McMaster University Lab Safety		
STANDARD OPERATING PROCEDURE		
Title: Safe Handling of Azides – The Hazards of "Click Chemistry"		
SOP No.:	**Revision No.: 1**	**Effective Date: April/2024**

1.0 INTRODUCTION

Azides constitute a highly reactive and versatile class of chemicals that are commonly used in chemical synthesis, in biomedical research applications and in the materials sciences.[1] Organic azides are especially useful in various types of synthetic conjugations or "Click Chemistry" and are increasing used in coupling reactions with alkynes and strained unsaturated organic materials.[2] Azides (inorganic and organic) possess toxic properties and can be potentially explosive and shock sensitive under certain conditions. Azides require precaution during preparation, storage, handling and disposal.

2.0 SAFETY

In addition to McMaster's mandatory health & safety training, all faculty, staff, students, visitors and volunteers who work with sodium azide, other metal azides, and any azide containing organic material (alkyl or aryl azide) must complete laboratory specific safety training with their supervisor or appropriate designate before handling these materials. Safety Data Sheets (SDS) should be reviewed to identify the specific hazards and necessary precautions and disposal protocols when working with particular azide compounds.

3.0 RELATED DOCUMENTS

3.1 McMaster University Risk Management Manual #100, 102, 300, and 301

3.2 Occupational Health & Safety Act (R.S.O. 1990, cO.1).

4.0 DEFINITIONS/ABBREVIATIONS

Definition/Abbreviation	Meaning
Inorganic Azides	Inorganic azides include commonly used commercial materials, most notably sodium azide. Other inorganic azides may be prepared in the lab via substitution or ion exchange methods. Many inorganic azides are explosive under certain conditions, and should be handled carefully and protected from light, shock, and heat. Azides in contact with metal components can form reactive mixtures. Substitute less reactive materials such as PVC for metal parts and/or metal instruments. Mixtures of inorganic azides and chlorinated solvents should be avoided. Dried mixtures of inorganic azides and organic materials should be considered highly hazardous. Mixing inorganic azides and acids must be avoided. Inorganic azides, such as

	sodium azide, should be purchased in the smallest quantity reasonably expected to be utilised for the current research project. It is often less expensive to purchase larger quantities of inorganic azides but this must be avoided. Experiments should be performed on the smallest scale feasible, often mg scale reactions are sufficient for many applications.
Organic Azides or Azidoalkanes or alkyl azides or aryl azides	Organic azides are often prepared in the laboratory and can be sensitive to violent decomposition from external energy sources such as light, heat, friction, and pressure. Organic azides may also be purchased commercially, often manufactured as the azido-linker component for coupling reactions. The stability of an organic azide is dependent upon its chemical structure, and the guidelines below should be reviewed prior to working with an organic azide. Always consider the *total* number of energetic functionalities ("explosophores") in a compound while making a stability assessment.
SAZ	Sodium azide: CAS Number 26628-22-8
Azidic Acid or Hydrogen azide	Hydrazoic acid: CAS Number 7782-79-8

5.0 BACKGROUND

Inorganic and organic azides are employed in various reaction types. These include but are not restricted to:

a) Substitution reactions. These include S_N2 reactions with alkyl or aryl electrophiles directly or in the presence of transition metal catalysts. These also include ion exchange reactions in conversion of sodium azide to other reactive metallic azides.

b) Azide-alkyne cycloaddition reactions. These are also known as **Click reactions or Huisgen reaction**. These may also be called Bioorthogonal reactions. These reactions can be carried out thermally or with a transition metal catalyst (usually copper).

c) Strain-promoted alkyne-azide cycloaddition, Bertozzi reaction/conjugation, and also as Bioorthogonal reaction.

The following two methods, C/N ratio and Rule of 6, may be used to assess stability of organic azides as a general guide. These considerations are only a guideline and due diligence and consultation with the laboratory supervisor must be carried out before any organic azide synthesis is conducted.

Carbon to Nitrogen Ratio (C/N)

With a few exceptions, the **number of nitrogen atoms should not exceed the number of carbon atoms in an organic azide**. Although some azides that have a C/N ratio between 1 and 3 can be synthesized in small quantities, the azides should be used or quenched as soon as possible. The azides should be stored at -18 °C, and in the absence of light (preferably in plastic amber containers). Concentrations should not exceed 1 M.

Rule of Six

Another method of assessing the stability of an organic azide is the "Rule of Six," which states that there should be no less than six carbons per energetic functional group. *Six carbons (or other atoms of about the same size) per energetic functional group (azide, diazo, nitro, etc.) provides sufficient dilution to render the compound relatively safe.* Less than six carbons per functional group **can result in the material being explosive**.

6.0 PPE REQUIREMENTS

Hand Protection: Appropriate gloves must be worn when handling azides. Nitrile gloves are recommended for handling azides of high toxicity.

Eye Protection**:** Safety glasses (solids) or splash goggles (in solution) must be worn when handling azides.

Skin and Body Protection**:** A lab coat must be worn when handling azides. Blast shields and a fume hood are required for all azides known to be or expected to be explosive (all azides unless data exists to suggest otherwise)

7.0 RULES FOR ALL PROCEDURES INVOLVING AZIDES

1. All reactions involving organic and inorganic azides must be carried out in a fume hood.
2. A blast shield is required for all azides known to be or expected to be explosive (see Carbon to nitrogen ratio and Rule of 6 above).
3. Azides should never be mixed with acidic and aqueous materials. This mixture can result in the formation of hydrazoic acid, which is highly toxic and explosive.[3]

4. Azides should never be mixed with metals as these mixtures can result in the creation of metal azides, which are highly unstable and explosive.

5. Azides should **not** be manipulated using metal utensils (e.g. metal spatulas), as this can result in the formation of metal azides. Do not weigh azides directly onto any metal balance or transfer device. Weigh directly into a glass flask and avoid all contact with ground glass surfaces.

6. Halogenated solvents (such as dichloromethane and chloroform) should never be used as reaction media with azides. Using these materials can result in the formation of di- and tri-azidomethane, which are extremely unstable.

7. All azide containing materials should be considered as sources of highly toxic and explosive materials such as hydrazoic acid (HN_3).[3]

8. Clean areas thoroughly where azides are used regularly.

8.0 CONTINGENCY PLAN AND REPORTING

Accident/injury response:

1. Contact Campus Safety Services immediately if medical assistance is required(Dial 88 on a campus landline phone, dial 905-522-4135 from a cellphone, use the “McMaster Security Emergency” tile in the McMaster University SafetyApp, or push the Panic Alarm in laboratories that have them. EFRT (Emergency First Response Team) will attend and call for further assistance as necessary. UHS/FHSSO will be contacted by Campus Safety Services if required.

2. Notify the supervisor of the laboratory and ensure an Incident/Injury Report is completed and signed by the appropriate people before submitting to uhs@mcmaster.ca within 24 hours of the injury.

Spills and Waste Disposal:

Ensure the appropriate spill kits are on hand and lab occupants are trained to use them. Dispose of all waste in the appropriate hazardous waste containers (see below) and label for removal by the waste contractor. See Waste under Lab Safety on the UHS website for general information on disposing of hazardous waste.

Waste containers for solid or solution waste dedicated to inorganic azides are labeled with “azide contaminated waste” to ensure no other incompatible materials (in particular acids, halogenated solvent or heavy metal salts) are added and potentially cause an explosion. **DO NOT co-mingle azide waste with any acid**.

Azide-containing waste streams **must be collected separately** and must be clearly labeled with a completed yellow WASTE CHEMICALS label **detailing the specific azide** and any additional compatible chemical constituents.

All azide containing materials should be considered as sources of highly toxic and explosive materials such as hydrazoic acid (HN_3).[3]

9.0 REFERENCES

9.1 BRÄSE, S., GIL, C., KNEPPER, K., ZIMMERMANN, V. "ORGANIC AZIDES: AN EXPLODING DIVERSITY OF A UNIQUE CLASS OF COMPOUNDS" *ANGEW. CHEM. INT. ED.*, 2005, *44*, 5188**.**

9.2 KOLB, H.C., FINN, M.G., SHARPLESS, K.B., "CLICK CHEMISTRY: DIVERSE CHEMICAL FUNCTION FROM A FEW GOOD REACTIONS," *ANGEW. CHEM. INT. ED.* 2001, *40*, 2004-2021.

9.3 TREITLER, D. S. LEUNG. HOW DANGEROUS IS TOO DANGEROUS? A PERSPECTIVE ON AZIDE CHEMISTRY. *J. ORG. CHEM.* 2022, 87, 11293−11295

ORIGINATOR:

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