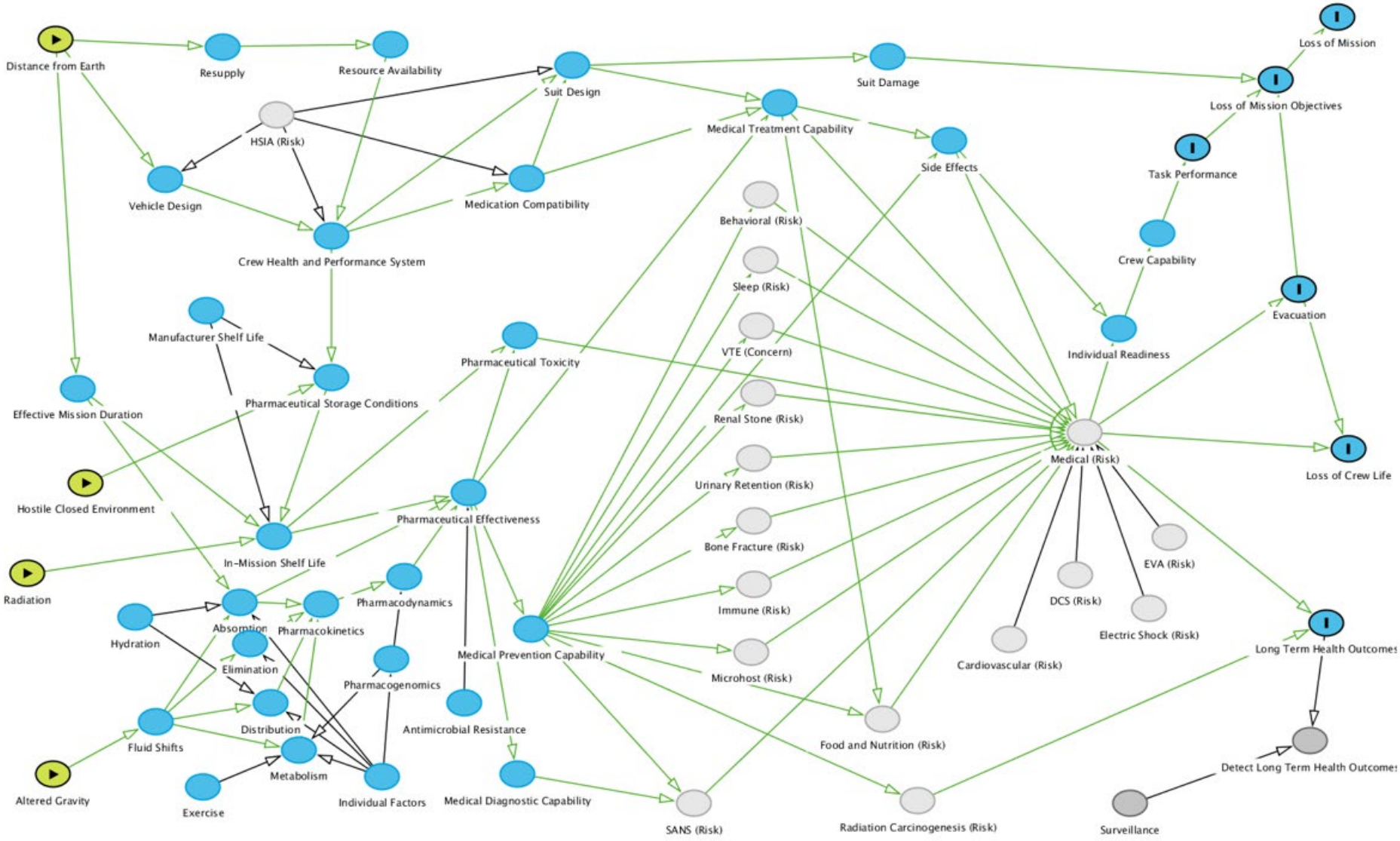
Risk of Ineffective or Toxic Medications During Long-Duration Exploration Spaceflight (Pharm Risk)



Pharm Risk DAG Narrative

DAG: Nodes Directly Affecting Pharmacokinetics.

- **Absorption**: How a drug enters the body.
  - Intestinal Absorption – For oral medications, most absorption occurs in the small intestine.
  - Gastric Emptying Time – The rate-limiting step of oral absorption.
- **Distribution:** The journey of the drug through the bloodstream to various tissues of the body.
  - Changes in total body water or Intravascular Volume.
  - Plasma protein binding.
- **Metabolism**: How the drug is biotransformed (broken down) in the body.
  - Hepatic Function, Hepatic Enzymes.
  - Other organs (e.g. Lungs, kidney, gastrointestinal (GI), skin).
- **Elimination**: How a drug is removed from the body.
  - Renal Function.
  - Hepatic Function.
  - Minor Pathways.

The Pharm Risk centers around **Pharmaceutical Effectiveness**. There are three basic things that contribute to this. 1. **In-Mission Shelf Life**, 2. **Physiologic Changes**, and **Antimicrobial Resistance**. Hazards affecting this risk include **Distance from Earth, Hostile Close Environment, Radiation and Altered Gravity.**

- **In-Mission Shelf** Life is defined from the time that medication is packed to whenever the medication is used or jettisoned. This is dependent on **Environmental Conditions** in the vehicle and **Pharmaceutical Storage Conditions** - i.e., refrigeration, packaging, etc. The **Manufacturer Shelf Life** refers to the labeled shelf life the medication would have without spaceflight exposure. **Effective Mission Duration** refers to how long the medications are exposed to the spaceflight environment.
- **Physiologic Changes** are the changes that the human body experiences that affect how a pharmaceutical functions within the body. Fundamentally this is broken into **absorption**, **distribution**, **elimination**, and **metabolism** of medications. **Metabolism** is affected by many factors including enzyme expression and **pharmacogenomics**. All lead to variations in **Pharmacokinetics** (the concentration of the active ingredient in the body over time) and **Pharmacodynamics** (how the target tissues use the medication). **Individual Factors** (age, sex, etc.), **Hydration**, and **Fluid Shifts** affect these physiologic changes.
- **Antimicrobial resistance,** including antibiotics, antivirals and antifungals**,** can affect the effectiveness of some pharmaceuticals.
- **Pharmaceutical Effectiveness** is upstream **of Medical Prevention Capability**, **Medical Diagnostic Capability**, and **Medical Treatment Capability**.
- **Medical Prevention Capability** in this case includes any medications used to prevent the effects of other risks. Examples include Potassium Citrate for Renal Stone Prevention, Bisphosphonates

for Bone protection, etc. There are 11 risks shown that have known potential pharmaceutical preventive cases.

- **Medical Diagnostic Capability** includes any medications used to assist in diagnosis. For example, proparacaine used to enable intraocular pressure measurements for the Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS) risk. Note that in this example proparacaine **In-Mission Shelf Life** is strongly affected by refrigeration (**Storage Conditions**).
- **Medical Treatment Capability** includes any medications used to treat medical conditions. This includes medications for symptoms including pain, nausea, fever, etc. as well as definitive treatments such as antibiotics for infections. Multiple risks include treatment needs including **Cardiovascular (Risk), EVA (Risk), Decompression Sickness (Risk), and Electric Shock (Risk)*.** Most of the risks shown in the **Preventive Medication Capability** pathway include a need for treatment as well i.e., pain control for renal stones, etc.
- **Medical Prevention Capability** and **Medical Treatment Capability** can affect the severity of **Side Effects** which then can affect **Individual Readiness, Crew Capability and Task Performance**, all which could lead to Loss of Mission Objectives or **Loss of Mission.**
- Additional paths included:
  - **Pharmaceutical Toxicity** can occur from two sources: 1) degradation products may be toxic; 2) dosing errors and other factors can lead to under-or over-dosing of a given medication. **In-mission Shelf Life** can reduce the amount of active pharmaceutical ingredients present or lead to degradation products that may cause **Pharmaceutical Toxicity.** Over-dosing of medication can lead to life-threatening toxicities including suppression of breathing in the case of opioid use or damage to organs such as liver failure in acetaminophen overdose.
  - **Medication compatibility –** This includes both the compatibility of medications of the vehicle environment (**Vehicle Design**) and the suit **(Suit Design).** It also includes the capability of the provision of a medication while wearing the suit. This affects what medications can be administered to the crew in suited operations.
  - Vehicle systems and suits that can be damaged by a medication therapy - I.e., topical medications that cause **Suit Damage.** We do not know what components of medications create problems for the suit and the atmosphere in the suit but continue to be asked by engineering for that information.
  - **Suit Design** that doesn't allow for proper **Medical Treatment Capability -** E.g., Orion 144-hour suit contingency allows for a small port in the helmet to administer a small number of oral medications. Not all medications fit.
  - **Resupply and Resource Availability – Distance from Earth** can affect the ability to **Resupply** in some DRMs can lead to a risk of inadequate medications. If **Pharmaceutical Effectiveness** is lessened through either degradation or PK/PD issues, crew may use more medications than originally planned and potentially run out sooner.
  - **Surveillance** enables us to **Detect Long Term Health Outcomes** and better characterize the risk as we gather more evidence.