UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
ENVIRONMENT HEALTH AND SAFETY/BIOSAFETY

HISTOPLASMA CAPSULATUM EXPOSURE/INJURY RESPONSE
PROTOCOL

Organism or Agent: Histoplasma capsulatum
Exposure Risk: Histoplasmosis
UCSF Occupational Health Services: 415/885-7580 (Available during work hours)
Exposure Hotline: 415/353-7842 (Available 24 hours)
Office of Environment Health & Safety: 415/476-1300 (Main number; available during work hours)
415/476-1414 or 9-911 (In case of emergency, via the UCSF Police Department; available 24 hours)

EH&S Public Health Officer: 415/514-3531
Biosafety Officer: 415/514-2824

In the event of an accidental exposure or injury, the protocol is as follows:

1. Modes of Transmission:
   a. Skin puncture or injection
   b. Ingestion
   c. Contact with mucous membranes (eyes, nose, mouth)
   d. Contact with non-intact skin
   e. Exposure to aerosols
   f. Respiratory exposure involving inhalation of the mold form

2. First Aid:
   a. Skin Exposure, immediately go to the sink and thoroughly wash the skin with soap and water. Decontaminate any exposed skin surfaces with an antiseptic scrub solution.
   b. Skin Wound, immediately go to the sink and thoroughly wash the wound with soap and water and pat dry.
   c. Splash to Eye(s), Nose or Mouth, immediately flush the area with running water for at least 5-10 minutes.
   d. Splash Affecting Garments, remove garments that may have become soiled or contaminated and place them in a double red plastic bag.

3. Treatment:
   a. In the event of an acute injury resulting from a laboratory incident which requires immediate medical care, the injured employee/student should report to the emergency department for medical treatment. The injured individual must take a copy of this entire protocol document to the Emergency Department, including information regarding the specific strain/serotype associated with exposure.
b. In the event of exposure, with or without an injury, call the Exposure Hotline pager in order to get access to medical care for the exposure. The hotline responder will provide guidance to the injured individual on necessary medical treatment and post exposure follow-up.

c. Post exposure prophylaxis with itraconazole is recommended for inhalational exposure to spores/conidia and exposure to the yeast form from percutaneous injury or mucous membrane exposure. See ISDS for details.

4. Follow up is needed in the event of any Laboratory Exposure:
   a. After first aid has been administered, immediately inform your supervisor of the exposure.
   b. In the event of a large spill, contact the emergency response team (9-911) for clean-up.
   c. Contact Occupational Health Services, after first aid is complete, for follow-up care.
   d. Contact the Biosafety Officer at 415/514-2824 to report the injury or exposure.
ROLES & RESPONSIBILITIES
ATRER ACCIDENTAL EXPOSURE TO HISTOPLASMA

1. Worker’s Responsibilities (Employee/Student Initial Self-Care)
   a. First Aid: Perform the recommended first aid and decontamination according to the posted instructions.
   b. Treatment: i) In the event of an acute injury resulting from a laboratory incident which requires immediate medical care, the injured individual should report to the Emergency Department for acute medical treatment. ii) In the event of an exposure, with or without an injury, call the Exposure Hotline pager in order to get access to medical care for the exposure and evaluation for possible post exposure prophylaxis.
   c. Access to Exposure Hotline: Call the Exposure Hotline pager in order to get access to medical care for the exposure. Dial 415/353-7842 to contact operator services. You will be asked to provide your name and two (2) contact numbers. Do not leave, wait for the call back. If the responder does not call back in 15 minutes, call again. If there is no call back the second time, proceed to the nearest Emergency Department with a copy of this protocol.
   d. Reporting: Inform your laboratory supervisor/principal investigator of the exposure. Complete an Employee Incident Report Form (http://ucsfhr.ucsf.edu/files/EIR.pdf)
   e. Secure the laboratory: Identify the equipment involved in the exposure and the mechanism of exposure. Make sure that the laboratory area has been secured and that notification of contamination has been posted to prevent other individuals from entering the area.
   f. Follow up: Contact Occupational Health Services (OHS) at 415/885-7580 for any needed follow up care.

2. Supervisor’s/PI’s Responsibilities
   a. First Aid and Decontamination: Verify that the worker has washed and decontaminated himself/herself. Ensure that appropriate medical treatment has been received.
   b. Secure the laboratory: Confirm that the laboratory area has been secured and that notification of contamination has been posted to prevent other individuals from entering the area.
   c. Laboratory clean-up (as needed): Contact the Office of Environment Health & Safety (EH&S) through the UC Police Department Emergency Dispatch (from a campus telephone 9-911, from a non-campus phone 415/476-1414).
   d. Report the exposure: Call the Biosafety Officer at 415/514-2824 during regular hours to discuss the exposure. A report summarizing any suspected Histoplasma exposure needs to be submitted to the Biosafety Committee by the Principal Investigator (PI). The report must include the following:
      • A brief description of the exposure event, a description of the area involved, and the extent of employee exposure
      • If applicable, specification of the amount of infectious material released, time involved,
and explanation of procedures used to determine the amount involved

- Corrective action taken to prevent the re-occurrence of the incident

- *Histoplasma* decontamination procedures

e. **Follow Up:** Confirm that the worker has called for an appointment at the UCSF Occupational Health Clinic.

SECTION I – Infectious Agent
Organism or Agent: Histoplasma capsulatum
Synonym or Cross Reference: Histoplasmosis; Ajeclomyces capsulatus
Characteristics: Dimorphic fungus, mold form in soil, yeast form in animals and human hosts

SECTION II – Recommended Precautions
Containment Requirements: Biosafety level 2 practices, safety equipment and facilities for specimens or cultures known or suspected to contain the yeast form. Biosafety level 3 practices, safety equipment and facilities for specimens known or suspected to contain the mold form. ABSL-2 practices, containment equipment and facilities for activities involving animals experimentally infected with the yeast form. ABSL-3 practices, containment equipment and facilities for activities involving animals experimentally infected with the mold form.

UCSF Required Personal Protective Equipment: gloves and lab coat for work with the yeast form. BSL 3 procedures for work involving the mold form.

SECTION III – Handling Information
Spills: Allow aerosols to settle; wearing protective clothing, gently cover spill with paper towel and apply 10% bleach (0.5% sodium hypochlorite) solution, starting at perimeter and working towards the center; allow sufficient contact time (30 min) before clean up.

Disposal: Decontaminate waste contaminated with known or suspected H. capsulatum in the mold form before disposal. Dispose as biohazardous waste.

Storage: Store in sealed containers that are appropriately labeled.

SECTION IV – Health Hazards
Pathogenicity: Systemic mycosis of varying severity with primary lesion in lungs; disease appears as a mild, flu-like respiratory illness with symptoms including malaise, fever, chest pain, dry or non-productive cough, headache, loss of appetite, shortness of breath, joint and muscle pain, chills; five clinical forms - asymptomatic, acute benign respiratory, acute disseminated, chronic disseminated, chronic pulmonary; some forms can be fatal; asymptomatic infection provides partial resistance to re-infection.

Epidemiology: Focal infections are common worldwide; clinical disease and severe progressive disease less frequent; hypersensitivity to H. capsulatum is common in eastern and central North America; outbreaks have occurred in families or groups exposed to bird or bat droppings, or recently disturbed contaminated soil; prevalence increases from childhood to 15 years of age.

Host Range: Humans, dogs, cats, cattle, horses, rats, skunks, opossums, foxes and other animals.

Infectious Dose: 10 spores lethal inoculum in mice. Unknown for laboratory strains, but lethal dose in mice is closer to 1,000,000 spores.
**Modes of Transmission:** Inhalation of airborne conidia; small size of infective conidia (< 5 µm) is conducive to airborne dispersal and intrapulmonary retention. The spores of H. capsulatum are of a respirable size.

**Incubation Period:** Symptoms appear within 3-18 days after exposure, commonly 10 days.

**Communicability:** Not transmitted from person-to-person.

**SECTION V – Viability**

**Drug Susceptibility:** Sensitive to amphotericin B, ketoconazole, itraconazole.

**Susceptibility to Disinfectants:** Susceptible to 1% sodium hypochlorite, phenolics, glutaraldehyde, formaldehyde; susceptibility to 70% ethanol questionable.

**Physical Inactivation:** Inactivated by moist heat (121° C for at least 15 min).

**Survival Outside Host:** Spores are resistant to drying and may remain viable for long periods of time.

**FOR THE USE OF THE EXPOSURE HOTLINE**

**SECTION VI – Medical**

**Surveillance:** Monitor for symptoms; confirm by culture, microscopic examination of specimens, and serologic response. Any pregnant or immune compromised worker should be evaluated by an infectious disease specialist.

**First Aid/Treatment:** Amphotericin B for disseminated or chronic pulmonary cases; conazole drugs may be added or used in rotation for therapy in immunocompromised patients because relapse is common.

**Immunization:** None.

**Prophylaxis:** Evaluate all exposures for prophylaxis according to the following criteria:

1. **Prophylaxis Recommended For:**
   a. Significant inhalational exposure to spores/conidia.
   b. Percutaneous injury with *Histoplasma*, materials contaminated by *Histoplasma*, or mucous membrane exposure.

2. **Prophylaxis Considered For:**
   a. Potential inhalational exposures to spores/conidia in individuals with risk factors for development of systemic disease.
   b. Potential mucous membrane exposure to either form of *Histoplasma*.

3. **Prophylaxis Not Recommended For:**
   a. Intact skin exposure associated with the yeast form of *Histoplasma*, where there is no inhalation or percutaneous or mucous membrane exposure.

Medication: Itraconazole – load with 200 mg TID for three days, then treat with 200 mg once daily for 30 days. Provide one week supply of medication.

This drug may have significant side effects and multiple drug interactions.

Itraconazole is contraindicated in pregnancy. If there is any question regarding early pregnancy, a pregnancy test should be performed before starting prophylaxis.

Prophylaxis should be started the day of exposure, but can be started up to 2 weeks after acute exposure. The rationale for this is that most severe cases would likely produce symptoms within 2 weeks. After 2 weeks, prophylaxis should be started with the development of symptoms, since severe disease would not be likely.
Follow-up: The exposed patient will need close follow up in UCSF Occupational Health Services.

**Reporting:** All laboratory exposures must be reported to the Biosafety Officer. Any known cases of histoplasmosis exposure must be reported to the Public Health Officer. Histoplasmosis communicable disease reporting to the San Francisco Department of Public Health is not required.

**SECTION VII – Laboratory Hazards**

**Laboratory-Acquired Infections:** Documented hazard in laboratories conducting diagnostic or investigative work; 71 reported cases with 1 death - pulmonary infection from handling mold from cultures, local infection from skin puncture during autopsy, accidental needle inoculation of viable culture.

**Sources/Specimen:** Infective stage (conidia) present in sporulating mold from cultures and in soil from endemic areas; yeast form in tissues or fluids from infected animals or humans (may produce local infection following parental inoculation).

**Primary Hazards:** Inhalation of infective conidia, contact with broken skin or mucus membranes, accidental parenteral inoculation.

**Special Hazards:** Collecting and processing soil samples from endemic areas has caused pulmonary infections in laboratory workers.

**FOR THE USE OF THE EMERGENCY DEPARTMENT**

**SECTION VIII – Emergency Medical Treatment**

**Treatment Indications:** Emergency department treatment will be required for injuries that require immediate medical care. The treatment needs to consist of the following: 1) decontaminate and debride wound, 2) repair wound, 3) consult with infectious disease specialist for high risk exposure, 4) contact the Exposure Hotline to discuss the need to start post exposure prophylaxis, if indicated (see section VI above), and 4) have patient follow up with UCSF-OHS.

**Exposure Indications:** In the event of an exposure, with or without an injury, the Exposure Hotline must be called.

**Decontamination:** The UCSF Emergency Department has requested a decontamination verification note for use at the Parnassus campus, which is included in this protocol. Other Emergency Departments may elect to sign the verification note. If so, the ED triage nurse will be asked to complete and sign the verification note indicating cleansing and decontamination of the patient and their clothing.

(Format/Content adapted directly from Canadian SDS and the 5th Edition of Biosafety in Microbiological and Biomedical Laboratories (BMBL), and recommendations from Dr. Joseph Wheat of Mira Vista Labs.)

**SECTION VIII – References**

http://www.phac-aspc.gc.ca/msds-ftss/msds82e-eng.php
I. RISKS IN LABORATORY WORKERS/CLINICAL SUMMARY

A. Overview

*Histoplasma capsulatum* is a thermally dimorphic fungus. It grows both as a yeast phase and a mold phase that undergoes sporulation. Histoplasmosis is acquired by inhalation of the spores of the organism. Some of the spores (also called conidia) are less than 5 microns in size, and may form an infective airborne aerosol when culture material or contaminated soil is disturbed. All work with the mold phase is performed in a BSL 3-level lab. The yeast form requires BSL 2-level protection and exposure to the yeast form may produce local infection. However, the potential for severe infection exists in the event of a BSL 3 laboratory accident. Workers in the lab will be aware when such an event occurs, and will present at the Emergency Department for evaluation.

Previous infection with *Histoplasma* provides some immunity, but host defenses are overwhelmed by exposure to high concentrations of the organism. Those individuals with any form of immune system compromise are especially susceptible to severe infections. Any exposed employee with defective cell mediated immunity is at greatly increased risk of disseminated disease. Severity of disease is determined both by the number of organisms inhaled and immune status. About 25% of adult exposures result in an influenza-like syndrome.

B. Diagnostic Tests

In the event of an exposure or suspicious symptoms, it is important to draw serum samples for fungal antigen titers. Immunodiffusion (ID) testing has a 4-6 day turn around time. Complement Fixation (CF) has a much longer turnaround time, since samples are sent to the state laboratory and then forwarded to the CDC. There is cross reactivity with coccidiodimycosis and blastomycosis. The tests may use two different antigen phases. “The ID test is slightly more specific than CF test; false-positive CF tests occur in patients who have lymphoma, tuberculosis, sarcoidosis, and other fungal infections. Both assays have a sensitivity of about 80%. Because CF antibodies can persist for years after infection, a single low CF titer means little other than that the patient was at some time exposed to *H capsulatum.*” (from Kauffman, Histoplasmosis, *Clin Chest Med*, 2009 Jun;30(2):217-25, v. PMID 19375629) Urine antigen testing may be used in acute cases, especially in immune compromised individuals, with disseminated Histoplasmosis. Urine antigen testing is available through Mira Vista Labs and Quest (turnaround time 1-2 days). Skin testing is not useful in the setting of acute exposure, and the reagent is not currently available in the US. Further, the skin test, as well as all currently available laboratory tests, does show cross reactivity with other systemic dimorphic pathogens.
C. Prophylaxis

With known airborne exposures in the BSL 3 lab, itraconazole prophylaxis is recommended. Prophylaxis is especially important in the event of exposure to high titers of organisms, which is more likely to result in symptomatic disease. The regimen for post exposure prophylaxis with itraconazole is 200 mg TID for three days as a loading dose, then 200 mg once daily for 30 days. It should be noted that for acute histoplasmosis, itraconazole is usually continued for 3 months, or, for disseminated histoplasmosis, one year. The medication is sometimes given with food and Classic Coke. Low pH aids absorption, patients should avoid medications that increase pH. This is based on a paper by McKinsey DS, Wheat LJ et al –PMID: 10452633. Even a short course of itraconazole of 2 weeks would likely provide substantial benefit, if side effects are tolerated. The most common side effect is GI upset.

Significant warnings exist for patients with a history of cardiac disease and hepatic insufficiency according to Mosby’s Drug Consult. Itraconazole should not be given to pregnant women or women who plan to become pregnant while taking the medication. In addition, there is a list of contraindications, warnings, and drug interactions that should be reviewed.

Prophylaxis should be started the day of exposure, but can be started up to 2 weeks after acute exposure. The rationale for this is that most severe cases would likely produce symptoms within 2 weeks. After 2 weeks, prophylaxis should be started with the development of symptoms, since severe disease would not be likely.

D. Attack rate

Up to 75% for groups of individuals exposed to barns/caves have developed symptomatic disease. Most disease is self-limited and the time of onset of symptoms varies with the severity of exposure. With the development of symptoms, a urine antigen test should be ordered. The test is positive in 75% of acute symptomatic cases. The rise in titer by Complement Fixation testing (CF) may take 1-2 months to occur, and is not useful for acute diagnosis. There is also a delay in developing a titer by Immunodiffusion testing (ID). Because of cross reactivity with other fungal antigens, it will be of great benefit to draw a baseline titer by ID so that subsequent increases in titer can be evaluated.

E. Risk Factors

“The major risk factors that portend an increased risk for disseminated infection with \textit{H capsulatum} are exposure to the organism as an infant before cell-mediated immunity is adequate to handle intracellular pathogens, AIDS with CD4 less than 150/μl, corticosteroids and other immunosuppressive agents given for various conditions, hematologic malignancies, and solid organ transplantation…With increasing use of tumor necrosis factor (TNF) antagonists, this form of therapy has emerged as a major risk factor for histoplasmosis. Not surprisingly, this cytokine is of integral importance in the cell-mediated immune response to histoplasmosis, and blockade, as occurs with etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira), results in widely disseminated histoplasmosis…Because it is an intracellular pathogen, \textit{H capsulatum} has the ability to remain viable in tissues for years in a latent state. If cell-mediated immunity wanes because of illness, organ transplantation, or
immunosuppressive drugs, the organism can reactivate and cause disease. This reactivation can occur years after the initial exposure and outside of the endemic area, making the diagnosis more difficult. Given its ability to remain latent in tissues, *H capsulatum* has been transmitted with donated organs.” (From: Kauffman, Histoplasmosis, *Clin Chest Med*, 2009 Jun;30(2):217-25, v. PMID 19375629)

All UCSF employees who work with *Histoplasma capsulatum* should be aware of the EH&S policy on workers with immune compromise/pregnancy. Please refer to Campus Research Exposure Protocols, Immune Compromised Worker:
http://www.occupationalhealthprogram.ucsf.edu/ohpEE.asp#EP
II. CDC/NIH RECOMMENDATIONS FOR LABORATORY EXPOSURE TO HISTOPLASMA

A. OCCUPATIONAL INFECTIONS

Laboratory-associated histoplasmosis is a documented hazard in facilities conducting diagnostic or investigative work. Pulmonary infections have resulted from handling mold form cultures. Local infection has resulted from skin puncture during autopsy of an infected human, from accidental needle inoculation of a viable culture, and from spray from a needle into the eye. Collecting and processing soil samples from endemic areas has caused pulmonary infections in laboratory workers. Conidia are resistant to drying and may remain viable for long periods of time. The small size of the infective conidia (less than 5 microns) is conducive to airborne dispersal and intrapulmonary retention. Work with experimental animals suggests that hyphal fragments are capable of serving as viable inocula.

B. NATURAL MODES OF INFECTION

The fungus is distributed worldwide in the environment and is associated with starling and bat feces. It has been isolated from soil, often in river valleys, between latitudes 45°N and 45°S. Histoplasmosis is naturally acquired by the inhalation of infectious particles, usually microconidia. Infections are not transmissible from person-to-person, but require common exposure to a point source.

C. LABORATORY SAFETY

The infective stage of this dimorphic fungus (conidia) is present in sporulating mold form cultures and in soil from endemic areas. The yeast form in tissues or fluids from infected animals may produce local infection following parenteral inoculation or splash onto mucous membranes.

D. Containment Recommendations

BSL-2 and ABSL-2 practices, containment equipment, and facilities are recommended for handling and processing clinical specimens, identifying isolates, animal tissues and mold cultures, identifying cultures in routine diagnostic laboratories, and for inoculating experimental animals, regardless of route. Any culture identifying dimorphic fungi should be handled in a Class II BSC. BSL-3 practices, containment equipment, and facilities are recommended for propagating sporulating cultures of *H. capsulatum* in the mold form, as well as processing soil or other environmental materials known or likely to contain infectious conidia.

E. SPECIAL ISSUES

Transfer of Agent Importation of this agent may require CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA/APHIS/VS. A DoC permit may be required for the export of this agent to another country. See Appendix C of the BMBL for additional information.

Taken Directly from: http://www.cdc.gov/biosafety/publications/bmbl5/index.htm
III. EMERGENCY DEPARTMENT TRIAGE

VERIFICATION OF EXPOSURE AND DECONTAMINATION NOTE

A. Confirm that the employee has had an exposure to *Histoplasma capsulatum* spores or yeast form working in a BSL 2/3 laboratory.

B. Confirm that the employee has carried out first aid for skin wound or skin surfaces (wound washed with hospital-approved disinfectant) if those sites have been exposed.

C. Confirm that the employee has carried out first aid for eye, nose or mouth splash (area flushed with running water for at least 15 minutes) if those sites have been exposed.

D. Confirm that the employee has removed garments that may have become soiled/contaminated and placed them in a double plastic bag.

E. If conditions in items B, C, and D are met, the employee can be roomed with no special precautions or may sit in the waiting room.

F. Confirm that the Supervisor and PI have been notified.

G. Confirm that Environment Health and Safety (EH&S) has been notified. Contact EH&S through the UC Police Department Emergency Dispatch (from a campus telephone 9-911, from a non-campus phone 415/476-1414) for laboratory clean-up as appropriate.

Signature of Nurse or other Triage Clinician: _________________________________________

Date: ________________________________
IV. Discharge Instructions for the Patient Exposed to *Histoplasma capsulatum*

A. Background Information

*Histoplasma capsulatum* is a fungus. It grows both as a yeast and a mold that can become airborne as spores. The disease of Histoplasmosis can be acquired by inhalation of the spores produced by the mold form. The disease can also be produced in animals by direct injection or mucous membrane exposure to either the yeast or mold forms. If you have worked in the BSL 2 lab, you have had contact with the yeast form, which could result in a local infection if you have had an accident. If you have worked in a BSL 3 lab, you have had contact with the mold form, and the potential for severe infection exists in the event of a BSL 3 laboratory accident. Therefore, the physician recommendation is that you take anti-fungal medication for a month following an exposure to prevent severe infection.

Those individuals with any form of immune system compromise are especially susceptible to severe infections. About 25% of adult exposures result in a “flu-like” syndrome. Up to 75% of individuals exposed to barns/caves where *Histoplasma* exists in spore form have developed symptomatic disease. Most disease is self-limited and the time of onset of symptoms varies with the severity of exposure. See comment question above.

B. Medication

With known airborne exposures in the BSL 3 lab, the medication itraconazole is recommended. Prophylaxis is especially important in the event of exposure to a high volume of organisms because this is more likely to result in symptomatic disease.

You will be given anti-fungal medication itraconazole 3 times a day for 3 days, then once a day for 30 days. If you develop symptoms of the disease, you may have to take the medication for 3 months, and for severe disease, for up to a year.

The medication is sometimes given with food and Classic Coke. This helps absorption.

Preventive medication should be started the day of exposure, but can be started up to 2 weeks after acute exposure. The rationale for this is that most severe cases would likely produce symptoms within 2 weeks. After 2 weeks, prophylaxis should be started with the development of symptoms. If you do not have symptoms at two weeks, severe disease would not be likely. You should not take the medication if you are pregnant or are planning to become pregnant.

C. Side Effects

The most common side effects include: skin rash and digestive system problems (such as nausea, bloating, and diarrhea). It is important that you report this to your provider. If you develop tingling or numbness in your hands or feet, call your provider right away. If you become unusually tired, lose your appetite, or develop nausea, vomiting, a yellow color to your skin or eyes, dark colored urine, or pale stools, call your provider. In rare cases, this medication may cause serious liver problems and these could be the warning signs. (*taken from Janssen Pharmaceutica* products, Patient Information)
Stop the medication and call your provider right away if you develop shortness of breath, have unusual swelling of the feet, ankles or legs, suddenly gain weight, are unusually tired, cough up white or pink phlegm, or have unusual fast heartbeats. In rare cases, patients taking this medication could develop serious heart problems, and these could be warning signs of heart failure.

D. Follow Up

It is important that you report as soon as possible to Occupational Health Services (415/885-7580) for follow up and workers’ compensation evaluation. For patients receiving medication, follow up will be conducted at 1, 3-6, and 8-12 weeks after exposure in the Occupational Health clinic at Mount Zion. This will include symptom review, assessment of your medical status, and repeat blood tests at 3-6 weeks after initial exposure and at 3 months after exposure. In case of development of flu-like symptoms, patients should return immediately for reevaluation. In the event that you think you may be pregnant, stop taking itraconazole and go to the Occupational Health Clinic at Mount Zion.