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Research Article International Journal of Pharmaceutical Sciences and Chemistry IJPSC-110
ISSN: 2641-712X

Optimization of the "Stockpile" of Sanitary Material (Drugs, Medical Devices, Personal Protective Equipment and Medicinal Oxygen) for the Management of Chemical Risk in Hospital Pharmacies Adjacent to Ethylene Oxide Production areas: An Operative Proposal

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Received Date: January 16, 2020; **Accepted Date:** January 22, 2020; **Published Date:** January 30, 2020

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Abstract

Chemical risk represents a current issue worthy of attention particularly in the field of pharmaceutical logistics. Currently, national management is delegated to the National Antidote Supply. The aim of this work is to propose are duction of health response times to a chemical-industrial accident defining strategic stocks in Hospital Pharmacies adjacent to the chemical production sites ethylene oxide falling within the SEVESOIII directive and the Prior Informed Consent regulation. In fact, the problem that a release of toxic substances may occur is an ever-present and real threat, just think of the disaster in Bhopal that led to the death of miles of people **[1]** or more simply to the release of toxic clouds like the one that happened in France **[2]**, hence the need to develop measures to reduce the damage on the population as much as possible. The study aspires to validate the hypothesized inventories on the basis of a chemical risk assessment obtained by a simulation of ethylene oxide release following a cyber-attack that will induce the opening of the valves of the implant and the release into the atmosphere of the whole substance stored within the production site (higher threshold requirements); clinical indicators generated by the aerial dispersion phenomena in gaseous state and the implant explosion will be evaluated. The release simulation was performed by the ALOHA® software (Environmental Protection Agency). The damage was estimated using quantitative methods, published by the TNO Organization in the Green Book. The quantification of toxicological properties of the substance was obtained through the consultation of "open" data including information on various databases and computational chemistry techniques (read-across analysis) obtainable through the Qsar Toolbox® software. The assessment of the minimum health material equipment to be made immediately available is performed taking into account the Resolution of 22 May 2003, which establishes the general criteria on the allocation of drugs and medical devices of a Level II Advanced Medical Post usable in case of catastrophe, the "Bioethics of Disasters" Document by the San Marino Committee of Bioethics and of the recent regulations dealing with medical oxygen as a drug and an antidote.

Keywords: Antidotes stockpile; Dual use; emergency medicine; Hazmat; prevention; Toxic industrial Chemicals

Introduction

In the course of history there have been important industrial accidents such as those of Bhopal **[1]** and Seveso **[3]** where the gas leak caused a high number of victims in Bhopal and major environmental disaster in Seveso. In Europe and Italy, the Seveso Directives and the last Seveso III (Italian Legislative Decree 26 June 2015, n.105) were created with the aim of reducing the possibility of accidents and risk on the population. Registration Evaluation Authorization of Chemicals (REACH Regulations (CE) n. 1907/2006) and Prior Informed Consent (PIC Regulations (CE) n. 649/2012) regulations were introduced in Europe to protect health and environment, respectively increasing the guarantee of the chemicals safe use and sharing the knowledge on the risk management. Growing international instability is increasing the risk of terrorist attacks through the use of chemicals **[4]**. The stuxnet virus experience and the ever-increasing

possibility of computer viruses interacting with industrial implants **[5]** have boosted the risk of toxic substances release following explosion or through the opening of valves that manage industrial processes.

Based on the considerations, this study proposes an operative plan for the optimization of resources already available on the territory towards the Hospital Pharmacies (HP), in terms of medical devices and drugs, including the medicinal oxygen in case they are adjacent to the ethylene oxide (EO) production sites. The objective of the study is to calculate the new stockpiles on the basis of what already defined by the Resolution of 22 May 2003, which establishes the maximum criteria for the allocation of drugs and medical devices for a Level II Advanced Medication Post (AMP), the Document of San Marino Committee on Bioethics "Bioethics of Disasters" **[6]** and the recent regulations that define medicinal oxygen as a drug (Italian Legislative Decree 219/2006) and an antidote **[7-8]**. The stockpiles' consistency, with suggestions of introduction or increase, is validated by means of computational chemistry simulations, with simulation software of the dispersions and vulnerability models. For the simulation of dispersion and the estimate of burn damage ALOHA® software developed by the Environmental Protection Agency was used, while for the simulation of lethal LC50 doses by inhalation on man Qsar Tool box developed by the European Chemicals Agency (ECHA) was employed.

Aim

The aim of this work is to adapt the stockpiles of drugs, medical devices and medicinal oxygen available into Hospital Pharmacies in order to face a chemical threat due to the release of ethylene oxide from a Seveso III company. The definition of needs is obtained by using level II AMP stocks already defined with the Resolution of 22 May 2003 and the allocations indicated in the Document of the Sammarinese Committee of Bioethics "Bioethics of Catastrophe" as basis for analysis, all in light of the regulatory re-classification of oxygen as a drug and antidote and of recent innovations in the field of emergency medical devices. The stockpiles composition will take into account two types of ethylene oxide damage: by inhalation after simple release and by burn following explosion.

Material and Methods

The Areal Hazards of Hazardous Atmospheres (ALOHA®) software from the Environmental Protection Agency (EPA) was used for the simulation of gas dispersion and burn damage. Google Earth software was used for map display while OECD Qsar Toolbox was used for the simulation of Lethal Concentration 50 (LC50) on man. Quantitative estimation models of damage contained in the "green book" published by the TNO Organization were used for the estimation of the damage of the people involved. The stockpiles estimation was hypothesized starting from the stocks listed in the resolution of 23 May 2003 and from the document of the San Marino bioethics committee "bioethics of catastrophes". The amount of released chemical substance was calculated considering the upper threshold requirements. Toxicological Information Is Retrieved From EPA, the European Chemicals Agency (ECHA) and the National Institute for Occupational Safety and Health (NIOSH) toxicological databases. Additional information was retrieved from the Safety DataSheet.

Scenario

The simulation took into account two exposure scenarios: the first with the release of a toxic cloud following the implant valves' voluntary opening, the second with the action range assessment of thermal waves starting from the cistern following an explosion.

Different colors have been used to identify different hazards. In both simulations, the same parameters have been applied to the cistern (51 tons of OE, 10 m height and 4 m diameter of the tank, for a total of 126 m^3 volume with an exit point 2 m above the ground). The atmospheric parameters were constant: 15 ° C, 3 knots wind speed, relative humidity of 50% and no thermal inversion.

Chemical Release Without flames

"OECD Qsar Toolbox" provided an Lc50 value equal to 691 ppm. The ALOHA® software was used to simulate the gas dispersion. When the chemical compound is released without Flames, O expands quickly and extensively. Different colors are visualized in GI Representation function of different gas concentrations. Red for the higher levels of concentration (in ppm) and yellow for the lowest concentration, as reported in (**Figure 1** and **Table 1)**.

Figure 1: Release of OE, in orange Lc50 691 ppm calculated with Read-Across method.

Zone	Threat Zone	Area	Perimeter
ORANGE - 800 ppm (IDLH)	1.8 km	3.36 km^2	7.03 km
RED - 691 ppm Lc50 From Read-Across	1.9 km	3.61 km^2	7.26 km
YELLOW - 200 ppm (AEGL3)	2.9 km	6.54 km^2	9.53 km

Table 1: EO distribution according to ppm and related areas.

Gas Effects After explosion

A simulation of thermal wave damage following the explosion of the cistern containing OE was carried out. In case of Boiling Liquid Expanding Vapor Explosion (BLEVE) generated by OE, we obtained three different areas divided in different colors by different thermal intensity. Red color for 10" of lethal thermal radiation, Orange for 2nd degree burns after 60" of explosion, and yellow for third degree burns in 60", as results reported in (**Figure 2** and **Table2)**.

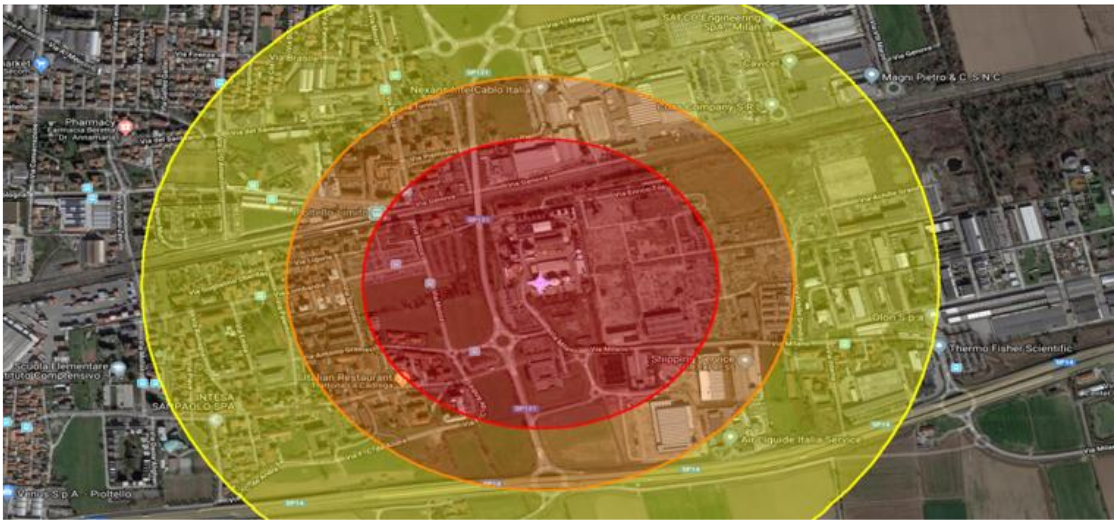

Figure 2: Bleve generated by OE.

Zone	Threat Zone	Area	Perimeter
RED - 10.0 kW/m2 potentially lethal within 60"	366 m	0.422 km^2	2.30 km
ORANGE - 5.0 kW/m2, 2nd degree burns within 60"	523 m	0.859 km^2	3.29 km
YELLOW - 2.0 kW/m2 pain in 60"	820 m	2.12 km^2	5.16 km

Table 2: Results of OE BLEVE release simulation.

Exposure Rates and Toxicological considerations

In this section the effects after exposure to the OE were calculated both in the case of the explosion- free release and in the case of BLEVE. In the first case, the gas leakage was simulated following a cyber-attack which led to the opening of the valves. The areas were divided according to the toxicological parameters (IDLH, Lc50, AEGL3). The assessment of the incidence of population was made through the Probit function originated by the Lc50 calculated with the QSar Tool box equal to 691 ppm, obtaining a parameter a = -12.65.

The function of Probit thus matched to the Lc50 is equal to:

$$Pr = -12,65 + 1 \ln(C^n t)$$

The function, taking into account the propagation curve of cloud concentration in space and its relative persistence in terms of minutes, made it possible to calculate the mortality rate at 200 m intervals for the length of the inhabited centre involved, as reported in (**Table 3)**.

Distance (meters)	External Concentration (ppm)	Time exposure (minutes)	% Mortality
400	71500	2	100
600	19600	4	100
800	7620	7	99
1000	3860	7	70
1200	2190	9	48
1400	1360	9	16
1600	920	10	5
1800	710	12	3

Table 3: Mortality rates as a function of distance.

In order to obtain the average Death-Rate, the harmonic mean of mortality was performed as a function of distance obtaining, as value, the mortality rate percentage of the inhabited centre, considering the outdoor concentration of 12.10. not being able to know the number of exposed people, the exposure estimation in terms of people involved was carried out on a second level AMP receptive capacity of 50 seats, generating 6 people at imminent risk of life of which 2 disabled, taking into account the percentage of people with disabilities in the population equal to 15% **[9]** and their double mortality compared to able-bodied people **[10]**.

The remaining part of the population involved (equal to 44 people) should be treated as a yellow code, taking into account the large extent of the area concerned at levels higher than those defined by the Acute Exposure Guideline Levels(AEGL3).

For thermal damage assessment, we divided the area in three different thermal exposure zones: 10 kW/m^2 as potentially lethal in 60", kW/m^2 for 2nd degree burns in 60" and 2 kW/m^2 able to cause pain in 60". We estimated the damage for each zone using a formula reported on Green Book available in two versions, one for the mortality rate and the other for the burns assessment. The formula for hydrocarbons exposure is:

$$Pr = -36.38 + 2.56 \ln (t * q^{4/3})$$

Where t is the time of exposure in seconds, q is the intensity of thermal wave in kW/m^2; the only variation between the first and the second version is in the q parameters: for the mortality rate is $q^{4/3}$ while for not mortal burn sis $q^{4/3}$=1.25. For a 10Kwsq/m exposure there results are 9% mortality, 99% 1st degree burns, 16% of 2nd degree burns, and 9% of 3rd degree burns.

Results

We compared the number of exposed people both after the gas release and after the heat wave, with stocks expected for level 2 AMP in the Resolution of 22 May 2003, taking into account the medical protocols for the treatment of oxide ethylene damage **[11]**.

In the case of ethylene oxide release as gas and of the epidemiologically most common type of damage (pulmonary edema) the result between the associated therapy and the hypothesized stocks is as follows **[12]**, (**Table4)**.

Medical drug/device typology	Stockpiles in the 22 may 2003 Resolution	Estimated needing for 6 red codes management
Furosemide	300 vials 20 mg/2ml	1500 mg (Max)
Nitroglycerin	30 vials 50 mg/50 ml	1000 mg (Max)
Morphine	450 vials 10 mg/ml	60 mg (Max)
Sol. Sodium chloride 0,9%	300 phials 500 ml	Up to 24 Phials 500 ml
Sol. Ringer Lactate	600 phials 500 ml	23 Phials 500 ml
Sol. Glucose 5%	50 phials 500ml	6 Phials 500 ml

Table 4: Comparison of present drugs and quantities estimated for acute pulmonary edema treatment.

The table shows that for acute pulmonary edema treatment the stock of 500ml physiological solutions usable for infusion treatments in case of hypovolemia and for any ocular chemical burn appears to be adequate; anyway it would be necessary to consider further uses of the physiological solution for infusion therapies or for the washing of possible wounds of various kinds and consequently, given the high versatility of use, an increase is suggested.

The 5% glucose infusion solutions for D & W / SRP and pulmonary edema treatment and Lactate Ringer appear to be appropriate as the pharmaceutical specialties Furosemide, Nitro-glycerine and Morphine. From the consultation of the list in the Resolution of May 22, 2003, these shortcomings emerge**:**

- Absence of walking aids for disabled persons such aswheelchairs;
- Lack of individual protection devices for first responders such as tyvek suits, FFP3 masks, gloves with chemicalprotection;
- Absence of emergency medical devices such as adult/ pediatric intraosseous infusion systems [13], disposable laryngoscope, adult/ pediatric manual respiratory units, nasopharyngeal and or pharyngeal\ tubes, nasal atomizer systems for the emergency administration ofdrugs;
- Absence of medicinal oxygen among the pharmaceutical equipment's to be always available and of the relative electro medicals for the administration (at least 6 portable pulmonary ventilators).

In particular, the absence of medicinal oxygen can be quantified considering the requirement of 15 L/ minute of medicinal oxygen to be administered to emergency patients as foreseen by the protocols **[14]**. The need for medicinal oxygen per patient can be summarized as per (**Table 5)**.

Oxygen cylinders	1 person	2 people	3 people	4 people	5 people	6 people
at 200 atm	24h	24h	24h	24h	24h	24h
2 liters	54	108	162	216	270	324
5 liters	22	44	66	88	110	132
7 liters	16	32	48	64	80	96
40 liters	3	6	9	12	15	18

Table 5: Consumption of cylinders of different sizes depending on the patients.

In the case of burn damage following the explosion, the results of comparison between the defined drug list and the simulated needs are the following**:**

- Introduction of drugs such as antibiotics like 2g ceftriaxone, thermo stable adrenaline with injector, gauze of silver sulfadiazine and connectives;
- Introduction of medical devices such as adult / pediatric suction and suction tubes, anti-burn paints of various sizes, sterile tongue depressors and personalizing visors.

Discussion

The simulations provided an estimation of the number of people exposed both to episodes of toxical inhalation and burn damage. Based on the processed numbers, the stocks of drugs and devices in the II level AMPs were then tested, revealing a total absence of the medical oxygen and related electro medical products useful for oxygen administration, even during the transport phases. A more general lack emerged in terms of non-modernization of medical devices usable in the emergency. Lacks have also emerged in terms of the aids that can be used by disabled people. Even at the level of the consistency of drugs and medical devices, taking into account the treatment protocols and the number of exposed persons, the consistency of stockpiles appeared to be improvable and necessary to increase for some items.

From this study emerges the need to modernize and expand the response capacity of Hospital Pharmacies adjacent to the production sites of SEVESO III substances such as ethylene oxide, encouraging the management of pharmaceutical warehouses together with the needs of hospital departments however based on criterion of efficiency and warehouse management originating from the First In - First Out method.

The greatest limit of the simulation consists in the inability of the software to estimate the three- dimensional conformation of the terrain (which takes into account the presence of building sor hills). The study also hypothesizes the management of "caregivers" generally associated with the presence of the disabled person.

Conclusion

European legislation and current laws increasingly aim to protect the environment and people, whether they are employees of companies at risk of a major accident than residents in the vicinity of the implants. On the other hand, the greater development of information technologies and relative risks of cyber-attacks have increased the risk of distorted use of the substances present the national territory against the civilian population. The current composition of the National Reserve Antidotes must therefore be adapted to new threats against population security, whether these are malicious or negligent nature.

The introduction of adequate stock of drugs like medicinal oxygen as a basic element in the treatment of intoxication from chemicals of industrial origin, and of medical devices that ensure a more rapid and safe administration of drugs is an ever-increasing priority, as is the adoption of personal protective equipment for First Responder understand dedicated aids for disabled people involved. It is also clear that considering as strategic stocks some pharmaceutical specialties of current use in HP in "sensitive" places leads to a reduction in the response times of pharmaceutical logistics, quickly facing a chemical event. Because of the possibility of several incidental scenarios, the essential task of the "competent" HP, which is appropriately identified, is attributable to the implementation of all the procedures necessary to allow adequate planning of the intervention and prevention, as much as possible, of the extension of damage to people, and constitutes a "resource" even the national strategic sphere.

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Citation: *Ciccotti M (2020) Optimization of the "Stockpile" of Sanitary Material (Drugs, Medical Devices, Personal Protective Equipment and Medicinal Oxygen) for the Management of Chemical Risk in Hospital Pharmacies Adjacent to Ethylene Oxide Production areas: An Operative Proposal. Int Jr Pharma Scie and Chem: IJPSC -110.*