University of St Andrews

Reaction Scale-Up: Safety Considerations

1. Introduction

Reaction scale can dramatically affect the risk associated with a given experiment. Whilst research experiments are commonly performed on small scale (e.g. <1 g of reactants), the impact of reaction scale should be considered as part of the risk assessment process.

2. Determining a Suitable Scale

Experience from Research Group: When deciding on a suitable reaction scale, prior knowledge within your research group is often an excellent starting point. As an example, if a similar (or identical) experiment has been performed previously using 0.5 g of each reactant without incident, this indicates that this is an appropriate reaction scale.

Literature Reports: If an experiment has been reported in the scientific literature, the scale adopted by the authors is a sensible starting point as we can reasonably assume they have performed the reaction on this scale without incident. If you plan to perform an experiment reported in the literature on an increased scale, a step-wise approach should be adopted (see section below).

New Reactions: In instances where an experiment is not reported in the literature and similar reactions have not been attempted in the research group, it is prudent to start on a small scale (as a rough guide, <1 g reagents; < 25 mL solvent). These exploratory experiments can be used to determine (i) whether a reaction is successful and (ii) provide information that would be useful if scale-up is required (see step-wise approach section below)

3. Step-wise Approach

Research experiments may need to be performed on a larger scale to (i) access suitable quantities of material or (ii) demonstrate the robustness of an experimental method.

When increasing the scale of an experiment, a step-wise approach should be adopted. As a rule-of-thumb, a reaction should only be scaled three times the amount used in a previous experiment (e.g. perform an initial experiment with 1 g starting material, increase to 3 g starting material, further increase to 9 g starting material. Do not move immediately from 1 g to 9 g of starting material).

When performing reactions on a smaller scale, consider the following questions:

- Is the reaction exothermic? What change in temperature do you observe?
- Does the reaction give off any gaseous by-products?
- Do you notice any pressure building up in the reaction vessel?
- Do you encounter any problems stirring the mixture effectively?

- Would the handling of reaction vessels or glassware for purification become problematic on a larger scale?

These questions can help identify if additional control measures are required when the reaction is being performed on a larger scale. The questions listed above are not exhaustive; make a note of any observations that may be significant.

4. Temperature

If a small-scale reaction is found to produce a significant exotherm, careful consideration should be given to how the reaction temperature will be controlled and whether the current cooling method will be effective on a larger scale.

Be aware that as the size of a reaction vessel increases, the volume : surface area ratio decreases and limits the rate by which heat can be transferred to the surroundings. If heat cannot be effectively removed from the reaction vessel, we run the risk of "reaction runaway" (a process by which an exothermic reaction goes out of control: the reaction rate increases due to an increase in temperature, causing a further increase in temperature and hence a further rapid increase in the reaction rate).

5. Liberation of Gases / Build-up of Pressure

If an experiment is known to produce a gaseous by-product, consideration should be given to whether the volume of gas released can be safely contained when performed on a larger scale. Reactions do not need to produce gas in order to result in a build-up of pressure; Heating large volumes of volatile solvents can generate internal pressure that could cause glass joints to separate and should be considered.

6. Presence of Hazardous Reagents / Emergency Response

If performing an experiment involving a highly hazardous material (e.g. a highly toxic reagent) on a large scale, careful consideration should be given to (i) the consequences of an unexpected release, (ii) whether the control measures used in previous reactions are still suitable and (iii) if specific emergency actions need to be developed.

As an example, compare a reaction using 100 mL versus 1 litre of diethyl ether. The fire risk associated with the larger-scale experiment is significantly higher. A safer alternative to diethyl ether would need to be identified or a robust emergency response be considered.

7. Reaction Monitoring

Large-scale reactions should be monitored continuously for temperature spikes, evolution of gases and problems with equipment (e.g. malfunction of an overhead stirrer or separation of glass joints). Constantly monitoring the reaction ensures we can take corrective action should a problem arise before a dangerous situation develops.

8. Time

The bigger the reaction, the longer the setup, run, and workup of the reaction will take. Allocate extra time for the experiment and do not rush.

9. Risk Assessment

Safety considerations associated with experimental scale should be included in the CHARM risk assessment for each experiment. Suggested inclusions are listed below:

- The maximum scale on which the reaction will be performed using the control measures described. Reactions performed on a larger scale should be reassessed to ensure the control measures described are still suitable.
- If the reaction has been reported in the research literature, provide a reference to the article / procedure as part of your risk assessment.
- If the reaction involves performing a literature procedure on an increased scale, outline whether the risk is likely to have increased and, if so, how this will be managed.
- If specific emergency procedures are needed based on the reaction scale this can be outlined here.

Illustrative examples are provided below:

*** Safety considerations associated with experimental scale.**

Highlight maximum scale before risk assessment is reviewed
Experiment will be conducted up to 10 mmol scale with regard to the starting acetic acid (<1 g acid). Experiments >10 mmol will be reassessed to ensure control measures are sufficient.

Example from literature:
Procedure adapted from "journal reference" (A.Nother) where it was conducted on a 20 mmol scale. Planned reaction will be conducted on 10 mmol scale and does not pose any significant change in risk

Increasing reaction scale:
Experimental procedure based on literature precedent conducted on 1 g scale of starting acid. Experiment will ultimately be performed on 20 g of acid, however, reaction will be scaled step-wise to determine if the exotherm generated is suitably controlled by experimental set-up or if additional cooling is required.

Sample procedures:
1. Example Chemical procedure Risk Assessment
2. Example Biological procedure Risk Assessment

10. Further Resources

The University of Illinois Urbana-Champaign and Stanford University have excellent pages relating to the reaction scale. The webpages are listed below:

- https://drs.illinois.edu/Page/SafetyLibrary/ScaleUpReactionSafety
- https://ehs.stanford.edu/wp-content/uploads/Scale-Up-Safety_FINAL.pdf

Additionally, a series of papers have been published relating to reaction scale safety that contain useful discussions. Examples are listed below:

- *Safe Chemical Reaction Scale Up, D. C. Hendershot and Aaron Sarafinas, Chem. Health Saf. 2005, 12, 6, 29–35 (doi:10.1016/j.chs.2005.07.011)*
- *From beaker to bucket: The safe scale-up of organic electrolyte materials, Trevor Dzwiniel, Krzysztof Pupek and Gregory Krumdick J. Chem. Health Saf.* 2014, 21, 3, 8–12 doi: 10.1016/j.jchas.2013.11.006