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

Brainstorming opportunities for post-marketing surveillance of chemicals

Workshop report

RIVM Letter report 2016-0169
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Synopsis

Brainstorming opportunities for post-marketing surveillance of chemicals
Workshop report

On behalf of the Ministry of Health a survey was prepared of possibilities for setting up a 'post-marketing surveillance' (PMS)-system for chemical substances in consumer products, including food. With such a system, (long-term) health effects of substances which are already on the market may be identified. Setting up such a system was advised by the Health Council of The Netherlands (GR) based on a report from 2014. In this report, GR concluded that PMS of chemicals is warranted given that certain health effects in humans may not become visible in animal studies used for risk assessment.

First, a preliminary overview of current PMS related activities in different areas of legislation, such as food, drugs and consumer products, was prepared. Existing experience in different legislative frameworks can feed into a new system. Relevant national stakeholders have contributed to the overview, and have discussed short and long-term opportunities for further development of PMS. Possible short-term options included sharing existing information, to connect different existing databases and to share new information about health effects of chemicals on an ad hoc basis.

For the longer term, exposure assessment directly in humans or for example in blood samples stored in biobanks were considered. In addition, more extensive registration of the use of compounds in consumer products was advised, as well as international harmonization of PMS data collection. It was advised to establish a working group with stakeholders to expand this initiative and to exchange ad hoc information on a regular basis.

Keywords: post-marketing surveillance, chemicals, consumer products, medicines, food, stakeholders, regulatory framework, signaling

Publiekssamenvatting

Post-marketing surveillance van stoffen

In opdracht van VWS heeft het RIVM een eerste inventarisatie gemaakt van mogelijkheden om een ‘post marketing surveillance’-systeem (PMS) voor chemische stoffen in consumentenproducten, inclusief voeding, op te zetten. Met een dergelijk systeem worden signalen over schadelijke (langetermijn)effecten van stoffen in kaart gebracht, *nadat* ze op de markt zijn gebracht. Aanleiding hiervoor is een voorstel van de Gezondheidsraad om een PMS in te richten. De raad concludeerde namelijk in 2014 dat mogelijk niet alle relevante effecten van stoffen op de volksgezondheid uit (proefdier)onderzoek worden opgepikt, waardoor ze niet vooraf in de risicobeoordeling worden meegenomen.

Voor de inventarisatie is eerst een globaal overzicht opgesteld welke post-marketing-surveillance activiteiten op het gebied van onder andere voeding, geneesmiddelen en consumentenproducten al worden uitgevoerd. Van de ervaringen uit deze ‘kaders’ kan immers gebruik worden gemaakt. Verschillende stakeholders binnen de overheid hebben het overzicht vervolgens aangevuld en hebben mogelijkheden voor aanpassingen op de korte en lange termijn besproken. Voor de korte termijn raden zij aan kennis uit verschillende kaders met elkaar te delen, bestaande databases aan elkaar te koppelen en elkaar te informeren over effecten van chemische stoffen die ad hoc worden gesignaleerd.

Voor de toekomst wordt meer aansluiting gezocht bij metingen van blootstelling direct in de mens, dan wel via metingen in bijvoorbeeld bloedmonsters die in biobanken zijn opgeslagen. Ook wordt een intensievere registratie van het gebruik van stoffen in consumentenproducten voorgesteld, en een methode om PMS-data internationaal op uniforme manier te verzamelen. Geadviseerd wordt om de input met de stakeholders te structureren in de vorm van een werkgroep.

Kernwoorden: post-marketing surveillance, chemicalien, consumenten producten, geneesmiddelen, voeding, stakeholders, regulatoir framework, signalering

Contents

Summary

The Health Council (GR) concluded in the report, "Risks of perinatal exposure to substances" of 2014 that certain relevant health effects for humans may not become visible in animal studies. The GR therefore advised to set up a "post-marketing surveillance system" to identify (long-term) effects of substances already on the market.

On behalf of the ministry of Health the possibilities for setting up a ‘post-marketing surveillance’ (PMS)-system for chemical substances in consumer products (including food) was explored. First, an overview of current PMS activities in different regulatory frameworks was prepared. Next, during a workshop with relevant national stakeholders the possibility of setting up a PMS system for chemical substances in more general was explored, using the overview of the already existing PMS activities as a starting point of the discussion.

During the workshop gaps and opportunities for short and long-term improvement of a more general and integrated post-marketing surveillance system were identified. Possible short-term options included coupling existing databases, sharing existing and new information and installing a national discussion group for regular and/or ad hoc information sharing. Potential longer-term options were international harmonization of regulations and terminology, and creating a registration system of the use and application of all substances in consumer products.

1 Introduction

1.1 Background

The general population is exposed to a large number of chemicals, food, consumer products and medicines on a regular basis. The majority of these substances are tested, some more extensively than others, for safety before they are placed on the market, However, the question remains whether they are all safe in real life in the human population and whether current surveillance systems are sufficient to detect possible safety problems.

The Health Council of the Netherlands expressed their concerns on the available post marketing surveillance (PMS) information of chemicals in a report focused on health effects of prenatal exposure (Gezondheidsraad, 2014). The Health Council wondered whether relationships between exposure to substances early in life and certain health effects may be missed under the current practice. Safety assessment of chemicals today is mainly based on *in vitro* and *in vivo* studies in animals, and sometimes on studies in humans. It cannot be excluded that certain relevant health effects caused by exposure to chemicals may not become visible in these studies, for example, because effects may be rare or only manifest later in life.

PMS may or may not be the best descriptive term of choice for the proposed activity. Terms like ‘early warning system’ and ‘new emerging risks’ are also being employed to describe new activities to improve the information level of the application, use and fate of chemicals, and their human exposure and possible health consequences. PMS information on health effects after exposure can be collected in a pro-active or reactive manner. Monitoring is an example of pro-active PMS. Reactive PMS refers to acting on health incidents/ adverse events that occur after (often acute) exposure. Only the pharmaceutical regulatory framework has a formal PMS system including pro-active and reactive PMS. Based on our first analysis, in 2015, of PMS activities in regulatory frameworks of medicines, food, cosmetics and industrial chemicals, we concluded that significant differences between the regulatory frameworks exist. For the food and chemical regulatory frameworks, no formal PMS system was in place that covered the entire life cycle of substances, but mostly only individual aspects of reactive PMS activities.

Given this current situation, and in view of the advice of the Health Council, it appeared both warranted and worthwhile to consider whether, to what extent and how a more formal system of PMS suitable for several regulatory frameworks should and could be defined and introduced. The aim of this project was to identify gaps in PMS activities and identify opportunities for improvement towards a general and integrated PMS system. To that end a workshop was organized with relevant stakeholders from governmental organizations. An initial overview of current PMS activities in view of relevant regulatory frameworks was prepared and used as supporting material for the workshop discussion.

1.2 Method

In 2015 we prepared first an inventory of the different stakeholders and their activities in pre-marketing / authorization and PMS of medicines, since for this regulatory area the most extensive PMS system is in place. We subsequently included in this inventory industrial chemicals, foods and cosmetics. In 2016, this inventory was expanded for other regulations: medical devices, other consumer products besides cosmetics, and different food-related regulations. This resulted in a general and not necessarily complete overview of the different stakeholders and their current pre-marketing / authorization and PMS activities related to these regulatory frameworks. Based on the regulatory frameworks included in this overview several national stakeholders were invited to take part in a workshop on the 13th of June 2016 at RIVM. During this workshop the overview of stakeholders and their activities were presented and the overview was used as supporting material for the discussion. The discussion focussed on the identification of gaps in PMS and the formulation of recommendations for further improvement of PMS in the non-pharmaceutical areas addressed.

2 Workshop preparation

2.1 Overview of post-marketing surveillance strategies

The workshop preparation comprised making an overview of current PMS strategies of several regulatory frameworks. This overview provided background information for the participants of the workshop without pretending or aiming to be complete in all possible detail, and was used to trigger the workshop discussion. The regulatory frameworks which were included in this overview were medicines, medical devices, consumer products and food. The regulatory frameworks of consumer products and food comprised different categories, as presented in Table 1.

Table 1: Different regulatory frameworks of consumer products and food-related categories

Consumer products categories	Food-related categories
Cosmetics (Co)	Plant protection products (PPP)
Chemicals/ REACH/ CLP (Ch)	Biocides (B)
Toys (T)	Veterinary medicinal products (VMP)
Detergents (D)	
General product safety (GPS)	Food contact materials (FCM)
	Novel foods (NF)
	Food additives (FA)
	Enzymes (E)
	Flavourings (F)
	Herbs (H)
	Feed additives (FeA)
	Contaminants (C)

Since pre-marketing and authorization are not the same for all regulatory frameworks, and since it can affect the activities performed during PMS, the stakeholders and their actions and responsibilities before a product is available on the market were also included. PMS activities were split into “notification”, “risk evaluation” and “risk management”. “Notification” describes the pro-active and re-active PMS and the stakeholders that are involved. The information collected during the “notification” is subsequently evaluated; especially the relationship between exposure and the health effect is assessed. “Risk evaluation” describes the stakeholders and their actions during this process. After the association between exposure and health effect is confirmed, the actions taken by the stakeholder to minimize the risk in the future are described in “Risk management”.

An overview of 1) pre-marketing and authorization, 2) notification, 3) risk evaluation and 4) risk management of different regulatory frameworks is presented in Attachment 1, including national and international stakeholders. Differences between regulatory frameworks were especially seen during the pre-marketing/ authorization phase, as we described in the previous report of 2015. Not only the stakeholders involved, but also the responsibilities and activities were not similar. This was important to realize during the workshop discussion. Since

notification is an essential step in a PMS strategy, this was the focus of the workshop discussion. Stakeholders involved in the notification were often also involved in the risk evaluation and/or risk management.

2.2 Selection of stakeholders for workshop

We identified national and international stakeholders. To start the discussion we choose to invite national stakeholders from governmental organisations. Some stakeholders were involved in more than one area of regulation. Relevant Dutch stakeholders of all areas of regulation were invited to the workshop PMS, as well as several experts on the different regulatory frameworks of three different centers of the RIVM, including Bureau REACH. The national stakeholders outside RIVM were the Ministry of Health, Welfare and Sport (VWS), Netherlands Food and Consumer Product Safety Authority (NVWA), National Poisons Information Centre (NVIC), Medicines Evaluation Board (CBG), The Netherlands Pharmacovigilance Centre Lareb (LAREB) and Health Care Inspectorate (IGZ). Participants are presented in Table 2.

Table 2: Participants of governmental organization at the Workshop postmarketing surveillance on the 13th of June 2016 at the National Institute for Public Health and the Environment (RIVM)

Governmental organisation	**Participants**
CBG	Ms Ineke Crijns
	Ms Anita Volkers
IGZ	Ms Sietske Eerens
LAREB	Ms Linda Harmark
NVIC	Mr Ronald de Groot
NVWA	Mr Dirk Van Aken
RIVM	Mr Walter Brand
	Ms Astrid Bulder
	Mr Arjan van Drongelen
	Mr Coen Graven
	Ms Joke Herremans
	Mr Elbert Hogendoorn
	Mr Dries de Kaste
	Mr Marcel Mengelers
	Ms Evelyn Olthof
	Ms Bernadette Ossendorp
	Mr Aldert Piersma
VWS	Mr Koen van der Kroef
	Mr Wouter Lips
	Mr Martijn Martena

3 Workshop Post-marketing surveillance

3.1 Opening and introduction

On 13 June 2016, the Workshop Post-marketing surveillance was organized at the RIVM in Bilthoven, the Netherlands. Participants of the workshop were representatives of the ministry of VWS, NVWA, NVIC, CBG, LAREB, IGZ and of the centers Centre for health protection (GZB), Centre for Nutrition, Prevention and Health Services (VPZ) and Centre for Safety of Substances and Products (VSP) of the RIVM, including Bureau REACH.

A general introduction and review was given of the table as presented in this report (Attachment 1). It was stipulated that the table was meant to provide a general overview of activities that might serve as possible components of what might in due course become a more integral PMS system for chemicals in the widest sense. It provided background to set the scene for the workshop discussion, without pretending or aiming to be complete in all possible detail. Subsequently, the three subgroups 1) chemicals/consumer products, 2) food, and 3) medicines/medical devices were formed at the workshop with experts from each area. They discussed opportunities for improvement for monitoring the fate of substances, from production to application and use, and including human exposure and possible health effects. Specific attention was given to the identification of possible quick wins on the one hand and to the formulation of possible strategies for the long term on the other hand.

3.2 Summary from discussion groups and general discussion

As expected, a number of existing formal and informal communication channels between different regulatory frameworks were identified in the breakout group discussions, which were not included in the table. A general recommendation was to make sure that any new PMS initiative does not duplicate activities already existing in well-functioning systems. However, whilst making optimal use of existing systems and processes, new activities should provide added value by connecting the entire production-to-use chain as well as including all regulatory frameworks. Substances may be employed under different legislation simultaneously, e.g. a substance may be used as a food additive and as a drug stabilizer as well. Therefore, signaling of a possible substance-related health issue occurring in one use category should be communicated to other areas of use to combine all available information and to efficiently decide on well-informed and harmonized action elsewhere as necessary. As an example, the melamine baby milk health issue in China was preceded a year earlier by a melamine health issue in the US in cat and dog feed.

Broader communication of the US information might have precluded the issue in China. Other examples mentioned include vitamins and pharmaceuticals and food supplements, plasticizers in medical devices and in toys, and exposure from medical devices to patients and health care workers.

The Dutch National Poisoning Information Center (NVIC) database contains extensive information on consumer product composition. Similar and complementary databases exist in other application areas and in different European countries. In addition, European research projects collect data on e.g. emerging risks and chemical mixtures. Challenges include identifying relevant data sources, connecting or cross-referencing information sources, stratifying their information level and to provide low threshold online search facilities. This can be considered initially at the national level, and broadened to the European and global levels in due course. Moreover, it was mentioned that in other countries well-functioning systems regarding components of such a system already exist that should be considered in advance to avoid reinventing the wheel.

Coupling of information between regulatory frameworks as well as between countries worldwide requires overall harmonization. This includes terminology, product categories, local legislation, quality control, and minimal information requirements. It was suggested that a harmonized app could be designed for self reporting of health issues, such as already exists for air pollution related health issues (http://ikheblastapp.nl/).

In the medicines area several information sources exist that deserve consideration in the wider context. Public registers of adverse events, as well as scientific societies and patient groups come to mind, all of which have extensive and often complementary information. In addition, information is increasingly shared via the internet. The Dutch Medicines Evaluation Board (CBG/MEB) interacts with patient communities to share information in both directions. The Personal Health Dossier (in addition to the Electronic Patient Dossier) is under development. This dossier will include lifestyle and environmental aspects of health. Important issues with these systems and their interaction are quality control and responsibility for keeping information up to date, as well as proprietary issues, not to speak of the necessary continuous financial support.

Worldwide many human cohort studies are ongoing in which substance exposure and health are monitored. These cohort studies could be expanded and streamlined in terms of parameters assessed based on health issues and substances of interest. Furthermore, cohort data could also be components of an integral substance information system that provides updated information on substance exposure and health. The ongoing European human biomonitoring project initiative could play a central role herein. Biobanks of human tissues sampled over the years can provide rich data sources for studying possible exposure-effect relationships.

It might be useful to install a register of substances for which risk regulation measures are in place, describing the related regulatory framework, the applicable risk regulation measure and the reasons for the restrictive action. Such information should be available and actively communicated so that timely and well-informed action can also be taken in other regulatory frameworks as necessary. It is currently still possible that a medicine is taken off the market after which the active substance reappears as a food supplement. Overall access to available safety

information will support timely further decisions and may preclude health issues.

Consumer awareness of the presence of chemical substances in consumer products should be stimulated, enabling the safe use and/or choice for alternatives. Data sources should be public and easily accessible and information should be understandable. One central counter (website) should be available, commonly accepted as the primary trusted information source and as the preferred place to signal issues.

3.3 Workshop recommendations

3.3.1 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.

3.3.2 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 safety information on substances between representatives from regulatory frameworks.

The central issues for information exchange: emerging issues, elaboration of explicit proposals, including feasibility assessment of quick wins and long-term goals as mentioned in this report.

4 List of abbreviations

B	Biocides
C	Contaminants
CBG	College ter Beoordeling van Geneesmiddelen
CE	Conformité Européenne
CESES	Consumer Exposure Skin Effects and Surveillance
Ch	chemicals/REACH/ CLP
CHMP	Committee for Medicinal Products for Human Use
Co	Cosmetics
CRD	Commissie Registratie Diergeneesmiddelen
CTGB	College voor de toelating van gewasbeschermings-middelen en biociden
D	Detergents
E	Enzymes
ECHA	European Chemical Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
EZ	Ministerie van Economische Zaken
F	Flavourings
FA	Food Additives
FCM	Food Contact Materials
FeA	Feed Additives
GPS	General Product Safety
GZB	Centrum voor Gezondheidsbescherming
H	Herbs
IGZ	Inspectie Gezondheidszorg
LAREB	Landelijke registratie en evaluatie bijwerkingen van geneesmiddelen
MRL	Maximum Residu Limit
NF	Novel Foods
NVIC	Nationaal Vergiftigingen Informatie Centrum
NVWA	Nederlandse Voedsel- en Warenautoriteit
PMS	Post-Marketing Surveillance
PPP	Plant Protection Products
PRAC	Pharmacovigilance Risk Assessment Committee
RASFF	Rapid Alert System for Food and Feed
RAPEX	The Rapid Alert System for non-food dangerous products
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
SCCS	Scientific Committee on Consumer Safety
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SCoPAFF	Standing Committee on Plants, Animals, Food and Feed
SVHC	Substance of Very High Concern
T	Toys
VMP	Vetenary Medicinal Products
VSP	Centrum Veiligheid van Stoffen en Producten
VPZ	Centrum voor Voeding, Preventie en Zorg
VWS	Ministerie van Volksgezondheid, Welzijn en Sport

5 Attachment

Attachment 1: Inventory of stakeholders and their pre-marketing/ authorization and post-marketing surveillance activities for different regulatory frameworks: medicines, medical devices, consumer products and food. - The regulatory frameworks of consumer products comprised different categories, including cosmetics (Co), chemicals/ REACH/ CLP (Ch), toys (T), detergents (D) and general product safety (GPS). Food-related regulatory frameworks which were described were plant protection products (PPP), biocides (B), veterinary medicinal products (VMP), food contact materials (FCM), novel foods (NF), food additives (FA), enzymes (E), flavourings (F), herbs (H), feed additives (FeA) and contaminants (C).

	PRE-MARKETING/ AUTHORIZATION		NOTIFICATION		RISK EVALUATION		RISK MANAGEMENT	
	Stakeholder	**Action**	**Stakeholder**	**Action**	**Stakeholder**	**Action**	**Stakeholder**	**Action**
MEDICINES	**CBG/ EMA**	Efficacy, safety, quality evaluation	**NVIC/LAREB**	Report adverse event (obligatory doctor/ pharmacist)	**NVIC/LAREB**	Evaluate causal relationship adverse event	**CBG/ EMA/ PRAC within EMA**	Adjustment Risk management plan or remove from the market
			Manufacturer	Pharmacovigilance				
	PRAC within EMA	Risk management plan (obligatory)	**IGZ**	Inspection	**CBG/EMA**	International evaluation adverse event	**IGZ**	Oversight on actions and intervention if needed
	CHMP	Safety specification	**EMA/CBG**	Report serious adverse events: EurdraVigilance database				
	Manufacturers	Testing, clinical evaluation, prepare documentation and market authorization	**Users/Health Care Professionals**	Notify problems/issues	**Manufacturers**	Perform risk evaluation	**Manufacturer**	Perform corrective actions if needed
	PRE-MARKETING/ AUTHORIZATION		NOTIFICATION		RISK EVALUATION		RISK MANAGEMENT	
	Stakeholder	**Action**	**Stakeholder**	**Action**	**Stakeholder**	**Action**	**Stakeholder**	**Action**
MEDICAL DEVICES	**Manufacturer**	testing, clinical evaluation, performing risk analysis, prepare documentation and authorization CE mark	**Manufacturers**	Receives information on safety and performance, importers and distributors involved, reports serious events to competent authority	**Manufacturer**	Evaluate safety and performance information: unforeseen risk? Higher risk than foreseen?	**Manufacturer**	recall of that product, a 'dear doctor' letter, and other corrective or preventive actions, e.g. change in design, changes in manufacturing.
	Notified body (if applicable)	CE mark/ authorization (class IIa, IIb and III)						
	Notified body + EMA/ CBG (if medicinal substance)	CE mark/ authorization (devices containing medicinal substance)	**Professional users, IGZ**	Severe adverse incidents reported by professional users of medical device	**IGZ**	Oversight of actions and decisions taken by manufacturer in case of serious events.	**IGZ**	Oversight of actions by manufacturer and action if needed
	IGZ	CE mark / notification registration (class I)	**Notified bodies**	Include PMS in audits			**Notified body**	Include PMS in audits
					Professional users	Quality registries		
	PRE-MARKETING/ AUTHORIZATION		NOTIFICATION		RISK EVALUATION		RISK MANAGEMENT	
	Stakeholder	**Action**	**Stakeholder**	**Action**	**Stakeholder**	**Action**	**Stakeholder**	**Action**
FOOD IN GENERAL (specified for a subgroup)	**CBG** (VMP)	Quality, efficacy, safety evaluation	**Producer/ sector/ consumer** (B, FCM, NF, FA, E, F, H, FeA, C)	Report adverse events	**NVWA/RIVM** (PPP, B, VMP, FCM, NF, FA, E, F, H, FeA, C)	Adverse event evaluation (VMP, FCM, NF, FA, E, F, H, FeA, C), post-registration dietary risk assessment (PPP, B)	**NVWA** (PPP, B, FCM, NF, FA, E, F, H, FeA, C)	Withdraw food product from market, RASFF
	University data	Compound evaluation (all legislations)					**CBG/EMA** (VMP)	Withdrawn from market
	CTGB (PPP, B)	Preparation evaluation active substance (PPP, B),	**NVWA** (PPP, B, VMP, NF, FA, H,	Targeted and random monitoring, inspection	**NVIC** (PPP, B, VMP, NF, H, FeA,	Evaluation, Treatment/ advise in case of	**SCoPAFF** (FA)&	Risk reduction measures, withdrawal from market

		MRL evaluation/proposal (PPP), product authorization (PPP, B)	FeA, C)	(PPP, B, VMP, NF, FA, H, FeA, C), Residue monitoring plan (VMP), Rapid alert system for food and feed (RASFF): international warning system	C)	accidents	EU Commission	Withdrawal active substance from the market (PPP, B) Withdrawal PPP or Biocidal products from the market. (PPP, B)
	CRD/EZ/VWS (VMP)	Authorization			**Centrum voor beroepsziekten** (PPP)	Evaluate adverse event	CTGB	Risk reduction measures, withdrawal from market Withdrawal active substance from the market (PPP, B) Withdrawal PPP or Biocidal products from the market. (PPP, B)
	European Commission (VMP, NF, F, FeA,B)	Final decision MRL (VMP), authorization (NF, F, FeA), compound registration (B)	**NVIC** (NF, H, C)	Report adverse event	**CBG/EMA** (VMP)	Adverse event evaluation		
	SCoPAFF EU Commission (C, PPP, FA, E)	Final decision, authorization, MRL decision (PPP), FCM, H, C	**Centrum voor beroepsziekten** (PPP)	Report adverse event	**EFSA** (C, FA, F, PPP)	Re-evaluation program (FA), international risk evaluation (F), monitoring (PPP)		
	EFSA (PPP, FCM, NF, FA, E, F, H, FeA, C biocides)	Compound evaluation (FCM, H, C, PPP, NF, FA, E, F, H, FeA, C), MRL evaluation (PPP), SML evaluation (FCM)	**CBG/ EMA** (VMP)	Report adverse event			VWS (FCM, H)	Risk reduction measures, withdrawal from market
	ECHA (B)	Compound evaluation (B)						
	EMA (VMP)	Assessment of MRL						
CONSUMER PRODUCTS IN GENERAL (specified for a subgroup)	**PRE-MARKETING/ AUTHORIZATION**		**NOTIFICATION**		**RISK EVALUATION**		**RISK MANAGEMENT**	
	Stakeholders	Action	**Stakeholders**	**Action**	**Stakeholders**	**Action**	**Stakeholders**	**Action**
	Manufacturer/Producer/downstream user (Co, Ch, T, D, GPS)	Safety evaluation (Co), only safe products on market (Ch, GPS), enable identification of toy/ product (T, GPS), labeling requirements (Ch, D)	**Consumer** (Co, T, D, GPS)	Report adverse event: in cosmeticaklachten.nl (NVWA) (Co), to NVWA (T, D, GPS)	**Manufacturer/Producer/downstream user** (Co, Ch)	Provide additional safety evaluation (Co), safety assessment (Ch)	**Manufacturer/ Producer** (Co, Ch, T, D, GPS)/ downstream user (Ch)	Voluntary risk management measures (Co, Ch, T, D, GPS), withdraw or recall product from market (T, GPS, D, Ch)
	Notified body (T)	CE marking (T)	**Producer/Sector/ Manufacturer (responsible person)/Downstream user** (Co, T, D, GPS)	Report serious adverse event (Co, T, D), collect (safety) complaints of consumers (T, D, GPS)	**NVWA** (Co, Ch, T, D, GPS)	Adverse event evaluation (Co, Ch, T, D, GPS)	**National government/ European commission** (Co, T, D, GPS)	Adjust regulation, (partial) ban (Co), reevaluation of harmonized standard (T), risk reduction (D), risk reduction e.g. by (revision of) European Product standards, ban, need for additional safety

								information (GPS)
	SCCS/ SCHEER (Co, T)	Safety evaluation (Co), Advice European commission: migration and safety limits (T)	**Dermatologist** (Co)	Report adverse event in CESES (voluntary in NL) (Co)	**NVIC** (Co, Ch, T, D, GPS)	Adverse event evaluation (Co, T, D, GPS), treatment/advice (Ch)	**Bureau REACH** (Ch)	Risk management options analysis (Ch)
	National Government (GPS)	National standards Voluntary standards (GPS)	**NVWA** (Co, Ch, T, D, GPS)	Report serious adverse event in European System for the rapid exchange of information (RAPEX) (Co, Ch, T, D, GPS) Targeted and random monitoring, inspection (Co, T, D, GPS)	**National government in SCCS/ SCHEER** (Co, T, GPS)	Safety evaluation (Co), Risk assessment (T, GPS)	**NVWA** (T, D, GPS)	Withdraw or recall product from market (T, D, GPS)
	Bureau REACH (Ch)	National implementation REACH (Ch)	**NVIC** (Co, Ch, T, D, GPS)	report (serious) adverse event (Co, Ch, T, D, GPS)	**Bureau REACH** (Ch)	Prioritize substance for (re-)evaluation internally or request to ECHA: substance evaluation/ restriction/identification as SVHC/authorization (Ch)	**ECHA**(Ch)	Proposal for risk management, classification (additional information, restriction on production/use of the substance) (Ch)
	ECHA (Ch)	Implementation REACH, authorization (Ch)	**Bureau REACH and ECHA** (Ch)	Identification of (emerging) risks, identification of substances of very high concern (Ch)	**ECHA** (Ch)	Prioritize substance for (Re-)Evaluation in the process: substance evaluation/restriction/identification as SVHC/authorization (Ch)	**European Commission** (Ch, D)	Adjust regulation, restriction, authorization (Ch), risk reduction measures (D)
	EU Commission (Co, T, D, GPS)	Safe concentration limits, conditions of use (Co), Final decision migration and safety limits (T), labelling requirements (D), safety recommendation (GPS)			**EU Commission** (Co, GPS)	Mandate safety evaluation (Co), risk evaluation (GPS)		
	EU standardization bodies (GPS)	Setting product standards (GPS)						

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Committed to *health and sustainability*