THE STABILITY OF DRUGS EXPOSED TO IONIZING RADIATION

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Project Context

- HRP Risk:
  - *Ineffective* or Toxic Medications during Long-Duration Exploration Spaceflight
- HSRB Risk:
  - **Contributing Factors: "**Drug stability (unknown deep space environment effects on drug stability), shelf life, packaging, storage conditions, drug compound formulation, **spaceflight radiation** environment…"
  - **LxC Risk Rationale: "**Vehicle specifications and capabilities to protect medications from environmental assault (e.g. temperature, humidity, oxygen, **radiation**) have not been characterized and could increase risk of ineffectiveness and possible toxicity."
- HRP Roadmap Gap:
  - Pharm-401: We need to perform further research to understand and characterize the active pharmaceutical ingredient and ***degradation profiles of medications*** for which we have low to moderate confidence in their safety and effectiveness for exploration missions

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Research Questions

- Past radiostability studies have focused on solid state drugs
  - Can we assume drugs in all forms are the same?
  - Do we need to test each formulation of a drug substance?
- How do we prioritize drug products for future testing?
  - Which have the greatest uncertainty

ExMC Exploration Formulary

Dosage form	Number of APIs
Aerosol	3
Capsule	22
Cream	9
Gel	5
Gelcap	4
Lozenge	2
Ointment	5
Pad	5
Patch	4
Powder	15
Solution	92
Suspension	3
Tablet	92

Study Approach

- Objective: Quantify the sensitivity of drugs to ionizing radiation.
- Approach: Use existing published pharmaceutical radiostability studies:
  - Model risk of drug failure
- Methods:
  - Systematic literature of research articles 1950 to present.
  - Inclusion requirements:
    - Use of quantitative stability-indicating (Chromatographic) analytical data
    - Radiation dose-response
    - Ionizing radiation: EM [X-ray or **γ-rays**], β-radiation [**e-beam**], charged nucleons
    - Excluded: Ecological (surface water), drinking water or waste water treatment studies, undefined drug content, non-quantitative studies, indirect measure of drug content… etc.

Results: Collected data summary:

Criteria	Solid state	Aqueous Solutions	Mixtures	Total
Total tests	436	388	222	1046
Gamma radiation	314	381	202	897
Electron beam	122	7	20	149
API treatments	153	92	43	288
Gamma radiation	121	90	37	248
Electron beam	32	2	6	40
Irradiated dose (kGy)				
Max/Minimum dose	0.1 / 800	0.001 / 160	0.001 / 79.37	0.001/800
Mean dose	82.73	15	11.384	41.327
Median dose	25	5	5	15.9

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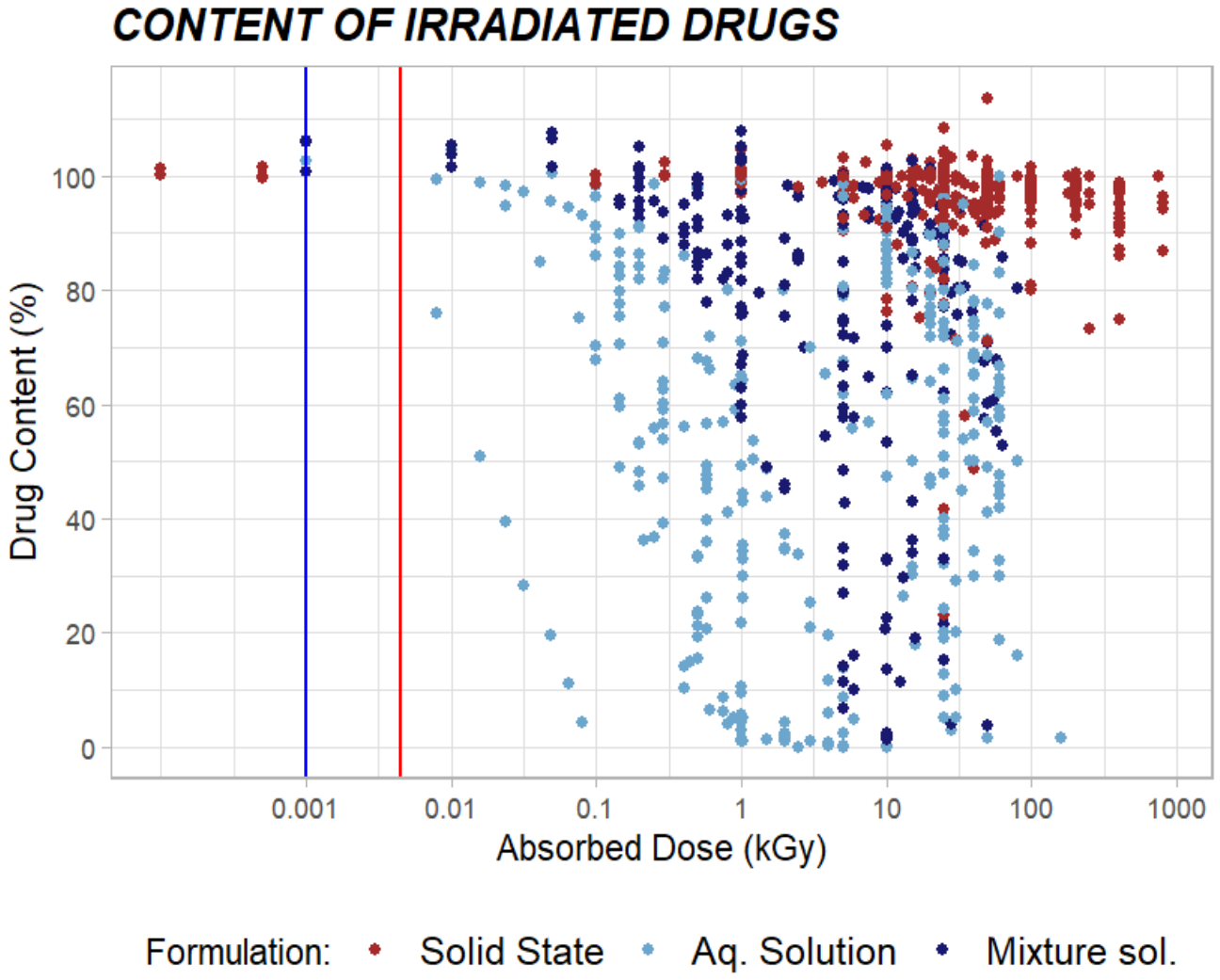
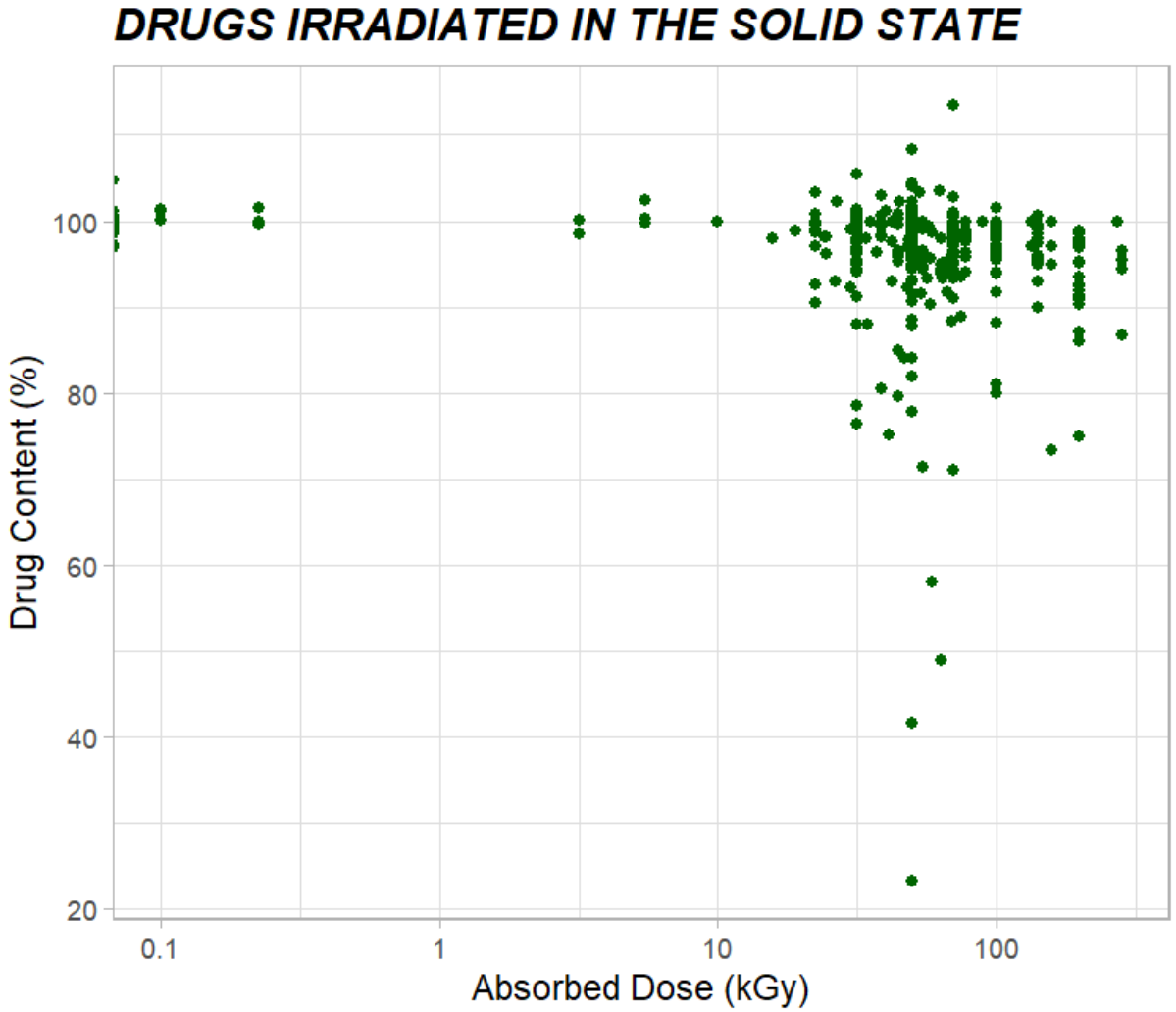
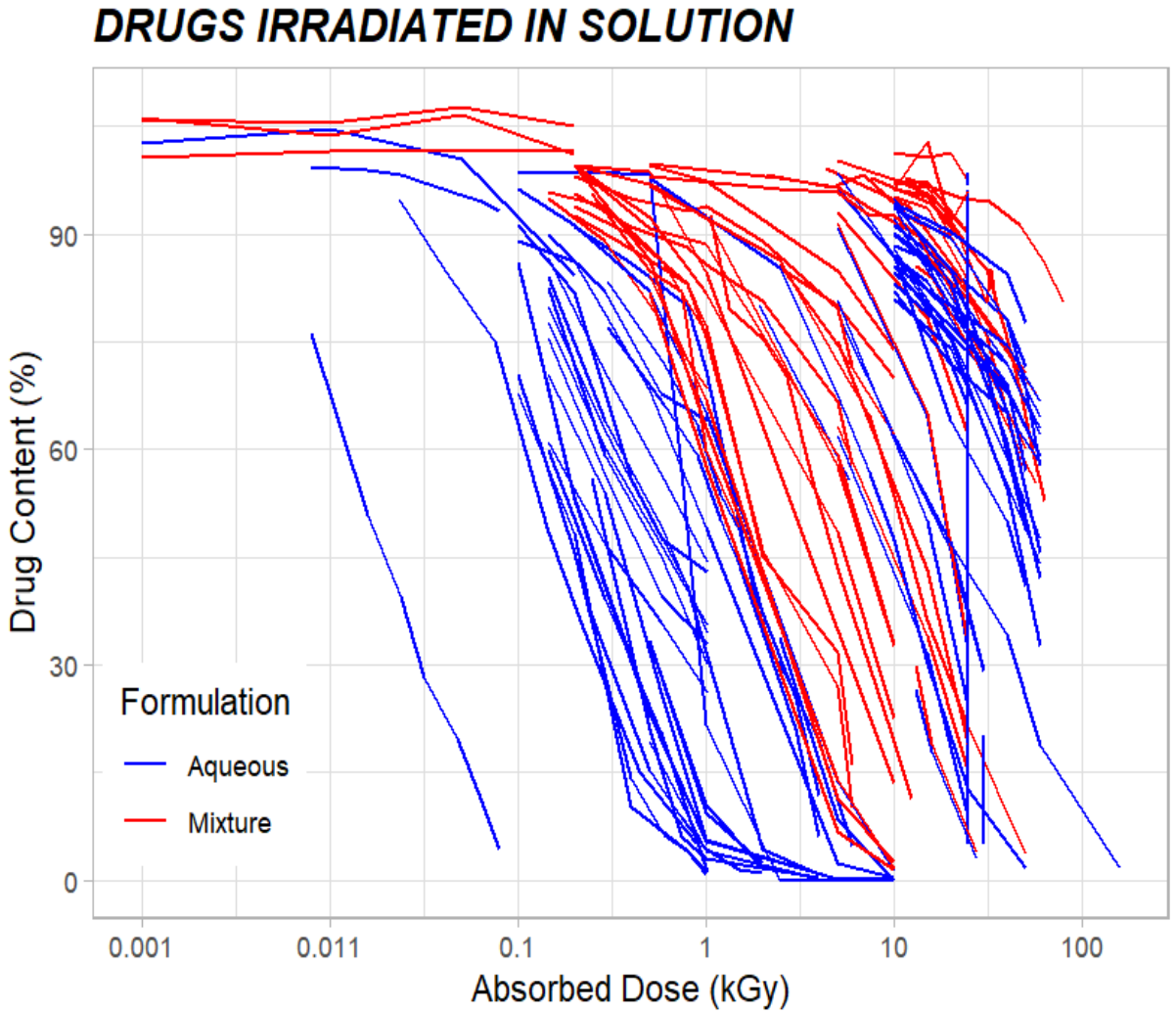
Drug Content After Irradiation

- Pale blue dots: Drug in aqueous solution (water) *without* additives
- Dark blue dots: Mixtures (drug solutions *with* at least additive)
- Red dots: Solid state pharmaceuticals
- Observations:
  - Liquid formulations are more sensitive than solids
  - Solid have a MoE of ~ 4 to 6 orders relative to the upper limit of a Mars mission
  - Aqueous drugs have MoE of ~ 1 to 3 orders
  - Excipients increase radiostability of drug solutions



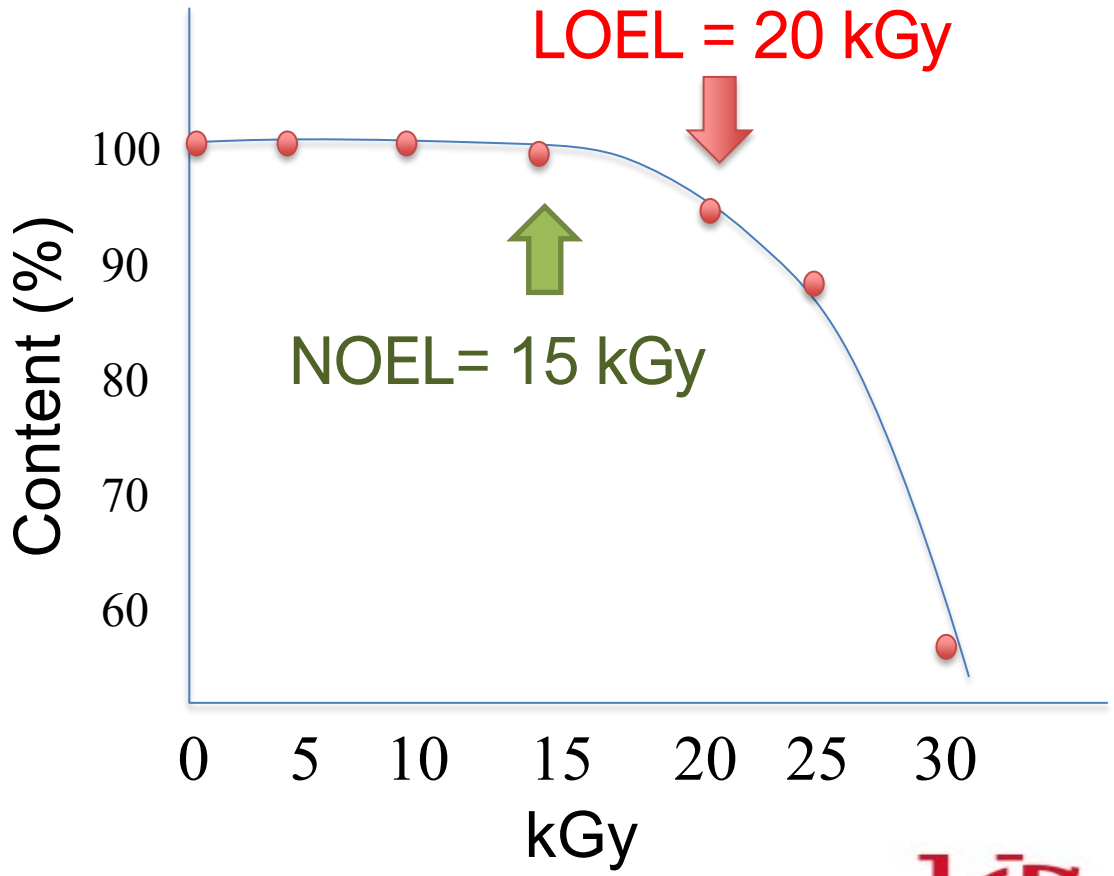
Solids and Solutions





Drug Failure Analysis

- Dichotomize radiation effect on drug content as pass / fail
  - Pass = Highest radiation dose with *no* observed effect (NOEL)
  - Fail = Lowest radiation dose where degradation *is* observed (LOEL)



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Drug Failure Analysis: Assumption

- There is no accepted standard for a NOEL/LOEL threshold
- NOEL is a change (loss) of API ≤ 5% of baseline API
- LOEL is the first dose that causes > 5% decrease in API content
- Justification
  - ½ the default USP lower acceptance criteria for API content (90%)
  - Pragmatic: We need to allow for experimental variability
  - 5% API loss is > 1.5 times the interquartile range (3.19) above the third quartile (2.32) of standard errors, which is 4.91

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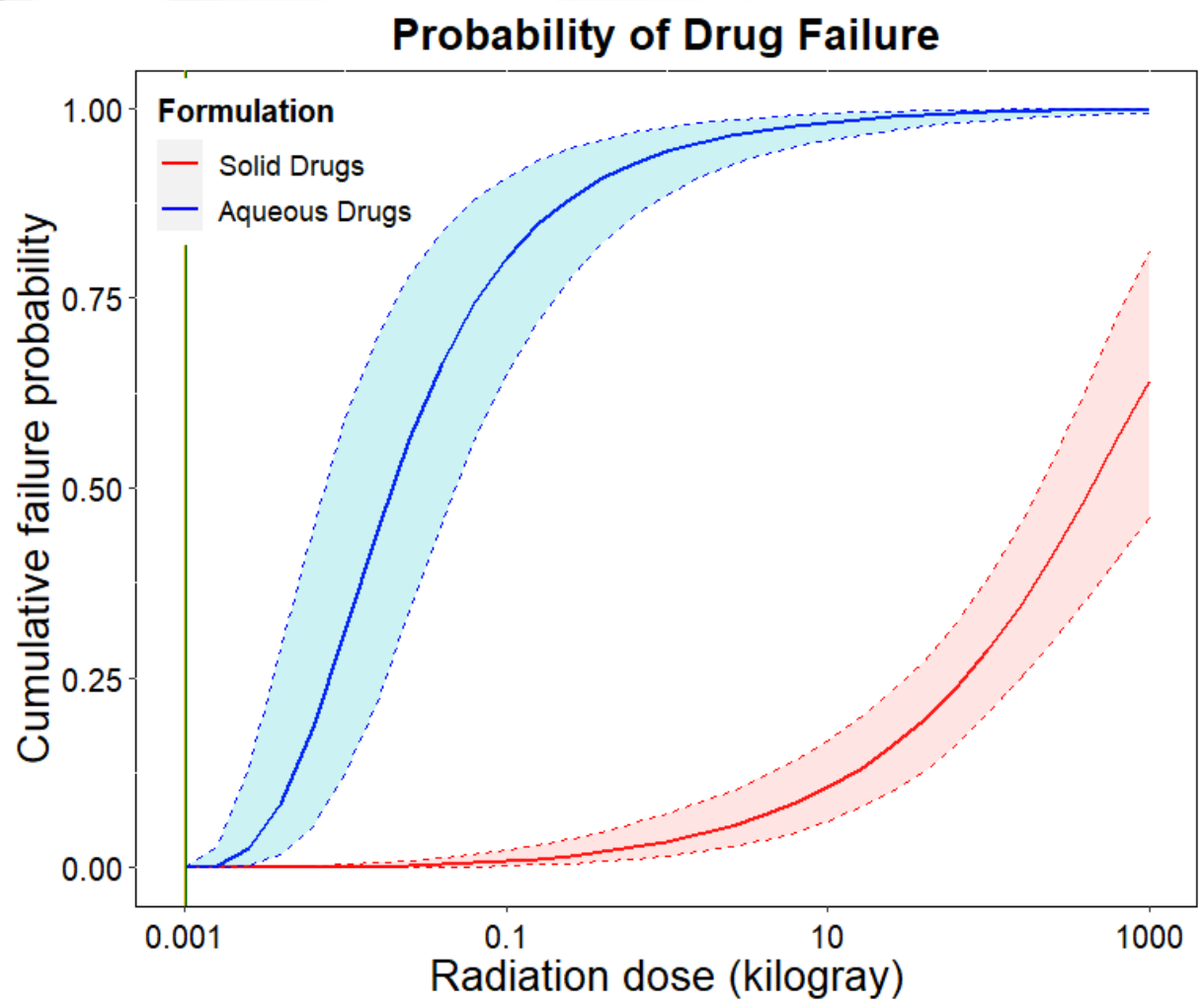
Parametric Failure Analysis



Failure Probability		
Radiation dose	**Solid State**	**Aqueous**
1 Gy (0.001 kGy)	0%	0%
10 Gy (0.01 kGy)	0.06%	25.7%
1000 Gy (1 kGy)	3.3%	95%

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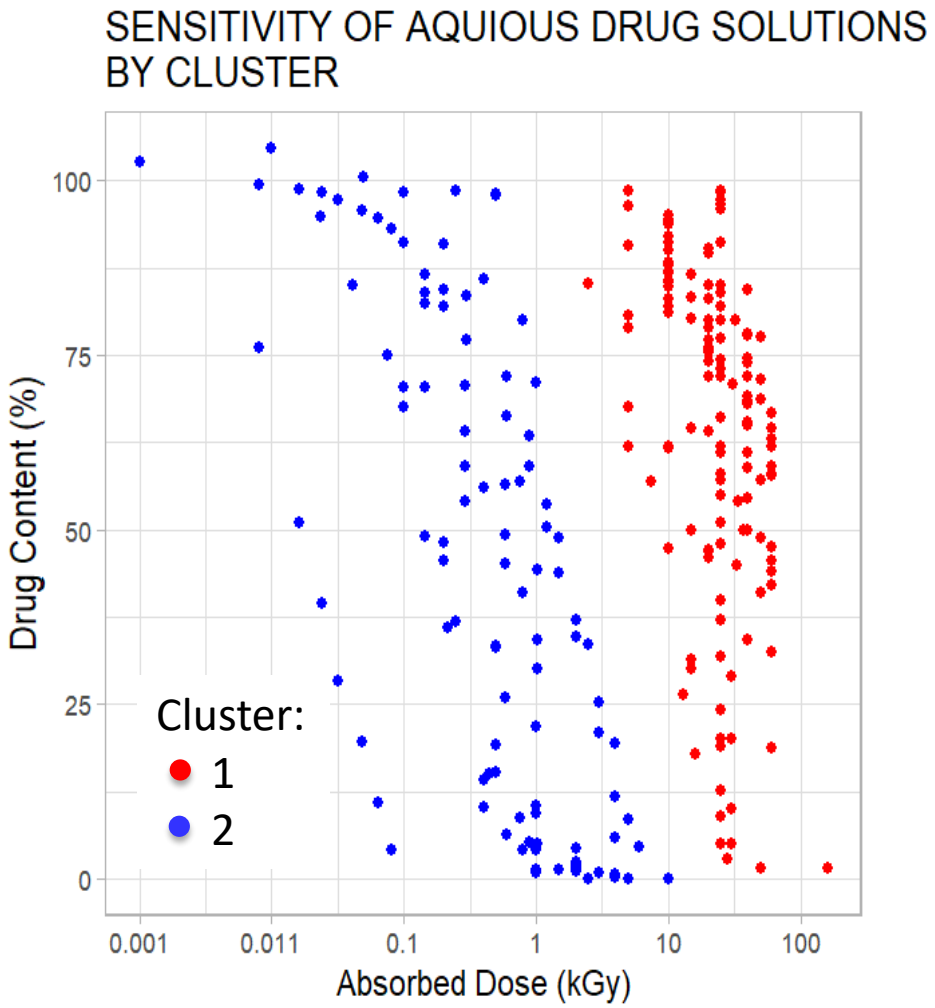
Drug Concentration Influences Radiation Stability



- Unsupervised cluster analysis of aqueous solutions
- Low concentration is associated with greater sensitivity to ionizing radiation.

Cluster	Mean Concentration (mg/mL)	Median Concentration (mg/mL)	Mean kGy	Median kGy
1	16.6	10	27.5	25
2	1.52	0.0206	0.927	0.29

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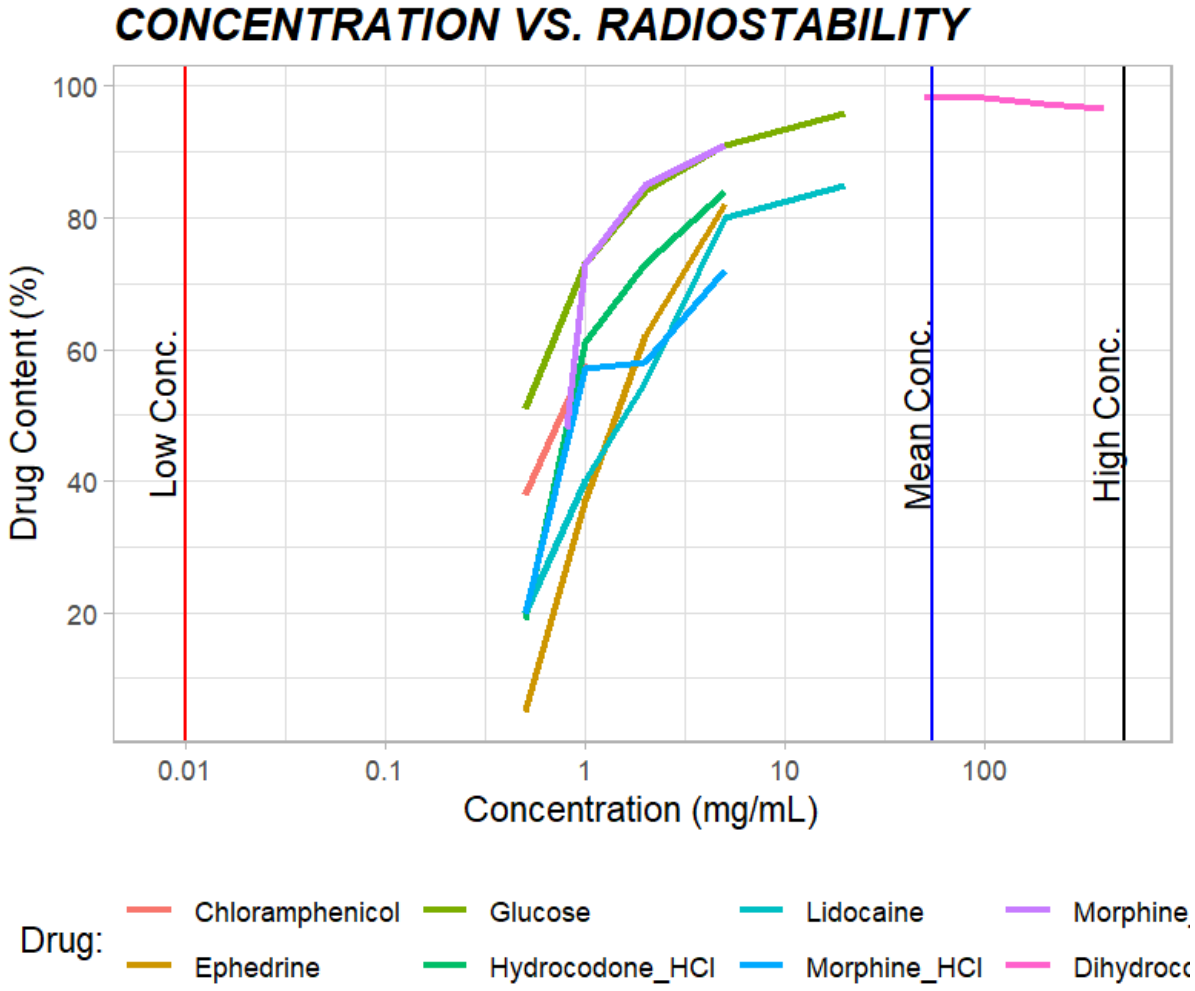
Radiostability Increases with Concentration

- Stability of drug solutions at different concentrations
  - All drugs exposed to 25 kGy gamma or β radiation
  - Increasing stability is observed over similar concentration range.



Preliminary Conclusions

- Drugs in solid state have a very low risk of degradation in the range of radiation exposures that are also acceptable for human health.
- Aqueous drug formulations also have a low risk – but the margin of exposure is much narrower – ***less room for uncertainty****!*
- Sensitivity of other non-solid drug formulations (creams, ointments) are unknown.
- Future studies should prioritize
  - Non-solid drug formulations over solid state drugs
  - Low concentration liquid formulations
  - Factors that can improve the stability of the most sensitive drugs, ie. excipients, temperature, protective packaging

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Backup slides

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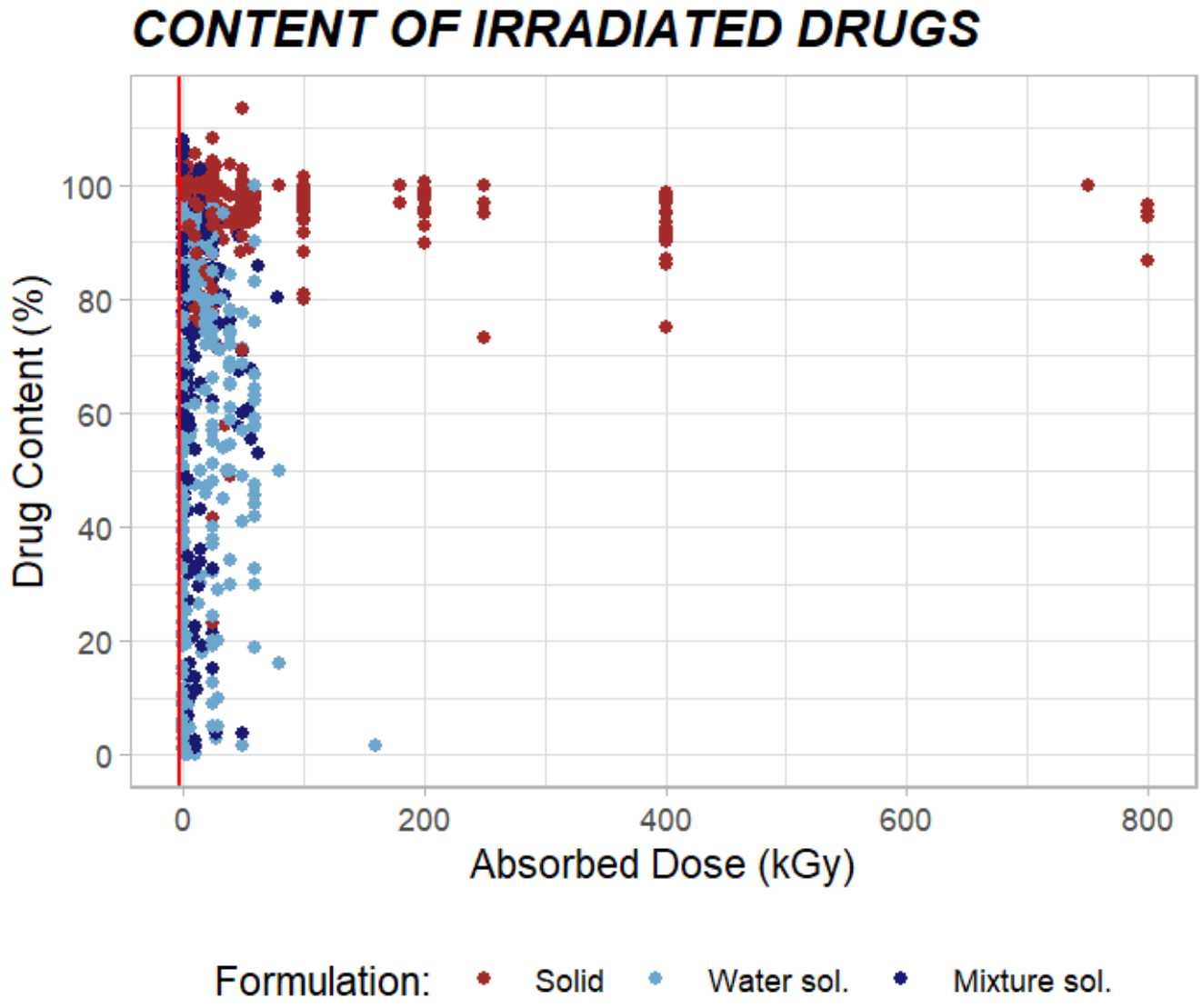
A Risk Factor For Spaceflight Drug Stability?

- Ionizing radiation damages important stuff, like DNA
- UV radiation degrades drugs (“Protect from light”)
- Ionizing radiation interacts with matter: directly (scission, excitation) and indirectly (reactive intermediates).
- Ionizing radiation degrades most drugs to some degree at a high enough absorbed dose
- Speculated to have contributed to degradation of *some* drugs in the only longitudinal pair-matched study by Du et al. 2011
  - Discussed in several published reviews
- No comprehensive NASA investigation of how ionizing radiation interacts with drugs

Loss of Drug Content with Radiation Dose



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Uncertainty

- **“The radiation environment in space is not like the environment on Earth!”**
  - It doesn’t need to be
    - Experimental radiation doses can be orders of magnitude higher than GCR
    - Dose-effect relationship is monotonic
    - Margin of exposure
    - **Mechanisms are essentially the same**
- Mechanism:
  - Chemistry in space is the same as on earth
    - **TEMPERATURE (energy)**
    - **TIME (Artemis is not that fast!)**
    - Moisture (hydrolysis)
    - Oxidation
    - Amorphous-crystal transitions

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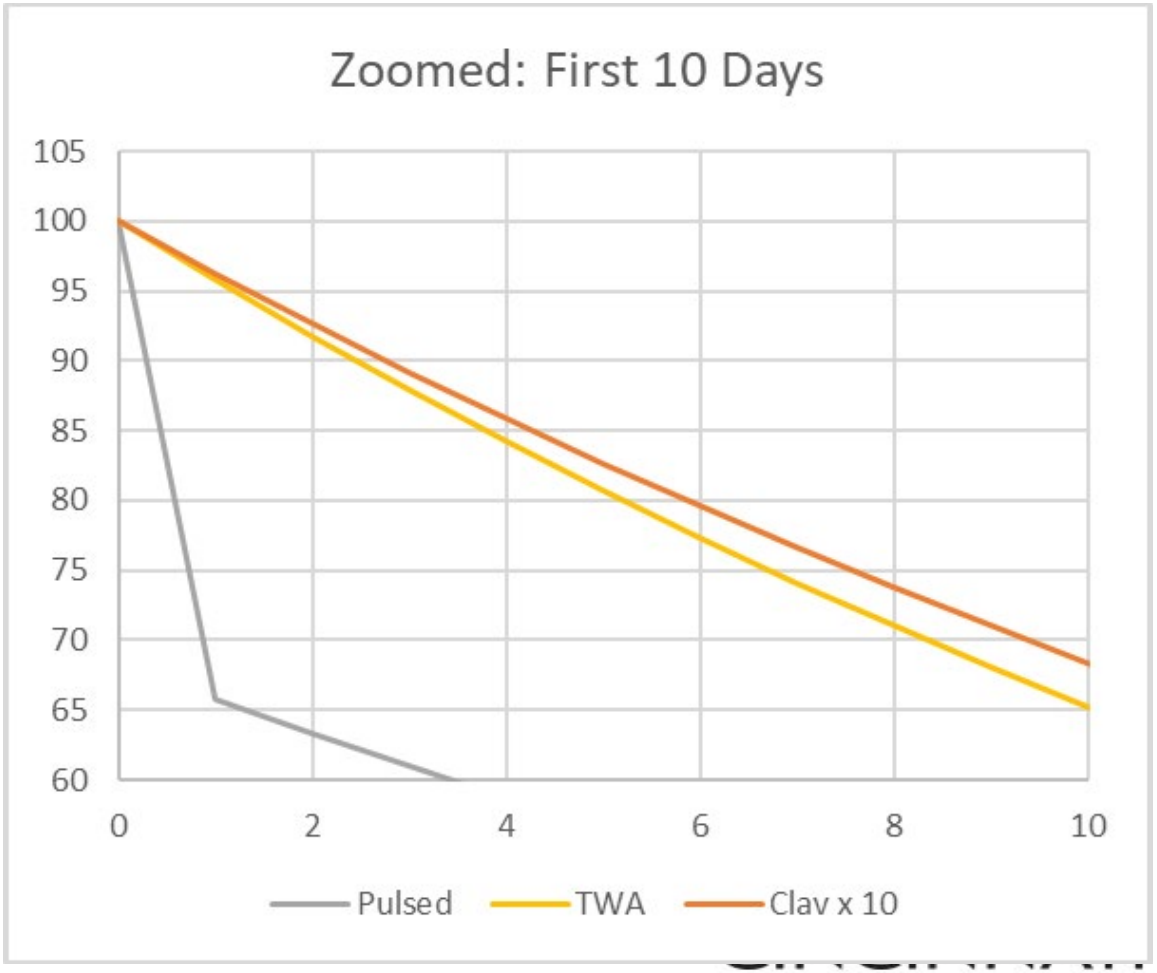
Effect of Slowly Delivering Radiation Dose

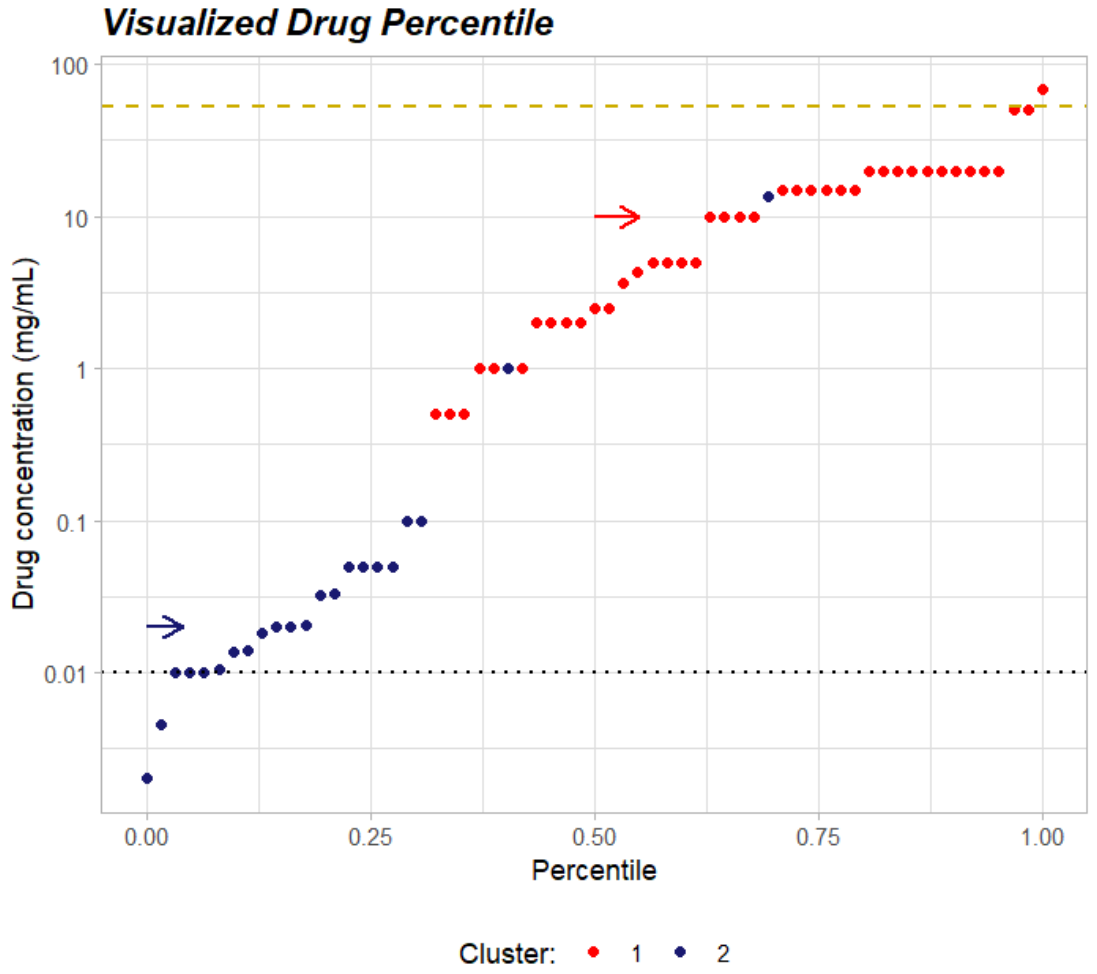
- Clavulanate: Du et al. (2011) control (red) degradation
- Assume:
  - 80 day mission
  - 10x clavulanate degradation rate
  - Hypothetically, radiation pulse increases degradation 500%
  - Same radiation as a TWA over mission
- Conclusions:
  - Terrestrial pulse studies using elevated radiation doses are likely protective.
  - Spaceflight studies necessary only to evaluate specific drug uncertainties



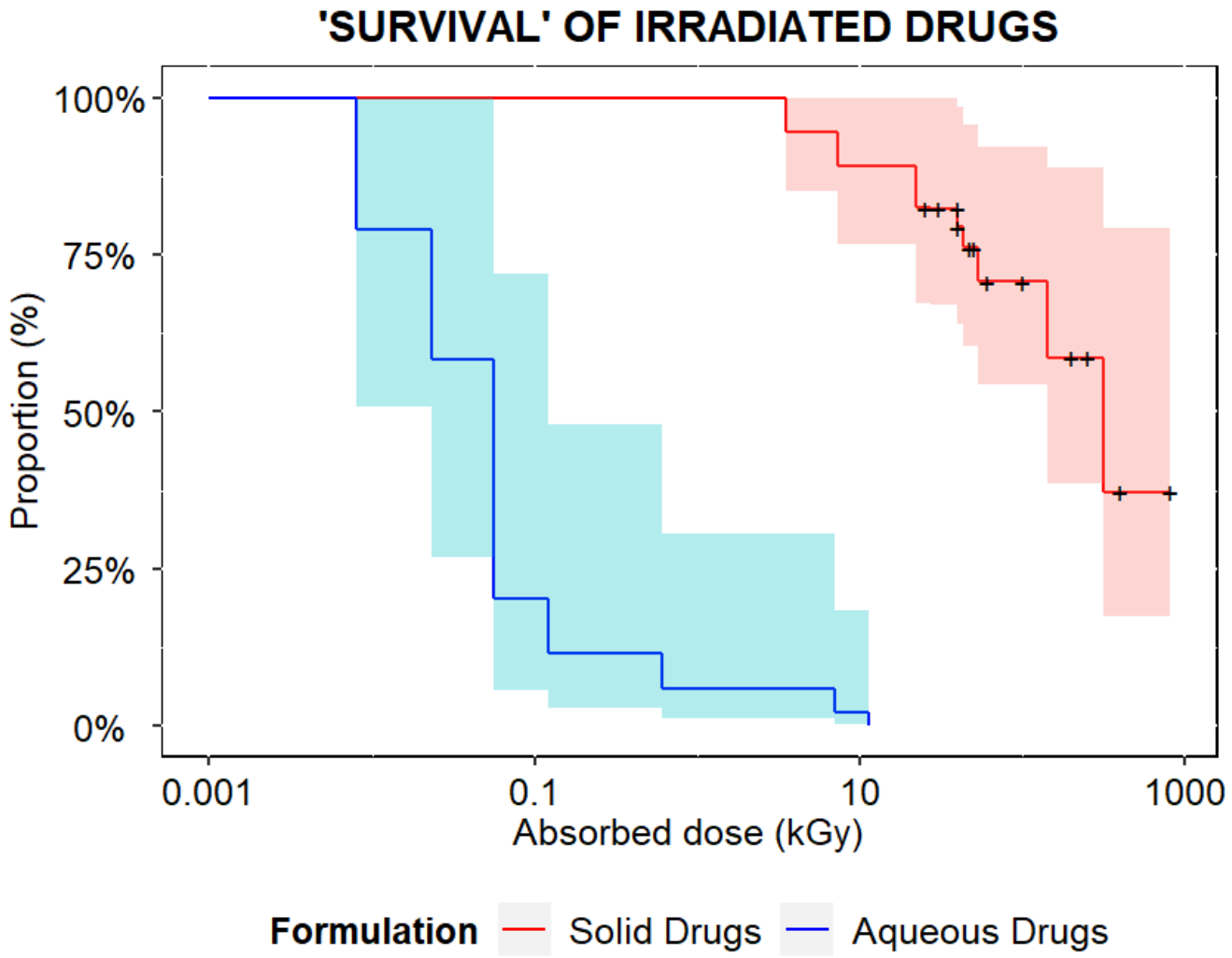
Comparison to NASA Formulary Drugs

Percentile ranking of starting drug concentration

- Cluster 1: high conc. (red)
  - Mean conc.: red arrow
- Cluster 2 low conc. (blue)
  - Mean conc: blue arrow
- NASA formulary
  - Mean drug conc.: Gold dashes line)
  - Lowest drug conc.: red arrow



Non-parametric Survival Analysis



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