tool for epidemiological research. Relationships between health effects and exposure and/or occupation can effectively (objectively and reproducibly) be studied, especially when exposure data are incorporated in the database. This type of research results in the formation of a hypothesis. Further research is necessary to investigate a possible causal relationship between the exposure and the health effect.

Questions related to the existence of a (national) database on (new and emerging) work-related health risks:

Does your country have (a) database(s) that allow research between work – exposure to substances – health effects?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If so, please give the name(s).....	
If so, please answer the next questions <i>In case there are more than one (national) databases, please copy this table</i>	
Which organization(s) manage and maintain(s) the database(s)?	<input type="checkbox"/> not applicable <input type="checkbox"/> please identify.....
Does research on identification of (new and emerging) work-related health risks take place?	<input type="checkbox"/> yes <input type="checkbox"/> no
Is the database available for other research/researchers?	<input type="checkbox"/> yes <input type="checkbox"/> no

Is an expert group on (new and emerging) work-related health risks available, discussing the causality between exposure and health effect?	<input type="checkbox"/> yes <input type="checkbox"/> no
How will research results be disseminated?	<input type="checkbox"/> not applicable <input type="checkbox"/> international papers <input type="checkbox"/> international symposia <input type="checkbox"/> other, please specify...

Use of biomarkers in health surveillance

The active detection of health effects via health surveillance of workers is a valuable tool. Biomarkers for exposure can be used to determine total (oral, inhalation, dermal) exposure to substances. Biomarkers for biological effects may be an indication of early health effects leading to occupational disease. This prospective method is useful since a causal relationship between the level of exposure and possible health effects is easier to prove.

Are you aware of any type of health surveillance using biomarkers in your country to identify possible (new and emerging) work-related health risks?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> If so, which ?.....
If so, which biomarkers <i>for identifying carcinogens or mutagens</i> are used, and for which (group of) substances?
Which organization takes the initiative to measure biomarkers for (new and emerging) work-related health risks	<input type="checkbox"/> research institutes <input type="checkbox"/> occupational health services <input type="checkbox"/> private parties <input type="checkbox"/> general practitioners <input type="checkbox"/> other; who.....
Are the results of the biomarkers collected in a for research available (national) database?	<input type="checkbox"/> yes <input type="checkbox"/> no If yes, please give the name:.....
How does the follow up of possible (new and emerging) work-related health risks take place?	<input type="checkbox"/> no follow up <input type="checkbox"/> national expert group <input type="checkbox"/> international expert group <input type="checkbox"/> if so, which one?

How to bring the possible (new and emerging) work-related health risks further?

Once a possible (new and emerging) work-related health risk has been identified by the methods mentioned above, there should be discussion in an expert group on the possibility of a causal relationship between the exposure and the reported health effect, and if (additional) research is needed to provide the necessary evidence.

Do you think that possible (new and emerging) work-related health risks should be discussed in an international group of experts?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, please specify how this should be organized according to you:	
If no, please specify why not:	

Question for names of policy advisers

Please, could you provide us with names and mail addresses of policy advisers of your country that should be invited to the international conference on how to ban work-related cancer in the EU according to you?
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Appendix C: How to bring possible NERCs further

Table 10: proposed ways of organization to bring possible NERCs further

Country	Way of organization of an international group of experts
Belgium	On a European level, a tripartite expert group on work related and occupational diseases should be established
Bulgaria	Studies at an international/EU level to estimate the health risks related to new or emerging work-related factors should be carried and further discussed in international expert groups.
Czech Republic	By the groups of specialists, such as MODERNET group, or participants of the countries organized by the European Commission
Finland	The French OccWatch system is a good starting point. It has been piloted and it can be further developed
France	A first selection has to be done at national level. The reflections and sharing of expertise within international group are essential to optimize ability to detect new diseases : - - Have the same definition of an emerging or new work related disease - Sharing expertise Perspective. - Capture and share about more events etc. Then cases could be shared on an online tool, as the OccWatch pilot tool designed by ANSES/ MODERNET.
Germany	regular meetings of relevant (national) institutes for health and safety
Hungary	Teleconferences/videoconferences.
Ireland	Need a Delphi type study as result of a conference or to be circulated in advance of a conference to determine a strategy
Italy	Periodical meetings and website to share opinion between pairs
Latvia	International grants for research works financed by various organizations
Luxemburg	They should be discussed in international platforms for occupational diseases (MODERNET for example) or in international advisory committees (UEMS for example) or in specific groups in ICOH so that the OHPs can be informed easily about the topic
The Netherlands	<ul style="list-style-type: none"> • The availability of expertise centers in every country, so that patients can consult occupational experts (both on exposure and health effect) to study whether the cancer is work or environmentally associated. • A group of experts financed by the EU and working on work related and occupational diseases. They could be organized like the SCOEL. • Discussion in SCENIHR: Scientific Committee on Emerging and Newly Identified Health Risks. This committee identifies and evaluates new and emerging risks, and advises the European Committee.
Macedonia	By developing of a network of experts with opportunities for exchange of experience, knowledge and skills

Country	Way of organization of an international group of experts
	with few core groups (for example; for development of the appropriate biomarkers, databases, literature review etc.) and organizing of annual conferences for a publishing the results of the national activities. Having on mind that the implementation of the measures for preventing of the work-related health risk mainly depends of the national policy this network should organize collection of the information for annual report from participating countries with intention to give the visibility of the summary report and opportunity for follow up of the progress. As the problem of new and emerging work-related health risk is much more presents in the non-EU countries, they should be forced to implement EU directives and standards and to participate in the network of experts
Norway	<ul style="list-style-type: none"> • May be on the same lines as SCOEL where experts financed by a EU mechanism get together. It is however important to include both scientists and the state authorities in such discussions (policy makers). • The commission has recently established a OCCUSTAT group and there are several representatives from MODERNET involved in this group. We believe that such existing infrastructures should be utilized for further work on NERCs.
Poland	We are very interested in any future collaboration in the topic of introducing early warning systems as you proposed
Romania	identification of existing country specific databases (containing data from regular surveillance/monitoring program or from research projects), - identification, selection and validation of new biomarkers of exposure/health effect, - follow up of the exposed workers after the exposure, - pooling the data for the analysis within large research consortia, - functional studies to identify plausible biological mechanisms
Serbia	Through merging available country data and through discussion of experts groups like it was the case in "MODERNET" project under EU COST action
Spain	possible NERCs should be discussed in an international group of experts on work related diseases
Sweden	This could be organized by the EU commission. There is an Expert Group on occupational diseases.
Switzerland	Contribution of signals in a database, topic specific conferences or workshops where member could contribute or further present cases
Turkey	You can directly try to contact with countries and also some international organizations such as ILO, WHO and OSHA have extensive data, information, statistics and analyses reports on countries profile. Organizing workshops and generating an international web platform may help to share experience and exchange of international information
United Kingdom	No answer

Appendix D: Overview of Spanish clinical watch systems

An overview of systems at the Spanish national level:

- CEPROSS and PANOTRASTSS which is a system not specifically designed to pick up NERCs.
- PIVISTEA which is a surveillance program of workers previously exposed to asbestos

An overview of system at the Spanish regional level:

A number of regions have created their own local/regional systems for registering occupational diseases and/or for promoting notification of Occupational Diseases (by doctors of their Regional Health Service; particularly by general practitioners). The system of Asturias is specific for detecting and registering occupational cancer. It includes an evaluation system (EVESCAP) and a specific register (cancERT). Navarre has a regional sentinel clinical watch system for Occupational Diseases that has been proven to be very good (García López, 2011.)

The rest of the Spanish Regional systems are for occupational diseases in general.

An overview of the Spanish regional systems is presented below:

- **ASTURIAS:** Valoración de sospecha de cáncer profesional (EVESCAP) (Resolución de 14 de junio de 2011, de las Consejerías de Salud y Servicios Sanitarios y de Industria y Empleo, por la que se crea y regula el funcionamiento del Equipo de Valoración de Sospecha de Cáncer Profesional (EVASCAP) del Principado de Asturias);
- **ANDALUCÍA:** Registro de enfermedades profesionales por los profesionales del Sistema Sanitario Público (Orden de 13 de mayo de 2010, por la que se crea el fichero con datos de carácter personal denominado Registro de comunicación de sospecha de Enfermedades Profesionales por los profesionales del Sistema Sanitario Público de Andalucía);
- **CATALUÑA:** Instrucción 01/2007 del ICAM (Valoración de la contingencia profesional a través de una instrucción del Instituto Catalán de evaluaciones médicas, Departamento de Salud, Generalitat de Catalunya);
- **GALICIA:** Registro de enfermedades profesionales del Instituto Galego de Seguridade e Saúde Laboral (ISSGA);
- **PAÍS VASCO:** Procedimiento de comunicación de casos sospechosos de origen profesional por parte de los facultativos de Osakidetza y de los servicios de prevención;
- **MADRID:** Programa de comunicación de sospecha de enfermedad profesional desde atención primaria (CSEP);
- **MURCIA:** Protocolo de actuación para la comunicación de diagnósticos de sospecha de enfermedades profesionales por parte de los profesionales sanitarios del Sistema Sanitario Público de la Región de Murcia;

- **NAVARRRE:** Institute of Public and Occupational Health of Navarre (ISPLN: Instituto de Salud Pública y Laboral de Navarra)
- **COMUNIDAD VALENCIANA:** SISVEL (Sistema de Información Sanitaria y Vigilancia Epidemiológica Laboral) desarrollado por la Dirección General de Salud Pública de la Consellería de Sanitat, a través del Servicio de Salud Laboral

