Refining the Adverse Outcome Pathway (AOP) for Radon -Induced Lung Cancer

Approaching the integration of genetic susceptibility and environmental co -exposures

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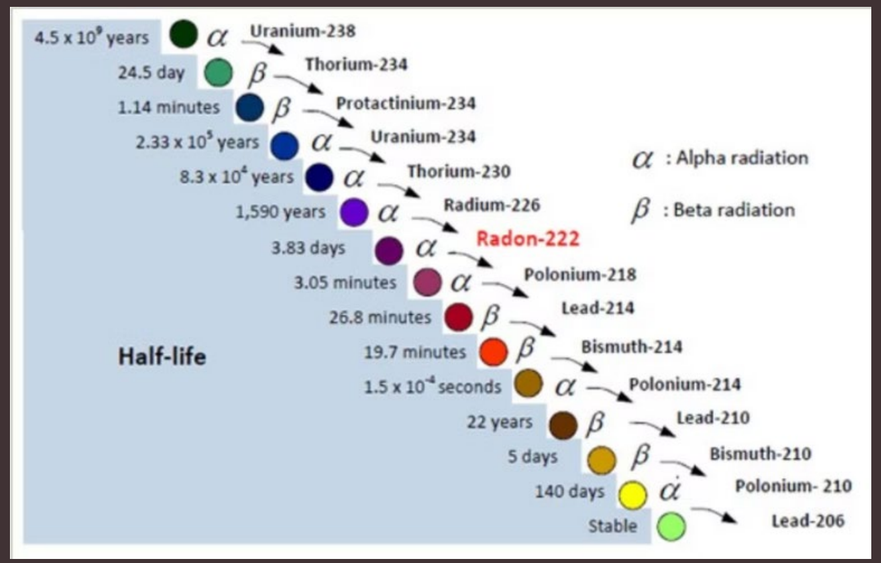
Understanding Radon: A Silent Threat

Radon is a naturally occurring, colorless, and odorless radioactive gas formed from the breakdown of radioactive materials in the earth. It poses a significant public health risk as it can accumulate indoors, particularly in basements, crawl spaces, and poorly ventilated areas.

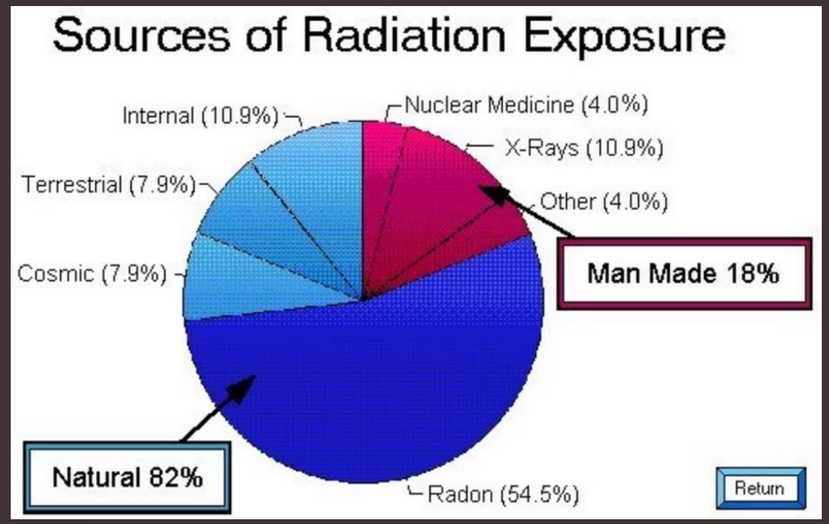
This gas is a leading cause of lung cancer, associated with an estimated 20,000 deaths annually in the United States, predominantly among smokers. While radon itself doesn't directly cause lung cancer, its radioactive decay byproducts are the culprits.

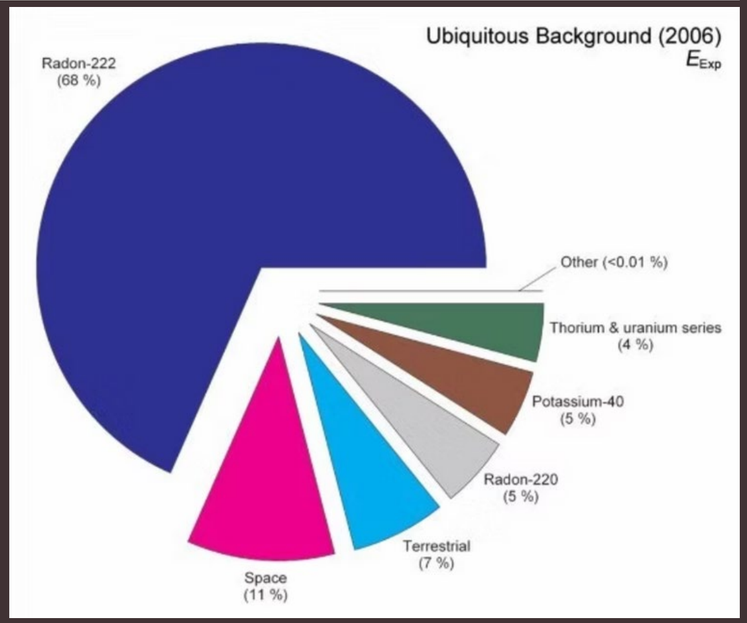
Radon originates from the decay chain of uranium -238 and thorium -232, progressing through radium -226 before producing radon -220 (thoron). Radon -222 is the most prevalent isotope and is strongly linked to lung cancer development.



The Significant Health Impact of Radon Exposure

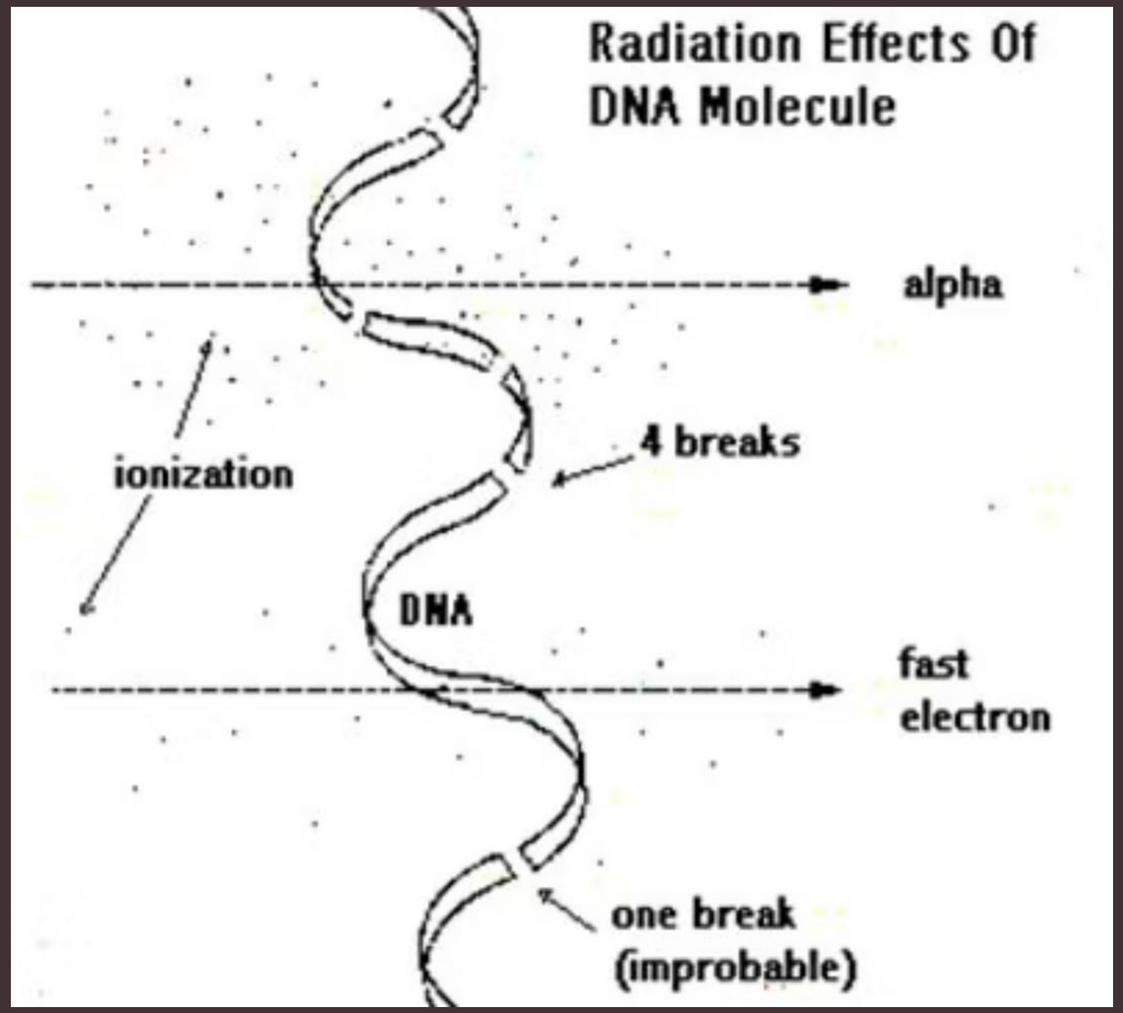
- Radon is recognized as the second leading cause of lung cancer globally, surpassed only by tobacco smoking. It's estimated to contribute to **3–14%** of all lung cancer cases worldwide.
- Exposure is prevalent in residential settings and occupational environments, particularly in mining and certain industrial facilities.
- The U.S. Environmental Protection Agency (EPA) has set an action level of 4 picocuries per liter (pCi/L) for indoor radon.





- It's crucial to understand that even levels below this action threshold carry some risk of lung cancer.
- However, **susceptibility varies widely among individuals**, suggesting biological and environmental modifiers.
- My research focuses on how **DNA repair deficiencies** and **co-exposures** (like smoking) **amplify this risk**, refining the Adverse Outcome Pathway (AOP) for radon-induced lung cancer.

Biological Mechanism of Radon Carcinogenesis



Radon's decay products, primarily alpha -emitting particles like polonium -218 and polonium -214, are the direct cause of cellular damage.

When inhaled, these radioactive particles adhere to the delicate cells lining the bronchial airways. They then emit high linear energy transfer (LET) radiation, leading to a cascade of cellular injuries:

- DNA double -strand breaks (DSBs)
- Oxidative stress via reactive oxygen species
- Chromosomal aberrations
- Chronic inflammation

The cumulative result of these damages is genomic instability, a critical factor in the initiation and progression of lung cancer.

Why this work matters?

- The **Adverse Outcome Pathway (AOP)** framework connects molecular events; like DNA damage and repair failure - to real health outcomes such as lung cancer.
- By identifying these key biological steps, AOPs help **translate complex toxicology into actionable public health guidance.**
- My work refines the radon AOP to include **genetic variability** and **co-exposures**, explaining why some people are more vulnerable than others.
- This approach supports **personalized risk assessment**, allowing regulators and clinicians to better **identify high-risk populations**.
- Ultimately, improving the AOP leads to **smarter prevention policies**, **targeted radon mitigation**, and a **healthier, more protected population.**

The Adverse Outcome Pathway (AOP) Framework

The AOP framework provides a structured approach to link a molecular initiating event (MIE) to an adverse outcome (AO) through a series of key events (KEs).

1. **Molecular Initiating Event (MIE):**
   DNA damage caused by alpha particles from radon decay.

2. **Key Event 1 (KE1):**
   Induction of oxidative stress within lung cells.

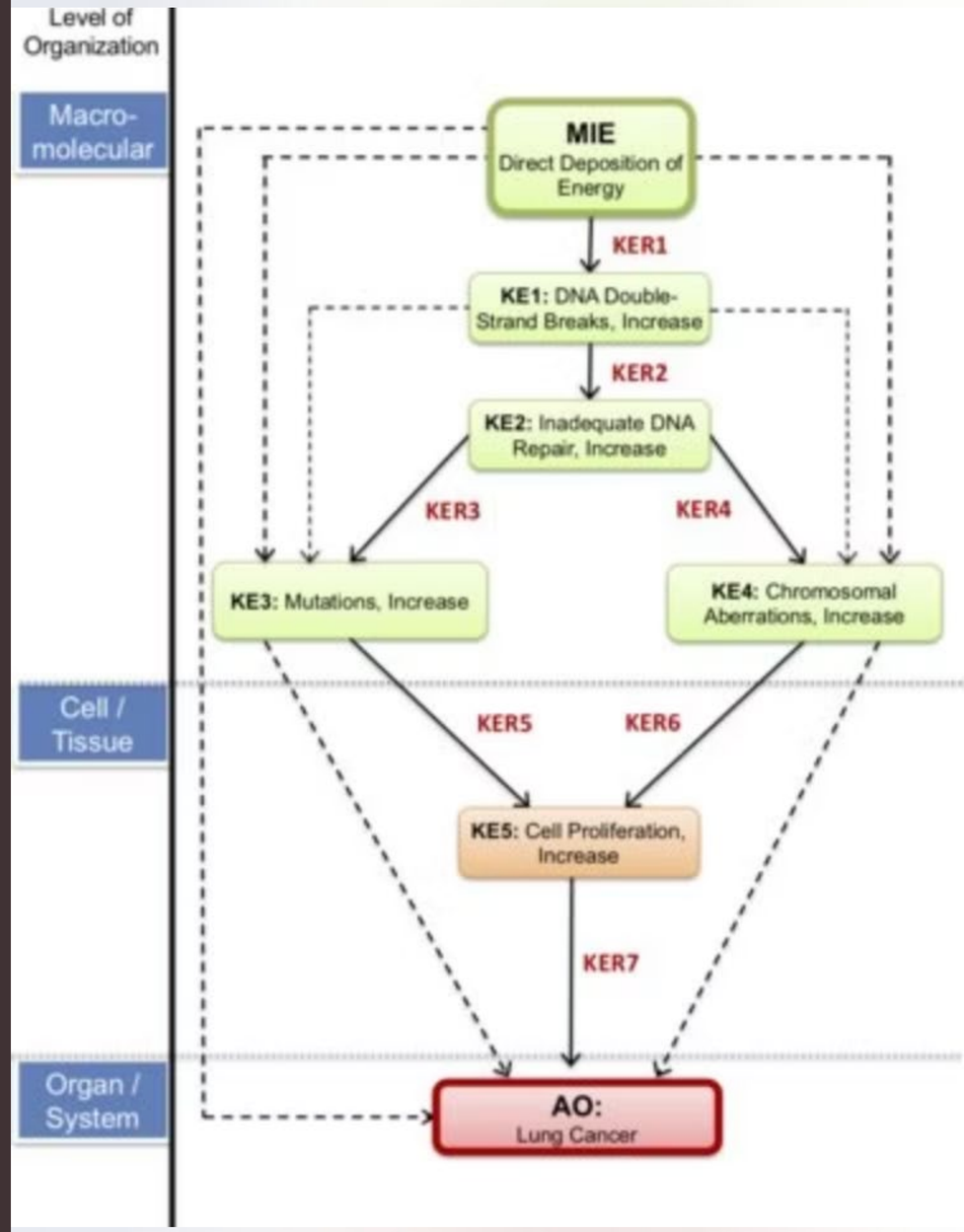
3. **Key Event 2 (KE2):**
   Failure or inefficiency of DNA repair mechanisms.

4. **Key Event 3 (KE3):**
   Development of chronic inflammation in the bronchial epithelium.

5. **Adverse Outcome (AO):**
   Progression to Non -Small Cell Lung Cancer (NSCLC).

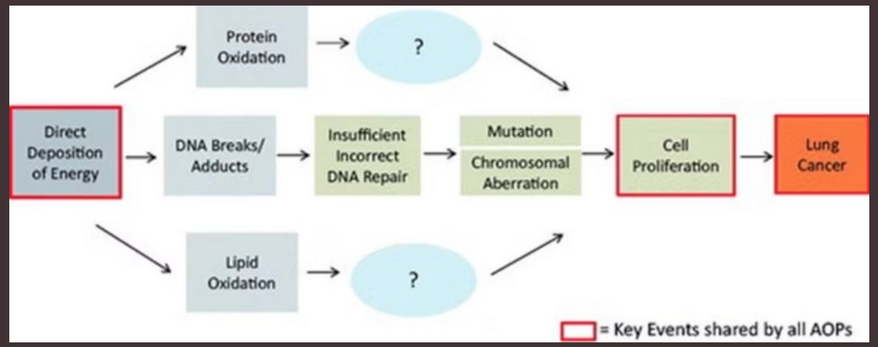
This framework is widely used by organizations like the OECD and EPA for mechanistic risk assessment, providing a clearer understanding of toxicological pathways.

Visual representation of an AOP, linking molecular events to adverse outcomes.



Key Focus Areas for Research and Intervention

This AOP framework helps visualize how radon exposure initiates a cascade of molecular and cellular damage, ultimately leading to cancer. It highlights why DNA repair, oxidative stress, and cell proliferation are critical focus areas for research and intervention.



Illustrative pathway showing radon exposure leading to DNA damage, oxidative stress, inflammation, and ultimately lung cancer.

Overall Aim: Using an AOP to Enhance Understanding about Radon -Induced Lung Cancer

Our overarching goal is to refine and improve the Adverse Outcome Pathway (AOP) for radon -induced lung cancer by integrating critical factors such as genetic variability, the impact of environmental co -exposures, and the framework's applicability in regulatory contexts.

Aim 1: Genetic Variability & DNA Repair

Integrating genetic variability and DNA repair deficiencies into the AOP model.

Aim 2: Environmental Co-Exposures

Developing a dynamic and predictive AOP model that incorporates environmental co-exposures.

Aim 3: Regulatory Applicability

Evaluating the feasibility of integrating the refined AOP framework into radon risk management and regulatory decision -making processes.

Aim 1: Genetic Variability in Radon AOP

Refining Existing AOP

This aim refines the current radon AOP by explicitly incorporating genetic variability among individuals.

DNA Repair Deficiencies

It focuses on DNA repair deficiencies as a crucial variability factor, challenging the assumption that everyone repairs radon -induced DNA damage equally.

Key Genetic Modulators

Highlights the roles of specific genes, such as **BRCA1, ATM, and XRCC1** , in modulating an individual's genetic variability to radon -induced lung cancer.

Personalized Risk Assessment

Supports the development of a more personalized approach to risk assessment, moving beyond population averages.

Benefit: Identifying Vulnerable Populations

Ultimately, this research helps to identify genetically variable populations who may be at higher risk, allowing for targeted preventative measures.

Main Focus for Aim 1: DNA Repair and Genetic Vulnerability

Key Event Focus: DNA Double - Strand Break (DSB)

Radon's alpha -particles primarily cause DNA double -strand breaks (DSBs), a highly damaging form of DNA lesion.

Impact on Risk Assessment and Management

Strengthens the radon AOP with a precisely defined molecular step (DSB repair failure) and supports risk characterization that accounts for genetic variability, guiding regulators and clinicians to identify high - risk subgroups and tailor mitigation strategies.

Goal: Map & Synthesize Evidence

To comprehensively map and synthesize evidence on how DSBs induced by radon are repaired (or fail to be repaired) in human cells.

Identify Genetic Variabilities

Identify specific genetic variabilities (e.g., in genes like BRCA1, ATM, XRCC1) that alter DNA repair efficiency and consequently increase lung cancer risk.

Mechanistic Insight

When DSB repair is deficient, cells accumulate mutations and genomic instability, creating a clear mechanistic bridge from radon exposure to lung carcinogenesis.

Aim 2: Co -Exposure with Environmental Hazards

Real -World Exposures

In real -world scenarios, individuals are exposed to radon alongside other environmental hazards, including particulate matter (PM2.5), tobacco smoke, and asbestos.

Amplified Harm

These co-exposures can lead to amplified oxidative stress, enhanced DNA damage, and persistent inflammation, accelerating the progression toward lung cancer.

Multi -Exposure Model

This aim focuses on creating a more realistic, multi -exposure model of lung cancer risk, reflecting the complex interplay of environmental factors.

Improved Risk Assessment

This approach supports improved risk assessment, particularly in environments with high pollution or multiple exposure sources.

Benefit: Targeted Policies, More effective interventions

The findings will inform targeted policies and interventions, allowing for more effective strategies to reduce overall pollutant exposures and protect public health.

Main focus for aim 2

Key Focus

- Smoking + radon: real -world combined exposure that strongly amplifies lung cancer risk.

Goal of This Aim

- Systematically map studies evaluating the joint effects of radon and smoking on lung cancer.
- Quantify dose –response and interaction between the two exposures.
- Refine the existing radon AOP by embedding smoking as a co -exposure modifier that influences multiple key events (e.g., oxidative stress, DNA damage, inflammation).

Mechanistic Insight

- Cigarette smoke adds additional carcinogens and reactive oxygen species, creating greater DNA damage and chronic inflammation than radon alone.
- Co-exposure may act as a multiple effector, impacting several steps in the AOP simultaneously.

Why This Matters

- Explains why risk estimates differ sharply between smokers and non -smokers even at the same radon levels.
- Makes the AOP more reflective of real -world mixed exposures rather than a single -agent model.

Impact

- Has the potential to strengthen risk characterization
- Supports science -based decision making and public health guidance for environments where radon and smoking overlap (e.g., residential, mining).
- Informs targeted mitigation and policies for high -risk populations who smoke and live in radon -prone areas.

Aim 3: Integration in Risk Managment

Evaluates the feasibility of using AOPs in radon risk management.

Aims to translate the radon AOP into actionable tools for policy and mitigation.

Assesses how genetic and environmental refinements improve decision -making.

Analyzes existing frameworks (e.g., EPA, WHO,OECD) for integration opportunities.

Seeks to bridge mechanistic science with real - world public health action.

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Ongoing Research & Future Directions

Current gap: Existing AOP explains how radon causes lung cancer but **ignores genetic variability and co -exposures** .

This work: Builds a **more personalized, mechanistic framework** by adding:

- **Genetic variability** — DNA repair deficiencies (BRCA1, ATM, XRCC1).
- **Environmental co -exposures** — especially **smoking** .

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Ongoing Scoping Reviews

- **Aim 1:** Map evidence on **radon -induced DNA double -strand breaks** and how repair deficiencies increase lung cancer risk.
- **Aim 2:** Synthesize **epidemiologic studies** on **radon + smoking** joint effects, dose –response, and interaction.

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Planned Next Step (Aim 3)

- **Integrate findings** from both scoping reviews to **refine and expand the radon AOP** .
- Build an AOP that reflects **real -world exposures and population variability** .
- **Improve risk characterization models** to support:
  - **More accurate risk estimates for high -risk subgroups** .
  - **Evidence -based radon mitigation and public health policy** .

Thank you!

Refining the Radon Adverse Outcome Pathway (AOP): Integrating Genetic Susceptibility & Environmental Co -Exposures

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