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RESEARCH ARTICLE

Analyzing occupational risks of pharmaceutical industry under uncertainty using a Bow-Tie analysis

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ABSTRACT

Risk analysis is a systematic and widespread methodology to analyze and evaluate risks which are exposed in many working areas. One of the Quantitative Risk Analysis (QRA) methods for risk assessment is Bow-Tie analysis which combines features of fault-tree analysis and event-tree analysis to identify the top event; its causes and consequences (outcomes); and possible preventive and protective control measures or barriers. This study proposes an occupational risk assessment approach, which is known as Fuzzy Bow-Tie analysis, for pharmaceutical industry processes and work units. The aim is to evaluate critical risks and risky pharmaceutical work units and take safety precautions against accidents which caused by risky conditions. Thus, this methodology combines the concept of uncertainty which comes from different (Decision Maker) DM's evaluations and the whole performance of the Bow-Tie analysis for hazard identification and risk assessment. To apply and validate the proposed method, a case study is performed for pharmaceutical industry processes and work units. Based on the computed risk score, which is calculated by multiplying probability ranking and impact ranking of criterion, the risks are prioritized and some measures are suggested for management to prevent accidents occur in the industry.

1. Introduction

Pharmaceutical industry is usually considered to have high quality levels since healthcare products require manufacturing processes in safe conditions, protection under a substantial control hygiene against chemical and biological contaminants, and keeping equipments at optimum working conditions [1]. Since the main aim is to produce medical substances with pharmacological processes, many factors in pharmaceutical Research and Development (R&D) and manufacturing are hazardous for employees. Pharmaceutical workers are at risk because occupational direct/indirect exposure is considered to be high among workers who used biological, chemical/radiological, or pharmacological agents in their working areas [2]. Risk factors and impact of these risks lead to occupational risks in Pharmaceutical industry. Fire or explosion risks during pharmaceutical production of dosage arrangements are associated with process safety. These processes are generally related to bed drying, slugging, granulation, blending, compounding and drying etc. and they produce pharmaceutical dusts due to flammable liquids. Coating, wet granulation, compounding operations may cause solvent vapor exposure. Also, once pharmaceutical workers expose to complex mixtures including high amounts of active drug substances, they are physically and chemically damaged. Moving machine parts (exposed equipment e.g., belts and shafts), manual handling of materials and equipments, unsafe energy systems (electrical, thermal, pneumatic, etc.); high-pressure vapor, hot water and heated areas; combustible and corrosive liquids; and high sound degree are other health and safety risks for workers during manufacturing process in pharmaceutical industry. These occupational risks cause illnesses, including occupational asthma, adverse reproductive concerns, pharmacologic impacts and dermatitis among pharmaceutical workers [2].

Appropriate mitigation measures need to be implemented for occupational risks in pharmaceutical industry to protect workers from industrial chemicals and drug matters throughout manufacturing, R&D and quality control processes [3,4].

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Consequently, in pharmaceutical industry, risk assessment methodologies play an important role to analyze occupational risks with other work environment components, including technical and organizational parts, production activities as well as implementation procedures [5].

The main objective of this paper is to propose a Risk Assessment framework and develop extensive risk analysis methodology to assess and prioritize risk factors for occupational safety in pharmaceutical industry. For this purpose, Bow-Tie risk assessment analysis, which includes two main risk assessment methods named Fault Tree Analysis (FTA), Event Tree Analysis (ETA), have combined with Fuzzy Set Theory (FST) to analyze the risk factors associated with the pharmaceutical industry. FST is used to handle data uncertainty in risk analysis. Thus, fuzzy linguistic probabilities are used for associating possibilities of failures, since probability theory alone was found insufficient to represent all types of uncertainties due to lack of ability to model human conceptualizations in the real world applications [6].

2. Literature review

Risk assessment is an efficient and methodological approach to assess and minimize the risks of an accident for any industry [7]. A quantity of qualitative and quantitative methods including Event Tree Analysis (ETA), Fault Tree Analysis (FTA), HAZOP analysis, and barrier block diagrams [8], Bow-Tie diagrams [9,10] have been used for risk assessment process [11].

The Bow-Tie diagrams and other risk assessment techniques have been used due to effective implementation in many real world applications such as accident risk assessment [12-17], human error risk analysis [18,19], dynamic risk analysis [20], risk management [21,22], safety barrier implementation [23-25]. However, the applications of all these techniques aren't efficient in terms of satisfying results because the safety risk data are often vague, imprecise or incomplete to determine risk levels [26]. Therefore FST, probability theory, and evidence theory etc. have been suggested to handle vagueness in risk analysis because of their efficiencies [27-32]. In this study, combination of FTA and ETA is introduced as Bow-Tie analysis to solve the risk assessment problem using fuzzy numbers to deal with uncertain and vague information.

The use of FST has been implemented in different fields of the process risk assessment [29,33-38]. However, uncertainty is seldom carried out in all other risk assessment studies, especially in consequence analysis [39]. The uncertainty-based methods of ETA, FTA and Bow-Tie analysis have been studied in literature for risk analysis of different systems [29,37,38,40-42].

Some researchers suggested certain novel methods to recognize barriers in Bow-Tie diagram [12, 23,24]. For instance, [24] presented a new approach using crossing matrices (checklist filled by experts) to suggest preventive and protective measures by considering the Bow-Tie construction. Aqlan and Mustafa Ali [43] proposed the Fuzzy Bow-Tie analysis to compute the aggregated risk scores for likelihood and impacts that have been used to decide the position of risk in risk prioritization matrix. Markowski et al. [44] presented a fuzzy based methodology for Bow-Tie analysis; however, this methodology is not useful to handle vagueness due to inconsistency in the knowledge. This study also was incapable to capture model uncertainty owing to the individual difference among the input events in FTA or ETA.

There is limited research in the literature related to workers health and safety assessment in pharmaceutical industry [1,5,45-49] since the quality risk management is commonly studied in this industry.

As it is evident in the previous studies in the literature, this paper is the first QRA study performing Fuzzy Bow-Tie for pharmaceutical industry to analyze and visualize risks, causes and consequences of potential risk events and their impacts with possible preventive and protective control measures or barriers in prospective manner.

Accordingly, the aim of the current study is to introduce a comprehensive framework based on Bow-Tie analysis and FST with three important points in risk analysis a) combination of multiple expert knowledge, and b) handling and managing uncertainty for risk analysis c) prioritizing risks based on probability and impact of the risks.

3. Risk analysis under uncertainty

3.1. Bow-tie analysis for risk assessment

Bow-Tie analysis was proposed by SHELL Company in the early nineties to analyze the whole scenario of an accident based on Swiss Cheese Model [9]. Bow-Tie analysis is a combined probabilistic method that assesses accident consequences due to evaluating the probability and impact of risk events [22].

Bow-Tie combines the features of fault and event trees used in QRA [50]. In the center of the diagram there is a top event. While the left side of the "Bow-Tie" diagram (fault tree) represents the potential parallel and consecutive combination of faults (causes), the right side of the ''Bow-Tie'' diagram (event tree) represents the potential consequences (outcomes) of corresponding top event [44]. After identifying risk events, hazards and consequences also preventive and protective measures or barriers are determined to mitigate hazards [50].

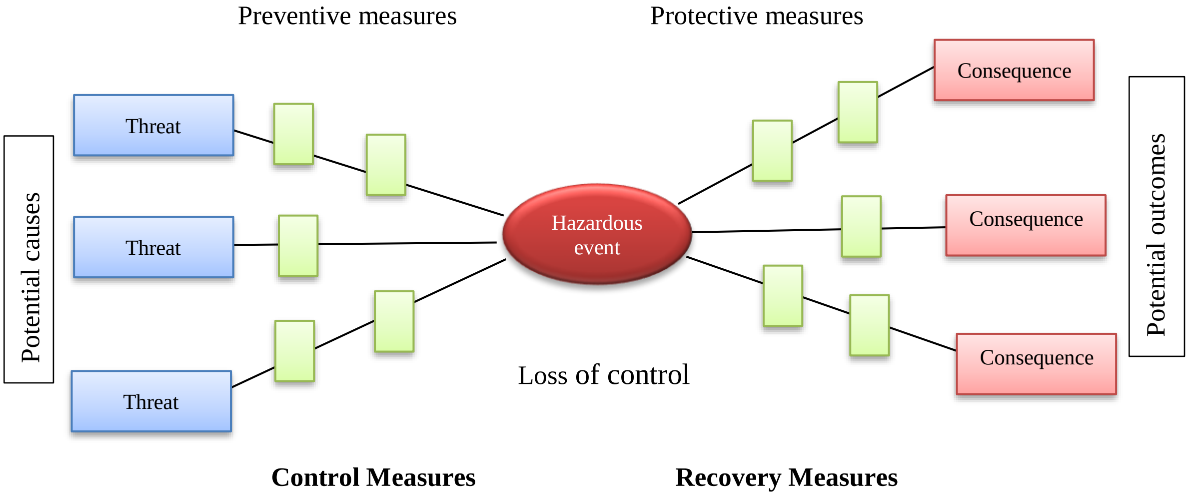

Figure 1. Implementation of Bow-Tie structure [9].

Figure 1 shows the implementation of Bow-Tie structure. As a part of Bow-Tie analysis, determination of preventive and protective barriers can be difficult since they are continuously contact with each other. Also, their performance depends on several criteria such as efficiency, being safe, ease of use and cost etc. [9].

The main advantage of performing the Bow-Tie analysis is that it ensures a visual illustration to evaluate and analyze the potential hazards and risks with their potential interactions. This relationship illustration provides many advantage when compared with word-based or tabular risk information in QRA [51]. However, data and model uncertainty are prevalent and generally inevitable, in fault tree and event tree and consequently in Bow-Tie analysis [52]. In the current study, to deal with the data and model uncertainty, Bow-Tie analysis is conducted based on the principles of FST.

3.2. Fuzzy set theory

The FST is suggested by L.A. Zadeh [53] in 1965. FST is performed to deal with vague and uncertain information. A FST in probability space symbolizes a fuzzy number which is between zero and one for the likelihood of an event. There are various representations of fuzzy numbers such as Triangular Fuzzy Number (TFN) and Trapezoidal Fuzzy Number (TrFN) which are generally used in reliability analysis. To quantify subjectivity of the DM's evaluations, TFNs are used in this study. A TFN can be represented by a vector (a_1, a_2, a_3) that shows the lower bound, most likely value, and upper bound.

A fuzzy set $\breve{A}$ identified on R must have the following features to represent a fuzzy number: [53-57].

(a) $\mu_{\breve{A}}(x) = 0$ for all $x \in (-\infty, c] \cup [d, \infty)$, where c<d.

(b) $\mu_{\breve{A}}(x)$ is hardly increasing on [c, a] and hardly decreasing on [b, d] for $c \le a \le b \le d$.

(c) $\mu_{\breve{A}}(x) = 1$ for all $x \in [a, b]$ ensured $a \le b$.

While a fuzzy number ($\breve{A}$) is represented as TFN, the membership function of fuzzy number A is denoted by the Expression (1):

$$\mu_{\tilde{A}}(x)=\begin{cases} 0 & if\ x \le a_1\ or\ x \ge a_2 \\ \frac{x-a_1}{a_2-a_1} & if\ a_1 \le x \le a_2 \\ \frac{a_3-x}{a_3-a_2} & if\ a_2 \le x \le a_3,\quad x, a_1, a_2, a_3 \in R \end{cases} \quad (1)$$

A triplet (a_1, a_2, a_3) might be used to illustrate any TFN seen above.

A trapezoidal fuzzy number $\breve{A}$ represented by a quadruple (a1, a2, a3, a4) can be identified as follows:

$$\mu_{\tilde{A}}(x)=\begin{cases} 0 & if\ x \le a_1\ or\ x \ge a_2 \\ \frac{x-a_1}{a_2-a_1} & if\ a_1 \le x \le a_2 \\ 1 & if\ a_2 \le x \le a_3 \\ \frac{a_3-x}{a_3-a_2} & if\ a_2 \le x \le a_3,\quad x, a_1, a_2, a_3 \in R \end{cases} \quad (2)$$

(TFN) $\breve{A}$ = (a, b, c) and (TrFN) $\breve{A}$ = (a, b, c, d) are illustrated in Figure 2.

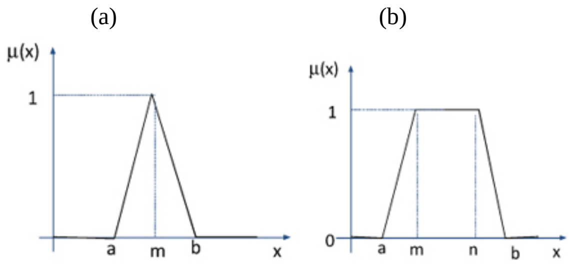

Figure 2. Illustration of (a) TFN and (b) TrFN.

Linguistic expression is representeed with words or sentences. For example, ''probability of failure'' might be shown with linguistic terms whose values are: ''very low'', ''low'', ''medium'', ''high'' and ''very high''. As shown in Figure 3, these variables can be represented by fuzzy numbers whose members are probability of risks [58].

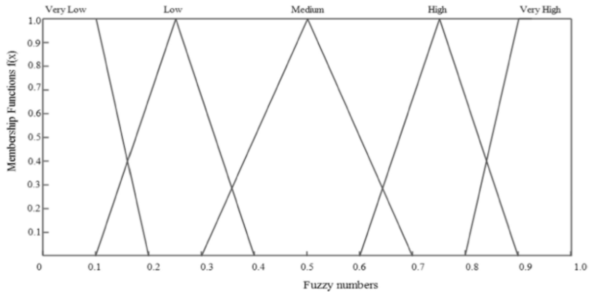

Figure 3. Linguistic values of fuzzy numbers.

In the implementation of the Bow-Tie analysis, the risk factors associated with each risk need to be identified. A fuzzy evaluation for the probability of occurrence and impact of the risk factors are determined. The probability of occurrence is calculated using the estimated evaluations given in Table 1. The impact or severity of each risk is also calculated. Table 2 shows the fuzzy probabilities for risk impacts.

Once two TFNs are summed, again a TFN is obtained. Likewise, when one TFN subtract from other TFN, a TFN is obtained again. Suppose $\breve{A}$ =(a_1, a_2, a_3) and $\breve{B}$ =(b_1, b_2, b_3) are two TFNs. The operations of TFNs are shown in Equation (3-5) [59].

$$\tilde{A} + \tilde{B} = (a_1+b_1,\ a_2+b_2,\ a_3+b_3) \quad (3)$$

$$\tilde{A} - \tilde{B} = (a_1-b_1,\ a_2-b_2,\ a_3-b_3) \quad (4)$$

The multiplication of two fuzzy numbers A=(a_1, a_2, a_3) and B =(b_1, b_2, b_3) represented as A*B can be denoted as:

$$\mu\tilde{A} * \tilde{B}(x) = \begin{cases} -D_1 + [D_1^2 + (x-P)/T_1]^{1/2} & P \le x \le Q \\ -D_1 + [D_{21}^2 + (x-R)/U_1]^{1/2} & Q \le x \le R \\ 0 & otherwise \end{cases} \quad (5)$$

where $T_1 = (a_2 - a_1)(b_2 - b_1), T_1 = a_1(a_2 - a_1) + ab_2(b_2 - b_1)$, $U_1 = (a_2 - a_1)(b_2 - b_1)$, $U_2 = b_3(a_2 - a_1) + a_3(b_2 - b_1)$, $D_1 = \frac{T_2}{2T_1}$, $D_2 = -\frac{U_2}{2U_1}$, $P = a_1 b_1$, $Q = a_2 b_2$, $R = a_3 b_3$

Supposing that the probability of a risk factor ‘i’ is assessed by n different number of DMs, the fuzzy probability can be computed as $\breve{P}(t) = (a_i - c_{1i}, a_i, a_i + c_{2i})$ where $i = 1,2,\dots,n;$ while $(a_i - c_{1i})$ is the minimum value of the fuzzy number, a_i is the mid value of the fuzzy number and $(a_i + c_{2i})$ is the maximum value of the fuzzy number. The fuzzy probabilities can be aggregated using aggregation operator. Thus, a single fuzzy probability has been obtained as $\breve{P}A(t) = (b - d_1, b, b + d_2)$ that best fits all DMs’ forecasts. The values of $b, d_1\ and\ d_2$ are estimated in such a way that $\breve{P}A$ has minimum variance with all $\breve{P}i(t)'s$. The square of deviations (S) can be computed as follows :

$$S_1 = \sum_{i=1}^{n} [2(d_1 - c_{1i})]^2 \quad (6)$$

$$S_2 = \sum_{i=1}^{n} [2(d_2 - c_{2i})]^2 \quad (7)$$

The minimum deviation can be computed using $d_1 = 1/n \sum_{i=1}^{n} c_{1i}$ and $d_2 = 1/n \sum_{i=1}^{n} c_{2i}$. The parameter b can be obtained by using equation $D = max_{1 \le i \le n}|b - a_i|$ where D is the absolute deviation. Then, D is the minimum for $b = min_{1<i<n} a_i + max_{1<i<n} a_i/2$ [43].

The fault tree consist of ‘AND’ and ‘OR’ gates. The ‘AND’ gate express that the out-put event will occur if all the input events occur, while the ‘OR’ gate express that the output event will occur if any one of the input events occurs. Therefore, in Bow-Tie analysis total probability for each failure is calculated when the connecting gate is either AND or OR [58].

In FTA, “AND gate” operator is: ($P_{AND} = \Pi P_i$) in which Pi (i = 1,2….n) recognizes the certain probability of the event i. Fuzzy operator for P_{AND} can be represented by the following equation:

$$P_{AND} = \prod_{i=1}^{n} P_i = [\prod_{i=1}^{n} a_i, \prod_{i=1}^{n} b_i, \prod_{i=1}^{n} c_i] \quad (8)$$

If the events are interdependent, then the mathematical expression is $P_{AND} = \min(P_1, P_2, \dots P_n)$.

In FTA, “OR gate” operator is: $P_{OR} = \Pi\ (1-P_i)$ in which Pi (i = 1,2….n) recognizes the certain probability of event i. Fuzzy operator for P_{OR} can be represented by the following equation:

$$P_{OR} = 1 - \prod_{i=1}^{n}(1 - P_i)$$

$$P_{OR} = 1 - \left[\prod_{i=1}^{n}(1 - a_i), \prod_{i=1}^{n}(1 - b_i), \prod_{i=1}^{n}(1 - c_i)\right] \quad (9)$$

if the events are dependent, then the algorithm is P_{OR} = max(P1, P2,…,Pn) [43].

4. Framework of the fuzzy Bow-Tie analysis

The proposed framework is applied to pharmaceutical industry to prevent occupational accidents in the pharmaceutical industry.

The aim is to propose a risk analysis framework which can be used in any pharmacy firm as a risk analysis tool. The steps of the proposed Fuzzy Bow-Tie risk analysis approach for pharmaceutical industry are explained in Figure 4. Before the implementation of this approach, five DMs, who actively work in the pharmaceutical industry, evaluated the risk events which can cause fatal or non-fatal occupational accidents. The DMs made judgments by expressing their opinions based on their experience, knowledge, and expertise. All potential occupational risk types and their impacts in any pharmaceutical industry processes are identified in Appendix A.

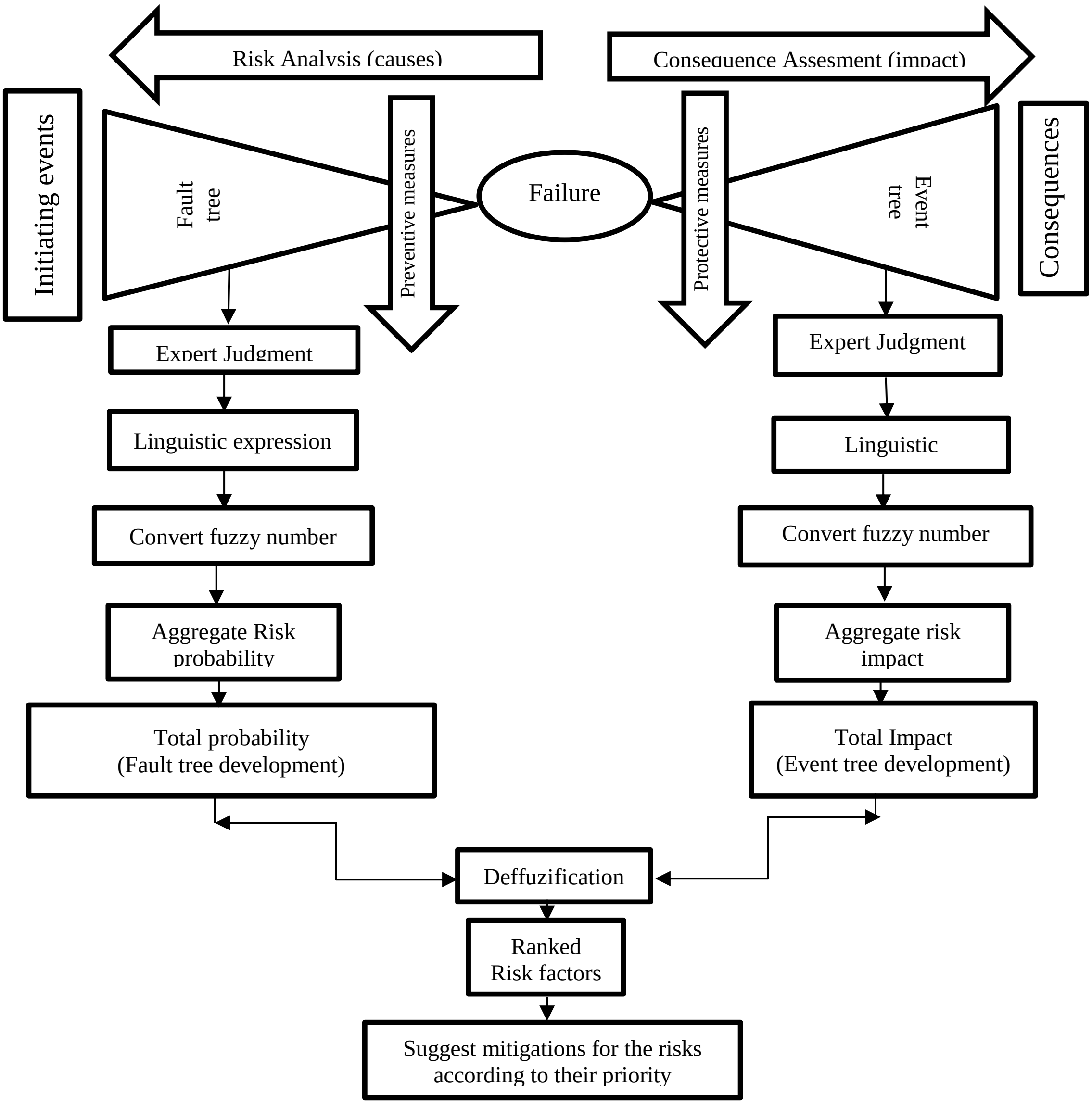

Figure 4. Implementation of Fuzzy Bow-Tie risk analysis approach.

The proposed framework based on FST and Bow-Tie analysis is as follows:

Step 1. Identify potential risks. The risks, risk factors, and risks' impacts are identified based on reported events and DMs' experience and knowledge in pharmaceutical industry.

Step 2. Collect linguistic expressions of DMs. DMs are interviewed about potential risk factors and their impacts by using qualitative linguistic terms because of the highly subjective and imprecise information. Therefore, DMs express their opinions for the probability of occurrence and impact of the risk events using linguistic variables. The linguistic expressions for the probability of occurrence of each risk event are 'Expected, 'Possible', 'Unlikely', 'Very unlikely' and 'Not expected'. The linguistic expressions for the impact of each risk event are 'High, 'Medium', 'Low', 'Very low' and 'None'.

Step 3. Convert linguistic variables into numerical values using TFNs. Each linguistic variable is converted into a TFN using Table 1 and Table 2 for the probabilities of occurrence and impacts of the risk events, respectively.

Step 4. Calculate fuzzy aggregated values for the probability of the occurrence and impact of each identified risk. If two or more DM judgments are available, it is needed to integrate their opinions into a single opinion to deal with non-homogeneous situations [60]. Accordingly, the individual DM fuzzy values are aggregated in this step. Fuzzy probabilistic value for the probability of the occurrence of each risk event is calculated using Equations (6) and (7). The same calculation is carried out for the impacts of the risk factors.

Table 1. Linguistic expressions and their corresponding fuzzy numbers for probabilistic occurrence [43,59].

Linguistic assessment variables	Corresponding fuzzy numbers	Characteristic function of fuzzy numbers
Expected (E)	$\widetilde{0.9}$	(0.7,0.9,1.0)
Possible (P)	$\widetilde{0.7}$	(0.5,0.7,0.9)
Unlikely (U)	$\widetilde{0.5}$	(0.3,0.5,0.7)
Very Unlikely(VU)	$\widetilde{0.3}$	(0.1,0.3,0.5)
Not Expected (NE)	$\widetilde{0.1}$	(0.0,0.1,0.3)

Table 2. Linguistic expressions and fuzzy numbers for impact of risks [43].

Linguistic assessment variables	Corresponding fuzzy numbers	Characteristic function of fuzzy numbers
High (H)	$\tilde{9}$	(7,9,10)
Medium (M)	$\tilde{7}$	(5,7,9)
Low (L)	$\tilde{5}$	(3,5,7)
Very low (VL)	$\tilde{3}$	(1,3,5)
None (N)	$\tilde{1}$	(0,1,3)

Step 5. Calculate the total risk probability for each identified risk event. In Bow-Tie analysis, after the probability of occurrence of each risk event is determined, the total risk probability for each event is calculated. The total probability value for each identified risk is calculated according to the relationship among risk factors (OR or AND). In the proposed framework, the total risk probability is calculated using Equation (8,9).

Step 6. Calculate the total impact for each identified risk event. The right side of the Bow-Tie diagram is event tree and it recognizes the estimated impact of each risk event. If the risk has multiple impacts $\widetilde{L_j}$ each with probability $\widetilde{P_j}(t)$, the total fuzzy impact can be calculated using Equation (10) in event tree diagram [43].

$$\widetilde{L_k} = \frac{\sum_{j=1}^{N} \widetilde{P_j}(t) * \widetilde{L_j}(t)}{\sum_{j=1}^{N} \widetilde{P_j}(t)} \quad (10)$$

Step 7. Defuzzify the fuzzy values for the probability of occurrence and the impact of each risk event. Defuzzification is the process of converting the fuzzy numbers into a crisp (exact) value. The aim is to determine the risk event priorities more easily using defuzzified values for the probability of occurrence, impact and total risk in the Fuzzy Bow-Tie analysis. The bigger the defuzzified value, the bigger the overall risk and the higher risk priority [58]

In this study, Centre of Area (COA) is used to defuzzify TFN output. A crisp output is obtained by calculating the center of symmetry of the area delimited by aggregating the consequences of such fuzzy set. A is a fuzzy set denoted on the output dimension (x), N is the number of quantization levels of the output. Equation (11) shows the COA formula [61].

$$x_0 = \frac{\sum_{j=1}^{N} \mu_A(x_0).\, x_0}{\sum_{j=1}^{N} \mu_A(x_0)} \quad (11)$$

Step 8. Calculate the risk score and prioritize the risk events. The aim of this step is to determine the risk level after calculating total risk score for each risk event. After defuzzification process, risk score is calculated by multiplying total risk probability and impact of the risks [43].

Step 9. Suggest risk mitigation strategies for safety management. After prioritizing risk events, appropriate mitigation plan can be implemented to reduce or eliminate the risk events.

4.1. Illustrative example

In this section, applicability and efficiency of the proposed Fuzzy Bow-Tie analysis is demonstrated through risk analysis in real pharmaceutical industry.

Step 1. Identify potential risks. Five DMs are organized as a team from pharmaceutical industry. These DMs are denoted as DM 1, DM 2, DM 3, DM 4, and DM 5. The DMs make judgments for potential risk events that cause the top event and their impacts based on their experience, knowledge, and expertise.

The profiles of DMs' from Pharmaceutical industry are shown in Table 3.

Table 3. The profile of DMs'.

DM	Age (years)	Education	Experience (years)	Professional Position
DM1	55	PhD	20	R&D manager
DM2	40	Bachelor	15	Synthesis/Process chemist
DM3	35	Master	10	Occupational safety expert
DM4	40	Master	10	Pharmaceutical operator
DM5	30	Bachelor	5	R&D Laboratory technician

Potential occupational risk events and their impacts during any pharmaceutical industry processes are identified as given in Appendix A. Risk factors, impacts, preventive and protective strategies are also identified by DMs as presented in Appendix A. According to their risk classification, the framework for risk assessment has been divided into six main risk types.

Step 2. Collect linguistic expressions of DMs. In this phase, DMs express their judgements and assessments for the probability of occurrence and impact of the risk events using linguistic variables.

Step 3. Convert linguistic variables into numerical values by TFNs. In this step, each linguistic expression has been transformed into a corresponding fuzzy number. Linguistic variables and corresponding fuzzy numbers for risk probability and risk impact are given in Table 1 and Table 2, respectively.

Step 4. Calculate fuzzy aggregated values for both the probability of occurrence and impact of each risk event. The individual DM fuzzy values for the probability of occurrence and impact of each risk event are aggregated with Equations (6) and (7). The aggregated fuzzy probabilistic values for the probability of occurrence of risk events are shown in Table 4. The estimation values for the impacts and associated probabilities are shown in Table 5.

Step 5. Determine the total risk probability for each identified risk event. Total probability for the identified risks is calculated using Equation (8-9). In Bow-Tie analysis, the left side is related to the relationship among the risk factors (OR or AND) for all the identified risks.

Step 6. Calculate the total impact for risk events. Total impact for each risk event is calculated using event tree diagram with Equation (10). The total risk probability of occurrence and total impact for each identified risk are given in Table 6.

Step 7. Defuzzify the fuzzy values for the probability of occurrence and the impact of each risk event. In order to obtain crisp value, TFNs are defuzzified using COA defuzzification method. The risk priority is obtained using defuzzified values for the probability of occurrence, impact and total risk in the Fuzzy Bow-Tie analysis. The results are seen in Table 7.

Step 8. Calculate the total risk score and prioritize the risks. In this step, total score for each risk event is calculated by multiplying total risk probability and impact of the risk after defuzzification process. The aim is to determine risk level of each risk event. Accordingly, Risk events are ranked based on the calculated total risk scores. Table 7 shows the total risk score and risk level for each risk event.

Step 9. Suggest mitigation strategies for safety management. After prioritize risks, appropriate mitigation plans must be implemented firstly for the high priority risks.

5. Results

According to the total risk scores, R1 is the most hazardous risk due to its higher score and the others have medium scores. The critical risks in descending order are R1, R3, R5, R6, R4 and R2. In order to mitigate the effect of risks, the risk mitigation plans must be developed for the high priority risks. However, managers have to identify preventive and protective mitigation measures to reduce risk scores to lower level. Preventive measures and protective strategies should be implemented to avoid the risk event occurs and minimize the impact of risk event, respectively. Hence mitigation plans related to R1 must be implemented firstly. R1 is associated with chemical hazards. According to this result, firstly, health and safety management team should implement a multifaceted prevention program and educate and inform employees about environmental health and safety risks, safe working instructions and the use of personal protective equipment and ventilators, gasmask etc. Training must include the drugs and chemical awareness. Chemicals must be stored in a separate storage area to reduce the risks of chemical practices, worker exposure to hazardous chemicals, and fire and explosion. Manual handling system must be replaced with an automated handling equipment for safety. Smoke or heat alarms and automated sprinkler systems must be installed to detect and prevent fire. Construction of suitable flooring, safe maintenance activities and appropriate cleaning and hygiene for work place are other key prevention and mitigation strategies for chemical risks. Other preventive protective measures about other risks are as follows:

Arrange design of workstations, hand tools, equipment etc.

Provide ergonomically designed equipment and furniture.

Install safeguards which protect workers against contact with potentially dangerous machine motions via physical guard.

Implement electrical safety program which designs and manages electrical installations.

6. Conclusions and discussions

The objective of this research is to propose a QRA framework which can be implemented effectively in any pharmacy company as a risk analysis tool. The Bow-Tie analysis is used to combine quality features of both FTA and ETA for risk assessment. It noticeably analyzes causes and consequences of an accident, then develops prevention and mitigation measures accordingly. Fuzzy sets and probability theories have been performed to handle the ambiguity of data since estimating the impact and occurrence probability of events are imprecise. Hence, this study combines the Bow-Tie analysis and FST to identify an initiating event; its causes and consequences; and potential preventive and protective control strategies or barriers to mitigate harms. The proposed methodology is easy to understand, clear, and practical that combines the features of handling vagueness, aggregation of different DM' data and prioritizing risks based on the probability of occurrence and impact of the risks.

The proposed method provides satisfactory risk assessment to evaluate and then prevent, control and mitigate occupational risks for pharmacy industry. A risk matrix, which shows the comparison of results obtained by above procedures, defines the level of risks related to ranking probability and impacts. In order to mitigate effect of risks, the risk mitigation plans must be developed for the high priority risks.

Table 4. The aggregated fuzzy probabilistic values for the probability of the occurrence of each risk event.

Risks	Factors	DM 1	DM 2	DM 3	DM 4	DM 5	Aggregated
R1	R11	P	P	U	P	P	(0.4,0.6,0.8)
	R12	U	U	U	U	VU	(0.2,0.4,0.6)
	R13	U	VU	P	U	U	(0.3,0.5,0.7)
R2	R21	NE	NE	NE	NE	NE	(0,0.1,0.3)
	R22	NE	NE	VU	NE	NE	(0.08, 0.2,0.4)
	R23	U	U	U	U	VU	(0.2,0.4,0.6)
R3	R31	U	U	U	U	VU	(0.2,0.4,0.6)
	R32	U	P	P	P	P	(0.4,0.6,0.8)
	R33	U	NE	U	U	U	(0.12,0.3,0.5)
R4	R41	VU	VU	U	U	U	(0.2,0.4,0.6)
	R42	NE	U	U	U	U	(0.12,0.3,0.5)
R5	R51	E	U	P	U	U	(0.5,0.7,0.88)
	R52	U	U	U	U	VU	(0.2,0.4,0.6)
	R53	U	NE	U	U	U	(0.12,0.3,0.5)
R6	R61	P	P	U	P	P	(0.4,0.6,0.8)
	R62	U	P	VU	U	U	(0.3,0.5,0.7)

Table 5. The estimation values for impacts and associated probabilities.

Risks	Factors	Impact /Probability	DM 1	DM 2	DM 3	DM 4	DM 5	Aggregated
R1	R11	Impact	L	M	H	M	H	(5,7.8.6)
		Probability	P	U	U	P	P	(0.4,0.6,0.8)
	R12	Impact	L	L	VL	M	M	(3,5,7)
		Probability	P	P	P	P	U	(0.4,0.6,0.8)
	R13	Impact	M	M	H	M	M	(6,8,9.8)
		Probability	P	P	U	P	P	(0.4,0.6,0.8)
	R14	Impact	M	M	H	M	M	(6,8,9.8)
		Probability	P	U	P	U	P	(0.4,0.6,0.8)
R2	R21	Impact	H	M	H	M	M	(6,8,9.6)
		Probability	P	E	P	P	P	(0.6,0.8,0.98)
	R22	Impact	L	L	L	VL	L	(2,4,6)
		Probability	NE	P	E	NE	P	(0.34,0.5,0.68)
	R23	Impact	L	M	H	M	H	(5,7,8.6)
		Probability	P	U	U	P	P	(0.4,0.6,0.8)
R3	R31	Impact	L	M	H	M	H	(5,7,8.6)
		Probability	P	U	U	P	P	(0.4,0.6,0.8)
	R32	Impact	L	L	VL	M	M	(3,5,7)
		Probability	P	P	P	P	U	(0.4,0.6,0.8)
	R33	Impact	M	M	H	M	M	(6,8,9.8)
		Probability	P	P	U	P	P	(0.4,0.6,0.8)
R4	R41	Impact	L	L	L	VL	L	(2,4,6)
		Probability	U	P	P	U	P	(0.4,0.6,0.8)

	R42	Impact	H	M	H	M	M	(6,8,9.6)
		Probability	P	E	P	P	P	(0.6,0.8,0.98)
R5	R51	Impact	M	VL	L	L	L	(3,5,7)
		Probability	U	U	U	P	E	(0.5,0.7,0.88)
	R52	Impact	M	M	H	H	M	(3,5,7)
		Probability	U	U	U	U	P	(0.4,0.6,0.8)
	R53	Impact	L	M	H	M	H	(5,7,8.6)
		Probability	P	U	U	P	P	(0.4,0.6,0.8)
R6	R61	Impact	L	M	L	L	L	(4,6,8)
		Probability	P	E	P	P	P	(0.6,0.8,0.98)
	R62	Impact	L	M	L	L	L	(4,6,8)
		Probability	U	P	P	U	P	(0.4,0.6,0.8)

Table 6. Calculated total probabilities and impacts for each risk.

Risk Type	Total Probability	Total Impact
R1	(0.66,0.88,0.98)	(5,7,8.8)
R2	(0.26,057,0.83)	(4.45,6.63,7.43)
R3	(0.58,0.83,0.96)	(4.67,6.67,8.47)
R4	(0.30,0.58,0.8)	(4.4,6.28,7.98)
R5	(0.65,0.87,0.98)	(4.4,6.28,7.98)
R6	(0.58,0.8,0.94)	(4,6,8)

Table 7. Determination of ratings for risk occurrence probability and impact.

Risk Type	Probability (COA)	Probability level	Impact (COA)	Impact level	Total risk score	Risk level
R1	0,84	VH	6,93	H	5,82	H
R2	0,55	H	6,17	M	3,42	M
R3	0,79	VH	6,6	M	5,22	M
R4	0,56	H	6,22	M	3,47	M
R5	0,83	VH	6,22	M	5,18	M
R6	0,77	VH	6	M	4,64	M

According to results, R1 is more hazardous risk due to higher its higher score. Hence mitigation plans related to R1 must be implemented at first. However, to reduce future risks, and human and material losses, other mitigation strategies must be implemented for other risks. Therefore, all risks needed to be reduced to low risk scores. For further research, the proposed approach can be used for safety and risk analysis in different industry areas that are faced with uncertainty in data and model.

References

[1] Attaianese, E. & Duca, G. (2012). The integrated assessment of occupational risks in a pharmaceutical manufacturing plant. *Work*, IOS press, 41, 1733-1738. DOI: 10.3233/WOR-2012-0377-1733.

[2] Keith, T. (1998). *Encyclopaedia of Occupational Health and Safety*. Fourth Edition Edited Jeanne Mager Stelman, International Labour Office, Chapter 79.

[3] Naumann, B., Sargent, EV., Starkman, BS., Fraser, WJ . Becker, GT & Kirk, GD. (1996). Performance-based exposure control limits for pharmaceutical active ingredients. *American Industrial Hyjgiene Association Journal*, 57: 33-42.

[4] Evelyn, N., Cristophe, R., Nathalie, B. & Alessandro, S. (2018). Chemical Risk Assessment Screening Tool of a Global Chemical Company. *Safety and Health at Work*, 9(1) 84-94.

[5] Binks, S.P. (2003). Occupational toxicology and the control of exposure to pharmaceutical agents at work. *Occupational Medicine*, 53:363–370.

[6] Shahriar , A., Sadiq, R. Tesfamariam, S. (2012). Risk analysis for oil & gas pipelines: A sustainability assessment approach using fuzzy based Bow-Tie analysis. *Journal of Loss Prevention in the Process Industries*, 25(3), 505–523.

[7] Khan, FI., Abbasi SA. (2001). Risk analysis of a typical chemical industry using ORA procedure. *Journal of Loss Prevention in the Process Industries*, 14, 43–59.

[8] Sklet S. (2004). Comparison of some selected methods for accident investigation. *Journal of Hazardous Materials*. 111 (1-3), 29-37.

[9] Couronneau, J.C., Tripathi, A. (2003). Implementation of the new approach of risk analysis in France. *Proceedings of the 41st International Petroleum Conference*, Bratislava, Slovakia.

[10] Jacinto, C., Silva, C. (2010). A semi-quantitative assessment of occupational risks using Bow-Tie representation. *Safety Science*, 48, 973–979.

[11] Khan FI, Abbasi SA. (1998). Techniques and methodologies for risk analysis in chemical process industries. *Journal of Loss Prevention in the Process Industries*, 11: 261–277.

[12] Delvosalle, C., Fievez, C., Pipart, A., Fabreg, C.J., Debray, B. (2006). ARAMIS project: a comprehensive methodology for the identification of reference accident scenarios in process industries. *Journal of Hazardous Materials*, 130, 200–219.

[13] Montano, D. (2014). Chemical and biological work-related risks across occupations in Europe: a review. Montano *Journal of Occupational Medicine and Toxicology* 2014, 9:28.

[14] Gowland, R. (2006). The accidental risk assessment methodology for industries (ARAMIS)/layer of protection analysis (LOPA) methodology: a step forward towards convergent practices in risk assessment? *Journal of Hazardous Materials*, 130, 307–310.

[15] Khan, F. (2001). Use maximum-credible accident scenario for realistic and reliable risk assessment. *Chemical Engineering Progress*, 11, 56–64.

[16] Chevreau, F. R., Wybo, J. L., & Cauchois, D. (2006). Organizing learning processes on risks by using the Bow-Tie representation. *Journal of Hazardous Materials*, 130(3), 276. doi:10.1016/j.jhazmat.2005.07.018.

[17] Khakzad, N., Khan, F., Amyotte, P. (2013). Quantitative risk analysis of offshore drilling operations: a Bayesian approach. *Safety Science*, 57, 108-117.

[18] Deacon, T., Amyotte, P.R., Khan, F.I. (2013). A framework for human error analysis of offshore evacuations. *Safety Science*, 51 (1), 319-327.

[19] Deacon, T., Amyotte, P.R., Khan, F.I. (2010). Human error risk analysis in offshore emergencies. *Safety Science*, 48 (6), 803-818.

[20] Khakzad, N., Khan, F., Amyotte, P. (2012). Dynamic risk analysis using Bow-Tie approach. *Reliability Engineering and System Safety*, 104, 36-44.

[21] Cockshott, J.E. (2005). Probability Bow-Ties: a transparent risk management tool. *Process Safety and Environmental Protection*, 83 (4), 307-316.

[22] Duijm, N. J. (2009). Safety-barrier diagrams as a safety management tool. *Reliability Engineering & System Safety*, 94(2), 332-341. doi:10.1016/j.ress.2008.03.031.

[23] Badreddine, A., Ben HajKacem, M.A., Ben Amor, N. (2014). A three stages to implement barriers in Bayesian-based Bow-Tie diagram. *27rd International Conference on Industrial Engineering and Other Applications of Applied Intelligent Systems, IEA/AIE* 2014, 32-41.

[24] Dianous, V., Fivez, C. (2006). ARAMIS project: a more explicit demonstration of risk control through the use of Bow-Tie diagrams and the evaluation of safety barrier performance. *Journal of Hazardous Materials*, 130(3), 220-233.

[25] Mokhtari, K., Ren, J., Roberts, C., Wang, J. (2011). Application of a generic Bow-Tie based risk analysis framework on risk management of sea ports and offshore terminals. *Journal of Hazardous Materials*, 192(2), 465-475.

[26] Preeda S., Min A. (2015). Development of Risk Assessment and Occupational Safety Management Model for Building Construction Projects. World Academy of Science. *Engineering and Technology International Journal of Civil and Environmental Engineering* Vol.9, No.9.

[27] Agarwal, H., Renaud, J. E., Preston, E. L., & Padmanabhan, D. (2004). Uncertainty quantification using evidence theory in multidisciplinary design optimization. *Reliability Engineering & System Safety*, 85(1-3), 281-294. doi:10.1016/j.ress.2004.03.017.

[28] Ayyub, B. M., & Klir, G. J. (2006). *Uncertainty modeling and analysis in engineering and the sciences*. Boca Raton, FL 33487-2742, US: Chapman & Hall.

[29] Wilcox, C.R., Ayyub, M.B. (2003). Uncertainty modeling of data and uncertainty propagation for risk studies. *IEEE Proceedings on Uncertainty Modeling and Analysis*, 184–191.

[30] Bae, H., Grandhi, R. V., & Canfield, R. A. (2004). An approximation approach for uncertainty quantification using evidence theory. *Reliability Engineering & System Safety*, 86(3), 215. doi:10.1016/j.ress.2004.01.011.

[31] Boudraa, A., Bentabet, A., Salzenstein, F., & Guillon, L. (2004). Dempster-Shafer's basic probability assignment based on fuzzy membership functions. *Electronic Letters on Computer Vision and Image Analysis*, 4(1), 1-10.

[32] Sentz, K., & Ferson, S. (2002). Combination of evidence in Dempster-Shafer theory. *Technical US Department of Energy*. Sandia National Laboratories.

[33] Gentile, M., Rogers, W. J., & Mannan, M. S. (2003). Development of an inherent safety index based on fuzzy logic. *Process Safety and Environmental Protection*, 81(6), 444-456.

[34] Markowski, A. S. (2006). Layer of protection analysis for the process industry. *Lodz: PAN, ISBN 83-86-492-36-8*.

[35] Salzano, E., & Cozzani, V. (2006). A fuzzy set analysis to estimate loss intensity following blast wave interaction with process equipment. *Journal of Loss Prevention in the Process Industries, 19, 343-*

352.

[36] Abrahamsson, M. (2002). *Uncertainty in Quantitative Risk Analysis—Characterization and Methods of Treatment. Department of Fire Safety Engineering.* Lund University, Sweden.

[37] Ferdous, R., Khan, F., Sadiq, R., Amyotte, P., Veitch, B. (2009). Methodology for computer aided fuzzy fault tree analysis. *Process Safety and Environment Protection*, 87(4), 217–226.

[38] Ferdous, R., Khan, F., Sadiq, R., Amyotte, P., Veitch, B. (2010). Fault and event tree analyses for process systems risk analysis: uncertainty handling formulations. *Risk Analysis: An International Journal*, 31(1), 86–107.

[39] Markowski, A., Sam Mannan, M., Kotynia, A. (Bigoszewska)., Siuta, D (2010). Uncertainty aspects in process safety analysis. *Journal of Loss Prevention in the Process Industries*, 23, 446-464.

[40] Ferdous, R., Khan, F., Sadiq, R., Amyotte, P., Veitch, B. (2011). Analyzing system safety and risks under uncertainty using a Bow-Tie diagram: an innovative approach. *Process Safety and Environmental Protection*, doi:10.1016/j.psep.2011.08.010.

[41] Tanaka, H., Fan, T.L., Lai, F.S., Toughi, K. (1983). Fault tree analysis by fuzzy probability. *IEEE Transactions on Reliability 32(5), 455–457.*

[42] Singer, D. (1990). A fuzzy approach to fault tree and reliability analysis. *Fuzzy Sets and Systems 34, 145–155.*

[43] Aqlan, F., Mustafa Ali, E. (2014). Integrating lean principles and fuzzy Bow-Tie analysis for risk assessment in chemical industry. Jou*rnal of Loss Prevention in the Process Industries*, *29, 39-48.*

[44] Markowski, A. S., Mannan, M. S., & Bigoszewska, A. (2009). Fuzzy logic for process safety analysis. *Journal of Loss Prevention in the Process Industries*, 22(6), 695-702. doi:10.1016/j.jlp.2008.11.011.

[45] Bhusnure, O. G., Dongare, R. B., Gholve, S. B., Giram, P. S. (2018). Chemical hazards and safety management in pharmaceutical industry. *Journal of Pharmacy Research*, Vol. 12, Issue 3.

[46] Gathuru, I.M., Buchanich, J., Marsh, G., Dolan, D. (2015). Health Hazards in the Pharmaceutical Industry. *Pharmaceutical Regulatory Affairs*, 4:3, DOI: 10.4172/2167-7689.1000145.

[47] Kumar, P., Shukla, J. (2010). Rısk Analysis and Risk Management In Pharmaceutıcal Industry. *Internatıonal Journal of Pharma World Research*, Vol. 1, Issue 1.

[48] Urushihara H, Kobashi G, Masuda H, Taneichi S, Yamamoto M, Nakayama T, Kawakami K, Matsuda T, Ohta K, Sugimori H. (2014). *Pharmaceutical company perspectives on current safety risk communications in Japan*. SpringerPlus, 3:51.

[49] Bhowmik, D., Durai Vel, S., Rajalakshmi A.N, Sampath Kumar, K. (2014). Recent Trends in Hazards in the Pharmaceutical Industry and Safety Precaution. *Elixir Pharmacy*, 69, 23688-23691.

[50] Patrick T.W., Guchelaar, H., Guchelaar, H. (2003). Risk assessment in clinical pharmacy. *Pharmacy World and Science*; 25(3), 98–103.

[51] Anthony P. Acfield and Dr. Robert A. Weaver (2012). Integrating Safety Management through the Bow-Tie Concept A move away from the Safety Case focus. *Australian System Safety Conferrence (ASSC 2012).*

[52] Shuang, C., Jinqiu, H., Laibin, Z. (2016). Risk analysis of refining equipment based on fuzzy theory and Bow-Tie model. *Proceedings of the 35th Chinese Control Conference July 27-29, 2016*, Chengdu, China.

[53] Zadeh, L.A. (1965). Fuzzy sets. *Information and Control*, 8, 339-353, 1965.

[54] Zadeh, L.A. (1978). Fuzzy sets as a basis for a theory of possibility. *Fuzzy sets and systems*, 1, 3-28.

[55] Lin, C., Wang, M.J. (1997). Hybrid fault tree analysis using fuzzy sets. *Reliability Engineering and System Safety*, 58, 205–213.

[56] Lee, K. (2005). *First Course on Fuzzy Theory and Applications*. Springer, ISBN 978-3-540-32366-2.

[57] L.X. Wang, (1997). *A Course in Fuzzy Systems and Control.* Prentice-Hall International Inc.

[58] Cheliyan, A.S., Bhattacharyya, S.K. (2018). Fuzzy fault tree analysis of oil and gas leakage in subsea production systems. *Journal of Ocean Engineering and Science*, 3(1), 38-48.

[59] Tyagi, S., Pandey D., Tyagi, R. (2010). Fuzzy set theoretic approach to fault tree analysis. *International Journal of Engineering, Science and Technology*, 2(5), 276-283.

[60] Sangaiah, A., Kumar, A., Thangavelu, A. (2013). An exploration of FMCDM approach for evaluating the outcome/success of GSD projects. *Central European Journal of Engineering*, 3(3), 419-435. DOI: 10.2478/s13531-012-0070-9.

[61] Tsenga, T., Konadaa , U., Kwon Y. (2016). A novel approach to predict surface roughness in machining operations using fuzzy set theory. *Journal of Computational Design and Engineering*, 3, 1–13.

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