What’s in That Medicine: An Inquiry-Based Activity to Introduce Medicinally-Active Natural Products and Metals

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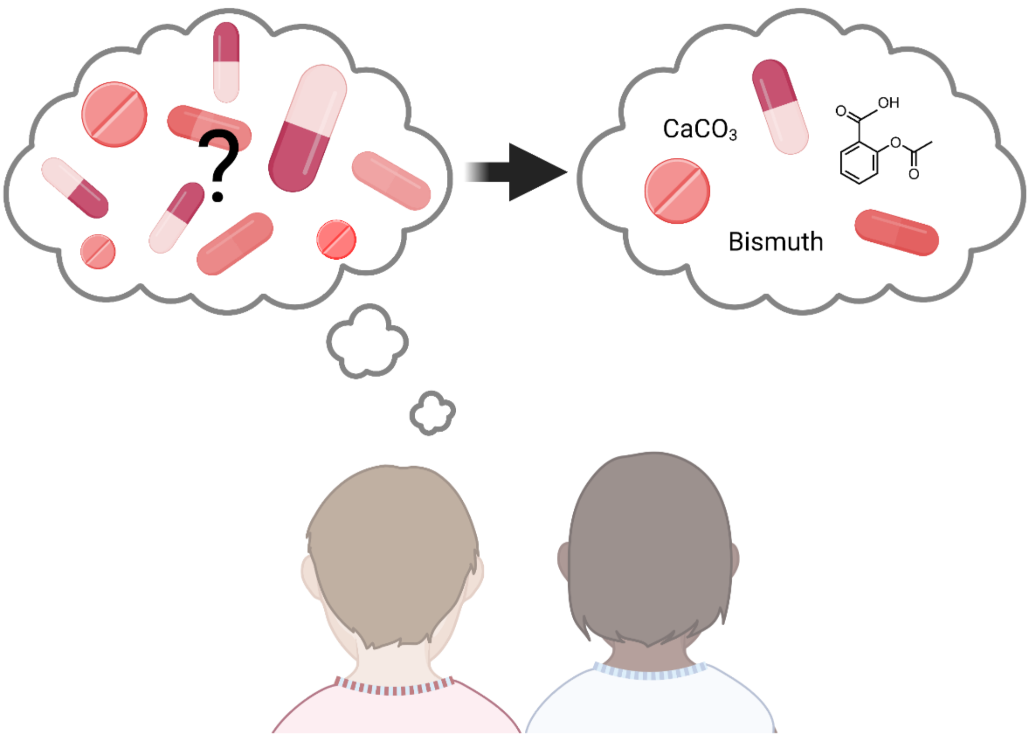
Abstract

Common over-the-counter medicines can be an exciting entry point for introducing students to the interesting chemistries that they encounter in their daily lives. In this inquiry-based activity, students are tasked with using a list of given supplies and information about four medications (Aspirin, Tums, Pepto-Bismol, and Tylenol) to design three experiments that will enable them to identify which mystery substance is which medication. This activity introduces students to several chemical concepts, including acid-base reactions, redox reactions, and chelation. Overall, comparing results of pre- and post- activity assessments, students learned about and became more confident in their knowledge of how natural products and metals can be used in medicine and were able to correctly identify their unknown medications. Additionally, a procedure-based activity for extracting bismuth from Pepto-Bismol is included.

GRAPHICAL ABSTRACT



KEYWORDS

High school/Introductory Chemistry, Public Understanding/Outreach, inquiry-Based/Discovery Learning, Consumer Chemistry, Drugs/Pharmaceuticals, Metals, Acids/Base, Natural Products

INTRODUCTION

Science classrooms and laboratories should continually strive to incorporate real-life scenarios that are relevant, interesting, and important to students. Integrating chemical concepts with real-life knowledge will improve science literacy, promote critical thinking, and encourage informed decision-making outside of the classroom. Laboratory lessons that revolve around medicine and pharmacology are ideal topics for developing real-life laboratory scenarios because they 1) call upon nearly universal experiences in taking medicines—enabling educators to reach a diverse student audience, 2) provide a foundation for finding and understand basic health information to make appropriately informed decisions, and 3) can initiate interest in health and pharmacology as a future area of study for students.[1-4]

Students may range in their familiarity with organic chemicals being used as drugs in their everyday medication, but most do not have appreciation for drug discovery, production, and analysis (*e.g.,* method development, quality control, statistical analysis), or how these medicines provide therapeutic benefits.[1] In addition to developing laboratory skills and understanding drug development, lessons around medicine also provide an opportunity for educators to address commercialization of science and have early discussions about social justice in medicine.[2, 5]

Inquiry-based learning has been shown to increase student knowledge and skills over traditional methods.[6] In traditional laboratory activities, students follow given instructions, which are often quite detailed, to get to a defined end. In contrast, with inquiry-based strategies students are responsible for integrating information and developing their own hypothesis, experimental design, and problem solving approaches. Inquiry-style activities are recognized as the best method for teaching the scientific method as the learning process is similar to laboratory-based investigations. Discussion and discovery with peers helps students to create new knowledge together, verbalize their explanation, and promotes collaborative behavior.[7] Inquiry-style laboratories do require more hands-on interactions with students, which may not be possible for every instructor due to limited instructor-to-student ratios. Inquiry-based activities can be more difficult to organize because they require more development, additional resources, and increased initial preparation in coaching students on how to best engage with non-traditional activities.[8-10]

Pepto-Bismol is the most-sold stomach relief remedy in the USA with over 20 million units sold in 2019. Despite such prevalence, the structure of the active ingredient, bismuth subsalicylate, has only recently been fully elucidated.[11] Bismuth has been the topic of other laboratory activities because of its unique and significant metal content.[12] There are some published traditional laboratory activities that address pharmaceuticals, although many are not suitable for high school students due to their need for specialized equipment,[3, 13, 14] and few address metals in medicine.[15]

The inquiry-based activity described herein evolved from an adapted traditional lab activity where students were given step-by-step instructions to isolate and quantify the amount of bismuth metal in Pepto Bismol.[16] (See Supplemental Information) The inquiry-style lab activity was designed to enable students to observe and discover the chemical differences between four commonly used over-the-counter pharmaceuticals: Pepto-Bismol, Aspirin, Tylenol, and Tums. Pepto-Bismol and Tums are typically taken to relieve symptoms of an upset stomach and Aspirin and Tylenol are common NSAID pain relievers. The key aspects in differentiating the pharmaceuticals that the students are tasked with is the presence of salicylic acid (Pepto-Bismol and Aspirin), calcium carbonate (Tums and Pepto-Bismol), and bismuth (Pepto-Bismol only). Tylenol contains none of these and will be non-reactive. Examining these differences introduced students to the concepts of acid-base reactions, coulometric assays, and redox reactions in an interactive and adaptable activity.

MATERIALS FOR THE ACTIVITY

Equipment and Chemicals

- One bottle each of: Aspirin, Tums (original or berry flavored), Tylenol, Pepto-Bismol
- Four 50 mL conical tubes or similar, sealable container
- Mortar and pestle
- Red food coloring
- Aluminum foil
- Small test tubes (glass or plastic)
- Disposable pipets
- Wooden stir rods
- Plastic scoopulas
- pH strips
- 70% ethanol in water solution
- 1 M aqueous HCl (pH 0)
- 1 M aqueous NaOH (pH 14)
- 5% aqueous iron (III) chloride
- Squeeze bottles

Note: Generic medicines are equally effective. Advil (ibuprofen) is a good replacement for Tylenol.

Preparation of Unknowns

All medicines used in this activity were purchased in tablet form. Dosage and use of generic brands do not impact this activity. It is important not to use children's Pepto-Bismol, as some of these formulas lack bismuth and only contain calcium carbonate as the active ingredient. To prepare the four medications to be the unknowns for this activity, it is important that they are all similar in color and appearance. Use a mortar and pestle to grind each medication individually to a fine powder.

Transfer the powder to a sealable container and add red food coloring several drops at a time. Seal the tub and vigorously shake, continue adding the food coloring until the powder is a consistent pink color and of similar intensity across all unknowns. (Note: some students could still identify the characteristic color of Pepto-Bismol, so addition of food coloring to Pepto-Bismol is still advised.) Divide the powdered medicine into conical tubes, marking each tube as Unknown A-D and keep an instructor's key.

SAFETY AND HAZARDS

Safety goggles and gloves should be worn for the entire duration of the activity. Participants should review safety measures at the beginning of the activity as part of the activity presentation. This activity requires the use of 1 M hydrochloric acid and 1 M sodium hydroxide. Acids and bases are corrosive and should be handled carefully. The use of squeeze droppers to minimize exposure to skin is recommended. If this activity is done with younger students (K-8), it is recommended that only the instructor handles the acids and bases. At the conclusion of the activity, acids and base solutions should be neutralized and disposed of following local health and safety guidelines. The pharmaceuticals used in this activity, while over-the-counter, can have side effects if ingested. Instructors should carefully monitor the "unknown" samples and remind students not to taste them.

DISCUSSION

This activity was conducted with high school students during the University of Minnesota's Discover STEM program. This is a group of rising high school juniors and seniors who are interested in STEM disciplines and are generally high achieving (**Figure S1**). The first implementation of the activity was a traditional lab-based experience that focused students on extracting and quantifying the amount of bismuth metal from Pepto-Bismol tablets (see Supporting Information). While students were successful at purifying the bismuth in the allotted 1-hour period, we were interested in making the activity more engaging and impactful. Therefore, we designed the described inquiry-based activity, which connected student learning with multiple pharmaceutical agents (see Supporting Information).

The activity begins with a short introduction presentation. The purpose of this presentation is three-fold. First, it introduces students to a brief history of how humans have used both natural products and metals as medicine. Second, it sets the stage for the activity. Students are given the role of pharmacists at a specialty compounding pharmacy. Their specialty: making boutique pink medications! Their technicians just finished making pink batches of Aspirin, Tums, Tylenol, and Pepto-Bismol, but did not take care to indicate which medicine was which. It is up to them, as the head pharmacist, to use their chemical knowledge of each medication to properly identify each batch. (Note: students are also given a disclaimer that this is a purely fictional scenario and all real compounding pharmacies have strict protocols in place including the use of unique, identifiable pill forms to ensure such a mix up does not occur.) The students then review their knowledge of each of the medicines, which is also available to them on their individual hand out for later review. Finally, the presentation covers important safety information for the proper handling of chemicals, first aid procedures, and required PPE.

The laboratory was designed to be conducted in 1-hour lab period and students were encouraged to work in pairs using the "think-pair-share" method.[17] Instructors walked around the room and asked each pair about their hypothesis and the design of their tests to differentiate the four unknown medications. The instructors were encouraged to direct students back to the provided information and lead a discussion about ideas, instead of supplying answers.

Through discussion and use of their provided handouts, the students should come up with variations of three basic tests. The first, to determine which unknowns contain the base calcium carbonate, using the provided acid to observe formation of bubbles indicating the release of gas. The second, to use the provided Fe^{3+} solution to determine which samples contain salicylic acid. With their handout, students should come to realize that all samples should be treated with acid first to free the salicylic acid from complexation with bismuth. Third, the use of aluminum metal to precipitate out bismuth metal. The precipitated bismuth is most readily visualized after the insoluble portions are allowed to settle in the tubes to not obscure the formation of the black solid. This reaction may take one minute to become clear (**Figure 1**).

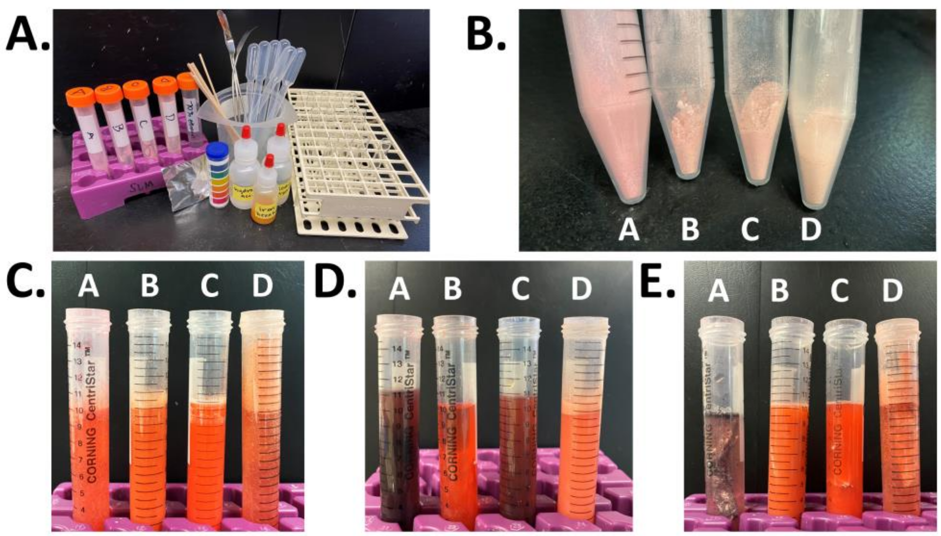


Figure 1: Experimental materials and results. A) The materials used for the experiment. B) The four unknowns in similar, powder form. Note: All unknowns were provided in roughly the same quantity. Unknown A (Pepto-Bismol) clung to the sides of the conical tubes. C) The four unknowns in acidic solution. Unknown A produces some bubbles and Unknown D produces numerous bubbles when dissolved in acid. D) The four unknowns in the presence of Fe^{3+}. Unknown A produces substantial purple color and Unknown C produces a moderately purple color. D) The four unknowns in the presence of acid and aluminum foil. Only Unknown A produces a black solid. The identity of the unknowns is A: Pepto-Bismol, B: Tylenol, C: Aspirin, D: Tums.

Assessment/Learning Outcomes

Student learning outcomes and evaluations were assessed through nearly identical surveys administered before and after both the traditional and inquiry-based activities (see Supporting Information). Analysis of pre- and post-survey data from both activities (traditional and inquiry-Based) are included below to examine if there were significant changes in outcomes. Students labeled their surveys with unique identifiers so that individuals could be tracked while keeping responses anonymous and encouraging honesty. Surveys included requests for minimal demographic information. Surveys contained free-response questions (1–3) and multiple-choice questions (4 and 5), followed by a request for students to rate their confidence in each answer. Confidence questions asked students to rate their confidence in their answers on a scale of 1 to 5. In the post-activity assessment, students were also asked to rank their understanding of the material, interest in the material, and the level of difficulty of the activity on a Likert scale (1 to 5). This study met the criteria for Institutional Review Board exemption.

Learning Gains

Student responses were categorized as correct (expressing understanding) or incorrect. For both the traditional and inquiry-based activity groups, students exhibited significant learning gains in nearly all questions (**Figure 2**). Question 2 asked students to give an example of a metal used in medicine or healthcare—a broad question which allowed for many technically correct answers. Understanding of the source of FDA approved drugs (question 1) was taught in the pre-activity lecture. Understanding of reduction potential was also addressed in the lecture and implemented in the activity (question 5). Learning gains tested in questions 3 and 4 were taught in the activity and tested students' ability to know the difference between drugs and their chemical identities. Student learning gains were generally comparable across activity styles (traditional vs inquiry-based). Students in the

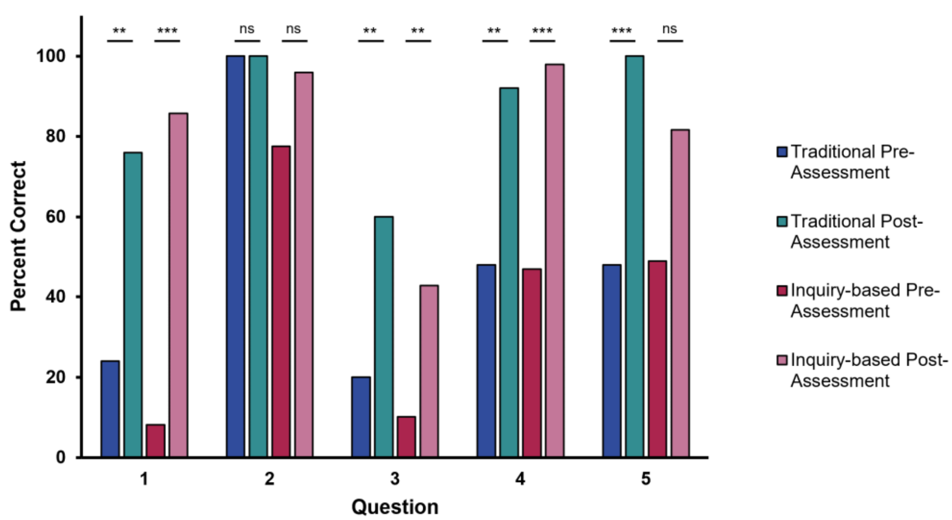


Figure 2: Percentage of students that answered each question correctly. Traditional $N = 25$; Inquiry-based $N = 49$. Significance was determined by a X^2 test where * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

inquiry-based lab struggled more with question 3, which asked them to conclude and recall complicated chemistry concepts and words from the activity. Inquiry-based learning requires the learner to generate their own knowledge, which may have been more difficult for students in this cohort.

Confidence Gains

Students had significant gains in their confidence across all questions (**Figure 3**). Even though there was no significant increase in accuracy for question 2 after the activity, there were significant gains in the confidence in their answers. In general, students had the least confidence in their answers to question 3 (about the difference between Pepto-Bismol and Tums), which may be due to the complexity of the question and the free response question design (**Figure S2**). There was no statistically significant difference in confidence gains between students who learned from the traditional or inquiry-based activities (**Figure 3**). The only difference in confidence gained between students in the traditional and inquiry-based activities revealed by the post-assessment was in

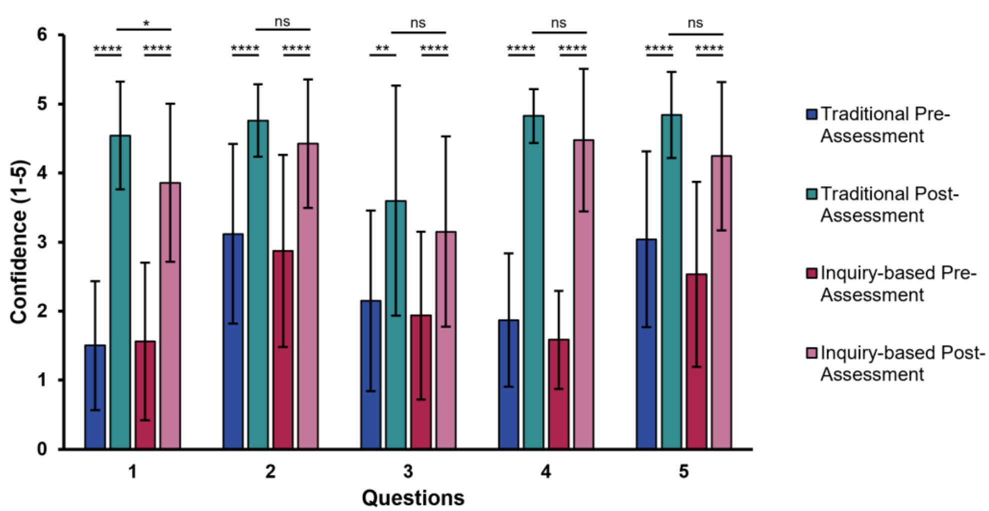


Figure 3: Student confidence for each question. Traditional *N* = 25 ; Inquiry-based *N* = 49 although if a student neglected to rank confidence in either pre-or post-assessment then their ranking for that question was taking out of consideration. Two statistical tests for significance were performed. First, statistical significance of confidence differences within an assessment group was determined by a paired t-test. Second, statistical significance of confidence differences between post-assessment groups was determined by an unpaired t-test, where * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

question 1, which is surprising as this learning outcome had been taught in lecture–not the activity. This may indicate differential lecture delivery or additional discussion in the traditional student group.

Confidence has been correlated with students' ability to perform well on exams, although there are negative consequences for over confidence in the classroom.[18, 19] We did notice a correlation between confidence and learning gains, which was strengthened after the activity (**Figure S3**). This indicates an improvement in metacognition around the test material. There were no statistically significant differences in confidence gained between pre- and post-assessment in self-identified male and female participants (**Figure S4**). Research has suggested that men report higher confidence when answering questions, but in our activity both groups made significant improvements in confidence and were not statistically different from each other.[20]

Reflections/evaluations

Students rated the activity favorably across both activity styles in both understanding and interest in learning about medicines through the activity (**Figure 4a, b**). The majority of students ranked the difficulty of the activity as "appropriate" (**Figure 4c**). Students who participated in the inquiry-based activity were more likely to find the activity difficult than those who participated in the more traditional, protocol activity design, which may have in turn affected their interest in the activity. Students reported that they were happy to witness the variety of chemical reactions that occur in the activity (color change, bismuth precipitation) and be trusted to independently plan their research experience (**Figure S5**). Students shared that they wished for more introductory information and

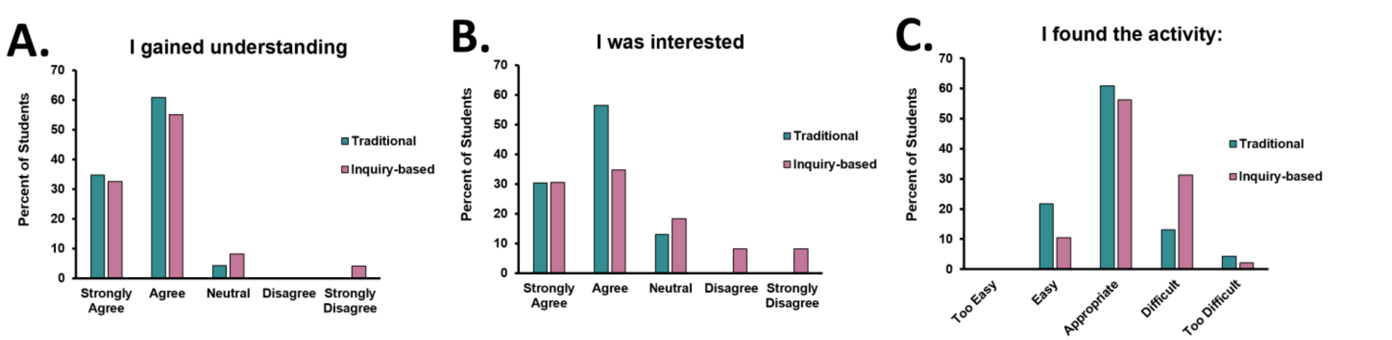


Figure 4: A) Student agreement with the activity increasing understanding and B) Student agreement with the activity increasing interest. C) Student ranking of the difficulty of the activity. Traditional $N = 25$; Inquiry-based $N = 49$.

would have been interested in handling other medications. Finally, students were happy to learn more about everyday items and handle the materials in atypical ways.

Conclusion

Here we report a new laboratory activity for students to engage with chemistry concepts like solubility, acid-base chemistry, colorimetric assays, and redox reactions using everyday items. This activity could be expanded to teach other chemistry lessons like gravimetric analysis,[12] equilibrium, bioavailability, crystallinity and crystal growth,[21] electrolysis, color,[22] and other medicinal chemistry topics.[23] Investigating common medications encourages students to reflect on content of medications, encourages critical thinking about health decisions, and promotes implementing problem-solving strategies. This laboratory activity enables students to design their own experiments to solve a medicine mystery. Students were able to successfully identify the each of the four unknown medicines based on their integration of provided chemical information. Student assessments show significant increases in student learning gains and confidence in the material. Students also expressed interest in the usage of natural products and metals in medicine.

Although our data suggests there is not a significant increase in learning gains with the inquiry-style activity over the traditional, protocol-driven activity, or vice versa, anecdotally, students engaged in more active discussion during the inquiry style laboratory. The goal of this comparison was not to call into question the validity of either model, but to illustrate the transition from a traditional lab activity to an inquiry-based activity did not negatively impact understanding. The differences in perceived difficulty between the traditional and inquiry-based activity suggest that prior experience with inquiry based activities or collaborative learning techniques could better prepare students for this activity. This is an activity which requires little to no previous chemistry experience to introduce students to the chemical basis of common medications and actively engage in the scientific method. Furthermore, it can be easily modified by the addition or removal of different medications to change the age level appropriateness or accommodate different learning goals.

ASSOCIATED CONTENT

Supporting Information

Compiled Supporting Information includes supplementary figures, the student handouts for both the inquiry based activity and traditional activity, and the student survey. The supporting information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.XXXXXXX. [ACS will fill this in.]

Compiled Supplementary Information (PDF,DOCX)

Activity Introduction Presentation (PDF)

NOTES

The authors declare no competing financial interest.

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ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under Grant No. CHE-2001611, the NSF Center for Sustainable Nanotechnology. The Center for Sustainable Nanotechnology is part of the Centers for Chemical Innovation Program. The authors would like to thank the University of Minnesota- Twin Cities Discover STEM program for the opportunity to be involved in their summer programming in 2018 and 2019. SLM gratefully acknowledges the support of the University of Minnesota's Doctoral Dissertation Fellowship during the development of this work. SLM and EJT would like to thank Natalie Hudson-Smith and Miriam Krause for their support and suggestions. BioRender was used to generate the TOC image.

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