# Hazardous Chemicals and Toxins in Biomedical Research

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# Disclosures

- None

# Learning Objectives

1. Identify the major hazardous chemicals and toxins commonly used in biomedical research laboratories.
2. Describe the mechanisms of toxicity and primary routes of exposure for each hazardous substance, with attention to both acute and chronic health effects.
3. Recognize the clinical manifestations of exposure to key research chemicals and biologic toxins.
4. Outline appropriate first aid measures, decontamination procedures, and evidence-based medical treatments for chemical and toxin exposures..
5. Discuss best practices for minimizing occupational exposure to these agents, including engineering controls, personal protective equipment (PPE), and safe handling protocols.

# Chemicals

# Potent Acids/Bases

Exposure Concerns:

- Injury severity depends on concentration, pH, volume, contact duration, and exposure site.
- Alkalis cause liquefaction necrosis, enabling deeper tissue penetration.
- Acids cause coagulation necrosis, potentially limiting depth but still causing severe damage.
- Acute skin or eye exposure may lead to pain, blistering, and full-thickness burns or corneal injury.
- Inhalation of acid or alkali vapors can cause asthma, chemical pneumonitis, or ARDS.
    - Water-soluble agents irritate the upper airway; less soluble agents affect the lower respiratory tract.

# Potent Acids/Bases

Treatment:

- Immediately remove contaminated clothing to prevent continued skin exposure.
- Irrigate affected skin with copious amounts of water for at least 15 minutes.
- Proprietary amphoteric solutions such as Diphoterine may be more effective than water for certain alkalis (sodium hydroxide and potassium hydroxide)

# Hydrofluoric Acid

Use in Research:

- Surface modification and etching of biomaterials, such as titanium and polyetheretherketone (PEEK), to enhance their biocompatibility and osteogenic properties.
- In solid-phase peptide synthesis (Boc-SPPS) as a cleavage reagent to remove side-chain protecting groups and release peptides from the resin.

# Hydrofluoric Acid

Exposure Concerns:

- Hydrofluoric Acid (HF) exposure causes both local tissue injury and potentially fatal systemic toxicity.
- Solutions ≥15% produce immediate symptoms; lower concentrations may have delayed onset but still cause severe burns.
- HF burns are extremely painful and often present with blanching, blistering, and surrounding erythema.
- Initial skin findings may underestimate the depth and severity of tissue damage.
- Fluoride ions bind calcium and magnesium, leading to hypocalcemia and hypomagnesemia.
- Hypocalcemia may trigger hyperkalemia, increasing the risk of cardiotoxicity.

# Hydrofluoric Acid

Treatment:

- Immediately irrigate the exposed area with copious water
- Remove contaminated clothing as soon as possible.
- Apply calcium gluconate gel promptly to neutralize fluoride ions and reduce toxicity.
- If persistent pain: consider intradermal calcium gluconate

For Significant Exposure consider admission:

- Monitor serum calcium, magnesium, and potassium levels in significant exposures.
- Continuous cardiac monitoring
- IV calcium and magnesium as needed

# Phenol

Use in Research:

- Serves as a protein denaturant and nucleic acid extraction reagent
- Utilized for antimicrobial properties in laboratory disinfection and as preservatives in certain reagents
- Studied for antioxidant, anti-inflammatory, and anti-neoplastic activities
- Phenol-based chemistries are used in the synthesis of nanoparticles and the development of biosensors for biomedical diagnostics

# Phenol

Exposure Concerns:

- Phenol is rapidly absorbed through the skin and can cause chemical burns, contact dermatitis, and depigmentation.
- Systemic absorption can lead to central nervous system dysfunction (agitation, seizures, or coma) and cardiac abnormalities (hypotension or dysrhythmias)
- Inhalation can cause mucous membrane irritation, headache, dizziness, and CNS depression at higher doses.
- Chronic or repeated exposure may alter immune function, behavior, and blood cell activity.
- Phenol can damage red blood cells, leading to oxidative injury and hemolysis.

# Phenol

Treatment:

- Decontaminate skin by thoroughly swabbing with low-molecular-weight polyethylene glycol (PEG 300 or 400).
- Follow PEG swabbing with copious irrigation using water.
  - Do not apply water before PEG, as this can spread phenol and increase absorption.
  - If PEG is unavailable, isopropanol or glycerol may be used as alternatives.
  - If there is a delay in obtaining PEG, begin irrigation with water, then switch to PEG when available.
  - Use large volumes of water, as dilute phenol solutions are more readily absorbed through the skin.

# 6-OHDA/MPTP

Use in Research:

- 6-hydroxydopamine (6-OHDA) rapidly autoxidizes, producing reactive oxygen species that can damage cells.
- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is metabolized to MPP+, which causes irreversible dopaminergic neuron loss.
- Used to induce selective dopaminergic neurodegeneration in animal models to study Parkinson's disease mechanisms and to test therapeutic interventions.

# 6-OHDA/MPTP

Exposure Concerns:

- 6-OHDA causes rapid, permanent degeneration of dopaminergic neurons.
  - Neurotoxicity from 6-OHDA is considered irreversible
- MPTP-induced neurotoxicity is generally irreversible in humans and non-human primates.
  - Recovery from MPTP toxicity depends on dose, duration, and extent of neuronal loss.
  - Reversibility is possible if compensatory mechanisms remain intact and damage is incomplete.

# 6-OHDA/MPTP

Treatment:

- Prompt Decontamination - Immediately remove contaminated clothing and wash exposed skin thoroughly with soap and water.
- Selegiline - selective MAO-B inhibitor with neuroprotective effects in experimental models.
  - Primarily through antioxidant activity and anti-apoptotic signaling.
  - MPTP - prevents formation of the toxic metabolite MPP+ if given before or immediately after exposure.
  - 6-OHDA **-** protective effects are observed with pre- or co-exposure administration

# Cyanides and Cyanogens

Use in Research:

- Inhibits cytochrome c oxidase (Complex IV), causing histotoxic hypoxia and ATP depletion.
- This mechanism is used to model mitochondrial dysfunction, oxidative stress, and apoptosis.

# Cyanides and Cyanogens

Exposure Concerns:

- Acute cyanide exposure can occur most commonly via inhalation; also skin absorption, or ingestion.
  - Symptoms may develop rapidly and include headache, confusion, and seizures.
  - Severe cases can lead to cardiovascular collapse, metabolic acidosis, and death.
- Chronic low-level exposure may result in neurotoxicity and organ dysfunction.
  - Long-term effects can include hepatic and renal impairment and metabolic disturbances.

# Cyanides and Cyanogens

Treatment:

- Decontamination: Immediately remove the individual from the exposure source and initiate airway, breathing, and circulation support.
  - Administer 100% oxygen as soon as cyanide exposure is suspected.
- If significant exposure: Call for ALCS certified EMTs
- Hydroxocobalamin (Cyanokit) is the preferred antidote due to rapid action and safety.
  - Hydroxocobalamin binds cyanide to form cyanocobalamin, which is excreted in urine.
- If hydroxocobalamin is unavailable, use sodium nitrite plus sodium thiosulfate.
  - Sodium nitrite induces methemoglobinemia to sequester cyanide; sodium thiosulfate promotes detoxification.
  - Sodium thiosulfate alone is not recommended for severe poisoning due to delayed onset.

# Ethidium Bromide

Use in Research:

- as a fluorescent nucleic acid stain for the detection and visualization of DNA and RNA
- as a probe for studying DNA structure, DNA-protein interactions, and the physicochemical properties of nucleic acids

# Ethidium Bromide

Exposure Concerns:

- Ethidium bromide is a potent DNA intercalator with high mutagenic and cytotoxic potential; It can deactivate DNA transcription and induce mutations in exposed cells.
- Acute exposure may occur via skin contact, inhalation of dust or aerosols, or accidental ingestion.
  - Health effects include local skin and mucosal irritation and potential systemic toxicity.
  - Severe acute poisoning is rare due to low working concentrations and established lab safety protocols.
- Long-term exposure may increase cancer risk.
  - Epidemiological data suggest possible links to non-Hodgkin lymphoma and bone cancer in exposed workers, especially in settings with multiple genotoxic agents

# Ethidium Bromide

Treatment:

- Immediately remove the worker from the exposure source.
- Promptly decontaminate affected skin or mucous membranes with copious amounts of water.
- Monitor for symptoms of systemic effects if exposure was significant.
- No specific medical management for acute systemic toxicity in humans, and no established antidote exists.

# Osmium Tetroxide

Use in Research:

- As a fixative and contrast agent for electron microscopy, a cytochemical marker, a reagent for mass cytometry barcoding, and a chemical probe for nucleic acid structure

# Osmium Tetroxide

Exposure Concerns:

- Highly potent oxidizer and corrosive agent.
- Severe ocular toxicity can occur, including chemical burns and potential vision loss.
- Inhalation may cause respiratory tract irritation and mucosal damage.
- Brief skin contact may lead to discoloration, erythema, and local irritation.
    - In some cases, dermal exposure can cause deeper tissue injury or granuloma formation.

# Osmium Tetroxide

Treatment:

- Immediately remove the worker from the exposure source.
- Promptly decontaminate affected skin or mucous membranes with copious amounts of water.
- Systemic toxicity is extremely rare
  - No specific antidote; treatment is supportive and symptom-based.

# Dichloromethane

Use in Research:

- used as a volatile organic solvent for the extraction of biomolecules and preparation of analytical samples.
- serves as a solvent in organic synthesis, including drug development and chemical reactions.

# Dichloromethane

Exposure Concerns:

- hepatically metabolized to CO
- Acute exposure causes CNS depression, presenting as light-headedness, nausea, headache, and respiratory depression.
- Skin and eye contact may cause chemical burns and corneal injury.
- It can sensitize the myocardium to arrhythmias, posing added risk to individuals with cardiovascular disease.
- Chronic exposure is linked to hepatotoxicity, neurotoxicity, and potential carcinogenicity.
  - DCM is classified as a Group 2A probable human carcinogen by IARC

# Dichloromethane

Treatment:

- Treatment is supportive and symptom-based.
- Prioritize airway, breathing, and circulation, with continuous monitoring for arrhythmias and CNS depression.
- DCM is metabolized to carbon monoxide; measure carboxyhemoglobin levels in symptomatic patients.
- Administer supplemental oxygen if carboxyhemoglobinemia is present or suspected.
- Monitor for delayed effects due to ongoing metabolism and potential systemic toxicity.

# Organotins

Use in Research:

- Organotin(IV) compounds exhibit potent cytotoxic and antiproliferative effects in cancer cell lines.
- Used to study endocrine disruption, neurotoxicity, and adipocyte differentiation.
- Some organotins influence epigenetic regulation by enhancing histone acetyltransferase activity.

# Chemotherapeutics

- **Alkylating agents** (e.g., cyclophosphamide, procarbazine, mechlorethamine)
- **Topoisomerase II inhibitors** (e.g., etoposide, doxorubicin, daunorubicin)
- **Platinum compounds** (e.g., cisplatin, carboplatin, oxaliplatin)

# Chemotherapeutics

Exposure Concerns:

- Potential for oncogenesis with high-risk exposures
- Most have concerns with repro-toxicity

Treatment:

- Standard for route of exposure
- Post exposure surveillance, USP 800, NIOSH

# Toxins

# Pertussis

Use in Research:

- Pertussis toxin (AB exotoxin)is used as a molecular tool to study G protein-coupled receptor (GPCR) signaling.
- Pertussis toxin is used as a protective antigen in acellular pertussis vaccines after inactivation and plays a key role in vaccine quality control to ensure safety and efficacy.

# Pertussis

Exposure Concerns:

- Potential systemic effects include leukocytosis, histamine sensitization, hyperinsulinemia, and increased vascular permeability.
- No human case studies, effects suggested in animal models and pertussis pathogenesis studies.

# Pertussis

Treatment:

- Current clinical guidelines do not provide specific protocols for exposure to isolated pertussis toxin.
- Management should be supportive and symptom-based, tailored to the route and severity of exposure.
- No specific antidote or post-exposure prophylaxis is available for isolated pertussis toxin.
- Provide Tdap every 5 or 10 years for researchers
- PEP with a macrolide antibiotic if also exposed to whole bacteria

# Tetanus

Use in Research:

- Tetanus toxin is used as a molecular tool to study synaptic transmission and neuronal connectivity.
- It irreversibly inhibits neurotransmitter release by cleaving synaptobrevin (VAMP).
- This selective silencing enables targeted manipulation of neuronal activity.

# Tetanus

Exposure Concerns:

- Tetanus toxin is extremely potent, with a human lethal dose estimated at ~1 ng/kg.
- Exposure can occur via needlestick injuries, cuts, or mucosal contact.
- High-risk scenarios include handling purified toxin or cultures of Clostridium tetani.
- The primary concern is development of tetanus, a life-threatening neuroparalytic disease.
  - Clinical features include muscle rigidity, painful spasms, and autonomic instability.

# Tetanus

Treatment:

- Immediate wound cleaning and debridement is critical to reduce infection and toxin production.
- Assess immunization status of the exposed individual.
  - Administer a tetanus toxoid–containing vaccine (Tdap or Td) if the primary series is incomplete or >5 years have passed since the last dose.
  - Use Tdap if the individual has never received it before, per ACIP guidelines.
  - For incomplete, unknown, or high-risk exposures, provide passive immunization with tetanus immune globulin (TIG) at a separate site from the vaccine.
  - The standard adult TIG dose is 250 units intramuscularly.
- Monitor all exposed individuals for symptoms of tetanus and provide supportive care if needed.
- Ensure follow-up to complete the vaccine series if not already done.

# Staphylococcus enterotoxin (A,B,C,D,E)

Use in Research

- Staphylococcal enterotoxins are widely used as model superantigens to study T-cell activation, immune regulation, and cytokine storm mechanisms and are used to develop therapeutics or vaccines targeting these pathways.
- Overall, staphylococcal enterotoxins are critical both as clinical virulence factors and as experimental tools for immunology and microbiology research.

# Staphylococcus enterotoxin (A,B,C,D,E)

Exposure Concerns

- Inhalation of staphylococcal enterotoxins, especially SEB, can cause fever, pulmonary symptoms, and gastrointestinal distress, and has been associated with toxic shock-like syndromes in laboratory-acquired cases.
  - Even small amounts can trigger severe systemic effects due to massive cytokine release.
- Ocular exposure can result in conjunctivitis and localized swelling, and may lead to gastrointestinal symptoms, as documented in laboratory workers.
- Ingestion is associated with rapid-onset nausea, vomiting, and diarrhea, typical of staphylococcal food poisoning.
- Staphylococcal enterotoxins are highly resistant to heat and proteolysis, increasing the risk of persistent contamination and accidental exposure.
- Laboratory workers handling purified toxins or cultures must use strict biosafety protocols, including personal protective equipment and engineering controls, to prevent inhalational, mucosal, or cutaneous exposure. Treatment is supportive care.

# Diphtheria

Use in Research:

- Diphtheria toxin is used primarily as a tool for targeted cell ablation and as a cytotoxic payload in the development of immunotoxins and targeted cancer therapies.

# Diphtheria

Exposure Concerns:

- Diphtheria toxin is highly potent; even minute quantities can be lethal if absorbed systemically
- Exposure may occur via inhalation, mucosal contact, skin puncture, or ingestion.
- Systemic effects include inhibition of protein synthesis, cell death, myocarditis, and neuropathy.
- Workers are at risk for acute diphtheria toxin intoxication and infection when handling toxigenic Corynebacterium diphtheriae, particularly if not fully immunized.

# Diphtheria

Treatment:

- Administer diphtheria antitoxin (DAT) immediately, ideally before symptom onset, to neutralize circulating toxin.
  - DAT availability is limited and accessed through the CDC under investigational protocol in the U.S.
- Initiate antibiotic therapy (erythromycin or penicillin) to eradicate Corynebacterium diphtheriae and prevent further toxin production.
  - Treat all exposures as potentially involving live bacteria, even if purified toxin was the known source.
- Monitor closely for complications such as myocarditis and neuropathy.
- Review vaccination status and give a Td or Tdap booster if >5 years since last dose or if immunization is incomplete.
  - For incomplete or unknown immunization, complete the primary series per standard guidelines.
  - For high dose Diphtheria toxin use, check Diphtheria Antibody before beginning research despite vaccination status
- Supportive care and close observation are essential in all cases of suspected exposure.

# Other hazards to consider

# Reproductive Hazards

Chemical

Biologics

# Category 1 Chemicals:
# Known or Presumed Human Reproductive Toxicants

| Chemical Name | CAS No. | Hazard Class | Hazard Code | Category |
|---|---|---|---|---|
| Benzene | 71-43-2 | Mutagen | H340 | 1B |
| 1,3-Butadiene (BD) | 106-99-0 | Mutagen | H340 | 1B |
| Cadmium Chloride | 10108-64-2 | Mutagen, Repr. tox., Teratogen | H340, H360FD | Muta. 1B, Repr. 1B |
| Chromium(VI) oxide | 1333-82-0 | Mutagen | H340 | 1B |
| Cyclophosphamide | 50-18-0 | Mutagen, Repr. tox. | H340, H360 | Muta. 1A, Repr. 1A |
| 1,2-dibromo-3-chloropropane (DBCP) | 96-12-8 | Mutagen, Repr. tox. | H340, H360F | Muta. 1B, Repr. 1A |
| Diglyme / Ethane, 1,1-oxybis[2-methoxy- | 111-96-6 | Repr. tox., Teratogen | H360FD | 1B |
| N,N-Dimethylformamide* | 68-12-2 | Teratogen | H360D | 1B |
| Ethyleneimine | 151-56-4 | Mutagen | H340 | 1B |
| Ethylene Oxide | 75-21-8 | Mutagen, Repr. tox. | H340, H360 | Muta. 1B, Repr. 1A |

# Category 1 Chemicals: Known or Presumed Human Reproductive Toxicants

| Chemical Name | CAS No. | Hazard Class | Hazard Code | Category |
|---|---|---|---|---|
| Formamide* | 75-12-7 | Teratogen | H360D | 1B |
| 8-Hydroxyquinoline /8-quinolinol | 148-24-3 | Teratogen | H360D | 1B |
| Imidazole* | 288-32-4 | Teratogen | H360D | 1B |
| Lead (& lead compounds) | 7439-92-1 | Repr. tox., Teratogen | H360FD | 1A |
| 2-Methoxyethanol | 109-86-4 | Repr. tox., Teratogen | H360FD | 1B |
| 1-Methyl-2-pyrrolidinone | 872-50-4 | Teratogen | H360D | 1B |
| Nickel Sulfate | 7786-81-4 | Teratogen | H360D | 1B |
| Potassium Dichromate | 7778-50-9 | Mutagen, Teratogen | H340, H360FD | Muta. 1B, Repr. 1B |
| Tamoxifen | 10540-29-1 | Repr. tox. | H360 | 1B |

# Category 2 Chemicals
# Suspected Human Reproductive Toxicants

| Chemical Name | CAS No. | Hazard Class | Hazard Code | Category |
|---|---|---|---|---|
| Carbon Disulfide | 75-15-0 | Suspected Repr. tox., Suspected Teratogen | H361fd | 2 |
| Chloroform | 67-66-3 | Suspected Teratogen | H361d | 2 |
| Ethidium bromide | 1239-45-8 | Suspected Mutagen | H341 | |
| Formaldehyde / Formalin | 50-00-0 | Suspected Mutagen | H341 | 2 |
| Phenol | 108-95-2 | Suspected Mutagen | H341 | 2 |
| Toluene | 108-88-3 | Suspected Teratogen | H361d | 2 |

# Biological Reproductive Hazardous Agents

| Biological Agent | Reproductive Hazards | Vaccine Available |
|---|---|---|
| Cytomegaly virus (CMV) | Teratogen, congenital infection causes mental retardation, vision and hearing impairment | NO |
| Ebola Virus | Increased risk of death to patient, bleeding, miscarriage, death of fetus | YES, for Zaire strain only. ERVEBO, live attenuated vaccines are generally contraindicated during pregnancy. |
| Hepatitis B virus | Liver damage to patient, fetal infection, prematurity, mental retardation | YES |
| Hepatitis C virus | Liver damage to patient, fetal infection, cirrhosis, prematurity, and mental retardation | NO, treatment available that can result in cure. |
| Hepatitis E virus | Liver failure to patient, Pre-term labor, and miscarriage | NO |
| Human Immunodeficiency Virus (HIV) | Affect fertility, infection of fetus | NO – however prophylaxis available |

# Biological Reproductive Hazardous Agents

| Biological Agent | Reproductive Hazards | Vaccine Available |
|---|---|---|
| Herpes- Simplex and Genital | Genital lesion may cause cesarian delivery to prevent transmission, neonatal herpes. | NO |
| Influenza | May cause severe illness and increased risk for influenza complications requiring hospitalization. | YES |
| Leishmania | Congenital transmission, miscarriage, premature delivery, and infection on infant. | NO |
| Listeria | Miscarriage, stillbirth, premature delivery, infant death. | NO |
| Malaria | Anemia and severe malarial disease to patient, miscarriage, premature delivery, low birth weight, fetal growth reduction, fetal death. | NO – however prophylaxis exists |
| Measles | Premature birth, low birth weight, and death. | YES |

# Biological Reproductive Hazardous Agents

| Biological Agent | Reproductive Hazards | Vaccine Available |
|---|---|---|
| Rubella (German Measles) | Risk to congenital rubella syndrome, severe birth defect, miscarriage, stillbirth. | YES |
| Parvovirus B19 (Fifth disease) | Miscarriage on rare occasion | NO |
| Toxoplasma gondii (Toxoplasmosis) | Blindness, mental disability, miscarriage | NO |
| Lymphocytic Choriomeningitis Virus | Miscarriage, mental retardation, hydrocephaly, vision problems | NO |
| Varicella zoster (chickenpox) virus | Congenital varicella syndrome, birth abnormalities, cause infant life-threatening infection | YES |
| Valley Fever (coccidioidomycosis) | Disseminated coccidioidomycosis may occur during pregnancy, especially during the third trimester. | NO |
| Zika Virus | Serious birth defects including microcephaly, seizures, hearing and vision loss | NO |

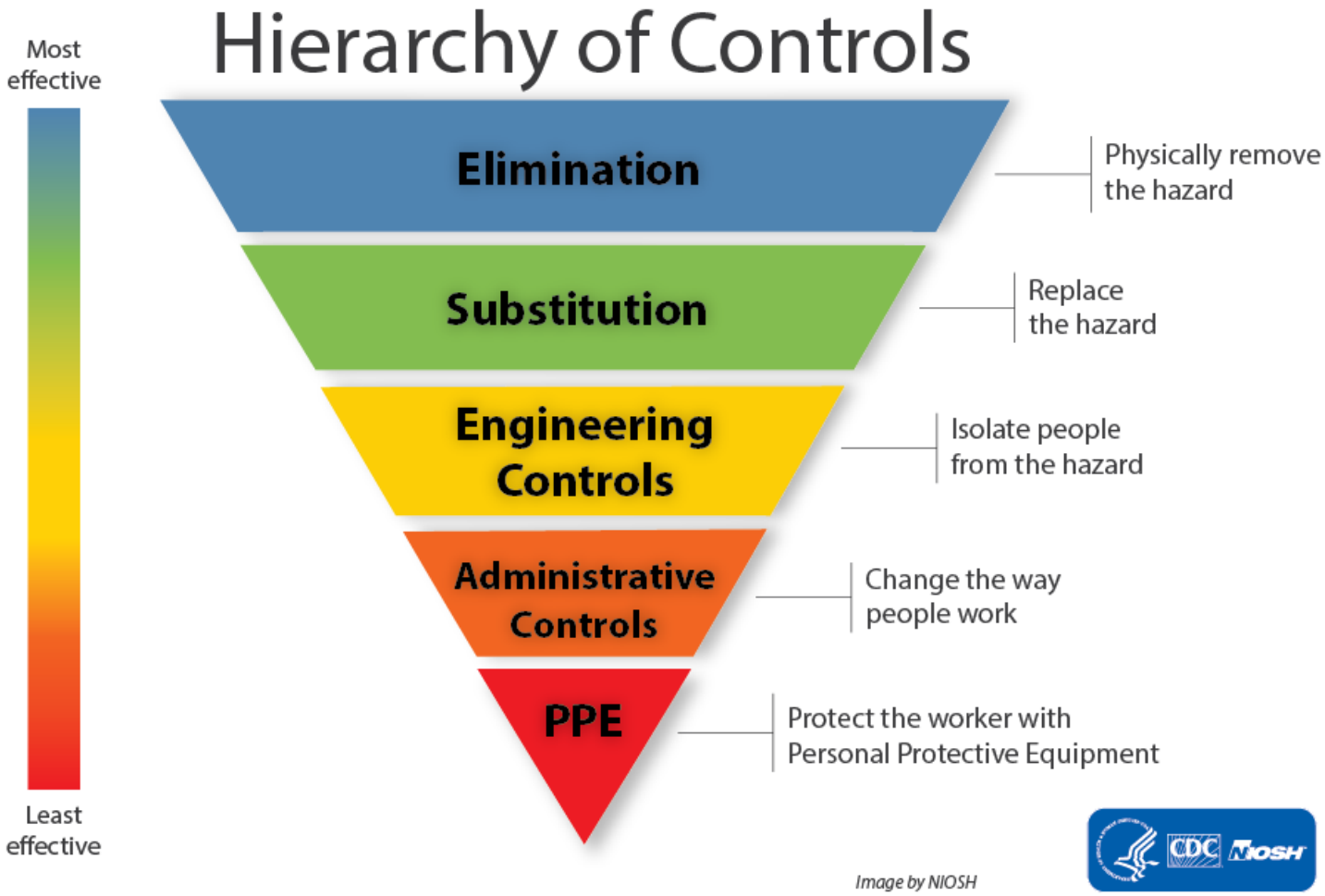
# Other hazards to consider

- Liquid Nitrogen
- Compressed Gases
- Water reactive chemicals
- Incompatible chemicals
- Nanoparticles

# Isoflurane

- Volatile halogenated ether inhalational anesthetic
- Delivered to rodents via infusion into box or nose cone
- Annual waste gas training programs provided, scavenging systems vary
- Excess exposure: dizziness, HA,, CNS depression
- 2 PPM 1 hr. TWA ceiling; 10 PPM TWA 8 hr. exposure limits (NIOSH)
- Repro tox risk

# Mitigation




https://www.cdc.gov/niosh/hierarchy-of-controls/about/index.html

# Elimination/Substitution

| Undesirable Solvent | Alternative |
|---|---|
| Pentane | Heptane |
| Hexane | Heptane |
| Di-isopropyl ether or diethyl ether | 2-MeTHF or *tert*-butyl methyl ether |
| Dioxane or dimethoxyethane | 2-MeTHF or *tert*-butyl methyl ether |
| Chloroform, dichloroethane, carbon tetrachloride | Dichloromethane |
| Dimethyl formamide, dimethyl acetamide, or N-methylpyrrolidinone | Acetonitrile |
| Pyridine | Et3N |
| Dichloromethane (extractions) | EtOAc, MTBE, toluene, 2-MeTHF |
| Dichloromethane (chromatography) | EtOAc/heptane |
| Benzene | Toluene |

# Engineering Controls

- Chemical Fume hood

# Administrative Controls

- Appropriate training
- SOPs for use and handling
- Exposure, decontamination, and spill protocols

# PPE

- Appropriate for the hazard?
- Correct and consistent use

# Resources

- https://www.bu.edu/research/ethics-compliance/safety/laboratory-safety/high-hazard-chemical-program-2/
- https://ehrs.upenn.edu/health-safety/lab-safety/chemical-hygiene-plan/standard-operating-procedures
- https://www.safety.duke.edu/documents?f%5B0%5D=select_topics%3A34

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# Thank you

Questions?