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

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

Vincent Bonneterre[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?

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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)
- *First publications in Spanish : 1994-1995*
- *First publication in English : Thorax 1996; 51(1):94-5*
- *Eur Respir J 1998;11:265-71 // Eur Respir J 1999;13:940-1*

KOREA 1998 : Primary Ovarian Failure and 2 bromo-propane

- **Cluster 16 cases, mean age : 24 years old, exposed 4 to 16 months**
- *Koh JM et al. Eur J Endocrinol. 1998 May;138(5):554-6.*

USA 1997-8 : Nylon flock Workers Lung Disease

- **Cases found in 5 different sites in US and Canada**
- *Kern. Ann Intern Med 1998;129:261-272 // Eschenbacher. Am J Respir Crit Care Med 1999, 159, 2003-8 // Kern. Chest 2000,117, 1,251-9*

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**
- *NJEM 2002;347:1980-82 / JOEM 2002;44:216-218*
- *MMWR Morb Mortal Wkly Rep. 2013 Apr 26;62(16):305-7*

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.**
- *Eur Respir J 2005;25(1):200-4 // Eur Respir J 2007, 29:317-324*

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**
- *Merget R. Am J Ind Med. 2010 Jan;53(1):42-6.*

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**
- *Kumagai et al. Occup Environ Med 2013; 70:508-510.*

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*
- *I : Heffler E. Ann Allergy Asthma Immunol. 2009;102(2):168-9*
- *F : Francuz, Clin Vaccine Immunol. 2010 Oct;17(10):1645-6*

USA 2009: Angiosarcoma of the liver in hairdressers and barbers due to former use of vinyl chloride propellant in hair spray

- *Infante PF. Int J Occup Environ Health. 2009;15(1):36-42.*

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 frequence of the exposure to other risk factors of the disease
- ++ Most of all : the Capture of the cases by people able to evoque the plausibility of work-relatedness -> importance to raise awarness of GP and specialists, and incite them to make secondary referrals to OD /WRD specialists

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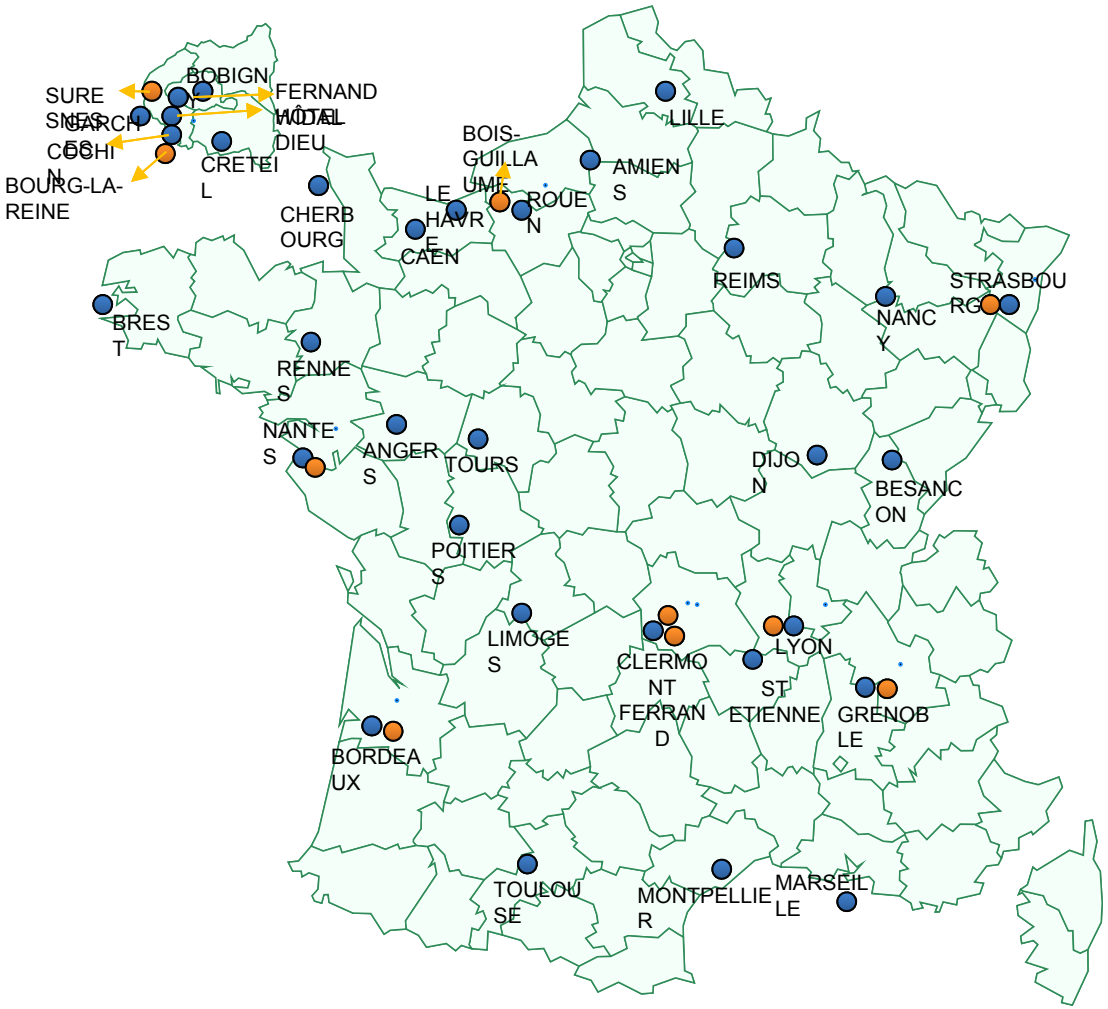
National initiatives for tracing new WRD

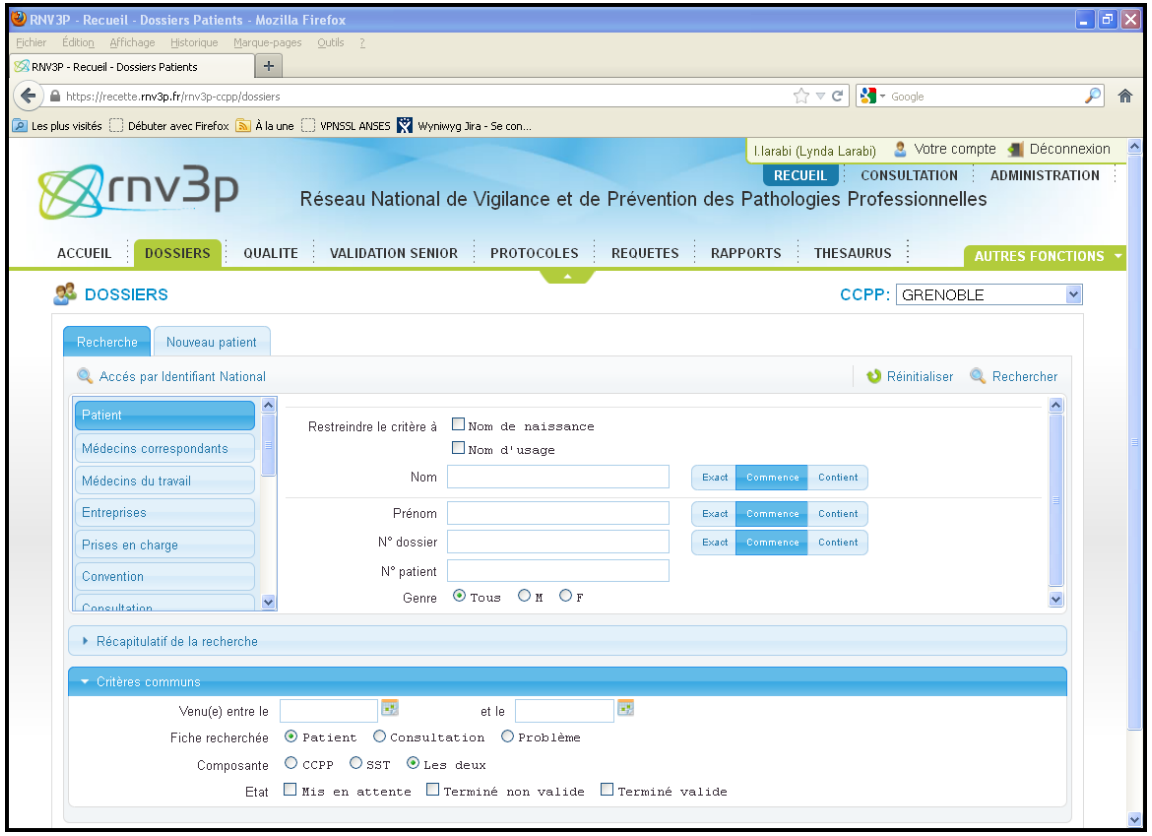
Example of the French approach

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

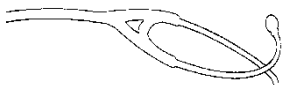
Tracing new WRD is one of RNV3P's aims

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

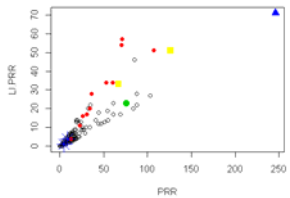
2014 : approach summarized and illustrated in our last scientific report

- 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

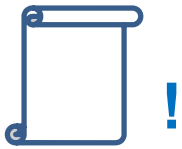
Information sources about new couples « disease x exposure » or new triads « disease x agent x circumstance of exposure »



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

Cases analysis (collective expertise)

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

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

Actions

excluded

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

Z= Intrinsic Imputability

Scores = Powers of 3

		S0	S1	S2	S3	S4
Very Likely	**I4**	0	27	54	108	216
Likely	**I3**	0	9	18	36	72
Possible	**I2**	0	3	6	12	24
Not impossible	**I1**	0	1	2	4	8
Impossible	**I0**	0	0	0	0	0

X= Severity

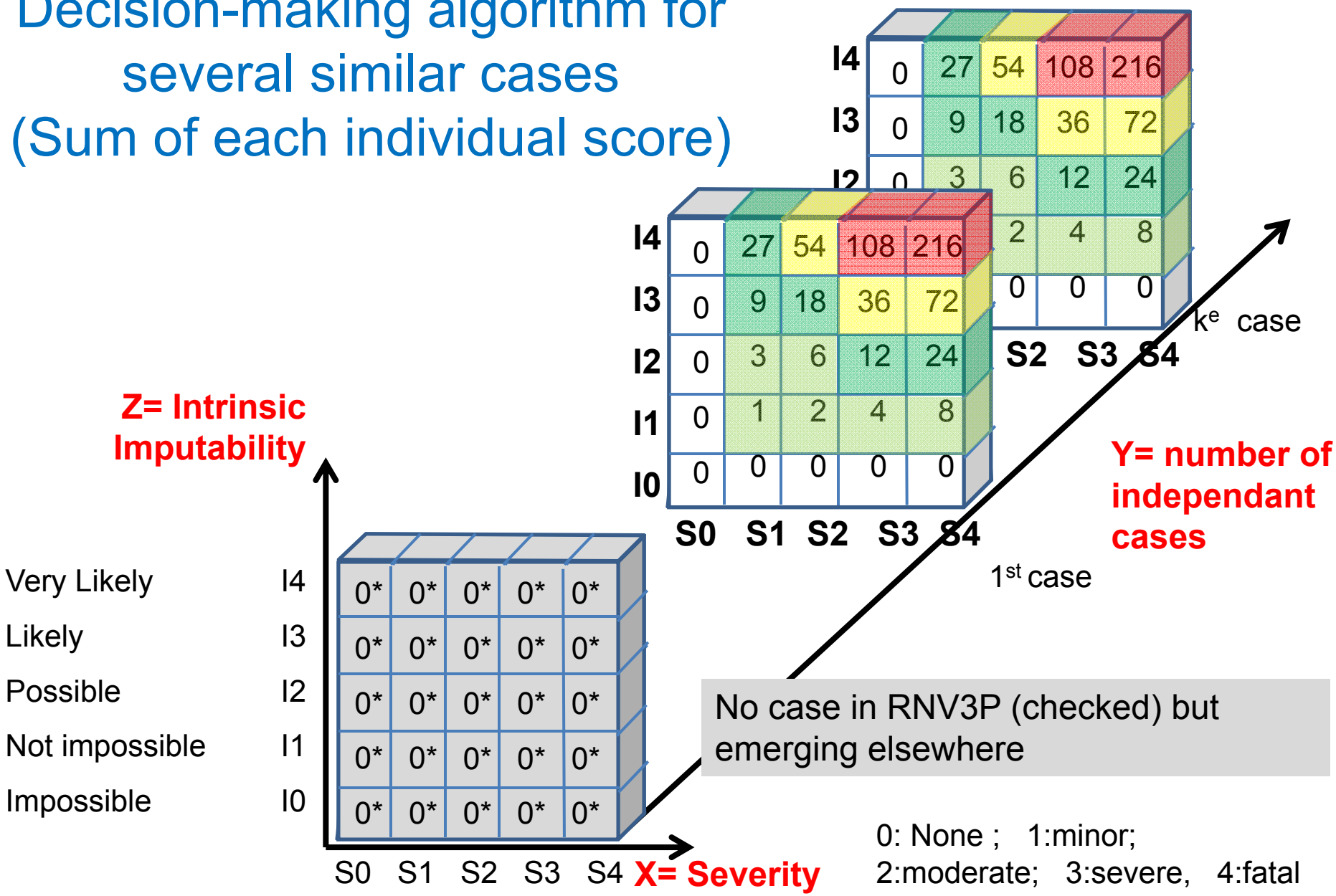
S0: None
S1: minor
S2: moderate
S3: severe
S4: fatal

Scores = Powers of 2

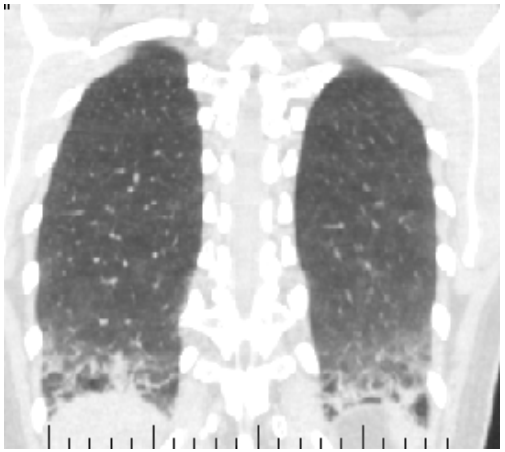
Excluded	**Level 1**	**Level 2**	**Transitional zone**	**Action level 3**
⊗	Notification to RNV3P physicians	Search for similar cases outside rnv3p (other physicians) + information RNV3P partners	According to extrinsic imputability, action of : <- level 2 or level 3 ->	LARGE INFORMATION THROUGH HEALTH SURVEILLANCE AGENCY (ANSES)

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)



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)

Score : 18 (cas index)

	S0	S1	S2	S3	S4
I4	0	27	54	108	216
I3	0	9	18	36	72
I2	0	3	6	12	24
I1	0	1	2	4	8
I0	0	0	0	0	0

Exemple: couple multiple proliferating skin lesions (pseudoepitheliomatous hyperplasia) x epoxy resins

Score : ∑ = 12< <36 (cas unique)

	S0	S1	S2	S3	S4
I4	0	27	54	108	216
I3	0	9	18	36	72
I2	0	3	6	12	24
I1	0	1	2	4	8
I0	0	0	0	0	0

- 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* »

Score : ∑ =54

	S0	S1	S2	S3	S4
I4	0	27	54	108	216
I3	0	9	18	36	72
I2	0	3	6	12	24
I1	0	1	2	4	8
I0	0	0	0	0	0

- 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)

Score : ∑ = 3x12+24=60

	S0	S1	S2	S3	S4
I4	0	27	54	108	216
I3	0	9	18	36	72
I2	0	3	6	12	24
I1	0	1	2	4	8
I0	0	0	0	0	0

- 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

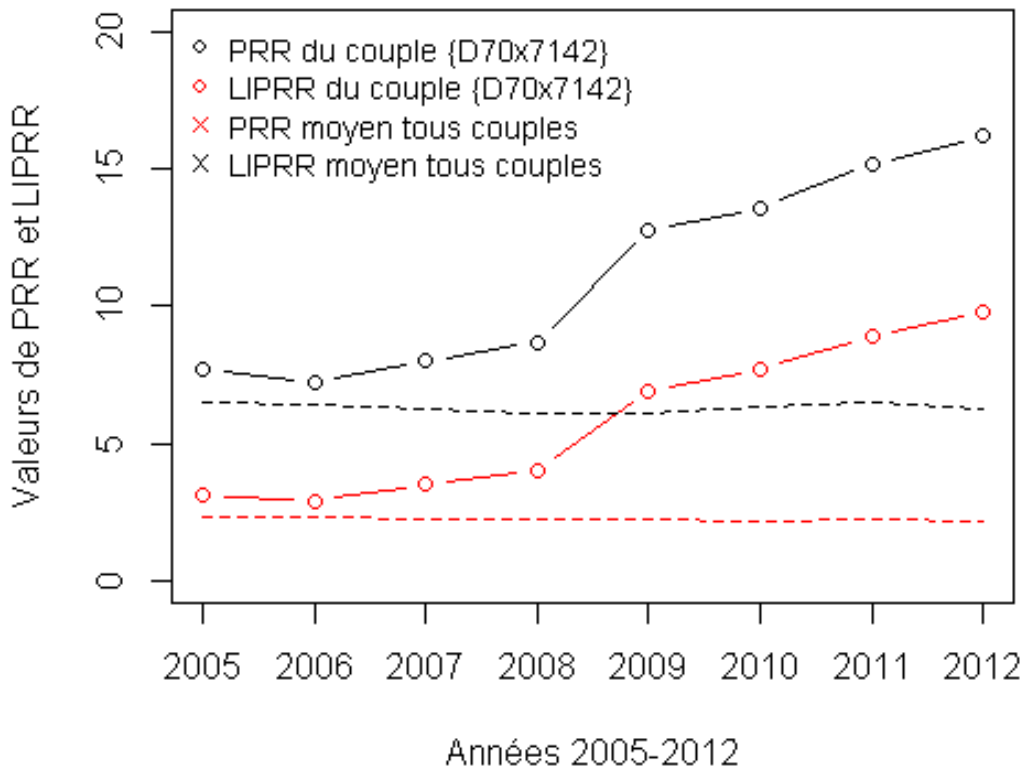
Methods:

- 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
- -> return to medical files for further investigation (21 cases altogether)



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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

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

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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

Date and Authors

Date of report *

Authors *

New disease - exposure association or new disease – exposure - occupational

First report checked ○ Yes ○ No *

Is it a new disease - exposure association? ○ Yes ○ No *

Is it a new triad? ○ Yes ○ No *

Merits of reporting? ○ Yes ○ No *

Please specify

Occupational exposure of high concern for health surveillance, as identified previously within Modernet?

Nanoparticles ○ Yes ○ No *

Endocrine Disruptors ○ Yes ○ No *

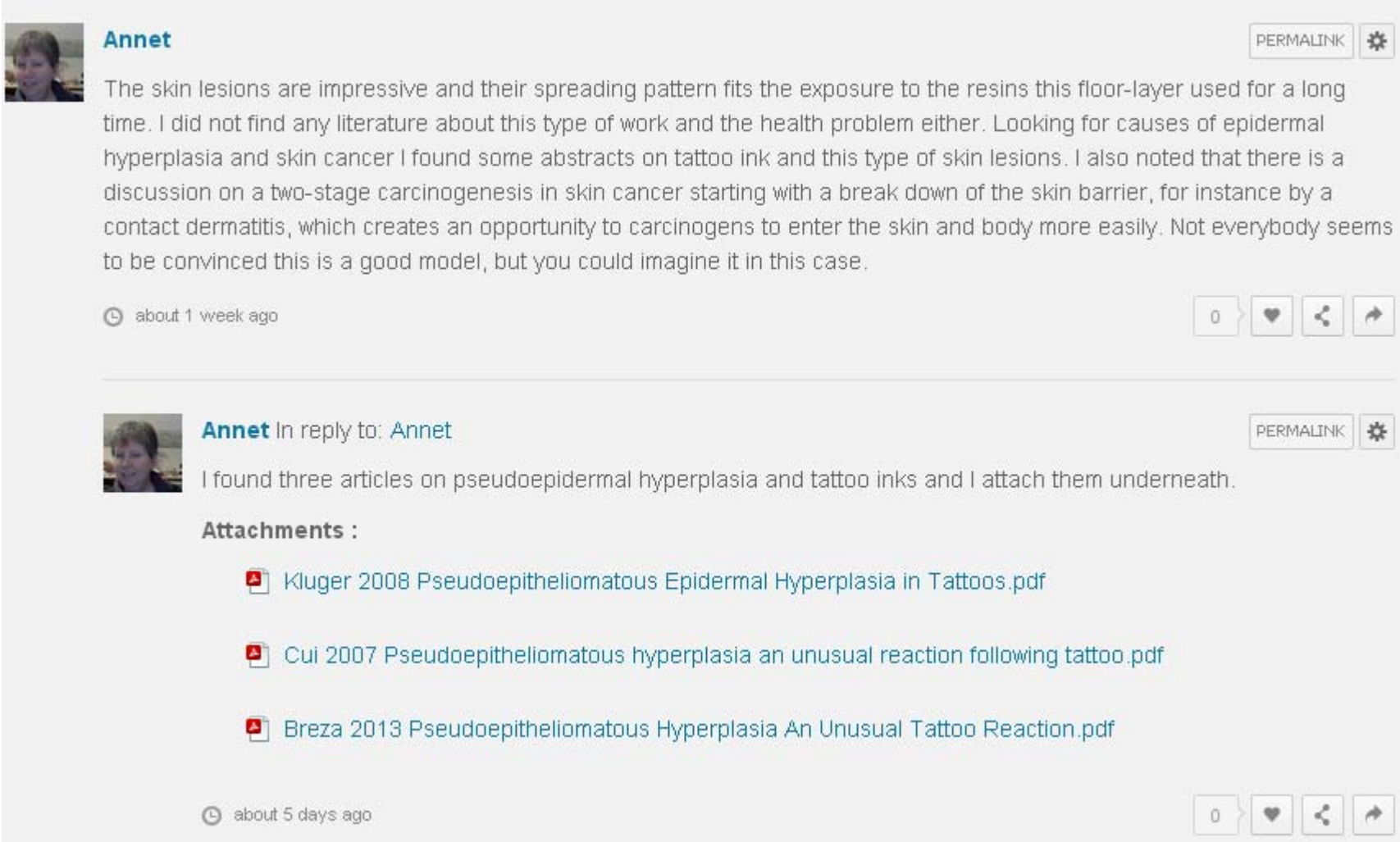
Multiple proliferating Skin lesions following long term contacts with EPOXY paints

Category: Case-reports DataBase Published: Tuesday, 24 September 2013 08:43 Written by BONNETERRE Hits: 85 Print Email Edit

- **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, I.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

Exemple: EXCHANGES & COMMENTS

Currently, well-argued/documented commentaries of 10 members from 7 other countries



Annet

PERMALINK

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

0

Annet In reply to: Annet

PERMALINK

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

Attachments :

- Kluger 2008 Pseudoepitheliomatous Epidermal Hyperplasia in Tattoos.pdf
- Cui 2007 Pseudoepitheliomatous hyperplasia an unusual reaction following tattoo.pdf
- Breza 2013 Pseudoepitheliomatous Hyperplasia An Unusual Tattoo Reaction.pdf

about 5 days ago

0

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

3 cases identified with previous signal	YEAR	Identifier	INDUSTRY (SIC+ TEXT)	JOB (SOC+ TEXT)	AGENT	Sex-Age
	2001	13 /666/2 /238	93-**FUNERAL**	5496-"**WREATH MANUFACTURE"**	ISOCYANATE (920)	F-24
	2001	13 /666/2 /239	93-**FUNERAL**	5496-"**WREATH MANUFACTURE"**	ISOCYANATE (920)	F-38
	2004	13 /666/2 /360	93-**FUNERAL**	5496-"**WREATH MAKER"**	ISOCYANATE (920)	F-34

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

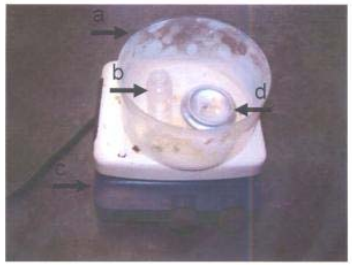
4th case identified	YEAR	Identifier	INDUSTRY (SIC+ TEXT)	JOB (SOC+ TEXT)	AGENT	Sex-Age
	2003	13 /666/2 /1023	36-"**WREATH MANUFACTURE"**	8139-"**GLUER"**	ISOCYANATE (920)	F-34

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

SWORD: 2nd Example of SIGNAL



2 cases identified	YEAR	Identifier	INDUSTRY (SIC+ TEXT)	JOB (SOC+ TEXT)	AGENT	Sex-Age
	2005	10/584/2/874	**POLICE**	"**FINGER PRINT** ENHANCEMENT OFFICER"	CYANOACRYLATE	F-47
	1995	10/584/2/10578	**POLICE**	"**FINGERPRINT** EXPERT"	CYANOACRYLATES	M-31

3 more cases retrieved with text search Fingerprint	YEAR	Identifier	INDUSTRY (SIC+ TEXT)	JOB (SOC+ TEXT)	AGENT	Sex-Age
	1994	10/584/2/9127	NA	"MET POLICE **FINGERPRINT** OFFICER"	ALUMINIUM	F-27
	2012	6/666/3/98	**SECURITY**	"**FINGER PRINT** SCIENTIST"	CYANOACRYLATE	F-34
	1997	10/584/2/12131	**POLICE**	"**FINGERPRINT** OFFICER (EX-)"	ALUMINIUM DUST	M-60

Coding issues: Was aluminium the good culprit in the other finger print experts? Probably not!

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

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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

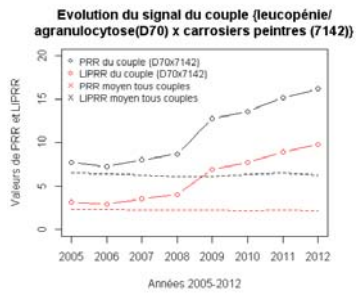
1- OccWatch

Occupational Diseases Sentinel Clinical Watch System

sharing new cases of potentially emerging work-related diseases

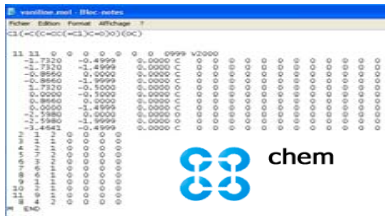
2- (Automatic) screening of existing WRD databases

- **Data mining**
- **Occupational exposome**
- **+ Signals within temporal trends**



Complementary sources of information

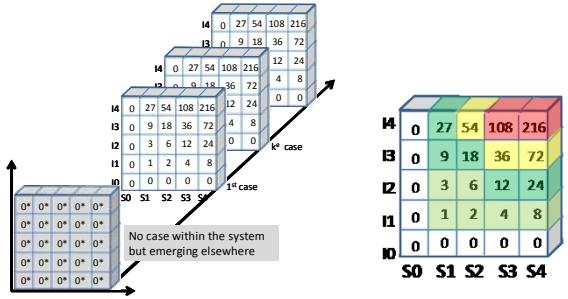
- QSARS
- Text Mining
- Bibliographic Watch
- Links with the emerging Drivers (ERO)



SIGNALS ASSESSMENT AND EXPERTISE

- **Matching up of information**
- **Exposure/Risk assessment**

- **Scoring (imputability, severity, number of cases)**



- **Briefing note including recommandations**

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

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

Thank you for your attention!

Acknowledgments

- Modernet members and supporters
- RNV3P and ANSES

Further Information

Links

- Modernet website: www.costmodernet.org/
- UK THOR surveillance scheme
- SIGNAAL NL and Be clinical watch system
- MALPROF Italy
- RNV3P page on ANSES website; RNV3P main publications: RNV3P OEM 2010, RNV3P Contact Dermatitis Trends Br J Dermatol 2014, Occ Asthma & rhinitis OEM 2013, RNV3P asthma trends OEM 2012; RNV3P publications regarding detection of new WRD: RNV3P scientific report on detection of new WRD, April 2014; RVN3P Emergence RST 2014