Hazard and Safety Management in Industrial Bio-based Processes

Valeria CASSON MORENO, Ph.D., Department of Civil, Chemical, Environmental and Materials, University of Bologna, via Terracini n.28, 40131 Bologna (Italy)
Valerio COZZANI, Professor, Department of Civil, Chemical, Environmental and Materials, University of Bologna, via Terracini n.28, 40131 Bologna (Italy)

Despite the importance that biotechnological process (bioprocesses) are assuming worldwide in the last decades, process safety aspects are not evolving at the same pace as the scale-up of related technologies. In the present paper, a novel methodology for hazard identification and safety management in biotechnological processes is described addressing both conventional hazards and specific biohazards. The focus is on major accidents prevention and safety management. The results of the methodology can be used, as shown in the present work, in the framework of emergency planning.

Biological hazard; Hazard Identification; Major accident hazard; Industrial biotechnological processes; Emergency Planning.

1. Introduction

Process safety management systems (PSMSs) were historically developed in the context of conventional chemical and process industry (e.g. oil&gas, fine chemicals, polymers and resins), and only recently others industries (such as pharmaceutical) adopted PSMSs even if no regulations require it except for Seveso Directives in Europe (European Parliament and Council, 2012). Even though bio-based processes might be perceived as safer technologies, having a lower impact with respect to traditional chemical processes, recent studies showed that in the recent years many accidents occurred in bioprocess industry (Casson Moreno et al., 2016b; Casson Moreno and Cozzani, 2015).

Indeed with respect to traditional chemical engineering processes, bioprocesses involve biological hazards (biohazards) associated to the presence of microorganisms, defined as infectious agents that present a risk, or potential risk, for human health, animals or environment. Biohazards are for bioprocess industry, a new specific process safety element to take care of, along with conventional risks, such as fires, explosions, etc (CCPS - Center for Chemical Process Safety, 2010).

A review on risk assessment methods made by the authors revealed that it is not available in literature a holistic technique for hazard identification specific to industrial scale bioprocesses (Casson Moreno et al., 2016a; Casson Moreno and Cozzani, 2018). Only few studies made a gap analysis about the application of conventional methods for risk assessment to bioprocesses (Angel et al., 2015; Harms et al., 2008; Mollah, 2005; Pietrangeli et al., 2013; Pinkenba and Statement, 2006; Salm et al., 2017). Several authors remarked that there is not a specific and standardized methodology to approach biological risk assessment in industrial processes (Caskey et al., 2010).

From one hand, existing methods and regulations (European Parliament, 2000; HSE, 2013; U.S. Environmental Protection Agency (EPA), 2007) addressing biohazards are mostly focused on the protection of workers from exposure to biological agents (Pietrangeli et al., 2013). On the other hand, these methods consist of conceptual steps similar to those conventionally applied in the framework process safety related to chemical and petrochemical industry (Bassett et al., 2012), as displayed in Figure 1: (1) biohazards identification, (2) biohazards characterization, (3) exposure (i.e. consequences) estimation, (4) biorisk characterization, (5) biorisk evaluation, and (7) risk reduction measures identification. Consequently, also in bioprocesses the hazard identification step plays a critical role, since all unidentified hazards will lead to unmanaged risks. Therefore, it is crucial to recognize the specific hazards related to new industrial bioprocesses to guarantee a safe scale-up and operation.

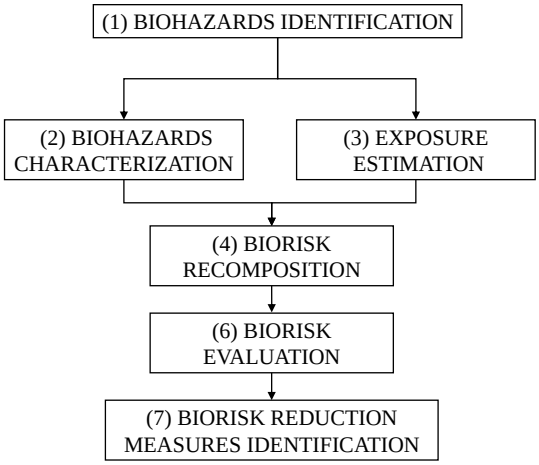

Figure 1: Steps of hazard identification and risk assessment in bioprocesses, deduced from literature review of existing methods and regulations aimed at protection of workers from exposure to biological agents.

For this reason, in the present work an ad hoc approach for hazard and safety management in biotechnological processes is described, with the aim of systematically assess in an integrated way conventional hazards and biohazards at industrial scale. The basic idea behind the creation of the methodology was to develop a tool able to identify hazards, focusing on major

accidents prevention and safety management, providing a guidance for safety improvements in the design and managing of the plant. Nevertheless, the results of the methodology can be used, as shown in the present work, as input for the preparation the emergency plan for the site.

The methodology has been applied to a biogas production plant via anaerobic digestion of animal manure, which represents a widespread bioprocess for energy production from renewable sources.

2. Methodology

The proposed methodology for hazard identification and risk management of industrial biological processes is composed by the main steps listed in Figure 2. The first two steps (performing the Bioprocess Checklist and BioHazOp) are aimed at hazard identification; the third and fourth steps (calculation of the Risk Priority Number and preparation of the Emergency Plan) are aimed at risk management. The last step is Monitoring and Reviewing, in agreement with the legal framework established by the Seveso III Directive (European Parliament and Council, 2012), that support a continuous improvement cycle of prevention, preparedness and response to major accidents.

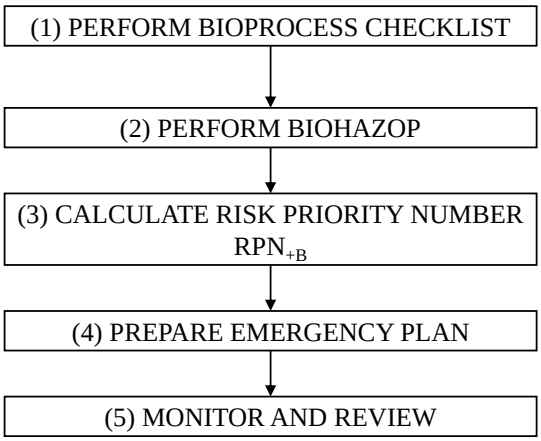

Figure 2: Steps of the present methodology for hazard identification and risk management of industrial biological processes.

More in details, the first step consists of a checklist, developed to recognize criticalities related to the engineering and biotechnological aspects of the process (e.g., pathogen agents and hazardous substances involved) for each process unit in the plant. The check list has been described in details elsewhere (Casson Moreno et al., 2016a). The main scope of using it is the collection of all possible information about the bioprocess (including hazardous substances and microorganisms involved) in order to perform a screening of the operating parameters and process conditions to be monitored.

The checklist is meant as a preparatory step for the BioHazOp: the main outcome of step 1 is a list of relevant parameters for the bioprocess that will be a used as input to step 2. More in details, the checklist is used to prepare a minimum set of relevant deviations that will be proposed for discussion to the team. This has to be intended as a minimum list of deviations that can be enriched during the brainstorming typical of HazOp sessions. The list of relevant deviations is produced with the support of the Relevant Deviation Matrix, shown in Table 1.

The Relevant Deviation Matrix was is created from the combination of standard set of guidewords (BRITISH STANDARD, 2001; Center for Chemical Process Safety - CCPS et al., 2008; Crawley and Tyler, 2015) and a general set of process parameters deriving from the application of the checklist as per step 1. The basic format of Table 1 can be modified any time the expert of the bioprocess required it, in order to add missing parameters significant for the biological process and microorganisms under analysis.

The BioHazOp (step 2) was recently developed by the authors (Casson Moreno and Cozzani, 2018) with the specific aim of including biohazards in the hazard and operability analysis. It was developed based on the model of MultilevelHAZOP (Cagno et al., 2002) and is structured into two levels: one considering the typical engineering process and one focusing on the biotechnological aspects.

Dealing with bioprocesses could imply a hidden relation between “conventional” deviations and “new type of consequences” with respect to conventional chemical processes. As a consequence, the relationship between cause-consequences, bio and not, is of paramount importance in hazard identification of bioprocesses to avoid unrecognized specific hazards. For this reason, in addition to conventional HazOp purposes, BioHazOp was designed to identify deviations from normal operating conditions specifically influenced by the presence of microorganisms (Casson Moreno and Cozzani, 2018).

The application of BioHazOp requires to introduce some changes in the composition of the standard HazOp team (BRITISH STANDARD, 2001; Center for Chemical Process Safety - CCPS et al., 2008; Nolan, 1994) by including a specialist of bioprocesses, expert of biohazards. In BioHazOp, no new guidewords are needed, since the approach of conventional HazOp studies allowed to perform the analysis in a satisfactory way (Casson Moreno and Cozzani, 2018). This makes BioHazOp user friendly to process safety experts that are familiar with this hazard identification technique.

Table 1: Relevant Deviations Matrix listing the possible combinations of guidewords and process parameters to be used in a BioHazop study. The parameter related to biological aspects of the process are displayed in italic. Adapted from (Casson Moreno and Cozzani, 2018).

	GUIDE WORDS					
PROCESS PARAMETERS	No Not	Less lower slower	More higher faster	More than	Reverse	Other than
Flow	✓	✓	✓		✓	✓
Temperature		✓	✓			
Pressure		✓	✓	✓		
Level		✓	✓	✓		
Time		✓	✓			
Composition	✓	✓	✓			✓
pH		✓	✓			
Viscosity		✓	✓			
Mixing	✓	✓	✓			
Reaction	✓	✓	✓			✓
State						✓
Volume	✓	✓	✓		✓	✓
Enzymatic activity	✓	✓				✓
Foam	✓	✓				✓
Biochemical oxygen Demand	✓	✓				✓
Oxidation-reduction potential	✓	✓				✓
Conductivity	✓	✓				✓
Osmolality	✓	✓				✓
Turbidity	✓	✓				✓

Step 3 of the methodology consists in calculating a Risk Priority Number (Trammel et al., 2001), namely RPN_{+B} (Casson Moreno and Cozzani, 2018). RPN_{+B} was originally developed to rank the risk reduction measures proposed during the BioHazOp, giving an indication about the prioritization of the counter measures to be implemented. RPN_{+B} is expressed as follows:

$$RPN_{+B} = (\sigma + \beta) \times \varphi \times \kappa \quad (1)$$

where σ represents the severity of the outcomes of the deviation, β accounts for the biohazards, φ represents the frequency of occurrence of the deviation, and κ the effect of existing counter measures in detecting and correcting it. The values of the parameters in Equation 1 are assigned by using the scoring chart displayed in Table 2.

In particular, the score of β is assigned depending on the cclassification of the biological agent into Risk Groups according to the Annex III of the European Directive 2000/54 (European Parliament, 2000), as follows:

- Risk Group 1: biological agent that is unlikely to cause human disease.
- Risk Group 2: biological agent that can cause human disease and might be a hazard to workers; it is unlikely to spread to the community; there is usually effective prophylaxis or treatment available.
- Risk Group 3: biological agent that can cause severe human disease and present a serious hazard to workers; it may present a risk of spreading to the community, but there is usually effective prophylaxis or treatment available.
- Risk Group 4: biological agent that causes severe human disease and is a serious hazard to workers; it may present a high risk of spreading to the community; there is usually no effective prophylaxis or treatment available.

Where no record on BioHazard is present, β is set to zero.

Table 2: Score chart for the calculation of the Risk & Biorisk Priority number (RPN_{+B}). Adapted from (Casson Moreno and Cozzani, 2018).

Score	**σ: severity**	**β: biohazard**	**φ: occurrence**	**κ: existing detection/correction measures**
1	- No effect on people, environment or asset - No negative effect on production - System failure that can be corrected within one shift		Very Unlikely $< 10^{-4}$ event/year	- On line-instrumentation - Automated control - AND - Regular maintenance

Score	σ: severity	β: biohazard	φ: occurrence	κ: existing detection/correction measures
2	- Slight effect on people, environment - OR - Negative effect on production - OR - Scheduled maintenance is required	Risk Group 1	Unlikely 10^{-3} to 10^{-4} event/year	- On line-instrumentation without automated control - AND - Regular maintenance
3	- One Injury / several minor injury - OR - Minor environmental damage - OR - Minor asset damage	Risk Group 2	Possible 10^{-2} to 10^{-3} event/year	- Manual control - AND - Regular maintenance
4	- Major health effect / one fatality - OR - Major environmental damage - OR - Major asset damage	Risk Group 3	Probable 10^{-1} to 10^{-2} event/year	- Maintenance based on operator inspections
5	- Several fatalities - Stop of the production	Risk Group 4	Very probable $> 10^{-1}$ event/year	- No control available

Being calculated for each deviation analyzed during the BioHazOp, the value of RPN_{+B} can be used also to rank the related top events, and select, among all, the Relevant Accident Scenarios, as required to prepare the emergency plan for the site (step 4 in Figure 2).

As in conventional risk assessment, the proposed approach requires that residual risk (i.e. the risk remaining after applying risk reduction measures) is managed and continuously monitored, being hazard identification a dynamic process based on the periodic review of the know hazards and the early warnings available (Casson Moreno et al., 2018; Paltrinieri et al., 2013).

In this perspective, Emergency Response is one of the tools for residual risk management, being a set of human resources, financial resources, technical equipment, procedures, decisions and actions, aimed at minimizing the impact of unexpected events. To be efficient, Emergency Response has to be prepared in advance and, for this reason, the last step of out methodology is related to the preparation of the Emergency Plan (both Internal and External).

A schematic procedure for emergency planning, developed on the basis of well-established existing guidelines (Gow and Kay, 2005; Health & Safety Executive, 1999; ISO, 2009) is proposed in Figure 3.

The preparation of the Emergency Plan (a written document) starts with the analysis of the scenarios related to the deviations identified during the BioHazOp. Among all, the Relevant Accident Scenarios (RAS) are selected based on the value of the corresponding RPN_{+B}. The level of emergency to assign to each RAS, is first of all related to the Risk Group of the microorganisms involved. If the microorganism belong to Risk Group > 2, there is a risk of spreading to the community; consequently, a specific emergency procedure for the RES has to be prepared, as well as an external emergency plan in collaboration with Public Authorities.

If biohazard is not particularly relevant for the RAS under analysis (Risk Group ≤ 2), the level of emergency has to be evaluated for "conventional scenarios" (e.g. fire, explosions, release, …). In this sense, it is important to define whether the scenario could involve (or escalate) to the entire plant or if it could be easily confined to part of the plant (e.g. a specific unit). If there could be the potential involvement of the entire site, an Evacuation Emergency Procedure (which is anyway to be included in the Emergency Plan) has to be followed, otherwise a specific procedure for that RAS has to be prepared. Following the specific procedure would avoid the escalation of the accident and thus the involvement of nearby units, besides ensuring the protection of workers.

Once all the scenarios have been analyzed, the procedures have to be implemented and tested by training and exercise, as a part of the preparedness cycle (according to (ISO, 2009). The Emergency Plan itself must be periodically updated, with respect to all kinds of changes in both the internal and external context.

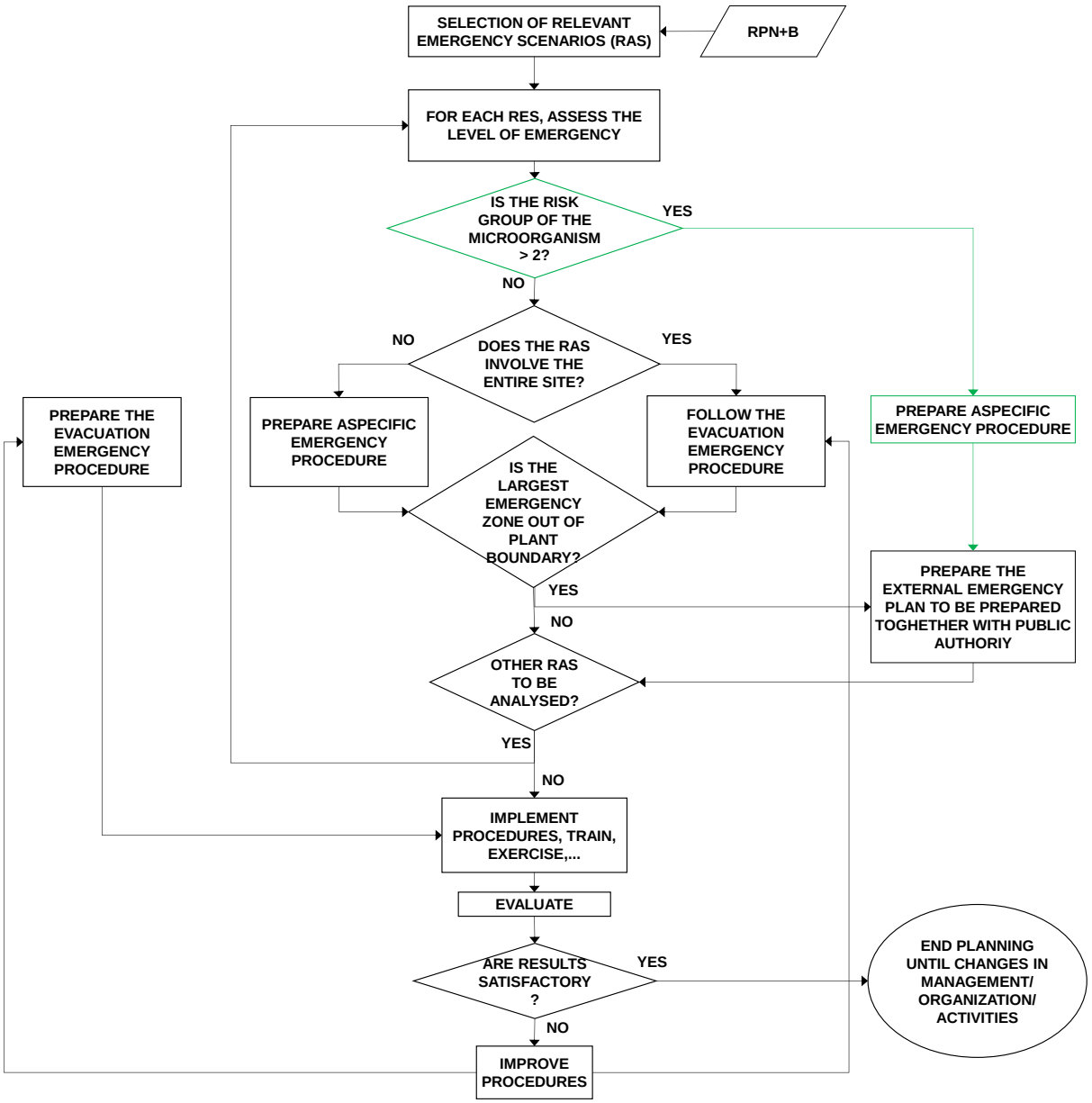

Figure 3: Steps of the preparation of emergency planning.

3. Case-study

The biogas production plant analysed used as a case study in the present work is shown in Figure 4.

The unit operations involved are: 1) anaerobic digestion; 2) biogas desulfurization, and 3) biogas dehumidification. The main equipment is the anaerobic digester (R-101), where the anaerobic digestion takes place and biogas is produced. The biogas is then sent to a gravel filter (F-201), where liquid droplets and foam are separated from the gas. Humidity is then reduced by means of a chiller (E-301). Finally, the biogas is sent by a blower (P-401) to the Combined Heat and Power (CHP) unit, where it is burned to cogenerate electricity and heat.

The anaerobic digester is constantly fed with substrate and mixed. Outlet streams are the digestate (i.e. reacted substrate), which is removed in the same quantity using an overflow, and the biogas. A flow controller, that measure the flow of biogas output stream, controls the feed to the digester. The operating temperature is maintained by hot water (thermal recovery from the CHP unit). The digester operating pressure is slightly above ambient pressure. Operating pressure is controlled regulating the biogas feed to the CHP unit, and a flare is used in case of critical overpressure. A hydraulic seal connected to a vent is also present, providing a passive emergency relief system as a second safety barrier. Biogas desulfurization is carried out inside the anaerobic digester. Since desulfurizing bacteria require oxygen to transform hydrogen sulfide to elemental sulfur, air is blown inside the top of the digester. Oxygen concentration is monitored and kept below 1% in volume, to avoid inhibition of anaerobic bacteria responsible for the production of biogas, and to prevent the formation of an explosive atmosphere inside the digester. Biogas humidification is carried out by a chiller used to condense water vapor, separating it from the desulfurized biogas.

Between the digester and the chiller, a grave filter is present to trap foams. A blower is then used to feed biogas to the CHP unit to cogenerate heat and electricity.

The main operating conditions are listed in Table 3 and 4. More details about the process scheme can be found in previous papers of the Authors (Casson Moreno et al., 2018; Casson Moreno and Cozzani, 2018).

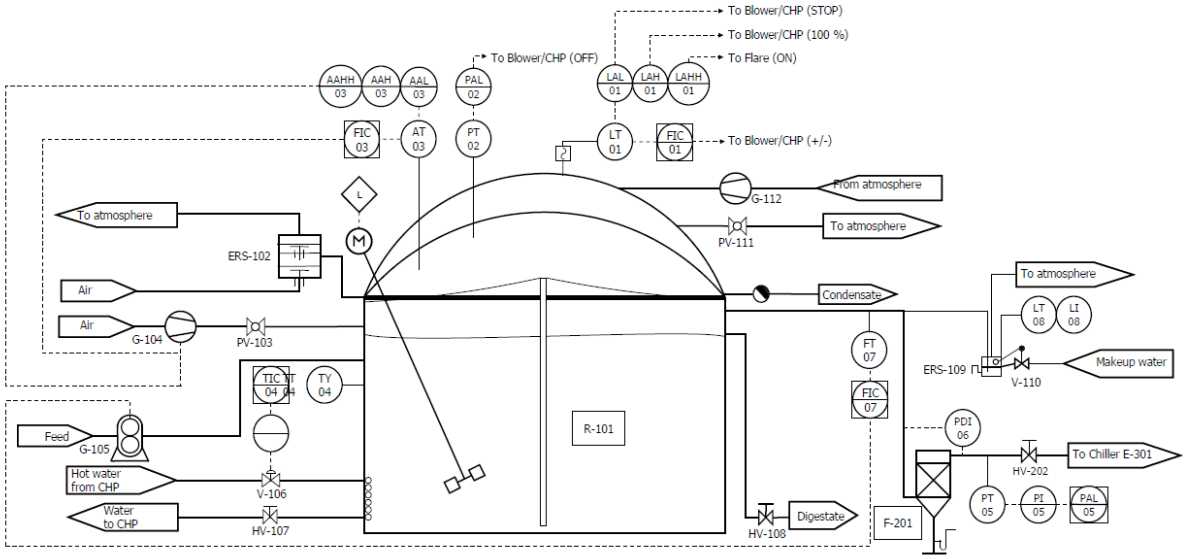

Figure 4: PI&D of the anaerobic digestion plant for biogas production analysed. Adapted from (Casson Moreno et al., 2018; Casson Moreno and Cozzani, 2018).

Table 3: Operating conditions of the equipment present in the biogas production plant analyzed. Adapted from (Casson Moreno et al., 2018; Casson Moreno and Cozzani, 2018).

	Volume [m^3]	Biogas flow rate [Nm^3/h]	Pressure [barg]	Temperature [°C]	CH_4/CO_2 [-]	H_2S [ppm_{vol}]
Digester	500	300	0.002	39	60/40	200
Gravel filter		300	0.002	15	60/40	200
Chiller		300	0.002	15	60/40	200
Blower		300	0.12	15	60/40	200

Table 4: Operating conditions of the pipelines present in the biogas production plant analyzed. Adapted from (Casson Moreno et al., 2018; Casson Moreno and Cozzani, 2018).

	Diameter [mm]	Biogas flow rate [Nm^3/h]	Pressure [barg]	Temperature [°C]	CH_4/CO_2 [-]	H_2S [ppm_{vol}]
Pipe from digester to gravel filter	150	300	0.002	39	60/40	200
Pipe from gravel filter to chiller	150	300	0.002	15	60/40	200
Pipe from chiller to blower	150	300	0.002	15	60/40	200
Pipe from blower to CHP or flare	150	300	0.12	15	60/40	200

4. Results

In order to apply the methodology to the case study just described, the team was composed by: (i) a senior process safety specialist, in the role of the team leader; (ii) a junior chemical engineer, in the role of the scribe; (iii) a bioprocess engineer; (iv) a site operation manager engineer, both experts of anaerobic digestion processes.

As a general result, the application of the developed checklist (step 1) confirmed that the anaerobic digester with integrated gasometer is the most critical piece of equipment, due to the hold-up of biogas (the highest in the entire plant), and to the presence of microorganisms. The digester is the equipment where flammable substances are present (CH_4) and where toxic substances (H_2S and NH_3) could be formed and accumulated in particular operating conditions. A detailed discussion is reported in (Casson Moreno and Cozzani, 2018). For this reason, for the sake of example, the results discussed below refer to the anaerobic digester only.

During the first step of the analysis, the relevant parameters related to the process have been identified and combined to the guidewords using the Relevant Deviation Matrix (as shown in Table 1) to obtain the set of relevant deviations to be analyzed by the BioHazOp team. A list of 25 relevant deviations was obtained and used as the starting point of the team discussion in the brainstorming session during the BioHazOp. The list is reported in Table 5.

Table 4: List of relevant deviations for the process under analysis.

1	no / less substrate in
2	more substrate in
3	no / less biogas out
4	more biogas out
5	no / less substrate out
6	more substrate out
7	reverse flow of biogas
8	higher pressure inside
9	lower pressure inside
10	higher pressure between the membranes of the gasometer
11	higher temperature inside
12	lower temperature inside
13	other composition of the inlet substrate
14	more c in the inlet substrate
15	more Carbon/Nitrogen in the inlet substrate
16	less C/N in the inlet substrate
17	more sulfur in the inlet substrate
18	more oxygen in the gas phase
19	less oxygen in the gas phase
20	more CO2 in the produced biogas
21	more H2S in the produced biogas
22	less CH4 in the produced biogas
23	more NH3 in the produced biogas
24	lower pH of the substrate
25	higher pH of the substrate

Performing the BioHazOp on the anaerobic digester, as per step 2, allowed us to identify the possible accidental scenarios, and the calculation of RPN_{+B} (step 3) allowed the selection of the Relevant Accident Scenarios to be discussed during the preparation of the Emergency Plan (step 4).

The most relevant scenario identified is the formation of flammable/explosive mixtures of biogas and oxygen inside the anaerobic digester, leading to an internal explosion causing the rupture of the gasometer and a consequent loss of containment. This top event can be generated by a deviation in the biogas production rate, or in a deviation of the pressure inside the digester. Correspondingly, the highest value of the RPN_{+B} is related to the implementation of the counter measure proposed for this top event: a rigid membrane (a third outer layer), acting as a layer of protection in case of rupture of the plastic-flexible membranes, that may also protect the flexible-plastic membranes from external stress due to particular weather conditions (e.g. snow or hail).

The BioHazOp allowed the identification of a second RAS related to this piece of equipment that is crucial from a process safety standpoint: the formation of the ammonia and hydrogen sulfide. In normal in conditions, these substances are present in the biogas in very small quantities. However, a specific combination of conditions and operating parameters can lead to their abnormal production. Some examples are: low pH and high concentration of sulfur in the fed substrate may lead to the formation of a high amount of H_2S; high pH, low C/N ratio of the feed, high temperature may lead to the formation of a high amount of ammonia. Consistently, high values of the RPN_{+B} are related to the implementation of the counter measures proposed to prevent deviations associated to the composition of the substrate fed to the anaerobic digester (e.g. analyzing the substrate composition), and to control parameters such as temperature and pH governing the biotechnological process.

During the next stage of our analysis, the results obtained were used for the preparation of the Emergency Plan (step 4).

In the present case study, the all microorganisms involved in the bioprocess of anaerobic digestion of animal manure belong to Risk Group 1, thus there is not a significant biohazard associated to this process; consequently, there is no need to prepare a Specific Emergency Procedure to mitigate the effect of a possible biohazardous contamination.

Still, according to Figure 3, during the preparation of the Emergency Plan, when the Risk Group ≤ 2, the level of emergency of the RAS has to be evaluated for "conventional scenarios" (e.g. fire, explosions, release …). In particular, "emergency zones" (or risk zones) associated to the scenario has to be evaluated, in order to decider weather an Evacuation Emergency Procedure only is needed or also the External Emergency Plan.

Following the above discussion about the RAS selected, the effects of fire, explosion and toxic release from the anaerobic digester in terms of damage distances have to be evaluated. Damage distances are intended as the maximum distances at which the effect of a given scenario equals a specific threshold value (different for each type of scenario). The threshold values applied in this study can be found elsewhere (Scarponi et al., 2016).

In the present case, to define the emergency zones, the maximum damage distances were calculated for the following losses of containment possibly involving the anaerobic digester: (i) small leak, continuous release from a 10 mm equivalent diameter

hole; (ii) catastrophic rupture, release of the entire inventory in 600 s, according to Scarponi et al (Scarponi et al., 2016, 2015). The results are displayed in Table 5.

The damage distances associated to the "conventional" RAS never fall out of the boundary of the site, therefore only the Internal Emergency Plan, containing a the Evacuation Emergency Procedure should be prepared.

Table 5: Maximum damage distance associated to a loss of containment of the anaerobic digester. Adapted from (Scarponi et al., 2016).

Loss of Containment	Maximum Damage Distance in case of Fire or Explosion [m]	Maximum Damage Distance in case of a Toxic Release [m]
Small leak, continuous release from a 10 mm equivalent diameter hole	21	-
Catastrophic rupture, release of the entire inventory in 600 s	100	8

5. Conclusions

The results obtained by the application of the methodology to a case study showed that this method allows a comprehensive exploration of both conventional hazards (e.g. formation of a flammable mixture inside the digester) and biological hazards (e.g. anomalous formation of toxic substance in the bioprocess) in an integrated and systematic way.

The checklist combined with the Relevant Deviation Matrix is an effective tool for the definition of an initial set of relevant deviations to be discussed by the team.

Performing the BioHazOp implies that the team has to focus simultaneously on conventional hazards and biohazards, being the latter harder to be unveiled, since they are probably well known only to the bioprocess expert, which is in turn usually less used to deal with process safety issues in systems scaled-up to industrial size.

The RPN_{+B} index supported effectively the selection of the Relevant Accident Scenarios as well as the prioritization of counter measures, providing a guidance for the preparation of the Emergency Plan.

The proposed approach thus represent a step forward in the safe implementation and management of large scale biotechnological processes.

References

Angel, M., Herrera, D.O., Severino, A., Carlos, A., Monte, E., Lemes, B., 2015. A structural approach to the HAZOP e Hazard and operability technique in the biopharmaceutical industry. J. Loss Prev. Process Ind. 35, 1–11. doi:10.1016/j.jlp.2015.03.002

Bassett, J., Nauta, M., Lindqvist, R., Zwietering, M., 2012. Tools for Microbiological Risk Assessment.

BRITISH STANDARD, 2001. British Standard Hazard and operability studies (HAZOP studies) — Application guide - BS IEC 61882:2001.

Cagno, E., Caron, F., Mancini, M., 2002. Risk analysis in plant commissioning: the Multilevel Hazop. Reliab. Eng. Syst. Saf. 77, 309–323. doi:10.1016/S0951-8320(02)00064-9

Caskey, S., Gaudioso, J., Salerno, R., Wagener, S., Risi, G., Kozlovac, J., Halkjær-knudsen, V., Prat, E., 2010. Biosafety Risk Assessment Methodology.

Casson Moreno, V., Cozzani, V., 2018. Integrated hazard identi fi cation within the risk management of industrial biological processes. Saf. Sci. 103, 340–351. doi:10.1016/j.ssci.2017.12.004

Casson Moreno, V., Cozzani, V., 2015. Major accident hazard in bioenergy production. J. Loss Prev. Process Ind. 35, 135–144. doi:10.1016/j.jlp.2015.04.004

Casson Moreno, V., Giacomini, E., Cozzani, V., 2016a. Identification of major accident hazard in industrial biological processes. Chem. Eng. Trans. 48, 679–684. doi:10.3303/CET1648114

Casson Moreno, V., Guglielmi, D., Cozzani, V., 2018. Identification of critical safety barriers in biogas facilities. Reliab. Eng. Syst. Saf. 169, 81–94. doi:10.1016/j.ress.2017.07.013

Casson Moreno, V., Papasidero, S., Scarponi, G.E., Guglielmi, D., Cozzani, V., 2016b. Analysis of accidents in biogas production and upgrading. Renew. Energy 96, 1127–1134. doi:10.1016/j.renene.2015.10.017

CCPS - Center for Chemical Process Safety, 2010. Guidelines for Process Safety in Bioprocess Manufacturing Facilities.

Center for Chemical Process Safety - CCPS, CCPS - Center for Chemical Process Safety, Center for Chemical Process Safety (CCPS), 2008. Guidelines for Hazard Evaluation Procedures, 3rd Editio. ed. American Institute of Chemical Engineers, New Jersey. doi:10.1002/9780470924891

Crawley, F., Tyler, B., 2015. HAZOP: Guide to Best Practice, Third Edition, 3rd Editio. ed. Elsevier.

European Parliament, 2000. Directive 2000/54/EC [WWW Document]. URL http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000L0054&from=EN (accessed 8.28.15).

European Parliament and Council, 2012. Seveso III, Directive 2012/18/UE.

Gow, H.B.F., Kay, R.W., 2005. Emergency Planning for Industrial Hazards. Elsevier, Barking, UK.

Harms, J., Wang, X., Kim, T., Yang, X., Rathore, A.S., 2008. Defining process design space for biotech products: case study of Pichia pastoris fermentation. Biotechnol. Prog. 24, 655–62. doi:10.1021/bp070338y

Health & Safety Executive, 1999. Emergency Planning for major accidents. Crown, Richmond, UK.

HSE, 2013. An update on HSE's work to consolidate legislation on human pathogens, animal pathogens and genetically modified organisms following the Callaghan and Löfstedt Reviews [WWW Document].

ISO, 2009. ISO 31000:2009, Risk management - Principles and guidelines.

Mollah, A.H., 2005. Application of Failure Mode and Effect Analysis (FMEA) for Process Risk Assessment. Bioprocess Int.

Nolan, D.P., 1994. Application of HAZOP and What-If Safety Reviews to the Petroleum, Petrochemical and Chemical Industries. William Andrew Publishing/Noyes.

Paltrinieri, N., Tugnoli, A., Buston, J., Wardman, M., Cozzani, V., 2013. Dynamic Procedure for Atypical Scenarios Identification (DyPASI): A new systematic HAZID tool. J. Loss Prev. Process Ind. 26, 683–695. doi:10.1016/j.jlp.2013.01.006

Pietrangeli, B., Lauri, R., Bragatto, P.A., 2013. Safe Operation of Biogas Plants in Italy. Chem. Eng. Trans. 32, 199–204. doi:10.3303/CET1332034

Pinkenba, P., Statement, I.A., 2006. Proposed Pinkenba Ethanol Bio-Refinery.

Salm, A.S.M., Casson Moreno, V., Antonioni, G., Cozzani, V., 2017. Dynamic Simulation of Disturbances Triggering Loss of Operability in a Biogas Production Plant. Chem. Eng. Trans. 57, 595–600. doi:10.3303/CET1757100

Scarponi, G.E., Guglielmi, D., Casson Moreno, V., Cozzani, V., 2016. Assessment of inherently safer alternatives in biogas production and upgrading. AIChE J. 62. doi:10.1002/aic.15224

Scarponi, G.E., Guglielmi, D., Casson Moreno, V., Cozzani, V., 2015. Risk Assessment of a Biogas Production and Upgrading Plant. Chem. Eng. Trans. 43, 1921–1926. doi:10.3303/CET1543321

Trammel, S.R., Davis, B.J., Cannon, W., West, D., 2001. Using a Modified Hazop / FMEA Methodology for Assessing System Risk, in: 2nd International Workshop on Engineering Management for Applied Technology, EMAT 2001. Elsevier Inc., pp. 47–53.

U.S. Environmental Protection Agency (EPA), 2007. A Compendium of Prior and Current Microbial Risk Assessment Methods.