ALERT AND SENTINEL APPROACHES TO DETECT WORK-RELATED DISEASES

RNV3P: National Network for Monitoring and Prevention of Occupational Diseases in France (*Réseau national de vigilance et de prévention des pathologies professionnelles*)

This discussion paper is part of a series aiming at describing alert and sentinel approaches for the early detection of work-related diseases (WRDs) in order to provide more insight into the way these systems function and into the drivers of and obstacles to the implementation of such systems. This article describes the National Network for Monitoring and Prevention of Occupational Diseases or *Réseau national de vigilance et de prévention des pathologies professionnelles* (RNV3P) in France and is based on EU-OSHA's project 'Alert and sentinel approaches for the identification of work-related diseases in the EU' (EU-OSHA, 2018) consisting of a literature review and an in-depth qualitative study and commissioned to a research team made of experts from the Catholic University of Leuven, the Coronel Institute, the Finnish Institute of Occupational Health, the University of Manchester and the University of Bologna.

Introduction to the approach

The National Network for Monitoring and Prevention of Occupational Diseases or *Réseau national de vigilance et de prévention des pathologies professionnelles* (RNV3P) is a network for monitoring and preventing occupational diseases (ODs) in occupational health (OH) in France.

Summary of main characteristics

- The National Network for Monitoring and Prevention of Occupational Diseases (RNV3P) is a network for monitoring and preventing ODs in OH.
- The network groups together the 30 occupational disease consultation centres (CPPs) in mainland France and, from 2018, a new centre in Réunion Island.
- This network aims to collect data (patient's demographic data, diseases, exposures, business sector, and profession) from each clinical consultation and to load it into a permanent national database on WRDs.
- The clinical expert at the network's university hospital who is responsible for the diagnosis can also investigate the occupational origins of diseases (this 'expert' assessment of causality is also registered in the database).
- The RNV3P is not only a platform for dialogue between clinicians and other OH professionals, but also a system that coordinates and generates knowledge for the purposes of monitoring, improving knowledge and preventing occupational risks.

Initiating organisation

The RNV3P network was an initiative of and is coordinated by ANSES (*Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*). ANSES, created in July 2010, is an administrative public establishment that is accountable to the French ministries of health, agriculture, the environment, labour and consumer affairs. ANSES undertakes monitoring, expert assessment, research and reference activities across a broad range of topics that encompass human health, animal health and wellbeing, and plant health. It offers a cross-cutting perspective of health issues by assessing health risks and benefits, often through the prism of the human and social sciences. Its monitoring, vigilance and surveillance work provide inputs for risk assessments.

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ANSES fully addresses all types of risks (chemical, biological, physical, etc.) to which a person may be subjected, intentionally or otherwise, at all ages and stages of life, including through exposure at work or in his or her private life. One of ANSES's specific missions is alerting and vigilance using the RNV3P network and database. Since the establishment of RNV3P, this mission also covers toxicovigilance (i.e. vigilance about toxic products), phytopharmacovigilance (i.e. the adverse effects of plant protection products), nutrivigilance (i.e. the side effects of dietary supplements), and vigilance in the context of ODs and health.

A working group, called 'emergence', is in charge of reporting any OH issues, emerging diseases or new WRDs to the network. The task of the working group is to evaluate the possible link between the disease and work, referred to as the degree of imputation (*imputabilité* in French; i.e. the level of certainty that the problem is related to the exposure). Specific methods are used to detect unusual or brand new diseases that are reported by physicians after OD consultations in the participating centres. These methods include a search through the RNV3P database that allows the working group to see if other participants have reported similar observations. The working group also applies data mining techniques in the database to detect signals. Depending on criteria, such as the degree of imputation, novelty, and implications for prevention, these signals are then further explored and reported. Reporting can range from communicating with regional prevention bodies to an alert to the ministries at the national level if regulatory action in France and Europe is required.

ANSES also employs two statisticians, a project manager and a data manager, who all work for the network. The RNV3P database includes more than 100,000 observations, all of which need verifications, controls and updates. To standardise all the encodings in the database, ANSES and senior physicians from the OD centres organise regular training sessions for the reporting parties in all the encoding centres.

History of the approach

The RNV3P network was set up in 2001 as an initiative of the former French agency for environmental and occupational health and safety (Afsset), later merged into the ANSES. At that time, the primary aim of the network was to pool data retrieved from physicians reporting on the results of their OD consultations in the participating centres. Another aim was to provide information on WRDs to the Caisse Nationale des Travailleurs Salariés (CNAMTS). The CNAMTS is the French health insurance system for occupational accidents and ODs.

At the outset, the network's driving force was the OD consultation in the teaching hospital *centre hospitalier universitaire* (CHU) of Grenoble. A first local database was implemented, in which OH issues were systematically registered and encoded by the OH physicians working in and around Grenoble. These issues were then subsequently transferred to the CHU consultation centre. Later, this system was extended to all the OD consultations of the CHUs in France (n = 32). Data were transferred from the other consultation centres to the CHU of Grenoble, which was responsible for data aggregation. Between 2007 and 2012, ANSES began to transform the local systems into a more global information system that contained a national database. This national database was then hosted by ANSES and integrated into its own information system. Today the system allows real-time data entry by the different consultation centres, which means that updates are immediately available in the national database.

Programme's aim and objectives

The primary aim of the network is to collect the data entered during OD consultations and to provide information on WRDs to the CNAMTS. The RNV3P database is a sentinel or alert system and is also used for emergence, which focuses on the detection of new OH issues or ODs. The RNV3P network encourages dialogue between different OH stakeholders and aims to obtain information on monitoring, detection and prevention.

Description of the programme's workflow and reporting

Reporting parties

The reporting physicians of the RNV3P are physicians who are employed in the 31 OD consultation centres of France's teaching hospitals (CHUs). Their main activity in relation to the RNV3P is assessing the work-relatedness of patients' diseases. Other consultation requests concern keeping workers in employment, assessing work capacity and fitness, or providing career guidance to employees (e.g. young people with asthma).

RNV3P reporting parties receive annual training to educate and motivate them. The focus of this training is to learn how to encode and enter qualitative data into the database. The interviewees mentioned that they also plan to develop online automated training or tutorials in the future. Until the time of writing, a computer engineer from the team of the University Hospital of Grenoble has been responsible for the education of newcomers. In the OD consultation centres, a 'buddy system' is applied. The senior physician coaches the junior residents and continuously validates or corrects their work and database entries. Background characteristics are coded and reported by administrative staff, whereas medical and other work-related data (e.g. disease, exposures, position and industry) are registered by the medical staff. Only data that are validated by a senior staff member are considered for inclusion in the database.

Work-relatedness evaluation

It is up to the network's university hospital experts to investigate the diseases and attribute them, if necessary, to a work-related origin (this 'expert' opinion on causality is also registered in the database).

The OH expert physician encodes the link between exposures, substances and medical conditions in the database, referred to as the degree of imputation. An association between disease and exposure, e.g. asthma and isocyanate, is scored on a scale from 'very likely' to 'impossible'. The degree of imputation is based on the types of exposures, their intensity, the chronology of symptoms, etc. A senior clinician always validates this imputability score.

Reporting mechanism

Most patients are referred to the OD centres by OH physicians who are employed in the local companies (i.e. 60 % to 70 % of the referrals) and who request a disease diagnosis. About 15 % to 20 % of the referrals come from GPs and medical specialists such as pulmonologists or rheumatologists. GPs mainly address occupational stress issues. Referrals regarding musculoskeletal disorders are becoming increasingly prevalent. In addition to GPs and medical specialists, medical advisors of the social security system also make use of the OD consultation centres' services to evaluate the work-relatedness of a disease.

First, patients are received by a secretary who collects a certain amount of administrative data and background details, such as date of birth, gender, address, treating physician, address of treating physician, current employer etc. The reason for the consultation is also specified during the first interview Possible reasons are an expert evaluation for the social security system, a WRD diagnosis, or issues related to work capacity. Other possible topics of discussion or investigation may relate to forensic medicine, recognition of ODs, actions to keep workers in employment etc. Subsequently, a physician investigates the medical condition of the patient, exposures and the possible link between these.

Information on each patient is available in his or her medical file, which is linked to the data that are entered into the RNV3P database. A trained physician enters the following data in the database: disease variables (ICD-10 codes ([1])), the patient's occupation (using the International Standard Classification of Occupations (ISCO code)), the type of industry (using the *Nomenclature d'activités*

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[1] http://www.who.int/classifications/icd/factsheet/en/

française (NAF code)), and occupational exposures using a specific thesaurus that was developed in France.

This thesaurus contains hierarchical codes that cover all types of exposure (chemicals, physical, biological, psychosocial) and explanations on how to use the codes. After quality control, a senior physician validates the data. Following the consultation, a report is sent to both the treating physician or OH physician and the patient.

Communication

Communication between reporting parties, experts and researchers is continuous. Experts and researchers from the emergence working group, for instance, evaluate the degree of imputation that is attributed to a case by the reporting parties. They perform searches in and outside the database, execute data analyses and evaluate if other colleagues have reported similar cases. If they detect a signal and an alert is needed, they communicate this to the reporting parties and all the appropriate authorities.

Data-storage

The RNV3P database has evolved over the years. The first database was located and managed by the CHU of Grenoble and it was later extended to all other French CHU occupational consultation centres. The CHU of Grenoble was responsible for collecting and merging all the registered data. Later (2007-2012), the system was transferred to the other CHU OH consultations across France. It then became a more global online information system containing the national database, accessible from anywhere.

Today the system allows real-time data entries by the different consultation centres and actors. After validation by senior clinicians, updates are immediately available in the national database. The database is well secured and protected. As with bank accounts, users need a token and a code to log in to the system.

Dissemination

The network produces activity reports and scientific reports on a regular basis, every two or three years:

- 2016 activity report: https://www.anses.fr/fr/system/files/RNV3P-RA-2016.pdf;
- 2014 scientific report: Réseau national de vigilance et de prevention des pathologies professionnelles Méthodes de détection et d'expertise des suspicions de nouvelles pathologies professionnelles (« pathologies émergentes »), Avril 2014. Available at: https://www.anses.fr/fr/system/files/RNV3P-Ra-Avril2014.pdf.

The interviewees mentioned that they published articles in top-tier scientific journals such as Occupational and Environmental Medicine, or public health journals. They also presented abstracts at important international conferences.

Financial aspects

The OD consultation centres do not carry out classic care consultations at the hospital. They are financed by two funds. The first funding source is called missions of general interest (MIG), managed by the *Direction générale de l'offre de soins* (DGOS) within the French Health Ministry. The DGOS distributes the funds across the different university hospitals. The RNV3P is a part of these missions of general interest. A second financial source is funding from the CNAM – through its regional levels, CARSATs). These OD consultations take more time than a classic consultation. The OH physician must question and investigate the employee thoroughly through several diagnostic tests and determine a link with the work situation for which a follow-up company investigation might be required. Subsequently, the physician must register and code the data in the RNV3P database. The convention allows the financing of staff such as a secretary and medical practitioners. Hence, the survival of this system is largely dependent on both sources of funding. The CNAM spends slightly over €1 million every year to finance the activities of the OD consultation centres, which is added to MIG funding by the DGOS from the French Health Ministry (about €8 million). The overall allocation of the MIG varies and depends on

the size of the consultation centre. The allocation can range from €50,000 to €400,000. An example of a large and important consultation centre is Créteil, which sees about 4,000 people each year.

ANSES, as the operator of RNV3P, covers all expenses related to the information system development and maintenance; gives a financial contribution to the centres for each new case recorded in the database; covers all expenses related to the working groups, coding school and scientific committees (experts' mission expenses); covers the wages of the RNV3P coordination team based in ANSES (such as the IT expert, RNV3P project manager, and statistician); and has specific research conventions (Conventions Recherche Développement).

Usage of data

The RNV3P database is intended for vigilance and collects cases. The database does not aim at being a representative sample for France; the RNV3P database is more a vigilance database (like pharmacovigilance spontaneous notification systems) than a database dedicated to epidemiological studies (Bonneterre et al., 2008; Bonneterre et al., 2010).

Each physician at an OD centre is able to access the database at any time to look, for instance, for cases in other centres that are similar to those he or she is currently investigating. RNV3P partners can also make requests and get summarised information regarding their field of interest.

Examples of data usage for informing policy and prevention

At the company level, following the OD consultation, feedback is given to the company's OH physician regarding the identification of a specific occupational exposure that requires preventive action. A recommendation to a company might be a risk evaluation or protecting the employee against an exposure.

When the RNV3P network brings to light a certain number of pathologies due to certain exposures, prevention in the regions and companies concerned becomes urgent. This also requires an alert to the CNAMTS, the National Research and Safety Institute for the Prevention of Occupational Accidents and Diseases (INRS) and the DGT (*Direction générale du travail*) Labour Ministry, to organise prevention and control at the national level. The agency can also use the data to suggest regulations about chemicals.

On a more macro level, the RNV3P network describes risk situations, for instance as part of the national cancer plan. The network was later asked to describe risk situations concerning certain cancers in the context of work. A report and communications targeting occupational physicians were based on this work.

Another example was the detection of numerous allergies, such as allergic dermatoses and allergies to methylisothiazolinone (methylisothiazolinone has replaced parabens in a certain number of cosmetic formulations) among hairdressers, beauticians etc. Hence, ANSES has suggested a measure under the European Union regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) to limit the use of methylisothiazolinone at the European level. France can thus be proactive and forbid this substance in cosmetics when it exceeds a certain concentration level.

Examples of data usage for detecting new/emerging WRDs

The RNV3P network is also used as a sentinel system for identifying new/emerging risks. Today, the alert system comprises a specific process of three stages. The three steps are risk detection, evaluation and action. Detection can be clinical: clinicians can identify and report a case that seems to be emerging, and this case is then discussed at national level. Detection can also be performed using information from statistics such as data mining and disproportionality signals or from a bibliographical search (Bonneterre, 2012). Detection can even be proactive, by searching for cases in response to alerts on new diseases from other sources or organisations, e.g. literature, the US National Institute for

Occupational Safety and Health (NIOSH) or Modernet ([2]). Subsequently, the signal is further explored and evaluated by the expert working group based on an algorithm containing three dimensions, which subsequently leads to an emergence score. Experts calculate a score for imputation (range: 'very likely' to 'impossible'), seriousness of the case (range: 'not severe' to 'fatal') and the frequency of occurrence of similar cases in and outside the RNV3P database. This provides a final emergence score. The algorithm and scoring system have already been validated based on the literature and in previous RNV3P cases. Depending on the score produced by the algorithm, the emergence score, the experts from the emergence group decide whether it is necessary to trigger an alert at the national level, whether this case should be internally consolidated or it should be discussed with foreign co-peers. A level 1 alert involves notifying only RNV3P physicians and recommending that the risk to and protection of the worker be evaluated. A level 2 alert requires that other clinicians and other RNV3P partners be informed and a search for similar cases outside the RNV3P network be made. Level 3 means that large-scale dissemination through health surveillance agencies and actions is required. This means that, for prevention, the reporting and the alert can be made at the regional level; to institutions, sanitary security agencies or bodies that are partners at the national level, such as the National Research and Safety Institute for the Prevention of Occupational Accidents and Diseases (INRS) or Santé Publique France; or straight to the ministries of labour and of health Another possibility is that ANSES takes the alert as a prompt to suggest regulatory changes.

On a case-by-case basis, the emergence working group highlights cases from the network, which are then subsequently redirected to the governing bodies. An example of a new case was a nail prosthetist who suffered from hypersensitivity pneumonia. The exposure in question was to ethylmethacrylate (EMA). Two cases of hypersensitivity pneumonia had already been described, but were linked to another exposure, to methyl methacrylate. A notification was sent to the physicians in and outside the RNV3P network. Wider dissemination would require a second similar case.

Another example concerns asthma patients who work in the coffee machine maintenance industry. Two of these cases were detected in the database. Subsequently, the association between asthma and exposure to a certain mould (*Chrysonilia sitophila*) has been documented. The exposure was already known in other industries and jobs such as woodwork. Similar cases were also published at the same time in Spain and Italy. Hence, wide dissemination was required, which led to an alert within the sector in question. The industry has since exchanged information with ANSES to determine how to better protect its employees.

A third example relates to the occurrence of non-Hodgkin lymphoma (NHL) in welders using anti-splash sprays containing methylene chloride, also known as dichloromethane (DCM). Four independent cases were detected, but they concerned different subtypes of NHL. DCM had already been classified as a carcinogen by the International Agency for Research on Cancer, especially because of the risk of NHL. A level 2 measure was required, meaning that information was exchanged with other clinicians. Wider dissemination may be mandatory if the degree of imputation increases.

Examples of other usage of data

Some researchers have analysed the geographical dimension of the RNV3P network. Using the geographical information system (GIS) they wanted to understand the spatial aspect of the RNV3P observations and of the related variables (patients' addresses, workplace addresses and the referring practice's address) (Delauney et al., 2015). The analyses have shown that, although the network covers the whole country, the density of observations decreased as distance from the 30 OD clinics (located in the main French cities) increased. Taking into account the underlying workforce, the study demonstrates large discrepancies in the probability of different OD clinics capturing an OD (assessed by rates of ODs per 10,000 workers). This capture rate might also show differences according to the disease (Delauney et al., 2016).

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[2] Monitoring Occupational Diseases and tracing New and Emerging Risks in a NETwork (Modernet):
http://modernet.org/

Based on the personal interests or research topics of researchers and experts, matrices are built to analyse possible associations between specific exposures, diseases, jobs, industries etc. Some researchers, for instance, are interested in workers who suffer from systemic scleroderma and look specifically at those who have been exposed to silica and solvents. Others might be interested in specific jobs and industries and construct a job versus exposure matrix to determine how many workers have been exposed.

Stakeholders' views

This article is partly based on qualitative, in-depth face-to-face or telephone interviews with three stakeholders of the system. The interviews reflect the views of different actors in the system (e.g. owner of the system, workplace actor reporting it, and researcher or other stakeholder using the resulting data from the system) on the drivers and obstacles (Table 1), the quality of data and the transferability to other countries of the system or approach.

Drivers and obstacles

Table 1: Drivers and obstacles

Drivers	Obstacles
The high quality of the data that are entered is guaranteed by appropriate training, which is given to all the different actors in the network and those who are involved in the standardisation, control and validation processes. Collaboration involves all stakeholders, such as the physicians from the OD consultation centres, the OH physicians who refer patients, the prevention actors who operate in the companies, and all the bodies that act on regulation or prevention at the national level following alerts. All these actors work together and are linked to each other, which of course necessitates constant, daily monitoring by the agency. Therefore, regular meetings are organised, which provide the opportunity to interact in real life and to move the system forward. This network makes people such as risk prevention experts, physicians and other OH care workers work together. *Stakeholder 1 (owner): 'So, distance means efforts and perseverance, and also maintaining the human link with people who are geographically far away, and the network needs leadership to stay vibrant and make everybody understand the sense the network gives to themselves and others, the mutual benefit, also in the true sense of the word.'*	*Maintaining necessary resources and means* OD consultations require a large investment of time as they often include a great deal of investigations and diagnostic tests. Entering the data into the database, validation by a senior clinician, administration and support are also time-consuming and generate large costs. *Stakeholder 1 (owner): 'Of course, for every consultation, to begin with, OD consultations are long, and on top of that we need people behind to enter the data into the database. And so that takes time, and then senior validation, that takes time and means, for both administrative and support functions, and means in medical time.'* OD consultations produce too little income for the hospital compared with other medical consultations and treatments, which charge per medical procedure. These financial concerns are important and often an issue of discussion with the Health Ministry, the DGOS and the CNAMTS to try to secure the daily operation of the consultation centres and of the network, and to guarantee their quality.
he upgrade to an online information system has helped the users a great deal, as the RNV3P database is being used continuously and is constantly changing. The system is also very responsive. New codes that relate to new exposures or substances can be added. *Stakeholder 2 (reporting party): 'That means that I am in charge of the emergence working group; if we identify new issues, we are going to say*	The researcher and clinician mentioned that it is important to **find a balance between asking reporting parties a lot of information and motivating physicians to continue to report cases**. *Stakeholder 2 (reporting party): 'That is so, but this is because we have to find the balance between wanting people to enter a lot of information, and it is more interesting afterwards*

Drivers	Obstacles
"well, caution, now, we have 3D printing, additive manufacturing, we have to be able to identify all the diseases that will occur, linked to these new types of exposures, these new types of use". But the issue is that with 3D printing you can use the methacrylates, you can use alloys of vanadium, titanium or whatever you want. So we won't find them by job, industry or exposure. So we need to be able to explain that the risk, for example exposure to titanium, will take place in additive manufacturing, so we have the code added.'	*when we analyse and the fact that in real life you can't spend 25 minutes encoding every single consultation.'*
International collaboration. The Modernet network provides the opportunity to be challenged by experts from other disciplines and countries, in turn providing a forum in which to exchange ideas and pathologies.	

Data quality

The data that physicians encode and register are entered using a standard form, to enable comparisons between entries and standardisation. After the data are entered, a number of automatic quality controls begin. Major or minor points, or missing data, mean that the reporting party immediately receives an alert. If the alert concerns major points (e.g. the type of industry is not entered), the data cannot be validated. To maintain a high quality of data registration, a senior clinician from the OD consultation centre always validates the data. Non-validated data are registered, yet will not be integrated into the national database and will be considered unresolved. The interviewees claimed that the quality of the data improved over time.

Stakeholder 3 (researcher): 'It means we can have the best statistics methods in the world, and the best epidemiologists to answer a question, or subject matter experts – if the data are ever biased, or low-grade data, I want to say, no pattern can fix low-grade data so what comes in, well, what comes out is as important as what comes in'.

The database also contains a standardised live thesaurus of occupational exposures. The thesaurus includes high-quality coding of products and substances. It was felt that the thesaurus should be shared at the national level and that there is a need for harmonisation at the European level. Yet building and maintaining a high-quality and standardised thesaurus takes a great deal of time and money. As new products that might have an impact on work life continuously emerge onto the market, vigilance is needed. Updating the thesaurus and coding within the RNV3P database is a part of the network's strategic plan.

Stakeholder 2 (reporting party): 'A heightened level of vigilance and a culture of quality has still spread, I would say, without a doubt, mainly since 2005.'

Transferability to other countries

Some countries already have similar systems to that of the RNV3P network and the RNV3P is completely willing to exchange information with other countries, for example with the THOR system in the United Kingdom. Creating networks between countries will enable the organisation of OH data as a basis for prevention. The RNV3P network has a scientific advisory committee, which consists of three to four people from other countries and different disciplines, such as epidemiologists, statisticians and OH professionals. To consolidate the RNV3P strategy in the years to come, it is important that people who have a good knowledge of both this type of network and of OH look outwards. Focusing outwards is essential in terms of strategic priorities: activities should not only be internal but also with external parties and scientists.

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Links for further reading

Information on RNV3P is available at: https://www.anses.fr/en/content/rnv3p-national-network-monitoring-and-prevention-occupational-diseases

Presentation on RNV3P at the meeting on MySignal.be at Fedris on 31 March 2017 in Brussels (BE) available at: https://www.fedris.be/sites/default/files/assets/NL/Presentaties/nisse_vanrullen_31mars2017_defv4.pdf

Presentation on RNV3P at the EU-OSHA project workshop in Brussels on 18 May 2017(BE) available at: https://osha.europa.eu/sites/default/files/seminars/documents/RNV3P%20system%20France%20Presentation%20Bonneterre%20%2526%20Vanrullen.pdf

Presentation on RNV3P at the EU-OSHA project workshop in Leuven on 31 January 2018 (BE) available at: https://osha.europa.eu/sites/default/files/seminars/documents/6.%20RNV3P_France_Van%20Rullen.pdf

The literature review report, the final report and summary report of the EU-OSHA's project 'Alert and sentinel approaches for the identification of work-related diseases in the EU', as well as two summaries of two seminars (18 May 2017 in Brussels (BE); and 31 January 2018 in Leuven (BE)) and the presentations given at the seminars are available from : https://osha.europa.eu/en/themes/work-related-diseases/alert-and-sentinel-systems-osh