New techniques for tracing newly occurring work-related diseases – sentinel and alert systems

Vincent Bonneterre\textsuperscript{1,2,3} on behalf of RNV3P and Modernet network

1. Grenoble University /CNRS (EPSP-TIMC) & Grenoble Teaching Hospital, France
2. RNV3P : French Network for WRD vigilance an Prevention
3. Modernet Network

Workshop EU OSHA on occupational burden of disease. Brussels, 10th of October 2014
Tracing new risks / tracing newly occurring work-related diseases (WRD)

A societal challenge in order to take appropriate actions in due time

1. Why is it important to rely also on sentinel approaches?
   – The need of a « diseases-first approach » complementary to the « risks-first approach » as conducted by the Emerging Risk Observatory (a priori risks identified by expert focus)

2. Example of National initiative: French RNV3P

3. Modernet initiative at EU level

4. What can we do for Europe?
Why is it important to rely also on sentinel approaches?

Lessons from the past: examples of primary identification of new WRD through clinical observations in the last 30 years.
Examples of Clinical identification of new "disease x exposure" associations (1/3)

SPAIN & ALGERIA 1992 : « textile sprayer’s lung » (Ardystil syndrom):
- 15 cases of interstitial lung diseases of which 2 died. Relation with spraying Acramin-FWN (polyamidamine)

KOREA 1998 : Primary Ovarian Failure and 2 bromo-propane
- Cluster 16 cases, mean age : 24 years old, exposed 4 to 16 months

USA 1997-8 : Nylon flock Workers Lung Disease
- Cases found in 5 different sites in US and Canada
USA 2002-2013: Bronchiolitis obliterans in popcorn-factory workers, … and in other food industry with food flavourings (last one: coffee industry)
- Several workers had to undergo lung transplantation. Some died. Cases found afterwards in other countries

JAPAN 2003 : Interstitial pulmonary disorders in indium-processing workers (Indium Tin Oxide ITO)
- New technology for LCD and plasma screens at the end of the 1990’s. Starting with the case of a young man, 27, who died. Other case description followed as well as epidemiological and toxicological studies.

USA 2007: Progressive inflammatory neuropathy among swine slaughterhouses.
- 12 cases initially described in several months -> finally 24 cases related to one specific activity, and related to auto-immunity reaction
  - CDC MMWR 2008;57:122-124

Germany 2010 : asthma x sel de Rhodium
- One only case with full demonstration
JAPAN 2013. Cholangiocarcinoma and offset printing with high 1,2 DCP exposure
- 11 young male workers (µ=36 years old, µ = 37 for the 6 who died) from a same Offset printing company in Osaka (62 male salaried workers and 11 female), all involved in the proof printing room with high dichloromethane and 1,2-dichloropropane exposure
- 1,2 DCP now classified by IARC as Group 1 carcinogen for these reasons

Examples of known « disease x exposure » couples identified in a new « activity sector » through clinical observation

SPAIN, ITALY, FRANCE 2009: Occupational asthma IgE mediated due to Chrysonilia sitophila in coffee industry.
- S : Monzón S et al. Allergy. 2009;64(11):1686-7

USA 2009: Angiosarcoma of the liver in hairdressers and barbers due to former use of vinyl chloride propellant in hair spray
Sentinel approach’s efficiency is related to many factors:

- **Discovery of Clusters**
  - Strong element to question the work-relatedness

- **Temporality of disease related to work**
  - Easier when it’s handling with acute toxicity (irritant dermatitis, burns, etc) or immuno-allergic diseases

- **Importance of Attributable Risk Fraction to the suspected occupational exposure** and frequency of the exposure to other risk factors of the disease

- ++ Most of all : the Capture of the cases by people able to evoke the plausibility of work-relatedness -> importance to raise awareness of GP and specialists, and incite them to make secondary referrals to OD /WRD specialists
National initiatives for tracing new WRD

Example of the French approach
RNV3P : French National Network for WRD Vigilance and Prevention Network

- 32 OD/WRD consultation centres (CCPP) located in (nearly) all teaching Hospitals in mainland France
- + 10 Occupational Health Services (SST)
  - Coordination: ANSES, the French Agency for Health Safety in Food, Work and Environment
  - Scientific Partners: CNAM-TS, SFMT, CCMSA, InVS.
  - Fully started in 2001 (after pilote phase)
Cases are recorded in a Web-based Information system, with coded variables

Some variables recorded:

- Disease (IC10)
- Occupation (ISCO code)
- Activity Sector (NAF code)
- Exposure (French Thesaurus)
- Imputability
- Company
- Demographic
- Which type of physician refers the patient
- Free text zone (summary)
- .../...

Database with about 200,000 work related health problems (OD & WRD for more than half of the database + work-fitness issues, medical surveillance after exposure to carcinogenic compounds, etc)

See RNV3P 2012 activity Report
Tracing new WRD is one of RNV3P’s aims

2009: a WG was created for that purpose. It developed progressively a 3 steps approach for Detection, Expertise & handling of new WRD

2014 : approach summarized and illustrated in our last scientific report

- **RNV3P scientific report on detection of new WRD, April 2014**

- **Summary for occupational physicians: Bonneterre et al. Repères en Santé au Travail, 2014 : RVN3P Emergence RST 2014**

- Publication awaited in Occupational Medicine
Information sources about new couples «disease x exposure» or new triads «disease x agent x circumstance of exposure»

Sentinel clinical approach: case reports from OD centres

Data Mining approach (rnv3p database): disproportionality signals

Notification from other sources: publications, Modernet, NIOSH -> look for similar cases within RNV3P

Expertise of each case (diagnosis / exposure / intrinsic imputability / extrinsic imputability / similar cases)

Ranking of each couple / triad through a decision-making algorithm: SET PRIORITIES AND ENSURE TRANSPARENCY and REPRODUCTIBILITY in actions proposed

Actions

1- Information to rnv3p physicians (only)
2- Information to other clinicians and to rnv3p partners
3- Large dissemination through health surv. agencies -> due actions
Decision-making algorithm (« Emergence score ») for a single case

Excluded Level 1 Notification to RNV3P physicians

Level 2 Search for similar cases outside rnv3p (other physicians) + information RNV3P partners

Transitional zone According to extrinsic imputability, action of: <- level 2 or level 3 ->

Action level 3 LARGE INFORMATION THROUGH HEALTH SURVEILLANCE AGENCY (ANSES)

Scores = Powers of 3

Scores = Powers of 2

Z= Intrinsic Imputability

Very Likely I4

Likely I3

Possible I2

Not impossible I1

Impossible I0

X= Severity

S0: None
S1: minor
S2: moderate
S3: severe
S4: fatal

NB : scores were tested on cases from the literature, and then validated on RNV3P cases
Decision-making algorithm for several similar cases
(Sum of each individual score)

\[ Y = \text{number of independant cases} \]

\[ Z = \text{Intrinsic Imputability} \]

\[ X = \text{Severity} \]

Very Likely: I4
Likely: I3
Possible: I2
Not impossible: I1
Impossible: I0

0: None; 1: minor; 2: moderate; 3: severe; 4: fatal

No case in RNV3P (checked) but emerging elsewhere
Exemple 1: « Hypersensitivity pneumonitis / nail technician »

- Number of RNV3P cases: n=1
- Diagnostic: OK
- Exposure: mainly Ethylmethacrylate (EMA)
- Work-relatedness / Intrinsic imputability: I3
  - Chronology with EMA exposure++
- Acute Severity: S2
- Extrinsic Imputability
  - 2 cases described with MMA
- Action: notification to physicians of RNV3P and outside
- Theoretically a 2nd similar case is needed before thinking to a large dissemination (as extrinsic imputability is quite high)
Exemple: couple multiple proliferating skin lesions (pseudoepitheliomatous hyperplasia) x epoxy resins

- Diagnostic: OK
- Number of RNV3P cases: n=1
- Chronic Severity: S3
- Exposure: Major skin contact with identified Epoxy resins

- Work-relatedness / Intrinsic imputability: I2 + lesions limited to the area previously in contact with the resins, initially concerned with contact dermatitis

- Extrinsic Imputability
  - Still low

- To be shared with other physicians
  - RNV3P, Modernet.... (-> OccWatch), publication of the case-report should be done
Exemple: triad « Asthma x maintenance worker for cafe-machines x *Chrysonilia Sitofila* »

- Diagnostic : **OK**
- Exposure: **OK**
- **Number of RNV3P cases : n=2**
- Work-relatedness / Intrinsic imputability: **I4**
  - Specific IgE
- Acute Severity: **S1**
- **Emergence Score= 2x27=54 : transitional zone**
- + High Extrinsic Imputability
  - C. Sitofila already an asthma risk factor in wood workers
  - cases published at the same time in Spain and Italy

-> **large dissemination**
- -> exchanges with the activity sector about prevention
Exemple : NHL x welders x anti-splashes sprays containing methylene chloride (dichloromethane)

- Diagnostic: **OK (but different subtypes)**
- Exposure: **OK**
- Number of RNV3P cases: n=4 (independant)
- Work-relatedness / Intrinsic imputability: I2

- Acute Severity: S3+ 1 S4 (fatal)
- Emergence Score= 3x12+24=60 : transitional zone
- + rather low Extrinsic Imputability
  - Long discussion. But DCM classified by IARC in 2014 as probable carcinogen (2A), especially because of NHL risk.

- Action level 2 : exchanges with other clinicians. Action level might change due to higher extrinsic imputability
RNV3P : Use of Data Mining tools

Objective: Systematic mining of RNV3P database trying to avoid missing early signals:

• Opportunity to retrieve and highlight similar cases reported only a few times, and by different physicians
• Explore « where problems can be according to our databases », and prioritize investigation of these cases
• No causal inference; bias related to recruitment of cases

Methods:
• Disproportionality metrics used in pharmacovigilance

Bonneterre et al. Safety and Health at Work 2012
Exemple of a Data Mining driven signal: couple \{occupation x leucopenia / neutropenia / agranulocytosis\}

- A signal not raised clinically, but raised by a high disproportionality measure… which also increases over time
- \(\rightarrow\) return to medical files for further investigation (21 cases altogether)
EU, Cost-funded (2011-2014), « Modernet » initiative for tracing new WRD
**Modernet** (EU COST Project 2011-2014)

“a network for development of **new techniques** for discovering trends in OD & WRD, and **tracing new and emerging risks**”

**Modernet WG3**

“**New techniques** for tracing **newly occurring WRD & OD**”

- **DEFINITION of « Newly occurring occupational diseases »**
  - New couple (disease x agent)
  - New triad (disease x agent x circumstance of exposure)

- **METHOD: Multiple complementary approaches**
  - **1st, Clinical: Sentinel Clinical Watch System: OccWatch Project**
  - **Data mining** within databases related to WRD. Lead = F (RNV3P)
  - + Development regarding **QSARS** (asthma). Lead = UK (Manchester Univ)
  - + Development regarding **Text mining**. Lead = NL (TNO)
Modernet group and invited experts, Paris, Oct. 2013

Modernet  www.costmodernet.org/
Monitoring trends in Occupational Diseases and new and Emerging occupation Risks
OccWatch OBJECTIVES

1. CAPTURE case-reports of potentially new WRD
2. EXCHANGE AND ANALYSE the relevance of clinical signals
   – Challenge diagnosis, exposure, work-relatedness, hypotheses on causative agents, physiopathology and prevention issues
   – Seek similar cases
3. SUMMARIZE: produce a common expertise
   – If possible within 2 months after the case has been posted
   – Reach a conclusion, regarding medical data but also including first information on risk assessment (population potentially exposed, severity), and proposals for actions to be taken if necessary
4. DISSEMINATE
   – (Not done at the moment). Possible dissemination of this briefing note to institutions concerned: national agencies, EU-OSHA. (these institutions might decide to raise alerts or not, take specific actions, etc)
https://occwatch.anses.fr/
MODERNET’s CASE-REPORT TEMPLATE
for sharing new cases of potentially emerging work-related diseases
(16th November 2012, version 2 for Modernet Members)

**Case Title**

<table>
<thead>
<tr>
<th>Date and Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of report</strong></td>
</tr>
<tr>
<td><strong>Authors</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New disease - exposure association or new disease - exposure - occupational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First report checked</strong></td>
</tr>
<tr>
<td><strong>Is it a new disease - exposure association?</strong></td>
</tr>
<tr>
<td><strong>Is it a new triad?</strong></td>
</tr>
<tr>
<td><strong>Merits of reporting?</strong></td>
</tr>
<tr>
<td><strong>Please specify</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupational exposure of high concern for health surveillance, as identified previously within Modernet?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nanoparticles</strong></td>
</tr>
<tr>
<td><strong>Endocrine Disruptors</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Multiple proliferating Skin lesions following long term contacts with EPOXY paints

- **Case Title**
  Multiple proliferating Skin lesions following long term contacts with EPOXY paints

- **Date of report**
  2013-09-05

- **Authors**
  V.Bonneterre1, J.Charles2, D.Salameire3, JL.Bourrain2, L.Templier2, JC.Beani2, MT.Leccia2, Grenoble Teaching Hospital, France (1-Occupational Disease Centre, 2- Department of Dermatology, 3- Department of pathology)

- **First report checked**
  yes

- **Is it a new disease - exposure association?**
  yes
Currently, well-argued/documentied commentaries of 10 members from 7 other countries

**Annet**

The skin lesions are impressive and their spreading pattern fits the exposure to the resins this floor-layer used for a long time. I did not find any literature about this type of work and the health problem either. Looking for causes of epidermal hyperplasia and skin cancer I found some abstracts on tattoo ink and this type of skin lesions. I also noted that there is a discussion on a two-stage carcinogenesis in skin cancer starting with a break down of the skin barrier, for instance by a contact dermatitis, which creates an opportunity to carcinogens to enter the skin and body more easily. Not everybody seems to be convinced this is a good model, but you could imagine it in this case.

*about 1 week ago*

---

**Annet** In reply to: Annet

I found three articles on pseudoepidermal hyperplasia and tattoo inks and I attach them underneath.

**Attachments**:

- Cui 2007 Pseudoepitheliomatous hyperplasia an unusual reaction following tattoo.pdf
- Breza 2013 Pseudoepitheliomatous Hyperplasia An Unusual Tattoo Reaction.pdf

*about 5 days ago*
SUMMARY regarding previous case (1/2)

- 11 members from 8 countries (France, NL, Italy, Finland, Belgium, UK, Norway, Spain) participated to the discussion
  - 3 looked at similar cases within national databases
  - 4 also asked advice of a leading dermatologist regarding WRD
  - 3 also made their own bibliographic search

- Disease:
  - No similar case reported in French, UK or Norway databases, nor known by expert. One very similar case published in 1982 in France.

- Discussion regarding Work-relatedness: Direct? Or possibly indirect as Pseudo-Epitheliomatous Hyperplasia might be triggered by chronic irritation, chronic wound healing, trauma

- CONCLUSION. No real public concern at the moment due to the wide use of epoxy and the quasi-absence of similar cases. Agreement on prevention measures / this activity. Worth publishing in scientific medical literature in order to be accessible to anybody facing similar case.
Test of Data mining in other EU databases : SWORD / ASTHMA SUBSET -> identification of signals

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Identifier</th>
<th>INDUSTRY (SIC+ TEXT)</th>
<th>JOB (SOC+ TEXT)</th>
<th>AGENT</th>
<th>Sex-Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>13 /666/2 /238</td>
<td>93-FUNERAL</td>
<td>5496-&quot;WREATH MANUFACTURE&quot;</td>
<td>ISOCYANATE (920)</td>
<td>F-24</td>
</tr>
<tr>
<td>2001</td>
<td>13 /666/2 /239</td>
<td>93-FUNERAL</td>
<td>5496-&quot;WREATH MANUFACTURE&quot;</td>
<td>ISOCYANATE (920)</td>
<td>F-38</td>
</tr>
<tr>
<td>2004</td>
<td>13 /666/2 /360</td>
<td>93-FUNERAL</td>
<td>5496-&quot;WREATH MAKER&quot;</td>
<td>ISOCYANATE (920)</td>
<td>F-34</td>
</tr>
</tbody>
</table>

Search of new cases within SWORD (Text search: « Wreath »)

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Identifier</th>
<th>INDUSTRY (SIC+ TEXT)</th>
<th>JOB (SOC+ TEXT)</th>
<th>AGENT</th>
<th>Sex-Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>13 /666/2 /1023</td>
<td>36-&quot;WREATH MANUFACTURE&quot;</td>
<td>8139-&quot;GLUER&quot;</td>
<td>ISOCYANATE (920)</td>
<td>F-34</td>
</tr>
</tbody>
</table>

BIBLIOGRAPHIC SEARCH (PUBMED): NO SUCH CASE REPORTED: possible NEW TRIAD “disease x agent x occupational setting”

((("Occupational Diseases"[Mesh] OR "Occupational Exposure"[Mesh]) AND ASTHMA) OR "Asthma, Occupational"[Mesh]) AND (isocyanat* OR HDI) AND (wreath* OR funeral or floral OR florist*)

INCENTIVE TO STRENGTHEN THE SIGNAL: SEARCH IN OTHER SURVEILLANCE NETWORKS
BIBLIOGRAPHIC SEARCH (PUBMED): NO SUCH CASE REPORTED: possible NEW TRIADS “disease x agent x occupational setting”

INCENTIVE TO STRENGTHEN THE SIGNAL: SEARCH IN OTHER SURVEILLANCE NETWORKS + Police occupational physicians
What can we do for Europe?
National initiatives of interest for tracing new WRD, with no links before Modernet

- French **RNV3P**
- UK: **THOR** Surveillance Scheme based on specialist physicians (ex: SWORD), GP (THOR-GP), and one scheme open to any WRD of interest, including new ones (Thor-extra)
- Italy: **MALPROF** (INAIL database)
- Other databases that could be searched to generate of confirm signals: **IDEWE** (Be), ...

- **NEW**: NL + Be: **SIGNAAL** recent clinical watch system, based on OccWatch structure (reporters: occupational physicians) to sort and investigate cases at national level first
Towards a systematic and integrated system for detection of emerging WRD issues? ("OSH/WRD Vigilance")

**DATA CAPTURE (« Incubator », « Soup »)**

- Clinically certified information
  - **OccWatch**
    - 1- OccWatch
    - 2- (Automatic) screening of existing WRD databases
      - Data mining
      - Occupational exposome
      - Signals within temporal trends

**SIGNS ASSESSMENT AND EXPERTISE**

- Matching up of information
- Exposure/Risk assessment
- Scoring (imputability, severity, number of cases)

**Complementary sources of information**

- QSARS
- Text Mining
- Bibliographic Watch
- Links with the emerging Drivers (ERO)

**DISSEMINATION**
EFSA as a source of inspiration

Mandate on emerging risks regarding Food:

- Regulation N°178/2002 of the EU Parliament and of the Council (28/01/2002) regarding European Food Safety Authority
  - Article 34 regarding identification of emerging risks

- An organisation build on that purpose
  - A dedicated unit with Human ressources (Emrisk unit)
  - Expert panels
  - Similar Process for detection, expertise and summarizing evidence

Need for EU-wide cooperation, and if possible a EU-wide system for detection, expertise and handling of potentially new WRD
Thank you for your attention!

Acknowledgments

• Modernet members and supporters
• RNV3P and ANSES

Further Information

Vبونترير@chu-grenoble.fr
Links

- Modernet website: [www.costmodernet.org/](http://www.costmodernet.org/)
- UK THOR surveillance scheme
- SIGNAAL NL and Be clinical watch system
- MALPROF Italy

**RNV3P page on ANSES website**: RNV3P main publications: