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

Post-marketing surveillance of chemicals: organisations and databases

Workshop report

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M. Bouwmeester (author), RIVM
A. van Drongelen (author), RIVM
C. Graven (author), RIVM
L. Hernandez (author), RIVM
J. Herremans (author), RIVM
D.de Kaste (author), RIVM
L. Razenberg (author), RIVM
R. Vandebriel (author), RIVM
A. Piersma (author), RIVM

Contact:
Aldert Piersma, aldert.piersma@rivm.nl

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www.rivm.nl/en

Synopsis

Post-marketing surveillance of chemicals: organisations and databases
Workshop report

The safety evaluation of chemicals is in general performed by the government, importer or manufacturer before marketing, and is based on (inter)national legislation. Less is known about the exact products in which chemicals are processed. Even though multiple institutions in the Netherlands are involved with various aspects of chemical safety after marketing, a concrete view on unforeseen effects is lacking.

The RIVM aims to improve the system to gain better insight on these effects. Therefore, several stakeholders in this area were brought together to exchange ideas for a more intense exchange of information on signals of possible adverse health effects and on information about existing databases. Actively communication adverse health effects was the focus here, as currently producers are informed after an effect occurred.

This report contains an overview of relevant databases, web addresses and contact information to facilitate exchange of information among relevant stakeholders in the field of post marketing surveillance of chemicals. Additionally, three concrete case studies were presented and discussed.

Keywords: Post-marketing surveillance, chemicals, risk assessment, databases, signaling, biocides, medical devices

Publiekssamenvatting

Post-marketing surveillance van stoffen: organisaties en databases
Workshop rapport

Voordat stoffen op de markt worden gebracht, beoordeelt de overheid, importeur of producent of het veilig is om deze stoffen te gebruiken. De manier waarop deze veiligheidsbeoordeling wordt uitgevoerd, is vastgelegd in (inter)nationale wetgeving. Maar meestal wordt niet gespecificeerd voor welke producten de stoffen worden gebruikt. In Nederland houdt een groot aantal instellingen zich bezig met de veiligheid van de producten waar de stoffen in zitten nadat ze op de markt zijn verschenen, de zogeheten post marketing surveillance. Een eenduidig zicht op onvoorziene gezondheidseffecten tijdens het gebruik ontbreekt echter.

Het RIVM werkt daarom aan een systeem om beter zicht op deze effecten te krijgen. Hiertoe hebben experts van organisaties die bijwerkingen en effecten van stoffen documenteren, gezamenlijk geïnventariseerd aan welke informatie behoefte is. De experts hebben ideeën uitgewisseld hoe beter bekend kan worden gemaakt welke informatie uit bestaande databases beschikbaar is en hoe die beter met elkaar kan worden uitgewisseld tussen organisaties die er belang bij hebben. De focus lag daarbij op mogelijkheden om signalen van mogelijk nadelige gezondheidseffecten actief uit te wisselen. Momenteel worden producenten pas geïnformeerd nadat een effect is optreden.

Dit rapport biedt een overzicht van relevante databases, webadressen en contactgegevens die uitwisseling tussen relevante partijen kan faciliteren. Ook zijn drie case studies uitgewerkt om hiaten bloot te leggen: metalen heuptransplantaten (medische hulpmiddelen), pesticiden voor mensen die werken in de agrobranche en consumentenproducten die voor andere doeleinden worden gebruikt dan waarvoor ze zijn beoordeeld, zoals een zuur in producten waar kinderen slijm mee kunnen maken.

Kernwoorden: Post-marketing surveillance, stoffen, risicobeoordeling, databases, signalering, biociden, medische hulpmiddelen

Contents

Summary

The safety evaluation of chemicals is in general performed before marketing, and is based on international legislation. The fate of chemicals after marketing is less transparent. This regards e.g. the application of chemicals in consumer products and possible unforeseen adverse health effects that may emerge after marketing. Nevertheless, after marketing multiple institutions are involved with various aspects of chemical safety.

This report describes a 2017 workshop at which several stakeholders in this area were brought together. Ideas were exchanged for a more intense exchange of data and on information about existing databases. Three concrete case studies were presented and discussed. This report contains an overview of relevant databases, web addresses and contact information to facilitate exchange of information among relevant stakeholders in the field of post marketing surveillance of chemicals.

1 Introduction

1.1 Background

The general population is exposed to various chemical substances, for example via food, consumer products and medicines. Before they are placed on the market, these different substances are tested for safety – some more extensively than others dependent on the legislation. The question remains if these substances, once on the market, are indeed safe to the human population and whether the current surveillance systems are sufficient to detect possible safety issues after marketing.

In a report focusing on health risks of prenatal exposures, the Health Council of the Netherlands expressed their concerns on the available post marketing surveillance (PMS) information of chemicals (Gezondheidsraad 2014). They questioned whether surveillance systems could play an important role in identifying relationships between exposure to chemical substances in early life and effects later in life, given the lack of test methods to fully cover all these effects during the pre-marketing safety assessment. It cannot be excluded that relevant health effects in humans may not be detected in the performed safety assessments, as these are often based on *in vitro* and *in vivo* studies.

PMS involves the identification of adverse health effects that occur after human exposure to substances on the market. Other terms to describe PMS are ‘early warning system’ and ‘new or emerging risks’.

Based on our first analysis of PMS related activities in regulatory frameworks of medicines, food, cosmetics and industrial chemicals in 2015, we concluded that there are major differences between PMS related activities in the different frameworks. Then we aimed to pinpoint gaps in PMS activities and to identify opportunities for improvement towards a general PMS system (Olthof ED et al. 2016).

Because databases are often used for the purpose of PMS, the workshop in 2017 discussed which databases can be used for PMS and how to facilitate communication between these sources of information. In addition, ideas and knowledge were shared on case studies in various PMS systems (medical devices, consumer products and occupational).

1.2 Method

1.2.1 Previous activities

In 2015, an inventory was prepared of the different stakeholders and their activity in pre-marketing or authorization and post-marketing surveillance of medicines, since this regulatory area has the most extensive PMS system. Subsequently, this inventory was expanded with known activities in the field of industrial chemicals, foods, and cosmetics. In 2016 other regulations were included, such as medical devices, other consumer products besides cosmetics, and different food-related regulations. An overview of the different stakeholders and their pre-marketing or authorization and PMS activities related to the before mentioned regulatory frameworks was generated. Several national

stakeholders identified in the overview were invited to take part in a workshop at RIVM in June 2016. During this workshop, the pre-marketing/authorization and PMS activities of the different stakeholders were presented and the overview of the different activities was used as supporting material for the discussion. The discussion focused on the identification of gaps in PMS and the formulation of recommendations for further improvement of PMS in the non-pharmaceutical areas addressed (Olthof ED et al. 2016).

The most important recommendations that were proposed in the 2016 workshop are:
Long term goals

- Connecting and expanding international activities in biobanking, biomonitoring and cohort studies.
- International harmonization of regulations, terminology, product categories, etc.
- Registration system of use and application of all substances.
- Streamlining information sources globally, harmonize quality, information content, search engines, etc.

Quick wins

- Coupling existing databases. This aims at combining complementary information sources to increase the overall information level.
- Share existing and emerging information and ad hoc signaling actions regarding substances and health issues between regulatory frameworks. This promotes sharing actions in an individual regulatory framework timely with other frameworks for consideration of additional regulatory action.
- Collect and share all existing and new information on databases, projects and regulations internationally as pertinent to the subject. This will keep all stakeholders up to date as to relevant developments.
- Install a national discussion group for regular and/or ad hoc exchange on safety information on substances between representatives from regulatory frameworks.

1.2.2 Workshop 2017

In 2017, an inventory of available databases that can be used for the purpose of post-marketing surveillance was prepared. This inventory was discussed in the second workshop concerning post-marketing surveillance at RIVM on the 26th of September 2017. During this workshop, three case studies were presented to demonstrate the broad applicability of a post-marketing surveillance system. Additionally, specific ideas on how to establish access to the different databases and to share knowledge on adverse effects of chemicals were discussed. Missing information in the proposed overview was identified and recommendations for improvement of this table and of the communication between different fields concerning post-marketing surveillance for chemicals were suggested.

2 Workshop preparation

2.1 Overview of databases

The workshop preparation comprised making an overview of databases (see Annex 2) made available by different organisations that may be applicable for PMS for chemicals. The table is based on the PMS for chemicals workshop at RIVM in 2016 and databases that are used by RIVM. Databases were categorised into regulatory frameworks, such as medicines, food (among which pesticides and additives), consumer products in general, and others. The purpose of this table is to provide an inventory of databases that are available, and where to find them.

2.2 Workshop participants

The participants list of the workshop was based on the workshop in 2016. Governmental organisations which participated in 2016 were invited and the invitation list was not further expanded.

The participating national stakeholders outside RIVM were the Ministry of Infrastructure and Water Management (I&W), Netherlands Food and Consumer Product Safety Authority (NVWA), Dutch Medicines Evaluation Board (CBG), Netherlands Center for Occupational Diseases (NCvB) and Health and Youth Care Inspectorate (IGJ). From RIVM the Centre for Health Protection (GZB), Centre for Nutrition, Prevention and Health Services (VPZ) and Centre for Safety of Substances and Products (VSP) participated. Participants are presented in Table 1.

Table 1. Participants of governmental organisations at the workshop post-marketing surveillance for chemicals in 2017 at RIVM

Governmental organisation	**Participants**
CBG	Ms Ineke Crijns Ms Anita Volkers
IGJ	Ms Sietske Eerens
I&W	Ms Heddy Lindeijer
NCvB	Mr Herman Bartstra
NVWA	Ms Jacqueline Castenmiller Mr Peter Dekker
RIVM - GZB	Ms Manon Bouwmeester Mr Arjan van Drongelen Mr Dries de Kaste Mr Aldert Piersma Mr Rob Vandebriel
RIVM - VSP	Ms Lya Hernandez Ms Joke Herremans
RIVM - VPZ	Ms Linda Razenberg

3 Workshop

3.1 Opening and introduction

On the 26th of September 2017, the second workshop concerning a post-marketing surveillance system for chemicals was organised at RIVM in Bilthoven, the Netherlands. Participants of the workshop are presented in Table 1.

The workshop was chair by Dr. A. Piersma. He opened the meeting and welcomed the participants and introduced the participants to the aim of the workshop. In brief, the outcome of the workshop on post-marketing surveillance for chemicals at RIVM in 2016 was reiterated. During this workshop, a list of initial short and long term recommendations for organisation and development of a post-marketing surveillance system for chemicals was proposed. As a follow-up and in preparation of the 2017 workshop, an overview was created of databases which can be useful in view of for post-marketing surveillance.

The focus of this workshop was to illustrate the broad applicability across regulatory frameworks of a post-marketing surveillance system for chemicals by presentations of three case studies by RIVM and NCvB. Additionally, the provided database overview was discussed: gaps were identified (missing databases/organisations or information) and thoughts were shared on how to use these databases. Finally, small steps that can be taken in the near future regarding improving connections and communication between organisations, and how the provided overview could assist in this improvement, were suggested.

3.2 Presentation of case studies

Three case studies were presented on different subjects illustrating the use of PMS in different fields.

3.2.1 Metal-on-metal hip implants and the relevance of PMS (Arjan van Drongelen, RIVM)

For medical devices, the current European legislation, which was published over 25 years ago and transposed into Dutch legislation, already required a PMS system, although the legislation did not contain a detailed description of these requirements. The system was mainly focused on dealing with adverse events and taking appropriate action. The responsibility for implementing such a system and performing PMS activities lies with the manufacturer of medical devices. RIVM has performed several file assessment studies for different types of medical devices, which indicated that PMS systems were often passive, relying mainly on complaints received, without manufacturers actively obtaining information on experiences with their product.
Metal on metal hip implants have metal surfaces for both articulating parts. Other combinations of surfaces are also in use, like metal on ceramic and metal on polyethylene. Metal on metal (MoM) hip implants have been developed over 30 years ago, but have not been regularly used. Over 10 years ago, the use of MoM hip implants grew more popular due to their durability and therefore suitability for younger

patients with a more active lifestyle. Due to friction, small metal wear particles can be formed, that can cause adverse tissue reactions and elevated levels of metal ions in the blood.
In 2010, one type of MoM hip implant of one manufacturer was recalled from the market in the USA due a higher failure rate than previously acknowledged. The data were available from a UK registry on implants and were confirmed by the data from an Australian registry. Although these data were available, they were not used by the manufacturer. Also other types and brands of MoM hip implants led to higher failure rates. The wear particles of MoM hip implants were shown to lead to adverse tissue reactions that could cause loosening of the implant. These complications also led to an increase in the rate of revision surgeries. The Dutch Health Care Inspectorate investigated this problem and in 2013 published a report containing an analysis of the problem and assessments of files of several MoM hip implants, performed by RIVM. The Dutch Orthopedic Association decided that the use of MoM hip implants in the Netherlands should be limited as far as possible and the need for a national implant registry became more apparent.
The file assessment indicated that there were often no criteria specified for the assessment of the PMS data and the methods used for the analysis were often not stated. Decisions on the acceptability of adverse outcomes were often justified by referring to similar outcomes for MoM hip implants of competitors. Moreover, the number of sources used for PMS were limited in most cases.
In the middle of 2017, the Dutch reporting point for side effects of medical implants was established to allow patients to report problems with implants. Analysing the reports and further investigation should allow early detection of possible problems with a specific type of implant. Such signals will be shared with the Dutch Health Care Inspectorate and the applicable associations of surgeons. Additionally, the signals will be published on the website of the reporting point for side effects of medical implants, allowing all stakeholders, including patients and manufacturers, to access such signals.

In conclusion, PMS is an important tool for medical devices to ensure their continued safety and effectiveness. It is however important that the appropriate information sources are being used. The manufacturer has to perform the PMS, but there is also a role for the authorities and the users to facilitate the correct performance of PMS. The data analysis of PMS needs to be performed correctly to allow adequate conclusions to be made and actions to be taken.
In the new European regulations for medical devices, the requirements for PMS have been considerably strengthened. This was initiated by the Dutch delegation during the negotiations, and supported by the other member states. An ISO guidance document for performing PMS by manufacturers of medical devices is currently being developed.

3.2.2 Signals of possible new risks – consumer products (Lya Hernandez, RIVM)

This presentation addressed a methodology for identifying new or emerging risks of chemicals (NERCs) of non-food products for consumers. In this methodology NERCs are identified according to the definition of the International Risk Governance Council (IRGC): "*a new risk or a familiar risk that becomes apparent in new or unfamiliar*

conditions" (IRGC 2015). The methodology for identifying NERCs is illustrated in Figure 1 and consists of a systematic data collection of potential cases retrieved by screening various post-marketing surveillance and pre-marketing information sources (i.e. literature search, network and consumer complaints) gathered in a database (Bakker J et al. 2015). The presentation is focused on the NERCs for consumers. Beginning with **signal identification** (Figure 1-1), the following information sources are systematically screened to obtain information on the possible link between chemicals in consumer products and health effects:
Post-marketing surveillance literature search including international government reports (Danish Environmental Protection Agency[1], the German BfR[2], Health Canada), *internet searches* including Dutch and international media reports, and *database searches* including ChemicalWatch[3], RAPEX[4] weekly report listings (EC RAPEX, rapid alert system for dangerous non-food products), and reports from the Dutch National Poison Centre (NVIC)[5]; For *pre-marketing surveillance literature search*, sources such as Cosmetics Design Europe[6] and consumer product trends were used; *Network* of experts which share signals; and *Consumer complaints* through the Consumer Exposure, Skin Effects and Surveillance (CESES) program[7], which was initiated at the request of the Netherlands Food and Consumer Product Safety Authority (NVWA) and the Ministry of Health, Welfare and Sport (VWS). In CESES, the reported consumer complaints from cosmetics use are assessed by dermatologists as part of a post-marketing surveillance system.

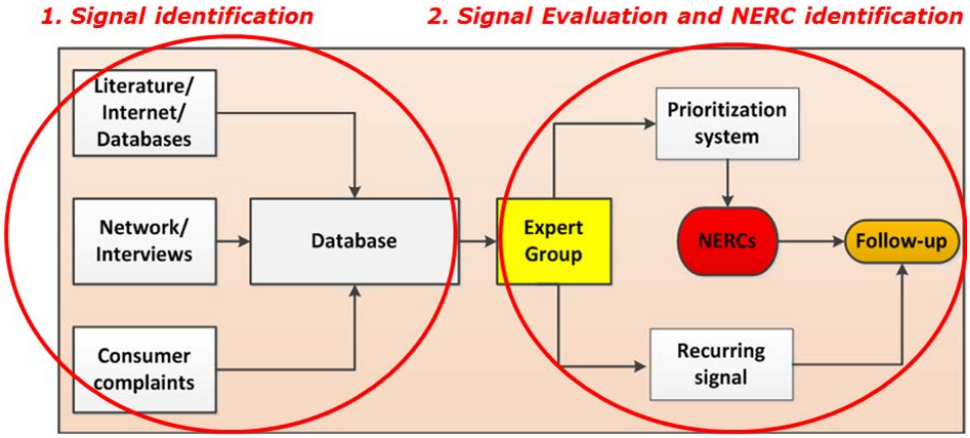

Figure 1. Schematic PMS methodology for consumer products

The identification of NERCs for consumers also includes collecting hazard, potency and exposure information of chemicals in consumer products with reported adverse effects. This information is gathered in a

[1] http://eng.mst.dk/
[2] http://www.bfr.bund.de/en/home.html
[3] https://chemicalwatch.com/
[4] https://ec.europa.eu/consumers/consumers_safety/safety_products/rapex/alerts/?event=main.listNotification
[5] https://www.umcutrecht.nl/nl/Subsites/Nationaal-Vergiftigingen-Informatie-Centrum-(NVIC)/Acute-vergiftigingen
[6] https://www.cosmeticsdesign-europe.com/
[7] http://www.cosmeticaklachten.nl

database consisting of chemicals in consumer products with reported adverse effects (Figure 1).
For **signal evaluation** and **NERC identification** (Figure 1-2), the information relevant for the identification of consumer risks and additional data on type of exposure and consumer product details as collected in this database is evaluated for further *prioritization* by an *expert group*. Information collected includes the severity of the effect as a result of product exposure, effects observed in a sensitive group (e.g. infants, children, elderly) and the probability of exposure. Product categories were assigned to discriminate between the different types of products and to better define various types of exposures. Important categories are 'cosmetics' (used on a daily basis), 'household products (used on a weekly or monthly basis) and 'toys' (used by sensitive groups). In addition, chemical categories were added to allow identification of important groups of chemicals (e.g. phthalates, flame retardants or parabens, CMRS (carcinogenicity, mutagenicity, reproductive toxicity and respiratory sensitization). Chemical categorization is useful to filter groups of chemicals for which regulatory measures have already been implemented and allows for the identification of products with the potential for high consumer exposure or high hazard potential. If a potential NERC is identified, additional information is gathered where possible on the identity of the substance, its classification (self-classification by the notifiers and/or harmonized classification), the use of the substance, the seriousness of the health effect, and the amount of the exposure to the substance in relation to the health effect reported.

In addition, an assessment is made as to whether the signal has previously been identified and actions or regulatory measures have already been implemented. A *recurring signal* is therefore defined as a known historical risk due to the presence of a substance in a consumer product (Figure 1). Where regulatory measures are implemented, the identified signal is forwarded to enforcement or inspection authorities.

Possible *follow-up actions* after identification of a potential NERC include a proposal for a risk management option analysis, a proposal for restriction of a chemical in the consumer product or a proposal for harmonized classification. The potential NERCs are also shared with the NVWA in a report twice per year.

During the workshop, 3 NERCs examples were illustrated: an unexpected exposure, an unexpected effect and examples of important trends in cosmetics.

Unexpected exposure: There have been several recalls by Health Canada[8,9] of boric acid found in slime toys and boric acid used to make slime at home. Health Canada's sampling and evaluation program has determined that the slime toys do not meet the Canadian toy safety requirements related to boric acid content. Boric acid exposure to children can occur if the slime toys licked or swallowed. Children are

[8] http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/59514a-eng.php
[9] http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/64040r-eng.php

more sensitive to boric acid toxicity than adults. High levels of boric acid ingestion may have long-term effects on a child's development and their future reproductive health. The concern is not with any single product, but rather multiple exposures from a variety of sources. Given the many sources of natural exposure to boric acid, sources of exposure to boric acid other than food and water should be minimized as much as possible, especially for children and pregnant women. In Europe boric acid is classified as Repro 1B by the CLP regulation (presumed human reproductive toxicant).

Unexpected effect: Common household chemicals (quats alkyl dimethyl benzyl ammonium chloride (ADBAC) and didecyl dimethyl ammonium chloride (DDAC)) have been linked to birth defects[10] in rodents. An increase in neural tube defects with exposure to ADBAC+DDAC is observed in both rats and mice. The neural tube defects persisted for two generations after cessation of exposure. Male exposure alone was sufficient to cause neural tube defects. In rodents ambient exposure from disinfectant use influenced the levels of neural tube defects to a greater extent than oral dosing. The substances ADBAC and DDAC, which are common household products, need further investigation given that they are not classified as being teratogenic in humans.

Trends in cosmetic products: Because emerging technologies are driving wave after wave of exponential innovation, actively searching for emerging risks is one way in which policy can keep up with innovations and novel products. The contribution to safe innovation, which also includes weighing of risks and uncertainties, is an important evaluation of emerging technologies. There is a trend in cosmetics for generating substances which target biological pathways or induce epigenetic changes. In cosmetic products, one novel substance Dextralip®[11] claims to induce genes involved in cell renewal and DNA repair, and inhibits genes involved in inflammatory pathways. Dextralip® is expected to reach the market in October 2018. The health implications of skin care products targeting genes that are also known to be mutated or involved in carcinogenesis need further investigation. Similar concerns are raised for substances such as RoyalEpigenP5[12], a new and biologically-active peptide that activates skin regeneration and glow by accelerating epidermal regeneration for a smooth skin, activating the cellular cleaning process and delaying cell ageing by applying new discoveries in epigenetic sciences. Although the first actor to ensure that only safe cosmetic products are placed on the market is the producer, the health implications of skin care products targeting epigenetic mechanisms need further investigation. These cross-border products (pharmaceutical and cosmetic) are an important trend that needs to be on the radar of regulators.

[10] Terry C. Hrubec, Vanessa E. Melin, Caroline S. Shea, Elizabeth E. Ferguson, Craig Garofola, Claire M. Repine, Tyler W. Chapman, Hiral R. Patel, Reza M. Razvi, Jesse E. Sugrue, Haritha Potineni, Geraldine Magnin-Bissel, Patricia A. Hunt**. Ambient and dosed exposure to quaternary ammonium disinfectants causes neural tube defects in rodents**. *Birth Defects Research*, 2017; DOI: 10.1002/bdr2.1064

[11] http://northamerica.in-cosmetics.com/en/Exhibitors/1253485/ChemSpec-Polymer-Additives-Safic-Alcan-Group/Products/979024/DEXTRALIP-10C/

[12] https://www.cosmeticsbusiness.com/news/article_page/RoyalEpigen_P5__Rejuvenation_through_epigenetic_science/117137/

There are many challenges in the identification of NERCs in consumer products. With regard to signal identification, we need to keep up with consumer product innovation in a proactive (pre-marketing) and reactive (post-marketing) way. In this regard, the exchange of signals with (inter)national partners is considered vital. With regards to signal evaluation and prioritization, our methodology can be refined as more hazard and exposure information becomes available. Finally, for timely follow-up actions, improvement of NERCs communication is needed .

Keeping up with NERCs in consumer products could benefit from: 1) a platform for signal sharing and strengthening, thereby improving signal identification; 2) active discussions of new or emerging risks to improve data evaluation and NERC identification; 3) the proposal of timely follow-up actions when necessary.

3.2.3 Estimation of historical individual exposure to pesticides. A difficult task. (Herman Bartstra, NCvB)

The Solvent Team is part of the Netherlands Center for Occupational Diseases and focuses on examination of patients with possibly chronic encephalopathy caused by occupational exposure to neurotoxic chemicals. Additionally, development of peripheral neuropathy, cerebellar ataxia and Parkinson's disease by occupational exposure is examined. The team, consisting of clinical occupational physicians, neuropsychologists and an occupational hygienist, assesses in a multidisciplinary setting whether health issues could be related to occupational exposure.

During the workshop, the following case study was presented and discussed: A 59 years old man who works in the agriculture (cucumbers) was historically exposed to pesticides between 1981 and 1994. The worker did not recall any product name or active substance name, the only information available is against what kind of insects the pesticides were used. Without detailed information, it is difficult to search for product name and active substances, and their safety evaluations in databases.

Five databases were searched, however each had its own deficiencies:

- Only pathogens were included in the database, not agents which could be used to fight them. It was not possible to search on active chemical or product.
- Large collection of websites/databases, easy to overlook the database suitable for this specific question
- In databases of manufacturer current products are included in the database; historical products are not included
- Information on age groups not relevant for this specific case
- Information on diseases and (acute) health effects, for this question and search not relevant starting points

The focus on pathogens did not retrieve information on used products. In addition, for this case it is necessary to know which products were used in the period between 19981 – 1994, which is hard to find in databases focusing on fighting pathogens at the present time.

Difficulties in establishing pesticide exposure:

- Exposure occurs to a mixture of chemicals

- Exposure is variable over time
- Reliability of anamnesis given by worker is uncertain
- Historical data is difficult to reconstruct (company records, interviews)

The optimal result is retrieved by a combination of extended occupational history supplemented with literature research and, if possible, company visit. In addition, pictures of the occupational setting or used products are helpful too.

Databases often show acute toxicity or reprotoxic/carcinogenic properties of substances. In these case studies, it is important to make a sufficient estimation of the exposure to active neurotoxic chemicals (or mixtures) and then to search if neurotoxic effects are described in humans.

Information and knowledge exchange with other experts could help to find more information in these complex case studies.

This case study illustrated the difficulty to estimate historical exposure to pesticides of an individual and to make an occupational disease plausible.

3.3 Databases

The workshop considered quick wins that could enhance the information level for interested parties and stakeholders dealing with activities related to post marketing surveillance of chemicals. A first action was identified in the area of availability and sharing of information that could be relevant among the stakeholder group.

Several organisations in different fields provide databases with information on chemicals, products, health effects, or others. In the beginning of 2017, within the framework of this project, an overview of available databases was prepared (see Annex 2). This overview could help interested parties to realize which databases are available, what kind of information they provide, and how they can obtain access to individual databases.

To stimulate information exchange, the overview presented in Attachment 2 can be used as an inventory of databases. This listing is not necessarily complete, and may need updating over time. Moreover, in the future, dependent on funding and willingness of stakeholders, the development of tools providing more direct connections between databases can be considered.

Besides the database overview, details on information provided in the databases, and relevant links for contacting and accessing databases are provided (Annex 1). This inventory thus provides an overview of existing information sources that can facilitate exchange among the stakeholder network in the area of post marketing surveillance of chemicals.

4 Recommendations

The focus of this workshop was to brainstorm on how small steps can be taken towards creating a post-marketing surveillance network for chemicals, given that setting up a post-marketing surveillance system is complex. We focused on improvement of communication between organisations and experts and thereby on the increase of knowledge on chemicals or products.

The overall consensus among participants was that this exchange of information was very helpful, and it was recommended to keep in touch; to improve communication and learn from knowledge and experience available within the group. The extended overview of databases and organisations might help to find the right database or organisation to answer questions or to solve case studies more efficiently. Another idea mentioned was to initiate a web-based platform or forum for posing questions to the network of stakeholders , which might provide a more efficient means of information exchange among the network. Continuation of these ideas and initiatives will depend on the availability of resources, such as has been provided by VWS for the current project.

The organisation of meetings or workshops in a broader field could also help to improve communication between different stakeholders and increase knowledge on specific cases. WHO, RIVM and ANSES are planning a workshop on emerging risks. That would provide an opportunity to find out how other countries organize post-marketing surveillance for chemicals.

5 List of abbreviations

CBG	Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen)
CESES	Consumer Exposure Skin Effects and Surveillance
Ctgb	The Dutch Board for the Authorisation of Plant Protection Products and Biocides (College voor de toelating van gewasbeschermingsmiddelen en biociden)
EC	European Commission
ECHA	European Chemical Agency
EDQM	European Directorate for the Quality of Medicines
EFSA	European Food Safety Authority
EMA	European Medicines Agency
FAO	Food and Agriculture Organization
GZB	Centre for Health Protection (Centrum voor Gezondheidsbescherming)
IGJ	Health and Youth Care Inspectorate (Inspectie Gezondheidszorg en Jeugd)
IRGC	International Risk Governance Council
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LAREB	Netherlands Pharmacovigilance Centre Lareb (Bijwerkingencentrum Lareb)
MoM	Metal-on-metal
NCvB	Netherlands Center for Occupational Diseases (Nederlands Centrum voor Beroepsziekten)
NERC	New or Emerging Risks of Chemicals
NIH	U.S. National Institutes of Health
NVIC	Dutch National Poison Centre (Nationaal Vergiftigingen Informatie Centrum)
NVWA	Netherlands Food and Consumer Product Safety Authority (Nederlandse Voedsel- en Warenautoriteit)
PMS	Post Marketing Surveillance
RAPEX	Rapid alert system for dangerous non-food products
REACH	Regristration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu)
VPZ	Centre for Nutrition, Prevention and Health Services (Centrum voor Voeding, Preventie en Zorg)
VSP	Centre for Safety of Substances and Products (Centrum voor Veiligheid van Stoffen en Producten)
VWS	Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport)
WHO	World Health Organization

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7 Annex

Annex 1: Organisations and their expertise

Organisation	Field of expertise	Web address	Contact details
CBG	Regulation of the quality, efficacy and safety of medicines, and encourages better use of medicines for the right patient	https://www.cbg-meb.nl/	+31 88 224 8000
Ctgb	Safety assessment of plant protection products and biocidal products	https://www.ctgb.nl/	+31 317 471 810
ECHA	Chemicals legislation and regulation	https://echa.europa.eu/	
EDQM	Quality standards for safe medicines and their safe use	https://www.edqm.eu/	
EFSA	Food and feed safety assessment, including animal health and welfare, plant protection and plant health	http://www.efsa.europa.eu/	
EMA	Evaluation and supervision of medicines	http://www.ema.europa.eu/ema/	
IGJ	Supervision of the quality, safety and accessibility of health care, and guards the rights of patients	https://www.igj.nl/	+31 88 120 5000
JECFA (WHO/FAO)	Risk assessment of food additives, flavouring agents, residues of vetinary drugs in animal products, contaminants, and natural toxins	http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/	
JMPR (WHO/FAO)	Risk assessment of pesticide residues	http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/	
LAREB	Identification of risks associated with the use of medicines in daily practice and is the Knowledge Centre for adverse drugs reactions (ADRs)	https://www.lareb.nl/	+31 73 646 9700
NCvB	National registration of occupational diseases	https://www.beroepsziekten.nl/ncvb	+31 20 566 5387
NVIC	Information on health	https://www.vergiftig	+31 30 274 8888

	effects and treatment in the case of poisoning	ingen.info/home.htm	
NVWA	Safeguards the health of animals and plants, animal welfare and the safety of food and consumer products and maintains the legislation in the field of nature	https://www.nvwa.nl/	+31 900 03 88
RIVM	Research and advice on public and environmental health	http://www.rivm.nl/	+31 30 274 9111
Zorginstituut Nederland	Health care in the Netherlands	https://www.zorginstituutnederland.nl/	+31 20 797 8555
Abbreviations: CBG: College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board; Ctgb: College voor de toelating van gewasbeschermingsmiddelen en biociden, the Dutch Board for the Authorisation of Plant Protection Products and Biocides; EFSA: European Food Safety Authority; EMA: European Medicines Agency; IGJ: Inspectie Gezondheidszorg en Jeugd, Health and Youth Care Inspectorate; LAREB: Bijwerkingencentrum Lareb, Netherlands Pharmacovigilance Centre Lareb; NCvB: Nederlands Centrum voor Beroepsziekten, Netherlands Center for Occupational Diseases; NIH: U.S. National Institutes of Health; NVIC: Nationaal Vergiftigingen Informatie Centrum, National Poison Centre; NVWA: Nederlandse Voedsel- en Warenautoriteit, Netherlands Food and Consumer Product Safety Authority; RIVM: Rijksinstituut voor Volksgezondheid en Milieu, National Institute for Public Health and the Environment; WHO: World Health Organization			

Annex 2: Overview of databases available for the purpose of PMS

Nr	Database subscription	Information details	Organisation	Website
Medicines				
1	(Veterinary) medicines	Information on medicines that are approved in the Nederlands, from scientific research to consumer information.	CBG	https://www.cbg-meb.nl/geneesmiddeleninformatiebank
2	Information on health effects and treatment in case of poisoning	Information on toxic substance(s) that are present in products	NVIC	https://www.vergiftigingen.info/stofmonografie_inzien.htm?execution=e2s1
3	Active substances in veterinary medicines	Maximum Residue Limit (MRL) assessment reports for active substances contained in veterinary medicines (open access tox data and – experimental – residu data) found in food products of animal origin.	EMA	http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/vet_mrl_search.jsp&mid=WC0b01ac058008d7ad
4	Medicines, human, veterinary and herbal	Scientific assessment reports.	EMA	http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=
5	Adverse drug reactions	Information on adverse drug reactions for medicines or vaccines	LAREB	https://www.lareb.nl/nl/databank
	European database on suspected side effects geneesmiddelen	Information on suspected side effects for medicines or active substances, including information on case studies.	EMA (EU)	http://www.adrreports.eu/nl/index.html
	Adverse effects of veterinary medicines		EMA	EVVet database http://eudravigilance.ema.europa.eu/veterinary/mah.html No public access

6	European Pharmacopoeia		EDQM	http://online.edqm.eu/EN/entry.htm Registration required
7	Martindale: The Complete Drug Reference	Information on drugs in clinical use worldwide, as well as selected investigational and veterinary drugs, herbal and complementary medicines, pharmaceutical excipients, vitamins and nutritional agents, vaccines, radiopharmaceuticals, contrast media and diagnostic agents, medicinal gases, drugs of abuse and recreational drugs, toxic substances, disinfectants, and pesticides.	Martindale Medicines Complete	https://www.medicinescomplete.com/mc/martindale/current/ Registration required
8	JECFA monographs	Toxicological evaluations of food additives and contaminants and of residues of veterinary drugs in food, produced by the Joint WHO/FAO Expert Committee on Food Additives JECFA	JECFA (WHO/FAO)	http://www.inchem.org/pages/jecfa.html
9	Information on medicines approved in the Netherlands	Information about medicines, such as composition, dose, side effects, interactions, use during pregnancy, or pharmacokinetic information	Zorginstituut Nederland	https://www.farmacotherapeutischkompas.nl/
Food				
10	Rapid Alert System for Food and Feed (RASFF)	Access to summary information about the most recently transmitted RASFF	European Commission	https://webgate.ec.europa.eu/rasff-window/portal/

		notifications as well as the ability to search for information on any notification issued in the past.		
Biocides / Pesticides				
11	Approved pesticides and biocides	Information on admission of approved products	Ctgb	https://toelatingen.ctgb.nl/
12	EU Pesticide database	Search based on active substances, products or pesticide residues	European Commission	http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=homepage&language=EN
13	Information on food contaminants, packaging materials and additives		European Commission	https://ec.europa.eu/food/safety/chemical_safety/contaminants_en
14	Pesticide database	Evaluation of pesticides	JMPR (FAO/WHO)	http://apps.who.int/pesticide-residues-jmpr-database http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/lpe/en/
15	ECHA database for REACH chemicals and biocides	Information on chemicals registered in Europe	ECHA	https://echa.europa.eu/nl/information-on-chemicals
16	Overview of databases	Links to different databases, such as information on agents, insects, crop diseases		http://gewasbescherming.startpagina.nl/
17	Overview of reports related to pesticide exposure and health effects	Reports which can provide information on pesticide exposure and related health effects, such as the module of pesticide illness	California Department of Public Health	https://www.cdph.ca.gov/Programs/CCDPHP/DEODC/OHB/OPIPP/Pages/PesticidePubs.aspx# , where you can find the module Pesticide Illness http://www.aoec.org/content/resources_1_3_1.htm

Additives				
18	Relevante informatie over additieven	This searchable database contains the summaries of all the evaluations of flavours, food additives, contaminants, toxicants and veterinary drugs JECFA has performed.	JECFA (WHO/FAO)	http://apps.who.int/food-additives-contaminants-jecfa-database/search.aspx http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/
19	EU register Food additives	Food additives approved for use in food in the EU and their conditions of use.	European Commission	https://ec.europa.eu/food/safety/food_improvement_agents/additives/database_en
20	EU register Feed additives	Documents on registration of feed additives	European Commission	http://ec.europa.eu/food/safety/animal-feed/feed-additives/eu-register_en
Consumer products in general				
21	Information on health effects and treatment in case of poisoning	Information on toxic substance(s) that are present in products	NVIC	https://www.vergiftigingen.info/stofmonografie_inzien.htm?execution=e2s1
Others				
22	Registration of occupational diseases	Information on occupational diseases: clinical effects, causes, and prevention	NCvB	https://www.beroepsziekten.nl/beroepenindex
23	Registration possible incidents with chemicals		NVWA	Confidential database of NVWA (MOS: Meldingenondersteuningssysteem)
24	Human and environmental chemical risk	Information per chemical	RIVM	http://www.rivm.nl/rvs/
25	Quality Programme for Agricultural Products (KAP) database about residue monitoring.	Information about residue monitoring in the Netherlands. The database contains information on meat and meat products, fruit and vegetables, fish, milk and feeding-stuffs.	RIVM	https://chemkap.rivm.nl/en/Topics/C/ChemKAP/ (no public access)

26	Hazardous substances database (HSDB)	Focus on toxicology of potentially hazardous chemicals. It provides information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, nanomaterials, and related areas.	NIH	https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm
27	OpenFoodTox - Chemical Hazards database	Compilation of a database, specific for the pesticide active substance and their metabolites, comprising the main genotoxicity endpoints	EFSA	https://dwh.efsa.europa.eu/bi/asp/Main.aspx?rwtrep=400 Doi:10.2903/sp.efsa.2017.EN-1229

Abbreviations: CBG: College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board; Ctgb: College voor de toelating van gewasbeschermingsmiddelen en biociden, the Dutch Board for the Authorisation of Plant Protection Products and Biocides; EC: European Commission; ECHA: European Chemical Agency; EDQM: European Directorate for the Quality of Medicines; EFSA: European Food Safety Authority; EMA: European Medicines Agency; FAO: Food and Agriculture Organization; IGZ: Inspectie Gezondheidszorg en Jeugd, Health and Youth Care Inspectorate; JECFA: Joint FAO/WHO Expert Committee on Food Additives; JMPR: Joint FAO/WHO Meeting on Pesticide Residues; LAREB: Bijwerkingencentrum Lareb, Netherlands Pharmacovigilance Centre Lareb; NCvB: Nederlands Centrum voor Beroepsziekten, Netherlands Center for Occupational Diseases; NIH: U.S. National Institutes of Health; NVIC: Nationaal Vergiftigingen Informatie Centrum, National Poison Centre; NVWA: Nederlandse Voedsel- en Warenautoriteit, Netherlands Food and Consumer Product Safety Authority; RIVM: Rijksinstituut voor Volksgezondheid en Milieu, National Institute for Public Health and the Environment; WHO: World Health Organization

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