



Safety Services Guidance



Guidance on risk assessments for chemical reactions - interpreting journal protocols, changing parameters and scaling up

Key word(s) : Exothermic, thermal runaway, pressurisation, mixing, temperature, cooling

Target audience : Local managers, PIs, Researchers

Contents

Introduction	2
Interpretation of Journal protocols.....	2
Changing reaction parameters	2
Scaling up	3
Initial Assessments.....	4
Safety Measures	5
Checklist for scale up from laboratory to pilot plant (>2L, >100g)	5
Checklist for scale up in laboratory setting (bench top, <2L, <100g)	7
Practical tips: Mixing.....	8
Practical tips: Apparatus	8
Practical tips: Thermal runaway	9
Training and Information.....	10
Further Reading	10

Management cycle	Useful paragraphs
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Plan	9, 10, 12, 13, 16
Do	11, 13, 14, 15, 17
Monitor	18
Review	

Introduction

1. Chemists and other researchers routinely refer to journal accounts of experimental protocols carried out by others to inform their current work. In designing their own protocols, these brief accounts are interpreted, key parameters are amended and varied and quantities and volumes are scaled up. The original accounts may have been based on acceptable practices and scientific knowledge many years old, carried out by very experienced experimentalists, in institutions with varying risk appetites and complying with very different national legislative requirements. Competent and informed assessments of risk are fundamental to converting this information into a safe system of working today. Principal Investigators are responsible for ensuring such assessments are carried out and kept up to date.
2. A majority of chemical reactions are exothermic (ie give out heat) even if they might need the application of some heat to initiate or start the reaction process. Therefore one of the main hazards of carrying out such reactions is the risk of thermal runaway when the heat generated by the reaction exceeds the heat removed. This surplus heat raises the temperature of the reaction mass which therefore causes the rate of reaction to increase thus increasing the rate of heat production and so on. Once control of the reaction is lost, temperature can rise rapidly leaving few options for correction.
3. There have been serious incidents at Higher Education Establishments involving run-away exothermic reactions and/or the uncontrolled release of toxic substances. Some of these are known to have arisen from errors in the interpretation of published data and also scaling up.

Interpretation of Journal protocols

4. Journal accounts seldom provide a step-by-step guide to all the practical details that need to be considered. They often do not include safety relevant information such as the size of reaction vessel, or size of stirring device. They may not explain the reason for the selection of a particular solvent, or know that the choice of a different solvent, perhaps offering better solubility, may completely alter the characteristics of the reaction.

Changing reaction parameters

5. The adjustment of journal procedures to suit a different research direction/purpose can have a devastating impact on the overall characteristics of the reaction. In one example, a research student changed the reaction solvent from dichloromethane to toluene. Dichloromethane is more dense than water,

toluene is not. The reaction was exothermic and the heat transfer characteristics of this particular three phase system when the solvents were switched changed fundamentally giving rise to local hot spots and a resulting detonation of hydrogen azide.

Scaling up

6. Increasing the volume/weight of reagents without considering the effects on a wide range of reaction parameters is known to be a factor in many catastrophic reaction failures, even at relatively small scale.
7. The main concerns include:
 - Runaway reactions.
 - Over-pressurisation.
 - Dust and vapour explosions inside vessels.
 - Fires due to overfilling of vessels.
 - Failure to identify all possible sources of ignition (including static).
 - Failure to assess the [ATEX](#)¹ requirements for electrical equipment this refers to the level of intrinsic protection of electrical equipment used in potentially explosive atmospheres.
 - Auto-ignition of flammable vapours.
 - Inadequate mixing.
 - Inadequate removal of heat.
8. The Health and Safety Executive's [analysis](#)² of the main causes of chemical reactions that run out of control lists the following:
 - Inadequate understanding of the process chemistry and thermochemistry.
 - Inadequate design for heat removal.
 - Inadequate control systems and safety systems.
 - Inadequate operational procedures, including training.

¹ <http://www.hse.gov.uk/electricity/atex/general.htm>

² <http://www.hse.gov.uk/pubns/indg254.htm>

Initial Assessments

9. For any chemical reaction, there are numerous risks to consider and the significant findings must be recorded. These assessments may include controls for risks from the chemicals themselves (both physical and health effects) and from the procedures that are being carried out which may be covered by local rules, standard operating procedures and safe systems of work. Any assessment of risk must include hazards that arise from the chemical process itself, most importantly:
- Thermal instability of any or all of the reactants, reactant mixtures and products, including intermediates, contaminants and by-products
 - Exothermic reactions leading to increased temperatures and production of decomposition reactions or violent boiling
 - Evolution of gas or vapour in sealed systems, leading to pressurisation and over-pressurisation.
10. Sources of useful information for initial assessment include literature surveys, predicting reactivity and stability from molecular structure and knowledge of the thermochemistry involved. HSG143 [Designing and operating safe chemical reaction processes](#)³ provides more guidance on each of these. Colleagues from other academic areas often possess expert knowledge about aspects of chemical reactions. Eg chemical engineers will be more familiar with the issues of scaling up, mixing, heat transfer than those used to working at smaller scale.
11. On a small scale, in the first instance, screening of the proposed reaction can take place using differential calorimetry or curius tube. For measuring reaction kinetics and heats of reaction, isothermal calorimetry can be used. Where reactions have the potential for thermal runaway, adiabatic calorimetry can be used.
12. Certain [molecular groupings](#)^{4, 5} should prompt more careful consideration. These include:
- Double and triple bonded hydrocarbons
 - Epoxides
 - Hydrogen and hydrides
 - Metal acetylides

³ HSE 2000 (reprinted 2008) ISBN 9780717610518

⁴ See also University of Manchester guidance on explosophoric and energetic chemicals.

⁵ Bretherick's Handbook of Reactive Chemical Hazards, 8th Ed, Urben and Pitt, 2017, ISBN 9780081009710

- Many nitrogen-containing compounds, eg amides, imides, azides, diazo, diazeno compounds, hydrazine-derived nitrogen compounds, nitrates, nitrites, nitroso- and nitro- compounds, N-metal derivatives (and more)
- Oxygenated compounds of halogens
- Peroxides

Safety Measures

13. Once the risks have been identified, appropriate controls can be selected to ensure safe operation. There are a number of ways this can be done:

- Use inherently safer methods which eliminate or reduce the hazard, eg substituting hazardous materials with safer ones; keeping less unreacted material in the reactor - using a continuous process, or a semi batch process (in which one of the raw materials is added over time) instead of a batch process; use a heating medium that has a maximum temperature that is too low for the reaction mixture to decompose.
- Process control, which includes the use of sensors, alarms, trips and other control systems that either cause automatic action or alert an operator to make a manual intervention to prevent the conditions for uncontrolled reactions occurring.
- Protective measures which do not themselves prevent a runaway but mitigate the consequences should one occur. They are intended to operate when the runaway has started, thus a detailed knowledge of the reaction is necessary for their effective specification and deployment. They could include: design to contain the maximum pressure; fitting emergency relief vents and ensuring the vented material goes to a safe place; making facilities available to crash cool the reaction if it moves outside set limits; addition of a reaction inhibitor to stop the reaction and prevent runaway or dumping the reaction into quenching fluid.
- Selecting the basis of safety, which is the combination of controls that are relied upon to ensure safe operation. The controls chosen for each particular case will depend on a number of factors, including: how easy it is to prevent runaway; how applicable the various methods are and their compatibility with the plant operation.

Checklist for scale up from laboratory to pilot plant (>2L, >100g)

14. The following is based largely on information from the [American Institute of Chemical Engineers](#) which lists the following key points to establish as part of the risk assessment process (more information about each is provided on the webpage):

- Know the heat of reaction for the intended reaction, and also any other potential reactions (wanted or not).
- Calculate the maximum adiabatic temperature for the reaction mixture. Assume a worst case scenario of no heat removal and 100% reactants actually react. If this temperature exceeds the boiling point of the mixture, then in theory at least, the vessel could become pressurised.
- Determine the stability of all individual components of the mixture at the maximum adiabatic temperature (worst case), to identify possible decompositions. Assess whether the decompositions could produce gaseous products, which would lead to pressurisation of the reaction vessel.
- Understand the means of heat transfer within the mixture (often two or three phases) and heat removal. Consider agitation, introduction of energy by the mixing technique and means of monitoring. Consider whether temperature is representative of the mixture, possible hot spots and that a thermometer can be seen accurately through the coolant etc.
- Avoid using a single temperature as the only means of monitoring the reaction rate, especially for exothermic reactions. The monitoring system is vulnerable to mechanical failure and operator error. It would be better to introduce multiple monitoring positions to be representative of the whole system.
- Identify possible contaminants and their effects on the reaction. Include ubiquitous ones such as water, metal ions such as sodium, calcium and others usually present in process water. (Note: azides react explosively with heavy metal ions).
- Consider "what if" questions – what if the water/electricity/heating/ etc fails? What if the quantity of one reactant is doubled by mistake?
- Remember that if the scale of the reaction is increased, the ratio of volume of reactant to surface area of the reaction vessel increases and cooling may become inadequate. Heat generation increases with the volume of the system (by the cube of the flask diameter). Heat is generally only removed through the external surface of the reactor, and the rate of removal therefore increases with the surface area of the system, (the square of the linear dimension).
Heat removal is therefore less efficient in larger vessels.
- Consider effects of changing the solvent which will also affect the following properties: density, vapour pressure, boiling point etc.
- Identify all heat sources connected to the reaction vessel and assess their maximum temperature (what if the thermostat on the heating plate/jacket is defective?)
- Determine the minimum temperature that could occur and what other hazards might arise, such as increased viscosity or freezing which might affect mixing and alter the process of heat transfer.

- For larger scale reactions, consider the potential for temperature gradients, which might be higher near the point of mixing.
- Understand the rate of all the chemical reactions that might occur which will potentially affect the rate of consumption of reactants and temperature of the reaction. If the reactants are consumed quickly with an increase in temperature, a control might be to limit the rate of addition of one of the reactants over time.
- Consider whether any vapour phase reactions could occur eg vapour phase decomposition of materials such as organic peroxides.
- Consider the properties of both reactants and products, intended and unintended, and whether they could degrade or attack materials such as the reactions vessel, tubing and pipework, gaskets, etc.

Checklist for scale up in laboratory setting (bench top, <2L, <100g)

15. It may not be practicable to implement the above checklist fully for smaller bench top scale ups, but the same principles should be applied. The checklist below should be reasonably practicable in most circumstances. If any measure cannot be implemented, the assessment of risk should document this and the reason and steps be detailed to address the risks from uncertain or unknown factors in other ways.

- Calculate changes in bond strengths between reactants and products which can predict whether strong exotherms are expected.
- When a new procedure is being trialled work on a small scale initially.
- Consult journals such as Organic Syntheses (available on line and free) or Inorganic Syntheses (not yet available in electronic format but available in the JRULM) to ascertain if there is a tested procedure similar to the one to be attempted. In these journals the apparatus is detailed and there are always safety notes and it is rare to be unable to find a model system. When a system is found it is better not to mix methods – keep to solvents with similar properties to those in the published methods and appropriate to that scale.
- Do not scale up ‘non-hazardous’ reactions more than five times that of a previously safe and successful reaction.
- Scale up of hazardous reactions should be carried out in smaller steps. (Hazardous reactions are defined as exothermic and / or heterogeneous [involving more than one phase] reactions).
- When carrying out a trial reaction, note all physical aspects of the reaction, including colour and phase changes, and in particular temperature changes within the reaction medium using an internal thermometer, preferably digital. It is also best practice to monitor the temperature of any cooling or heating baths which can indicate significant thermal events during the reaction (thus it

is preferable to carry out the initial trial reaction vessel in a heating / cooling bath rather than a heating / cooling mantle to enable these changes to be recorded.

- When the risk assessment is being carried out, consider the impact of scale on the potential exposure to chemicals hazardous to health (toxic, irritant, corrosive, carcinogenic, mutagenic etc). Sources of data include Safety Data Sheets (SDS).
- The practicalities of large scale disposal of chemical residues should also be considered as well as methods for containing and clearing up any potential spillages.
- In an exothermic reaction, be aware that the heat produced in reaction mass increases with volume, ie is proportional to the cube of the reaction vessel diameter; whilst the heat lost to surroundings depends on surface area of the vessel available for heat transfer, ie is proportional to the square of the reaction vessel diameter. For example⁶, the time taken for a 1 degree drop in temperature due to natural cooling from an initial temperature of 80°C when the surroundings are 20°C:
10mL test tube – 10 seconds
100mL glass beaker – 20 seconds
1000mL glass dewar – 60 minutes
- Be aware of both the mechanistic and physicochemical nature of the reaction, including unavoidable or potential side-reactions, which may vary depending on the purity of the starting materials (note bulk chemicals often contain more impurities than laboratory grade chemicals, mild steel contains more impurities than stainless steel etc).

Practical tips: Mixing

- If there are no baffles in a flask or beaker (ie they have smooth straight sides), fast stirring doesn't actually mix the contents.
- Magnetic stirrers are unsuitable for larger scale applications as they will not stir efficiently and may damage the flask; use mechanical stirring paddles.
- An overhead (preferably compressed air) stirrer should be used for reaction volumes of 2L or more.
- For larger scale reactions, slower agitation will provide adequate mixing compared to that used on a small scale.
- Overhead stirrers must be used for heterogeneous reactions which are heated to reflux.

Practical tips: Apparatus

⁶ Adapted from HSG143, para 50

- With larger volume 'Quick-fit' flasks, the minimum size of ground glass joint should be B29 (this makes it easier to remove solid products and to prevent condensers from flooding).
- Do not overfill flasks. Calculate the total volume of all reagents plus solvents, including quench solutions, before deciding flask size – it is recommended that the total volume of reactants should not exceed 50% of the flask volume.
- A large bore condenser (B24 or grater) must be used for reactions heated to reflux to avoid flooding of the condenser.
- When using a solvent bath cooled with solid carbon dioxide (cardice), industrial methylated spirit (IMS) is preferable to acetone (subject to the desired temperature) as addition of cardice to IMS causes less foaming.
- Some exothermic reactions with long initiation times, eg nitrations can be better scaled up if the reaction is run at elevated temperature so that when reactants are added in aliquots they are consumed at a faster rate and the initiation period is reduced. However, during aliquot addition of a reagent always allow the reaction temperature to return to a predetermined level before introducing more material.
- For large flasks, separating funnel and chromatography columns, standard bosses and clamps are inadequate and more robust support is required.
- Cannulas (flexi-needles) should be used to transfer, under inert gas pressure, air / moisture sensitive liquids from tared bottles to the reaction vessel. The use of a suitable pressure regulator to control the inert gas pressure is required to allow a steady and controllable flow of liquid from one vessel to another.
- When transferring viscous solutions or suspensions, do not use a normal cannula, instead use a wide bore glass or plastic tubing device, Use as wide a bore needle for the inert gas inlet as possible in order to reduce the pressure of inert gas to transfer the fluid.
- Do not leave a fluid which is being transferred by cannula unattended. Always ensure the vessel from which the liquid is being transferred is positioned below the reaction flask as otherwise as soon as a flow is established the transfer will continue by a siphoning effect regardless of whether there is a positive pressure of inert gas applied or not.

Practical tips: Thermal runaway

- An exothermic reaction can lead to thermal runaway, which begins when the heat produced by the reaction exceeds the heat removed. The surplus heat raises the temperature of the reaction mass which causes the rate of reaction to increase, which in turn increases the rate of heat production. An approximate rule of thumb is that reaction rate – and hence the rate of heat generation – doubles with every 10°C rise in temperature.

- Thermal runaway can occur because, as the temperature increases, the rate at which heat is removed increases linearly but the rate at which heat is produced rises exponentially. Once control of the reaction is lost, temperature can rise rapidly leaving little opportunity for correction. The reaction vessel may be at risk from over-pressurisation due to violent boiling or rapid gas generation. The elevated temperatures may initiate secondary, more hazardous runaways or decompositions.

16. If thermal runaway is a possibility, the assessment of risk must address all reasonably practicable means of eliminating the risk through process controls but will probably also have to specify precautionary measures to minimise the damage caused by such an event. These might include:

- Designing equipment to contain the maximum pressure – eg fit emergency relief vents and ensure that the vented material is discharged in a safe place.
- Having a facility to crash cool the reaction mixture if it moves outside predetermined limits.
- Being able to add a reaction inhibitor to stop the reaction and prevent runaway.
- Having a dump of quenching fluid to hand (and the means to move the reaction to it!).

Training and Information

17. All those at risk from the reaction should be given sufficient information about the risk to be able to respond appropriately. The researchers directly involved will obviously need to know the most about setting up the procedure, understanding the reaction thermodynamics (quantifying where necessary) and should receive information and training in responding to emergencies or non-planned outcomes. Those working nearby should also be given sufficient information to enable them to respond safely in the event of an emergency.

18. Training and information given should be recorded, either as part of the risk assessment, in laboratory notebook or by updating training records held electronically.

Further Reading

19. Safety Issues in the Scale-up of Chemical Reactions – Royal Society of Chemistry, Environment, Health and Safety Committee <http://www.rsc.org/globalassets/04-campaigning-outreach/realising-potential-of-scientists/regulations-health-safety/safety-issues-in-the-scaleup-of-chemical-reactions.pdf>

Document control box	
Title	Guidance on risk assessments for chemical reactions - interpreting journal protocols, changing parameters and scaling up
Link to Policy or Chapter	University Health & Safety Arrangements Chapter
Date issued:	August 2018
Issued by:	Safety Services
Implementation date:	v1.0 March 2009 v1.1 February 2012 v1.2 August 2018
Version:	1.2
Next review date:	Upon significant change
Owner of this document:	Head of Safety Services, Dr Patrick Seechurn
Lead contact:	University Safety Coordinator, Elaine Armstrong