Practical Training Exercise

ANALYZING AND MANAGING RISKS IN LIFE SCIENCES RESEARCH

Based on the article by Siddique, N. et al. “Sequence and phylogenetic analysis of highly pathogenic avian influenza H5N1 viruses isolated during 2006–2008 outbreaks in Pakistan reveals genetic diversity.” Virology Journal. 2012; 9: 300.

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ADVANCING SCIENCE, SERVING SOCIETY

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Learning Objectives

1. Develop the skills to think critically about risks and risk mitigation strategies needed in your own scientific environment;

2. Enhance your ability to identify risk management strategies and approaches that minimize identified risks and maintain the high-quality and utility of the scientific activity; and

3. Apply the risk analysis framework to your own or your peers' scientific activities.

Participant Expectations

By the end of this exercise, you will have familiarity with:

1. The definitions of different types of risks associated with laboratory, field, and public health research.
2. The process of risk analysis—risk identification, assessment, management, and communication—including:
   - How to identify and assess risks by considering the possible likelihood and consequences of risks, and the risks versus benefits of a research activity,
   - Strategies for managing risks, and
   - Who, when, and how to communicate risks.
3. How to apply the risk analysis framework to your own scientific activities.

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Ground Rules for Participation

Prior to starting this exercise, participants should have read the case study article.

Ask the facilitator to clarify questions about the case study article.

Focus on understanding and analyzing the diverse risks involved in the research rather than on critiquing the methodologies or research choices of the authors.

Interact with one another in a way that encourages open communication and exchange of ideas. For example, listen to everyone's ideas respectfully.

You may want to take your own notes to enhance your ability to actively participate in the training activity.

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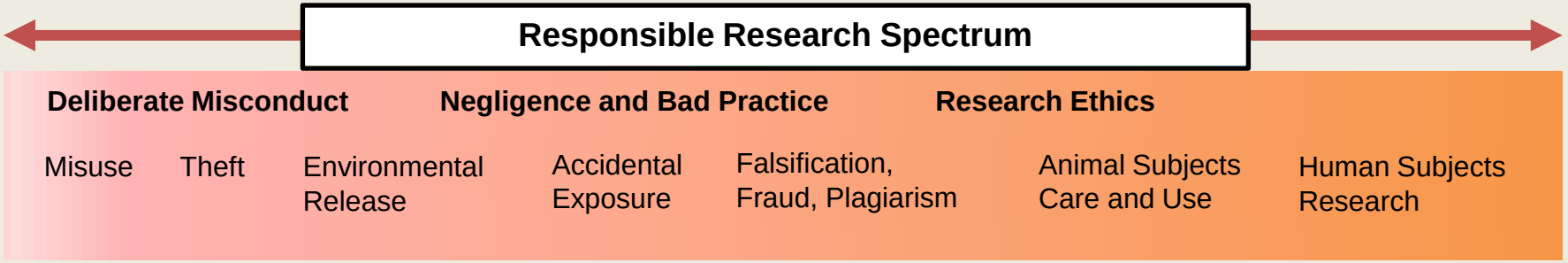
Biorisk Glossary

These definitions are from the WHO's *Responsible Life Science for Global Health Security: A Guidance Document*.



- Bioethics
- Biorisk
- Biorisk reduction
- Laboratory biosafety
- Laboratory biosecurity
- Dual-use life sciences research
- Research excellence

<u>Additional concepts:</u>

- Protection of human subjects
- Protection of animal subjects
- Responsible research/responsible conduct of research

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Risk Analysis Framework

Your risk review will follow these 4 stages:

1. **Risk Identification**
2. **Risk Assessment**
3. **Risk Management**
4. **Risk Communication**

1. Risk Identification

process by which researchers consider all possible internal, external, and organizational risks.

Asks the question:

- ***What are the possible risks associated with the research?***

2. Risk Assessment

process by which researchers identify needed resources and consider biosafety/biosecurity recommendations.

Also defined as the “process of evaluating the risk(s) arising from a hazard(s), taking into account the adequacy of any existing controls and deciding whether or not the risk(s) is acceptable).” (OHSAS 18001: 2007)

Asks the questions:

- ***How likely are the risks to occur?***
- ***What are the potential consequences if the risks occur?***
- ***Do the risks outweigh the benefits?***

3. Risk Management

process by which researchers consider regulations/guidelines, training, and SOP compliance issues.

- Asks the question:

  What risk management strategies could minimize the likelihood that the risk will occur or the consequences if the risks occurred?

- Possible strategies: physical barriers, personnel training or vetting, regulations and laws, and/or alternative experiments

4. Risk Communication

process by which researchers consider communication strategies, non-compliance issues and approval/modification processes.

- Asks the questions:

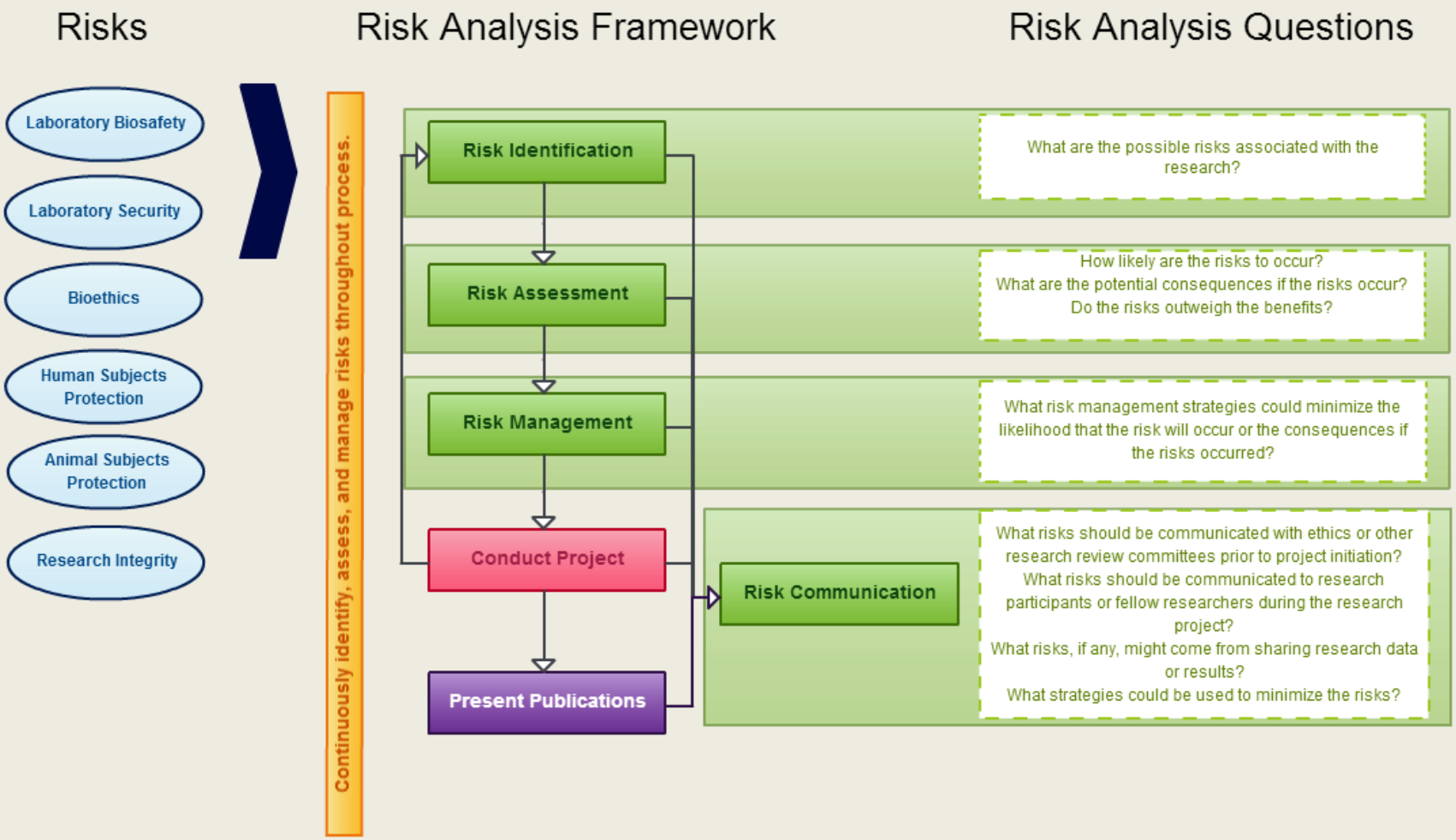
  What risks should be communicated with ethics or other research review committees prior to project initiation?

  What risks should be communicated to research participants or fellow researchers during the research project?

  What risks, if any, might come from sharing research data or results?

  What strategies could be used to minimize the risks?

Risk Analysis Chart



CASE STUDY

Sequence and phylogenetic analysis of highly pathogenic avian influenza H5N1 viruses isolated during 2006-2008 outbreaks in Pakistan reveals genetic diversity

Siddique, N. et al. “Sequence and phylogenetic analysis of highly pathogenic avian influenza H5N1 viruses isolated during 2006–2008 outbreaks in Pakistan reveals genetic diversity.” Virology Journal. 2012; 9: 300.

Outline of Case Study

Part 1: Research Question/Hypothesis

Part 2: Background Information Overview

Part 3: Research Methodology

Part 4: Risk Analysis in the Research Article

Part 5: Research Results and Conclusions

Research Question/Hypothesis

Research Statement:

“The present study was designed to carry out sequence and phylogenetic analyses of HPAI H5N1 isolates recovered during 2006–08 from different wild, domestic and commercial poultry populations in Pakistan.”

The goal is to understand the genetic relationship of Pakistani highly pathogenic H5N1 strains with strains isolated from other parts of the world to better understand the geographic origins of the Pakistani viruses.

Background Information Overview

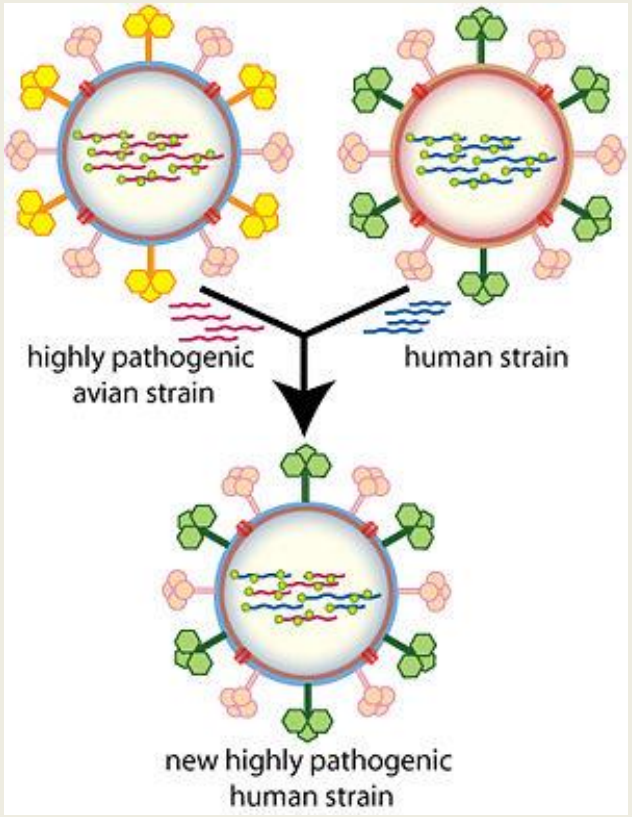
Avian Influenza Virus

- Avian influenza viruses are characterized as highly pathogenic (HPAI) if they cause significant disease in birds.
- Avian influenza viruses are characterized as low pathogenic (LPAI) if they do not cause disease in birds.
- HPAI H5N1 viruses originate from Asia.
- LPAI H5N1 viruses originate from North America.
- The Asian HPAI and North American LPAI H5N1 strains are not closely related.
- Influenza A viruses are classified by their hemagglutinin and neuraminidase proteins. Sixteen hemagglutinin (HA) subtypes and 9 neuraminidases (NA) subtypes of Influenza A virus have been identified.

Background Information Overview

How Influenza Mutates

- Has 2 surface glycoprotein genes
  - HA – hemagglutinin
  - NA – neuraminidase
- Virus undergoes natural mutations
  - Antigenic drift: mutations within individual genome
  - Antigenic shift: exchanging genes between 2 viruses during co-infection (genetic recombination)

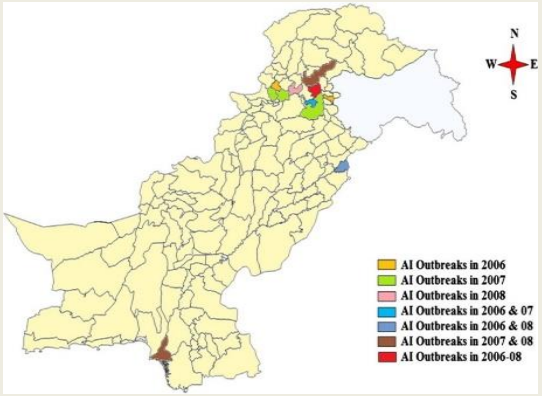


Influenza Genetic Shift
Photo Credit: Wikipedia, 2012

Background Information Overview

H5N1 in Pakistan

- The Indus Flyway (an international migratory route) brings 0.7-1.2 million birds to Pakistani wetlands each year.
- Influenza A viruses have been identified in Pakistani poultry since 1995.
- HPAI H5N1 was first identified in Pakistan in 2006 (Siddique et al.)
- Since 2006, HPAI H5N1 infected domestic poultry through backyard interactions with infected wild birds.
- Vaccination and biosecurity measures were undertaken to control H5N1 circulation in Pakistani birds.
- Between 2006-2008, only Abbottabad experienced continuous H5N1 infections.



HPAI H5N1 outbreaks in Pakistan during 2006–08.

Photo Credit: Siddique et al.

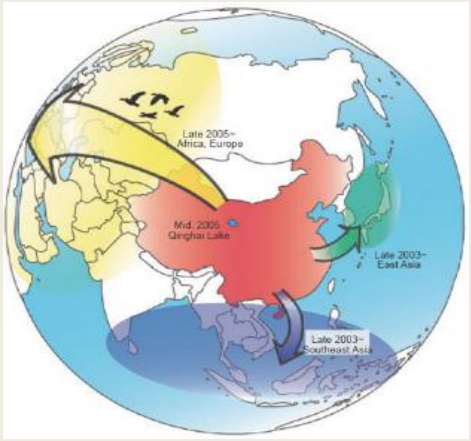


Photo Credit: Neumann et al., 2010

Research Methodology

- **Collection and Isolation.** Organs and throat swabs from dead birds were received by provincial surveillance units. Viruses were cultured from samples using fertilized chicken eggs. Allantoic fluid from inoculated embryos was harvested.

- **RNA extraction and genome sequencing.** Viral RNA extracted from clinical samples and alliotic fluid using a commercial kit.
  - Real-time PCR was performed to detect H5 virus in the samples and alliotic fluid.
  - Reverse Transcriptase PCR (RT-PCR) was used to create and amplify cDNA of the virus.
  - The purified cDNA PCR products were sequenced.

- **Phylogenetic analysis.** Using the online BLAST algorithm, sequences from the GenBank database that were closely related to the Pakistani H5N1 viral sequences were selected for phylogenetic analysis. The Pakistani H5N1 viral sequences were compared to the selected GenBank H5N1 sequences using commercially available software.

Risk Analysis in this Research Article

While risk analysis is an important part of science, few scientific publications include in-depth descriptions of how the authors assessed and managed risk.

Today your task is to perform a risk analysis based on this research article.

To begin, answer the following question:

Based on your current knowledge of the experiment procedures and research purpose, what risks might be important to consider in designing, carrying out, or communicating this research?

Risk Identification

Sequence and phylogenetic analysis of highly pathogenic avian influenza H5N1 viruses isolated during 2006-2008 outbreaks in Pakistan

Questions
What, if any, are the potential safety risks to researcher and staff? Consider: surveillance teams gathering samples, sample transportation and sample preparation?
Does this research pose any potential risks to human health in Pakistan? Can any of this research be used to intentionally harm people or animals?
Are there any risks associated with collecting and analyzing samples from wild birds versus a domestic chicken or other livestock?

Risk Assessment

Sequence and phylogenetic analysis of highly pathogenic avian influenza H5N1 viruses isolated during 2006-2008 outbreaks in Pakistan

Question
What methodological steps, if any, in this research are most likely to cause a deliberate or accidental incident with severe, negative consequences? How likely is such an incident?
What steps in this study present the greatest biosafety threats to the research team? What steps in this study present the greatest biosecurity threats to the research team? How does working with a pathogen of global health concern, such as H5N1, change this assessment?
What are the resources, expertise, training, and tools that could be useful in assessing the risks identified for this research project?

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Risk Management

Sequence and phylogenetic analysis of highly pathogenic avian influenza H5N1 viruses isolated during 2006-2008 outbreaks in Pakistan

Question
Are there any international, domestic, or institutional laws and regulations that would help manage risks from this experiment?
What standard operating procedures (SOPs) in sample collection, storage, transport, and analysis should be employed in this research project to mitigate any safety or security risks?
How could researchers in this or a similar project minimize potential negative impacts of expected outcomes without changing the research question or the quality of the science?
What, if any, specialized competencies, skills, and training are needed to safely and successfully carry out this laboratory experiment?

Research Results and Conclusions

Results

- All the HPAI H5N1 viruses in the study were “related to those circulating in poultry populations of South Asia, East Asia, Middle East and Europe since late 2005,” but Pakistani virus most closely related to those from neighboring countries.
- Pakistani H5N1 isolates have a “high rate of sequence identity”, which indicates rapid dissemination throughout the country from a single introduction in Pakistan in 2006.
- The Pakistani H5N1 isolates from 2006-2008 are genetically diverse, having several mutations in important antigenic and receptor binding sites.

Conclusions

The Pakistani H5N1 isolates from 2006-2008 were closely related to isolates from Afghanistan and neighboring Eurasian countries.

The authors state that that transportation through legal and illegal poultry trade cannot be ignored

Risk Communication

Sequence and phylogenetic analysis of highly pathogenic avian influenza H5N1 viruses isolated during 2006-2008 outbreaks in Pakistan

Question
What are the risks that should be communicated during this research? To whom?
What are some strategies for communicating the risks and research findings with public and animal health experts and government stakeholders?
When working with pathogens of concern to human health or agriculture, SUCH AS H5N1, what tools are available to aid researchers in evaluating the risks of communicating the research findings?
Are there any circumstances under which researchers should not share all or some of their findings with other scientists and the public?

Final Exercise: Risk in Your Own Research

Perform a risk analysis of your own research. Choose one past, ongoing, or future research project to analyze:

1. Identification: What are the primary risks you face in your research? Think about the risks to you and other researchers and technicians in the field, clinic, and/or lab, the general public, the environment and economy, your institution, and human and animal subjects.
2. Assessment: What are the consequences of the identified risks if they occur? How likely are they to occur? Based on your assessment of the potential consequences, are there are there any risks that could harm people, animals, crops, or the economy? What resources, capabilities, and skills are needed to mitigate these risks?
3. Management: What strategies could you use or resources you could refer to minimize or mitigate these risks? (These strategies should not decrease the quality of the research.) For ideas of possible strategies and resources, consider those discussed in this practical exercise and from your own experiences. Are there any risks associated with your research that cannot be adequately mitigated?
4. Communication: What risks, if any, are associated with communicating your research during the design or conduct of the research? What risks, if any, are associated with communicating the research results at scientific conferences and in publications? What strategies could you use to mitigate the risks? Are there any stakeholders with whom you must share or should share the risks of your research? Your findings?

Example Risk Analysis Strategy

Communicate

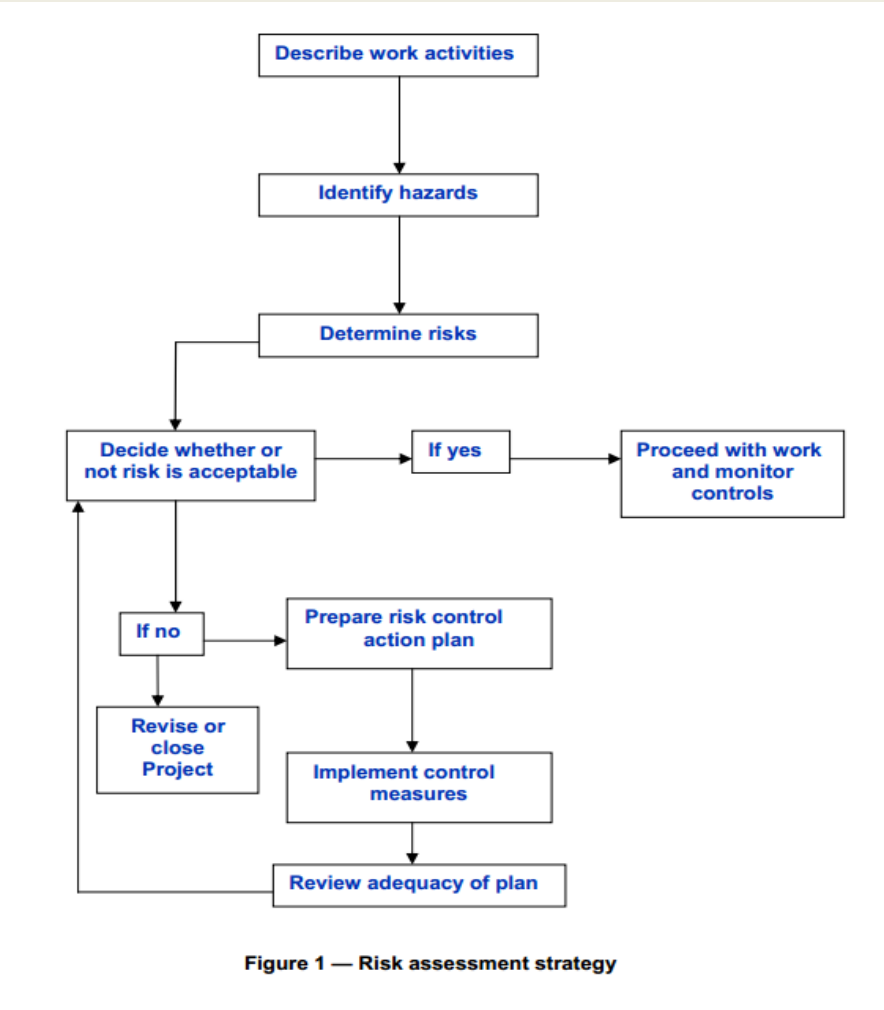

Figure 1 — Risk assessment strategy

"Laboratory risk management." CWA 15793: 2011

Reference List

Background Information

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Diagrams and Images

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