

## Chemical reactivity assessments in R&D

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### Abstract

The evaluation of reactive chemical hazards at the pilot and manufacturing scale, using laboratory testing, is increasingly used and has been well documented. However, reactive chemical hazard evaluation at the R&D scale presents special challenges. The typical hazard testing program requires a significant amount of sample, often takes time (>3 days) to complete, and is can be quite costly. On the other hand, the synthesis of new molecules in the R&D environment often produces only a few grams, occurs quickly (<2 days), may only happen once and many synthetic reactions may be carried out before a suitable candidate for scale-up will be found. However, with each new synthesis there is the risk of injury, possibly serious or fatal, caused by unexpected and maybe violent reactivity.

While it may not be possible at the R&D stage of product development to define the critical limits of temperature, pressure, concentration, and safe dosing rates of processes it is possible to identify the potential hazards of the planned synthesis.

This paper describes a staged approach for chemical reactivity hazard evaluation and assessment applicable to an R&D environment. We will describe these initial phases of the R&D hazard evaluation process that rely on only data that can be obtained from the open literature. We will also indicate how the need for additional assessments can be determined from this initial hazard review.

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### 1. Introduction

When an accident involving loss of containment, explosion or fire occurs in a laboratory people are often seriously hurt. The layers of personnel protection typically found in a pilot-plant or manufacturing facility are not normally present in the lab because quantities handled are generally small (< 25 l for example) and hence the risks are believed to be lower.

Chemical process hazard evaluation at the manufacturing and pilot-plant scale is a well-defined process with much open literature documentation available for guidance. Formal hazard evaluations are rarely performed for lab operations for a variety of seemingly sound reasons. However, when accidents occur the investigation findings often point to the absence of a hazard analysis as a contributing factor.

This paper describes the use of a simple fill-out form, Fig. 1, that is designed to highlight the potentially haz-

ardous situations that could arise from the use and handling of chemicals during the synthesis, why particular data is being recorded, and how the potential level of risk may be inferred from that data. The form is constructed so that a potentially hazardous situation is immediately flagged and the user is directed towards a more formal review.

Recently, the Center for Chemical Process Safety (CCPS) published a book devoted to management practices for dealing with chemical reactivity hazards [1]. Chapter 3 in their book provides a screening tool designed to help determine if a chemical reactivity hazard exists at a facility. The procedures described in this presentation may be viewed as a follow-on to the CCPS screening tool using specific data as part of the reactivity hazard review and evaluation.

*Caution:* This approach does not explicitly address the synthesis reaction being performed, except by considering, in a general sense, the type of reaction (esterification, nitration, Friedel Craft, etc.) being performed. Evaluation of the thermal hazards of the reaction requires a more detailed and extensive investigation of the desired reaction(s) and any

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<b>1 Run Ref #</b>	_____ / _____	<b>2. Synthesis Type:</b>	_____	<b>3. Date</b>	_____
<b>4. Description:</b>	_____		<b>5. End Use:</b>	_____	
<b>7. Physical Properties</b>	<b>6. Chemicals to be used – Sample, Reactants, Solvents</b>				
B Pt / M Pt / VP @ 20 °C	_____ / _____ / _____	_____ / _____ / _____	_____ / _____ / _____	_____ / _____ / _____	_____ / _____ / _____
Fl Pt / Al / MIE	_____ / _____ / _____	_____ / _____ / _____	_____ / _____ / _____	_____ / _____ / _____	_____ / _____ / _____
LEL / UEL	_____ / _____	_____ / _____	_____ / _____	_____ / _____	_____ / _____
Dust Explosion Severity	_____	_____	_____	_____	_____
<b>8. Chemical Overview</b>					
Stability/Reactivity	_____	_____	_____	_____	_____
Toxicity/Exposure	_____	_____	_____	_____	_____
NFPA/HMIS Ratings	_____	_____	_____	_____	_____
Incompatibilities	_____	_____	_____	_____	_____
Spill Clean-up Material	_____	_____	_____	_____	_____
PPE Required	_____	_____	_____	_____	_____
Specific Hazard (Note 1)	_____	_____	_____	_____	_____
<b>9. Function in synthesis</b>					
<b>10. MDS Sheet Reviewed</b>	Signed: _____	Date: _____			
<b>11. Classified as a Non-Routine Operation (check relevant categories)</b>					
High toxicity / Low exposure limits	<input type="checkbox"/>	Chemical Handled (Air/water sensitive, Corrosive)	<input type="checkbox"/>		
Flammability (Fl Pt<10 °C; LFL<10%)	<input type="checkbox"/>	Extreme Reaction Temperature (> 150 °C; < -30 °C)	<input type="checkbox"/>		
Flammability (Al<200 °C; MIE < 0.5mJ)	<input type="checkbox"/>	High Temperature Feed (> 50 °C)	<input type="checkbox"/>		
High Hazard Reaction or Functional Group	<input type="checkbox"/>	High Pressure Reaction (>10 bar)	<input type="checkbox"/>		
High/moderate hazard reaction performed ≤ 2 times	<input type="checkbox"/>	High Pressure Feed (>2 bar)	<input type="checkbox"/>		
<b>12. Potential Hazard Level</b>	Routine: Y <input type="checkbox"/> N <input type="checkbox"/>	Non-Routine: Y <input type="checkbox"/> N <input type="checkbox"/>			
<b>13. Synthesis by</b>	Name: _____	Sign: _____	Date: _____		
<b>14. Hazard Review by</b>	Name: _____	Sign: _____	Date: _____		
<b>15. Non-Routine Hazard Review</b>	Schedule Date : _____	Date Completed : _____			

**Note 1:** Enter as many codes as needed to describe the Special Hazard: RDX – Oxidizer/Reducer; PYR – Pyrophoric; POL – Polymerizes; EXP – Reacts explosively; HS – Sensitive to heat; WAT – Water reactive; PER – Peroxide former; INH – Inhibitor required; IMP – Impact/friction sensitive; TCN – Temperature control needed; GRP – Functional group

#### Instructions for Use of Form

Use this form as a check-list and review of potential hazards involved in the synthesis. Each section requires responses, as detailed below:

1. Reference number 2. Technique 3. Date filled out 4. Describe Synthesis 5. Product end-use 6. List each chemical used in the run – use a new form as needed; 7. Physical properties – use MSD sheet, Saxes, Merck Index and “Sources of Ignition” (Bond) 8. Summarize listed properties as available from reference materials, mostly MSD sheets 9. Function of each chemical in the synthesis, ie reactant, solvent, catalyst, etc. 10. MSDS reviewer, when; 11. What led to a Non-Routine classification? Check all appropriate boxes 12. What is the assessed potential hazard – Routine or Non-Routine 13. Who will perform the synthesis; when? 14. This hazard review; when? 15. If Non-Routine, when is detailed hazard review scheduled; when completed? Non-Routine hazard review notes must accompany this form with risk reduction recommendations activities as needed.

Fig. 1. Preliminary R&D reactive chemicals hazard review form.

undesired reactions, together with an analysis of possible equipment upsets or procedural short-comings [2–6].

## 2. Data requirements for chemical reactivity assessment

### 2.1. Sections 1–5, 10, 13–15: documentation of hazard review

These sections record basic information for documentation purposes, including the names of chemicals to be handled. It is important in all hazard evaluation exercises to maintain a traceable record of the nature and extent of any risk assessment activities undertaken as part of chemical handling. Items 13–15 also show who will be doing the work and if additional reviews are needed.

### 2.2. Sections 6 and 7: physical properties of the chemicals

The physical properties of each chemical represent the basic information that is used for this initial hazard assessment. If all of the information requested in Sections 6 and 7 of the Preliminary R&D Reactive Chemicals Hazard Review form is available, it will be possible to obtain a reasonable overview of the potential hazards that will allow appropriate risk reductions measures to be put into place.

Realistically, not all the data will be available. The melting and boiling points, flash point and flammable limits of the material constitute a minimum set of physical properties to establish the conditions for safe operations. Table 1 provides the definitions for each of the physi-

Table 1  
Physical properties definitions for preliminary hazard evaluation

Property	Definition
M. Pt. and B. Pt. VP, vapor pressure Fl. Pt., flash point	Melting and boiling point of the substance. Vapor pressure, usually at 20 °C, is a quantitative measure of vapor in the atmosphere. The flash point of a liquid is the minimum temperature at which the liquid gives off sufficient vapor to form an ignitable mixture with air near the surface of the liquid or within the test vessel used. Mists, dusts, and foams present unique hazards because they are flammable below the Fl Pt temperature of the fuel.
LFL, UFL, lower /upper flammable limits.	Flammable limits are the lower and upper concentrations (volume %) of a vapor in air ignitable by an ignition source. Ignition will not occur above the upper limit and below the lower limit. Also known as lower and upper explosion limits, LEL and UEL.
AIT, auto-ignition temperature	The AIT of a solid, liquid, or gas is the minimum uniform temperature required to cause self-sustained combustion in the absence of an external ignition source. AIT is also referred to as <i>self</i> or <i>spontaneous ignition</i> temperature (SIT).
MIE, minimum ignition energy	The MIE of a solid, liquid or gas is the lowest amount of energy to ignite a mixture at its most easily ignitable concentration.
DE, dust explosion severity	Dust explosion testing measures the pressure and pressure rise rate of the explosion caused by the ignition of a dispersed dust sample. The pressure data are used to determine the $K_{st}^a$ value and $S_t$ hazard class <sup>b</sup> of the material. These parameters may be used for the purpose of designing dust explosion protection measures and equipment.

<sup>a</sup>  $K_{st}$  is numerically equal to the experimentally determined pressure rise rate ( $\text{bar m s}^{-1}$ ).

<sup>b</sup>  $S_t$  classifies dusts having a particular  $K_{st}$  value into one of three categories.  $K_{st} < 200 \text{ bar m s}^{-1}$   $S_t = 1$ ;  $200 < K_{st} < 300 \text{ bar m s}^{-1}$   $S_t = 2$ ;  $K_{st} > 300 \text{ bar m s}^{-1}$   $S_t = 3$ .

Table 2  
Chemical properties and their role in preliminary hazard evaluation

Concern	MSDS Section	Significance to chemical reactivity hazard assessment and evaluation
Stability/reactivity	10	Does the particular chemical react unexpectedly?
Toxicity/exposure	3, 4, 8, 11, 15	Are there any highly toxic materials or exposure thresholds that require additional PPE or special handling?
NFPA/HMIS ratings	3	The NFPA and HMIS rating systems provide general warnings about chemical handling.
Incompatibilities	7	Specific incompatibilities are noted here that are known to the chemical supplier. No information does not guarantee complete compatibility.
Spill clean-up	6, 13, 15	Information about recommended and prohibited spill clean-up chemicals are provided. Be careful if sawdust is planned for use; it is a water-laden organic material that reacts with many chemicals and supports combustion.
Personal protective equipment (PPE) required	8	Specific details are provided for PPE. Compare recommendations made in MSDS Section 8 with the toxicity and exposure data provided elsewhere in the MSD sheet and quantities to be handled.
<u>Specific hazard</u>		
Oxidizer/reducer	10	Special precautions are needed for the stronger oxidizers (e.g. >50% $\text{H}_2\text{O}_2$ ) or reducers (e.g. $\text{NaBH}_4/\text{MeOH}$ ).
Pyrophoric	10	Solids, liquids or gases that spontaneously combust in air at temperatures greater than 130 °F.
Polymerizes	10	Do any reactants polymerize unexpectedly at ambient conditions, especially if the inhibitor is removed?
Reacts explosively	10	Does the particular chemical react unexpectedly at a high reaction rate, especially at moderate temperatures?
Inhibitor required	7, 10	See "Polymerizes".
Impact/friction sensitive	10	Impact or friction sensitivity could lead to injuries during handling of solid reactants, inhibitors and catalysts. The impact sensitivity of the product should also be established.
Temperature control needed	7, 10	Material may be liquid only at $T < \text{ambient}$ requiring refrigerated storage. Is the refrigerator temperature alarmed?
Sensitive to heat	7, 10	Small temperature changes may cause violent reactions.
High hazard reaction or functional group	10	See Tables 5, 6 and 7 for examples of potentially hazardous reactions and hazardous atom groupings.
Water reactive	10	Many classes of organic and inorganic compounds are highly reactive with water. For example, acyl chlorides and metal hydrides react violently with water evolving gas extremely rapidly ( $\text{HCl}$ and $\text{H}_2$ respectively).
Peroxide former	10	Bretherick [7] and CCPS [8] lists organic compounds that will form peroxides with air which are often impact sensitive.

Table 3  
Reactions having a high hazard potential

Reaction	Example of concern
Curtius rearrangements	Use of acyl azides, nitrous acid or hydrazine.
Decarboxylation	Removal $-\text{COOH}$ with $\text{CO}_2$ evolution—possible pressure hazard.
Diazotizations	Especially if followed by reduction to the hydrazine ( $\text{SnCl}_2$ reaction); replacement with a $-\text{OH}$ or to replace the $-\text{NH}_2$ with $-\text{H}$
Displacements	Uses oxalyl chloride to displace $-\text{OH}$ . ( $\text{CO}_2$ , $\text{CO}$ , $\text{HCl}$ generated)
Epoxidations	Epoxides are high energy strained rings
Esterification	When using oxalyl chloride
Friedel Crafts ( $\text{AlCl}_3$ )	Friedel Crafts reactions and their quenches due to use of $\text{AlCl}_3$ , $\text{BCl}_3$ , $\text{H}_2\text{SO}_4$ , $\text{HF}$ .
Grignard reactions	Reactions require an activation period and are highly exothermic.
Hydrolysis	Hydrolysis of a cyano to an amide oxidatively using $\text{H}_2\text{O}_2$
Metallations	Uses <i>n</i> -BuLi, <i>t</i> -BuLi, LDA, NaHMDS
Nitrations	Uses nitric acid and strong acids like sulfuric or triflic acid (trifluoromethane–sulfonic acid). Nitrations are very exothermic. The potential for thermal runaway, initiating violent decompositions and explosions exists.
Oxidations	Use of Jones reagent [ $\text{K}_2\text{Cr}_2\text{O}_7/\text{H}_2\text{SO}_4$ ], $\text{O}_3$ , $\text{H}_2\text{O}_2$ , $\text{KMnO}_4$ (with large exotherms), peroxy acids, cleavage using sodium periodate
Peptide formations	Use of HOBT (1-hydroxybenzotriazole hydrate).
Quenches	When $\text{PCl}_5$ or $\text{POCl}_3$ have been used in a previous step and water is the quench
Reductions	Any nitro compound or high energy functional group reduction. Reductions using $\text{LiAlH}_4$ , Fe or Zn powder with $\text{HCl}$ or acetic acid, hydrazine in caustic; hydrogenations by generating $\text{H}_2$ in-situ using hydrazine, $\text{NaBH}_4$ in $\text{CH}_3\text{OH}$ or $\text{C}_6\text{H}_{12}$
Sulfonation	Sulfonation of an amine to form sulfonamide

cal properties listed in Section 7 of the hazard evaluation form.

### 2.3. Sections 8: chemical overview, mostly from MSD sheets

This section gathers specific information about each chemical used in the synthesis. It is also important to note the chemical's role in the synthesis. Does it function as reactant, solvent, catalyst (to be added), inhibitor (to be removed)? Table 2 lists the chemical properties required and provides a brief explanation of the link(s) between that information and hazard evaluation.

Several of the consequences of mis-handling chemicals, in particular solvents, can be assessed from physical property data, as that shown in the solvent data table, Table 4. For example, the flash point, LFL, UFL, and MIE dictate the way a solvent is chosen or handled. Diethyl ether and heptane are more hazardous to handle than other common solvents because of key differences in these four flammability parameters. Whenever possible it is prudent to select solvents with decreased ignition sensitivities.

Table 4  
Flammability characteristics of common solvents

	Fl. Pt. (°C)	AIT (°C)	B. Pt. (°C)	VP @ 20°C (mm)	LFL (Vol. %)	UFL (Vol. %)	MIE (mJ)	NFPA class
Diethyl ether	−45	160	35	442	1.8	36	0.19	Class IB
Heptane	−4	215	98	40	1.1	6.7	0.26	Class IB
CAN	6	524	81.6	72.8	4.4	16.0	–	Class IB
MeOH	10	385/455	64	97	6.7	36	0.14	Class IB
DMF	55	440	152	3.3	1.8	15.2	–	Class II
NMP	86	346	202	0.29	1.3	9.5	–	Class IIIA
DMSO	95	215/270	189	0.6	2.6	29.5/40	–	Class IIIB

ACN: acetonitrile; MeOH: methanol; DMF: dimethylformamide; NMP: *N*-methylpyrrolidinone; DMSO: dimethylsulfoxide.

### 2.4. Hazards of synthetic reactions and functional groups

Reactions may be classified as having a high hazard potential (Table 3) because one or more of the following conditions are characteristic of the reaction:

- Reactants or products contain functional groups or atom groupings that confer explosive properties to the molecule. Examples are shown in Table 4; Bretherick [9] provides a fuller list of groups that infer potentially explosive characteristics to the molecule;
- The rate of reaction can increase to a thermal explosion if any of the control systems (cooling, agitation, addition controllers, etc) fail;
- The reaction has a long and unpredictable initiation period and is strongly exothermic;
- Reactants or reagents are highly toxic or have very low personal exposure limits;
- Reactants or reagents react vigorously or explosively with air or moisture, under ambient or near-ambient conditions;

Table 5  
Reactions having a moderate hazard potential

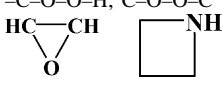
Reaction	Examples of concern
Acylation	Use of acetic anhydride or acid chloride acylations of amines.
Additions	Additions of alkyl metals to ketones or aldehydes, cyano groups, carboxylic acids or esters, or any other functionalities.
Alkylations	Alkyl halide or amine (aromatic or aliphatic) used with a phenol.
BOC protections-deprotections	BOC ( <i>t</i> -butoxycarbonyl) used to protect/deprotect amines. Unreacted BOC anhydride in waste streams can liberate CO <sub>2</sub> and isobutylene.
Condensations	C–C bond or C–N bond formation with elimination of small molecules.
Cross coupling reactions	These reactions involve the use of a metal to mediate a C–C bond formation, usually a Pd(0) species (Pd(triphenyl-phosphine) <sub>4</sub> ); Suzuki coupling; zincate coupling by transmetalating a Grignard or a lithium species with zinc chloride.
Dealkylation	Demethylation of methoxy group using HBr or HCl to generate methyl bromide or methyl chloride. BBr <sub>3</sub> and BCl <sub>3</sub> used at low temperatures.
Displacement	Displacement of –OH with –Cl using PCl <sub>5</sub> ; reactions are heated, the distilled PCl <sub>5</sub> is difficult to quench due to the delayed water reaction. Use of LiCl in NMP to displace a triflate (CF <sub>3</sub> SO <sub>3</sub> <sup>–</sup> ).
Esterification	Using oxalyl chloride and acid followed by alcohol addition. Reaction liberates CO and HCl—pressure hazard. Also by using acid and SOCl <sub>2</sub> and then adding the alcohol.
Ether formations	Ethers formed via Williamson synthesis by alkylating with alkylhalide.
Halogenations	Reactions of alkyl or aryl groups with halogens such as Br <sub>2</sub> , Cl <sub>2</sub> or I <sub>2</sub> .
Hydrolysis	Reaction of a cyano with Lewis acid (e.g. BF <sub>3</sub> ). See other categories for hydrolysis/quench reactions.
Peptide formations	Coupling of an amine with an acid using EDC, EEDQ ( <i>N</i> -ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline), or alkyl-chloroformate mediated peptide coupling, or <i>N</i> -hydroxy succinamide.
Reductions	Use of triethylsilane, NaBH <sub>4</sub> (except with methanol), tri-acetoxyborohydride, B <sub>2</sub> H <sub>6</sub> generated in-situ via BF <sub>3</sub> /NaBH <sub>4</sub> . Birch reductions with Na or K is category. Reductions using H <sub>2</sub> and Pd, Pt, Raney Ni, Ru, Ir.
Sulfonation	Use of SO <sub>2</sub> Cl <sub>2</sub> with an alcohol (plus base) to form a mesylate or tosylate. Use of triflic anhydride to form a triflate

- Reactants or reagents, in particular catalysts, are pyrophoric;
- Side reactions can over-run the main reaction leading to thermal explosion or detonation;
- Product workups involve highly exothermic quenches.

Table 5 lists reactions that may be viewed as having a moderate potential hazard.

Drawing the line between highly hazardous (Table 3) and moderately hazardous (Table 5) is, to a large degree, linked with the experience that lab personnel may have with the particular synthesis. This aspect is probed in the hazard evaluation form, Section 11. A proposed synthesis that uses a reaction listed in Tables 3 and 5, involves the introduction of an functional group known to confer explosibility (Table 6), and has only been performed a few times should be considered as non-routine and identified as requiring a formal hazards review [10].

Table 6  
Atom groupings that indicate or enhance molecular instability

Atom grouping with molecule	Example of functional group	
	Structure	Name
C–C and C–N triple bonds & their metal salts	–C≡C–; –C≡N	Acetylenic; cyano
Adjacent N–O atoms many combinations	C–NO <sub>2</sub> ; C–O–N=O	Aryl, alkyl nitro; alkyl nitrite
Adjacent and consecutive N atom pairs, triplets and higher	–C–N≡N; –N–N≡N	Diazo; azide
Adjacent O–O pairs	–C–O–O–H; C–O–O–C	Peroxyacids; peroxyesters, peroxides
Adjacent C atoms bridged by O or N and many ring combinations of 4 or less atoms		Epoxides, azetidine
O–X atomic pairs	–O–X; –ClO <sub>3</sub>	Hypohalites; chlorates
Many N–metal atomic pairs	=N–M	N–metal salts

### 3. Transforming data to the hazard potential

The chemical and physical property data gathered, from the open literature and interpreted as a whole, provide a reasonably comprehensive view of the potential hazards of handling the chemicals involved in the synthesis. As noted earlier, hazard analysis for the synthesis reactions are conducted using a more complex approach that may include hazard testing.

This final step in the process compares the data gathered with company-defined safety boundaries and risk tolerance. This part of the process is somewhat subjective. Senior management to whom the lab supervisors report will, on behalf of the company, assign a Window of Safe Operations for the lab. For example, Section 11 of the Review Form (Fig. 1) shows a typical set of flammability, temperature and pressure limits for the reaction conditions that define a Window



of Safe Operations. The actual limits imposed by the HSE department and management are governed by the technical expertise of the synthesis group as well as the absolute hazard of a particular set of operating conditions or properties of a particular molecule.

If one or more of these predetermined boundaries are crossed the synthesis is classified as non-routine and additional detailed review before any laboratory work is started.

### 3.1. Sections 11 and 12: routine or non-routine synthesis?

#### 3.1.1. Toxicity and exposure data

Federal regulations govern the personal protective measures that must be taken by a company tied to the published toxicity and exposure limit data for a particular chemical. Furr [11] has edited an encyclopedic reference book that addresses toxicity and exposure issues as well as many other safety issues concerning the handling and use of chemicals in the laboratory. The experience that a company has in handling highly toxic materials will determine whether or not the properties of any chemical used in synthesis constitute a routine or non-routine synthesis.

Increasing the level of required PPE is often the response to elevated toxicity or exposure hazards. However, it is better practice to determine if the synthesis can be adapted to an inherently safer process rather than simply donning more protective gear. There is also the concern of whether lab personnel are experienced in the use of, and able to safely work in this additional PPE.

#### 3.1.2. Flammability data

**3.1.2.1. Melting point, boiling point and vapor pressure.** It is important to know the physical form of the material under the conditions of operation. If liquid, the vapor flammability and ignitability is of primary concern; melting of the solid during the synthesis should also be considered. The vapor pressure of a liquid is directly linked to the flammability hazard of that material and developing a flammable atmosphere at that temperature.

**3.1.2.2. Flash point.** Operating at temperatures at or above the flash point of a solvent invariably requires precautions to prevent the formation of a flammable atmosphere. NFPA uses flash point and flammable limits data to link the presence of flammable or combustible liquids in the work area to the area's electrical classification. A number of National Fire Protection Association (NFPA) publications provide guidance in this area. NFPA 325 [12] gives formal descriptions of the various flammability terms and provides fire hazard properties for about 1500 compounds; NFPA 30 [13] provides the code that is the legal basis for regulation; NFPA 45 [14] is the standard applicable to laboratories where chemicals are stored or handled. For example, when planning to conduct a synthesis it is important to know if the solvents, reagents, and reaction conditions require explosion-proof

electrical fittings and equipment. Therefore, the choice of a solvent may be ultimately determined by the electrical area classification of the laboratory.

**3.1.2.3. Lower/upper flammable or explosion limits.** Knowledge of the flammable limits, in particular the LFL, indicates directly the concentrations of the organic vapor and air (oxygen) required to create a flammable, and therefore potentially explosive atmosphere. If a flammable atmosphere can occur, then usually adding an inerting gas, such as nitrogen, argon, and sometimes CO<sub>2</sub>, will mitigate the hazard.

The familiar fire triangle is invariably interpreted as all three sides being required for an explosion to occur. Does that mean that by eliminating ignition sources the hazard can also be mitigated? No matter how diligently ignition sources are eliminated, there is no guarantee of 100% success. It is inherently easier to control the presence and the absence of flammable vapor mixtures by adding an inert gas to the head space.

The LFL can be estimated from the vapor pressure of the fuel at the flash point temperature. If the vapor pressure (VP) at the flash point is expressed in atmospheres and the total pressure is one atmosphere, then the LFL can be calculated in volume or mol % as  $LFL = 100 \times VP$  (in atmospheres at the flash point temperature).

**3.1.2.4. Auto Ignition temperature.** AIT values range from 180 to 650 °C for most hydrocarbons and their derivatives, and are used as one indication of the potential explosion hazard in the absence of sparks. AIT can be significantly lowered by adsorption of an organic material on to a high surface area solid such as vessel insulation and spill adsorbents. Therefore, liquids with AIT < 200 °C are particularly vulnerable to self-ignition if accidentally spilled on a hot surface or warm insulation.

**3.1.2.5. Minimum ignition energy.** For gases or vapors, the MIE values range from 0.01 to 100 mJ, compared to 10–10,000 mJ for dusts and mists. Static sparks from equipment can be as high as 200 mJ, and the human body can carry up to 40 mJ. The lower the MIE the more care that should be exercised with common operations that generate static electricity—pouring, scooping, use of plastics, especially flexible tubing, in the synthesis equipment. Paying particular attention to grounding and bonding of the equipment is one way to lessen the risk. Low MIE values should trigger a review covering grounding and bonding issues including inspection and testing of all equipment planned for use.

**3.1.2.6. Dust explosion severity.** Combustible, dusty materials, with particle sizes less than approximately 200 mesh, can explode if a sufficient concentration in air is present along with an ignition source. Ignition sources range from 20 to 200 mJ (common static spark) to hundreds of Joules (arcing electrical equipment). Thus, dust explosion testing

is often performed to determine if grounding or inerting synthesis areas and equipment is necessary. The cost of the dust explosion testing to determine ignition energies and the severity of dust explosion is a small fraction of the costs of upgrading an area to Class 1 division I in the belief that it might be necessary.

### 3.1.3. Reactivity concerns and reaction conditions

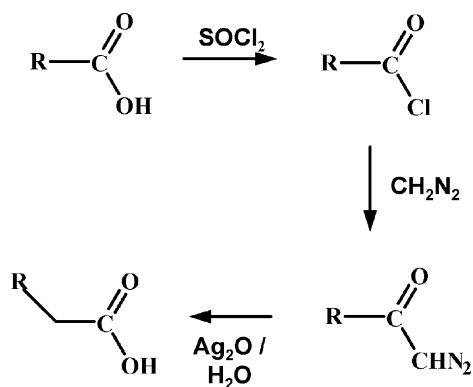
**3.1.3.1. Air/water sensitivity, corrosivity.** This section addresses the common incompatibilities that could be experienced while handling reactants. As an example, the common reducing agents based on metal hydrides are all water reactive, some more so than others. Therefore, consideration must be given to maintaining a water-free environment when performing this type of synthesis. Part of the pre-startup review would therefore include an examination of the integrity of all shut-off devices for water sources in the immediate area.

### 3.1.4. Operating conditions

Are temperature or pressure conditions required by the synthesis outside of the “normal” operating range routinely practiced by the lab? It is common practice to designate all high pressure reactions (“high” implying  $P < 5$  bar for example) as potentially hazardous requiring special review. High temperature reactions or reaction feeds may lead to hot surfaces that can become unexpected ignition sources. Extremely low temperatures can lead to unexpected loss of flow of critical coolants, reactants or quenches if not properly reviewed. Premature embrittlement is always a concern with low temperature work.

## 4. Example

Here is an example of the use of the assessment form, Fig. 1. Lab personnel plan to extend the carbon backbone chain of an aliphatic carboxylic acid by adding a single methylene group. The proposed reaction scheme is:



The reaction sequence has been conducted only once before by the lab personnel. The conversion is in fact a three

Table 7  
Hazard scores for Sections 7, 8, and 11

Section	Item	SOCl <sub>2</sub> Rxn	CH <sub>2</sub> N <sub>2</sub> Rxn
7	FI Pt/AI/MIE	n.d.	2
7	LEL/UEL	n.d.	8
8	Stability/reactivity	7	8
8	Toxicity/exposure	7	9
8	Incompatibilities	7	7
8	Spill clean-up	6	9
8	PPE required	6	9
11	Chemical handling	7	9
11	Extreme reaction <i>T</i>	1	1
11	High temp feed	1	1
11	High press reaction	1	1
11	High press feed	1	1
11	High toxicity	7	9
11	Flammability	2	9
11	High hazard reaction	4	9
11	Hazard Rxn done $\leq$ twice	2	9

step reaction involving the use of thionyl chloride, SOCl<sub>2</sub>, diazomethane CH<sub>2</sub>N<sub>2</sub>, and aqueous suspension of silver oxide. The procedures discussed in the previous sections are used to assess the three steps of the chemical synthesis. The details of the data gathering from the open literature are shown as entries into the hazard evaluation table, Fig. 2.

The principle hazards incurred in the conversion to an acyl chloride, using SOCl<sub>2</sub> involve the violent reactions of SOCl<sub>2</sub> with water/moisture, its highly corrosive nature, and the low TLV. The conversion of the acyl chloride to the azide uses diazomethane which is highly toxic, extremely flammable and can detonate under certain circumstances. Silver oxide is relatively benign provided that it does not come into contact with aqueous ammonia (potential for the formation of impact sensitive silver azide).

The initial assessment strongly indicates that the proposed reaction should not be performed without a detailed hazard review designed to reduce the potential hazards involved with the handling of thionyl chloride and diazomethane.

A simple hazard scoring scheme may be used to identify the degree of the handling and reactivity hazard(s) for each chemical and the reaction(s). Table 7 shows the scores for each item of Sections 7, 8, and 11 of the Hazard Evaluation form. Table 8 summarizes the scores for each reaction, focusing on the key chemical in each step.

The numerical scoring was 1–3 (low hazard), 4–6 (moderate hazard), 7–9 (high hazard). Although this is a subjective approach it provides a reasonably reliable way of risk ranking the reaction steps and highlighting the potential hazards.

Table 8  
Summary of hazard scores by reaction step

Section average	SOCl <sub>2</sub>	CH <sub>2</sub> N <sub>2</sub>
Section 7	n.d.	5
Section 8	6.6	8.4
Section 11	2.9	5.4
Number and percentage of “High” Ratings for Sections 8 and 11 (max 14)	5 (36%)	10 (71%)

7. Physical Properties	6. Chemicals to be used – Sample, Reactants, Solvents		
	Thionyl Chloride	Diazomethane	Silver Oxide, aq.
B Pt / M Pt / VP @ 20 °C	76 / -101 / 0.6	-23 / no data	Not applicable
FI Pt / AI / MIE	No data	Flam gas / 100	Not applicable
LEL / UEL	No data	Flammable	Not applicable
Dust Explosion Severity	Not applicable	Not applicable	Not applicable
8. Chemical Overview			
Stability/Reactivity	Violent with water	Explosive / Shock	None
Toxicity/Exposure	TLV- 0.2ppm	TLV – 0.2ppm	None
NFPA/HMIS Ratings	3 / 1 / 4	Not Rated	Not Rated
Incompatibilities	Any active hydrogen	Many	None
Spill Clean-up Material	Sand	Evacuate	Eye protection
PPE Required	Respirator	SCBA	None
Specific Hazard (Note 1)	Highly corrosive	Explosion Hazards	None
9. Function in synthesis			
10. MDS Sheet Reviewed	Signed: _____		Date: _____
11. Classified as a Non-Routine Operation (check relevant categories)			
High toxicity / Low exposure limits	Y	Chemical Handled (Air/water sensitive, Corrosive)	Y
Flammability (FI Pt<10 °C; LFL<10%)	Y	Extreme Reaction Temperature (> 150 °C; < -30 °C)	N
Flammability (AI<200 °C; MIE < 0.5mJ)	Y	High Temperature Feed (> 50 °C)	N
High Hazard Reaction or Functional Group	Y	High Pressure Reaction (>10 bar)	N
High/moderate hazard reaction performed ≤ 2 times	Y	High Pressure Feed (>2 bar)	N
12. Potential Hazard Level	Non Routine	Non-Routine	

Fig. 2. Completed hazard evaluation form for the addition of a methylene group to an aliphatic carboxylic acid.

The obvious conclusion is that both reaction steps are potentially hazardous but that the use of diazomethane introduces a significant hazard. A good case can be made at this point for investigating an inherently safer synthetic approach. The hazard potential would be lower if the synthesis had been performed more often by the group implying that some hazard evaluation had already been performed.

## 5. Summary and conclusions

The process described in this paper is intended to be the first hazard review for any lab work that involves reactive chemicals. This paper has shown that deciding if a synthesis is routine or non-routine may be determined by assembling and assessing a collection of readily available information about the physical and chemical properties of the chemicals that will be used in the synthesis. The one page Preliminary R&D Reactive Chemicals Hazard Review Form acts as both the documentation tool as the information is being assembled and the means by which the decision regarding routine vs. non-routine is made. The assessment of the actual synthesis is a separate process. It is predicated on the results of this preliminary assessment.

The form is designed to be used by a chemist or chemical engineer with a knowledge-level sufficient to safely handle the chemicals and equipment used. Some training may be needed by process hazard experts to show how the information links together. However, the form is designed to be

more of a self-audit for day-to-day use by lab personnel. Any synthesis that is flagged as non-routine should be assessed in a formal review using an appropriately trained and experienced facilitator [10].

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