Practical Training Exercise

ANALYZING AND MANAGING RISKS IN LIFE SCIENCES RESEARCH

Based on the article by Ben Salah, G, et al. “An Interethnic variability and functional prediction of DNA repair gene polymorphisms: the example of XRCC3 (pThr241>Met) and XPD (pLys751>Gln) in a healthy Tunisian population.” Mol Biol Rep. 2012; 39: 9639-9647.

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ADVANCING SCIENCE, SERVING SOCIETY

This exercise was developed by Center for Science, Technology and Security Policy at the American Association for the Advancement of Science (AAAS).

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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.

Ground Rules for Participation

1. Prior to starting this exercise, participants should have read the case study article.
2. Ask the facilitator to clarify questions about the case study article.
3. Focus on understanding and analyzing the diverse risks involved in the research rather than on critiquing the methodologies or research choices of the authors.
4. Interact with one another in a way that encourages open communication and exchange of ideas. For example, listen to everyone's ideas respectfully.
5. You may want to take your own notes to enhance your ability to actively participate in the training activity.

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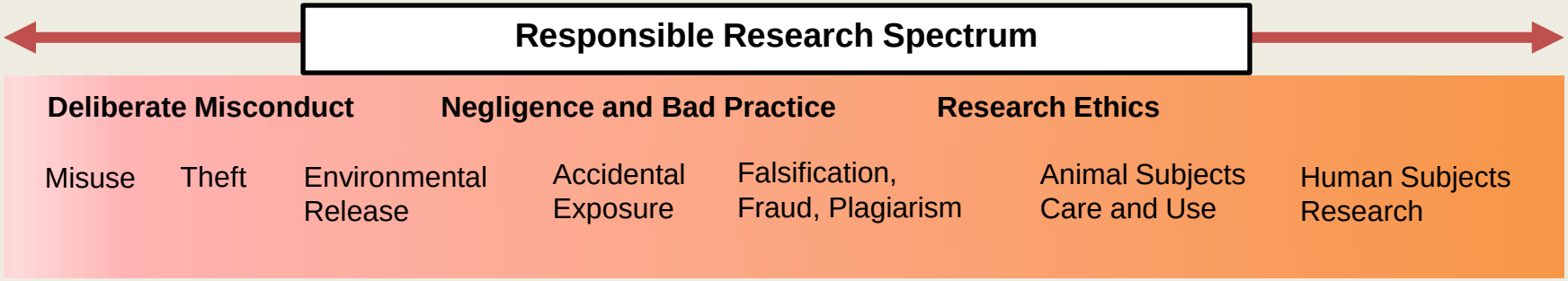
Biorisk Glossary

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?***

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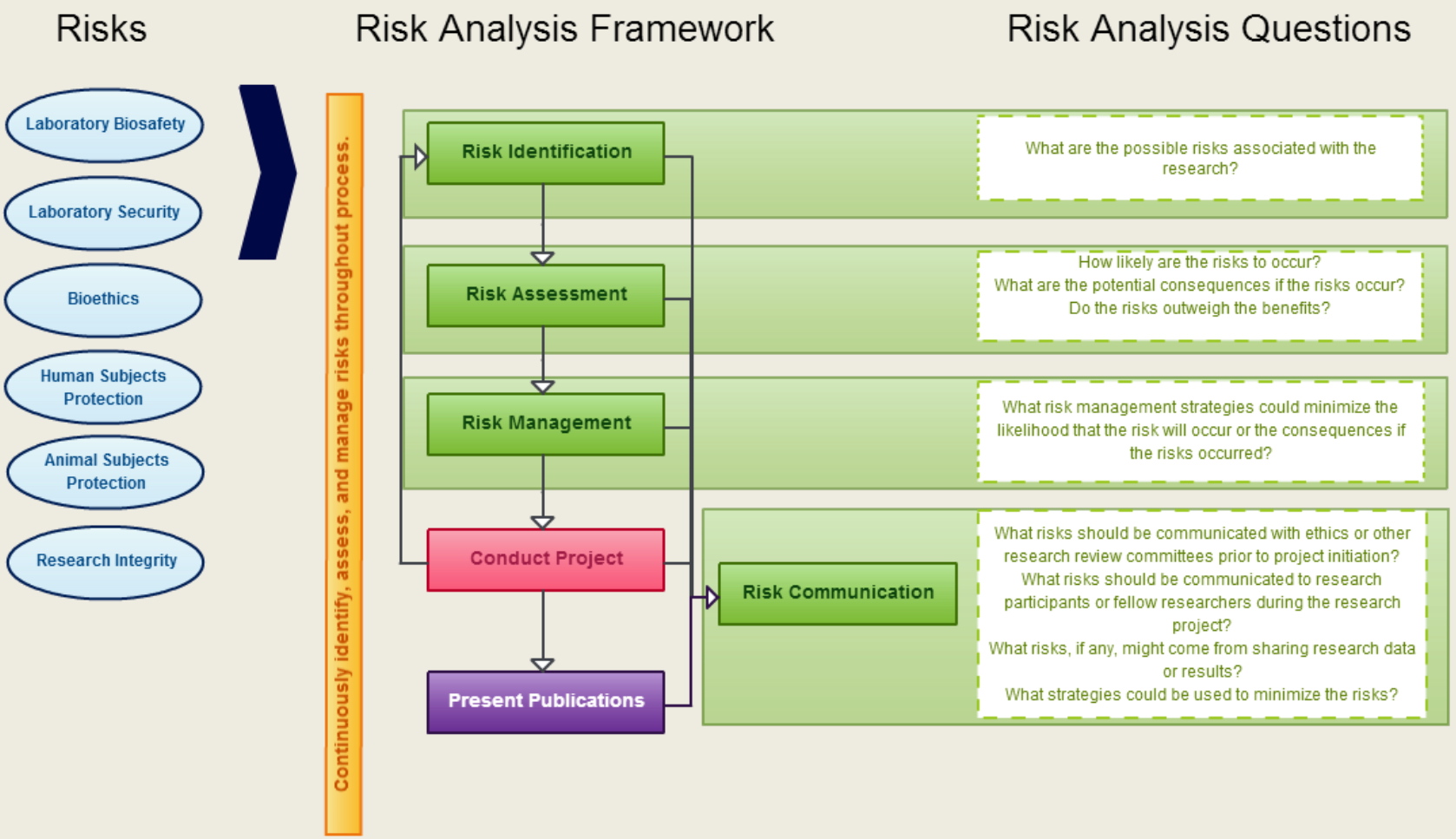
Risk Analysis Chart



CASE STUDY

An Interethnic variability and functional prediction of DNA repair gene polymorphisms: the example of XRCC3 (pThr241>Met) and XPD (pLys751>Gln) in a healthy Tunisian population

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Ben Salah, G, et al. “An Interethnic variability and functional prediction of DNA repair gene polymorphisms: the example of XRCC3 (pThr241>Met) and XPD (pLys751>Gln) in a healthy Tunisian population.” Mol Biol Rep. 2012; 39: 9639-9647.

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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:

DNA repair is critically important for maintaining genome stability and normal cellular and organismal functions.

Mutations in the protein XRCC3 (involved in homologous recombination repair) and XPD (involved in nucleotide excision repair) have been linked to cancer.

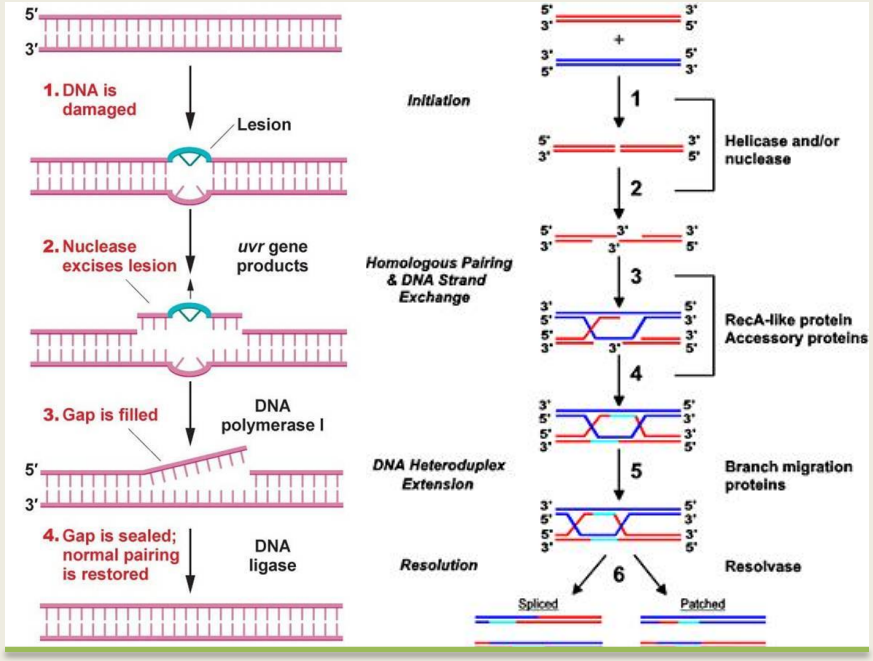
The prevalence of these mutations “are not randomly distributed throughout the human population, but follow diverse ethnic and/or geographic-specific patterns.”

The authors proposed to examine the prevalence of these mutations in the Tunisian population and carry out bioinformatic analysis to assess whether the mutations are deleterious in the Tunisian population.

Background Information Overview

DNA Repair

- Changes in DNA can occur through individual base deletions, additions, or substitutions; single stranded breaks; and double stranded breaks.
- DNA repair is a critical cellular function to fix breaks in the DNA before they cause major damage.
- Repair can be done through correcting individual bases (nucleotide excision repair) or repairing major damage (homologous recombination repair).



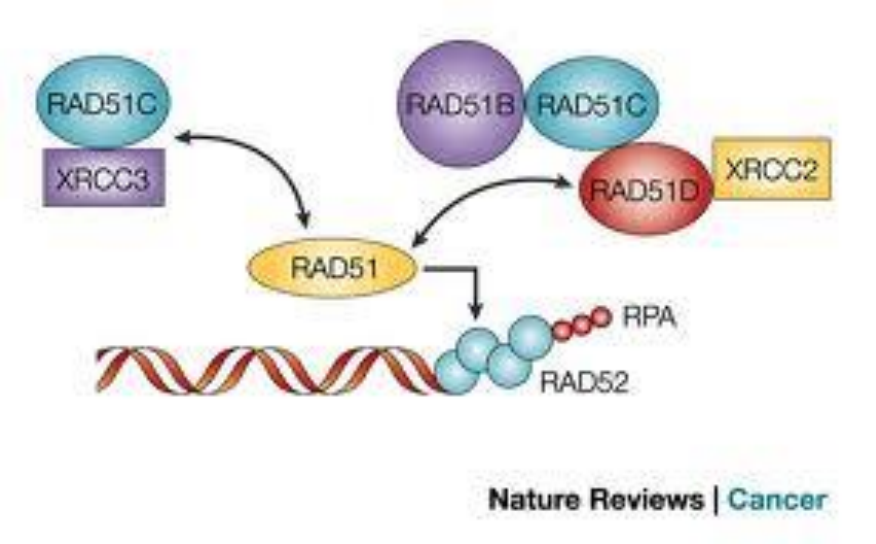
Nucleotide Excision Repair
Photo Credit: Laura Mitchell, 2011

Homologous Recombination
Photo Credit: Bianco et al., 1998

Background Information Overview

XRCC3 and Homologous Recombination Repair (HRR)

- XRCC3 is *X-ray repair cross-complementing group 3*
- XRCC3 is thought to repair chromosomal fragmentation, translocations, and deletions
- XRCC3 is a member of the Rad-51 family of proteins and interacts with other family proteins to carry out its role in homologous recombination repair
- The Thr241>Meth is the most common mutation and is associated with low DNA repair capacity, which could lead to cancer.



XRCC3 and HRR.
Photo Credit: Skorski, 2002.

Background Information Overview

XPD/ERCC2 and Nucleotide Excision Repair

- XPD is *xeroderma pigmentation complementation group D*
- It is a ATPase/helicase involved in nucleotide excision repair and transcription
- The Lys751>Gln mutation is linked to lower DNA repair capacity by altering the properties of the DNA repair enzyme, which is a complex of proteins.

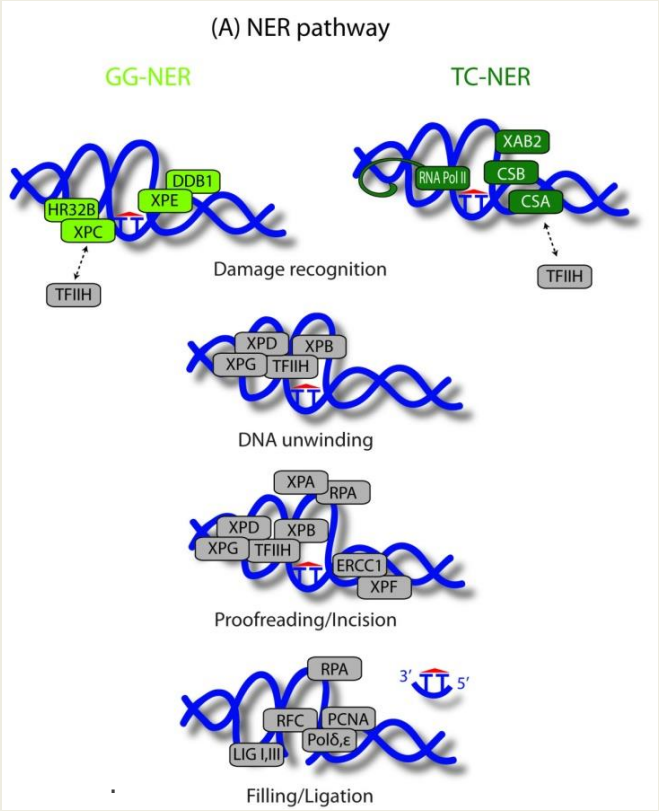


Photo Credit: Cameroni, et al, 2010

Research Methodology

- **Patient Inclusion:** Healthy, unrelated individuals (154 men and women from South Tunisia) were recruited to participate in the study. Participants provided their social habits and health problems on a standard questionnaire. Individuals with a history of cancer were excluded.
- **DNA Extraction and Sample Genotyping:** Blood samples were collected from participants and DNA was extracted using standard procedures. Fragments from the XRCC3 and XPD genes were amplified by polymerase chain reaction (PCR). Restriction fragment length polymorphism (RFLP) analysis was conducted on the amplified fragments.
- **Bioinformatics Analysis:** The HapMap database was used to determine which mutations/polymorphisms were associated with different ethic and geographic groups. Sorting intolerant from tolerant (SIFT) software and analysis was used to predict whether the mutations might affect protein function. The SIFT predictions were verified by Polymorphism Phenotyping, version 2.2 software.
- **Statistical Analysis:** Standard statistical analyses were conducted on the data to calculate the allele frequency and compare the relatedness between alleles found in the Tunisian and HapMap populations.

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 experimental procedures or research purpose, what risks might be important to consider in designing, carrying out, or communicating this research?

Risk Identification

An Interethnic variability and functional prediction of DNA repair gene polymorphisms: the example of XRCC3 (pThr241>Met) and XPD (pLys751>Gln) in a healthy Tunisian population

Questions
What, if any, are the potential biosafety risks (including collection and handling of human blood samples) to researchers and staff?
What, if any, are the possible safety and ethical risks to the patients who participate in this study? What risks, if any, are associated with collecting information about study participants?
Could this research be used to cause harm, either misuse of research information, materials and results?

Risk Assessment

An Interethnic variability and functional prediction of DNA repair gene polymorphisms: the example of XRCC3 (pThr241>Met) and XPD (pLys751>Gln) in a healthy Tunisian population

Question
What aspect of this research or procedural steps might pose the most severe consequences to patients? What are those consequences and how likely are they?
What aspect of this research or procedural steps might pose the most severe consequences to researchers? What are those consequences and how likely are they?
What are the resources, expertise, training, and tools that could be useful in assessing the risks identified for this research project?

Risk Management

An Interethnic variability and functional prediction of DNA repair gene polymorphisms: the example of XRCC3 (pThr241>Met) and XPD (pLys751>Gln) in a healthy Tunisian population

Question
What international, national, and institutional laws, regulations, policies, and best practices could minimize the identified risks of the research project?
What are the minimum laboratory safety and security protocols and infrastructure (including equipment) that should be in place before beginning this research project?
What additional approaches could be used to minimize the identified risks of the research project?
What, if any, specialized competencies, skills, and training are needed to successfully carry out this research?
What could the research team do in advance to limit the risk of sensitive personal information being accessed?

Research Results and Conclusions

Results

- According to genetic analyses of the *XRCC2* and *XPD* genes, the Tunisian population is closely related to the Caucasian population from European ancestry.
- The XPD genetic analysis suggests a relationship between the Tunisian population and people who originated from Gujarat, India.
- The p.Thr241>Met mutation of XRCC3 is potentially damaging and could affect ATP-binding and DNA repair efficiency. This mutation affects homologous recombination repair.
- The pLys7521>Gln mutation of XPD might be tolerated. The mutation affects the ATP-binding site of XPD and destroys his helicase activity. Although this mutation affects nucleotide excision repair, it does not affect transcription activity.

Conclusions

- The data provides the foundation to further study the relationship of the *XRCC3* and *XPD* mutations to cancer risk and DNA repair variability in the Tunisian population.

Risk Communication

An Interethnic variability and functional prediction of DNA repair gene polymorphisms: the example of XRCC3 (pThr241>Met) and XPD (pLys751>Gln) in a healthy Tunisian population

Question
What are the risks that should be communicated during this research? To whom?
How would you communicate the risks and risk management steps to an IRB or ethics committee?
What data and information protection measures should be implemented to protect the safety and anonymity of research participants?
What, if any, social or cultural sensitivities are associated with the study? What approaches can be used to minimize these sensitivities when research results are discussed at conferences, between project researchers, and in publication?
What approaches could be used to communicate any risks and risk mitigation strategies to other researchers 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

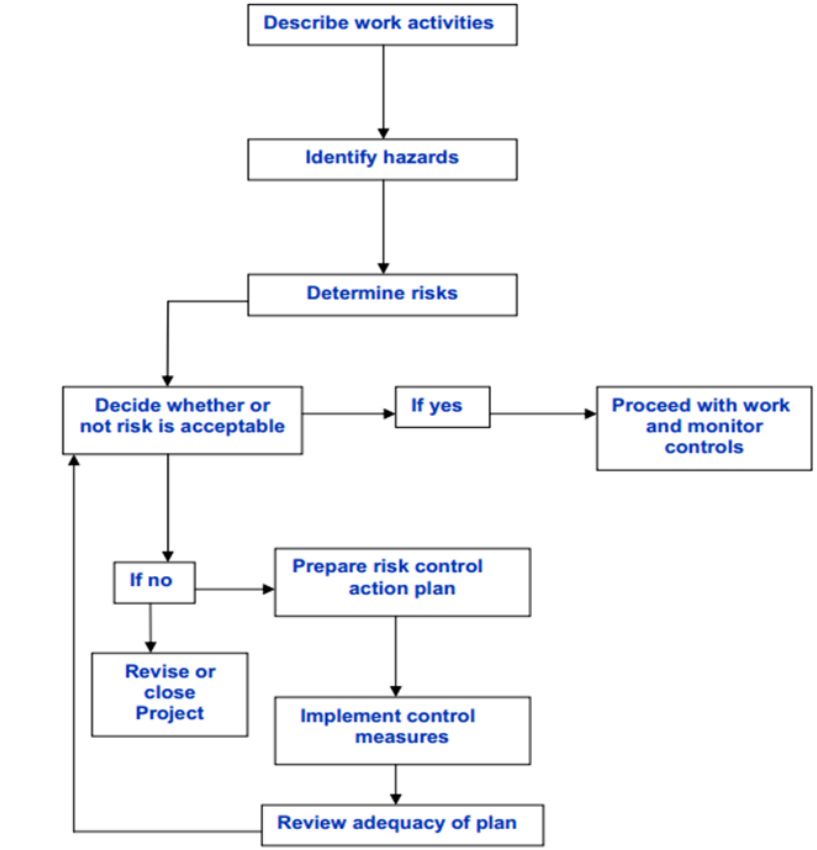


Figure 1 — Risk assessment strategy

"Laboratory risk management." CWA 15793: 2011

Reference List

Background Information and Data

Ben Salah, G, et al. “An Interethnic variability and functional prediction of DNA repair gene polymorphisms: the example of XRCC3 (pThr241>Met) and XPD (pLys751>Gln) in a healthy Tunisian population.” Mol Biol Rep. 2012; 39: 9639-9647.

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Diagrams and Photos

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