



Evaluation and Management of Patients with Methomyl Poisoning – A Case Report

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Abstract

The Apulian Poison Centre (PC) of Foggia, Italy, annually manages numerous consultations concerning certain or suspected poisonings from pesticides, starting at the same time a careful activity related to the risk assessment phase. The management of the exposure to pesticides and to other chemicals, and the alerting of the “National center for chemicals, cosmetics and consumer protection” at the Istituto Superiore di Sanità (ISS), actively contributes to the improvement of products quality and safety. Thus, leading to a reduction in the number of intoxications - and therefore of the accesses to the emergency services - allows greater protection for workers, bystanders, residents and consumers. The reported case of methomyl poisoning has been of fundamental importance both from the medical point of view and for the management of the intoxicated patient, both for the risk assessment actions, and for cooperation with the competent authorities, generating discussion points on the regulations in force between PCs and National Competent Authority. It follows that the feedback of intoxication in an emergency can lead to improvements in the management and risk mitigation measures in order to reach a greater protection of human, animal, and environmental health. In addition, the regulatory feedback deriving from these reports is an input to the increase product quality improvement (mixtures, labels, packaging, and risk communication) leading to a greater protection of potential exposed subjects. The importance of creating an information and management network that allows the optimization of the flow of information deriving from PCs arises. The actions taken are therefore described, both relating to the management of the emergency, and relating to the subsequent information flow and to the measures for containing the consequent risks.

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Background

The National Poison Centres (PCs) are services of the National Health System dedicated to the treatment, prevention of intoxication and adverse effects due to the exposure to chemical substances (including those considered of abuse) [1]. According to the requirements of the World Health Organization, the PCs are specialized structures in providing the community with information and toxicological advice [2], [3]. In the national Official Journal G.U. No. 65 of March 18, 2017 was issued the Prime Minister Decree of January 12, 2017, which defines new essential levels of assistance (ELA) [4]. In the new legislation, the PCs were inserted (art.36, par.1, letter h) between the areas of activity and hospital assistance (Chapter V, art.36), in this context art.46 shows: The National Health Service guarantees through the PCs specialist consultancy activities for highly complex toxicological problems, to support first aid operative units and other hospital and territorial services, as well as adequate surveillance, vigilance, and alert systems.

The inclusion of the PCs in the ELAs highlighted the importance of the specialist toxicological activities

in favor of the emergency urgency system and of all the territorial services, in addition to the consolidated contribution in the field of surveillance, vigilance, and alert.

PCs peculiar characteristics are the management of poisoning, toxicological analysis, surveillance, vigilance and alert, as well as scientific research, and training. In the surveillance, they are actively involved in the development, implementation, and evaluation of measures for the prevention of intoxication or chemical incidents.

They on average represent from 40% to 61% of cases of poisonings that a PC annually manages, all in close collaboration with institutions and authorities such as Ministries, Istituto Superiore di Sanità (ISS), AIFA, Regions, Universities, Hospitals, ASL, 118 (equivalent to the 911 phone number of other countries), first aid, public forces, civil protection, and other organizations or private companies (chemical, pharmaceutical chemists, factories in general) and private citizens. In addition, monitoring of adverse drug reactions, warning deriving from contaminated food, and beverages is active, including the sophistication and study of new psychoactive substances and smart drugs.

The operation of the PCs benefits from the cooperation between the centers themselves, at national and international level, as well as from other institutional bodies involved in prevention and intervention in the event of intoxication. The predominant activity of a PC is the management of acute intoxication. They are linked to prevention, vigilance, and reporting actions applied to various fields. From the environment to food, from drugs to chemicals, while the environment of exposure to these substances varies from the workplace to the domestic one, the latter counts the greater number than cases of exposure/intoxication given the lack of knowledge of the most common safety, product, and labeling rules.

To be recognized overall national territory and to become part of the capillary network of National PCs, nine in Italy, a PC should be able to meet specific quality and confidentiality requirements.

The D.Lgs. of March 14, 2003, No. 653 (implementation of the Directives 1999/45/CE and 2001/60/CE, subsequently repealed by the European Regulation (EC) n. 1272 of 16 December 2008 (CLP) [5] in Annex XI part D reports the quality and confidentiality criteria to be assured by PCs (Table 1) [6].

These criteria represent the foundation of the PCs and allow the performance on the innumerable work and research activities to which a PC is called.

In addition, a PC to operate as such needs recognition from its own region, of the Ministry of Health and the Ministry of Economic Development.

Furthermore, the definition of PC represents the access key for the consultation of the hazardous preparation archive (HPA) of the ISS [1.S].

In addition to the medical-toxicological activities necessary for continuous clinical research, PCs show a need to link to the evolution and updating of chemical risk assessment and management. It makes essential to include the figure of the specialist (evaluation and management of chemical risk) since this figure would be the link between PC and national competent authorities and regions in the field of risk assessment [4]. Therefore, the specialist should be able to be included among the regional competent authorities and related technical committees. A PC daily manages various consultations related to exposures, certain or suspected poisonings,

accidents, as well as all the activity related to prevention and vigilance. Even from a single case, it emerges cues for reports, supervisory activities and related assessments on chemicals. The risk management and assessment phase is fundamental for the protection of human, animal, and environmental health, improving the protection of workers and consumers against the risks that derive or may derive from exposure to chemical agents [7], [8], [9], [10], [11], [12].

Case Report

The health workers of the 118 station of Trinitapoli (BT) contacted the Apulian PC of the Azienda Ospedaliero Universitaria OO.RR. of Foggia, due to the accidental ingestion of an unknown amount of a mixture contained in a dark colored plastic bottle (from subsequent investigations, it has been ascertained that the bottle previously contained mineral water). From a first contact, the 118 operator, following an interview with the company owner, reports to the PC staff that the mixture contained a basic plant protection product of the active ingredient Methomyl (CAS 16752-77-5) [2.S], unspecified quantity. The first phase of data collection refers to the patient's cardio-respiratory arrest: On the spot and in itinerary a resuscitation assistance is provided with respiratory support, cardiac, and continuous monitoring. Upon arrival of the patient in the Emergency Room, the medical staff contacted the PC again and the PC specialist advised that emergency measures and support for airway patency and assisted ventilation if necessary, treatment of the coma and cardiorespiratory arrest and as an antidote treatment atropine and pralidoxime had to be administered empirically. In addition, blood sampling and instrumental continuous monitoring of hepatic-pancreatic-renal function and pseudocholinesterase (PChE) function, in addition to RX-Thorax and RX-Abdomen were prescribed. Subsequently, chest and abdomen CTs were performed without contrast medium. The PC staff setted a follow-up schedule to monitor the patient (Table 2).

Management of the suspected intoxication

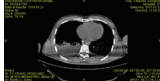
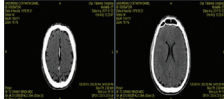
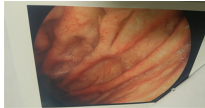
In all cases of suspected or ascertained intoxication by dangerous substances/mixtures and detergents, the Apulian PC of Foggia proceeds to the risk assessment and a careful investigation, so as to be able to better manage the exposure/intoxication/incident and improve the management of the intoxicated patient, deepening the knowledge and activities of supervision and prevention.

The research to individuate the chemical risk was carried out by an initial research on the

Table 1: The quality and confidentiality criteria of Italian PCs

Quality and confidentiality criteria of Italian PCs. D. Lgs n°65, 14 March 2003
Premises and equipment exclusively dedicated to the PC
Activities 24 hs a day
Juridical state that characterizes the PC as a recognized structure within the National Health Service
Registration of all the interventions carried out
Dedicated personnel with adequate professional competence
Direct access to telephone counseling for the general population
Adequate IT structures that are not accessible on the web
Incoming telephone line dedicated to the PC, as well as telephone line for telematic connection
Activity documented for at least 2 years in accordance with the resolution CEE 90/C and 329/03
Formal responsibility for the use of confidential information to be implemented through customized access keys

Table 2: The investigations' results

Hematochemical tests/ instrumental examinations	Levels/reports
AST	371 U/L
ALT	390 U/L
LDH	656 U/L
PChE	1 st day – 4504 (normal range 5320-12920) 25 th day – 5290 28 th day – 5412
Pancreatic amylase	153 U/L
Lipase	145 U/L
CPK	303 U/L
RX thorax	Left mediastinal parenchyma consolidation
CT scan of the lungs (without contrast)	Right lobe parenchymal consolidation areas affecting the dorsal segment of the upper lobe and most of the lower lobe. Associated with perifocal and ground-glass opacities. Right pleural effusion with ground-glass opacities in lingula pulmonis
	
CT scan head (without contrast)	Diffuse edema with loss of the normal gray-white differentiation of the two cerebral hemispheres. The surface of the brain appears smooth
	
Endoscopic examination	24 January, 2017: Distal esophageal mucosa ulcerated and easily bleeding. Lesser curvature erosion. Normal pylorus. Nothing against the first and second parts of the duodenum. Distal erosive esophagitis, diffuse gastropathy 2 March 2017: Endoscopic aspect compatible with the evolution of the demarcations of gastric wall lesions
	
Exitus	Thirty-third day

toxicological and chemical-physical properties of the active substance in the international Micromedex Solution® database, Hazard Management Information section [3.S]. It has emerged that the active substance in question belongs to the carbamate family, less toxic active organophosphorus molecules but with similar clinical effects [13], [14], [15], [16], [17], [18].

They also inhibit the enzyme acetylcholinesterase with a nicotinic symptomatologic manifestation but of short duration and reversible action, with the possibility of specific antidote treatment that involves the use of atropine and pralidoxime, the latter, empirically administered in case of high quantities ingested or in the suspicion of the presence of other substances with nicotinic and muscarinic action (e.g., organophosphorus).

After identifying, the nature of the intrinsic properties of the active substance and taking into account the dangers from the same, we have searched for plant protection products that contain this active ingredient [19], [20], [21].

Thus, making a complete evaluation taking into consideration also other substances present as co-formulants, agronomic antidotes, synergists, etc., that could have toxicological properties and therefore played a role in the accidental intoxication of the worker.

Since the commercial name was not available initially, the investigation was carried out by doing a research on the database of plant health products of the Ministry of Health.

The research was carried out by entering the name of the active substance and as administrative status only authorized products, leaving free the item of parallel import and that of products for ornamental plants and

edible plant products, resulting in three plant protection products containing the active substance methomyl.

Since, according to the labels, the mixtures were classified as dangerous in agreement to the EC 1272/2008 (CLP), they were searched also in the HPA of the National Health Institute (formerly ISS), where several dangerous preparations containing the active ingredient methomyl have been found.

They were assessed for the management of intoxication both for the active substance and for the presence of other possible dangerous substances. The evaluation of the safety data sheets (SDS), the compositions reported in the HPA and the evaluation of the current legislation authorizing the active substance methomyl, has produced fundamental data.

In particular, starting from the Directive 2009/115 / EEC, consideration has been given to paragraphs 7 and 10 (Table 3), from which important points of discussion emerged, such as the requirement to incorporate substances with emetic activity in case of intentional or accidental poisoning and to use methomyl products only for professional purposes.

Thus, it remained to check the substance(s) with emetic properties.

The research on the HPA allowed immediately the identification it in the sucrose octaacetate (CAS 126-14-7) and the confirmation was made with the evaluation of the intrinsic properties carried out on the Hazard Management Information section of the international Micromedex Solution® bank. There it was reported that it does not produce significant toxicity but which could be irritating to the eyes and skin and have a mechanical-irritating effect on the mucous membranes.

Then, the staff of the PC had only to understand what the cause of the cardiopulmonary arrest was and how it had arrived at such an important pulmonary and cerebral damage. The collection of this information allowed the chemical risk expert and the PC doctor to arrive to the following conclusion: "The accidental intoxication and therefore the cardiorespiratory arrest were definitely caused by the substance activates methomyl, for which the patient has been treated". Anyway the death has occurred due to causes not related to the active substance but to secondary damages (pulmonary effusion and diffuse bihemispheric edema) probably caused by the induced emesis of the coformulant. The induced or self-induced emesis, in fact, is always discouraged by all the guidelines of the national and international PCs since the second passage of the toxic could cause further damage.

In this specific case, there was a rise (second step) of the product causing shocking, loss of consciousness and subsequent pulmonary effusion, factors that have led to an important cerebral anoxia producing irreparable and irreversible damage.

The expertise of the chemical risk to carry out a correct and complete evaluation has followed the research

Table 3: European Commission Directive 2009/115/EC of August 31, 2009 amending Council Directive 91/414/EEC to approve the active substance methomyl

Par. 7	In the new dossier, the notifier submitted new data and new information and a re-evaluation was carried out, as shown in the supplementary report and in the EFSA Scientific Report on methomyl. It has, therefore, been shown that acceptable levels of operator exposure can be achieved by wearing additional protective devices compared to those indicated in the initial dossier. As regards risks to workers and bystanders, it has been clarified that no unacceptable risks are connected to the uses indicated in the new file. Finally, the risks to birds, mammals, aquatic organisms, bees, and non-target arthropods can be considered acceptable provided that the lowest dose among those indicated is duplicated and that appropriate risk management measures are implemented
Par. 10	However, to exclude any risk of intentional or accidental poisoning, it is appropriate to require that repellents and/or emetic agents be incorporated into plant protection products containing methomyl and that only the professional use of such plant protection products be authorized

of the two substances (methomyl and the co-formulating agent) on international databases, on the institutional site of European Chemicals Agency (ECHA), on SDS and the labels of several plant protection products.

This to understand if the accident had been caused only by human distraction (misuse) or if there were causes attributable to wrong information on the label or the SDS, packaging or the dilution of the mixture at the preparation site.

Evaluation of substances

The evaluation began with a study of the risk management section of the international Micromedex Solution[®] database from which both the chemical-physical properties and all the information concerning the uses were considered, as in the clinical case management phase, to the workplace exposure limit values, to the lethality values of the test substances, and to all useful information for one.

The study and characterization of the properties of the two test substances have been compared with the classification reported on the institutional site of the European Agency for Chemical Substances (ECHA).

It can be pointed out that only the active ingredient methomyl is classified (acute and chronic toxic to aquatic organisms category (1), and acute toxic category (2) for humans).

In the SDS of the mixture, in section 4, first aid measures; point 4.1, description of first aid measures, it is recommended to induce vomiting in case of ingestion, this procedure is not congruous as previously stated.

Finally, the evaluation of the labels of the plant protection product has brought to light another point of discussion for the competent authorities that the product before use must be previously diluted and that often the residual diluted mixture is stored in unsuitable containers as in the clinical case mentioned above (misuse).

Reporting for National Technical authorities and the Regional and National competent authority

After the closure of the clinical case and its assessment, the chemical risk expert of the PC of

Foggia has notified, through a report, the case to the competent regional and national authorities and to the national technical competent authority.

The purpose was not only of bringing the above-mentioned authorities to the attention of the specific case but also to possibly take preventive measures and care to reduce risks and accidents in the workplace.

Thus, implementing what is reported in article 45 of regulation (EC) 1272/2008 (Reg. CLP) paragraph 2 letter b (... to start a statistical analysis to examine any need to improve risk management measures) [22], [23], [24], [25], [26], [27], [28], [29], [30], [31].

The case was examined by the national technical body that provided a response to the notifying PC, reporting that – until today – it is mandatory, given the dangerousness of the active substance methomyl, to insert in the formulated mixtures of substances with an emetic action, with the sole purpose to remove the toxic in the shortest possible time [32], [33], [34], [35], [36], [37], [38].

Considering the event, there was also a great sensitivity to bring this issue on the European technical tables to be able to re-evaluate the danger of mixtures containing methomyl and the related mandatory prescriptions.

For labeling and preparation and preservation procedures of the mixture, it was definitely agreed that the good phytosanitary practices were not complied with.

Conclusions

The clinical case of mixture poisoning containing the active ingredient methomyl has been of fundamental importance from the medical point of view for the management of the intoxicated patient, and for the risk assessment, as well as for comparisons with the competent authorities, generating discussion points on regulations and regulations in force between PCs, national technical body, and national authority. This is really important to better define the best procedures for the manipulation of phytosanitary products and, eventually, for possible management of patients which accidentally or voluntary ingest such products.

From this, it follows that the feedback of an intoxication in emergency leads to improvements in management measures and containment of the risk to a greater protection of human health, animals, and the environment and to a significant improvement of products (mixtures, labels, and packaging) and a greater protection of potential exposed.

The importance of creating a network that allows the optimization of the flows of information deriving from PCs arises.

Authors' Contributions

All the authors equally contributed.

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