



RAPPORTI ISTISAN 26|23

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**SIN-SEPI - National informative system
for the surveillance of dangerous exposures and poisonings**

Definition, evaluation and management of sentinel events, alerts and non-compliance: operational manual

English version of the *Rapporto ISTISAN 25/25*

L. Attias, F. Giordano, L. Lanciotti, R.M. Fidente, R. Lavallo,
C. Ferranti, E. Attolini, R. Draisci, D. Quarto, P. Rossi, D. Leone, G. Bortone
and the Poison Centres' experts of the Sentinel working group



AMBIENTE
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ISTITUTO SUPERIORE DI SANITÀ

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English version of the *Rapporto ISTISAN 25/25*

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SIN-SEPI – National informative system for the surveillance of dangerous exposures and poisonings: Definition, evaluation and management of sentinel events, alerts and non-compliance: operational manual. English version of the *Rapporto ISTISAN 25/25*.

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2026, v, 60 p. Rapporti ISTISAN 26/23

As part of SIN-SEPI activities, this report revises the criteria and workflows for reporting three distinct categories of cases (Sentinel event, Alert, and Non-compliance) supported by examples and reporting processes flowcharts. It also identifies key interaction points between the information flows of the Poison Centres Network and the Network of Chemical Control Laboratories, both coordinated by the National Centre for Chemicals, Cosmetic Products, and Consumer Protection of the Istituto Superiore di Sanità (the National Institute of Health in Italy). These connections aim to facilitate information sharing and ensure the timely implementation of preventive measures. The manual provides an innovative tool to harmonize the reporting of exposures/poisonings to chemicals, emphasizing collaboration among all the stakeholders involved in case management (Poison Centres, Laboratory Control Network, Competent Authorities) and promoting process simplification.

Key words: Sentinel surveillance; Poison control centres; Public health surveillance

Istituto Superiore di Sanità

SIN-SEPI - Sistema informativo nazionale per la sorveglianza delle esposizioni pericolose e delle intossicazioni. Definizione, valutazione e gestione di casi sentinella, alert e non conformità: manuale operativo. Versione inglese del *Rapporto ISTISAN 25/25*.

Leonello Attias, Felice Giordano, Lucrezia Lanciotti, Rosanna Maria Fidente, Roberta Lavallo, Carolina Ferranti, Ettore Attolini, Rosa Draisci, Daniela Quarto, Pasqualino Rossi, Daniele Leone, Giuseppe Bortone e gli esperti dei Centri Antiveneni del Gruppo di lavoro Sentinella
2026, v, 60 p. Rapporti ISTISAN 26/23 (in inglese)

Nell'ambito delle attività del SIN-SEPI, il rapporto ridefinisce criteri e flussi per consentire la segnalazione di tre tipologie distinte di casi (Evento sentinella, Alert e Non conformità) fornendo anche esempi e diagrammi di flusso dei diversi processi di segnalazione. Vengono identificati inoltre i nodi di interazione tra flussi della Rete dei Centri Antiveneni e della Rete dei Laboratori di controllo dei *chemicals* coordinate dal Centro Nazionale Sostanze Chimiche, Prodotti Cosmetici e Protezione del Consumatore dell'Istituto Superiore di Sanità, per condividere informazioni e consentire l'attuazione tempestiva di azioni preventive. Il manuale fornisce uno strumento innovativo per armonizzare la segnalazione di casi di esposizione/intossicazione da prodotti chimici, evidenziando l'interazione con tutti gli attori potenzialmente coinvolti nella gestione di tali casi (Centri Antiveneni, Rete dei Laboratori di controllo, Autorità Competenti) e la semplificazione dei processi.

Parole chiave: Sorveglianza degli eventi sentinella; Centri Antiveneni; Sorveglianza in sanità pubblica

The document was developed within the framework of the PNC-PNRR Project "The national system for the control and surveillance of chemicals for the protection of public health" – Lead partner: AReSS Puglia (Project Scientific Coordinator: Dr. Ettore Attolini) – in which the National Institute of Health (Italian Istituto Superiore di Sanità-ISS) serves as an Operational Unit.

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PNC-PNRR project

“The national system for the control and surveillance of chemicals for the protection of public health”

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ACRONYMS

APP	Archive of Hazardous Preparations
ASL	Local Health Authority
BPR	Biocidal Products Regulation
CLP	Classification, Labelling and Packaging
CNSC	<i>Centro Nazionale Sostanze Chimiche, prodotti Cosmetici e protezione del Consumatore</i> (National Center for Chemicals, Cosmetic Products, and Consumer Protection)
DPCM	Decree of the President of the Council of Ministers
EuPCS	European Product Categorisation System
IHR	International Health Regulations
IRCCS	Scientific Institutes for Research, Hospitalization and Healthcare
ISS	National Institute of Health
ELC	Essential Levels of Care
NAS	Carabinieri Units for Health Protection
PC	Poison Centres
PCN	Poison Centre Notifications
PNC	National Complementary Plan
NRRP	National Recovery and Resilience Plan
PSS	Poisoning Severity Score
RASFF	Rapid Alert System for Food and Feed
RCA	Root Cause Analysis
REACH	Registration, Evaluation, Authorisation and Restriction of chemicals
HDR	Hospital Discharge Records
SDS	Safety Data Sheets
SEMOS	Sentinel Event Measure Of Success
SIMES	Information System for Monitoring Errors in Healthcare
SIN-SEPI	National informative system for the surveillance of dangerous exposures and poisonings
SNAP	National Early Warning System on Drugs
NHS	National Health Service
RHS	Regional Health Systems
UFI	Unique Formula Identifier
WG	Working Group
WHO	World Health Organization

INTRODUCTION

This report falls within the scope of surveillance activities on hazardous exposures and poisonings caused by chemical products conducted by the National Centre for Chemical Substances, Cosmetic Products and Consumer Protection (*Centro Nazionale Sostanze Chimiche, prodotti Cosmetici e protezione del Consumatore*, CNSC) of the Istituto Superiore di Sanità (ISS, the National Institute of Health in Italy), in collaboration with the network of Italian Poison Centres (PCs).¹

The document first provides an overview of surveillance activities, the stakeholders involved, and the current state of the art of the different types of reporting relevant to public health (Appendix A).

The definitions and concepts identified are applied to the context of surveillance of exposures and poisonings caused by chemical substances and products, which are the focus of this manual, providing operational guidance for PC physicians in order to ensure timely and accurate reporting and assessment of cases of interest:

- Sentinel events;
- Alerts;
- Non-compliance.

To enhance clarity and understanding, Appendix B provides examples of case studies for each type of reporting.

¹ It should be noted that, as of 2026, the activities and responsibilities of the CNSC, including SIN-SEPI surveillance, have been transferred to the Department of Environment and Health of the ISS. The CNSC structure is no longer in place.

SURVEILLANCE OF CHEMICAL PRODUCTS: AN OVERVIEW

The World Health Organization (WHO) (1) defines surveillance as the ongoing systematic collection, analysis, and interpretation of health data essential for the planning, implementation, and evaluation of public health practice. Surveillance is therefore a fundamental component of public health and requires reliable and effective systems to be implemented.

The terms *toxicovigilance* and *toxicological surveillance* are commonly used.

According to the WHO guidelines on poison centre's activities (2020) (2), the increasing global reliance on chemicals requires the health sector to expand its traditional roles and responsibilities to address the medical and public health issues associated with chemical use and its effects on human health. Acute harmful exposure (intentional or unintentional) to toxic substances and products represents a significant health risk. This burden can be reduced through the timely identification of emerging trends or new patterns of use, thereby enabling the implementation of appropriate preventive measures.

The WHO (2) defines toxicovigilance as the active identification and evaluation of the risk of toxicity arising from exposure of a community or population to consumer products, pesticides, pharmaceuticals, environmental and industrial chemicals, controlled substances, and natural toxins. Information collected through toxicovigilance activities enables monitoring of exposure trends in specific population subgroups (e.g., different age groups, sex, occupational and domestic settings), thereby allowing for differentiated risk assessment of exposure and poisoning. This supports the development of targeted prevention interventions (Evidence-Based Prevention), the proposal of risk management measures, and the evaluation of their effectiveness. Toxicovigilance activities may also identify events such as intentional or unintentional product contamination that require an immediate response from the competent authorities.

Therefore, the objective of toxicovigilance is to provide information to support timely actions aimed at preventing, treating, and mitigating harm, as well as managing risks associated with toxic exposures of concern for public health (2).

Toxicological surveillance generally refers to the monitoring of a specific toxic threat or toxidrome. In many countries, this term is used to describe the same activities as toxicovigilance (2).

Within the framework of toxicovigilance activities, Poison Control Centres (PCs) are the healthcare facilities actively involved in the development, implementation, and evaluation of poisoning prevention measures.

PCs: roles, organization, and activities

PCs have been established worldwide to provide a dedicated response to the needs for treatment and prevention of poisonings and the harmful effects of chemical substances. At the global level, there are no regulatory frameworks that uniformly define the functions and structure of PCs; however, over time, a few guidelines, international recommendations, literature reviews, and legislative acts have been developed to harmonize and define their roles and functions.

The main international reference documents on PCs are listed below:

- European Community, *Resolution 90/C 329/03* (3)
Member States express the political will to adopt the necessary measures to improve the prevention and treatment of acute human poisoning, including increasing the availability and accessibility of antidotes;
- McGuigan MA, *Quality management for poison centres* (4)
PCs should adopt quality management criteria consistent with the ISO 9000 series guidelines. The adoption of quality standards provides PC staff with a framework to improve the overall quality of the services delivered;
- WHO, *Guidelines for establishing a poison centre* (2)
Poisoning is a major global public health problem. WHO estimates that, in 2016, unintentional poisoning caused 106,683 deaths and the loss of 6.3 million healthy life years (disability-adjusted life years). In many countries, poisoning is among the leading causes of emergency department visits. Poisoning is a time-critical emergency and, like infectious diseases, may require specialist expertise for appropriate diagnosis and treatment. In many countries, PCs are established to provide specialized expertise in support of healthcare professionals working in emergency settings, who cannot be expected to be familiar with the toxicity of every substance and chemical product, and to serve as a focus for toxicological research. PCs also play an important role in implementing the International Health Regulations (IHR, 2005), which require countries to have the capacity to monitor, detect, and respond to public health events caused by chemical substances. Much of this capacity can be provided by a well-resourced PC. The guidelines for establishing a poison centre provide information on the services that can be offered by a PC, as well as detailed practical guidance on planning and operations. This publication is an update of the guidelines for poison control and prevention issued by WHO in 1997. The update reflects the renewed emphasis on PCs arising from the implementation of the IHR (2005), as well as technological advances and the increased experience and expertise of PCs since 1997;
- WHO, *At least one poison centre in each country: summary for policy makers* (5)
A PC is a specialized unit that provides advice and assistance in the prevention, diagnosis, and management of acute and chronic poisoning. PCCs contribute to reducing the burden of disease associated with exposure to hazardous chemicals, both in emergencies and in everyday life;
- WHO, *Poison centres as essential unit for poisoning prevention and sound chemicals management: technical summary* (6)
This publication summarizes key information on PCs, including their role in poisoning management, public health preparedness and emergency response, implementation of international health regulations, and their contribution to the sound management of chemicals. It also includes examples demonstrating the importance and value of PCCs for health systems.

In Italy, the State-Regions Agreement No. 56/CSR of 28 February 2008 (7) defines the characteristics and functions of a PC. This Agreement, together with the Essential Levels of Care (ELC) established in 2017 (8), in which Italian PCs are included, constitutes the current national regulatory framework governing PCs (establishment, definitions, roles, functions, and operations).

PCs are therefore essential specialized clinical services within the healthcare system, operating 24 hours a day. Specialist advice is provided both remotely (by telephone) and directly (e.g., in hospital wards where PCs are located) to any requester (e.g., physicians working in emergency services, pre-hospital emergency systems, primary care, authorities, law enforcement, and private citizens).

Any suspected or confirmed exposure to a chemical substance may constitute grounds for requesting specialist consultation from a PC, although most requests concern poisoning cases or preventive enquiries related to pharmaceuticals, chemicals (mixtures/products), food/mushrooms, substances of abuse, plant toxins (excluding mushrooms), and animal venoms.

With specific regard to chemicals, the Decree of the Ministry of Health of 28 December 2020 (9) indirectly highlights the key role of PCs in the management of exposures or poisonings from hazardous chemical substances. Consultations requested from PCs for issues involving chemicals, intended as mixtures and chemical products of various types, account for approximately 10-45% of all consultation requests (data derived from a survey conducted among PCs in 2023).

In addition to specialist consultation, PCs (in accordance with the State–Regions Agreement) perform other activities of fundamental importance within the healthcare system. The main categories of activities characterizing PCs are as follows:

- specialist toxicology consultation for clinical toxicology emergencies within the National Health Service (NHS) and Regional Health Systems (RHS);
- direct clinical activity (outpatient and/or inpatient care);
- managerial and organizational activities related to public health issues;
- non-emergency specialist consultations for national and regional administrations, public bodies, and companies requiring toxicological support (prevention, organizational aspects);
- antidotes (scientific research, availability, stock planning and management);
- clinical toxicological analytical activities, both emergency and non-emergency;
- research (for PCs operating within scientific institutes for research, hospitalization and healthcare (Italian *Istituti di Ricovero e Cura a Carattere Scientifico*, IRCCS);
- teaching and training (academic and non-academic).

PCs, in their capacity as specialist consultants, perform a range of activities primarily aimed at hospitals, physicians, citizens, and institutions other than those in which they are formally established (for some centres, this includes all regions and the entire national territory). PCs are co-responsible for the management of tens of thousands of patients per year; they support the NHS and the RHS in all toxicological issues and are expected to be fully organized to ensure specialist operational capacity also in the context of large-scale emergencies of both conventional and non-conventional nature.

In this regard, PCs carry out surveillance, vigilance, alert, and prevention activities for all existing toxicological issues (including food, plant and animal toxins, environmental contamination, pharmaceuticals, drugs of abuse, chemicals, cosmetics, etc.) and provide data to all national and regional authorities requiring such information.

Furthermore, one of the core functions of PCs, explicitly established in the State–Regions Agreement and reflected in international documentation, is to ensure the availability of all relevant antidotes in support of the entire NHS; PCs should also have access to specific and uncommon diagnostic tests not routinely available within the NHS.

Moreover, PCs activities extend well beyond the interests of the individual institution or region in which they operate.

Key definitions across different contexts

Sentinel event

PCs physicians are at the forefront of identifying, among the totality of reported cases, those events in which the cause of exposure can be attributed to an agent for which effective preventive measures can be implemented or, in extreme cases, for which the product may be withdrawn from the market to protect public health. Such decisions fall within the remit of the Competent Authorities.

These events are referred to as “sentinel events”, although their definition varies according to the objectives and needs of the organization adopting them.

Definitions of sentinel events (or sentinel cases) found in literature depend on the field of application (Appendix A1): sentinel events are described in hospital settings, occupational settings, and, more broadly, the WHO (2) provides a definition applicable to exposures resulting from the release, whether accidental or intentional, of chemical products into the environment (e.g., during a chemical attack, but also indirectly, for example, during the bombing of chemical facilities). In many cases, such events are easy to detect (e.g., leakage from a fuel tank), whereas it is more difficult to ascertain whether individuals have been exposed; this role, particularly for acute effects, lies within the toxicovigilance and toxicological surveillance activities of PCs.

In general, these are major incidents whose management by Competent Authorities and PCs involves a set of interventions: prevention, preparedness and training in case of exposure, identification of exposures and reporting to Competent Authorities, provision of responses to physicians and citizens, and recovery actions (2). Therefore, for the detection of exposures and reporting to Competent Authorities, it is useful to implement systems for the identification of sentinel events in order to timely understand the health impact of a chemical incident on the surrounding population.

WHO (2) defines a sentinel event as the identification of a preventable disease, disability, or premature death whose occurrence signals that a hazardous environmental exposure may have occurred or may be occurring. The purpose of sentinel events local monitoring is to identify chemical releases that have not been reported or have been considered harmless.

One of the earliest publications on this topic is undoubtedly the one written by Rutstein *et al.* (1983) (10), which provides a general definition of a sentinel event and then focuses on environmental exposures in the occupational setting. The general definition is as follows: a *sentinel event* is a preventable disease, disability, or premature death whose occurrence serves as a warning signal that preventive or healthcare actions within the health system require improvement. The definition adapted to the occupational context is instead as follows: an *occupational sentinel event* is a disease, disability, or premature death related to occupational exposure, the occurrence of which may: (1) provide input for epidemiological or industrial hygiene studies; and (2) serve as a warning signal highlighting the need for substitution of materials, implementation of engineering controls, adoption of personal protective equipment, and appropriate medical care.

Rutstein *et al.* (10) developed a table listing a range of preventable occupational diseases whose occurrence is considered avoidable and therefore suitable for surveillance through health data sources, such as Hospital Discharge Records (HDR). A similar table had previously been developed by Rutstein *et al.* (1976) (11) for preventable diseases not limited to the occupational setting.

Carr *et al.* (1989) (12), based on the list of preventable diseases compiled by Rutstein *et al.* (1976), conducted a search for sentinel cases (diseases or deaths) among hospital discharge

records from a hospital in New York State in 1983. It is noteworthy that three types of sentinel cases were identified, depending on the condition being monitored:

1. severe diseases for which a single case is sufficient to trigger an alert (e.g., botulism);
2. diseases showing an increase in frequency above expected levels (e.g., deaths from diabetes);
3. medical-social problems (e.g., alcoholism, suicides) and psychiatric conditions whose causes, and therefore prevention strategies, require in-depth investigation.

Moreover, some diseases or deaths are considered sentinel only when they occur in specific population subgroups (e.g., deaths from acute respiratory diseases in individuals under 50 years of age).

Aldrich and Leverton (1993) (13) identified additional types of sentinel events related to diseases associated with environmental etiological factors:

- *Single events*
based on a single case (e.g., oral cancer in a person under 30 years of age);
- *Localized clusters of rare events*
based on a small number of cases of a disease, often sharing a common environmental risk. While the occurrence of a rare disease may be acceptable in a large community, two cases occurring in a population living near an industrial site may not be attributable to chance;
- *Changes in a “logical” pattern*
based on the observation of diseases/deaths that are normally frequent in the general population but, if occurring in subgroups generally considered at low risk, may indicate sentinel events (e.g., deaths from stroke are generally common in older populations, but if observed with some frequency in populations under 30 years of age, they may indicate an excess of cases to be considered sentinel; studying the causes of these events may also help identify sentinel cases in older populations);
- *Surrogate events*
when a cluster of a small number of disease cases lacks sufficient statistical power to be classified as sentinel (e.g., rare tumours), until cases of another condition (e.g., congenital malformations) occur that share a common aetiology. Taken together, the two clusters may identify a shared environmental etiological factor.

In the healthcare setting, it is particularly important to monitor medical errors that result in patient injury or death. Preventing such events is crucial, as their occurrence undermines public trust in healthcare systems (14).

In this regard, the Joint Commission (15) defines a sentinel event as an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof. Serious injury specifically includes loss of limb or function. The phrase “or the risk thereof” includes any variation in the process of care that could carry a significant chance of a serious adverse outcome. These events are termed *sentinel* because they signal the need for immediate evaluation and response.

The Joint Commission is a United States-based accreditation body for healthcare organizations that voluntarily seek accreditation. Accreditation is granted if specific standards of good clinical practice are consistently met over time (<https://www.jointcommission.org/what-we-offer/accreditation/>). Among these standards, considerable importance is placed on reducing medical errors that may compromise patient trust. Following the occurrence of such events, a Root Cause Analysis (RCA) should be conducted, followed by the identification of optimal strategies to reduce the risk of recurrence. An evaluation phase is also useful to verify whether

the preventive measures implemented have been effective (Sentinel Event Measure of Success, SEMOS) (15). Friedman (1998) (16) emphasized the importance of sharing reports of sentinel events within healthcare organizations accredited by the Joint Commission through periodic publications, allowing the experience of a single institution to inform others and reduce the likelihood of similar occurrences. Since 2013, reportable harmful events have also included those affecting healthcare staff, visitors, and hospital vendors (17). The systematic collection of such data has led to numerous scientific studies on different types of reported sentinel events (18, 19).

The sentinel event guideline issued by the Maine Department of Public Health (20) highlights that, within a sentinel event reporting system, it is beneficial to establish a dedicated team responsible for implementing criteria for the identification and management of sentinel events. In addition, training activities of reporting personnel is essential.

Similarly, in Italy, a National Observatory for sentinel events occurring in healthcare facilities and affecting patients operates within the Ministry of Health. Its aim is to provide Regions and healthcare organizations with a standardized approach to surveillance and management of such events across the national territory, to ensure the ELC. Reporting is carried out through a dedicated information platform: the Information System for Monitoring Errors in Healthcare (SIMES). Within the monitoring protocol, a sentinel event is defined as follows:

“un evento avverso di particolare gravità, potenzialmente evitabile, che può comportare morte o grave danno al paziente e che determina una perdita di fiducia dei cittadini nei confronti del servizio sanitario. Il verificarsi di un solo caso è sufficiente per dare luogo ad un'indagine conoscitiva diretta ad accertare se vi abbiano contribuito fattori eliminabili o riducibili e per attuare le adeguate misure correttive da parte dell'organizzazione” (14) /

A sentinel event is an adverse event of particular severity, potentially preventable, that may result in death or serious harm to the patient and that leads to a loss of public confidence in the healthcare system. The occurrence of even a single case is sufficient to trigger an investigation aimed at determining whether preventable or reducible factors contributed to the event, and at implementing appropriate corrective measures by the organization (14).

Sentinel events include:

- an occurrence that may lead to subsequent harm (e.g., a fall);
- the harm itself (e.g., maternal death);
- an indicator of activity or process (e.g., under-triage);
- any act of violence affecting healthcare staff or patients.

Given their severity, the occurrence of even a single event is sufficient to warrant, on the part of the organization: (a) an immediate investigation to determine which preventable or reducible factors caused or contributed to it; and (b) the identification and implementation of appropriate corrective measures.

Across all systems considered, the term *sentinel event* is used both for the occurrence of chronic diseases (e.g., cancer) and for incidents involving exposures and acute symptomatology. PCs predominantly manage cases of acute exposure, such as poisonings due to chemical products.

Alert

Distinguishing between a sentinel event and an *alert* case can be crucial from an event management perspective. Indeed, a sentinel case may represent an indicator of a potentially critical condition requiring assessment and subsequent action by the Competent Authorities. In contrast, an alert case may require a prompt response and immediate corrective action by the bodies responsible.

The literature allows for the identification of various definitions of *alert* (also referred to as “alert notification”) across different fields, sometimes referring to situations of serious risk to health and, in other cases, to scenarios that may overlap with those classified as sentinel events (Table A2).

A common element emerging from many studies and institutional documents (21–27) is the need for the *timely* reporting and management of alert cases, thereby defining a *maximum timeframe for action* by all stakeholders involved in the process. Another crucial aspect is the *direct involvement of Competent Authorities*, which can promptly implement the necessary measures (21, 24, 26–29).

For example, the “Guidelines for the operational management of the alert system for food, feed, and materials intended to come into contact with food” (30) emphasize that the *Rapid Alert System for Food and Feed* (RASFF) has undergone several regulatory updates aimed at ensuring its proper functioning both in cases where a serious risk to health can be identified and in cases where the risk identified is less severe or less urgent, yet still requires efficient information exchange among members of the RASFF network. In this document, *notifying an alert to the Competent Authority* means reporting a risk that requires, or may require, rapid action in one or more Regions or Member States. It is also stated that the creation of a notification must occur *without undue delay* and, in any case, *within 48 hours* from the moment the risk becomes known.

In the “Piano strategico-operativo nazionale di preparazione e risposta a una pandemia influenzale (PanFlu 2021-2023)” (31) – strategic-operational plan for preparedness and response for an influenza pandemic in Italy – developed following the recent experience of the SARS-CoV-2 pandemic, the *alert phase* is defined as the period in which:

“l’influenza causata da un nuovo sottotipo è identificata nell’uomo. Una maggiore sorveglianza epidemiologica e virologica e un’attenta valutazione del rischio, a livello locale, nazionale e globale, sono le attività caratteristiche di questa fase”. (31) /

an influenza caused by a new subtype is identified in humans. Enhanced epidemiological and virological surveillance, along with careful risk assessment at the local, national, and global levels, are the defining activities of this phase (31).

Therefore, in this phase, surveillance systems (rapid alert systems) play a fundamental role in enabling timely and targeted response actions.

In the 2020 WHO guidelines on Poison Centres (2), it is stated that alerting authorities is among the toxicovigilance roles of a PC, with the aim of enabling Competent Authorities to implement the necessary preventive and/or corrective measures. The document provides several examples of cases that a PC may identify and report to Competent Authorities, including:

- a high number of poisoning cases associated with a newly marketed product;
- new cases occurring within a specific population group (e.g., analgesic poisoning in children);
- cases occurring under particular circumstances;
- cases occurring during specific periods of the year;
- issues related to product safety or labelling.

Finally, the *rapid and efficient sharing of information* among all stakeholders involved in the reporting and management of an alert represents another key element for the protection of public health. In this regard, the national early warning system on drugs (the Italian *Sistema Nazionale di Allerta Precoce*, SNAP) (27) relies on a *platform* that facilitates the activities of all involved entities, with the aim of conducting analyses, verification processes, disseminating information, and providing a timely operational response within an integrated system. This system allows all

reports to be collected in a single repository accessible online by authorized users, ensuring that information is promptly available to all relevant authorities.

In light of the existing framework, within the scope of this document it is necessary to distinguish between sentinel events and alert cases in the context of exposures to hazardous chemical products, and to define their respective evaluation criteria and information flows, in order to ensure efficient management within appropriate timeframes.

Near miss

Implementing systems to protect public health also requires the ability to accurately and rapidly identify all those cases in which a harmful event could have occurred but, due to a series of circumstances, did not take place. Such situations are commonly referred to as *near misses*.

The concept of a *near miss* originates from the aviation context, referring to situations in which two aircrafts fly in very close proximity without causing harm, yet raising concern (32). In the literature, various definitions of *near miss* can be found, primarily in healthcare and occupational settings, emphasizing the potential of the event to cause harm, even though harm did not occur (Table A3).

Kessels-Habraken *et al.* (33) highlight that *an optimal definition of near miss may be context-dependent*, varying according to the organizational setting in which it is applied. The literature review presented in this Dutch study suggests that identifying and reporting near misses offers several advantages: their high frequency allows for the rapid accumulation of a large body of data for analysis, a point also emphasized by Van der Schaaf (1995) (34). Moreover, since the causes leading to a near miss and to an adverse event are often the same, acting on near misses means acting preventively on potentially harmful events. The study identifies three types of events described in the literature:

- Events that did not reach the patient (e.g., a nurse identifies an error in a prescription and requests correction by the physician);
- Events that reached the patient but did not cause harm (e.g., administration of therapy to the wrong patient who, fortunately, required the same treatment);
- Events that reached the patient and caused harm.

Thus, within the definition of *near miss*, a crucial aspect appears to be the distinction between “patient not reached/reached” and “patient reached without harm/with harm”

Some studies show that the identification of near misses can lead to a proactive, prospective, and improvement-oriented approach to risk management in healthcare services (35, 36), enabling preventive modification of protocols before harm occurs to patients (37-39). Given the importance of timely and accurate identification of near misses, Kang *et al.* (2017) (40) suggest that reporting rates for such cases could be increased through the implementation of *standardized protocols that simplify the entire process*.

In light of these considerations, within the context of exposures to hazardous chemical products addressed in this document, it would be appropriate first to distinguish between exposure (without symptoms) and poisoning (exposure with symptoms), and subsequently to identify cases that may fall within the definition of *near miss*. This approach may support the development of a body of information useful for implementing preventive actions by Competent Authorities.

National informative system for the surveillance of dangerous exposures and poisonings

For several years, the CNSC of the ISS has been implementing the National Information System for the Surveillance of Hazardous Exposures and Poisonings (*Sistema Informativo Nazionale di Sorveglianza delle Esposizioni Pericolose e delle Intossicazioni*, SIN-SEPI) in Italy, recognized as a system of national relevance by the Prime Ministerial Decree of 3 March 2017 on the “Identification of surveillance systems and registries of mortality, cancer, and other diseases” (41).

In accordance with the Prime Ministerial Decree of 3 March 2017, Article 45 of Regulation (EC) No. 1272/2008 (Classification, Labelling and Packaging, CLP) (42), and the Decree of the Ministry of Health of 2 March 2016 concerning the organization and functioning of the ISS (43), the CNSC is entrusted with the management of notifications of hazardous mixtures and detergents placed on the market through the Archive of Hazardous Preparations (Italian *Archivio dei Preparati Pericolosi*, APP), pursuant to the CLP Regulation, Legislative Decree No. 65/2003 (44), Legislative Decree No. 21/2009 (45), and subsequent amendments. In addition, it is responsible for activating surveillance actions on exposures to chemical substances and hazardous products, with the aim of providing the Ministry of Health with tools to support the development of prevention programmes.

SIN-SEPI activities also contribute to verifying compliance with the requirements set out in the European legislation, particularly those concerning the hazard classification of mixtures and the information necessary to ensure their safe use. In fact, Regulation (EC) No. 1907/2006 (REACH) (46), concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals, and the CLP Regulation (42), require the collection of large amounts of data to assess chemical risk and to achieve the objectives of understanding and reducing the impact of hazardous substances on human health and the environment. This includes surveillance of potentially hazardous exposures to chemical agents intended for consumer, professional, or industrial use.

SIN-SEPI operates in collaboration with PCs identified by national and regional authorities in accordance with the Agreement reached at the State–Regions Conference on 28 February 2008 (7) and recognized as eligible to access information for emergency health response contained in the ISS Archive of Hazardous Preparations.

The data feeding SIN-SEPI are collected through two modalities:

- *Annual consultation database*

Data submitted by PCs are validated, analysed, and published in annual reports that are useful for guiding prevention professionals toward emerging issues. Therefore, such reports are, at best, published only in the following year.

- *Real-time reporting via the online surveillance form (47)*

Toxicologist physicians voluntarily report in real time exposure/poisoning events that may potentially be classified as “sentinel” when one or more of the following agreed conditions occur:

- the colours and/or shape of the product packaging resemble those of other products;
- the route of exposure is unusual;
- the symptoms are unusually severe for the hazard class of the product;
- the frequency of observed cases is unusually high over time or within a specific area.

At present, the confirmation or rejection of these cases is carried out by ISS personnel, who classify them as follows:

- *Non-case*
none of the above conditions are met;
- *Possible*
one or more of the above conditions are met, but there is reasonable doubt that contributing factors related to improper use by the operator may have played a role;
- *Probable*
one or more of the above conditions are met, and no errors in product use by the operator can be identified;
- *Confirmed*
when evidence of a possible or probable sentinel case is subsequently validated through epidemiological analyses based on large datasets, using the annual consultation data provided by collaborating PCs under formal agreements with the ISS.

These assessments are periodically transmitted to the Directorate-General for Health Prevention of the Ministry of Health for the actions within its remit. In many cases, technical modifications can improve product safety by reducing the risk of hazardous exposure; in other cases, the only solution may be permanent withdrawal from the market. Data from PCs, when analysed prospectively following the implementation of a preventive measure, are also useful for assessing the effectiveness of the actions undertaken. In some instances, an event may take on the characteristics of an *alert* and is evaluated by the ISS within a short timeframe and brought to the attention of the Ministry within a maximum of one week. For the current minimum dataset used, reference is made to Chapter 6.

The system described above has clearly demonstrated its effectiveness and sensitivity in detecting issues that pose a risk to health, including during the recent public health emergency caused by the COVID-19 pandemic (48). Nevertheless, over the years of its implementation, the need has emerged to optimize certain key aspects, including types of reporting (e.g., intentional cases, non-compliance), timelines for case management, and the sharing of information with all central and regional bodies responsible for protecting public health.

Control and surveillance of chemicals for the protection of public health: an *ad hoc* project

Among the interventions identified by the Mission 6 – Health of the National Recovery and Resilience Plan (*Piano Nazionale di Ripresa e Resilienza*, PNRR), the CNSC of the ISS promoted the submission of the Project proposal entitled “Il sistema nazionale per il controllo e la sorveglianza dei chemicals a tutela della salute pubblica / The national system for the control and surveillance of chemicals for the protection of public health” (hereinafter referred to as “Project”), which was approved for funding on 30 September 2022 by Ministerial Decree (49). The Project has a duration of four years (2023-2026) and involves the Regional Agency for Health and Social Care of Apulia (Italian AReSS Puglia) as the lead partner, together with 15 Operational Units distributed across the national territory, including the CNSC itself and five Italian PCs (Foggia, Pavia, Milan, Naples, Florence).

The Project aims to establish an integrated system for the surveillance and control of chemicals, with the objective of fostering interaction and collaboration among PCs, the network of laboratories responsible for chemicals control, and national regulatory bodies, thereby facilitating the sharing of information, expertise, procedures, and methodologies.

To effectively improve the protection of public health and related intervention strategies, the systems involved in surveillance and control activities require greater simplification, harmonization, data sharing, and interaction. This objective will be achieved through the development of an IT platform that will enable:

- more effective communication, planning, and reporting of surveillance and control activities;
- more efficient responses from the networks involved;
- more active and productive exchange of requests and information between central and local Competent Authorities.

This operational manual aims to *simplify* and *harmonize the reporting process* undertaken by PCs by distinguishing cases according to their type, providing *differentiated workflows* for case management, and proposing an integrated management system that enables timely action and information sharing among all stakeholders involved in the surveillance and control of chemicals.

**Operational manual
for reporting by PCs**

1. SCOPE AND PURPOSE

1.1. Objective

This operational manual provides guidance to PC toxicologist physicians to enable the timely reporting of cases of exposure/poisoning due to chemicals, based on shared criteria and differentiated information flows according to the type of report. In the context of hazardous exposures to chemical products on the market, it is essential to assess the risk associated with their use, investigate the underlying causes, and implement targeted preventive and/or corrective actions aimed at protecting public health. To ensure accurate and efficient reporting, assessment, and management of exposure cases, it is necessary to distinguish between different types of reports, assign priority to specific cases, and identify the most appropriate management approaches.

Within the scope of this document, reports can be classified into three main types: *Sentinel Events*, *Alerts*, and *Non-compliance* with regulations. The document provides definitions for each type of report and the corresponding evaluation criteria and establishes different timelines for case management according to the assigned priority. In addition, it describes the reporting flows and identifies the relevant addressees responsible for implementing appropriate preventive, monitoring, and corrective actions.

To facilitate understanding of the processes and promote easier application of the recommendations, examples (case studies) and flow diagrams are provided for each type of report.

The feasibility of the proposed system builds on an existing reporting framework already operating at the national level, which requires further development and enhancement. In particular, one of the most relevant innovations is the possibility of reporting *alerts*, which are currently managed independently by each PC in coordination with the appropriate Competent Authority.

The document also aims to preliminarily define the interaction flows between the PC-ISS network and the network of chemicals control laboratories coordinated by the CNSC (now Department of Environment and Health), in order to promote the sharing of information, expertise, procedures, and methodologies, and to enable the timely implementation of the necessary actions.

1.2. Target population and intended users

This document is addressed to PCs personnel who, in accordance with the 2008 State–Regions Agreement (7), are required to report cases of hazardous exposures/poisonings related to specific chemicals that require timely assessment to implement prevention, control, and monitoring strategies in coordination with the Competent Authority. Reports include cases of confirmed or suspected human exposure to chemicals.

This document may represent a valuable methodological framework that can be transferred to and implemented in other countries and comparable systems.

1.3. Expected benefits

The implementation of this document is expected to promote effective knowledge sharing among all stakeholders involved in the assessment and management of cases of exposure/poisoning due to chemicals, with the aim of improving the services provided to the population in terms of:

- effectiveness and efficiency in the management of exposure/poisoning cases, also through continuous exchange among PCs;
- reduction of inappropriate access to hospital emergency services and of unnecessary hospital admissions (6);
- rapid identification of the most appropriate strategies to guide *Evidence-based Prevention* interventions, propose risk management measures, and verify the compliance of marketed chemicals with European regulatory requirements;
- interaction with the activities of the Network of Control Laboratories for potential actions on non-compliant products reported by PCs;
- collaboration with chemical manufacturers to ensure the placing on the market of increasingly safer products, minimizing risks associated with their use.

2. ORGANIZATION AND METHODOLOGY

The following sections outline the expert group responsible for developing the manual and the process through which the manual was developed.

2.1. Expert group

Within the framework of the Project, the “Sentinel” Working Group (WG) was established to implement the process for the assessment and management of cases reported by PCs through the ISS Online Reporting Form.

The WG reflects the multidisciplinary nature and the representativeness of the stakeholders involved in the drafting and revision of the document, as it is composed of toxicologist physicians from PCs currently accredited across the national territory, as well as chemists and biologists with expertise in the prevention, surveillance, and control of chemicals, affiliated with institutions engaged in the protection of public health (e.g., ISS). The entities participating in the WG and their respective contributions to the development of the manual are listed below:

- ISS (drafting and revision);
- Apulia PC (drafting and revision);
- Pavia PC (drafting and revision);
- Milan PC (drafting and revision);
- Naples PC (revision);
- Florence PC (revision);
- Bergamo PC (revision);
- Bambino Gesù Paediatric Hospital PC - Rome (revision);
- Gemelli PC - Rome (revision);
- Verona PC (revision).

2.2. Development process

The “Sentinel” WG convened to define the preparatory activities required for the implementation of the system and to outline new criteria and information flows.

Based on the identified challenges and needs, an outline was developed and topics were assigned to the Operational Units involved in the Project.

The PCs of Foggia, Pavia, and Milan, which have been involved since the first year of the Project, established a sub-working group and proceeded with a further allocation of specific topics, each according to their respective areas of expertise.

2.2.1. Bibliographic research

To identify studies and materials useful for the development of these recommendations, several searches were conducted across major biomedical databases (PubMed, Web of Science, Google Scholar). In addition, a search was carried out using Google Chrome® to identify relevant documents within the grey literature.

After compiling a comprehensive list of the retrieved materials, an initial selection was performed based on titles and abstracts in relation to the topic of interest. Subsequently, the selected materials were further examined through full-text review.

The results obtained, summarized in the tables in Appendix A, enabled the identification of elements useful for the evidence-based development of the text. The search queries were constructed using the following keywords in various combinations: *Sentinel Event, Public Health, Definition, Alert, Authority, Near miss, Healthcare*.

2.2.2. Strengths and limitations of the scientific evidence

The scientific evidence identified, although referring to different contexts, provides a solid basis for the development of recommendations concerning the reporting of exposures/poisonings due to chemicals.

In the reviewed studies, sentinel cases, alerts, and near misses primarily relate to healthcare/hospital settings, proposing definitions and case management protocols that vary according to the needs of the adopting organization. In the context of chemicals, in addition to defining criteria and information flows for sentinel cases, alerts, and potential near misses, it is also necessary to identify appropriate pathways for reporting, assessment, and management of cases of *non-compliance* with regulations.

Indeed, hazardous exposures to chemical products may be caused or exacerbated by several factors, including inconsistencies between the information reported on labels (e.g., composition, hazard statements), packaging, and the outcomes of exposure (e.g., unusually severe symptoms), as well as discrepancies between the label and the Safety Data Sheet (SDS), or between the label and the information provided at the time of product notification prior to placing on the market.

Identifying, assessing, and managing such cases within appropriate timeframes is essential to effectively support the implementation of regulatory oversight and corrective actions by Competent Authorities and to minimize the risk of future exposures.

2.2.3. Development of recommendations

Priority topics to be addressed in the document were discussed and agreed upon during several operational meetings of the “Sentinel” WG. In line with the provisions of the PNC-PNRR Project and in agreement with all WG participants, the Operational Units directly involved in the first year of activities were identified, and the different sections of the document were subsequently assigned.

The outputs produced by each Operational Unit were shared with the entire Group; emerging issues were discussed, and consensus was achieved through continuous interaction among all parties.

2.2.4 Implementation and monitoring

The validation of the new system implemented through the reporting and management of cases will make it possible to assess its effectiveness and to carry out any necessary revisions and updates to the manual. Where appropriate, the WG, and, where relevant, the Authorities concerned, will be convened to agree on the required modifications.

3. TYPE OF REPORT

3.1. Sentinel event

This document proposes a new definition of a sentinel event in the context of chemicals:

An unexpected accidental event involving human exposure to a chemical product which, due to its intrinsic chemical/physical characteristics or its packaging, results in an increased risk of hazardous exposure within the population.

The consumer involved in the event is misled:

- *with direct evidence*
 - the colour and/or shape of the packaging resembles the one of other products (food, food products, other chemical products, dietary supplements, medicines, toys, etc.);
 - the colour, shape, smell, or consistency of the content resembles the one of other products (food, food products, other chemical products, dietary supplements, medicines, toys, etc.);
 - the presence on the label of wording typically used for medicines and dietary supplements (e.g., tablets, pills, capsules);
 - incorrect or unclear instructions for use reported on the label;
 - the presence on the label of images or text resembling those of other products;
 - inadequate packaging/safety closure/cap/label for the type of product;
 - instructions for use or claims reported on the label/SDS or in advertising lead the consumer to incorrect use;
- *with indirect evidence*
 - an unusual route of exposure to the product;
 - unusually severe (or atypical) symptoms in relation to the product hazard class;
 - a high frequency of cases over time or within a specific geographical area.

A sentinel event therefore represents a warning signal that may indicate the need to replace or modify certain chemical products to protect public health.

3.2. Alert

An *alert* (or alert notification) is a mechanism to be activated when a PC identifies the need to communicate to the relevant Authorities/Institutions an issue related to exposure to chemical substances, provided that all the following conditions, according to the checklist below, are met:

- the clinical case of exposure to one or more chemical substances has resulted in fatal or potentially fatal consequences in humans;
- the exposure is associated with factors that may lead to recurrence of the event in other individuals;

- urgent interventions can be implemented by Institutions/Authorities to prevent recurrence of the event;
- the exposure results in fatal or potentially fatal consequences arising from (at least one of the following conditions):
 - correct use, according to its intended purpose, of an adulterated product;
 - incorrect/improper use or abuse of a product for purposes other than those intended;
 - use of a product associated with an emerging phenomenon encouraging its improper or unsafe use.

The use of a checklist (Table 1) allows verification of whether the criteria defining a case as an alert are met. Based on the score obtained after completing the checklist, the system will permit two options:

- score $(a + b + c + d) \geq 4$
= the system allows progression to the “alert pathway”;
- score $(a + b + c + d) < 4$
= the system automatically refers to the “sentinel case or non-compliance pathway”.

Table 1. Check-list for identifying alert cases of chemical exposure

Criteria	Score
a) Exposure resulting in fatal or potentially fatal consequences	1 point
b) Exposure associated with factors that may lead to recurrence of the event	1 point
c) Presence of urgent interventions that can be implemented by Institutions/Authorities to prevent recurrence of the event	1 point
d) Exposure resulting in severe consequences arising from (<i>at least one of the following conditions</i>):	
correct use, in accordance with the intended purpose, of an adulterated product	1 point
incorrect/improper use or abuse of a product for a purpose other than the one intended	1 point
use of a product associated with an emerging phenomenon	1 point

3.3. Non-compliance with current regulations

Participation in regulatory oversight activities, in collaboration with the Ministry of Health, Regions, and other institutionally competent bodies, is one of the key functions and roles of PCs as defined in the 2008 State–Regions Agreement (Rep. Acts No. 56 CSR) (7), contributing to the enhancement of human health and environmental protection.

The purpose of this section is to provide guidance and operational support to PCs for reporting suspected cases of non-compliance with European regulations, including REACH, CLP, and Regulation (EU) No. 528/2012 on Biocidal Products (BPR), among others (46, 42, 50). These reports may arise from both clinical and non-clinical cases that could lead to accidental toxicological exposures or difficulties in managing emergencies related to exposure to substances, mixtures, or other types of hazardous products. Scientific and epidemiological research conducted by several PCs, also in collaboration with the CNSC of the ISS, has yielded important results that support the development and improvement of reporting procedures and the establishment of a robust information flow among all stakeholders involved.

Reporting procedures will be carried out by PC personnel authorized to access the web platform. Reports will be submitted using the updated surveillance reporting form.

Reports submitted by PCs concerning suspected non-compliance (where non-compliance is not the direct cause of exposure) will refer to:

- labelling;
- packaging;
- safety data sheets (SDS);
- product type/intended use;
- product not notified in the APP/PCN Portal;
- incorrect notification;
- colours and shapes resembling those of other products (e.g., cosmetics or toys).

In the future, if appropriate, the platform may also allow the reporting of near miss cases. This term refers to situations in which a PC receives a request for information regarding a potentially non-compliant product in the absence of a clinical case (i.e., no exposure has occurred).

4. ASSESSMENT OF THE TYPE OF REPORT

Cases reported by PCs will be uploaded to the dedicated IT platform and will be available in real time to all relevant stakeholders. Reports of sentinel events and non-compliance will be reviewed by a team of experts (detailed below), who will assess them based on shared criteria within the established timelines. Due to their severity, alert reports will be transmitted directly to the Competent Authorities for appropriate and timely action.

4.1 Assessment team

Within the framework of the Project, and in compliance with the expected outcome indicators and timeline, a panel of experts was established to assess and manage sentinel events and non-compliance cases reported by Italian PCs.

The team is composed of eight experts distributed as follows:

- *Italian AReSS Puglia*
1 expert;
- *ISS*
4 experts, of whom 3 are responsible for aspects related to SIN-SEPI and 1 for coordination with the Network of Control Laboratories;
- *Apulia PC*
1 expert;
- *Pavia PC*
1 expert;
- *Milan PC*
1 expert.

The experts were nominated by the Directors of their respective institutions and approved through a vote during a plenary meeting of the “Sentinel” WG. The composition of the team may be subject to modification if necessary.

4.2. Sentinel event

4.2.1. Not a case

None of the conditions set out in Section 3.1 are met.

4.2.2. Possible

At least one of the conditions described in Section 3.1 is met; however, there is uncertainty regarding potential operator responsibility due to improper use of the product.

4.2.3. Probable

At least one of the conditions in Section 3.1 is met, and no operator-related errors have been identified.

4.2.4. Confirmed

Evidence of a probable or possible sentinel event is further substantiated through epidemiological analyses, including large-scale data evaluations, using information from annual consultations submitted by collaborating PCs to SIN-SEPI under formal agreements with the ISS.

4.3. Alert

Reports of alert cases must be submitted *directly* to the Competent Authorities/Institutions (e.g., ISS, Ministry of Health, Carabinieri Command for the Protection of Health-Italian NAS, Regions) for the appropriate actions to be undertaken. Reference is made to Section 5.2 (Figure 1) for the alert reporting flow.

4.4. Non-compliance with current regulations

Following submission, the report will enter the processing phase. The assessment team will receive the report, which will be evaluated within the timeframes established by the specialists.

After evaluation, the team will determine whether the report constitutes:

- *validated non-compliance*: initiation of surveillance procedures;
- *non-validated non-compliance*: with justification provided by the team.

Any surveillance actions undertaken will also be shared with users of the dedicated platform. All data will in any case be transmitted to ISS (SIN-SEPI group) for the processing of statistical and epidemiological information.

Within the assessment procedure for non-compliance, the expert team may decide to involve the Network of Control Laboratories coordinated by the ISS (51) for qualitative and quantitative evaluations of hazardous products.

5. INTERVENTION WORKFLOWS AND TIMELINES

The three types of reporting are outlined below, together with their respective intervention workflows and expected timelines. For each report, it will be necessary to enter the required information in the dedicated electronic form, accessible via personal credentials, and to select the appropriate type of report.

5.1. Sentinel event

Identification, dissemination and control of sentinel events within the PC – example of internal management:

- *Identification of the event*
 - staff training within each PC to raise awareness on event identification.
- *Dissemination of the event within the PC*
 - “Sentinel event” form template included in the data collection record of the centralized PC database.
 - linkage of the form template to an email notification sent to the manager/director or designated reporting contact or group of reporters (which may include specific individuals or all staff involved in the data collection interface).
- *Monitoring of reported sentinel events through the form template*
 - possibility of using a query to extract sentinel events from the centralized PC database.
- *Monitoring of sentinel events not reported through the form template*
 - periodic extractions of the chemicals category.

PCs notify the event as soon as possible, and the report is visible to all platform users. Specifically, a notification is sent to the Team/Authority/PCs/Institutions involved in the event assessment and management processes.

Each Team member submits their assessment within 7 days of the report.

The shared assessment is published within 15 days of the report.

The diagram below illustrates the reporting workflow for sentinel events (Figure 1).

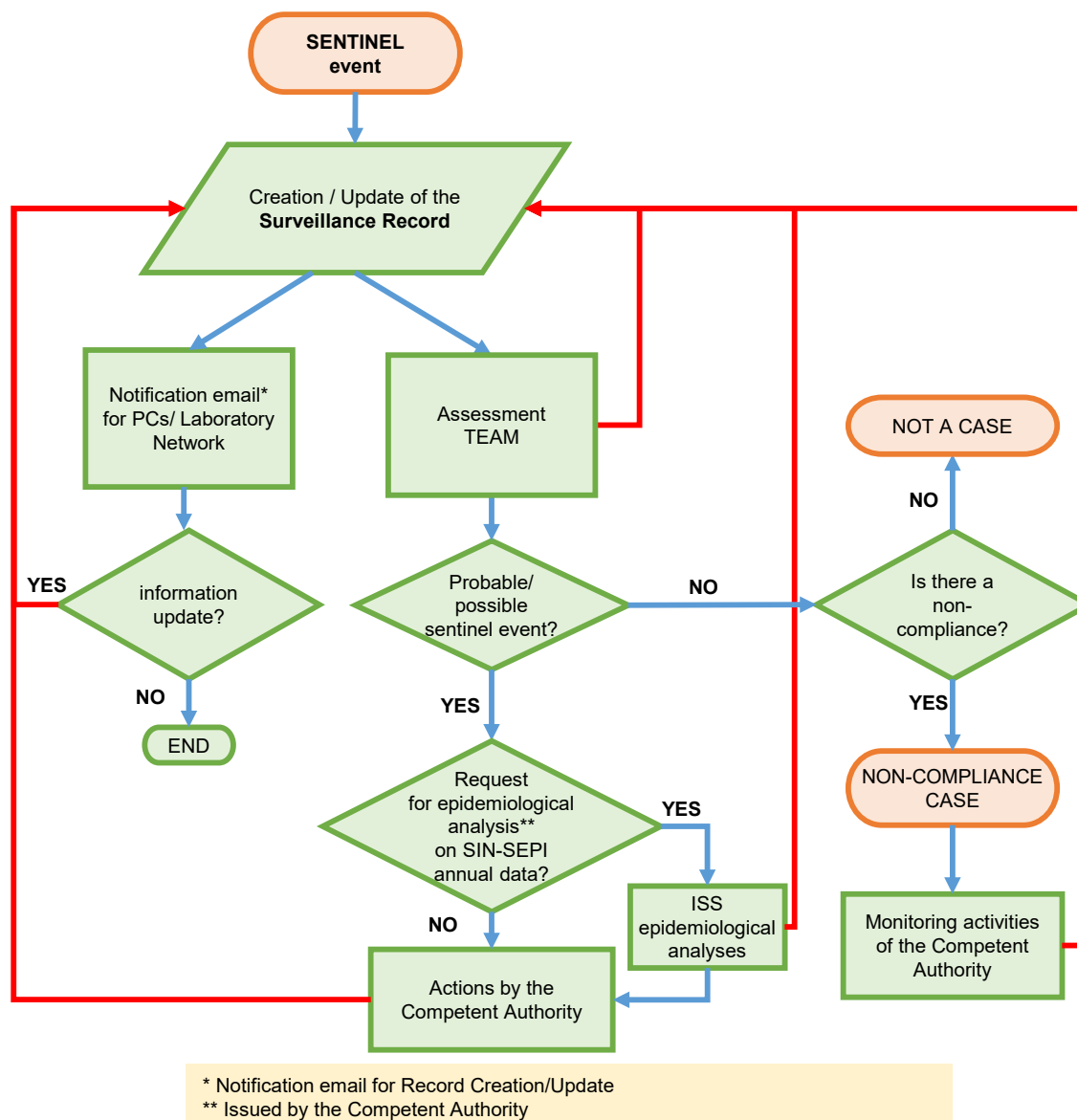


Figure 1. Diagram illustrating the reporting workflow for sentinel events (or cases)

5.2 Alert

The alert (or warning) report must be received, as rapidly as possible and without intermediaries, by the competent Authorities/Institutions. Such reporting falls under the exclusive responsibility of the PC Director or their delegate.

The reporting system must include an acknowledgment/feedback mechanism confirming receipt by the competent Authorities/Institutions to which it is addressed. Through the reporting system, other PCs must also receive the alert notification in order to raise their level of attention with regard to their cases and the identified product(s). Other PCs may supplement the alert report with any similar cases.

The reporting workflow for alerts (or alert notifications) is outlined below (Figure 2).

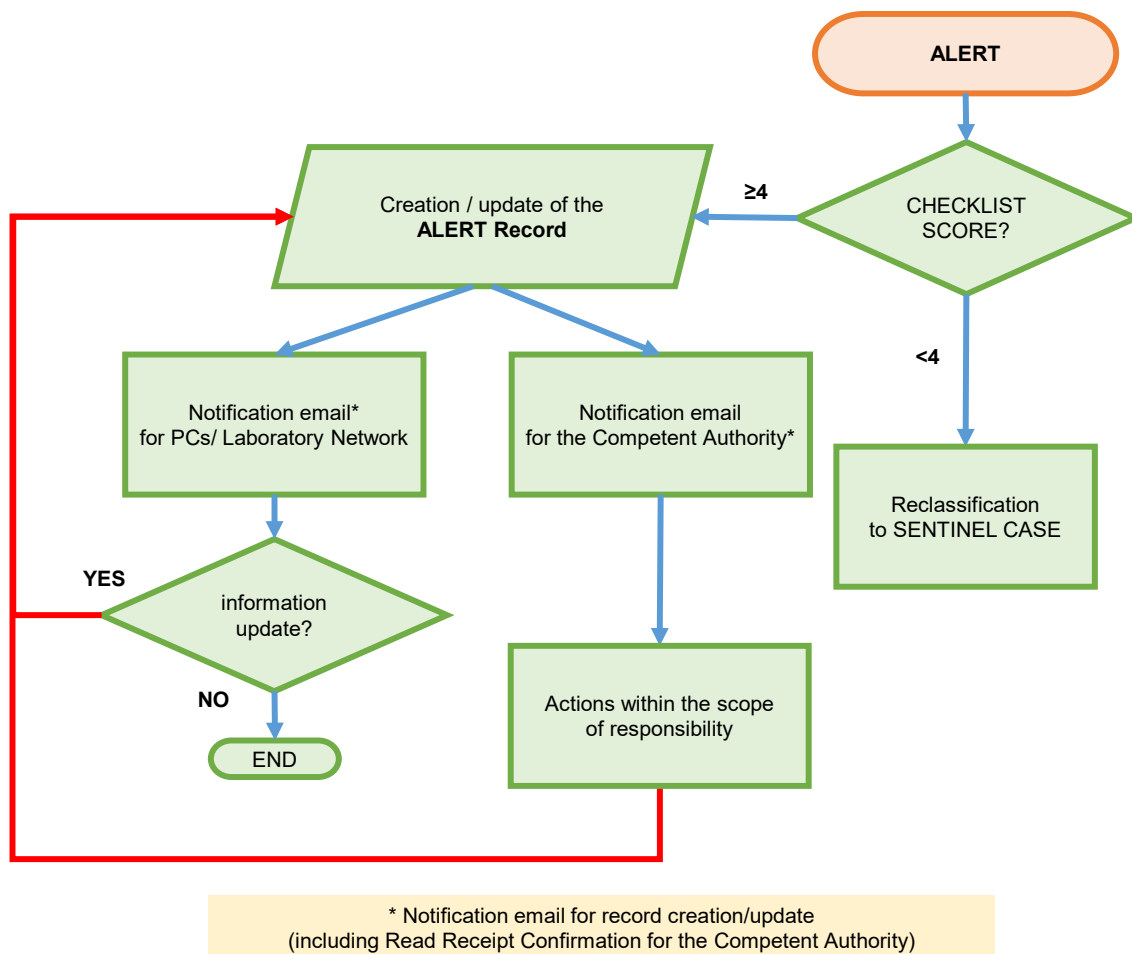


Figure 2. Diagram illustrating the reporting workflow for alert notifications (or warnings)

5.2.1. Flowchart - Contact directory

A contact directory will be established, in coordination with the Competent Authorities (e.g. Ministry of Health, Regions), in order to identify the relevant offices (at least including email addresses and telephone numbers) for alerts concerning:

- biocides / Italian medical-surgical devices;
- plant protection products;
- detergents;
- cosmetics;
- toys;
- tobacco and related products, including electronic cigarettes and refills;
- medical devices;
- other categories of chemical products;
- substances (e.g. sodium nitrite).

5.2.2. Access to the reporting system and identification of the reporter

Reporting is carried out through the platform via restricted access, providing for a single account per PC (with the possible option of using a digital signature to be evaluated).

The reporter must be the head of the service or a delegated person operating within the PC. In all cases, the reporter's details must be clearly visible in the alert report submitted to the competent Authorities/Institutions.

The availability of the reporter or their delegate(s) must be ensured during the 48 hours following submission, to allow interaction with the Competent Authorities/Institutions. Telephone availability may be ensured through a dedicated 24-hour contact number.

5.2.3. Status of progress of the report

The reporting system will include a record/archive of all alert reports submitted, associated with a status identifier indicating the progress of the reporting process:

- Status 1 → alert under preparation (managed by the reporting PC);
- Status 2 → alert submitted (with the possibility of integration by other PCs);
- Status 3 → alert received by the Competent Authorities (linked to feedback from the Authorities);
- Status 4 → alert archived (completion of the process).

The system must allow alerts to be saved in standby mode, with the possibility of subsequent modification and/or integration (depending on the stage of progress).

5.3. Non-compliance with current regulations

The reporting of non-compliance is carried out by PC representatives through a short form, as it is not necessary to provide detailed information on exposed individuals (such as personal data, symptoms, or any treatment undertaken). It is possible to select the type of non-compliance and provide a brief textual description. This information may also be supplemented by attaching documents such as SDSs, labels, etc.

In the dedicated form, the following steps are required:

- Select the type of non-compliance (e.g. labelling, packaging, SDS, etc.)
- Complete the minimum dataset required for the selected item:
 - text field for a brief description
 - field for uploading files (labels, SDSs, photos, etc.)
- Close the report and submit it to the expert team.

When the report is under processing, it will be visible to all PCs, which may view but not modify it; this is allowed in cases where another PC has identified the same situation, with the possibility of supporting the evidence through a second report.

After assessment by the team, the outcome will be visible to all users of the platform. The diagram below illustrates the reporting workflow for non-compliance cases (Figure 3).

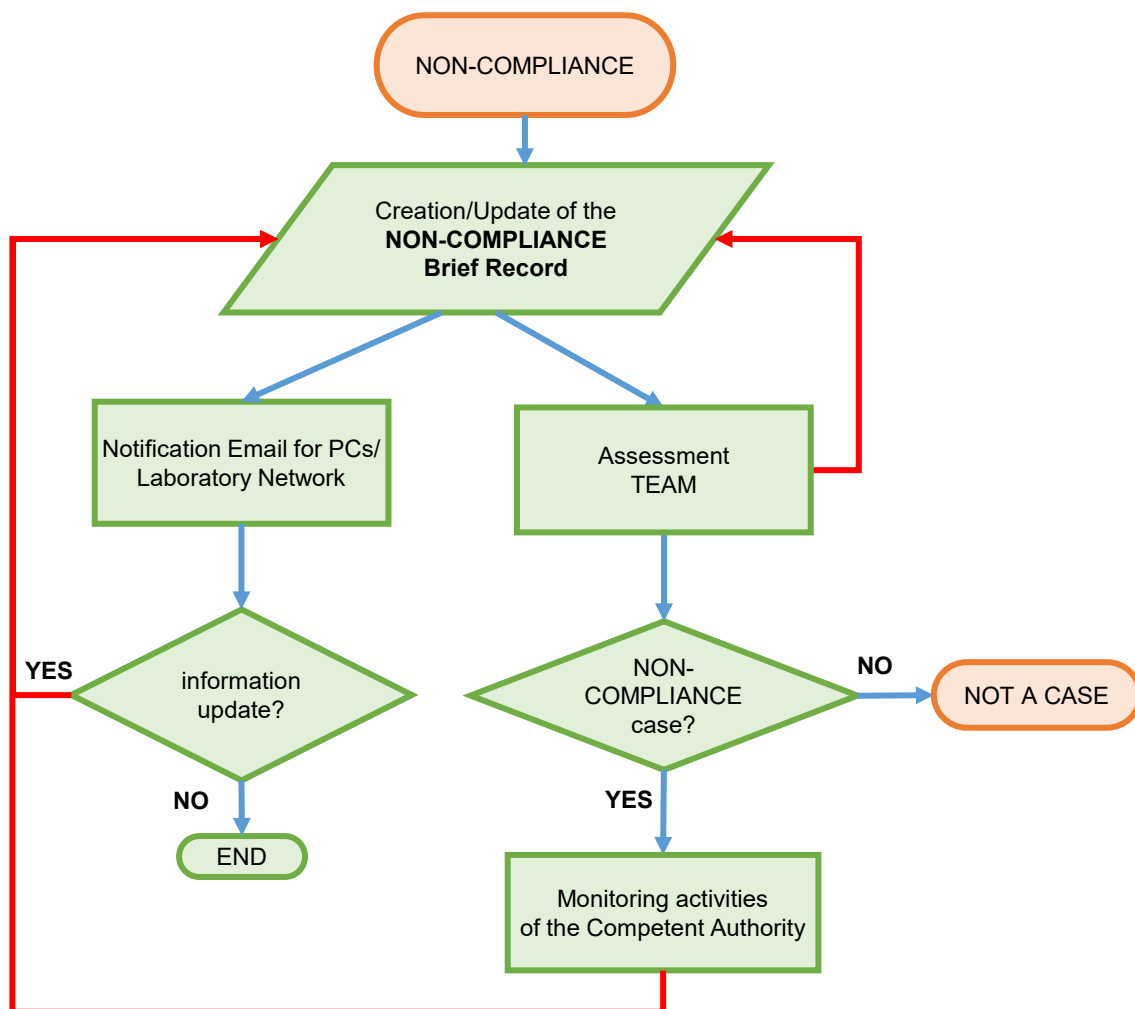


Figure 3. Diagram illustrating the reporting workflow for non-compliance cases

6. INFORMATION TO BE PROVIDED IN THE ONLINE SURVEILLANCE FORM

6.1. Sentinel event

The variables useful for describing the sentinel event are listed below. Some are drawn from the minimum dataset set out in Annex II of the State-Regions Agreement No. 56/CSR of 28 February 2008 (7) for the recording of exposures managed by PCs, while others are newly introduced variables aimed at providing a more detailed characterization of the sentinel event:

- *Reason for reporting*
 - Packaging colours/shape resemble those of other products (food, food product, other chemical product, dietary supplement, medicinal product, toy, other);
 - The colour/shape/smell/consistency of the contents resemble those of other products (food, food product, other chemical product, dietary supplement, medicinal product, toy, other);
 - Unusual route of exposure;
 - Symptoms unusually severe in relation to the hazard class of the product;
 - High frequency of cases over time or within a specific area;
 - Packaging/safety closure/cap/label not appropriate for the type of product;
 - Presence on the label of wording typically used for medicinal products and dietary supplements (e.g. tablets, pills, lozenges);
 - Incorrect or inappropriate instructions for use reported on the label;
 - Presence on the label of images or text resembling those of other products.
- *Caller*
 - Private citizen;
 - Hospital;
 - General practitioner / paediatrician;
 - Veterinarian;
 - Pharmacist.
- *Type of request*
 - Sentinel event (case).
- *Route of exposure*
 - Ingestion;
 - Oral mucosa;
 - Inhalation;
 - Dermal;
 - Ocular.
- *Symptoms*
 - Oropharyngeal;
 - Gastrointestinal;
 - Respiratory;
 - Cutaneous;
 - Ocular;
 - Nervous system;

- Cardiovascular;
- Haematological;
- Metabolic;
- Hepatic;
- Renal.
- *Circumstance of inadvertent exposure – level 1*
 - Occupational;
 - Non-Occupational.
- *Circumstance of inadvertent exposure – level 2*
 - Normal use;
 - Uncontrolled access (children <12 years / individuals lacking capacity);
 - Environmental contamination;
 - Misuse: improper mixing;
 - Misuse: use without precautions;
 - Misuse: unintended use;
 - Misuse: inappropriate transfer;
 - Therapeutic error: confusion with a medicinal product;
 - General error: confusion with food/food product;
 - General error: confusion with a dietary supplement;
 - General error: confusion with another product.
- *Exposure setting (place)*
 - Domestic environment;
 - Healthcare setting;
 - Workplace;
 - Public place;
 - Agriculture;
 - Other.
- *Frequency of exposure*
 - Single;
 - Repeated.
- *Use of protective equipment*
 - Yes;
 - No;
 - Unknown.
- *Identification of the agent involved* (with the possibility of uploading an image of the product/substance and any other relevant documents)
 - Commercial name of the product
 - Main agent category according to EuPCS (52) and non-EuPCS (cosmetics, tobacco and related products, toys, self-defence devices).
 - Point of purchase of the product
 - Supermarket
 - Home care store
 - DIY store
 - Internet
 - Market

- Physical state of the product
 - Solid
 - Liquid
 - Gaseous
- Product form
 - Powder
 - Granules
 - Solid tablets
 - Single-dose units with liquid and solid components (capsules)
 - Single-dose liquid units (capsules)
 - Liquid
 - Liquid spray
 - Gel
 - Aerosol
 - Other.
- *Treatment setting*
 - Home treatment;
 - Medical examination;
 - Hospitalization;
 - Other.
- *Type of treatment*
 - Stabilization of vital functions;
 - Decontamination;
 - Symptomatic treatment;
 - Antidote therapy;
 - Elimination techniques.
- *Toxicological risk*
 - Non-toxic (symptoms not related);
 - Possible poisoning;
 - Confirmed poisoning (symptoms present and consistent).
- *Poisoning Severity Score (PSS) (53)*
 - PSS 0: no poisoning;
 - PSS 1: minor poisoning;
 - PSS 2: moderate poisoning;
 - PSS 3: severe poisoning;
 - PSS 4: fatal.

6.2. Alert

The fields for the description of the alert, listed below, must enable a timely and clear description of the issue to be brought to the attention of the Competent Authority:

- description of the clinical case;
- patient's clinical condition;

- circumstances of the event (inadvertent or intentional);
- place;
- products/substances involved (with the possibility of uploading an image of the product/substance and any other relevant documents).

6.3. Non-compliance with current regulations

The variables for non-compliance cases must specifically describe the type that led to the report. Detailed information on the characteristics of the exposed individual is generally not required.

The types of non-compliance are listed below.

- *Reports concerning labelling*
 - likely label and pictogram size not appropriate for the packaging capacity;
 - product name on the label different from the one reported in the SDS;
 - absence of an indication of the substances contributing to the classification of the mixture with respect to acute toxicity, skin corrosion or serious eye damage, germ cell mutagenicity, carcinogenicity, reproductive toxicity, respiratory or skin sensitization, specific target organ toxicity (Specific Target Organ Toxicity, STOT), or aspiration hazard;
 - pictograms that differ or are missing between the label, the notification in the APP/PCN Portal, and the SDS;
 - verification of the UFI (Unique Formula Identifier): consistency between the UFI on the label and the one notified in the APP, and verification of the presence or absence of the UFI in accordance with the requirements of the aforementioned European regulations.
- *Reports concerning packaging*
 - the packaging does not prevent leakage of the contents;
 - the material constituting the packaging and its closure are deteriorated due to contact with the contained mixture;
 - failure or loosening of the packaging and its closure;
 - the packaging has a shape or design that may attract and arouse the curiosity of children;
 - the packaging has a shape or design that may mislead consumers;
 - the packaging has a shape or design similar to that used for food, medicinal, or cosmetic products, such as to be misleading;
 - packaging that should be equipped with a child-resistant closure;
 - whether single-use soluble packaging is contained in rigid outer packaging;
 - the soluble packaging dissolves rapidly, releasing the liquid contents in less than 30 seconds;
 - the soluble packaging does not have sufficient compressive strength to prevent breakage following accidental compression by a child.
- *Reports concerning the Safety Data Sheet (SDS)*
 - possible inconsistencies and non-compliance in the SDS, across all sections and parts.

- *Reports concerning product type/intended use*
 - product type: presented as a disinfectant (biocide or Italian Medical-Surgical Devices) but actually a detergent or cosmetic product;
 - medical device classified as a detergent or disinfectant (occupational setting), etc.
- *Reports concerning products not notified in the APP/PCN Portal*
 - following verification, the product is not present in the APP/PCN Portal
- *Reports concerning probable incorrect notification*
 - all possible cases of probable incorrect notification or products/substances notified under a commercial or chemical name that prevents proper identification.
- *Reports concerning colours and shapes resembling those of other products (e.g. cosmetics or toys) – excluding sentinel cases.*

It should be noted that, if there is a need to report a sentinel event whose causative agent also presents regulatory non-compliance, it is possible to open a sub-form within the “Sentinel event” section.

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APPENDIX A
Scientific evidence identified in literature
on sentinel events, alerts, and near misses

Literature searches were conducted in 2023, and the results are presented in chronological order in each table according to the type of report.

A1. Scientific evidence on sentinel events

Author (year)	Type	Country	Setting	Definitions
Rutstein <i>et al.</i> (1983)	A	USA	G/O	<i>Sentinel event</i>: a preventable event of disease, disability, or premature death whose occurrence acts as a warning signal that the quality of preventive and/or therapeutic medical care may need improvement. <i>Occupational Sentinel event</i>: disease, disability, or premature death related to the occupational setting, the occurrence of which may: – prompt epidemiological or industrial hygiene studies; – serve as a warning signal that substitution of materials, engineering controls, personal protective measures, and medical care may be required.
Carr <i>et al.</i> (1989)	A	USA	G	<i>Sentinel event</i>: adverse health outcomes such as diseases, disabilities, and deaths that are considered preventable given current knowledge and technologies in medical and public health practice. The occurrence of such events serves as a warning signal of potential deficiencies in one or more areas of healthcare. The event may: - be based on a single case that requires the implementation of preventive actions for the entire population (e.g. botulism); - be based on epidemiological analyses showing increased frequency of diseases associated with other conditions (e.g. vascular complications leading to death in individuals with pre-existing diabetes); - address medical-social issues (e.g. alcoholism, suicide) and psychiatric conditions requiring in-depth investigation.
Aldrich & Leverton (1993)	A	USA	ENV	<i>Statistical Sentinel event</i>: based on the occurrence of multiple events in temporal and geographical clusters. The following can be identified: - single events; - localized clusters of rare events (a single event in a population may be physiological, but even two events in a given area, in the presence of a risk factor for the disease, may qualify them as sentinel); - changes in a “logical” pattern, used to study common diseases that are rare in specific age groups; - surrogate events: when a cluster of a few cases of a disease does not have sufficient statistical power to be considered a sentinel event, until cases of another disease occur that share a similar etiology. The two clusters, considered together, identify a risk linked to the persistence of a common etiological factor, often of environmental origin.
Reilly <i>et al.</i> (1996)	A	USA	O	A case definition is provided for inclusion in the study, based on the association between asthma and occupational exposure.
Friedman (1998)	A	USA	H/ HOSP	It draws on the work of the Joint Commission.
Henry <i>et al.</i> (1999)	A	USA	H/ HOSP	No definitions are provided.
Saufl (2002)	A	USA	H/ HOSP	No definitions are provided.
Flink <i>et al.</i> (2005)	A	USA	H/ HOSP	No definitions are provided.
Min. of Labour, Health and Social Policies (2009)	P	Italy	H/ HOSP	<i>Sentinel event</i>: adverse event of particular severity, potentially preventable, that may result in death or serious harm to the patient and leads to a loss of public confidence in the healthcare system. The occurrence of even a single case is sufficient to trigger an in-depth investigation aimed at determining whether avoidable or reducible factors contributed to the event and to implementing appropriate corrective measures by the organization. List of sentinel events.

Author (year)	Type	Country	Setting	Definitions
Maine Dept. of Health and Human Services (2015)	GL	USA	H/ HOSP	<i>Sentinel event:</i> - serious and preventable health events; - unexpected death or transfer of a patient to another healthcare facility not related to the natural course of the disease; - permanent loss of function not related to the natural course of the disease or to any other underlying condition of the patient; - unexpected death or permanent loss of function occurring within 48 hours after a treatment or procedure in a healthcare facility, not related to the natural course of the disease or to any other underlying condition of the patient; - patient suicide occurring within 48 hours of discharge from a healthcare facility; - unexpected perinatal death or severe permanent loss of function in a newborn with a birth weight greater than 2,500 grams, not related to the natural course of the disease or to any other condition affecting the newborn or the mother, nor to appropriate treatment of the disease or other condition in a healthcare setting.
Safer Care Victoria (2019)	GL	Australia	H/ HOSP	<i>Sentinel event:</i> a patient safety adverse event that is entirely preventable and results in unnecessary or avoidable harm to a patient. Harm implies impairment of body structure or function and/or any detrimental effect arising from disease, injury, suffering, disability, or death.
Steelman <i>et al.</i> (2019)	A	USA	H/ HOSP	No definitions are provided.
Lazio Region (2021)	GL	Italy	H/ HOSP	<i>Sentinel event:</i> a particularly serious adverse event that results in death or severe harm to the individual and/or undermines public trust in the National Health Service (NHS) and healthcare professionals. Following its occurrence, an immediate investigation is required to determine any avoidable or reducible contributing factors, with subsequent implementation of appropriate corrective measures and their monitoring.
Patra & de Jesus (2023)	A	USA	H/ HOSP	It draws on the definition established by the Joint Commission and highlights that, since 2013, reportable adverse events also include those involving staff, visitors, and hospital suppliers.
McGowan <i>et al.</i> (2023)	A	USA	H/ HOSP	<i>Sentinel event:</i> specific subcategory of the broader concept of “medical error”.
Rodziewicz <i>et al.</i> (2023)	A	USA	H/ HOSP	It draws on the definition established by the Joint Commission and emphasizes errors committed by healthcare personnel in hospital settings affecting patients, which are often underreported for a variety of reasons (e.g. reputational concerns, fear of penalties).
Joint Commission (2025)	GL	USA	H/ HOSP	<i>Sentinel event:</i> an unexpected event involving death or serious physical or psychological harm, or the risk thereof. Serious injury specifically includes loss of limb or function. The phrase “risk thereof” includes any process variation for which a recurrence would carry a significant chance of a serious adverse event. Such events are termed <i>sentinel</i> because they signal the need for immediate evaluation and response. Each organization should establish its own definition of a sentinel event, tailored to its specific context.

A: Article; GL: Guideline; P: Protocol

G: General; O: Occupational; ENV: Environmental; H: Healthcare; HOSP: Hospital

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A2. Scientific evidence on alerts

Author (year)	Type	Country	Setting	Definitions
WHO (2003)	Web site	International	PH	<i>Alert</i> : hospital-acquired disease affecting three or more individuals in the same healthcare unit who meet the clinical case definition for SARS, with disease onset occurring within the same 10-day period.
Ministry of Health (2006)	P	Italy	PH	No definitions are provided.
Berry <i>et al.</i> (2014)	A	Canada	PH	<i>Alert</i> : a condition that may lead to an increase in morbidity and mortality within a region.
Denecke & Atique (2016)	A	Switzerland	PH	No definitions are provided.
Mercado-Mallari (2018)	A	Canada	H/HOSP	No definitions are provided.
WHO (2020)	G	International	PH	The document states that reporting alerts to the Competent Authorities is part of the toxicovigilance responsibilities of a Poison Centre, in order to enable the Authorities to implement the necessary preventive and/or corrective measures.
Sarthak Vage <i>et al.</i> (2020)	A	India	PHS	No definitions are provided.
Presidency of the Council of Ministers (2021)	LG	Italy	PHS	<i>Alert</i> : Notification to the Competent Authority of a risk that requires, or may require, rapid action in one or more Regions or in one or more Member States. The notification must be issued without undue delay and, in any case, within 48 hours from the moment the risk becomes known.
CDC (2022)	Web site	USA	PH	Several newsletters from the HAN system are available concerning potential emerging health risks (e.g. the spread of new viruses).
Malik <i>et al.</i> (2023)	A	Pakistan	PHS	No definitions are provided.
Alameda County Public Health Department (2023)	Web site	USA	PH	<i>Alert</i> : a notice conveying the highest level of importance and ensuring immediate action or attention.
ISS (2023)	Web site	Italy	PH	No definitions are provided.
European Commission	Web site SARR	Europe	PH	<i>Alert/Warning</i> : the competent authorities for the EWRS (Italian SARR) or the European Commission issue an alert when a serious cross-border health threat: - is unusual or unexpected with respect to place and time; - causes significant morbidity or mortality, or spreads rapidly; - exceeds national response capacity and affects more than one EU country; - may require a coordinated response at EU level.
European Commission	Web site RASFF	Europe	PH	<i>Alert</i> : notifications issued when a food or feed posing a serious risk to health is placed on the market and rapid action is required.

A: Article; GL: Guideline; P: Protocol

PH: Public Health; PHS: Public Health and Safety

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A3. Scientific evidence on near misses

Author (year)	Type	Country	Setting	Definitions
Van der Schaaf (1995)	A	The Netherlands	O	<i>Near miss</i>: Situations in which an operator, manager, or team behaves in an unexpected manner and prevents a system breakdown or restores standards of safety and reliability. <i>Near misses</i>: - are more frequent than actual incidents (providing a broad database); - contain important information about how the system functions, as they show why things did not go wrong, thereby offering the opportunity to implement control measures across the entire process; - serve as a psychological reminder of the need to remain vigilant for one's own safety and for that of others.
Wilson (1998)	A	United Kingdom	H/HOSP	<i>Near miss</i> : an event that, without luck or effective management, would likely have resulted in an incident.
Berry <i>et al.</i> (2000)	A	USA	H/HOSP	<i>Near miss</i> : events that were identified and averted before evolving into adverse events (in line with the Joint Commission definition)
Nashef (2003)	A	United Kingdom	H/HOSP	<i>Near miss</i>: - the adverse event occurs but does not result in harm because the systems in place to detect and correct it function properly; - the adverse event occurs but does not result in harm despite one or more detection and correction systems failing; - the adverse event occurs (with one or more detection and correction systems failing) and results in harm, although not reaching the worst possible outcome.
WHO (2005)	GL	International	H/HOSP	<i>Near miss</i> : a serious error or incident that could lead to an adverse event but does not do so, either by chance or because it is intercepted (also referred to as a potential adverse event).
Jeffs <i>et al.</i> (2008)	A	Canada	H/HOSP	<i>Near miss</i>: - a metaphor for system vulnerability; - a constructive interruption in the pathway of clinical error; - the illusion of a patient-centered care system that does not actually ensure patient safety. Patients' relatives may feel compelled to monitor the patient because they perceive them as not being safe.
Alamgir <i>et al.</i> (2009)	A	Canada	O	<i>Near miss</i> : an event that nearly affected a healthcare worker and could have caused harm, but did not occur due to chance or, if it did occur, did not necessitate medical treatment or emergency care.
Kessels-Habraken <i>et al.</i> (2010)	A	The Netherlands	H/HOSP	<i>Near miss</i>: - an event that did not reach the patient; - an event that reached the patient but caused no harm; - an event that reached the patient and caused harm.
Cure <i>et al.</i> (2011)	A	USA	H/HOSP	<i>Near miss</i> : events that had the potential to harm patients but did not, due to prompt intervention or favorable circumstances. The reporting of near misses has become an increasingly important tool in advancing patient safety, as it provides insight into potential system risks before patients are affected by adverse outcomes.
Jeffs <i>et al.</i> (2012)	A	Switzerland	H/HOSP	<i>Near miss</i> : events with potentially significant consequences for patient safety that have been prevented. Near misses arise when an initial failure (organizational or technical) or a human deviation is identified and mitigated, without causing harm or a negative outcome.
Marks <i>et al.</i> (2013)	A	USA	H/HOSP	<i>Near miss</i>: - an event that did not reach the patient; - an event that may have reached the patient but caused no harm (due to specific interventions or by chance); - an event that may have reached the patient but did not result in serious harm (due to specific interventions, preventive actions, or chance).
Sheikhtaheri (2014)	LE	Iran	H/HOSP	<i>Near miss</i>: - an incident that does not reach the patient due to formal and planned interventions and programs (previously established by the organization); - an incident that does not reach the patient due to a chance or unplanned intervention.

Author (year)	Type	Country	Setting	Definitions
Kang <i>et al.</i> (2017)	A	Korea	H/HOSP	<i>Near miss</i> : an event, situation, or error that occurred but was identified and intercepted before reaching the patient (also referred to as a close call).
Pfroh <i>et al.</i> (2021)	A	USA	H/HOSP	<i>Near miss</i> : an event or situation that did not result in harm to the patient, but only by chance. This luck may reflect the patient's resilience or a timely and fortuitous intervention. A near miss is also referred to as a close call.
Australian Commission on Safety and Quality in Health Care (2021)	GL	Australia	H/HOSP	<i>Near miss</i> : An incident or potential incident that was prevented and did not result in harm, but had the potential to do so.
Isaksson <i>et al.</i> (2022)	A	Sweden	H/HOSP	<i>Near miss</i> : what could have happened to the patient but did not occur.
Feng <i>et al.</i> (2022)	A	China	H/HOSP	<i>Near miss</i> : an incident that does not reach the patient. Near misses are more frequent than adverse events and can provide timely indications of system vulnerabilities without any cost to the patient, constituting a valuable source of learning for healthcare organizations. Moreover, learning from near misses is essential for adopting a prospective and proactive risk management approach.
Woodier <i>et al.</i> (2022)	A	United Kingdom	H/HOSP	<i>Near miss</i> : events that almost led to a significant outcome but were prevented by human intervention before reaching the patient, in the absence of physical or engineering controls. This definition facilitates the identification of areas for improvement where, either by chance or through human oversight, potential harm was averted.
OSHA (2022)	Web site	USA	O	<i>Near miss</i> : a situation that is immediately and instinctively recognized, often accompanied by a surge of adrenaline and a sense of relief (close call).
University of Sunshine Coast, Australia (2023)	GL	Australia	H/HOSP	<i>Near miss</i> : an incident that had the potential to cause injury or illness to individuals, pose a health hazard, and/or result in damage to property or the environment.
Rodziewicz <i>et al.</i> (2023)	A	USA	H/HOSP	<i>Near miss</i> : - any event that could have had adverse consequences for the patient but did not; - potential adverse events that could have caused harm but did not, either by chance or because someone or something intervened. <i>Near misses</i> provide opportunities to develop preventive strategies and actions and should receive the same level of analysis as adverse events.
Chafik <i>et al.</i> (2023)	A	Morocco	H/HOSP	<i>Near miss</i> : an event in which a woman nearly died but survived a complication occurring during pregnancy, childbirth, or within 42 days following the termination of pregnancy.
Santos & Jones (2023)	A	USA	H/HOSP	<i>Near miss</i> : an unplanned event that almost occurred and has the potential to result in patient harm. The analysis of near misses allows healthcare systems to identify and revise protocols before adverse outcomes take place.
AHRQ (2024)	Web site	USA	H/HOSP	<i>Near miss</i> : an event that had the potential to result in adverse consequences but did not, and was otherwise indistinguishable from actual adverse events except in its outcome. In a near miss, an error occurred, but the patient did not experience clinical harm, owing to early detection or chance.

A: Articolo; GL: Guideline; LE: Letter to Editor
H: Healthcare; HOSP: Hospital; O: Occupational

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APPENDIX B

Case studies

B1. SENTINEL EVENTS

CASE STUDY 1

Inadvertent ingestion of a chemical product whose shape and colour resemble those of a dietary supplement

Ingestion of a solution obtained from a chemical product (“bleach tablets”) due to confusion with a multivitamin dietary supplement in effervescent tablet form (Figure B1). The product label includes the term ‘tablets’, which is commonly used for medicinal products and dietary supplements.

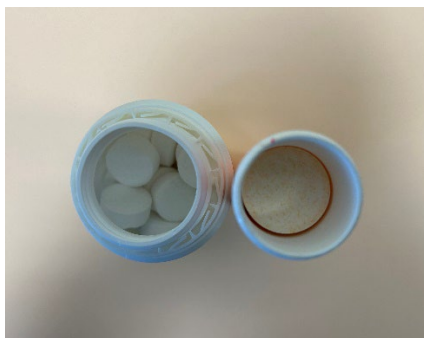


Figure B1. Chemical product resembling a dietary supplement in shape and colour: bleach tablets (right) and dietary supplement tablets (left).

CASE STUDY 2

Inadvertent ingestion of a gel toilet product in a cage container whose size and colour resemble those of a food product (candy)

Example 1. A 10-month-old child: while crawling, the child reached the product placed in the toilet. He experienced three episodes of vomiting: one immediately, one during transport, and one in the emergency department. In the emergency department, the oral cavity was unremarkable and respiratory examination was negative. He was treated with simethicone drops (Mylicon), a mucosal protective agent (magnesium–aluminium hydroxide), followed by ranitidine (Ranidil). He was discharged after 8 hours of observation.

Example 2. A 1 year and 5 months-old children: she detached the cage from the toilet and put her hands into the accessible gel component. After putting her hands in her mouth, she developed oral hyperaemia and sore throat. Gastroprotective treatment was administered at home.



Figure B2. Gel toilet product resembling a food item (candy) in size and colour: pink gel cages (right) and pink lollipops (left)

CASE STUDY 3

Inadvertent ingestion of a laundry product in water-soluble single-dose capsules

Example 1. A 90-year-old woman with senile dementia bit a liquid laundry detergent capsule in water-soluble single-dose form, mistaking it for a chocolate/candy. She did not vomit but developed respiratory distress, requiring endotracheal intubation. The patient died 10 days after the exposure².

Example 2. An 81-year-old man with senile dementia opened a package of purple single-dose liquid detergent capsules. He bit the capsule, mistaking it for a plum. He immediately developed coughing and foaming, followed by sore throat and a single episode of diarrhoea within two hours after exposure. Gastroprotective treatment was administered at home.

Example 3. An 82-year-old man with senile dementia cut open a purple single-dose liquid detergent capsule and ingested its contents, mistaking it for a plum. He experienced two episodes of diarrhoea within three hours after exposure. Gastroprotective treatment was administered at home.



Figure B3. Water-soluble single-dose liquid laundry detergent capsules resembling candies

CASE STUDY 4

Inadvertent ingestion of a household chemical product (“bleach tablets”) with a cap of the same colour as that of a pharmaceutical product (“effervescent digestive granules”)

The label indicates, among the instructions for use, that the product can be placed directly in the dishwasher to facilitate the removal of organic residues and to keep the dishwasher clean. For this purpose, consumers typically store it in the kitchen. The product label features the image of a lemon.



Figure B4. Household chemical product (“bleach tablets”) with a cap of the same colour as that of a pharmaceutical product (“effervescent digestive granules”):
on the right, the cap of a container with effervescent antacid digestive granules;
on the left, the cap of a container with effervescent bleach tablets

² Celentano A, Bissoli M, Sesana F, Scaglione F. Why are adults exposed to liquid laundry detergent capsules? *Clinical Toxicology* 2023;61(11):999-1000.

CASE STUDY 5**Inadvertent ingestion of a household chemical product (“granular drain cleaner”) packaged in a container similar in size and shape to a food product (“table salt in a dispensing jar”)**

A 95-year-old woman confused a container of effervescent digestive granules with the one of a ‘granular drain cleaner’. She was transported to the emergency department presenting with hyperaemia and oedema of the oral cavity, glottic oedema, and respiratory distress. The patient developed severe injuries and complications during hospitalization and died two weeks after exposure³.

The product is intended for clearing kitchen drains. For this purpose, the consumer had left the product on the kitchen counter next to the salt.



Figure B5. Household chemical product (“granular drain cleaner”) packaged in a container similar in size and shape to a food product (“table salt in a dispensing jar”): on the right, a salt container with dispenser; on the left, the drain cleaner

CASE STUDY 6**Inadvertent exposure to a cosmetic product whose shape, colour, and consistency resemble those of a food item**

Example 1. An 82-year-old woman bit a piece of the product “Marron Hennè”, mistaking it for a chocolate bar (Figure B6). She experienced two episodes of vomiting.



Figure B6. Marron Hennè product, mistaken for a chocolate bar.

Example 2. A 12-year-old boy ingested a solid highlighter product (“Splendido splendente”), mistaking it for a chocolate candy (Figure B7), and subsequently developed two episodes of diarrhoea.

³ Celentano A, Bissoli M, Sesana F, Scaglione F. Accidental exposures to caustic drain cleaners. In 41st International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 25-28 May 2021, Virtual Meeting. *Clinical Toxicology*. 2021;59(6):568-569.



Figure B7. Solid highlighter product (‘Splendido splendente’) mistaken for a chocolate candy.

Example 3. An 80-year-old man bit a body wash product (‘Passion Fruit Delight’), mistaking it for a sweet (Figure B8). He experienced a single episode of vomiting immediately after ingestion.



Figure B8. Body cleansing product (‘Passion Fruit Delight’) mistaken for a sweet

CASE STUDY 7

Inadvertent exposure to a cosmetic product whose packaging shape and content colour resemble those of a food item.

Example 1. Ingestion of a body wash whose packaging size and content colour resemble those of a bottle of white wine (Figure B9).



Figure B9. Body wash resembling a bottle of white wine in terms of packaging size and content colour: food product (wine bottle) on the right and cosmetic product (body wash) on the left.

Example 2. Ingestion of a body wash whose packaging size and content colour resemble those of a bottle of rosé wine (Figure B10).



Figure B10. Body wash resembling a bottle of rosé wine in terms of packaging size and content colour: food product (wine bottle) on the right and cosmetic product (body wash) on the left

B2. ALERT

CASE STUDY 1

Adulterated/counterfeit product

Severe and fatal methanol poisoning in alcohol abuse

Over the course of a few days, the PC managed three cases, admitted to three different hospitals of poisoning from an unknown substance characterized by severe metabolic acidosis. Clinical findings and laboratory results led clinicians to suspect methanol poisoning.

Biological samples were therefore sent to a specialized laboratory, which confirmed the diagnostic suspicion. In the meantime, the PC was contacted by other hospitals regarding similar cases.

The cases shared the following characteristics: (1) all patients were admitted to hospitals in the Sicily region; (2) they involved individuals (predominantly young women) of Romanian nationality.

Further anamnestic investigation revealed that the patients had the habit of adding denatured ethanol to spirits in order to increase their alcohol content.

Accordingly: (1) an alert was issued to the competent national and regional authorities; (2) a diagnostic and therapeutic protocol for the management of methanol poisoning was prepared, distributed, and made available to all hospitals in Sicily and other regions; (3) guidance was provided on the procurement of specific antidotes. Subsequent investigations revealed that a local company was marketing a product intended for cleaning purposes containing methanol instead of ethanol.

In the following months, a further 18 cases of similar poisonings occurred within Romanian and Polish communities in the same region, resulting in fatal outcomes (13 out of 18 cases) or severe permanent sequelae.

CASE STUDY 2

Product used for purposes other than those for which it is registered

Cases of severe acute poisoning (some with fatal outcomes) due to nitrites used for harmful/self-harm purposes

Over a four-month period, the Pavia PC was contacted regarding six cases of patients presenting to hospital facilities in six different cities across the country, all with severe methemoglobinemia due to voluntary ingestion of sodium nitrite purchased online.

The Forensic Medicine Service of the Verona University Hospital (a) had already reported to the Judicial Authority two previous cases of death due to nitrites/nitrates, and (b) was able to confirm, through a separation analytical technique (capillary electrophoresis), the high presence of nitrates and nitrites in some of the acute poisoning cases with methemoglobinemia identified by the Pavia PC.

The products used (nitrites) had been mainly purchased via the web: there are websites online providing instructions on the use of sodium nitrite for self-harm purposes ('suicide kits'). The PC issued an alert regarding this increasing issue and the need to equip emergency medical services (ambulances/advanced life support vehicles) with the specific antidote, namely methylene blue.

B3. NON-COMPLIANCE

CASE STUDY 1

Product not notified in the APP/PCN Portal

Patient accidentally exposed to a chemical product classified as hazardous and not notified in APP or the PCN Portal. In this case, the cause of exposure is not related to the lack of notification; therefore, once it has been verified that the product falls within the categories requiring notification to the APP or PCN Portal, a report should be submitted through the appropriate platform for suspected non-compliance.

CASE STUDY 2

Product classified as a Biocide or Italian Medical-Surgical Device but notified as a detergent or cosmetic product

A patient was accidentally exposed to a chemical product classified as a biocide or Italian Medical-Surgical Device but notified as a detergent or cosmetic product. In this case, the exposure is not attributable to incorrect categorization. After verifying the correct classification, a report for suspected non-compliance should be submitted through the appropriate platform.

Example 1. The product is a surface detergent but is marketed with claims of effectiveness against coronavirus and bacteria (Figure B11). The instructions for use indicate application of the product as such, a characteristic typical of disinfectants, rather than involving physical and/or mechanical action as required for detergents (Regulation (EU) No 528/2012, Article 3(1)(a)). The product was notified as a detergent.

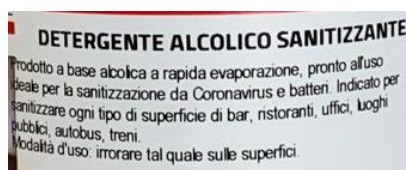


Figure B11. Detergent product claiming disinfectant properties on the label

Example 2. Hand sanitizing gels, classified as cosmetic products, bearing the label “antibacterial” (Figure B12). As presented, the product appears to have disinfectant properties (biocide or Italian Medical-Surgical Devices); however, it has been notified as a cosmetic product.



Figure B12. Hand sanitizer bearing an “antibacterial” claim on the label

CASE STUDY 3

Labelling

Patient accidentally exposed to a hazardous chemical product with:

- likely label and pictogram size not appropriate for the packaging capacity;
- product name on the label different from that reported in the Safety Data Sheet (SDS);
- absence of an indication of substances contributing to the classification of the mixture with respect to acute toxicity, skin corrosion or serious eye damage, germ cell mutagenicity, carcinogenicity, reproductive toxicity, respiratory or skin sensitization, specific target organ toxicity (STOT), or aspiration hazard;
- pictograms that differ or are missing between the label, the notification in the APP/PCN Portal, and the SDS;
- UFI verification: consistency between the UFI on the label and the one notified in the APP, and verification of the presence or absence of the UFI in accordance with the requirements of the aforementioned European regulations.

CASE STUDY 4

Packaging colours and shape

Reports concerning packaging, colours, and shape of the contents or packaging must derive from non-clinical cases; otherwise, a sentinel event report should be submitted.

Examples derived from non-clinical cases are provided below.

Example 1. Report derived from a non-clinical case. Slime products (toy category) presented in packaging resembling food items (Figure B13). In addition, fragrances and colours resemble food products such as caramel, sugar, and chocolate.



Figure B13. Slime (toy category) presented in food-like packaging (chocolate).

Example 2. Report derived from a non-clinical case. Slime (toy category) presented in food-like packaging; its fragrance and colour also resemble a food product, such as tomato sauce (Figure B14).



Figure B14. Slime (toy category) presented in packaging resembling food items (tomato purée)

GLOSSARY

Biocides: see definition in Article 3 of Regulation (EU) No 528/2012 of 22 May 2012⁴.

Chemicals: in the context of this document, it refers to substances, mixtures, and products that may have intrinsic hazardous properties and pose a risk arising from their use by consumers and in occupational settings.

Claim: an action or property attributed to a product and stated on the label. No characteristics may be attributed to the product that it does not possess and cannot possess in accordance with the applicable legislation.

Clinical case: a consultation referring to a new episode of human exposure, confirmed or suspected, involving one or more individuals.

Competent Authority: Central and regional authorities involved in surveillance, vigilance, control, and prevention activities in the field of chemicals.

Detergents: see definition in Article 22 of Regulation (EC) No 648/2004 of 31 March 2004⁵.

Exposure: an event that occurs when there is contact between a human being and a chemical at a given concentration and for a given period of time.

Inadvertent/Accidental event: an exposure episode in which the contact between the agent and the exposed individual is recognized as inadvertent/accidental or unintentional. Therefore, it refers to exposures with no intention to harm oneself or others.

Italian medical-surgical devices: a product that claims on its label an activity falling within the definitions set out in Article 1 of Presidential Decree No. 392 of 6 October 1998 and in the Ministry of Health Decree of 5 February 1999⁶.

Medical Devices: see definition in Article 2 of Regulation (EU) 2017/745 of 5 April 2017⁷.

Mixture: a mixture or solution composed of two or more substances (Article 2 of Regulation (EC) No 1272/2008 of 16 December 2008).

Near miss (context of chemicals): cases in which a report is received by a Poison Centre regarding the potential risk associated with the use of a product, without any actual exposure occurring. Such reports may suggest preventive measures capable of avoiding hazardous exposures to the product.

⁴ Europe. Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products Text with EEA relevance. *Official Journal of the European Union* L 167 27/6/2012, p. 1–123.

⁵ Europe. Regulation (EC) No 648/2004 of the European Parliament and of the Council of 31 March 2004 on detergents (Text with EEA relevance). *Official Journal of the European Union* L 104 8/4/2004, p. 1-35.

⁶ Italy. Ministry of Health. Provvedimento 5 febbraio 1999. Approvazione dei requisiti della domanda e relativa documentazione da presentare ai fini dell'autorizzazione all'immissione in commercio ed alla variazione di autorizzazioni già concesse per i presidi medicochirurgici. *Gazzetta Ufficiale – Serie Generale* n. 34 11/2/1999.

⁷ Europe. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance). *Official Journal of the European Union* L 117 5/5/2017, p. 1-175.

Packaging: see Article 35 of Regulation (EC) No 1272/2008 of 16 December 2008⁸.

Poisoning: exposure to a chemical agent resulting in related symptoms.

Product: in the context of this document, it refers to a substance/mixture placed on the market under a specific trade name and trademark, indicated on the label of a specific packaging.

Request for information: a consultation concerning the hazard characteristics of agents of various types, in the absence of a confirmed or suspected exposure event.

Substance: a chemical element and its compounds, in the natural state or obtained by any manufacturing process (Article 2 of Regulation (EC) No 1272/2008 of 16 December 2008).

Tabs: single-dose powder detergent tablets.

⁸ Europe. Regulation (EC) No 1272/2008 of the European parliament and of the council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. *Official Journal of the European Union* n. L 353 31/12/2008.

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