Signals of new occupational health risks: an impetus for health and safety vigilance

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Summary

Continuous changes in work and working conditions give rise to new occupational health risks and possibly to new occupational diseases. Research shows that social partners and the government have a need for timely and specific knowledge about new risks. In cases where there is insufficient knowledge of these risks, opportunities for intervention and prevention are missed. Although a great deal of effort goes into risk assessment in order to manage the risks brought on by new technologies, it is a good idea to also be signalized to new and undesirable side effects of work on health.

This report uses the definition of 'new risk' formulated by the European Agency for Safety and Health at Work:

- The risk was previously unknown and is caused by new processes, new technologies, new types of workplaces, or social or organizational change, or
- A long-standing issue is newly considered a risk due to a change in social or public perceptions (for example, stress or bullying), or
- New scientific knowledge allows a long-standing issue to be identified as a risk.

In society, the need to identify new health risks more quickly and more effectively has grown particularly fast over the past decade. It is continually emphasized that identifying new risks is a process that involves many uncertainties, in which a balance must be found between a dynamic and a careful approach. The challenge is to prevent any occupational damage to health without creating unnecessary concern.

Various methods exist to identify the occurrence of occupational diseases. This sometimes leads to detection of new occupational health risks. A number of these methods are discussed briefly in this report. These vary from the active NIOSH HHE approach in the United States to the 'Vigilant Physicians Networks' (*Waakzame Artsen Netwerken*) in the United Kingdom, France and the Netherlands, and the active search for 'lost cases' in Italy.

To find new ways of organizing vigilance of new occupational health risks (health and safety vigilance), it seems useful to use experiences with pharmaceutical control or pharmacovigilance: the science of collecting, monitoring, studying and evaluating information about the side effects of drugs. This concerns detecting and interpreting signals, in which a signal can be described as a hypothesis about a connection between exposure and a health problem, supported by data and arguments.
Four phases can be distinguished in this process, which also seem to apply to health and safety vigilance:

- Signal detection: the identification of possible relevant links between work/working conditions and health problems.
- Signal strengthening: preliminary assessment of available information and arguments (evidence).
- Signal validation: follow-up and further research.
- From signal to action: communication, follow-up research and measures.

First of all, several methods are discussed which can be used to detect signals of new occupational health risks (signal detection). The subsequent subjects addressed are the registration of spontaneous reports of possible connections by physicians/occupational physicians, reports from workers, the periodic screening of literature, data mining in databases, links between databases, the active investigation of health effects and the secondary analysis of patient information which was collected for other reasons. The advantages and disadvantages and limitations of these methods are then examined.

There are various types of association between exposure and health problems. These connections relate, for example, to the seriousness and nature of the health problems and the strength of a causal connection with the specific exposure. The methods discussed vary in terms of their suitability for identifying various types of association. It is therefore not possible to use only one method to signal all new occupational health risks. One should use methods that complement each other (triangulation).

After signals of associations between work/working conditions and health have been discovered, the signal must first be assessed preliminary before a more final evaluation is made of the signal itself and the supporting information: signal strengthening and signal validation. For that reason, additional information must be collected at both an individual and aggregate level. The first question addressed here is whether similar associations have been identified in registries or described in the literature. Next, the established hypothesis about a association must be further studied using epidemiological or experimental research. Actually international cooperation is always desirable in this context. Therefore it is important that a platform exists for rapid international discussion, such as analogous to the Review Panel of pharmacovigilance experts. Ultimately, a judgment (preliminary or final) must be issued about the new risk, varying from certain to unlikely, or unclassified due to lack of data.

Once it has been decided that a possible association is actually a signal, action must be taken. The necessary steps constitute the phase 'from signal to action'. This includes communication with parties directly involved, communication with external parties, initiating further research, and, where necessary, amending guidelines, protocols, legislation and regulations. The actual details of this phase depend largely on the nature, seriousness and scale of the signal.

It can be concluded that, besides anticipating risks by analyzing the work and the workplace, it is important to signal new occupational health risks so that measures can be taken in time to prevent loss or damage. Monitoring the adverse consequences of work, referred to as health and safety vigilance, must be given a prominent place in the field of health and safety.

Because no single method is suitable to signal all potential new occupational health risks, a series of complementary methods (triangulation) must be selected. Because it is not known in advance which method will best detect a new signal, the range of signaling methods should be rather extensive.

Once possible new occupational health risks have been discovered, this must result in a preliminary and later a final assessment. To this end, information will be collected at both an individual and aggregate level. Actually international cooperation is always desirable and necessary in this context, in order to make the best possible use of the available information and resources (including research). For this reason, opportunities for rapid and low-threshold international discussion are highly important.

It is recommended to intensify the duties of the Netherlands Center for Occupational Diseases (NCvB) in the organization of monitoring new occupational health risks (Center for Health and Safety Vigilance- *Centrum voor Arbovigilantie*). The following possible activities have been identified:

- Creating a system in which new risks can be reported by occupational physicians and possibly other parties (GPs, medical specialists, workers).
- Conducting regular focused literature surveys and drawing up reports on this.
- Experimenting with data mining techniques in the Dutch National Occupational Disease Registry.
- Studying cases and clusters, for example by forming ad hoc multidisciplinary teams to investigate suspected cases and clusters.
- Analyzing existing databases (of the NCvB or in cooperation with other organizations, such as the Netherlands Institute for Health Services Research (NIVEL), the Employee Insurance Administration Agency (UWV), the Institute for Asbestos Victims (IAS) in other databases).
- Disseminating knowledge and information about new risks.

Furthermore, the importance of a national and international network for knowledge exchange is emphasized. This will involve making the best possible use nationally of existing expert groups, as well as promoting internationally the cooperation between the institutes in the various countries that are charged with the detection and evaluation of new health risks by means of:

- Developing a platform for questions and discussion on the subject of new occupational health risks.

- Collectively gathering cases.
- Starting and evaluating experiments that can lead to the harmonization of detection methods between participating countries.
- Dividing up activities in the screening of the scientific literature.

1. Introduction

Continuous changes in work and working conditions give rise to new occupational health risks and new occupational diseases. The health consequences of new technologies, as well as the currently unknown effects of existing technologies, create reasons for concern among the working population, people professionally involved in work and health, policymakers and insurers.

There is insufficient knowledge about possible new occupational health risks, as confirmed in, for example, a report by the Social and Economic Council of the Netherlands (SER) entitled 'Advisory report on the approach to and the insurability of occupational health risks' *('Advies over de aanpak en de verzekerbaarheid van nieuwe arbeidsgerelateerde arbeidsrisico's*) [1]. As a result, new risks are detected too late and the opportunities to prevent or treat the resulting damage to health are impeded. By conducting risk assessments in a timely manner, an attempt is made to control the risks of new technologies. The European REACH program, which came into effect on 1 July 2007, is an example of this. REACH stands for the Registration, Evaluation, Authorization and Restriction of Chemical Substances. Companies are required to test the substances that they produce or use for possible hazards to human and environmental health. Another example is the establishment of the European Agency for Health and Safety at Work in Bilbao, Spain as a 'Risk Observatory' with a special focus on 'Emerging Risks'. One of the methods used by the agency involves taking an inventory of expert opinions on occupational health risks. Three Expert Forecasts have been published on physical risks [2], biological risks and psychosocial risks (http://osha.europa.eu/en/riskobservatory/risks/forecasts).

Complementary to risk management, it is important to detect new, adverse occupational health consequences: incident notifications of cases or clusters of possible occupational diseases that are assessed, weighted and translated into preventive actions. This approach is comparable to analyzing and learning from occupational accidents, which is now common practice. We can also learn from experiences with identifying the adverse effects of drugs: although drugs have undergone extensive testing for safety in the research phase, they may produce unexpected and sometimes serious adverse effects after introduction to the market. Examples include the epidemic of congenital birth defects due to the sedative thalidomide (Softenon) in the early 1960s, and the serious congenital abnormalities caused by diethylstilbestrol (DES). Many countries have therefore set up national centers for reporting the side effects of medicines (in the Netherlands, LAREB, www.lareb.nl) and for registering congenital abnormalities in systems such as EUROCAT (www.eurocatnederland.nl).

More than 30 years' experience of identifying the adverse effects of drugs within and outside the Netherlands has shown that a notification system can make a valuable contribution to post-marketing surveillance. 'Pharmacovigilance' has thus become an important source of information.

In France, principles of pharmaco-epidemiology have been successfully applied to reports of unusual cases of occupational diseases [3]. Now that pharmacovigilance has been the focus of attention, it seems high time that serious action is taken with respect to health and safety vigilance.

The scope of this report is restricted to the detection of new occupational consequences of work on health. This perspective is complementary to risk analyses and expert forecasts, as carried out by the EU Risk Observatory in Bilbao. Because the risk-management approach is based on experience and knowledge from the past, it can be unsatisfactory in terms of identifying and tackling new occupational risks. Moreover, the occurrence of a health effect is often the first indication of a new occupational risk.

This publication does not deal with all aspects of new risks. For example, measures to prevent health effects and treat occupational health problems are mentioned, not discussed. This report does not address the social theme of the insurability of and responsibility for new risks. Recently, the Scientific Council for Government Policy in the Netherlands issued an advisory report on the allocation of responsibilities relating to 'uncertain safety'. The report advocates a proactive approach to uncertainty in order to formulate future-proof policies for dealing with

risks. The detection of new occupational health effects is an example of proactive searching for potential risks and is in line with the 'precautionary principle' [4]. The Health Council of the Netherlands has also issued an advisory report on the substance of the precautionary principle and its application in policy, including working conditions policy and environmental management [5].

It is the wish of social partners and the government that there should be an early warning system of specific knowledge about new occupational diseases. This is evident from, among other things, a survey into the need of stakeholders for information about occupational diseases (2006). In the opinion of the stakeholders, the Netherlands Center for Occupational Diseases (NCvB) fulfils an important role in identifying, gathering and transferring this knowledge [6]. For this reason, an invitational conference was organized on the subject of detecting new risks: 'Identifying the side effects of work, role of notification of (new) occupational diseases for identification of new occupational risks' (13 December 2007, Appendix 1) and the theme was the subject of the Heijermans Lecture (14 December 2007; presentations, see www.beroepsziekten.nl).

Reading guide

This report builds on the results of this invitational conference and the study of various reports and scientific articles. This publication contains the following:

- The background to identifying new risks, including definitions, typology, social debate and discussions of various methods for identifying health risks related to work and working conditions (Chapter 2).
- An overview of methods for identifying new occupational health risks, with an indication of the advantages and limitations of each method, and examples (Chapter 3).
- A description of the possibilities for further strengthening and validating the signals of new risks, including a discussion of the subsequent knowledge transfer and communication processes (Chapter 4).
- Conclusions about the possible approach to identifying new occupational health risks (Section 5) and recommendations for further policy (Chapter 6).

2. Background

2.1 Defining 'new risks'

Several definitions exist for the term 'new risks', varying from a broad interpretation of the term from the perspective of insurers, to descriptions that are confined to new occupational health risks.

In the introduction to the ESB dossier on new risks, De Bruin [7] defines new risks from the perspective of insurers. In this context, new risks have the following characteristics:

- they cannot be detected by the human senses
- they can therefore arise unexpectedly
- they lack scientific substantiation
- they usually have a long incubation period
- they can affect anyone
- they are large-scale and cross-border in nature, and can be a serious threat to society
- due to their nature and scale, it is difficult to incorporate them in traditional insurance solutions.

Examples given are DES, BSE (mad cow disease), Organic Psycho Syndrome and mesothelioma. In any case, these new risks often have a solid scientific basis and these afflictions primarily affect those who are subject to the highest levels of exposure. This interpretation of new risks does not make a sufficient distinction between hypothetical and real risks, but is understandable from the position of insurers, which is aimed at providing timely cover for new risks.

In the SER report 'Advice on the approach to and insurability of new occupational health risks' *('Advies over de aanpak en de verzekerbaarheid van nieuwe arbeidsgerelateerde arbeidsrisico's*')[1], 'new risks' are taken to mean: new occupational health risks to which employees are exposed due to changes in production processes and work methods, or to changes in working conditions. This includes risks that are already known or should be known, as well as risk that are (as yet) unknown, but are discovered through new information. Risks that have been known for some time, and for which the process of signals, prevention and recovery is largely in place, are outside the scope of this description.

The European Agency uses the term 'emerging OSH risks': risks that can be both new and increasing.[2]
By 'new' is meant:

- The risk was previously unknown and is caused by new processes, new technologies, new types of workplaces, or social or organizational change, or
- A long-standing issue is newly considered as a risk due to a change in social or public perceptions (for example, stress or bullying), or
- New scientific knowledge allows a long-standing issue to be identified as a risk.

By 'emerging' is meant:

- An increase in the number of risk factors.
- An increase in exposure to these risk factors (increase in exposure level and/or the number of people exposed).
- An increase in the effects on workers' health (an increase in the seriousness of the health effects and/or the number of people affected).

There is a striking similarity between the objectives of the European Agency and those of pharmacovigilance. The aims of pharmacovigilance [8] are stated as follows:

- The early detection of unexpected, unknown adverse effects.
- The detection of any increase in the frequency of a side effect.
- The identification of risk factors (including risk groups) and the mechanisms of side effects.
- The quantitative assessment of side effects.
- The interpretation of data and dissemination of information.

When this report refers to occupational health risks, this involves new (and not increasing) risks as defined by the European Agency of Occupational Safety & Health Risk Observatory.

2.2 Typology of new occupational diseases

New occupational diseases are being discovered all the time, although they might not be as new as may be suspected. Such cases often involve an already known syndrome, caused by recent changes in work and working conditions. New occupational diseases can be categorized in various ways. An example is shown below (see Table 1 after Pal [9]). There are more or less new syndromes caused by changes in work and working conditions, whereby a possibly new combination of health complaints arises as the result of causes previously unknown for these symptoms. Examples are Popcorn Disease and Progressive Inflammatory Neuropathy (PIN). There are also health problems that turn out to be due to known forms of specific stressors (such as breast cancer due to night shift work or respiratory illness caused by fine dust). There is a special category of disorders that can occur in offspring when parents have been exposed to harmful substances before or during the pregnancy.

Table 1: Categories of new occupational diseases, with examples

Category	Examples
New diseases due to changes in work and working conditions	• Progressive Inflammatory Neuropathy (PIN) in swine slaughterhouse workers • Popcorn disease • Legionnaires' disease • Allergy to preservatives (paint, adhesive) • Allergy to biological pesticides • Repetitive Strain Injury (RSI) due to computer work
New risks from known forms of stress	• Breast cancer due to night shift work • Cardiovascular diseases caused by fine dust • Lung infections due to welding fumes
Consequences of parents' occupational exposure on their offspring	• Congenital abnormalities • Cancer in children • Delayed neuropsychological development

Detecting new occupational health risks requires different instruments from those used for monitoring occupational diseases. For those looking for unexpected connections, registries of occupational diseases which are based on registration guidelines that set out how a causal association between health problems and exposure must be assessed, are a less suitable option. Furthermore, the choice of instrument is determined by characteristics of the health problems to be investigated, such as the nature and seriousness and the strength of the causal link with the possible cause.

That is why it is not possible to detect new occupational health risks using a single method; several complementary methods are required. If the situation involves a signal of a rare disease with a high etiological fraction (work is an important cause of these complaints), then a large group of signal physicians and others are more suitable than epidemiological research (popcorn disease, PIN). Stimulating and registering 'spontaneous reports' by physicians or employees would be a good instrument in such cases. In the case of frequently occurring illnesses with a low etiological fraction (work is *a* cause, but there are many other causes too), epidemiological research among large groups of employees is more valuable than individual reports (breast cancer due to night shift work, cardiovascular disease due to fine dust).

New risks from existing forms of stress: breast cancer related to night shift work

Various scientific studies show an increased risk of breast cancer among nurses and flight attendants. For women who have worked night and irregular shifts over a long period of time,

the risk of breast cancer is 1.5 to 1.8 times higher than for women who were not exposed to shift work.

A possible explanation is the disruption of the biorhythm as a result of *light at night.* It is known from animal experiment research that exposure to *light at night* decreases melatonin levels. Melatonin is important for the sleep-wake cycle, but also serves to slow down tumor growth. If less melatonin is produced, there is therefore less deceleration of tumor growth.

The first convincing studies date from 2001, and others followed later. These findings are recorded in the Signal Report of Occupational Diseases (*Signaleringsrapport Beroepsziekten*) 2002 [10]. The Health Council of the Netherlands was asked to provide its recommendations on this report [11]. In 2007, the International Agency for Research on Cancer (IARC) concluded: 'shift-work that involves circadian disruption is probably carcinogenic to humans' and included shift-work in its list of Group 2A carcinogenic agents.[12]

This new link between work and health was identified through epidemiological research (cohort study among employees).

2.3 Social discourse on the theme of new risks

International:

In 1992, the **WHO** introduced the theme 'New Epidemics in Occupational Health' into its Workers Health Program. The WHO planning group took the initiative to gather information on early signs of occupational health problems that are not or not yet regarded as epidemics, but which have been signaled as case reports, clusters of changes in morbidity trends. This information was discussed at an international symposium in Helsinki.[13] The chosen approach was one that lies between intuitive predictions and scientific observation; an approach that was more proactive than reactive. Subjects discussed in Helsinki included sudden unexplained death in the workplace, occupational reproductive disorders, cancer caused by work and multiple chemical sensitivity. More strategic subjects were also discussed, such as communication on uncertain safety and the researching of disease clusters in a particular group or sector.

European Union: The European Agency Occupational Health and Safety Risk Observatory was established in Bilbao in 1996. New occupational risks are expected as a result of new technologies, changing work organizations, the feminization of work, ageing, globalization and increasing work pressure and information supply. It is important to identify and tackle these new risks at an early stage. Since 2005, the European Agency has published Expert Forecasts [2] on certain themes such as physical risks, biological risks and psychosocial risks.

EUROGIP in France produced an overview of new occupational health risks based on a survey and a literature study.[14] The report explores a number of themes such as work stress, the position of contractors (those who provide services to employers on a contract basis), new communication techniques and nanotechnology. The recommendation is to link the introduction of new technologies and substances to research into possible health effects and prevention methods. EUROGIP also calls for better international information exchange so that measures can be introduced quickly.

In the Netherlands:

In 1998, the **Dutch Association of Insurers** held a conference on new risks, thereby placing the subject on the agenda in the Netherlands. There is a report of the conference in a theme number of 'Economic Statistic Reports' (*Economisch Statistische Berichten)* [7], in which the theme is discussed from various perspectives in contributions from, among others, Paul Schnabel ('On the desire for security and the need for trust' ('*Over het verlangen naar zekerheid en de noodzaak van vertrouwen*')), Arnold Heertje ('New Risks, a public-private problem ('*Nieuwe Risico's, een publiek-privaat probleem*')) and Lucas Reijnders ('The anatomy of new risks' ('*De anatomie van nieuwe risico's*)).

In 2001, in response to this, the **Council for Public Health and Health Care** published an advisory report.[15] The council stated that new risks are a precarious subject in terms of policy and interesting for various reasons in terms of strategy. 'They (new risks – ed.) can result in collective but also individual threats. The causes are difficult to identify and it is therefore difficult to allocate responsibilities. Early detection requires considerable research capacity and a substantial stand-by facility for detection. New risks are surrounded by uncertainty – uncertainty regarding time, place, scale, seriousness and point of engagement. The consequences of exposure to the risks may not manifest themselves until future generations, and in that case, investments will only generate returns in the long run.' It is clear that new risks are discussed here in a far broader perspective than the new occupational risks.

In its 2002 advisory report on new risks, the **Social and Economic Council of the Netherlands (SER)** restricted itself to occupational aspects.[1] The Council stated that knowledge is lacking on new occupational health risks. This hampers both how fast new risks can be detected and how effectively the damage to health resulting from these risks can be prevented and treated.

The Council states that policy for detecting new risks focuses on risk identification and evaluation and on monitoring occupational diseases. At the same time, other instruments should be used, such as epidemiological research, the development of early diagnostics and the monitoring of knowledge about new risks at a national and international level.

In the Council's opinion, knowledge of new risks is also important for the prevention of possible health problems. The knowledge is necessary in order to properly assess the seriousness and scale/extent of new risks. It is also required for developing and implementing effective preventive measures.

With regard to the treatment of occupational health problems, the Council observes that there is insufficient expertise in the curative healthcare sector. A number of recommendations are made for businesses, employees, sector associations and the government.

KnocoM, AStri: KINA (Knowledge Infrastructure for New Occupational Risks), 2005. Proposal for improving the notification process and the dissemination of knowledge about new occupational risks.[16] KnocoM and AStri were commissioned by the Ministry of Social Affairs and Employment (SZW) to assess how the notification and knowledge infrastructure for new occupational risks is organized. They also advised on improvements. A distinction is made between two largely separate processes: the detection process and the knowledge process. The detection process is not operating optimally because various parties (employers, employees, professionals in the occupational health and safety sector and the curative sector) appear to have no direct interest in detecting new risks. In addition, the knowledge process does not function smoothly because a clear 'chain' approach is lacking; there are many different websites and central control is lacking.

Four related recommendations are made:

- Reinforce the signal function of the (NCvB).
- Reinforce the control function of the Dutch Occupational Health and Safety Platform (*Arbo Platform Nederland*).
- Further development of the website www.arbo.nl.
- Set up a national expertise network for new occupational health risks.

On this basis, Henk van Hoof, the then State Secretary of Social Affairs and Employment, stated that it would not be expedient to establish processes specifically for new occupational risks, but that this could be realized within existing structures (May 9, 2005, letter accompanying the report to the Lower House of the Dutch Parliament).

A committee of the **Health Council of the Netherlands** [5] has advised on the substance and application of the 'precautionary principle' (*voorzorgsbeginsel*, VZB), also regarding working conditions. The various descriptions of the principle have four elements in common: an element of threat, an element of uncertainty, an element of action, and an element of urgency. The precautionary principle must be applied to issues characterized by substantial uncertainty about dangers, exposure, and the nature and extent of risks, etc., for which a threat and a causal

relationship are plausible. In doing so, the challenge is to create a reasonable balance between a dynamic and cautious approach and a fair distribution of costs and benefits among groups. Part of dealing with uncertain risk issues should be monitoring the effects which, if necessary, lead to changes in policy.

The **Scientific Council for Government Policy (WRR)**[4] has advised on the allocation of responsibilities with regard to uncertain safety. These recommendations have called for the so-called 'precautionary principle' to be added to the classic risk-management approach. The arguments for the addition of the precautionary principle are based on the statement that 'the vulnerability of people, society and the natural environment require proactively dealing with uncertainties'.

In the classic risk-management approach, the key question was 'How large are the risks that confront us and how can they be controlled?'. The new approach to risks is based on the question: 'How should we structure our organization (or society as a whole) so that the uncertainties that we face are able to be discussed and, if possible, become manageable risks?'. Identifying new occupational health effects and detecting early warnings are examples of proactive searching for potential risks, and are in line with the precautionary principle advocated by the Scientific Council for Government Policy.

It is evident from this brief overview of national and international statements that there is growing recognition of the need to identify new health risks faster and more effectively. At the same time, it is clear that such a process will involve a great deal of uncertainty and must find a balance between a dynamic and cautious approach. The constant challenge will be the timely prevention of damage to health, without creating unnecessary concern.

2.4 Identifying occupational health risks

Various methods exist to identify the occurrence of occupational diseases. These methods may sometimes result in the discovery of new occupational health risks. A number of these will be discussed briefly in this section. The methods vary from the active NIOSH HHE approach in the United States to the "Vigilant Physicians Networks" in the United Kingdom, France and the Netherlands, and the active tracing of 'lost cases' in Italy.

2.4.1 NIOSH Health Hazard Evaluation (HHE) Program

In 1971, the National Institute for Occupational Safety and Health (NIOSH) in the United States introduced a program for identifying chemical, biological or physical risks in the workplace. Multidisciplinary teams are stationed at five different locations in the U.S., and carry out this research at the request of employers, employees or employee representatives, and other public-sector agencies. The teams comprise physicians with various backgrounds, occupational health specialists, epidemiologists, technicians, psychologists and statisticians. When a request is received, the program staff members decide on an appropriate response and, depending on the nature of the problem, assign the relevant experts. It has emerged that the engagement of the teams is mainly useful for the evaluation of new problems, such as cases of diseases with an unknown cause, or exposure to substances or processes for which no regulations exist.

The strength of the NIOSH HHE program lies in the ability to quickly engage expertise and a broad field of focus: aimed not only at analyzing and solving the problems in the organization concerned but also, when necessary, in the sector or chain of organizations.
Another strong point is the low-threshold nature of the program: in the case of a Health Hazard Evaluation (HHE) at the request of employees, an application submitted by at least three employees is sufficient, provided that initial discussions confirm the existence of a serious health problem that is likely work-related. The financial support by the government also ensures that the access to the program is easy. Consequently, the study can commence as soon as possible, the parties may not selectively search for research agencies and the reports are not limited to the company. After presentation at the company concerned (management and employees), the results are published on the NIOSH website. Since the launch of the program, more than 13,000 HHEs have been carried out.

Popcorn disease

In 2003, an HHE was carried out following reports of several cases of serious respiratory problems among employees in a popcorn factory. The rare lung disease (bronchiolitis obliterans) seemed to originate from exposure to a volatile flavoring: diacetyl (butter flavoring). For this reason, this occupational respiratory disorder is known as 'popcorn disease' or 'popcorn lung'.

After the association was confirmed, measures were taken to reduce exposure to diacetyl. A monitoring program was set up with periodic lung function evaluations for exposed employees. Information about the health problems was issued to the producers and users of the flavoring. As a result, an evaluation was carried out at a diacetyl producer in the Netherlands, and three cases were discovered.[17]

2.4.2 Vigilant physicians networks

2.4.2.1 The Health and Occupation Reporting Network (THOR)

The United Kingdom has a long tradition in the field of epidemiology, related to intelligence, the collection, analyzing and interpretation of 'enemy' information. This kind of intelligence is also organized in the field of occupational diseases. In addition to the official registration of occupational diseases which are eligible for compensation, as well as the more than 150 years of existing death statistics which also state the individual's last profession, a number of complementary surveillance projects have been established. THOR is an example of a voluntary reporting system for occupational diseases. Each year, approximately 2,200 physicians send in about 24,000 notifications electronically or by post.

Within THOR, there are a number of surveillance systems with various notifiers:

- SWORD: Surveillance of Occupational & Occupational Respiratory Diseases
- EPI-DERM: Occupational Skin Surveillance
- OPRA: Occupational Physicians Reporting Activity
- THOR-GP: The Health and Occupation Reporting Network - General Physicians
- MOSS: Musculoskeletal Occupational Surveillance Scheme
- SOSMI: Surveillance of Occupational Stress and Mental Illness
- SIDAW: Surveillance of Infectious Diseases At Work
- OSSA & ENT: Occupational Surveillance Scheme for Audiological & Ear, Nose & Throat Physicians.

Within this network, it is possible to carry out fast, current analyses of trends in occupational diseases and signals of possible new occupational diseases.

2.4.2.2 French National Occupational Illness Surveillance and Prevention Network

The French national occupational illness surveillance and prevention network, RNV3P (*Réseau National de Vigilance et Prévention des Pathologies Professionelles*) is a network of 29 occupational disease clinics which are based in each university medical centre. Patients can be referred to these clinics by occupational physicians, GPs or medical specialists. In addition to cases that clearly identify occupational diseases which are eligible for compensation, many patients are referred with health problems for which the connection between exposure and health problems is less clear. In all cases, a systematic assessment is made with a good assessment of the exposure and the illness. This is entered, in a standardized format, in a central database managed by the University of Grenoble.

2.4.2.3 NCvB: National Occupational Disease Registry and Surveillance Projects

Since 1999, the detection of occupational health risks has been an important task of the Netherlands Center for Occupational Diseases (NCvB). Important methods for this are the National Occupational Disease Registry and the Surveillance Projects (*Nationale Beroepsziekteregistratie en Peilstations*).

National Occupational Disease Registry: Since November 1999, Occupational Health Services and occupational physicians are required to report occupational diseases to the NCvB. The reports from this National Occupational Disease Registry provide insight into the occurrence of occupational diseases in the Netherlands and have mainly a signaling function. They can be used to develop activities to prevent occupational diseases or for further study into the causes and consequences of occupational diseases. The value of the figures from the National Occupational Disease Registry is limited due to underreporting and the lack of data about the size of the population at risk [18].

Surveillance projects: A surveillance project is where a selected group of notifiers report certain occupational diseases. Within the surveillance projects, intensive contact is maintained with the notifying parties in order to keep up their motivation to continue reporting. This is done by means of newsletters and theme meetings. As such, there is a surveillance project for occupational skin diseases (dermatologists), occupational respiratory diseases (lung specialists) and a Surveillance Project for Intensive Notification (*Peilstation Intensief Melden - PIM*) (motivated occupational physicians).

2.4.3 'Lost cases' of Occupational Diseases

After discrepancies were observed in Italy between the number of officially reported cases of occupational diseases and the number that could be expected based on epidemiological estimates, an active effort was undertaken to find these 'lost cases' of occupational diseases. The Institute for Occupational Diseases at the University of Milan initiated a project in cooperation with the Lombardy region in the context of a European Recommendation[1]. In addition to increased attention for occupational diseases in regular medical education and in the refresher and post-graduate training of GPs and medical specialists, information about 'lost cases' was gathered in various ways: linking databases on diagnoses and professions, research into special disease registries (such as the mesothelioma registry and the paranasal sinus carcinomas registry) and the identification of clusters. An example of this last approach is a study of a cluster of mesotheliomas on Sicily. This study revealed the causal role of fluoradenite, a mineral similar to asbestos.

[1] Recommendation 2003/670/CE … it is necessary 'to promote the active contribution of the National Health System at the prevention of occupational diseases, in particular through an improved awareness of the occupational health physicians and public health personnel of the need of an improvement of the knowledge on occupational diseases and their diagnosis'

3. Signal detection

Giving some further thought to possible ways of organizing the monitoring of new occupational health risks (health and safety vigilance), it seems useful to use experiences with pharmaceutical control or pharmacovigilance: [19].

Pharmacovigilance
Around 1970, in response to the disabling birth defects from the use of the sedative thalidomide (Softenon), notification centers were set up in many countries to allow the reporting of suspected adverse effects of medicines. People realized that, even if a medicine is approved for use, not all of the adverse effects are necessarily known, despite all the previously conducted research. In the Netherlands, the Bureau for the Adverse Effects of Drugs (*Bureau Bijwerking Geneesmiddelen*) was established, which later became the Netherlands Pharmacovigilance Centre (the LAREB foundation - *Landelijke Registratie en Evaluatie Bijwerkingen Geneesmiddelen*).

The Netherlands Pharmacovigilance Centre and similar centers continually receive a wide range of more or less plausible signals on adverse drug reactions. These signals must be assessed to determine whether measures must be taken. This process is called pharmacovigilance: the science of collecting, monitoring, studying and evaluating information about the adverse effects of drugs to prevent damage to the users and to track down new risks involving drugs. This concerns detecting and interpreting signals, in which a signal can be described as a relationship between exposure and a health problem, supported by data and arguments.

A distinction can be made into four phases in pharmacovigilance: *signal detection, signal strengthening, signal validation*, and *from signal to action*.

- *Signal detection*: the identification of possible relevant links between work or working conditions and health problems. This phase involves tracking down possible relevant connections in different sources of information. A signal contains a hypothesis about a possible relationship and is accompanied by supporting data and arguments.
- *Signal strengthening*: preliminary assessment of available data and arguments (evidence). This phase involves collecting supporting information, such as an increasing number of reports nationally or from other countries, and studying the biological and other plausibility of the signal.
- *Signal validation*: follow-up and further research. This phase involves attempting to substantiate the possible connection using, for example, more detailed literature, epidemiological and/or experimental research.
- *From signal to action*: communication, follow-up research and measures. This phase involves the dissemination of information about the signal to all interested parties. If necessary, follow-up studies are initiated and/or intervention or prevention measures are taken.

This chapter will discuss several methods to detect signals of new occupational health risks (signal detection). Various methods exist to track down possible relationships between work or working conditions and health problems. The registration of spontaneous reports of possible relevant relationships by occupational and other physicians is one of the most common methods for this. However, there are other, possibly supplemental, methods, such as: reports from employees, the periodic screening of literature, data mining in databases, links between databases, the active investigation of health effects and the secondary analysis of patient information which was collected for other purposes. The following chapter (Chapter 4) will examine the phases after detection, summarized as signal management. This focuses mainly on the further assessment of the signals found and the possible follow-up steps necessary.

3.1 Spontaneous reports of possible relevant connections

The registration of “spontaneous” reports of possible relevant connections by occupational or other physicians is the most common method of tracking signals. Certainly with respect to new connections, it is important that the system has a wide reach of potential notifiers requiring a national or international system in which reports can be made. In this case, a report relates to a suspicion on the part of the notifier that a relationship exists between exposure at work and a certain health complaint.

The detection of new risks involves mainly unknown and unexpected relationships with serious health complaints (leading to a serious disorder, possibly permanent limitations, hospital admittance or death). The reports should be made voluntarily and confidentially, with respect for privacy and medical confidentiality and with the option of adding as much relevant information as possible. If the same suspicion of a connection is reported by two or more notifiers independently of one other, this serves to significantly strengthen the signal.

While a system of spontaneous reports is an effective manner of gathering data, it also has its limitations. A report can contain various forms of bias, and underreporting is also a problem. In addition, privacy aspects play a role when publishing case reports. Great care is needed to guarantee the confidentiality of the data and the involvement of the notifiers.

Progressive Inflammatory Neuropathy (PIN) among swine slaughterhouse workers

In late 2007 12 men were admitted to the Mayo Clinic, a leading academic hospital in the U.S. with branches in Arizona, Florida and Minnesota, with an inexplicable neurological disorder with symptoms varying from weakness and sensory disorders in the arms and legs to paralysis. Thanks to the attentiveness of health care personnel, it was established that all the men were suffering from a new syndrome, which was named Progressive Inflammatory Neuropathy (PIN) [20].

It turned out that all the men worked in a pork slaughterhouse, in the same department at the same company. The company had switched over to a new method of processing pig heads. The process involved brain matter being blown out of a pig’s skull using a compressed-air device through a hole in the back of the pig’s head. Inhaling the aerosol containing brain matter particles seems to be the most probable cause of the disorder. It is not yet clear whether an immunological or infectious process is involved.

When the possible cause became clear, this working method was stopped immediately, and no new cases developed. Two other slaughterhouses used the same process, and workers there also developed neurological complaints. All neurologists in the U.S. were asked to be on the signal for this new disorder and to report it if necessary.

3.1.1 By occupational physicians

As specialists in the field of work and health, occupational physicians are expected to be able to detect signals about new, adverse effects of work. They do this by reporting such connections to the National Occupational Disease Registry, but also sometimes by posing a question to the NCvB helpdesk. Each year, the occupational disease specialists of the NCvB answer around 800 questions, and 60% of these come from occupational physicians. Several times a year, these questions relate to possible new connections between health problems and work.

Occupational physicians have identified new occupational diseases

In 1969, Dr. Stumphius, an occupational physician, described a situation in which 22 of the 25 patients with mesothelioma who were diagnosed in Walcheren between 1962 and 1968 had worked at a large shipyard. Most of these men worked as insulation installers or ship

carpenters, and were exposed significantly to asbestos. The serious medical problems resulting from asbestos exposure were clearly demonstrated in the Netherlands as a result of these cases [20].

Dr. Van den Bogart (1990) saw patients with extrinsic allergic alveolitis who had inhaled a large amount of fungi spores during their work in mushroom cultivation. This was further studied in cooperation with lung specialists. His dissertation on Mushroom Worker's Lung led to preventative action being taken in this sector [21].

Dr. Elders (1999) described the paralysis of a shoulder muscle due to the pressure of scaffolding equipment on the *nervus thoracicus longus*; strain on the nerve also plays a role in this disorder. A patented shoulder protector has been developed for scaffolding builders to prevent this disorder [22].

Unlike the United Kingdom, the Netherlands does not have a method of separately reporting suspicions about new connections between work or working conditions and health. In the United Kingdom, the THOR system (The Health and Occupation Reporting Network) as discussed in Chapter 2, also has the THOR-Extra unit, where all THOR participants can submit reports of new and interesting connections between exposure and work. If a certain connection is reported more than once, the notifiers can be brought into contact with each other to determine whether the situation involves a relevant signal.

Advantages:
Occupational physicians have access to the workplace and knowledge of the relationship between occupational exposure and health problems.

Limitations:
Underreporting from which the actual scope is unknown and that has many causes. Workers do not consult a physician for their occupational health problem. GPs and medical specialists do not focus on work or working conditions as a cause of a complaint. Workers do not visit an occupational physician because of their problem, especially if the problem does not involve absenteeism (especially long term). This is sometimes also the worker's own choice, and moreover, approximately one million working people do not have access to occupational physicians in the Netherlands; for example, because they are temporary employees or self-employed. Furthermore, occupational physicians do not always recognize that a complaint is work-related. And even if the complaint is identified as work-related, it is not always reported, due to reasons as lack of time, fear of legal problems or lack of motivation.

3.1.2 By GPs

The data from GPs can be used in various ways for signals of new occupational diseases: through spontaneous reports of exceptional cases or clusters and through secondary analysis of GP registries, as described below. The United Kingdom has had good experiences with notifications of occupational diseases by GPs within THOR: THOR-GP (The Health and Occupation Reporting Network in General Practice) [23]. This is probably furthered by the fact that, in contrast to the Netherlands, many GPs in the United Kingdom also have occupational health duties as part of their practice. Occasionally, exceptional cases or clusters are reported by GPs to the NCvB helpdesk and through working group discussions.

Advantages:
There is low-threshold access to GP care, which means that also self-employed and retired people consult their GP about possibly work-related health problems.

Limitations:
GPs are less focused than occupational physicians on work or working conditions as the cause of health problems.

3.1.3 By medical specialists

The Netherlands has few medical specialists who are specialized in clinical occupational health. If so, they are mainly dermatologists, allergologists and lung specialists. THOR in the United Kingdom has various registries for medical specialists, such as lung specialists; dermatologists; rheumatologists; infectious disease specialists; ear, nose and throat specialists / audiologists and psychiatrists. In other countries, there are facilities for second-line health and safety care, such as clinics for occupational diseases. In these clinics further examination of people for whom a connection is suspected between their work and their health problems can take place. This is often also linked to a claim in a compensation system for occupational diseases.

Advantages:
A notification from a medical specialist is usually more complete with respect to the medical diagnosis than a report from an occupational or general physician. In many cases, more extensive investigation has also taken place into the possible causes, such as for occupational allergic skin or respiratory disorders.

Limitations:
Medical specialists with a demonstrable interest in occupational matters are rare. Besides, extensive diagnostics with contact allergy research or provocation tests are only performed as an exception due to the lack of structural financing for this type of testing.

3.2 Notification by workers

Reports from workers can result in signals for potentially new occupational health risks. There have been good experiences with patients reporting on the adverse effects of drugs [24, 25]. In the U.S. as well, reports from workers can lead to the start of an investigation into new effects on health as a result of work, as discussed in Chapter 2 in the NIOSH Health Hazard Evaluation Program.

Advantages: the person who is the most involved serves as the primary source of information.

Limitations: possibility of irrelevant information that must be filtered out.

3.3 Periodic literature screening

Systematic literature searches in large scientific literature databases can be conducted periodically. Once keywords have been used to determine a good search strategy, periodic searches can be conducted in Medline (PubMed). The results can be received automatically by means of email updates. In this context, an example is presented below of the search strategy developed by the NCvB used to detect new health risks with respect to occupational reproductive disorders.

Results of search strategy of pregnancy and work:

”Pregnancy Outcome”[MeSH] OR “Abortion, Spontaneous”[MeSH] OR “Labor, Premature”[MeSH] OR “Infant, Low Birth Weight”[MeSH] OR “Infant, Very Low Birth Weight”[MeSH] OR “Abnormalities”[MeSH] OR “Nervous System Malformations”[MeSH] OR “Fetal Death”[MeSH] OR “Gestational Age”[MeSH] OR “Infant, Small for Gestational Age”[MeSH] OR “Pregnancy Complications”[MeSH] OR Pregnancy complication* [all fields]
AND
”Occupational Exposure”[MeSH] OR “Occupations”[MeSH] OR “Employment”[MeSH] OR “Workload”[MeSH] OR “Work”[MeSH] OR “Workplace”[MeSH]

Similar searches can produce a set of new scientific articles periodically (every year, every six months). These articles must then be evaluated for relevance by people who are experts on the subject. In the event of new possible connections, attention will also have to be paid in particular to case reports and analyses of clusters of occupational health risks. This literature data must be interrelated if possible with data from other sources (such as information on

general and specific websites, notifications at conferences, notifications in networks of experts, questions from the field through a helpdesk or other channels). Ultimately, the information will be summarized and discussed.

Advantages:
Systematic current summaries of international scientific articles, which make up-to-date knowledge of occupational health risks accessible.

Limitations:
It usually takes some time before a signal is described in the scientific literature (case report, cluster report, etc.).
The so-called 'gray literature' is difficult to retrieve. This concerns reports and other publications that are not found in scientific journals, but may still be relevant.

3.4 Data mining in databases

A method that has already demonstrated its usefulness in pharmacovigilance involves data mining in existing databases. New signals can be generated by regularly searching in databases for disproportional associations using specially developed methods. This is described as automated quantitative signal detection with the following characteristics:
It is suitable for the analysis of large or extremely large quantities of combinations of exposure and consequences; it can automatically select interesting combinations using quantitative disproportionality; and it:

- makes it possible to search in specific sets of data
- involves minimal human resources
- does not have researcher' bias
- is objective, transparent and reproducible
- is flexible and easy to adapt
- is suitable for explorative research in databases.

Advantages:
Enables the generation of hypotheses about new connections between exposure and health effects within existing databases in a fast, inexpensive, objective and reproducible manner.

Limitations:
There is no information about the size of the risk population.
The quality of the signal strongly depends on the quality of the report and the notifier (use of guidelines, coding, diagnostics, determination of exposure, etc.)
No statements can be made about causality without extensive assessment of the relationship and further research.

Data mining for occupational diseases in French database

Bonneterre has successfully used data mining in the RNV3P (*Réseau National de Vigilance et Prévention des Pathologies Professionnelles*), the French database that includes all reports of occupational diseases.[3]

He calculated proportional reporting ratios (PPR) for all reported combinations of health complaints and reported risks that occurred more than twice. The PPR is equal to the ratio between the probability of having a specific exposure and the probably of having the specific health complaint in the case of exposure to any risks other than the specific exposure.

Between 2001 and 2005, 24,785 reports in the RNV3P were analyzed. Some 3830 combinations were found, of which 47% were eligible for compensation. Of these, 1344 different combinations of illness and exposure were reported more than twice, of which 922 were eligible for compensation and 422 were not.

In 162 cases, the calculated PPR met the criteria established in advance; this was therefore higher than expected. These 162 cases may likely form a signal and must be further analyzed.

Further analysis is currently taking place, for example, of the relationship between trichloroethylene and kidney tumors, larynx cancer and asbestos, and sarcoidosis and dust exposure. Bonneterre concluded that the use of data mining methods for detecting possible new occupational diseases is promising and should be further studied.

3.5 Linking databases

In the Scandinavian countries, the use of record linkage (for example, of cancer registration and personnel files) has shed a great deal of light on new occupational health risks. In the Netherlands, this type of research faces problems in the implementation stage in connection with privacy aspects. The Advisory Council for Health Research (Raad voor Gezondheidsonderzoek - RGO) recently recommended promoting the record linkage for scientific research as far as possible within the limits of privacy legislation [26]. To study the risk factors of disease, the available public health data in the Netherlands can be used. Linking records by making use of people's citizen identification numbers can serve to significantly improve the quality and expediency of this type of research. With respect to monitoring privacy, the RGO is advocating the establishment of a trusted third party to link the records from the various databases. This trusted third party should be an agency that is independent of the data managers and the researchers who will be using the linked records.

Advantages:
Availability of large databases with unique data about characteristics of work and health parameters.

Limitations:
Privacy aspects and the risk of false-positive findings. If searches take place in databases without a hypothesis being established in advance about a possible relationship between a specific cause (such as a chemical substance or an occupation) and a specific effect (such as an illness or a defect), this is referred to as an epidemiological 'fishing expedition'. Research has shown that such fishing expeditions often generate false-positive findings [27].

3.6 Active detection of effects on health

Active detection of effects on health in specific, well-defined risk groups is an elegant but labor-intensive research method. It can be conducted in the form of a cohort study based on a suspicion of a health problem. It can also be utilized proactively as a form of post-marketing surveillance: the health of a group of workers is followed after the introduction of a new substance or new working method.

Also a project can started up aimed at active case finding. This involves usually the quantification of known effects, often linked to preventive measures. In the Netherlands, research was conducted this way into the prevention of silicosis in construction workers with a relevant exposure to quartz particles, such as those performing masonry work, foundry work and asphalt milling [28]. The bakery sector has also conducted research into bakers' asthma, where active cases were detected in a step-by-step manner: first with a questionnaire about health complaints, followed by further investigation among those with asthma-related health complaints. [29]

Advantages:
The workers' exposure can be successfully characterized and specific effects on health can be studied. This results in good quality and high reliability.

Disadvantages:
Often large groups are necessary (especially in the case of relatively rare health effects) in addition to a long follow-up period, in order to arrive at reliable results. This makes it an expensive form of research.

Allergy to biological pest control

Bell pepper producers in the Netherlands were worried because many of their employees were suffering from a runny nose, sneezing fits, red eyes and shortness of breath. It was possible that these symptoms were associated with their work. A number of workers was diagnosed with allergic rhinitis (hay fever) or asthma, and some were forced to quit their jobs. The trade association therefore asked the Allergy department of the Erasmus University Medical Center in Rotterdam to investigate the situation.

The researchers found that some 40% of the bell pepper workers suffered from rhinitis, 26% from conjunctivitis and 12% from asthma, all related to work. The allergy tests showed that 34.5% were sensitive to pepper pollen, but also – rather unexpectedly – that 23.3% were allergic to the predatory mite Phytoseiulus persimilis [30]. This predatory mite is used for biological insect control, so its waste products can become airborne and therefore can be inhaled. Breathing protection is rarely used when working with this biological pest control method [31] .

After the study, the airborne particulate control in the greenhouses was improved. In addition, bees were successfully used to pollinate the plants. As such, it was no longer necessary to mechanically vibrate the plants for pollination, which prevented clouds of pollen from being released.

This study illustrates the importance of involving the people that actually work in the target situation in detecting, scheduling and control of occupational health problems.

3.7 Secondary analysis of patient data

3.7.1 LINH/NIVEL database

The electronic medical files used by GPs can serve as a continuous source of data about health complaints, medication, the number of contacts with the GP and referrals. If this information is linked with information about the patient's occupation, it is possible to get an impression of the presence of health complaints in specific occupations. The National Information Network of General Practice (LINH) is a general practice system that can be used for this type of research.

The LINH contains data of about 85 computerized general practices, with nearly 340,000 registered patients [32]. There was no record made of the patients' occupations to date. However, in the context of a National Study into Diseases and Activities in General Practice (*Nationale Studie naar Ziekten and Verrichtingen in de Huisartsenpraktijk*), information was collected about the patients' occupations (coding according to the methods used by Statistics Netherlands (CBS)). This study was conducted most recently in 2005.

Monitoring work and health through primary care

NIVEL and NCvB conducted a pilot study to determine the usefulness of linking data from GPs and patients' occupations [33]. This revealed that a good impression can be obtained if the situation involves frequently occurring occupations as well as frequently occurring diseases.

For example, it emerged that cleaners clearly suffer more from respiratory problems, farmers more from cases of hand eczema and teachers from mental disorders. This is in line with risks reported elsewhere. The system is not suitable for an analysis of occupations that occur less frequently; for example, only 121 bakers were registered in the LINH, which makes this group too small for reliable analyses. In addition, the risk population is almost always too small for the detection of rare disorders.

However, the primary care networks seem to be useful for detecting specific health complaints as a result of a certain exposure (for example health complaints after environmental exposure, such as the firework disaster in Enschede) or in a certain region (consequences of the

occurrence of animal diseases in a certain area, such as swine fever, mad cow disease or bird flu).

Advantages:
Every person in the Netherlands is registered with a primary care practice, which means that the prevalence of disorders in specific occupational categories can be calculated and compared to other occupational categories and the total workforce.

For GPs, other than for occupational physicians, there is not a conflict between the medical interests of the worker and the interests of the employer. In addition, the self-employed and those people who have difficulty accessing occupational health care can easily obtain care from their GP (no threshold).

It is possible to use the LINH, a nationally representative random sample of electronic files from primary care practices; this makes it possible to collect data about work and care simply and efficiently. The system can easily be expanded to risk areas; for example, aimed at the detection of zoonoses.

Limitations:
In general, GPs focus little on working conditions as a cause of disease, party due to the separation of treatment and control in the Dutch healthcare system. This can be an obstacle for the spontaneous reporting of exceptional cases and clusters. It's not a problem for the secondary analyses of the primary care registration system.

The LINH is less suited for rare diseases or occupations, despite the source population of minder of around 340,000 people.

It is not standard to record data about the patients' occupation, so an extra step is needed to complete the data. More precise data about exposure than the patients' job title suggests, cannot be obtained through this system.

Secondary analyses do not generate incidence data for occupational diseases, but generate attributive risks due to occupational factors in certain occupations instead.

3.7.2 Other potential databases

In addition to the NIVEL/LINH registries, there are also other potential sources of information about occupational diseases, such as cause-of-death statistics, disease registries, the mesothelioma registry or files from the Employee Insurance Administration Agency (UWV). However, closer inspection has revealed that various disadvantages are associated with the use of these files.

Cause-of-death statistics. In the Netherlands, death certificates do not contain any information about the deceased's work/occupation. Such information was included in death certificates in the United Kingdom for more than 150 years (http://www.hse.gov.uk/statistics/overall/ohsb0203.pdf). Although this seems to be a good source of information, it is nowadays becoming an increasingly less relevant source, due to the fact that people change their occupation and activities more frequently during their career. Consequently, there is not sufficient reason to call for stating a person's occupation on the death certificate in the Netherlands.

Disease registries: These often do not contain any information about work or working conditions or exposure. It is true that this information is already available and therefore analysis might be relatively quick and inexpensive, but these registries are not set up for the objective you would want to use them for in the second analysis. This often limits the options.

Mesothelioma registry: In most cases of mesothelioma, an appeal is made to the Institute for Asbestos Victims (IAS). The evaluation of claims for the IAS involves both verifying the diagnosis and systematically establishing the person's past exposure to asbestos. This data, however, are not entered into a database, which means they are only available for the

assessment of individual cases and not for epidemiological research. Furthermore, the Asbestos Chart (Asbestkaart), with an overview of activities and jobs associated with asbestos exposure in the past, has not been updated based on the above data.

Employee Insurance Administration Agency (UWV) files: In files, for example, of occupational disability evaluations, a person's medical history/diagnosis is known and data are also collected about the person's occupation. However, this information is not easily accessible for analyses.

Method	Sources	Advantages	Limitations
Spontaneous reports	General	Effective, continuous, fast, relatively inexpensive and may cover a large area (all of the working population, all exposures, all health complaints)	It's about suspicions Underreporting and possible bias Low sensitivity for connections with long latency periods Little information about the size of the group at risk (denominator) No causal evidence Further research is often necessary
By	Occupational physicians	Access to the workplace, knowledge of the connection between work and health	Underreporting due to diverse causes
By	GPs	Low-threshold access; GPs also see patients who do not have an occupational physician	Little detailed information, less focused on work as a cause of health complaints
By	Medical specialists	Complete medical information	Often minimal focus on work as a cause of health complaints
By	Workers	Information from the people most directly involved	Higher risk of irrelevant information due to lack of knowledge about the connection between work and health
Periodic literature screening	Scientific literature databases	Systematic, current overview of international scientific articles	Lag in information Gray literature is difficult to retrieve
Data mining	Databases such as notification registries	Enables the generation of hypotheses of new connections between exposure and health within existing databases in a fast, inexpensive, objective and reproducible manner	No information about the size of the risk population Quality of the signal strongly depends on the quality of the notifier's report No judgment about causality is possible without extensive evaluation of the relationship and further research
Active detection	Workers	Exposure of workers can be successfully characterized It is possible to look for specific health effects, which produces a good level of quality and reliability	In many cases, large groups are necessary (mainly for relatively rare effects on health) along with a long follow-up period, in order to arrive at reliable results Expensive form of research
Secondary analysis of other sources	Electronic files from GPs	No biased information due to conflict of interests	Exposure often only can be derived from occupation, therefore very general
	Cause-of-death statistics	Already available	No information about occupation on form where cause of death is stated
	Disease registries	Information is already available, therefore relatively fast and inexpensive	Not set up with the objective for which they are now used, so not every type of analysis is possible
	Mesothelioma registry	Already available	No information about exposure is included in database
	Employee Insurance Administration Agency (UWV) files	Systematic records of data about work and health	Difficult to retrieve electronically

Table 2: Various sources of information for the detection of new occupational health risks with advantages and disadvantages

4. Signal management

4.1 Methods for strengthening signals

Once possible connections between work or working conditions and health complaints have been reported or discovered, the first step involves making a preliminary evaluation of the information available. This serves to determine the relevance of a signal. The following (and other) considerations may play a role in this:

- Early warning. The signal should result in alerting the parties involved quickly (serious problems with clear opportunities for prevention).
- Social perspective: The signal demands quick action on the part of the government because it involves a frequently occurring work situation or exposure and the risk group is large, because it concerns a serious health problem or because the number of reported cases is rising quickly.
- Interesting signal from a scientific or educational perspective.

One part of signal strengthening concerns the follow-up of individual cases, for which the following five-step plan may be used:

Step 1. *Determine the health damage*. First of all, the disease must be made objective; individual research and the retrieval of data and consultation with GPs or specialists must provide insight into the specific nature and course of the disorder.

Step 2. *Determine the relationship with work*. Next, it should be examined what kind of relationship is possible between this disease and the work. The interpretation of epidemiological research findings plays an important role in this.

Step 3*. Determine the exposure*. An estimate of the exposure can be obtained by having someone who is well informed about the past and current working conditions of a particular occupation take a systematic and chronological career history from the worker. It is important to examine the relationship between the health complaints and exposure over time: Do the complaints disappear after ending the exposure? Do the complaints get worse during the course of the week at work? Did the complaints arise following a change in the work? Does the latent period correspond to what is known about the situation? Sometimes it is necessary to conduct an investigation at the workplace, or to reconstruct a past working situation in cooperation with a specialist in the field of working conditions, such as an occupational health specialist. In other cases it is possible and desirable to purposely provoke symptoms, such as when diagnosing occupational asthma and occupational skin conditions, and in a number of cases, occupational disorders of the locomotor apparatus.

Step 4. *Are other explanations possible?* This should be examined with respect to the medical diagnosis and with respect to the exposure. A differential diagnosis must therefore be drawn up along with an evaluation of causes other than work.

Step 5. Finally, a *conclusion* must be reached and an associated *report* issued*.* Due to the multiple causes that usually exist in the case of occupational diseases, the conclusion is stated in terms of: probable, possible and unlikely.

In addition to this approach based on individual notification, it is important to determine whether the connection has been reported more frequently: both domestically and internationally. On the one hand, this can take place by conducting a rough literature survey to discover whether such a report is present in the scientific literature. On the other hand, it is important to determine whether the same connection has been found elsewhere. An international network is essential for this. Here as well, agencies that focus on the adverse effects of drugs can serve as an example. They have been involved in intensive cooperation for many years, and have such resources as, for example, the common restricted electronic discussion forum Vigimed. This forum is used to ask and answer questions. An evaluation of the system demonstrated that there are an average of six relevant responses to every question [34]. The Uppsala Monitoring Centre (European center for research into the adverse effects of drugs) also utilizes expert

evaluations, in its Review Panel, in which 40 experts participate worldwide. This panel evaluates signals, determines which possible connections qualify for follow-up and publishes information about signals.

With respect to occupational diseases, the NCvB is currently also part of an international network in which information is exchanged with agencies abroad on the subject of occupational diseases. Examples include the Collaborating Centers in Occupational Health of the World Health Organization (WHO), scientific committees of the International Conference on Occupational Health (ICOH) and participation in the European Commission, the European Forum for Occupational Diseases and Accidents at Work. The NCvB also cooperates intensively with the University of Manchester: together they took the initiative to establish MODERNET: **M**onitoring trends in **O**ccupational **D**iseases and New and **E**merging **R**isks **Net**work. The Finnish Institute of Occupational Health (FIOH), the University of Milan, the National Institute in Prague and the University of Grenoble have also joined this network.

4.2 Methods for validating signals

At first, a signal is still a hypothesis about a possible connection. Further study must demonstrate whether the hypothesis can be proven or must be rejected. In some cases, a causal relationship can be established relatively easily, such as for allergic occupational diseases, with the use of a provocation test with the suspected substance on the skin or the respiratory system. However, often much more research is needed to substantiate the nature and strength of the suspected connection (cohort studies, patient-control studies, animal experiments, etc.).

In the assessment of a signal, all the available data must be included and the relationship among various pieces of data must be interpreted. There are a number of qualitative and quantitative arguments that often have an influence on this:

- The *strength of the signal:* for example, the number of notifications or, in epidemiological studies, the association between the risk and the disease. In most cases, this involves doubling of the risk of developing the disease at the work and/or exposure concerned.
- *Consistency* of the data*:* different studies point towards the same results.
- *Specificity*: the specific risk concerned is associated with a clearly defined disease.
- *Sequence:* there is a clear plausible sequence of events between the exposure and the development of the disease over time.
- *Biologic gradient*, also called the dose-effect relationship: the higher the exposure, the greater the risk of the disease occurring.
- *Biologic plausibility*: does the clinical picture match up with what is known about how the disease develops?
- *Analogy*: such as corresponding experiences with related material.
- *Nature and quality of the data*: for example, the objectivity of the observations, and the preciseness of the documentation.

Ultimately, pharmacovigilance involves one of the following five causality categories [8].

Certain

- The connection identified has a plausible connection with the exposure over time.
- The health complaints identified cannot be explained by other exposure.
- Improvement occurs if exposure is stopped.
- The health complaints are objective and specific.
- It is possible to provoke the health complaints.

Probable

- The connection identified has a reasonable connection with the exposure over time.
- It is improbable that the health complaints identified can be explained by other exposure.
- Some improvement occurs if exposure is stopped.
- The health complaints are objective and specific.

- It is not necessary to provoke the health complaints.

Possible
- The connection identified has a reasonable connection with the exposure over time.
- The health complaints identified could also be explained by other exposure.
- There is no information about the effect of stopping the exposure.

Unlikely
- The connection identified does not have a clear connection with the exposure over time.
- The health complaints identified can also be explained by other exposure.

Unclassified
No connection has been observed, but more data are needed to provide a good assessment.

4.3 From signal to action

Once it has been decided that a possible connection is actually a signal, action must be undertaken in this context. The steps needed form the phase *from signal to action*. This includes the following:

Communication with parties directly involved. The parties that are considered 'directly involved' in a certain signal strongly depend on the connection found. Obviously, this will include occupational physicians and occupational health professionals who can act as intermediary between employers and employees, as well as organizations which are actively involved in branches or companies, the government, GPs and medical specialists, etc. Each of these groups has its own communication channels: occupational physicians can be contacted directly by e-mail and specialist literature; there are regular forms of consultation with the government; employers and employees can be reached through their sector organizations; and the medical sector is easily reached through their professional associations or a general platform like the Royal Dutch Medical Association (KNMG).

Communication with external parties, such as through general media, the professional media and/or scientific literature. The signal itself and, for example, the urgency of broad knowledge of the signal, determine to a large extent whether the decision must be made to publish the relevant information in the general media (such as by issuing a press release or news reports on the website). If a signal is only relevant to a particular sector or occupational group, then the relevant information can be published in the appropriate professional journals. Ultimately, the goal will always be to publish this information in the scientific literature in order to contribute to the dissemination of knowledge about signals, also internationally.

Initiation of further research. Further research will almost always be needed. It is a good idea to report this in all communications about the new signal. It seems useful to describe the desired follow-up research as specifically as possible.

Where necessary, **amending guidelines, protocols, legislation and regulations.** Depending on the consequences and the 'hardness' of the new signal, it can be indicated which guidelines, protocols, legislation and regulations may be affected by the new insights.

4.4. Signal management summarized

In summary, this leads to the following approach to signal management, which will ultimately result in the dissemination of information and possible actions:
- Selecting the relevant data (case reports) and formulating the signal (hypothesis)
- Literature screening
- Assessing the available data, identification of missing data and unanswered questions
- Collecting the missing information (follow-up of cases, focused research)
- Internal discussion of the data found
- International discussion of the data found

- Final weightening up of all data
- Writing a report that includes the following:
    - Summary of the signal
    - Presentation of original data
    - Presentation of additional information
    - Discussion with attention for all positive and negative arguments
    - Hypothesis (preliminary conclusion)
    - Suggestions for further research.

Based on this report, decisions can be made for the relevant parties. The report also serves as the basis for the further dissemination of information (to the parties involved and in the scientific literature).

5. Conclusions

The importance of signals

Identifying signals of new occupational health risks is important. New occupational health risks arise because of continuous changes in work and working conditions. Research has shown that the social partners and the government have a large need for early, specific knowledge about these new risks. In cases where there is insufficient knowledge of these risks, opportunities for intervention and prevention are missed.

It is clear that activities that anticipate risk control, such as the assessment of the risks of new technologies, working methods and substances before their introduction into the working environment, are important. It is appropriate that significant attention is directed towards risk analyses at a European level, such as in the REACH program and the Expert Forecasts. However, complementary to this, it is also a good idea to actively search for the occurrence of new and adverse side effects of work on health.

In the same way that pharmacovigilance has developed in conjunction with the launching of new drugs on the market and post-marketing surveillance, monitoring the side effects of work – referred to as health and safety vigilance – should be given a more prominent place in the field of work and health.

A wide range of detection methods

It is not possible to utilize only one method to detect all new occupational health risks. For this reason, use must be made of methods that complement each other (triangulation), taking into account that each method has its own advantages and limitations.

The suitability of a method depends on such things as the nature of the disease: if the situation involves a rare disease with a high etiological fraction, stimulating and registering ‘spontaneous reports’ by physicians or employees would be a good instrument. In the case of more frequently occurring illnesses with a low etiological fraction, occupational epidemiological studies and monitoring and trend analysis are more suitable tools. Because it is not clear under which category a new signal will fall, the range of signal methods must be quite extensive.

International cooperation

After possible new occupational health risks have been found, a preliminary assessment must precede a more final evaluation. To this end, additional information must be collected at both an individual and aggregate level. The first question addressed here is whether a signal has already been identified in registries or described in the literature. Next, the established hypothesis about an association must be further studied using epidemiological or experimental research.

International cooperation is virtually always desirable and necessary in this context, in order to make the best possible use of the available information and resources (including research). For this reason, opportunities for rapid and low-threshold international discussion are highly important.

6. Recommendations

Strengthening of the NCvB's duties in organizing the vigilance for new occupational health risks (Center for Health and Safety Vigilance)

Various activities can be performed in this context:

- Creating a system in which new risks can be reported by occupational physicians and possibly other parties (GPs, medical specialists, workers).

  Because occupational physicians have knowledge on both illness and work, they are well equipped to identify signals of new occupational diseases. However, they must also be challenged to do so. This can be achieved by drawing attention to the importance of reporting exceptional and unexpected cases, by making the notification process as simple as possible, by ensuring good post-notification feedback, by guaranteeing confidentiality and by offering training.

  The NCvB infrastructure can be used to offer GPs and medical specialists the ability to report exceptional cases of potential new occupational diseases. Rapid feedback and providing support options for the analysis of a case or cluster of cases are also important in this regard. Experiments can be conducted in which GPs signal new occupational diseases.

  To signalize new occupational diseases by the workers themselves is also an interesting option. Sectors with specific risks come to mind. When creating a pilot study in this area, it is desirable to involve employer and employee organizations in the sector in the setup and implementation of the process.

- Conducting periodic literature screening and generating associated reports.

- Experimenting with data mining techniques in the Dutch National Occupational Disease Registry.

- Studying cases and clusters, for example by forming ad-hoc multidisciplinary teams to investigate suspected cases and clusters.

- Analyzing existing databases (of the NCvB in cooperation with other organizations, such as the Netherlands Institute for Health Services Research (NIVEL), the Employee Insurance Administration Agency (UWV), the Institute for Asbestos Victims (IAS) in other databases).

- Disseminating knowledge and information about new risks.
  The NCvB has a reasonably large amount of experience with disseminating knowledge and information to target groups, both to health and safety professionals and to the curative sector or industry. The means to do this include websites, newsletters, articles in scientific and general media, generating signals and news items, presentations at conferences and other meetings and refresher and post-graduate training. In view of the importance of signaling new risks for the Health and Safety Inspectorate, the joint establishment of a signal system is also in interesting option.

National and international network for knowledge exchange

- National: use existing expert groups (infectious occupational diseases, allergic occupational diseases, reproductive disorders) better to discuss and, where necessary, strengthen and validate unusual findings.

- International: promote cooperation between the institutes in different countries charged with the detection and evaluation of new health risks.

  This can be achieved by, for example:

  - Developing a platform for questions and discussions on the subject of new occupational health risks. On this platform, questions can be discussed quickly and confidentially to strengthen and possibly validate signals of connections.

  - Gathering sufficient cases in the phase of signal strengthening and validation. This is important particularly in the research into rare disorders or risks in less common occupations or work situations.

  - Starting and evaluating experiments that can lead to the harmonization of detection methods between participating countries.

  - Dividing up activities in the screening of the scientific literature about subjects like chemical and biological risks, radiation, psychosocial risks, physically demanding work, risks for offspring, genetic sensitivity, etc.

Glossary

ESB: *Economisch Statistische Berichten*, ('Economic Statistic Reports'), a leading journal in the field of economics and policy

Etiologic fraction: the proportion of the occurrence of or death from a certain disease in the population, which can be attributed to exposure to a specific risk factor

EUROCAT: European Surveillance of Congenital Anomalies. The member registry for the Netherlands is UMCG Groningen medical center. The aim of EUROCAT is to prevent congenital abnormalities by means of registration, scientific research and monitoring

FIOH: Finnish Institute of Occupational Health

IAS (*Instituut Asbest Slachtoffers)*: Institute for Asbestos Victims

LAREB (*Stichting Landelijke Registratie and Evaluatie Bijwerkingen Geneesmiddelen*): Netherlands Pharmacovigilance Centre

LINH: *Landelijk Informatie Netwerk Huisartsenzorg* (Netherlands Information Network for General Practice)

NCvB (*Nederlands Centrum voor Beroepsziekten*): Netherlands Center for Occupational Diseases

NIVEL (*Nederlands instituut voor onderzoek van de gezondheidszorg*): Netherlands Institute for Health Services Research

MODERNET (Monitoring trends in Occupational Diseases and New and Emerging Risks Network): European consortium of institutes in the field of occupational disease signals

PIN: Progressive Inflammatory Neuropathy, a neurological disorder among swine slaughterhouse workers, defined in 2008 as a new occupational disease.

Popcorn disease or popcorn lung: occupational lung disease (*bronchiolitis obliterans*) developed through exposure to a volatile flavoring: diacetyl (butter flavoring).

REACH: **R**egistration, **E**valuation, **A**uthorization and Restriction of **Ch**emical substances. EU regulation that came into effect on 1 July 2007.

RGO (*Raad voor Gezondheidsonderzoek*): Advisory Council on Health Research

RNV3P (*Le Réseau National de Vigilance et Prévention des Pathologies Professionelles)*: the French network of university clinics for occupational diseases

RVZ (*Raad voor de Volksgezondheid en Zorg):* Council for Public Health and Health Care

SENSOR: Sentinel Event Notification System for Occupational Risk (USA)

STIGAS: *Stichting Gezondheidszorg Agrarische Sectoren* ('Foundation for Health Care in the Agricultural Sectors')

THOR: The Health and Occupation Reporting Network (UK)

VZB (*voorzorgbeginsel):* Precautionary principle

WRR (*Wetenschappelijke Raad voor het Regeringsbeleid*): Scientific Council for Government Policy

Zoonosis: any infectious disease that can be transmitted from animals to humans.

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