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Performing Hazard Analyses and Setting Triggers for Reevaluation in Lab-Scale Chemical Reactions

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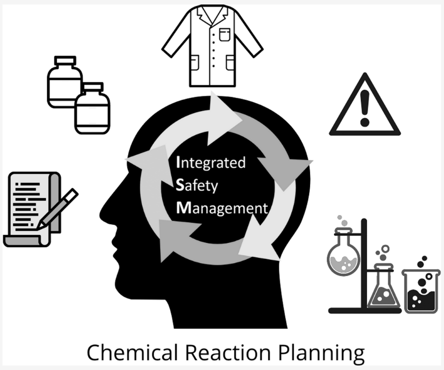

ABSTRACT: Laboratory chemical synthesis research typically lacks the preplanned hazard responses found in production-scale industrial laboratories. Chemical safety management is a known challenge in education-based facilities, which is concerning for academic and national laboratory environments working with inexperienced student researchers. At the Molecular Foundry, a U.S. Department of Energy (DOE) user facility, a chemical safety management form has been developed that follows DOE's Integrated Safety Management (ISM) process, which evaluates the risks and hazards associated with all forms of work. An ISM form for chemical synthesis is described here in detail. It is regularly used to guide chemical safety discussions between researchers and supervisors, to plan accident responses, and to establish triggers, at which point a reevaluation of the work is needed. The form makes it straightforward to know what limits researchers may work within and makes it clear which procedure changes will require a new safety assessment and discussion before work continues. The ISM form for synthesis is being successfully used in three fields of chemistry: Inorganic, Organic, and Biological. The form has also been adapted for liquid sample preparation in electron microscopy. Upper management, supervisors, students, and general users are engaged in this process. It is hoped that sharing this knowledge will enable educational institutions and other laboratories to develop similar methods to help researchers and supervisors understand the hazards as well as the working limits of any protocol, helping researchers to work more independently and safely within the laboratory.

KEYWORDS: *Safety, Hazards, Laboratory Management, Safety Culture, Laboratory Safety, Safety Practices, Best Practices, Hazard Evaluation, Communication, Writing*

The safety practices in academic laboratories were brought to the world's attention in 2009 when a University of California student lost her life as a result of chemical reaction accident.[1] While extracting *tert*-butyllithium (tBuLi), the plunger of a syringe came out of the barrel, and this pyrophoric material spontaneously burst into flames, severely burning the student. Poor planning for an emergency response, the safety culture, and poor house-keeping were all contributors in escalating the consequences that resulted in a loss of life. This incident also highlighted the need to develop a safety management process where researchers and supervisors understand the potential hazards and know how to minimize the risks involved in chemical research. Many changes may have saved this student's life (training, lab technique, experimental design, safety assessment, etc.). The last line of defense when research planning fails is a person's personal protective equipment (PPE), and it is possible that wearing a flame-resistant lab coat could have saved her life.

Though progress in safety policies has been made, it is clear that improvements are still needed. In 2010, an explosion in a biochemistry laboratory injured four people at the University of Missouri when too much hydrogen prematurely entered an anaerobic growth chamber.[2] The T-connector to the gas supply had been temporarily changed to one that did not have a toggle switch, which could have prevented the simultaneous flow of nitrogen and hydrogen. A leak check and confirmation that the equipment contained the necessary components would have prevented the incident. In the same year, a graduate student at Texas Tech University lost three fingers when an energetic material exploded.[3] The student scaled the reaction from 100 mg to 10 g and removed his safety glasses. The sample exploded, resulting in eye injuries that may have been prevented or lessened in severity with proper PPE and a smaller scale. The U.S. Chemical Safety and Hazard Investigation Board gave several recommendations for improvements.[4] In 2016, a postdoctoral researcher at the University of Hawaii lost an arm when an ungrounded tank

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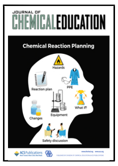

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containing hydrogen, oxygen, and carbon dioxide exploded due to static discharge.[5] The explosion happened after the researcher modified the method and no risk assessment was performed, even after the researcher noted a small ignition the day before the accident. In 2018, three students at Beijing Jiaotong University were killed when a spark from a mixer containing magnesium powder and phosphoric acid exploded. The initial explosion further ignited nearby magnesium powder and combustibles.[6] With a hazard analysis and proper planning for magnesium storage, these fatalities may have been prevented. It was recently stated that "the past two decades have seen a rise in university laboratory accidents in China,"[7] a concerning trend for future generations of scientists. The examples stated here are the most visible and well-known, likely due to severity, and there are many less visible accidents with a broad array of consequences that are less known, visible, reported, or not reported. In all cases mentioned above, a hazard analysis of reaction changes would likely have prevented severe injuries and loss of lives.

Process chemistry in industry is well-established with documented standard operating procedures and preplanned hazard responses. However, exploratory reactions in lab-scale research, especially those found in educational institutions, often lack established protocols for new chemistry. There is often no chemical safety management planning or guidance regarding changes to procedures. Creating new regulations and increasing safety inspections are common methods that attempt to improve safety[8] but do not account for the entire reaction planning process. Safety leadership, training, and review processes for new and modified reactions need improvement.[9] Collaborations have been built between industry and academia to help students develop good safety practices, but the passing of knowledge must be continuous and not through a one-and-done model.[10] Though a few processes have been published as tools to help undergraduate students minimize risk,[11] laboratories need to design more robust processes to understand chemical hazards, authorize work, and establish when researchers must stop and reevaluate their project.

The Department of Energy (DOE) follows an Integrated Safety Management (ISM) process to assess the risks and hazards associated with all forms of work.[12] The process is continuous, requiring constant reevaluation of processes and associated hazards. The core functions of the ISM risk cycle are illustrated in Figure 1. Workers are expected to define their scope of work, analyze the hazards, develop and implement controls, perform work within the established controls, and provide feedback and continuous improvement. Each step is analyzed before, during, and after the procedure, and workers move forward or backward in this cycle depending on the outcome of each stage.

The ISM process helps researchers assess hazards and plan accident responses. At the Molecular Foundry, a DOE-funded nanoscience user facility, we have developed a safety form for chemical synthesis based on the ISM work cycle. It is not a formal work authorization but helps frame the safety discussion between researcher and supervisor. During orientation, researchers learn how to access a blank form and completed example online.

The Molecular Foundry assists roughly 1000 users with their science every year, including undergraduate and graduate students, faculty, staff scientists, and industry leaders. It is a multidisciplinary facility with a unique opportunity to apply the same safety assessment methods to multiple fields of chemistry. The Molecular Foundry's ISM form for synthesis has been used since 2016 and applied to inorganic chemistry, organic chemistry, biochemistry, and liquid microscopy experiments.

Figure 1. Illustration of the core functions of the Integrated Safety Management (ISM) work cycle.

The ISM form could be adapted for educational facilities, starting with chemical reactions that are already in the curriculum with well-known hazards. The process would start in entry-level laboratory classes by providing students with the chemical reaction in advance. Asking students to read and become familiar with safety data sheets and published literature on the chemicals involved would give them exposure to written resources that would initially be provided by the instructor. As students become more familiar with chemical mechanisms and interactions, they could retrieve relevant documents as homework and start incorporating additional hazard assessments in later courses. These skills would take students through graduate school, postdoc, and fulltime research careers.

This manuscript explains each section of the ISM form for chemical synthesis, broken down into segments that fit within the core functions of the ISM process. As seen in Table 1, each stage of the ISM cycle has a set of items that must be considered, documented, and discussed with the supervisor. It is crucial that researchers understand what they are allowed to do independently, what conditions can be changed, and by how much. When there is a desire to exceed the limits set in the ISM form, this triggers a requirement to engage with the supervisor and have a new safety discussion before making changes. It is hoped that sharing our successes and best practices will help those in academic and exploratory research laboratories to refine their chemical safety and work authorization practices.

DEFINE SCOPE OF WORK

Plan Chemical Reaction and Identify Byproducts

When defining the scope of work, it is important to identify the intended, balanced chemical equation, as well as potential side

Table 1. General Integrated Safety Management (ISM) Applied to Chemical Synthesis

ISM − general guidance	ISM − applied to chemical synthesis
1. Define scope of work	• plan chemical reaction and any byproducts
	• establish reaction conditions
	• establish purification and waste procedures
	• identify needed equipment/resources
2. Analyze hazards	• analyze hazards of chemicals, reaction and disposal
	• identify failure modes and plan responses
3. Implement controls	• obtain required authorizations and training
	•establish triggers for reevaluation[a]
4. Perform work	• perform chemical reaction
	• purify material and manage disposal
5. Feedback and improve	• evaluate reaction outcome
	•determine if desired improvements exceed established triggers[a]

[a] Triggers for reevaluation include a set of predetermined changes that are allowed to be adjusted independently (i.e., a range of temperatures or precursor volumes). Plans to exceed these triggers requires a new safety discussion before proceeding.

reactions or byproducts. It is possible the side reactions may be more hazardous than the intended chemistry, which must be considered when planning the reaction. As part of the planning process, researchers must search journal articles and books to explore similar, previously reported reactions.

While comparing the planned reaction to what has been reported in the literature, it is vital to consider potential chemical substitutions from the chemistry and safety perspectives. Not all substitutions behave the same. Take the common hydride reducing agents as an example. Sodium borohydride ($NaBH_4$) is a weak reducing agent, reducing aldehydes, ketones, and acid chlorides to alcohols and carbonyl groups to hydroxyls. In contrast, lithium aluminum hydride ($LiAlH_4$) reacts very strongly and is an unselective reducing agent that reduces the esters, amides, and carboxylic acids that $NaBH_4$ cannot.[13] Replacing $NaBH_4$ with $LiAlH_4$ may have unintended consequences, reducing more groups than intended and causing a violent reaction.

Substitutions also present hazards in biochemistry. For example, a researcher substituting human serum albumin (HSA) for bovine serum albumin (BSA) in a binding assay may not realize that they will be subjecting themselves to new risks since HSA is sourced from humans and may harbor human disease. Defining the allowed materials and conducting a hazard analysis on the substituting material may prevent researchers from taking unnecessary risks.

The ISM form is meant to encourage open discussions about safety and science, so if researchers cannot solve an intended chemical equation or are struggling to determine what substitutions may lower the hazard level, they must talk with others who are more experienced. This may include instructors, group members, local experts, and the responsible supervisor.

Establish Reaction Conditions

This section of the ISM form is for planning the reaction conditions and deciding which factors will be variable. For instance, if a researcher intends to heat a material, a predetermined temperature range must be listed. This requires some chemical awareness that is achieved by reading published articles and safety data sheets (SDSs). Table 2 provides a few examples. $NaBH_4$, the reducing agent mentioned above, is also a source of boron in solid state chemistry. If solid $NaBH_4$ is heated, it is important to know that hydrolysis can cause a dramatic increase in pressure, as this material can release up to four moles of hydrogen per one mole of sample.[14] $NaBH_4$ also decomposes and evolves all of its hydrogen at 534 °C.[15] An intended reaction with a maximum temperature of 250 °C would be far below the point of total hydrogen release, significantly reducing the overpressurization risk.

Table 2. Sample Table of Variable Conditions and Allowable Ranges

variable conditions (i.e., heat, stir time, precursor)	allowable range (i.e., temperature)
heat	150−250 °C
inert gas	argon or nitrogen
reaction time	10 min −3 h
$NaBH_4$ quantity	0.5−2.0 g

If there are multiple gases allowed or changes to reaction times, these should be included in the table and the potential safety implications evaluated. The quantities of materials to be used are documented here or in the section below listing chemical hazards. Researchers must be mindful of reaction scale. It is strongly recommended that a reaction be performed consistently and reliably on a small scale several times before planning a larger scale. When increasing the reaction size, it is not possible to keep everything constant, which is a fundamental concern.[16] Equipment size directly influences reaction kinetics, so scaling up reactions may increase mixing times and different mixing methods may be required. Additionally, flow rates may change and the larger volumes of gas may increase the pressure beyond safe limits.[16,17] The Molecular Foundry focuses on exploratory research and not full-scale production, which is also the case in academic laboratories. Within our facility, revising the ISM form and holding safety discussions are required for scale-up.

Establishing allowed variable conditions helps researchers to work more independently. When someone wishes to go beyond the set limits of the ISM form, known as "triggers for reevaluation," a new analysis is needed before work continues.

Establish Purification and Waste Procedures

The researcher must plan in advance how the final material will be purified. This might be accomplished through processes such as precipitation, rinsing with solvent, or crystallization. The ISM form includes a plan for safe disposal of all waste, noting that some materials require special treatment, such as quenching. The researcher must consider the compatibility of the waste container material with the waste chemicals. For example, some materials will etch glass and must be disposed of in acid-resistant plastic. If the person completing the ISM form is not experienced enough to identify methods for cleaning or to select proper containers for disposal, then the scientist overseeing and approving the work must be consulted. The cleaning and waste process also must be considered as part of the resources planning described in the next section.

Identify Needed Equipment/Resources

The resources required are documented here. This may include, but is not limited to, heater and bath types, Schlenk

Table 3. Sample Table of Chemicals and Their Associated Hazards, Including Reagents Name, Allowed Scale/Range, Hazards Documented in the Safety Data Sheet, and Any Special Handling

reagents/ chemicals needed	range/scale and concentrations of quantities planned	hazards associated (read Safety Data Sheets)	special handling (i.e., treat residue with alcohol before disposal, etc.)
$NaBH_4$	1 mg−2 g	acutely toxic, corrosive, flammable with water exposure	quench with methanol prior to disposal, extinguish fire with dry powder
NaCl	5 mg−2 g	nonhazardous	no special handling
t-BuLi (1.7 M in pentane)	0.1−3.0 mL	pyrophoric (flammable in air), corrosive, toxic	handle in an inert atmosphere glovebox or on Schlenk line using rigorous air-free techniques, quench with methanol, extinguish fire with dry sand, dry chemical or alcohol-resistant foam
MeOH, anhydrous	20−50 mL	highly flammable liquid and vapor, toxic, causes eye damage	keep away from sparks and flames, handle in fume hood or glovebox

lines, cell plates, growth chambers, stir plates, fume hoods, needle types and sizes, waste containers, spill kits, and more. There may be multiple tools that can accomplish the same task, such as a tube furnace versus an oven. If multiple tools will be available, they must be listed here and described in the section on reaction conditions.

This section also lists required PPE, such as goggles or safety glasses, glove types, acid-resistant aprons, and more. When selecting PPE, researchers must be aware of chemical compatibility issues and breakthrough times. For example, it is important to select a glove type that will stop or slow down how quickly a chemical can permeate through the material.[18] A lab coat should be selected according to the highest hazards involved.[19] When working with flammable materials, it may be a good idea to wear a flame-resistant lab coat, while it may be more appropriate to use a poly/cotton coat when working with biological materials. One must also take into consideration the fit and comfort to the users.[20] If the selected PPE is too uncomfortable, hot, or difficult to move in, then researchers may become noncompliant in favor of their personal comfort.

■ ANALYZE HAZARDS

Analyze Hazards of Chemicals, Reaction, and Disposal

Even without considering the intended reaction, chemicals have inherent hazards and storage requirements that must be considered. Table 3 shows a chemical hazard table containing a short chemical list on an ISM form, including the chemical names, intended range/scale, hazards, and notes on special handling. It is important to plan the quantities of materials, which is tied not only to the hazards involved but to the scale of the equipment (flask size, chamber size, etc.). This portion of the ISM form requires researchers to look at references[21] and read the SDS for every chemical involved in the planned reaction. There are known inconsistencies in SDS forms,[22] but these documents are still a valuable starting point for gathering information about chemical materials. For researchers new to reading SDSs, it is important for the supervisor to ask questions to confirm understanding of the process.

Here, the researcher documents the relevant hazards and comments on special handling, which may include the need for specific glove types, storage conditions, special cleanup considerations, and known incompatibilities to be avoided. As seen in Table 3, this is done for both hazardous and nonhazardous chemicals. For example, $NaBH_4$ is corrosive, potentially flammable in moist air, and should be quenched prior to disposal, while sodium chloride (NaCl) is nonhazardous and requires no special handling. *Tert*-butyllithium (*t*-BuLi) is pyrophoric and catches fire in air, so it requires handling in an inert atmosphere while anhydrous methanol (MeOH) is flammable and should be kept away from ignition sources.

Researchers completing the ISM form should also consider the hazards of the chemical reaction itself. When balancing a chemical equation, it may have been determined that a gas may form, causing overpressurization concerns. It is also important to look at the potential hazards of disposal. Oftentimes, starting materials in a reaction may not be fully consumed or the final product may need special treatment prior to disposal. The hazards of the materials to be disposed of, container types, and waste compatibilities must all be considered. This information may also be documented in the section of the ISM form focused on analyzing potential failure modes.

Incompatibilities between the intended chemicals and the equipment being used must also be considered. Researchers should be aware of experiments happening in shared equipment and know how possible cross contamination might lead to unintended consequences. Consider a gas manifold (Schlenk line) with a solvent trap. If one researcher performs a reaction and collects ammonium in the trap and a second researcher uses the same setup and collects hydrochloric acid in the same trap, then an unintended acid−base reaction occurs, creating an unsafe environment. It is important to also consider and plan the best route for communication when working in a shared space. This is typically discussed in person, so it is not always captured on the ISM form. However, it is still a vital part of the ISM process.

Beyond chemical hazards, researchers must be aware of the physical hazards involved in their research. It is common in laboratories to see pokes from needles, burns from hot plates, cuts from removing tubing from glassware, lacerations from razor blades, and more. Inexperienced researchers who are learning about working in a laboratory in addition to learning chemistry are encouraged to document those hazards here, as well as in the section on implementing controls.

Identify Failure Modes and Plan Responses

This section of the ISM form gives researchers an opportunity to brainstorm what could go wrong in their procedure, identifying where and how the reaction could cause harm, and planning a response ahead of time. Researchers learn where emergency equipment is located, how to use it, and when to seek professional emergency services for help. Industrial laboratories often use what is called a Failure Modes and Effects Analysis (FMEA)[23] when evaluating how a process might fail, which can be anything from repairing equipment to running a chemical reaction. The FMEA identifies where a

Table 4. Sample Table of Failure Modes Describing What Could Go Wrong, How to Prevent the Problem, and What Response Will Be Followed if Prevention Methods Fail

What could go wrong?	How to prevent the problem?	Response if this problem occurs?
$NaBH_4$ catches fire when in contact with water (moist air)	handle under inert atmosphere	evacuate the lab, pull fire alarm and dial 911. If fire is small and contained, a class D fire extinguisher may be used.
	limit time in air	
	quench with methanol prior to disposal in flam can	
contact with skin causes irritation	wear nitrile or rubber gloves	immediately and thoroughly rinse with water for 15 min, dial 911

system might fail and determines what the impact would be. This process is simplified in the ISM form, and a table is used to document the potential failure modes. This table asks what could go wrong, how the problem might be prevented, and what will be the response if hazard prevention fails. In the example below (Table 4), if $NaBH_4$ makes contact with water or moist air it can potentially catch fire. This fire might be prevented by handling the material under inert atmosphere. However, if a fire does occur, the researcher will respond by evacuating the laboratory and contacting emergency services. If trained and within the scope of what is allowed by the institution, the researcher might also use an appropriate fire extinguisher to extinguish a small fire. The second example in the table is in regards to a known skin irritant. It is noted that skin irritation may occur upon contact, which may be prevented by using rubber or nitrile gloves. If contact does occur, the researcher knows from this planning process to rinse with water for 15 min and contact emergency services. Please note that Table 4 lists calling 911 as the emergency phone number because this is what is done at the Molecular Foundry. Your own institution may have a different number in their emergency response plans.

IMPLEMENT CONTROLS

Obtain Required Authorizations and Training

In the United States, the Occupational Health and Safety Administration (OSHA) has an established standard for laboratories that perform science at nonproduction scales.[24] This laboratory standard (29 CFR 1910.1450) requires that all researchers are aware of the hazards in their workplace and that workers are protected from chemical exposure.[25] Every institution develops educational methods to inform people of workplace chemical hazards in addition to developing site-specific training. At the Molecular Foundry, all work is authorized through a Work Planning and Control system, which is a database that lists work activities (i.e., chemical synthesis) and ties activities to specific hazards (i.e., pyrophoric chemicals, biologics, pressure systems, etc.). Some hazards require specialized training to both inform researchers of potential harm and to ensure the work is done safely. This training is delivered either through prerecorded online classes or on-the-job training. Every workplace, university, and national laboratory has their own set of training policies and guidelines that researchers must follow.

Including a list of the common activities for the laboratory and required training on the ISM form with check boxes has been found to be the most effective means of determining what training requirements must be met prior to starting the planned reaction. Researchers complete the ISM form, learn about the hazards in the process, and may then check the boxes next to the training that must be completed before the supervisor approves the work. The ISM form for chemical synthesis is nearly identically for all fields of chemistry within our institution. However, there are noticeable differences in this section of the ISM form for different fields of chemistry because some processes are not relevant to everyone. For example, inorganic chemists do not typically need to worry about handling biological samples, and organic chemists are not dealing with heavy metals. Small laboratories and educational institutions may have less strict training and documentation requirements. However, there are a few important points to highlight when planning chemical reactions to ensure a safe work environment. Researchers must be trained to recognize the hazards in their workspaces. This is an important aspect of on-the-job training, where a class with a test may not capture the specific hazards in the relevant lab space. Researchers must complete the minimum training requirements of their institution and be given in-person instruction on proper chemical handling. On-the-job training is an important step, where a supervisor or more experienced researcher may observe chemical handling skills and determine whether or not a researcher is competent enough to work independently. Proving competency may involve answering questions about identifying laboratory hazards, being directly observed handling chemicals, or performing a chemical reaction safely under supervision.

Researchers using an ISM form should also be aware of the engineered controls that are important and often overlooked. PPE should be the last line of defense, intended to protect researchers when other controls have failed. Chemistry laboratories typically have access to fume hoods and local exhaust available for protection. Blast shields can be used in case of an explosion. Chemical reactions can also be engineered to be safer, reducing scale or substituting hazardous chemicals for nonhazardous or less hazardous options. The engineering controls are tied to the location of where the work will take place and should be documented on the ISM form.

Establish Triggers for Reevaluation

When a researcher is performing chemistry and recognizes a need to go beyond the established limits discussed on the ISM form, it is considered a trigger for reevaluation. The ISM form requires researchers to list allowed ranges and limits in which they are authorized to work, and the need to go beyond these limits triggers the need to stop work and reevaluate. Triggers include but are not limited to temperature ranges, reaction scale, chemical substitutions, equipment size, change in containment, and cell cultures. In order to make changes to the ISM process, the researcher must perform a hazard assessment of the changes and have a new discussion with the supervisor to determine whether authorization will be given to proceed with the changes. This method of using triggers allows workers the opportunity to work independently and safely in the laboratory, while assuring the supervisor that the researcher understands the hazards and allowed scope of work.

This section of the ISM form is starred in the subheading in order to stress how critical this process is to maintaining a safe laboratory environment. In fact, this section is often moved to the top of the form and is the last component completed to ensure that the limits are not overlooked in the planning process. Exploratory chemical research is an educational experience and it is well-known that people develop and improve their skills when given freedom to learn independently.[26] However, there must be limits set in order to ensure worker safety. This is especially true for new researchers and students who lack experience.

Perform Planned Chemical Reaction

After completing the ISM form and gaining authorization to work, the chemical reaction may proceed. Though the hazards have been analyzed and thoroughly discussed, it is important to be constantly questioning and reevaluating the full process, especially with regard to safety. Workers should not ignore the potential hazards upon completing the form and must always be aware of what could go wrong. Researchers are expected to make note of how the reaction proceeds and to recognize when reaction behaviors are different than anticipated. If a problem is observed, it is important that the researcher immediately stops the work and reevaluates the project. There is always the risk that something could go wrong, regardless of how well hazard assessments have been done. Even if working within the established triggers for reevaluation, a new assessment and discussion with the supervisor is required if at any point the reaction raises questions about safety.

Purify Material and Manage Disposal

Upon completion of the chemical reaction, researchers are expected to follow the purification and waste procedures that were outlined in the scope of work section of the ISM form. Again, if safety concerns or a desire to work outside of the established triggers occur at this stage of the process, the researcher is required to open a dialogue with the supervisor.

■ FEEDBACK AND IMPROVE

Evaluate Reaction Outcome

Upon completion of the reaction, it is important to evaluate how the full process went. This involves analyzing the final material to ensure that the right product was formed, looking at whether any expected or unanticipated hazards occurred, and determining if modifications should be made if the reaction is to be repeated. If any safety concerns arise, the researcher must contact the supervisor to discuss the concerns and decide what changes need to be made to the project.

Determine if Desired Improvements Exceed Established Triggers

If the worker realizes upon completing a reaction that better results may be achieved by exceeding the established limits in the ISM form, this triggers a need for a new hazard assessment. In our experience, it is very common for researchers to want to explore their chemistry beyond their original limits, such as increasing the temperature, performing a chemical substitution, increasing the reaction scale, etc. Thus, it is important to incorporate these changes and review the full ISM process in order to assess any potential new hazards and establish new triggers for reevaluation.

■ ISM BEYOND TRADITIONAL SYNTHESIS

The use of the ISM form has been invaluable to the safe planning of reactions at the Molecular Foundry, and hundreds of researchers have participated. The process has expanded beyond chemistry and biology laboratories. Our multidisciplinary facility includes the National Center for Electron Microscopy (NCEM), which now uses their own version of the ISM form for cutting-edge imaging experiments.

Electron microscopy is typically performed on nanoscale samples in the solid-state, which are mostly nonhazardous. The samples are normally prepared a day in advance, often in a separate lab, and at the end of the experiment, the samples are retrieved by the user and stored for future use. Unlike what is found in chemistry and biology laboratories where chemical reactions are being performed, the operating protocol in most microscopy laboratories assumes sample handling and disposal will not be of significant concern. However, as the field has evolved, microscopists have increased the scope of their experiments. Liquid cell microscopy and air-free microscopy have necessitated the need for ISM evaluations.

Liquid cell microscopy normally involves sandwiching a tiny droplet of solution (~1−5 nL) between two substrates. When performing these experiments, scientists often come to the lab with a significantly larger volume of solution (up to ~100 mL) than what is needed for their measurements, which poses new safety concerns. Furthermore, parameters such as pH, salt concentration, and the vapor pressure of the liquid are critical in predicting any adverse outcome, which may arise when the liquid specimen is loaded onto a sample holder and transported into the microscope. The choice of the appropriate sample holder for the chemistry of the liquid being studied is an additional concern.

Similarly, air-free microscopy of air-sensitive samples, such as lithiated battery electrodes, involves the use of a glovebox and dedicated sample holders. In such cases, it is critical to consider the chemical compatibility of the specimens being studied, as well as their physical properties. For instance, some samples outgas and cross contaminate specimen holders, others may be so brittle that they turn to powder when transported into a pressurized glovebox. Additionally, most air-sensitive chemicals are also very reactive, and normal precautions when handling reactive materials must be followed at all times during such experiments. All of these aspects must be considered by researchers in advance of their experiments in addition to reading the SDS of any associated chemical being used. Even though these experiments involve no chemical reactions, there are compatibility concerns arising from potential cross contamination. An increase in overall sample size (from nanoscale to macroscale) creates new hazards, which are constantly monitored and reevaluated within the scope of the ISM.

Users are asked to list all parameters in a Scope Authorization Form, NCEM's version of the ISM form for synthesis, which narrowly defines the scope of work they are undertaking. This form is then reviewed by the lab scientists before work is authorized. Any change in materials being used, in terms of chemistry or volume, triggers the need for a reevaluation of the protocol and the submission of a new Scope Authorization Form. The process of assessing the chemical hazards, establishing limits or triggers for reevaluation, and the requirement to continually evaluate and improve are the same for microscopists as they are for chemists, making the ISM form for laboratory experiments extremely versatile.

In conclusion, the Molecular Foundry has developed an ISM form for chemical synthesis that has been used in multiple fields of chemistry, Inorganic, Organic, and Biological, and has been modified for microscopy work. The document follows DOE's ISM process, which asks workers to define the scope of work (identify the full reaction process and needed resources), analyze the hazards (identify areas of concern, failure modes, and create a response plan), implement controls (complete training and establish triggers/limits), perform the work (conduct the experiment), and get feedback and improve (assess the reaction results and determine if changes will exceed allowed limits). This process has fostered continual safety conversations between workers and their supervisors. It has helped students and researchers to better understand the safety aspects of their work and what they are authorized to do and has given those working in the laboratory more independence. It is hoped that outlining the ISM process we use for chemical reactions will help provide guidance to others who wish to improve the chemical safety conversations in their own institutions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.3c00017.

Blank ISM form used at the Molecular Foundry (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kemsley, J. N. Learning From UCLA. *Chem. En. News* **2009**, *87* (31), 29−34.

(2) Banken, M. J. *Investigation Of Schweitzer Hall Explosion Complete | News Bureau, University Of Missouri*; New Bureau (University Of Missouri), 2010. Https://Munewsarchives.Missouri.Edu/News-Releases/2010/0709-Investigation-Of-Schweitzer-Hall-Explosion-Complete/ (accessed 2022-02-28). Kemsley, J. Research Lab Explosion Injures Four People. *Chem. Eng. News* **2010**.

(3) Kemsley, J. N. Texas Tech Lessons. *Chem. Eng. News* **2010**, *88* (34), 34.

(4) *Texas Tech University Laboratory Explosion*; U.S. Chemical Safety and Hazard Investigation Board, 2011.

(5) Benderly, B. L. Report On UH Lab Explosion Reveals Deep, Systemic Safety Failures. *Science* **2016**.

(6) Keju, W. Negligence Blamed In Deadly Laboratory Explosion On Campus. *China Daily* **2019**.

(7) Silver, A. Fatal Lab Explosion In China Highlights Wider Safety Fears. *Nature* **2022**, *601* (7892), 176−177.

(8) Chen, C.; Reniers, G. Chemical Industry In China: The Current Status, Safety Problems, And Pathways For Future Sustainable Development. *Safety Science* **2020**, *128*, 104741. Staehle, I. O.; Chung, T. S.; Stopin, A.; Vadehra, G. S.; Hsieh, S. I.; Gibson, J. H.; Garcia-Garibay, M. A. An Approach To Enhance The Safety Culture Of An Academic Chemistry Research Laboratory By Addressing Behavioral Factors. *J. Chem. Educ.* **2016**, *93* (2), 217−222. Ayi, H.-R.; Hon, C.-Y. Safety Culture And Safety Compliance In Academic Laboratories: A Canadian Perspective. *J. Chem. Health Saf.* **2018**, *25* (6), 6−12.

(9) Ezenwa, S.; Talpade, A. D.; Ghanekar, P.; Joshi, R.; Devaraj, J.; Ribeiro, F. H.; Mentzer, R. Toward Improved Safety Culture In Academic And Industrial Chemical Laboratories: An Assessment And Recommendation Of Best Practices. *ACS Chem. Health Saf.* **2022**, *29*, 202.

(10) Pollet, P.; Cunefare, K. A.; Davis, D. J.; Lisk, R.; Nair, S.; Alford, T. Academia-Industry Partnership For R&D Safety Culture: The Partners In Lab Safety (PALS) Initiative. *ACS Chem. Health Saf.* **2022**, *29* (1), 79−86. Huston, E. M.; Milligan, J. A.; Powell, J. R.; Smith, A. M.; Neal, D.; Duval, K. M.; DiNardo, M. A.; Stoddard, C.; Bell, P. A.; Berning, A. W.; Wipf, P.; Bandik, G. C. Development Of An Undergraduate Course In Chemical Laboratory Safety Through An Academic/Industrial Collaboration. *J. Chem. Educ.* **2018**, *95* (4), 577−583.

(11) Finster, D. C. RAMP: A Safety Tool For Chemists And Chemistry Students. *J. Chem. Educ.* **2021**, *98* (1), 19−24. Finster, D. C.; Jackson, P. Comprehensive Undergraduate Safety Instruction. *J. Chem. Educ.* **2021**, *98* (1), 39−44. Willey, R. J.; Carter, T.; Price, J.; Zhang, B. Instruction Of Hazard Analysis Of Methods For Chemical Process Safety At The University Level. *Journal Of Loss Prevention In The Process Industries* **2020**, *63*, 103961.

(12) Weitzman, D. *Integrated Safety Management Policy - DOE Directives, Guidance, And Delegations*; U.S. Department Of Energy, 2011. https://www.directives.doe.gov/directives-documents/400-series/0450.4-APolicy-a (accessed 2020-12-14).

(13) Ambrosi, A.; Chua, C. K.; Bonanni, A.; Pumera, M. Lithium Aluminum Hydride As Reducing Agent For Chemically Reduced Graphene Oxides. *Chemistry Of Materials* **2012**, *24* (12), 2292−2298.

(14) Schlesinger, H. I.; Brown, H. C.; Finholt, A. E.; Gilbreath, J. R.; Hoekstra, H. R.; Hyde, E. K. Sodium Borohydride, Its Hydrolysis And Its Use As A Reducing Agent And In The Generation Of Hydrogen. *J. Am. Chem. Soc.* **1953**, *75* (1), 215.

(15) Martelli, P.; Caputo, R.; Remhof, A.; Mauron, P.; Borgschulte, A.; Züttel, A. Stability And Decomposition Of $NaBH_4$. *Journal Of Physical Chemistry C* **2010**, *114* (15), 7173−7177.
(16) Hendershot, D. C.; Sarafinas, A. Safe Chemical Reaction Scale Up. *Chem. Health Saf.* **2005**, *12* (6), 29−35.
(17) Yang, C.; Wang, T.; Muzzio, D. J.; Cleaf, S. V.; Phillips, E. M.; Fine, A. J.; Vickery, T. P.; Kalinin, A.; Dalby, S. M.; Furman, T. R.; Flessner, R.; Rosario, A.; Zhao, R.; Roth, M. Safety Assessments Supporting Scale-Up Of Chemistry Involving Hydrogen. *Org. Process Res. Dev.* **2021**, *25* (8), 1979−1987. Rossetti, I.; Compagnoni, M. Chemical Reaction Engineering, Process Design And Scale-Up Issues At The Frontier Of Synthesis: Flow Chemistry. *Chem. Eng. J.* **2016**, *296*, 56−70.
(18) Banaee, S.; Hee, S. S. Q. Glove Permeation Of Chemicals: The State Of The Art Of Current Practice, Part 1: Basics And The Permeation Standards. *J. Occup Environ. Hyg.* **2019**, *16* (12), 827−839.
(19) Lindstrom, M.; Fucillo, J.; Hernandez, F.; Herrick, D.; Ide, S.; King, A.; Liberman, R.; Malconian, S.; Miele, M.; Petricone, D.; Ranken, E.; Wetzel, S. Improving Lab Coat Selection, Use, And Care: Lessons Learned From One University's Comprehensive Lab Coat Initiative. *J. Chem. Health Saf.* **2015**, *22* (6), 3−9.
(20) Mcpherson, D. Balancing PPE Protection With Comfort, Fit & Style. *Professional Safety* **2008**, *53* (3), 50−52.
(21) Urben, P. G. *Bretherick's Handbook Of Reactive Chemical Hazards*; Academic Press, 2006.
(22) Eastlake, A.; Hodson, L.; Geraci, C.; Crawford, C. A Critical Evaluation Of Material Safety Data Sheets (Msdss) For Engineered Nanomaterials. *J. Chem. Health Saf.* **2012**, *19* (5), 1−8. Kolp, P.; Sattler, B.; Blayney, M.; Sherwood, T. Comprehensibility Of Material Safety Data Sheets. *American Journal Of Industrial Medicine* **1993**, *23* (1), 135−141.
(23) Hendricks, C.; Williard, N.; Mathew, S.; Pecht, M. A Failure Modes, Mechanisms, And Effects Analysis (FMMEA) Of Lithium-Ion Batteries. *Journal Of Power Sources* **2015**, *297*, 113−120. Jiang, Y.; Jiang, H.; Ding, S.; Liu, Q. Application Of Failure Mode And Effects Analysis In A Clinical Chemistry Laboratory. *Clin. Chim. Acta* **2015**, *448*, 80−85.
(24) *Laboratory Safety Guidance*; Occupational Safety And Health Administration, 2011; Vol. *3404−11R*.
(25) *1910.1450 - Occupational Exposure To Hazardous Chemicals In Laboratories*; Occupational Safety and Health Admin., Labor, 1991.
(26) Lyall, R. J. Practical Work In Chemistry: Chemistry Students' Perceptions Of Working Independently In A Less Organised Environment. *Chem. Educ. Res. Pract.* **2010**, *11* (4), 302−307. Cukurova, M. An Investigation of an Independent Learning Approach in University Level Chemistry: The Effects on Students' Knowledge, Understanding and Intellectual Attributes. PhD Thesis, University Of York, 2014.

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