Exploring inherent process safety indicators and approaches for their estimation : a systematic review

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Abstract

The index-based approach is one of the most popular ways to measure the inherent safety degree of a chemical route or process during the early design stages. One of the main shortcomings of current indices is the limited set of aspects which are considered and are influencing inherent safety. In addition, the minimal knowledge of process designers regarding inherent safety hazards can exacerbate this problem. In this study, we identify the inherent safety indicators (within the period 1990-2017) used to measure the inherent safety degree of a process, and describe existing approaches to estimate these indicators. Bibliographic sites, including the Web of Science, ScienceDirect, Springer, ACS publications and Online Library, were searched based on various search strategies. A total of 62 resources were selected, and 35 indicators were found that were classified into six categories: (i) the 'chemical and physical properties of a chemical substance (11 indicators); (ii) the 'process conditions' (5 indicators); (iii) the 'equipment' (5 indicators); (iv) the 'reaction/decomposition properties' (3 indicators); (v) the 'activities and operations characteristics' (4 indicators); and (vi) the 'consequences' (7 indicators). We also found six estimation approaches, including the relative rating, an advanced mathematical approach (statistical, numerical descriptive and fuzziness), the risk-based, graphical, equational (or formula) based approach and the hybrid approach. This study can provide a quick guide for non-experienced researchers being enthusiast to work on inherent safety measurements using an index-based approach.

Key words: inherent safety, measurement, index-based, indicators, process

Abbreviations

ISD	Inherently Safer Design	**NFPA**	National Fire Protection Association
PIIS	Prototype Index of Inherent Safety	**ERPG**	Emergency Response Planning Guideline
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses	**AP**	Atmospheric Pressure
FP	flash Point	**VP**	Vapour Pressure
BP	Boiling Point	**PP**	Process Pressure
LFL/LEL	Lower Flammability/Explosion Limit	**F&EI**	Fire and Explosion Index
UFL/UEL	Upper Flammability/Explosion Limit	**OSBL**	Outside (Offsite) Battery Limit Area
TLV	Threshold Limit Value	**ISBL**	Inside Battery Limit Area
R-phrase	Risk Phrase	**VCEs**	Vapour Cloud Explosions
LD	Lethal Dose	**BLEVE**	Boiling Liquid Expanding Vapour Explosion
LC	Lethal Concentration	**RR**	Relative Ranking
RFD/C	Reference Dose/Concentration	**AMM**	Advance Mathematical Methodologies
IDLH	Immediately Dangerous to Life or Health	**HYB**	Hybrid
EQB	Equation Based Approach	**RBA**	Risk Based Approach
GR	Graphical Approach		

1. Introduction

To ensure the safety of a process, a hierarchical strategy is suggested as follows from low to high effectiveness: 1) a procedural strategy that utilizes administrative controls, such as standard operational procedures, training, and emergency response planning procedures; 2) an active strategy that provides safety through technological (engineering) controls, such as sprinklers, alarms, and safety instrumented systems; 3) a passive strategy that offers safety using design characteristics of the design process or equipment without active functions, such as a dike wall around storage tanks; and 4) Inherently Safer Design (ISD) strategies that reduce or eliminate hazards using the ISD principles (Bollinger and Crowl, 2009; Kletz and Amyotte, 2010; Crowl and Louvar, 2011).

ISD is at the top of the hierarchy for process safety strategies and it is regarded as one of the main future directions for loss prevention in the chemical and process industries (Reniers and Amyotte, 2012), with the goal of reducing or eliminating intrinsic hazards during early design stages of a process plant instead of controlling them using “add-on” technologies (Kletz, 2003). ISD emerged after being published in Flixborough's accident investigation report. The four main principles suggested for ISD include (but are not limited to): minimization (the reduction of chemical inventory), substitution (replacing substances with less hazardous ones or eliminating them), attenuation (conducting processes under more facile conditions) and simplification (designing simplified processes for the reduction of human errors) (Kletz and Amyotte, 2010; Khan and Amyotte, 2002; Eini et al., 2015; Eini et al., 2016a; Eini et al., 2016b).

The first ISD priority is to eliminate hazards, and if this is unachievable, one needs to try to mitigate hazard consequences. Its implementation begins at the conceptual design and at the selection synthesis route and extends into other process design phases, although the efficiency of this process decreases near the end of the design life cycle, such as in the piping and instrumentation diagrams (P&ID) and during construction (Hendershot, 1997, 2006; Srinivasan and Natarajan, 2012).

One of the biggest challenges of ISD implementation is determining the inherent safety degree of a plant. Measuring the inherent safety degree can aid the stakeholders to come up with the effective strategies for coping with the residual risks and also for improving the aspects of ISD requiring modifications (Hendershot, 1997; Rahman et al., 2005; Nhan, 2006).

The approaches for assessing inherent safety are classified into three categories: a) *models* that focus on the properties of materials or operations in experimental, computational and mathematical environments, (but their applicability is limited), b) *qualitative reviews* that evaluate hazards using techniques such as brainstorming and checklists; and c) *metrics* that quantitatively (in most cases) or qualitatively assess the inherent hazards of a specific process, displaying better applicability than other approaches (Srinivasan and Natarajan, 2012). Metrics (or index-based approaches) have been widely used since they are user-friendly and time effective than other approaches, they require levels of information which mostly are available in early design stages, they can be integrated with process simulator or similar assessment tools, they can consider the trade-offs among various alternatives for design of a specific process and other benefits (Nhan, 2006; Rahman et al., 2005; Koller et al., 2001; Warnasooriya and Gunasekera, 2017).

The first index, called "Prototype Index of Inherent Safety (PIIS)", was introduced by Edward and Lawrence (1993) for ranking the inherent safety degree of synthesis routes (Edwards and Lawrence, 1993). This is an inspiring index for researchers interested in developing and introducing novel methodologies with the goal of overcoming the limitations of IS degree measurements (Gentile et al., 2003a; Khan and Amyotte, 2004; Cozzani et al., 2007; Hassim and Hurme, 2010a; Shariff and Zaini, 2010; Rathnayaka et al., 2014).

Beside their advantages, index-based approaches suffer from several shortcomings (Nhan, 2006; Rahman et al., 2005). There is no golden standard (such as a metre for distance measurements for instance) to measure the real degree of inherent safety of a process. Thus, the accuracy and sensitivity of the index results can be ambiguous. Additionally, few scientific studies have proposed the minimum criteria for developing a comprehensive index. Therefore, the difference among the results of various indices was considerably influenced by the extent to which inherent safety indicators have been covered. Index-based tools have specific structures that include indicators (sub-index), indices (sets of sub-indices) and overall indices (set of indices). The diversity of the indices can also be attributed to the various indicator calculations and how these indicators aggregate into an overall index. A study by Koller et al. (2002) showed that the similarity between two studied indices, when ranking a safety process, was 75% due to the diversity in their coverage of sub-indices (Koller et al., 2000). Whenever an index covers high numbers of inherent safety indicators, its results will be more realistic. It should be noted that there is no comprehensive index that covers all of the inherent safety indicators, although, typically, some indices give more convincing results (Koller et al., 2000; Rahman et al., 2005; Srinivasan and Natarajan, 2012).

The best efficiency for ISD implementation can be achieved during the early design stages of a process route or process plant (Khan and Amyotte, 2003). Therefore, the roles of design teams and researchers for avoiding hazards during these stages are crucial. Some studies have pointed out that lack of awareness and knowledge regarding ISD principles and its measurement methods remain as one of the main barriers to the implementation of inherent safe designs (Gupta and Edwards, 2002; Jafari et al., 2017; Kletz, 2003; Kletz and Amyotte, 2010). To overcome this problem, experts, especially designers, their knowledge should be increased regarding the sources of hazards with the goal of reducing or eliminating possible hazards and developing evaluation strategies to measure the extent to which inherent safety has been achieved (using index-based approaches). Therefore, informative resources are required to achieve these goals. However, to the best of our knowledge, few studies have been conducted from 1990 to date that systematically gathered and discussed inherent safety indicators from validated resources to provide the required information for non-experiensed researchers (Roy et al., 2016; Hassim, 2016; Khan and Amyotte, 2002; Khan and Amyotte, 2003). Thus, our study is the first systematic attempt to identify inherent safety indicators that can be used to measure the inherent degree of safety of a process plant. First, we identify the safety indicators and describe the existing estimation approaches for each indicator. Then, we categorize the inherent safety indicators into several categories within a framework.

2. Methods

2.1 Data sources

This study was conducted by reviewing the literature and reports on inherent safety measurements using index-based approaches. For this purpose, resources published from 1990 to February 2017 were sought and scanned to identify relevant papers. Relevant studies (see section 2.3) were identified using electronic searches in Web of Science, ScienceDirect, Springer, ACS publications and Online Library databases using defined search strategies. The "Snowball method" (finding more references from the citation section of each reference) (Fatemi et al., 2017) was also utilized to find other supplementary resources from the references of papers.

2.2 Search strategy

Inherent safety specific search terms (inherent safety, chemical route selection, process design, synthesis route, ISD, sustainability, and occupational health) were combined with index-based related terms (index, indicator, indices, tools, methodology, and technique) in all of the searches in the databases. These terms were derived via consultation with process safety experts (who had more than 20 years' experiences in process safety). Our priority was to search in the "title" and "keywords" of each resource because this could direct us to find more relevant papers.

2.3 Inclusion and exclusion criteria

A set of the following inclusion and exclusion criteria was determined by the research team (based on our objectives) to obtain better results:

- **Publication periods:** The articles that were published in peer-reviewed journals from 1990 to February 2017 were included in the study.

- **Type of article:** Only peer-reviewed original articles were included. All articles published in conferences and so on were excluded. Review articles were also considered to benefit from their relevant references.
- **Research question:** According to our objectives, each relevant paper had one of the following criteria:

a) presenting inherent safety indicators

b) introducing methodologies for calculating inherent safety indicators

c) validating the case studies by conducting tests

d) excluding the articles with the goal of designing inherently safer equipment or describing the theoretical aspects of ISD

- **Language:** We included only articles written in the English language.

2.4 Quality appraisal

To obtain better results, two independent authors were involved throughout the study to assess the applicability of the articles to the inclusion criteria. Once the searches were completed, the abstracts of the papers were read with care and the full text of the candidate articles was reviewed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. PRISMA provides a graphical and step-by-step procedure to refine high numbers of articles to achieve high-quality studies based on a set of minimum items for reporting systematic reviews. PRISMA includes three steps for qualitative synthesis, including identification, screening and eligibility (Moher et al., 2009), as depicted in Fig. 1.

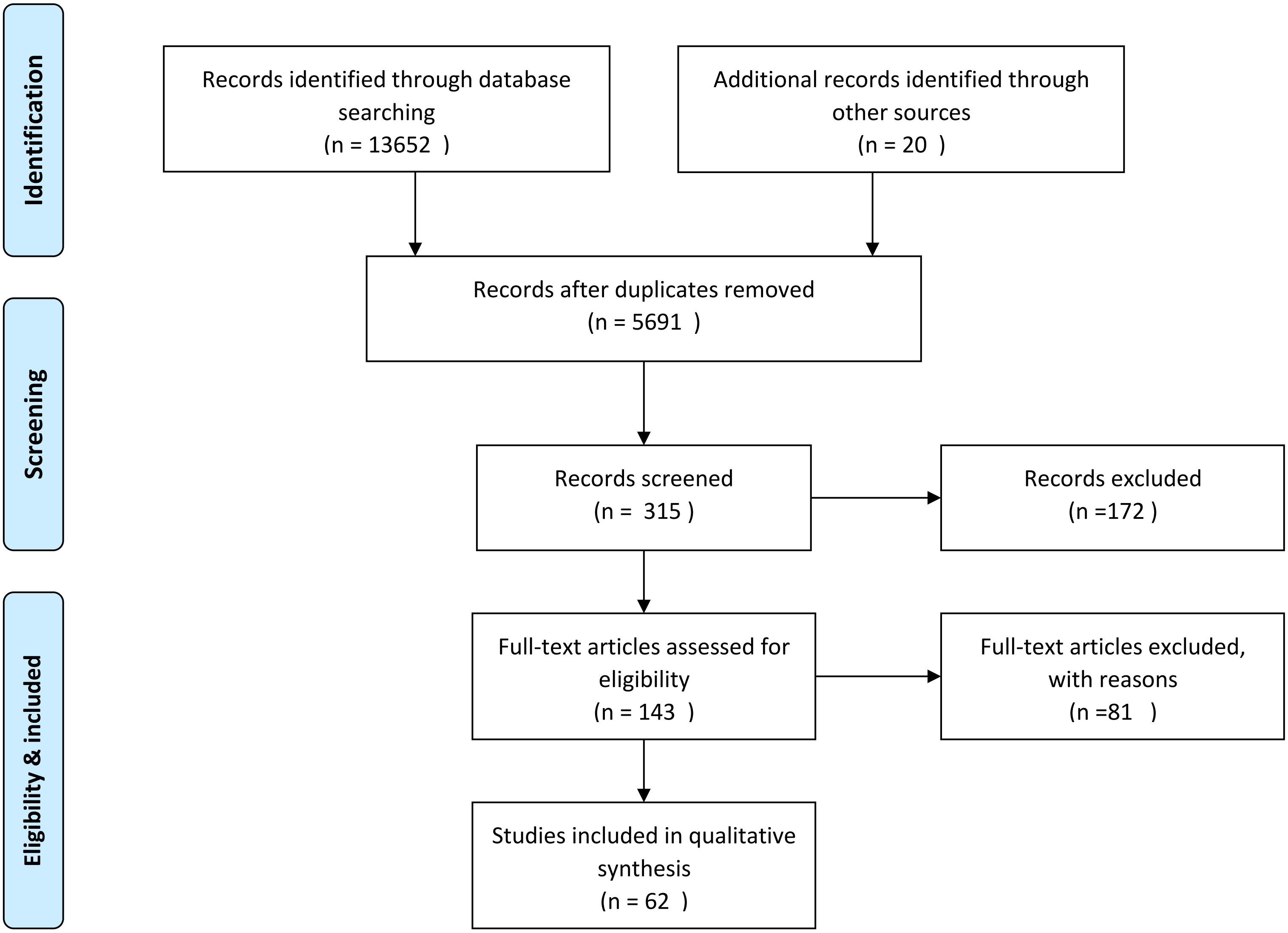

Figure 1 – PRISMA diagram for search and selection of paper

2.5 Data extraction

Once the relevant studies were identified, the characteristics of each study were summarized as follows: the author names, publication year, country of first author, case study and estimation approach. All of the indicators were identified, as well as their estimation methods. Once all of the indicators were identified, they were classified into groups based on their similarity.

3. Results

A total of 62 studies met the inclusion criteria that were included in this study (Appendix 1). Most of the researchers were inclined to validate their indices by testing the chemical synthesis routes of methyl methacrylate (MMA). Most of the included studies were performed in developed countries.

A total of 35 ISD indicators were identified, and they were sorted into six categories based on their similarity:

a) Chemical and physical properties of chemical substances: 11 indicators
b) Process conditions: 5 indicators
c) Equipment: 5 indicators
d) Reaction/decomposition properties: 3 indicators
e) Activities and operations characteristics: 4 indicators
f) Consequences indicators: 7 indicators

3.1 Estimation approaches:

We identified six categories for the estimation of ISD indicators (Fig 2) and linked the studies with one or more categories (Appendix 1). To better describe our analysis, we first start with the estimation approaches and then focus on the ISD indicators (See references in Appendix 1 and Appendix 2).

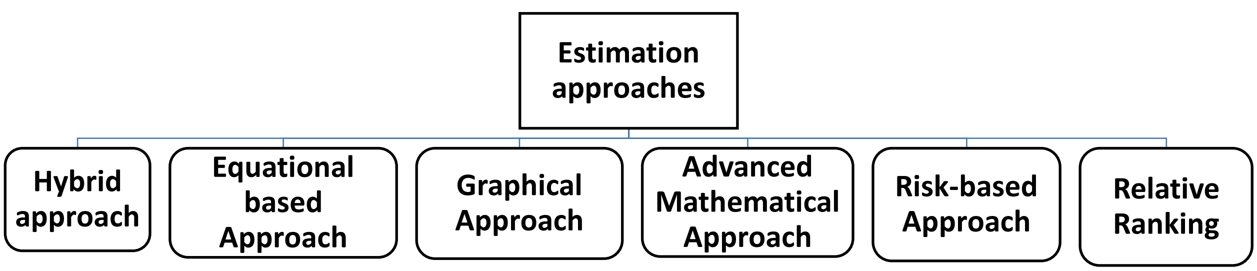

Figure 2 – estimation approaches for estimation of ISD indicators

3.1.1 Relative Ranking: A ranking system is created based on the possible quantitative values of each indicator. The extent of each rank is always determined through expert judgement, and each rank gains a score (each score is also thoroughly defined). The values of the indicators are then compared with this ranking system to specify their score (Heikkilä, 1999).

This is the approach which is the easiest to use; it requires minimal information and time and is most user-friendly, although it is based on the expert judgment. The relative ranking approach covers the assessment of most of the inherent safety indicators. It is a suitable choice to integrate with another estimation approach (Rahman et al., 2005; Hassim, 2016; Koller et al., 2001).

3.1.2 Advanced mathematical approach: This approach is based on advanced mathematical methodologies including statistical, numerical and fuzziness methods.

3.1.2.1 Statistical method: A statistical method is based on the data obtained from several databases in which a proposed formula for each indicator is solved by substituting constants or relative ranks into the formula. The output of each formula is valued from 0 to 1, and the lower scores indicate inherently safer options (Nhan, 2006; Srinivasan and Nhan, 2008).

3.1.2.2 Numerical descriptive method: This method is based on the logistic equation, which consists of X (indicator value) and Y (score of each indicator) variables and three constants: A (equation based on the gathered data from previous studies), B (same as A) and C (maximum limit of the scores). By solving the proposed equation, the score of each indicator is obtained (Ahmad et al., 2014).

3.1.2.3 Fuzziness method: Each indicator is represented by a linguistic function, and the range of an indicator is divided into a fuzzy set (0 (absence of intrinsic hazards) and 1 (extreme hazards)). The fuzziness method can overcome the uncertainty of expert judgement. It covers inherent safety aspects such as fire, explosions and human toxicity (Gentile et al., 2003a; Gentile et al., 2003b; Ng et al., 2013).

Although several benefits are attributed to these methodologies, their applicability in the real assessments is more time consuming and requiring to have great knowledge and expertise about advanced mathematical methods (Gentile, 2004).

3.1.3 Risk-based approach: The risk-based approach focuses on estimating the main consequences of inherent hazards, including the type of fire, the type of explosions and the dispersion of hazardous chemicals (Cozzani et al., 2009). When all of the possible scenarios are identified, the risk of each scenario can be estimated using the severity and probability obtained from the models and formulas (Tugnoli et al., 2008a,b; Tugnoli et al., 2009; Tugnoli et al., 2012). The risk-based approach also provides reliable and applicable results, requiring a number of initial assumptions, however it is more time consuming and has a more complex estimation procedure than other calculation approaches such as expert judgement (Rathnayaka et al., 2014). Recently, the focus on consequences analysis has received great attention, as conducting quantitative risk analysis is a critical requirement in the design of process facilities, layout and spacing, and land-use planning (Yuan et al., 2013).

3.1.4 Graphical approach*:* In this approach, the actual value of each indicator is employed and plotted for the various synthesis routes. The indicators are calculated using variables that are depicted in a graphical form using a simple graphical method or reactive layers. This approach can provide a visual comparison among inherent safety indicators or process design alternatives (Gupta and Edwards, 2003; Shah et al., 2003; Koller et al., 2000; Hassim et al., 2013). Most of the researchers tend to employ this approach as supplementary with other approaches (Khan and Amyotte, 2004, 2005).

3.1.5 Hybrid approach: This approach integrates or employs combinations of the aforementioned approaches to estimate the indicators (for example, a relative ranking and a risk-based approach). Through overlapping several approaches, a hybrid approach may provide more satisfying results than an individual approach. Hence, it represents an area for indicator assessment (Cozzani et al., 2009; Khan and Amyotte, 2004; Rathnayaka et al., 2014; Ruiz-Femenia et al., 2017).

3.1.6 Equational (or formula) based approach: In this approach, experimental or proposed equations are used for the estimation of indicators (equations not included in the above methodologies). In some cases, a simplified equation can eliminate the request for employing complex modelling. It should be noted that reliable equations which have already acquired from research studies or equations which are proposed in accordance with scientific principles are the reasonable choices in this approach (Shariff and Wahab, 2013; Shariff et al., 2016; Cordella et al., 2009).

Appendix 2 shows the extracted indicators along with the current approaches for their estimation. 35 ISD indicators are depicted into the figure depicted in Appendix 3, described below and described in Section 3.2. Possible ISD indicators are also indicated Appendix 3. We describe only some important points about the indicators in the next section.

3.2 Chemical and physical properties of the chemicals

This section addresses the physical and chemical properties of the raw materials, as well as of intermittent substances, final products and by-product chemicals. There are a number of these properties, but their applicability depends on the availability of information during the early process design stages, whether the chemicals are considered individually or as a mixture. The influence of the chemicals on eliminating or reducing inherent hazards and the ability to estimate their behaviour during the design phase is taken into consideration. In addition, the chemical and physical properties of the chemicals are related to the substitution principle of inherent safety, which recommend replacing highly hazardous materials or processes with less hazardous ones. Lowering the values of these indicators can mitigate the consequences of major accidents, such as huge fires, explosions and toxic clouds. There are many informative resources that facilitate accessibility to chemical properties, such as material safety data sheets, literature, and encyclopaedias. The most common indicators in this category are mentioned and explained below.

3.2.1 Flammability: Flammability indicates the means in which a solid, gas or liquid material easily burns in air. If a material or mixture has a lower flash point (FP) than the ambient, storage or operative temperatures, it may pose a safety risk that results in fire or an explosion (Heikkilä, 1999; Heikkilä et al., 1996). In most of the studies, the flash point and boiling point (BP) is employed for the flammability estimation (Edwards and Lawrence, 1993; Heikkilä, 1999; Palaniappan et al., 2002a; Palaniappan et al., 2002b; Hassim et al., 2013). The National Fire Protection Association (NFPA) flammability class is an available source for each substance, and each class receives a number (0 to 4) based on its BP and FP (Khan and Abbasi, 1998; Khan and Amyotte, 2004; Khan et al., 2001; Khan and Amyotte, 2005). The relative ranking approach consider these variables in its scoring system. The flammability is also estimated by comparing the process temperature with the flash, fire and auto-ignition points of materials for each processing unit (Khan and Abbasi, 1998; Khan et al., 2001). The flammability of the chemicals in a mixture can be acquired using the lower flammability limit (LFL) and upper flammability limit (UFL) of the components with the appropriate equations (Shariff et al., 2012; Shariff and Zaini, 2010). The other approaches, including the advanced mathematical approach, the hybrid approach, and the graphical approach, are also used to estimate the temperature indicator (Ahmad et al., 2014; Gupta and Edwards, 2003; Rusli et al., 2013; Srinivasan and Nhan, 2008).

3.2.2 Explosiveness: The explosiveness indicator refers to the ability of a material to make an explosive mixture with air when its concentration falls between the lower explosive limit (LEL) and the upper explosive limit (UEL) (Heikkilä, 1999). The more common variable for assessing the explosiveness of a material is the difference between the UEL and LEL (UEL-LEL). An extended range indicates a higher probability of explosion. For individual chemicals, we found two numerical rating systems in which the range (0-100%) was divided into eleven (score of 0 to 10) (Edwards and Lawrence, 1993) and five (score of 0 to 4) ranks (Heikkilä, 1999). As with the flammability estimation, the same procedure is used for estimating the explosiveness of a mixture. Regarding streams, the combustibility of a stream is calculated and then divided by the average combustibility of all streams (Shariff et al., 2012).

The statistical, fuzziness, numerical, and hybrid approaches can be employed for this indicator (DOW chemical, 1994; Ahmad et al., 2014; Nhan, 2006; Serna et al., 2016). After estimating the explosiveness for each chemical synthesis route, the alternative route with the lower possibility of explosion can be chosen.

3.2.3 Toxicity: The toxicity indicator is one of the most studied ISD indicators dealing with the properties of chemicals that interfere with bodily organs to cause undesirable acute and chronic effects (Hassim, 2016; Heikkilä, 1999). In an accident involving toxic chemicals, the acute toxicity of the materials is often regarded as a safety problem, although also chronic exposure has undesirable effects on human health and should be considered. Included studies thus focus on the toxicity of chemicals from the viewpoint of acute and chronic toxicity. A set of suggested variables to estimate the toxicity are the following: the TLV or exposure limit, R-phrase, LD_{50} oral (mg/m^3), LD_{50} dermal (mg/m^3), LC_{50} inhalation (mg/m^3), RfD, RfC, CSF, IDLH, ERPG 3, health factor (NH) obtained from NFPA-49, OSHA GHS, GK, EC classification and so on (references are presenting in Appendix 2 and Appendix 3). Criteria and abbreviations used for toxicity assessment are given in Table 1. Lower values of these variables (except for the NFPA category) represent the higher toxicity of the chemicals. Other considered physical chemical properties include the molecular weight, the Henry constant, the boiling point for acute toxicity, the octanol-partition coefficient, the overall persistence time (for chronic toxicity), the physical state of the involved chemicals, the quantity of chemicals involved in the units, the process operating conditions and the site characteristics (Cordella et al., 2009).

The most common approach for estimating toxicity is relative ranking. Other estimation methods include statistical, graphical, numerical, and hybrid approaches (Ahmad et al., 2014; Gupta and Edwards, 2003; Koller et al., 2000; Nhan, 2006; Shah et al., 2003; Srinivasan and Nhan, 2008; Khan and Amyotte, 2005).

Table 1- Some criteria using for toxicity assessment

<table>
<tr><th colspan="3">Abbreviation</th><th>definition</th><th>Reference</th></tr>
<tr><td colspan="2">TLV</td><td>Threshold limit value</td><td>Allowable concentration for exposure with a substance for 8 h in day, 5 days in week and 48h per week.</td><td>(American Conference of Governmental Industrial Hygienists, 2015)</td></tr>
<tr><td colspan="2">R-phrase</td><td>Risk phrase</td><td>Specify the risk related of a chemical substance</td><td>(ECHA, 2015)</td></tr>
<tr><td rowspan="2">LD_{50}</td><td>Oral</td><td rowspan="2">Lethal dose</td><td rowspan="3">A dose/concentration of a chemical that kills 50 percent of subjects animal through ingestion, dermal or inhalation injection.</td><td rowspan="3">(United States Environmental Protection Agency, 1992)</td></tr>
<tr><td>Dermal</td></tr>
<tr><td>LC_{50}</td><td>Inhalation</td><td>Lethal concentration</td></tr>
<tr><td colspan="2">RfD</td><td>Oral Reference Dose</td><td rowspan="2">((maximum acceptable oral/inhalation dose of a toxic substance))</td><td rowspan="2">(United States Environmental Protection Agency, 2002)</td></tr>
<tr><td colspan="2">RfC</td><td>Inhalation Reference Concentration</td></tr>
<tr><td colspan="2">CSF</td><td>Cancer Slope Factor</td><td>Chance of cancer occurring per unit of dose of a chemical substance</td><td>(United States Environmental Protection Agency, 1992)</td></tr>
<tr><td colspan="2">IDLH</td><td>Immediately Dangerous To Life Or Health</td><td>((A situation that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment))</td><td>(National Institute for Occupational Safety and Health, 2013)</td></tr>
<tr><td colspan="2">ERPG 3</td><td>Emergency Response Planning Guidelines</td><td>((Maximum airborne concentrations below which nearly all individuals can be exposed without experiencing health effects for 1-hour exposure.))</td><td>(American Industrial Hygiene Association, 2016)</td></tr>
</table>

3.2.4 Corrosiveness: Corrosion is a great challenge in the process industry threatening mechanical integrity. Only relative ranking considers the estimation of this indicator (Heikkilä, 1999). Corrosiveness is estimated based on the construction materials, the ability of chemicals to cause corrosion and the corrosion rate per year

(Hassim and Hurme, 2010a; Jia et al., 2015; Pandian et al., 2015). The indicator is also indirectly considered in the health category based on the assumption of the ability of the materials to affect steel and other incompatible materials (Koller et al., 2000; Shah et al., 2003)

3.2.5 Volatility: Volatility is the ability of a chemical substance to disperse in the air. The vapor pressure and physical state of a material are regarded as criteria for the relative ranking of volatility (Hassim and Edwards, 2006; Hassim and Hurme, 2010a; Hassim and Hurme, 2010b; Hassim et al., 2013; Zainal Abidin et al., 2016a; Zainal Abidin et al., 2016b).

3.2.6 Material state: The various forms of chemicals may have different dispersion patterns and hazards. This indicator is assessed using relative ranking in which a special score belongs to each physical form of a material (Hassim and Edwards, 2006; Hassim and Hurme, 2010a; Hassim and Hurme, 2010b; Hassim et al., 2013; Zainal Abidin et al., 2016a; Zainal Abidin et al., 2016b).

3.2.7 Solubility: The solubility of a chemical in water and in other solvents is another property of chemicals, and it is rated as the ability of a chemical to solubilize in water (Hassim and Edwards, 2006).

3.2.8 Ability to precipitate: This factor is considered based on the ability of a chemical to precipitate (Hassim and Edwards, 2006).

3.2.9 Viscosity: This factor is rated as 'low', 'medium' or 'high' based on the viscosity value (Hassim and Edwards, 2006; Zainal Abidin et al., 2016b).

3.2.10 Density: The differences between chemical densities are ranked as 'low', 'medium' and 'high' (Hassim and Edwards, 2006). The density of a stream is calculated and subsequently divided by the average density of all the streams (Shariff et al., 2012). The relative vapor density is obtained by dividing the vapor density by the air density (Khan and Abbasi, 1998; Khan and Amyotte, 2004, 2005; Khan et al., 2001).

3.2.11 Volume change: Changes in the volumes of the chemicals are (subjectively) ranked as 'low', 'medium' and 'high' (Hassim and Edwards, 2006).

3.3 Process/ unit Conditions

The process parameters that can pose inherent risks during normal work conditions are assessed. Kletz and Amyotte (2010) proposes that it is better (or safer) to develop processes under attenuated conditions, such as lower pressures and temperatures (the "attenuation" principle) and with a lower chemical inventory (the "minimization" principle)(Kletz and Amyotte, 2010). The indicators in the following sub-section correspond to these two principles.

3.3.1 **Temperature:** The temperature of a process is an indicator of the thermal energy in a system, and higher temperatures indicate higher energy and more hazardous conditions. In total, hazardous consequences can be expected for both very high and very low temperatures (lower than zero centigrade). From the point of view of estimation, the first estimation approach is relative ranking in which the process temperatures are divided into 13, 5, 2 and 4 classes (Edwards and Lawrence, 1993; Heikkilä et al., 1996; Hassim and Edwards, 2006; Hassim and Hurme, 2010a). The estimates are also obtained by comparing process temperatures with the flash point, fire point or auto-ignition temperature of the chemicals (Khan and Abbasi, 1998; Khan and Amyotte, 2004; Khan et al., 2001). Other approaches, including statistical, numerical, fuzziness, hybrid and graphical approaches, are also considered for estimating the temperature (Ahmad et al., 2014; Gentile et al., 2003a; Gentile et al., 2003b; Gupta and Edwards, 2003; Srinivasan and Nhan, 2008). Finally, the temperature is also considered indirectly in the risk-based estimation approach.

3.3.2 Pressure: A process with a higher operating pressure (higher energy) poses a higher risk for chemical leakage, fire and explosion. Hence, a designer should tend to choose chemical routes with lower pressures. The effect of pressure on the inherent safety of a process can be assessed using the process pressure, vapor pressure and atmospheric pressure. As with most indicators, relative ranking is the most frequent approach for estimating the pressure of a process (Edwards and Lawrence, 1993; Hassim, 2016; Hassim and Edwards, 2006; Hassim et al., 2013; Heikkilä, 1999; Pandian et al., 2015). Other approaches include statistical, numerical, fuzziness, hybrid and graphical estimations (Ahmad et al., 2014; Gupta and Edwards, 2003; Khan and Abbasi, 1998; Khan et al., 2001; Koller et al., 2000; Nhan, 2006; Srinivasan and Nhan, 2008).

3.3.3 Inventory: Inventory is related to the quantity of chemicals that exists as feedstocks, raw materials, intermittent products and by-products. Higher amounts of materials in a plant lead to more severe accident outcomes, such as fires, explosions and chemical leaks. Calculating the total inventory in a plant during the early design phase is difficult, although it can be estimated based on the mass balance, residence time, and size of the equipment. The quantity of flammable materials was first considered using the DOW Fire and Explosion Index (F&EI) (DOW chemical, 1994)) . Next, the other relative rankings consider the amounts of chemicals (tons) and types of equipment (Edwards and Lawrence, 1993; Heikkilä, 1999). The inventory can also be obtained from the capacity of units (thousands of tons) as well as the ratio of the flammability to the reaction rank (NF/NR) can be drawn in a graph for various processing units (Khan and Abbasi, 1998; Khan and Amyotte, 2004; Khan et al., 2001; Rusli et al., 2013; Zainal Abidin et al., 2016b). The graphical approach can also be employed to estimate the potential of danger (Gupta and Edwards, 2003). In the risk-based approach, the quantity of materials can be directly used to estimate the amount of chemicals released during leakage accidents.

3.3.4 Yield: A desirable condition is that the yield of a reaction is sufficient to meet the expected production rate. Lower yields require the use of supplementary processes that, in turn, potentially increase the inventory. Hence, a high yield reaction is favourable from the inherent safety point of view. The relative ranking approach and the statistical methodology are utilized to estimate this indicator. Ten classes of yield are supported (Edwards and Lawrence, 1993; Nhan, 2006).

3.3.5 Mode of Process: This indicator is proposed by Hassim and Hurme (2010). They consider the mode of a process as an indicator to measure the inherent safety degree of a chemical route: continuous, semi continuous, semi batch and batch modes (Hassim and Hurme, 2010a). The continuous process mode is considered to be safer than the other process modes due to the minimum requirement for manual operations and the lower emissions of chemicals. In the INSET toolkit, this indicator is qualitatively employed to consider the complexity of the indicator (Mansfield et al., 2001).

3.4 Equipment and unit Process

This category is proposed due to the possibility of equipment or unit failure in which the chemical contents and process conditions can be regarded as a hazard with destructive consequences. For the direct comparison of equipment safety, Heikkila (1999) proposes this category to measure the possible failure of equipment pieces, except for the piping, valves and instruments developed by other researchers (Heikkilä, 1999). The relative ranking approach is used for estimating this category with the indicators explained hereafter.

3.4.1 Inside Battery Limit Area (ISBL): This is the area in which raw materials, under the process conditions, are converted into the intended products, and it includes a low inventory, high number of equipment pieces, small-sized equipment and low scatter in the layout. Heikkila (1999) ranks it into five groups (0 to 4 scores), including the safest group (equipment that handles non-flammable and nontoxic materials), common equipment processes (such as heat exchangers and pumps), hazardous equipment, more hazardous equipment (handling materials above their ignition temperatures) and equipment with ignition sources (Heikkilä, 1999).

3.4.2 Outside (Offsite) Battery Limit Area (OSBL): This indicator is for plants with a large quantity of flammable/toxic materials. The main risk of OSBL is related to the high inventory of flammable and toxic materials. Heikkila (1999) proposes four ranks, including the safest group, equipment with pressure gauges lower than 1 bar, equipment with possibly flammable gas, and equipment with ignition sources. For both ISBL and OSBL, lower scores indicate safer equipment (Heikkilä, 1999).

3.4.3 Safe Process Structure: This item is related with the safety information that is available for various alternatives of process configurations. Heikkila (1999) proposes five groups of scores based on the knowledge of their safety behaviour during operation: standard, suggested and solution processes are available; well-known and reliable process alternatives are used; safety data are unavailable or processes are neutral; configurations are used with a debatable safety level; and minor or major incidents are expected and documented during the process (Heikkilä, 1999).

3.4.4 Complexity: A lower complexity of a process plant leads to lower chances of human error (simplification principle). Abedi and Shahriari (2005) suggests an estimation approach that considers the number of equipment, the number of degrees of freedom, the number of measurement readings, the number of input and output streams, the number of interactions, and the number of external disturbances (Abedi and Shahriari, 2005). The INSET toolkit also considers the complexity as qualitative, based on the fact that batch and continuous processes are different, and their complexity is different as well (e.g., the number of inputs to the process, outputs from the process, and temperature changes) (Mansfield et al., 2001). *Rusli and Mohd Shariff (2010)* also consider the complexity indicator as a function of the number of vessels and auxiliary units, the frequency of transportation and the complexity of maintenance (Rusli and Mohd Shariff, 2010).

3.4.5 Layout: The layout and configuration of the units and equipment is considered to minimize the effects of probable failures. *Abedi and Shahriari (2005)* consider layout indicators based on the accessibility to equipment, the spacing of the processes and unit operations within a process, the shape factor and the connection factor (Rusli and Mohd Shariff, 2010). *Khan et al.* also quantify the locations of the nearest hazardous units as the distances from the other hazardous units. Additionally, the density of the units is also considered, and is defined as the space occupied by the unit in an area of a 30 m radius from the unit (Khan and Abbasi, 1998; Khan and Amyotte, 2004; Khan et al., 2001). *Cozzani et al. (2009)* also calculates the distance and layout for a process plant using a risk-based approach (Cozzani et al., 2009). Khakzad and Reniers (2017) for instance indicate how to allocate safety measures in a cost-effective way and taking into account land-use planning (Khakzad and Reniers, 2017).

3.5 Reaction/decomposition Properties:

This category addresses the reaction/decomposition related properties that can influence the safety of a reaction. The main reactions occur in a reactor, and if they run out of control (runaway reaction), their consequences are terrible. Reactions producing high amounts of heat can be more hazardous than reactions with less heat. The indicators that fall into this category and their estimation approaches are described below:

3.5.1 Reactivity (interaction): This indicator considers the unwanted reactions between chemicals outside of a reactor and considers the reactivity of each chemical.

The relative ranking is the more frequently used approach for estimating the categorization, such as the EPA matrix and type of reaction and reactivity in NFPA-704. Enthalpy and oxygen balance are other variables that are employed to judge the reactivity. Enthalpy has an important role in exothermic reactions. The oxygen balance has an important effect on the self-oxidation processes of chemicals being categorized as follows: value higher than -100% (detonation explosive hazard), between -100% and -200% (susceptible to detonation) and greater than -200% (not susceptible to detonation) (Heikkilä, 1999). In a graphical method, the interactions between chemicals are considered as "Intended Reaction" and "Incompatible Reaction" layers, and the risk of runaway reactions is also considered (Koller et al., 2000; Shah et al., 2003). The INSET toolkit also suggests a Reaction Hazard Index (RHI) based on the reaction risk category (Mansfield et al., 2001).

3.5.2 Heat of main reaction: Exothermic reactions with the capability to produce higher quantities of heat represent hazardous conditions. The relative rankings based on the heat released from the main reaction (J/gr) are proposed as five groups: thermally neutral, mildly exothermic, moderately exothermic, strongly exothermic and extremely exothermic. In the case of several main reactions, the assessment is made based on the total reaction. In the cases with several reactors, the reactor with the highest heat release is considered to be representative of the main reaction. The statistical approach is also used to consider this indicator (Heikkilä, 1999). The heats of combustion of the materials that are not available in the HYSYS databank can be obtained from the composition of the released chemicals (Leong and Shariff, 2009; Shariff et al., 2012).

3.5.3 Heat of side reaction: The estimation of the heat of each side reaction is obtained from a similar approach that is employed for the heat of the main reactions (Heikkilä, 1999).

3.6 Type of operation/ activities:

This category was first introduced by Hassim and Hurme (2010) to assess occupational health hazards using a relative ranking approach (Hassim and Hurme, 2010a). It assesses the activities or operations that cause dangerous chemicals to enter the workplace and consequently threat the health of workers in the long term. It should be noted that each operation and activity that causes chemical release can be important from both an occupational health and process safety standpoint, although the recommended criteria for occupational health (such as the TLV) differ from those for process safety (such as the LEL). This category was suggested for occupational health but it appears that it can also be regarded for process safety. The main indicators in this category are summarized below:

3.6.1 Transport: The type of transport is categorized into pipes, bags, drums and vibrations, and pipeline transport is regarded as the safest transportation method (Hassim and Hurme, 2010a; Mansfield et al., 2001).

3.6.2 Venting or flaring: This relative scaling includes effluent vents from scrubbing (the safer option), venting or flaring above the occupiable platform level and venting or flaring on the occupiable platform level (Hassim and Hurme, 2010a).

3.6.3 Maintenance works: If maintenance activities are required, then the process is assigned a score of 1; otherwise, it is assigned a score of 0 (Hassim and Hurme, 2010a).

3.6.4 Other activities or operations: Other activities (not included above) that can pose safety and health hazards are categorized as agitation, sieving, filtering, solid handling, size reduction, extrusion and open air mixing (Hassim and Hurme, 2010a).

3.7 Consequences category

The previous categories focus on the source of the safety hazard influencing inherent safety without considering its consequences. The category 'consequences' is specifically focused on the consequences of accidents, such as fires, explosions and chemical releases, instead of hazards.

There are studies proposing the use of damage radii (m), showing the intensity of a fire scenario in contrast to damage radii without considering the type of fire (Rathnayaka et al., 2014; Zainal Abidin et al., 2016a; Khan and Amyotte, 2005). In turn, some studies also focus separately on the type of fire, such as a pool fire, jet fire, and fireball (Cozzani et al., 2007, 2009; Tugnoli et al., 2008a,b; Tugnoli et al., 2009; Tugnoli et al., 2012). Similar to those for fire, estimation methodologies exist for proposing damage radii for explosions. Damage radii are also estimated based on the amount of energy released during an explosion scenario for a liquid, gas, and dust explosion separately (Khan and Amyotte, 2005; Khan et al., 2001).

The types of fire and explosion consequences can be differentiated due to their different natures. The main approach employed for estimating these indicators is called the "Quantitate Risk Assessment (QRA)" or "Risk-based approach", which provides the severity of the consequences integrated with the probability of fatality (obtained from for instance a probit equation) and the quantitative value of the risk. The heat flux and transmissivity of the atmosphere are also considered. As a total rule, the heat of radiation (Kw/m^2) and overpressure (kPa) are ultimate criteria for determining fire and explosion intensities, respectively (Cozzani et al., 2009). The main identified indicators and their estimation approaches are described below:

3.7.1 Fireball: This occurs when a liquefied flammable gas or flammable gas is stored under pressurized conditions and its duration is limited (5 to 20 s). The intensity of a fireball (fireball radius) is calculated based on the inventory of the chemicals. With the estimation of the heat radiation, an inherent safety distance can be obtained from a plotted figure (Cozzani et al., 2007, 2009; de Lira-Flores et al., 2014; Martinez-Gomez et al., 2016; Rathnayaka et al., 2014; Tugnoli et al., 2008a,b; Tugnoli et al., 2009; Tugnoli et al., 2012).

3.7.2 Pool fire: This occurs when a pool of flammable liquid burns. The intensity of this type of fire is dependent on the pool area (m^2), inventory of the chemicals, and type of liquid (heavy or light liquids). In the risk-based approach, the inherent safety distance and inherent safety region can be estimated after adding this information in a plotted figure (Cozzani et al., 2007, 2009; de Lira-Flores et al., 2014; Martinez-Gomez et al., 2016; Rathnayaka et al., 2014; Tugnoli et al., 2008a,b; Tugnoli et al., 2009; Tugnoli et al., 2012).

3.7.3 Jet Fire: Jet fires occur after releasing a pressurized volume of hydrocarbons resulting in impinging flames with significant momentum. The intensity of this type of fire is dependent on the flame length (m), pressure (bar), leakage diameter and chemical inventory (kg). After adding this information in a plotted figure, the inherent safety distance and inherent safety region can be obtained, which are suitable for the layout of other equipment (Cozzani et al., 2007, 2009; de Lira-Flores et al., 2014; Martinez-Gomez et al., 2016; Rathnayaka et al., 2014; Tugnoli et al., 2008a,b; Tugnoli et al., 2009; Tugnoli et al., 2012).

3.7.4 Vapor Cloud Explosions (VCEs): This type of explosion occurs when a created large vapor cloud reaches a spark and releases its energy. The items in contact with the vapor cloud are greatly endangered. The inherent safety distance from the vapor cloud can be obtained from plots created using the equipment volume, mass of the chemicals and the total energy. The distance from the centre of the explosion is regarded as the intensity of escalation. For VCEs, the peak overpressure of the explosion wave is the main cause of damage, and critical equipment should not be located within this distance (Cozzani et al., 2007, 2009; de

Lira-Flores et al., 2014; Tugnoli et al., 2008a,b; Tugnoli et al., 2009; Tugnoli et al., 2012).

3.7.5 Boiling Liquid Expanding Vapor Explosion (BLEVE): This occurs when a tank containing liquids with a temperature higher than the boiling point ruptures/explodes due to a sudden drop of pressure. Their estimation is analogous to that for the VCEs (Cozzani et al., 2007, 2009; de Lira-Flores et al., 2014; Tugnoli et al., 2008a,b; Tugnoli et al., 2009; Tugnoli et al., 2012).

3.7.6 Confined vapour cloud explosion: This type of explosion is the same as a VCE, but it occurs in a confined space. Its estimation process is analogous to that for VCEs and BLEVEs (Cozzani et al., 2007, 2009; de Lira-Flores et al., 2014; Tugnoli et al., 2008a,b; Tugnoli et al., 2009; Tugnoli et al., 2012).

3.7.7 Dispersion (toxic chemical leakage): To estimate the amount of leaked chemicals, a few equations have been proposed in which the released mass of gases is obtained from parameters such as the discharge coefficient, the pressure at the source, the molecular weight, the heat capacity ratio, the initial temperature, the ideal gas constant, the stability class, and the downwind speed. For liquids, this indicator is dependent on the fraction of liquids, pressure at the source, height and diameter of the release point, and temperature of the source (Shariff and Zaini, 2010; Rathnayaka et al., 2014; Zainal Abidin et al., 2016a; Shariff and Zaini, 2013; Shariff et al., 2016; Ribeiro and Machado, 2013). Damage radii are also suggested for chemical dispersions.

The summary of ISD indicators extracted from this study is depicted in Appendix 3.

4. Discussion

A set of 35 indicators were identified in this paper for measuring the inherent safety degree of chemical processes during early design stages which placed into six categories. Furthermore, six approaches for ISD indicator estimation are also identified and discussed.

From the six indicator categories, two major categories can be distinguished: the first major category is comprised of classes focusing on the source of inherent hazards. The second major category focuses on the consequences of inherent hazards. In most of the cases, inherent hazard indicators are utilized for estimating the consequence-related indicators (especially for severity assessment).

Researchers tend to seek the estimation approaches with the desirable characteristics to achieve more realistic results. We should be considered that any estimation approach has particular characteristics which should be carefully considered during its application (Koller et al., 2001). Among the individual estimation methods, relative ranking and risk-based approaches receive higher attention than others. Given the limitations of the individual methods for assessment of various indicators (Rahman et al., 2005; Koller et al., 2001; Adu et al., 2008), hybrid approach can be regarded by researchers as the preferred method with the ability for broad coverage of various indicator assessment (Appendix A and B).

This study focuses on the diversity of the identified indicators and their estimation methodologies; therefore, how these indicators could combine together to form of an overall index is not discussed in this paper.

Conclusions

The present study attempts to shed some light on the current ISD indicators and their estimation approaches existing within scientific literature. We found 35 ISD indicators and six estimation approaches. The outcome of this study can steer process designers, process safety engineers, chemical engineers and other stakeholders toward choosing the correct the indicators related to measuring inherent safety.

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Appendix 1 – Details of the included study

Code	Authors/Reference	Year	Country	Title/name	Estimation approach/s	Case study
1	(Gentile et al., 2003b)	2003	USA	Fuzzy logic-based Inherent safety index	Advanced mathematical methods (Fuzziness)	A tank contained solvent
2	(Liew et al., 2015)	2015	Malaysia	Systematic framework for sustainability assessment on biodiesel production: Preliminary engineering stage	Advanced mathematical methods (Fuzziness)	Biodiesel production
3	(Gentile et al., 2003a)	2003	USA	Inherent Safety Index Based on Fuzzy Logic	Advanced mathematical methods (Fuzziness)	A tank contained solvent
4	(Ahmad et al., 2014)	2013	Malaysia	umerical Descriptive Inherent Safety Technique (NuDIST) for inherent safety assessment in petrochemical industry	Advanced mathematical methods (Numerical)	MMA
5	(Srinivasan and Nhan, 2008)	2008	Malaysia	A statistical approach for evaluating inherent benign-ness of chemical process routes in early design stages	Advanced mathematical methods (statistical)	Acetic Acid and Methyl Methacrylate (MMA)
6	(Serna et al., 2016)	2016	Columbia	Multi-criteria decision analysis for the selection of sustainable chemical process routes during early design stages.	Advanced mathematical methods (statistically)	Ethyl acetate
7	(Shariff and Zaini, 2010)	2010	Malaysia	Toxic release consequence analysis tool (TORCAT)	Equation based	ammonia Purification Column
8	(Shariff et al., 2012)	2012	Malaysia	process stream index (PSI)	Equation based	Acrylic Acid
9	(Andraos, 2013)	2013	Canada	Safety/Hazard Indices: Completion of a Unified Suite of Metrics for the Assessment of “Greenness” for Chemical Reactions and Synthesis Plan	Equation based RR	phenyl isocyanate dimethyl carbonate phenol aniline
10	(Mohd Shariff and Zaini, 2013)	2013	Malaysia	Using integrated toxic release consequences analysis tool for inherently safer design of process plant at preliminary design stage	Equation based Risk based	Ammonia release
11	(Tugnoli et al., 2008a)	2008	Italy	Safety assessment in plant layout design using indexing approach: part I	Equation, graphical	Introducing an approach

Code	Authors/Reference	Year	Country	Title/name	Estimation approach/s	Case study
12	(Koller et al., 2000)	2000	Switzerland	safety, health, and environmental impact (SHE) index	Graphical	Amino dimethyl Ergolin
13	(Gupta and Edwards, 2003)	2003	UK	simple graphical method for measuring inherent safety	Graphical	Reactivity of water and runaway reaction
14	(Shah et al., 2003)	2003	Switzerland	Hierarchical approach for the evaluation Of chemical process aspects from the Perspective of inherent safety	Graphical	Azo Dye Intermediate Acrylic Resins
15	(Shah et al., 2005)	2005	Switzerland	Assessment of chemical process hazards in early design stages	Graphical	acrylic monomers
16	(Hassim et al., 2013)	2013	Malaysia	Simple graphical method for inherent occupational health assessment	Hybrid (graphical, RR)	Tertiary butyl alcohol acetic acid
17	(Ten et al., 2016)	2016	Malaysia	A novel chemical product design framework with the integration of safety and health aspects	Hybrid (RR, equation)	Gas sweetening process
18	(Khan and Abbasi, 1998)	1998	India	Hazard Identification And Risk Assessment (HIRA)	Hybrid (RR, graphical, equational, risk based)	Sulpholane
19	(Khan et al., 2001)	2001	Canada	Safety Weighted Hazard Index (SWeHI)	Hybrid (RR, graphical, equational, risk based)	Sulpholane
20	(Khan and Amyotte, 2004)	2004	Canada	Integrated Inherent Safety Index (I2SI)	Hybrid (RR, graphical, equational, risk based)	MMA
21	(Khan and Amyotte, 2005)	2005	Canada	Integrated Inherent Safety Index (I2SI)	Hybrid (RR, graphical, equational, risk based)	MMA
22	(Cozzani et al., 2007)	2007	Italy	Prevention of domino effect: from active and passive strategies to inherently safer design	Hybrid (RR, graphical, equational, risk based)	Offshore separation train for oil extraction Tank farm of gasoline and propane
23	(Tugnoli et al., 2008b)	2008	Italy	Safety assessment in plant layout design using indexing approach: implementing inherent safety perspective. Part 2-Domino Hazard Index and case study	Hybrid (RR, graphical, equational, risk based)	acrylic acid process

Code	Authors/Reference	Year	Country	Title/name	Estimation approach/s	Case study
24	(Cozzani et al., 2009)	2009	Italy	The development of an inherent safety approach to the prevention of domino accidents	Hybrid (RR, graphical, equational, risk based)	off-shore separation train for oil extraction tank farm of gasoline and propane
25	(Rusli et al., 2013)	2013	Malaysia	Evaluating hazard conflicts using inherently safer design concept	Hybrid (RR, graphical, equational, risk based)	nitration of toluene
26	(Rathnayaka et al., 2014)	2014	Canada	Risk-based process plant design considering inherent safety	Hybrid (RR, graphical, equational, risk based)	biodiesel production
27	(Zainal Abidin et al., 2016a)	2016	Malaysia	Resolving inherent safety conflict using quantitative and qualitative technique.	Hybrid (RR, graphical, equational, risk based)	Modification of Union Carbide
28	(Etowa et al., 2002)	2002	Canada	Quantification of inherent safety aspects of the Dow indices	Hybrid (RR, graphical, risk based)	Bhopal process
29	(Zainal Abidin et al., 2016b)	2016	Malaysia	Three-Stage ISD Matrix (TIM) Tool to Review the Impact of Inherently Safer Design Implementation	Hybrid(RR, graphical, risk based)	Ammonia supply system
30	(Ruiz-Femenia et al., 2017)	2017	Spain	Systematic Tools for the Conceptual Design of Inherently Safer Chemical Processes. I	Hybrid(RR, graphical, risk based)	Chlorination of Benzene Methanol Production
31	(Edwards and Lawrence, 1993)	1994	USA	Fire and explosion index (F&EI)	Hybrid(RR, graphical, risk based)	MMA
32	(Suardin et al., 2007)	2007	USA	The integration of Dow's fire and explosion index (F&EI) into process design and optimization to achieve inherently safer design	Hybrid(RR, graphical, risk based)	reactor and distillation column system
33	(Palaniappan et al., 2004)	2004	Singapore	Selection of inherently safer process routes	Relative ranking	Acetic acid
34	(Edwards and Lawrence, 1993)	1993	UK	Prototype Index of Inherent System (PIIS)	Relative Rating (RR)	Methyl Methacrylate (MMA)
35	(Heikkilä et al., 1996)	1999	Finland	Inherent Safety Index (ISI)	Relative Rating (RR)	MMA
36	(Palaniappan et al., 2002a)	2002	Singapore	Expert System for the Design of Inherently Safer Processes I	Relative Rating (RR)	Acetic acid

Code	Authors/Reference	Year	Country	Title/name	Estimation approach/s	Case study
37	(Palaniappan et al., 2002b)	2002	Singapore	Expert System for the Design of Inherently Safer Processes II	Relative Rating (RR)	Acetic acid
38	(Hassim and Edwards, 2006)	2006	UK	Methodology for Assessing Inherent Occupational Health Hazards	Relative Rating (RR)	MMA
39	(Leong and Shariff, 2008)	2008	Malaysia	Inherent safety index module (ISIM)	Relative Rating (RR)	Acrylic acid
40	(Cordella et al., 2009)	2009	Italy	Inherent safety of substances: Identification of accidental scenarios due to decomposition products	Relative Rating (RR)	Tetrabromobisphenol A (TBBA)
41	(Hassim and Hurme, 2010a)	2010	Finland	Occupational chemical exposure and risk estimation in process development and design	Relative Rating (RR)	MMA
42	(Hassim and Hurme, 2010b)	2010	Finland	Inherent occupational health assessment during process research and development stage	Relative Rating (RR)	MMA
43	(Rusli and Mohd Shariff, 2010)	2010	Malaysia	Qualitative Assessment for Inherently Safer Design (QAISD) at preliminary design stage	Relative Rating (RR)	toluene nitration
44	(Li et al., 2011)	2011	USA	Incorporating exergy analysis and inherent safety analysis for sustainability assessment of biofuel	Relative Rating (RR)	biodiesel production
45	(Zheng et al., 2012)	2012	USA	Incorporating Sustainability into the Conceptual Design of Chemical Process-Reaction Routes Selection.	Relative Rating (RR)	propylene oxide (PO) carbon dioxide ethanol
46	(Gangadharan et al., 2013)	2013	USA	Methodology for Inherent Safety Assessment in the Process Design Stage	Relative Rating (RR)	Biodiesel and MMA
47	(Ng et al., 2013)	2013	Malaysia	Process synthesis and optimization of a sustainable integrated biorefinery via fuzzy optimization.	Relative Rating (RR)	Oil palm
48	(Ribeiro and Machado, 2013)	2013	Portugal	Holistic Metrics for Assessment of the Greenness of Chemical Reactions in the Context of Chemical Education	Relative Rating (RR)	Syntheses of Iron(II) Oxalate Dihydrate

Code	Authors/Reference	Year	Country	Title/name	Estimation approach/s	Case study
						Tetraamminecopper(II) Sulfate Monohydrate
49	(Jia et al., 2015)	2014	China	Integrated sustainability assessment for chemical processes.	Relative Rating (RR)	Ethanol production process
50	(Pandian et al., 2015)	2015	Malaysia	Designing an inherently healthier process based on inherently safer design (ISD) concept: research and development stage	Relative Rating (RR)	MMA
51	(Leong and Shariff, 2009)	2009	Malaysia	Process route index (PRI)	Risk based Equation based	MMA
52	(Medina et al., 2009)	2009	Spain	Process design optimization and risk analysis	Risk based	BLEVE/fireball in a chemical plant
53	(Tugnoli et al., 2009)	2009	Italy	Key performance indicators for inherent safety: application to the hydrogen supply chain	Risk based	Hydrogen
54	(Tugnoli et al., 2012)	2012	Italy	Supporting the selection of process and plant design options by Inherent Safety KPIs.	Risk based	LNG
55	(Shariff and Wahab, 2013)	2013	Malaysia	Inherent fire consequence estimation tool (IFCET)	Risk based	Loading of LPG
56	(Shariff and Zaini, 2013)	2013	Malaysia	Inherent risk assessment methodology in preliminary design stage: A case study for toxic release.	Risk based	Purification of Ammonia
57	(Ordouei et al., 2014)	2014	Canada	New simple indices for risk assessment and hazards reduction at the conceptual design stage of a chemical process	Risk based	Chlorination of methane Hydrogenation of unsaturated hydrocarbon
58	(de Lira-Flores et al., 2014)	2014	Mexico	A mixed-integer non-linear program (MINLP) for layout designs based on the domino hazard index	Risk based Equational	Acrylic Acid production plant
59	(Shariff et al., 2016)	2016	Malaysia	Assessing the ha(Eini et al., 2015)zards from a BLEVE and minimizing its impacts using the inherent safety concept	Risk based	Propane storage vessel

Code	Authors/Reference	Year	Country	Title/name	Estimation approach/s	Case study
60	(Martinez-Gomez et al., 2016)	2016	Mexico	Involving economic, environmental and safety issues in the optimal purification of biobutanol	Risk based	Biobutanol
61	(Mansfield et al., 2001)	2001	EU	INSET toolkit	RR Hybrid (RR, equations)	Some examples
62	(Abedi and Shahriari, 2005)	2005	Canada	Inherent safety evaluation in process plants – a comparison of methodologies	RR, equation	MMA

Appendix 2- Details of the ISD indicators and their estimation approaches

Indicator		**Meaning or Variable required for calculation of the indicator**		**Estimation approach**					**Reference(code of studies from appendix 1)**
			RR	**AMM**	**HYB**	**EBA**	**RBA**	**GR**	
Toxicity	Toxicity	NFPA health TLV, R-phrase, OEL, ERPG, IDLH	+	+	+	+	+	+	13, 62, 6, 3, 1, 5, 34, 31, 13, 35, 18, 19, 20, 21, 61, 28, 36, 37, 33, 42, 41, 38, 40, 44, 45, 9, 46, 16, 47, 48, 4, 26, 49, 50, 17, 27, 30
	Acute Toxicity	LD50, LC50, MW, H, BP, R-phrase	+	+	+		+	+	12, 14, 15, 62,6, 5, 61, 42, 38, 40, 30
	Chronic Toxicity	RfD, RfC, Kow, To, Kow, To, CST	+		+	+	+	+	12, 14, 15, 42, 38, 40
Flammability		NFPA fire Flash point and BP OSHA GHS EU Directive 67/548 S=(LFL-UFL)	+	+	+	+		+	13, 62, 6, 3, 1, 5, 2, 34, 31, 35, 18, 19, 20, 21, 28, 36, 37, 33, 51, 44, 8, 45, 9, 46, 47, 48, 25, 4, 26, 49, 17, 27
Explosivity (explosiveness)		Explosive ranges (UEL-LEL)	+	+	+	+	+	+	13, 12, 14, 15, 62, 6, 3, 1, 5, 2, 34, 31, 35, 18, 19, 20, 21, 28, 36, 37, 33, 39, 51, 44, 8, 45, 9, 46, 47, 4, 26, 49, 17, 27
Corrosiveness		Based on construction material	+		+				31, 35, 62, 42, 38, 44, 45, 9, 46, 47, 49, 2, 17
Volatility		Vapour pressure and physical state of a material	+		+				42, 38, 16, 2, 17, 27
Material phase		State of material (gas, powder and etc.)	+						42, 38, 16, 2, 17

Solubility	Solubility of a chemical in water and other solvents	✚						38
Ability to precipitate	Ability to precipitate	✚						38
Viscosity	Viscosity of fluids	✚						38, 27
Density	Density of fluid, relative density (density of chemical divided into the air) and density of fluid into a stream	✚		✚	✚			18, 19, 20, 21, 38, 51, 8, 27
Volume change	Changes in the volumes of the chemicals	✚						38
Temperature	Temperature of process or in comparison with flash point, auto-ignition temperature	✚	✚	✚		✚	✚	13, 62, 6, 3, 1, 5, 2, 34, 31, 35, 18, 19, 20, 21, 28, 36, 37, 33, 32, 42, 38, 39, 51, 44, 45, 9, 46, 16, 47, 25, 4, 26, 49, 2, 27, 29
Pressure	Pressure of a process (Kpa, Bar, PSI or atm)	✚	✚	✚	✚	✚	✚	13, 62, 6, 3, 1, 5, 2, 34, 31, 35, 18, 19, 20, 21, 28, 36, 37, 33, 32, 42, 38, 39, 51, 44, 45, 9, 46, 16, 47, 25, 4, 26, 49, 2, 27, 29
Inventory	Quantity of material in a process or plant as Tons or Kg	✚	✚	✚	✚	✚	✚	12, 14, 15, 62, 6, 3, 1, 5, 2, 34, 31, 35, 61, 28, 32, 51, 42, 44, 8, 38, 9, 46, 25, 4, 26, 49, 29, 27, 30
Yield	yield of a reaction	✚	✚					62, 6, 5, 5, 2, 34, 36, 37, 33, 38
Mode of process	Continuous, Semi Continuous, Semi Batch And Batch Modes	✚		✚				61, 42, 16
Chemical interaction	Interaction of chemicals into/outside of reactor	✚		✚				31, 18, 19, 20, 21, 61,62, 46, 47, 26, 27

Reactivity		NFPA reactivity Runaway temperature	✚	✚	✚			✚	12, 14, 15, 62, 6, 3, 1, 5, 2, 31, 18, 19, 20, 21, 61, 36, 37, 33, 9, 46, 48, 25, 4, 26, 49, 27
Heat of the main reaction		heat released from a main reaction (J/gr)	✚	✚	✚				62, 6, 3, 1, 5, 2, 61, 36, 37, 33, 43, 44, 47, 25, 4
Heat of the side reactions		heat released from a side reaction (J/gr)	✚	✚	✚				62, 6, 3, 1, 5, 2, 61, 36, 37, 33, 43, 44, 47, 25, 4
ISBL		Equipment inside Battery Limit Area	✚	✚					35, 3, 1, 62, 44, 46, 47, 49
OSBL		Equipment outside Battery Limit Area	✚	✚					35, 3, 1, 62, 44, 46, 47, 49
Safe Process Structures		Safety information that are available for various alternatives	✚						35, 44, 46, 47, 49
Complexity		Complexity of plants based on the outputs and inputs	✚			✚			61, 62, 23
Layout		Layout of equipment in a unit or plant as distance (m)	✚				✚		61, 62, 23, 24, 54
Type of fire	Fire	Without consideration type of fire			✚				31, 18, 19, 20, 21, 61,11, 26, 27
	Fireball	chemical inventory (kg), heat or radiation (Kw/m^2), safe distance (m)			✚	✚	✚		22, 23, 24, 52, 53, 54, 26, 58, 60
	Pool fire	pool area (m^2), type of liquid, chemical inventory (kg), heat or radiation (Kw/m^2), safe distance (m)			✚	✚	✚		22, 23, 24, 52, 53, 54, 26, 58, 60

	Jet fire	flame length (m), pressure (bar), leakage diameter and chemical inventory (kg), heat or radiation (Kw/m^2), safe distance (m)			✚	✚	✚		22, 23, 24, 52, 53, 54, 26, 58, 60
Type of explosion	Explosion	Without consideration type of explosion			✚	✚	✚		18, 19, 20, 21, 61, 26, 27
	Vapor Cloud Explosion (VCE)	equipment volume, mass of the chemicals and the total energy, peak overpressure of the explosion wave, safe distance (m)			✚	✚	✚		22, 23, 24, 52, 53, 54, 26, 58, 59, 60,
	Boiling Liquid Expanding Vapor Explosion (BLEVE)	Same as VCE			✚	✚	✚		22, 23, 24, 52, 53, 54, 26, 58, 60
	Confined explosion	Same as VCE			✚	✚	✚		22, 23, 24, 52, 53, 54, 26, 58, 59, 60
Dispersion (toxic chemical leakage)		Based on the different variables as separately for gas and liquids			✚	✚	✚	✚	12, 14, 15, 18, 19, 20, 21, 61, 22, 23, 52, 7, 54, 10, 56, 57, 26, 58, 60
Transport		Type of chemical transportation	✚						38, 61
Venting or flaring		Venting or flaring of effluents	✚						38
Maintenance works		Required to maintenance works	✚						38
Other activities or operations		Activities not included above	✚						38

✚: This indicator can be estimated by the mentioned approach. The blank cell means an indicator cannot be estimated by the approach.
Abbreviations: RR: relative ranking; AMM: advance mathematical methodologies; HYB: hybrid; EQB: equation based approach; RBA: risk based approach; GR: graphical approach
Reference: To avoid duplicate citing, codes from Appendix 1 employed as reference (without considering referencing format).

Appendix 3 -ISD indicator extracted from this study (indicators with red color are possible indicators that can be consider for ISD assessment)