Risk of Acute Radiation Syndrome Due to Solar Particle Events: Risk to BFO and Skin

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Questions for Consideration

• How well is the risk understood? What, if any, are the major sources of disagreement in the literature pertaining to this risk?

• Does the evidence report provide sufficient evidence, as well as sufficient risk context, that the risk is of concern for long-term space missions?

• Does the evidence report provide evidence that the named gaps are the most critical presented? Are there any additional gaps or aspects of existing gaps that are not addressed for this specific risk?

• Does the evidence report address relevant interactions among risks?

• Is the breadth of the cited literature sufficient?

Conflict of Interest

Have served as the Chair of 2 Scientific Advisory Committees for NSBRI (CARR and CSRR)
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Level of Understanding of the Risk – BFO Humans

• Majority of our understanding comes from clinical experience (e.g. BMT patients), accidents – low LET (p11, Reviews of Human Data, etc.)
• Threshold for effects defined as dose required to cause 1% incidence (ICRP)
• Threshold for lowest level of ARS is ~0.1-0.3 Gy (minimal hematopoietic effects, mild prodromal) – seen in most at-risk populations
Best Estimates – LD$_{50/60}$

- Acute TBI, no medical support = 2.5-3.5 Gy
- Acute TBI + supportive care = 4.5-8 Gy
- Acute TBI + BMT = 10-11 Gy
## Prodromal Syndrome

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>Nausea, vomiting</th>
<th>Time of onset</th>
<th>Duration</th>
<th>Lymphocyte count</th>
<th>CNS function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1 Gy</td>
<td>None</td>
<td>None</td>
<td>&lt;24 hr</td>
<td>Minimally affected</td>
<td>No impairment</td>
</tr>
<tr>
<td>1 - 2 Gy</td>
<td>5 - 50%</td>
<td>3 - 6 hr</td>
<td>&lt;24 hr</td>
<td>Minimally decreased</td>
<td>No impairment</td>
</tr>
<tr>
<td>2 - 6 Gy</td>
<td>50 - 100%</td>
<td>2 - 4 hr</td>
<td>&lt;24 hr</td>
<td>&lt;1000 at 24 hr</td>
<td>Impairment for 6 - 20 hr</td>
</tr>
<tr>
<td>6 - 8 Gy</td>
<td>75 - 100%</td>
<td>1 - 2 hr</td>
<td>&lt;48 hr</td>
<td>&lt;500 at 24 hr</td>
<td>Impairment for &gt;24 hr</td>
</tr>
<tr>
<td>10 - 30 Gy</td>
<td>90 - 100%</td>
<td>&lt;1 hr</td>
<td>&gt;48 hr</td>
<td>Decreases in hrs</td>
<td>Rapid incapacitation</td>
</tr>
<tr>
<td>&gt;30 Gy</td>
<td>100%</td>
<td>Minutes</td>
<td>N/A</td>
<td>Decreases in hrs</td>
<td>Rapid incapacitation</td>
</tr>
</tbody>
</table>
## Latent Phase of Acute Radiation Syndrome (ARS)

<table>
<thead>
<tr>
<th>Degree of ARS and approximate dose of acute WBI (Gy)</th>
<th>Mild (1–2 Gy)</th>
<th>Moderate (2–4 Gy)</th>
<th>Severe (4–6 Gy)</th>
<th>Very Severe (6–8 Gy)</th>
<th>Lethal (&gt;8 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency period (d)</td>
<td>21–35</td>
<td>18–28</td>
<td>8–18</td>
<td>7 or less</td>
<td>None</td>
</tr>
<tr>
<td>Lymphocytes (G/L) (days 3–6)</td>
<td>0.8–1.5</td>
<td>0.5–0.8</td>
<td>0.3–0.5</td>
<td>0.1–0.3</td>
<td>0.0–0.1</td>
</tr>
<tr>
<td>Granulocytes (G/L)</td>
<td>&gt;2.0</td>
<td>1.5–2.0</td>
<td>1.0–1.5</td>
<td>≤ 0.5</td>
<td>≤ 0.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>None</td>
<td>None</td>
<td>Rare</td>
<td>Appears on days 6–9</td>
<td>Appears on days 4–5</td>
</tr>
<tr>
<td>Epilation</td>
<td>None</td>
<td>Moderate, beginning on day 15 or later</td>
<td>Moderate or complete on days 11–21</td>
<td>Complete earlier than day 11</td>
<td>Complete earlier than day 10</td>
</tr>
<tr>
<td>Medical response</td>
<td>Hospitalization not necessary</td>
<td>Hospitalization recommended</td>
<td>Hospitalization necessary</td>
<td>Hospitalization urgently necessary</td>
<td>Symptomatic treatment only</td>
</tr>
</tbody>
</table>

*This chart is adapted from “Diagnosis and Treatment of Radiation Injuries,” International Atomic Energy Agency, Vienna, 1998.*
Level of Understanding of the Risk – Skin

- Skin may be at greater risk than BFO of adverse irradiation due to depth dose distributions of SPE particles – predictions suggest 5x higher dose; greater if EVA versus craft exposure

<table>
<thead>
<tr>
<th>Dosimetry quantities</th>
<th>August 1972 SPE</th>
<th>October 1989 SPE</th>
<th>September 1989 SPE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVA 0.3 g/cm²</td>
<td>EVA 0.3 g/cm²</td>
<td>EVA 0.3 g/cm²</td>
</tr>
<tr>
<td></td>
<td>Spacecraft g/cm²</td>
<td>Spacecraft g/cm²</td>
<td>Spacecraft g/cm²</td>
</tr>
<tr>
<td>$D_{\text{skin}}$, cGy</td>
<td>2859.27</td>
<td>2416.88</td>
<td>716.83</td>
</tr>
<tr>
<td>$G_{\text{BFO}}$, cGy-eq</td>
<td>138.65</td>
<td>95.70</td>
<td>37.94</td>
</tr>
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</table>

- Skin damage can aggravate/increase response to radiation injury (known complications from radiation combined injuries)
Questions for Consideration

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Bone marrow effects:
For low LET exposures: acute risk (dose range) is reasonably well understood. Growing understanding of the role played by the microenvironment vs. HSCs; differential effect on HSCs (ST-HSC vs. LT-HSC)

For SPE-like exposures: limited data (animal). Most comprehensive – recent work from CARR (NSBRI/NASA: Kennedy group) comparing mice, ferrets (prodromal) and mini-pigs (skin);

CSRR: Boerma – mice, rabbits (cardiovascular/eye)
Mouse:
~150 MeV protons – dose rate 0.5 Gy/min
Transient though significant response at 2 Gy (lowest response at 0.5 Gy – confirmed by CSRR)

Ferret:
- Fully modulated protons – dose rate 0.5 Gy/min
- 100% mortality following 2 Gy – disseminated intravascular coagulopathy

CARR Findings – 3 Animal Models

Krigsfeld IJROBP 88:940-6, 2014.
CARR Findings – 3 Animal Models


Pig:
6 MeV electrons – high skin dose; BFO dose <5%
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SPE bone marrow effects:
Mouse data suggests that SPE induces similar effect to low LET – current triage criteria would indicate minimal concern


Confirmed by ferret vomiting data
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SPE bone marrow effects:
• Large animal data: both ferret and mini-pig are possibly overtly radiation sensitive (endothelial cell)
• or do protons induce a differential response?
• Varying RBE calculations for SPE protons
• Granulocyte model: Failure to take into account differential effects at stem/precursor cell level and heterogeneity across skeleton volume
• What and by how much additional conditions may impact bone marrow?
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SPE skin effects:
Pig data suggests that SPE induces similar effect to low LET

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SPE skin effects:
Pig data suggests that SPE induces similar effect to low LET – immune response?

Pig: Hypersensitivity response (4 days post-radiation)

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SPE immune effects:
Mouse data supports exaggerated acute immune response due to combined stressors

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The report provides evidence of risk. And I believe there is a risk – uncertain as to whether the actual acute risk has been clearly defined as yet.
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   Personal opinion: possibly not!

GAPS: Role of additional stressors in altering response to SPE; response in the context of GCR – are the decrements described confirmed on ISS?; extrapolation between models to humans; dose rate!
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See previous
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  Breadth – yes; current status - no
Summary: Acute Risks from SPEs

- Report provides evidence of risk to astronauts of acute events
  - Actual risks that may affect mission/astronaut health (prodromal/manifest) not yet defined

- Critical Gaps
  - Role of additional stressors on acute response (chronic GCR, microgravity, infection, etc.)
  - Dose rate effect/dose-latency relationships
  - Slow development of reasonable/practical countermeasures. Will those being developed against high dose, low LET injury be appropriate?
  - Adequacy of animal models/availability of experimental conditions to answer outstanding questions