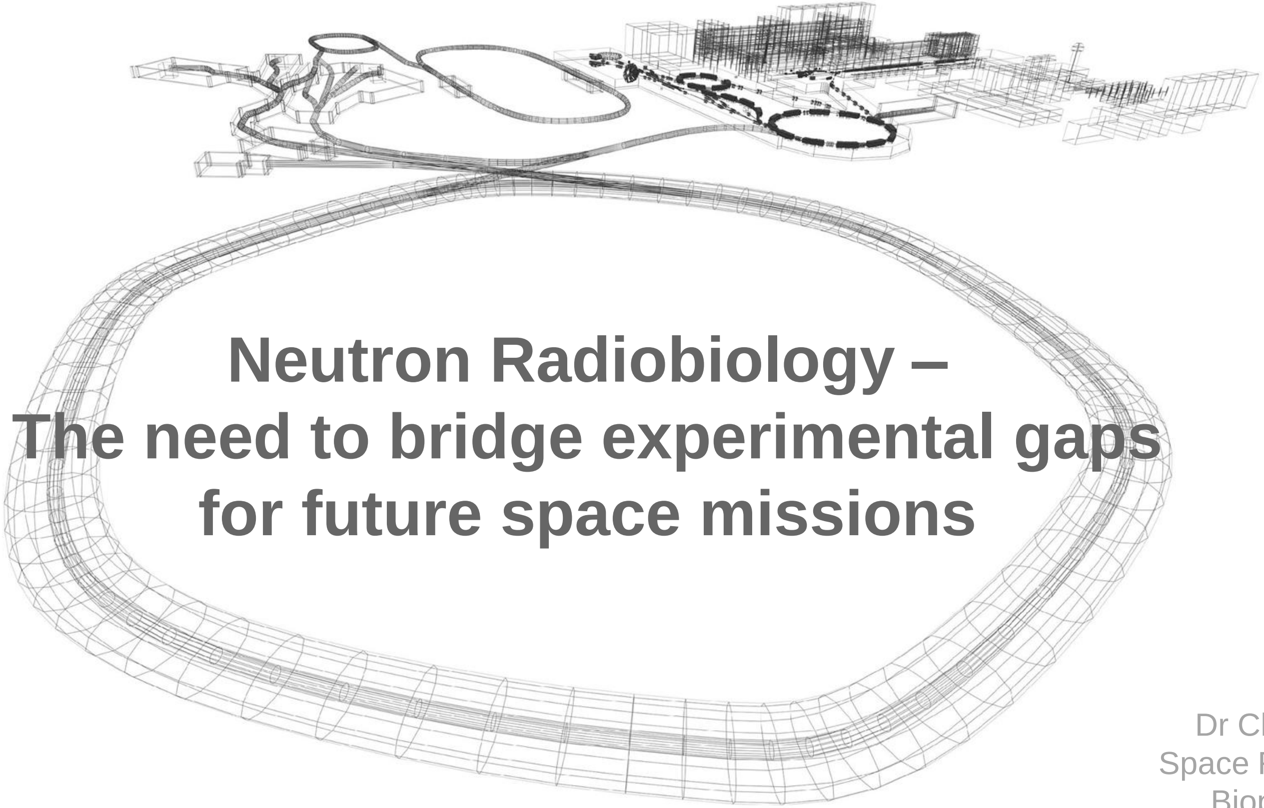


Neutron Radiobiology – The need to bridge experimental gaps for future space missions

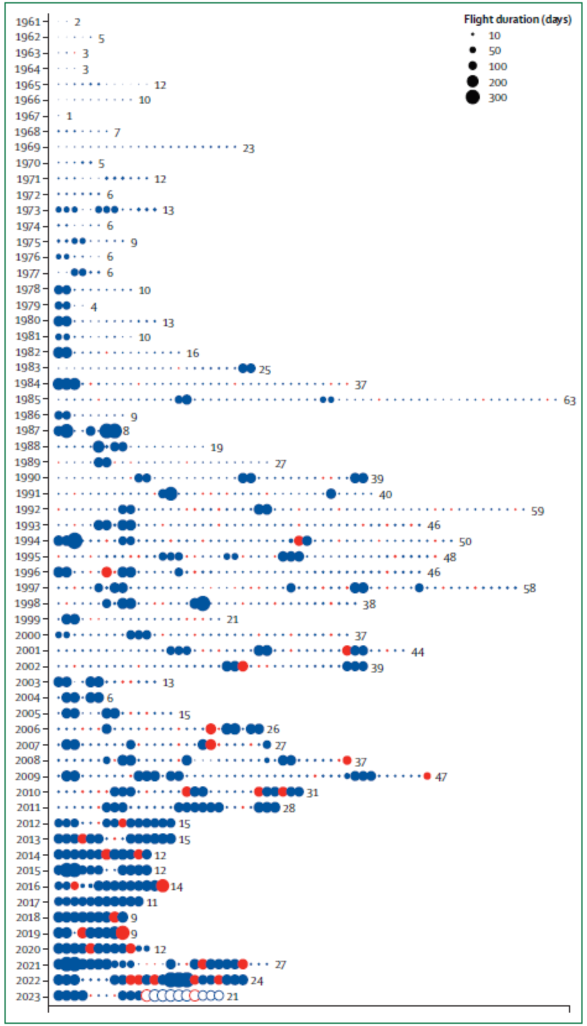
Dr Charlot Vandevoorde
Space Radiobiology Group
Biophysics Department

Background setting

Why is it important to improve radiation risk estimations for space missions?

- Missions from April 1961 – March 2024:
  - Increase in duration
  - Increase in number
- We aim to go beyond Low-Earth-Orbit (LEO):
  - Only short-term Space Shuttle missions
  - Mainly ISS missions within LEO
  - Small sample sizes

Accurate prediction of space radiation risks beyond LEO is hampered by the lack of relevant human data



Seidler et al. – Lancet Neurol 2024

Background setting: Space Radiation beyond LEO

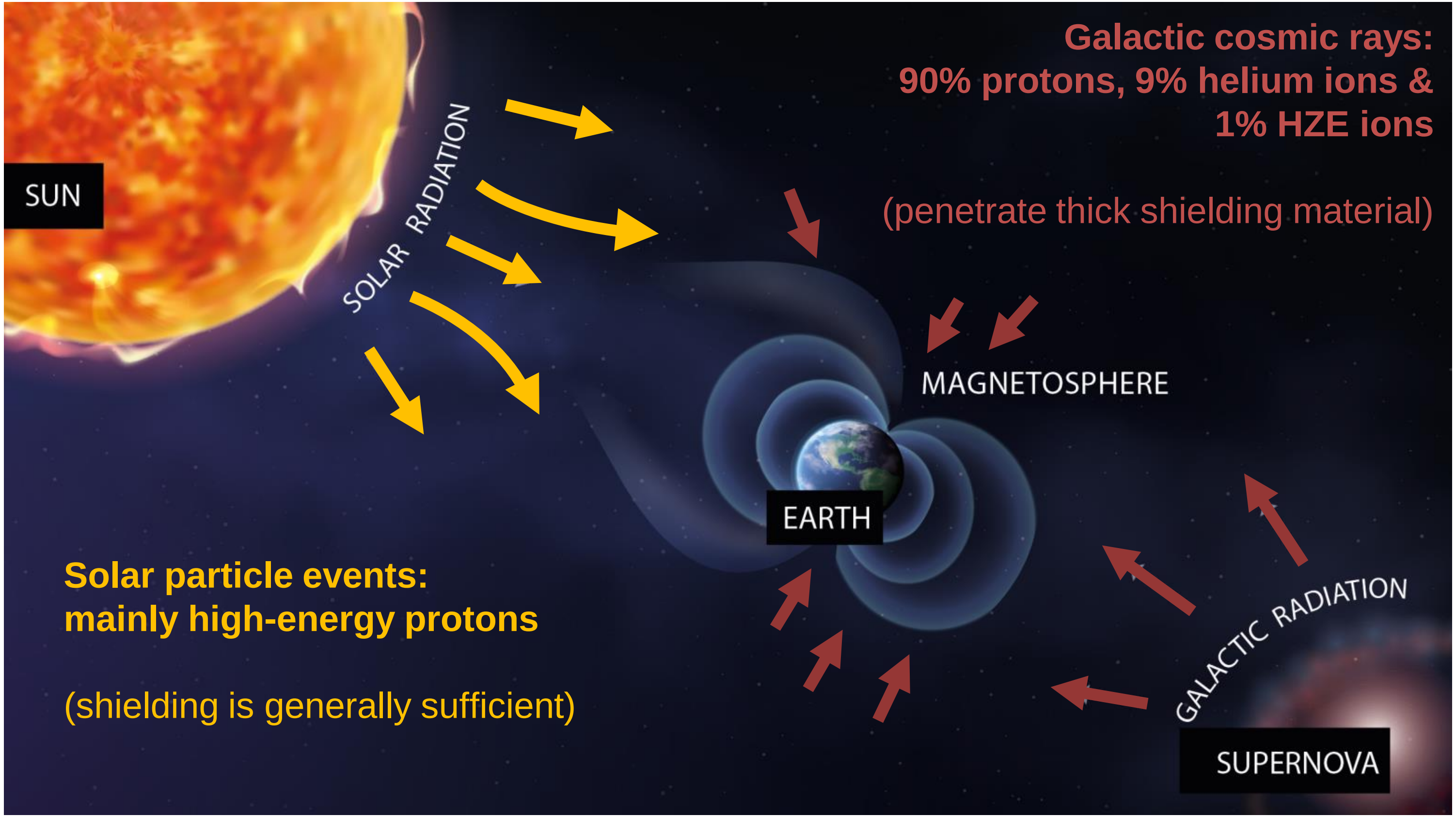
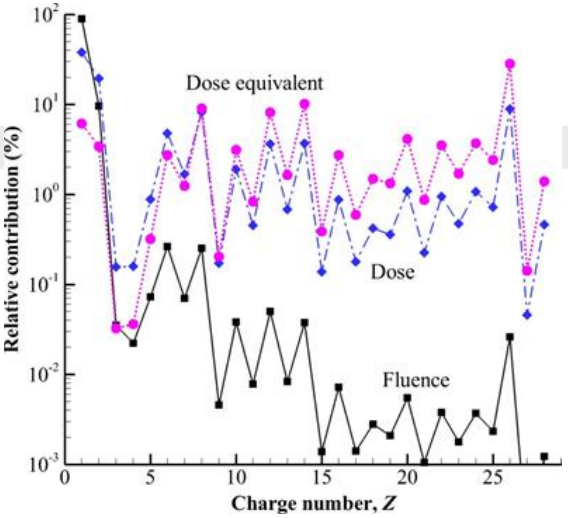


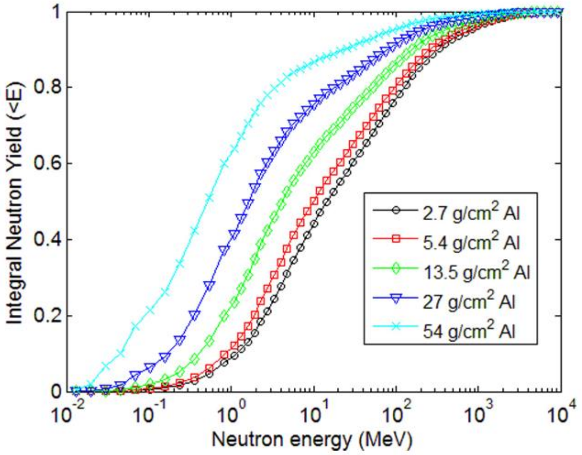
Image: modified from IAEA

Background setting: Space Radiation beyond LEO

Secondary radiation:

- Interaction of GCR with body tissue, spacecraft shielding material…
- **Neutrons** can penetrate thick shields and deep into organic tissues before interacting with nuclei
- Significant fraction of the **neutron fluence lies in the region > 20 MeV** up to several hundred MeV as a result of GCR interactions with a variety of simple shielding configurations

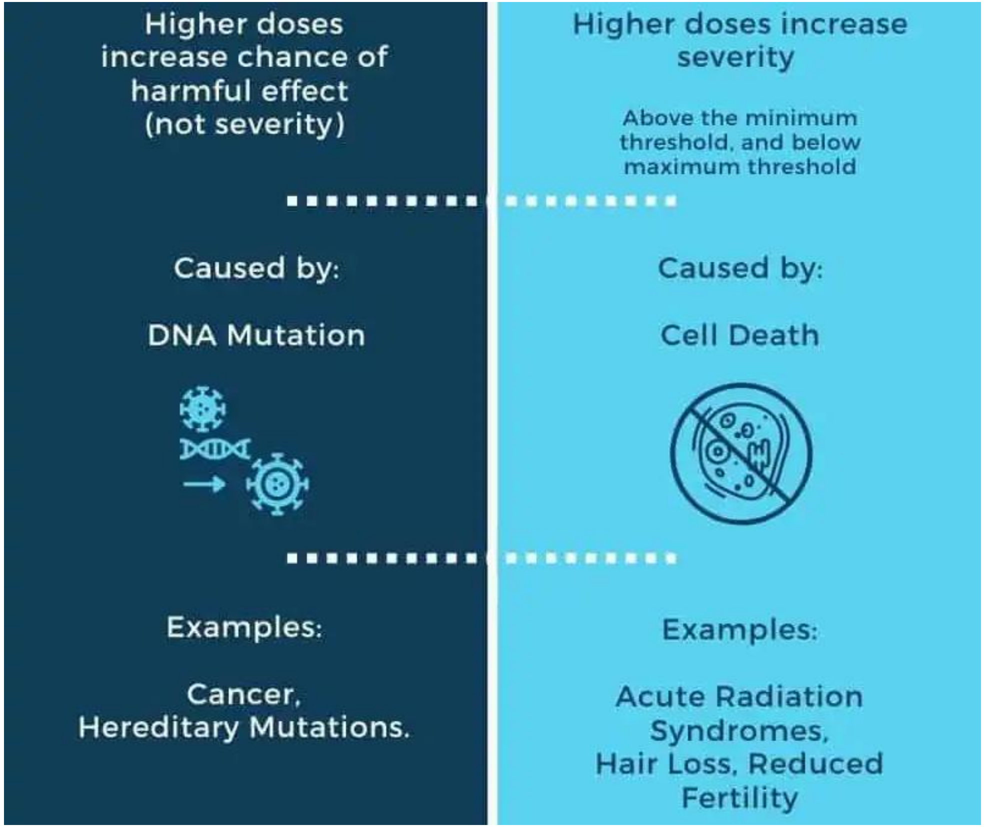




Simonsen et al. – PLoS Biol 2020/ Heilbronn et al. – Life Sci Sp Res 2015

Radiobiology: key concepts

Stochastic Effects

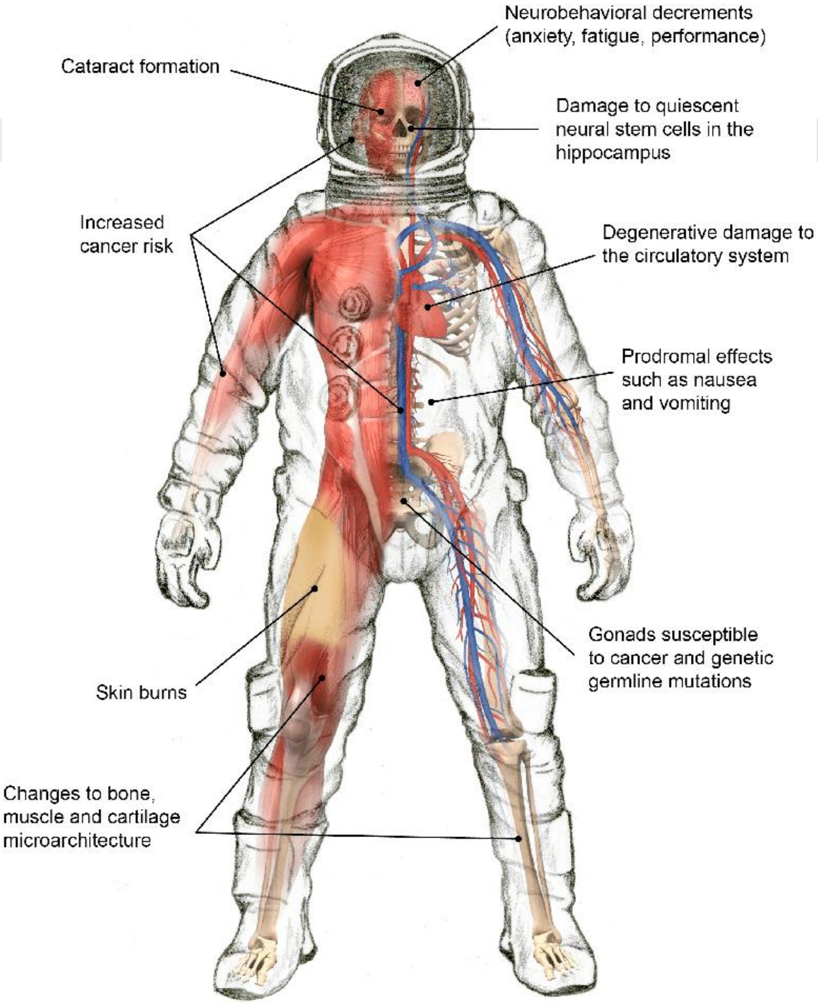


Deterministic Effects

Radiobiology: key concepts

Space radiation induced health risks:

- Acute radiation syndrome
- Degenerative tissue effects (cataract, cardiovascular risks…)
- Central nervous system deficits
- Cancer



Chancellor et al. – Life 2014

Radiobiology: key concepts

Not all ionizing radiation is equal:

LET = Linear Energy Transfer

In contrast to the stopping power, which focuses on the energy loss by a charged particle moving through a medium, LET focuses on the linear rate of energy absorption by the absorbing medium as the charged particle traverses the medium.

ICRU definition: *"LET of charged particles in a medium is the quotient dE/dl, where dE is the average energy locally imparted to the medium by a charged particle of specified energy in traversing a distance of dl."*

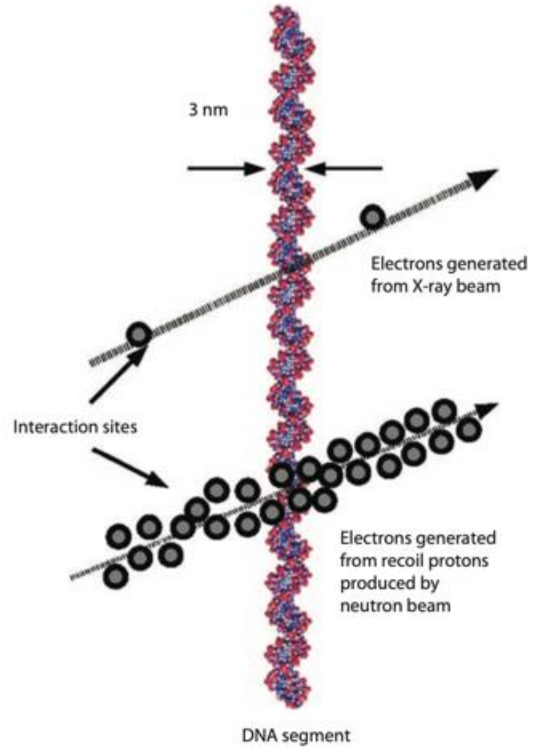


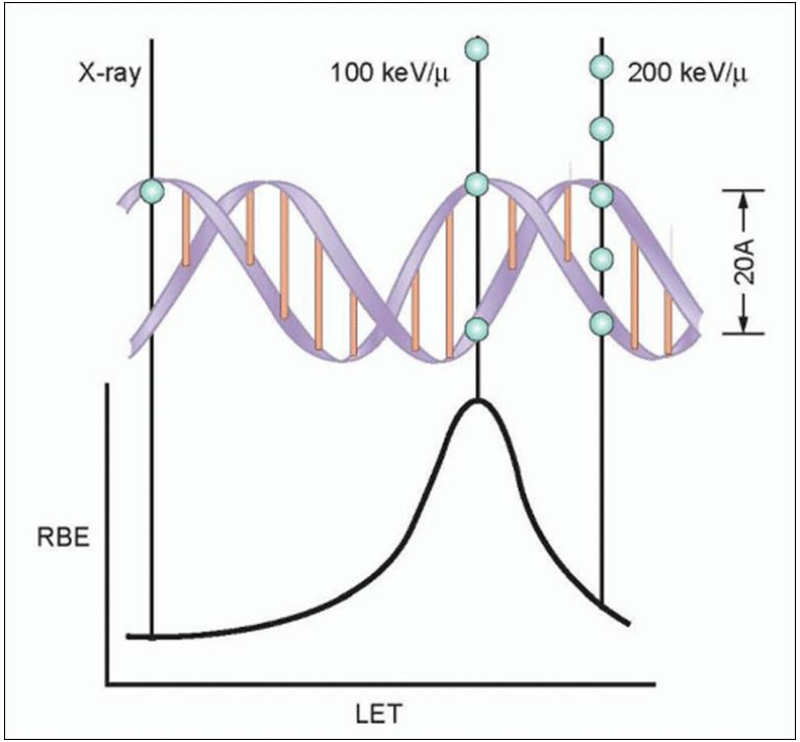
Figure 6.2 The greater DNA damage caused by the higher density of charged particles following irradiation with neutrons compared with photons.

Radiobiology: key concepts

Not all ionizing radiation is equal:

RBE = Relative Biological Effectiveness

As the LET of radiation increases, the ability of the radiation to produce biological damage increases



Radiobiology: key concepts

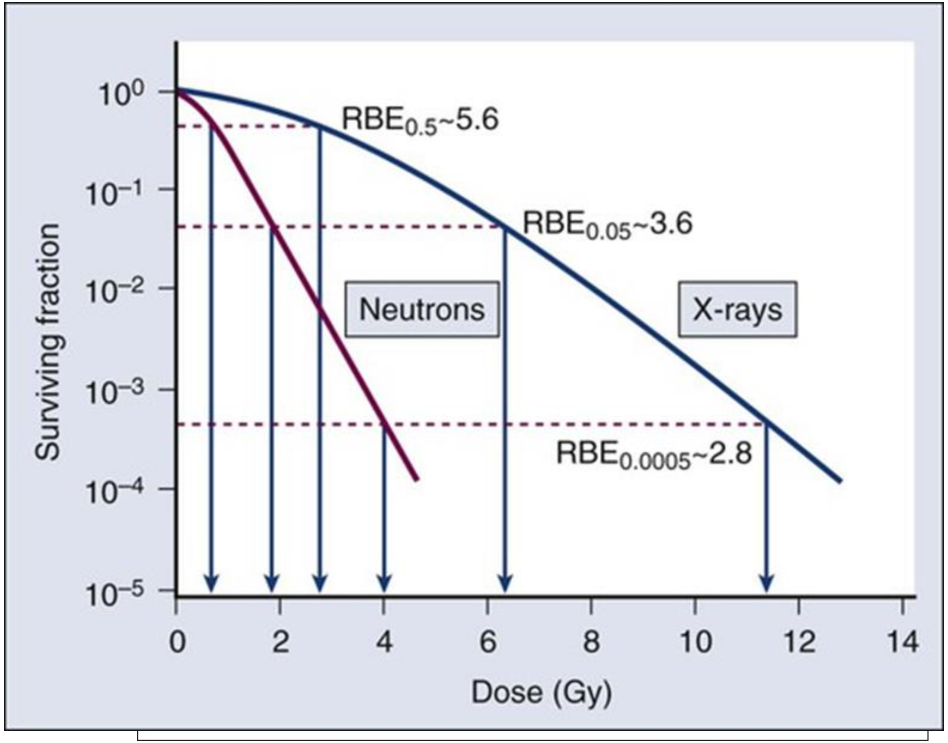
Not all ionizing radiation is equal:

RBE = Relative Biological Effectiveness

Comparison of dose values at isoeffect

Historically, 250 kVp X-rays or Cobalt-60 gamma-rays are used as reference radiation quality

$$RBE = \frac{D_\gamma}{D_{Ion}}\bigg|_{Isoeffect}$$

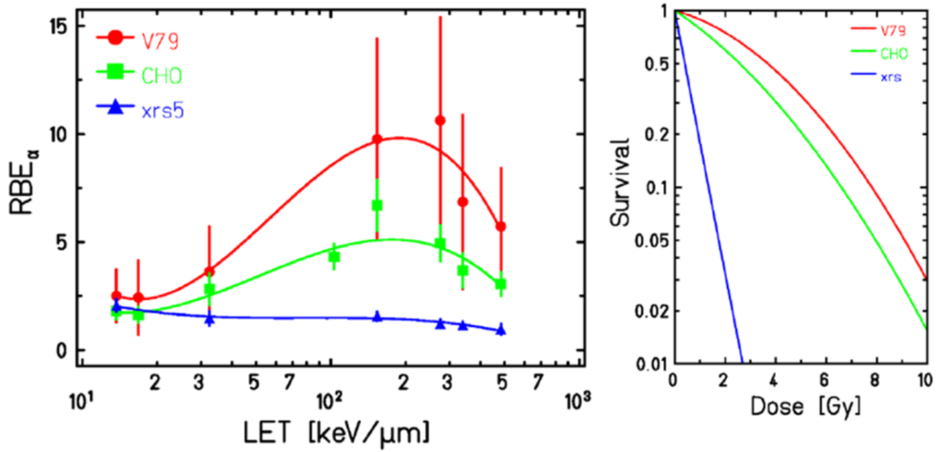


Relative Biological Effectiveness: depends on…

Biology

- Biological endpoint
- Tissue microenvironment (oxygen, scavengers, …)
- Genetic radiosensitivity
- Cell-cycle phase

Cell line dependence of RBE



Weyrather et al. 1999

Relative Biological Effectiveness: depends on…

Biology

- Biological endpoint
- Tissue microenvironment (oxygen, scavengers, …)
- Genetic radiosensitivity
- Cell-cycle phase

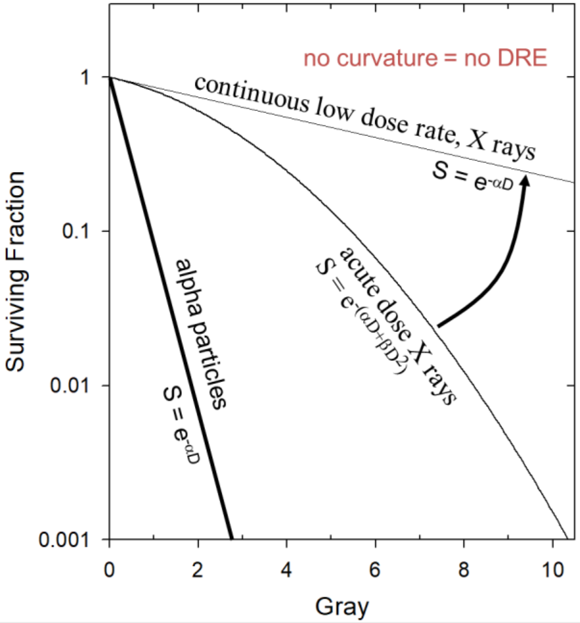
Physics

- LET
- Energy/Charge
- Dose
- Dose rate

Radiobiology: key concepts

Relative Biological Effectiveness: depends on…

Dose rate effects for low- and high LET radiation



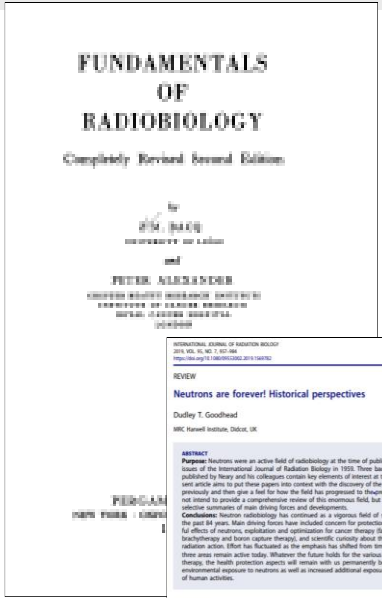
Physics

- LET
- Energy/Charge
- Dose
- Dose rate

Neutron Radiobiology: an old story

Neutron radiobiology: Past or Future?

- Studied in the early days of radiobiology
  - Protection of workers in nuclear power plants
  - Use of fast neutrons in radiotherapy
  - Exposure of atomic bomb survivors
- Emerging field of radiobiology research at accelerator-based research facilities:
  - Particle therapy
  - Space radiobiology

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2019, VOL. 95, NO. 7, 957–984
https://doi.org/10.1080/09553002.2019.1569782

Taylor & Francis

REVIEW

Neutrons are forever! Historical perspectives

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ABSTRACT

Purpose: Neutrons were an active field of radiobiology at the time of publication of the first issues of the International Journal of Radiation Biology in 1959. Three back-to-back papers published by Neary and his colleagues contain key elements of interest at the time. The present article aims to put these papers into context with the discovery of the neutron 27 years previously and then give a feel for how the field has progressed to the present day. It does not intend to provide a comprehensive review of this enormous field, but rather to provide selective summaries of main driving forces and developments.

Conclusions: Neutron radiobiology has continued as a vigorous field of study throughout the past 84 years. Main driving forces have included concern for protection from the harmful effects of neutrons, exploitation and optimization for cancer therapy (fast beam therapy, brachytherapy and boron capture therapy), and scientific curiosity about the mechanisms of radiation action. Effort has fluctuated as the emphasis has shifted from time to time, but all three areas remain active today. Whatever the future holds for the various types of neutron therapy, the health protection aspects will remain with us permanently because of natural environmental exposure to neutrons as well as increased additional exposures from a variety of human activities.

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Neutron radiobiology; neutron therapy; boron neutron capture therapy (BNCT); neutron brachytherapy; neutron radiation protection; neutron health risks; history of neutron radiobiology

Introduction

In 1920, Ernest Rutherford suggested the existence of heavy neutrally-charged particles within the atomic nucleus and that they were composed of a proton and an electron bound in some way (Rutherford 1920). The neutral particle was discovered experimentally in 1932 by James Chadwick (Chadwick 1932), for which he received the Nobel Prize for physics in 1935. He called the particles 'neutrons' because they had no electrical charge (Chadwick 1932), although this name had been used for a variety of other concepts since as early as 1899 (Feather 1960). The discovery of the neutron and its properties was the key to the extraordinary developments in atomic and nuclear physics that occurred rapidly over the next few decades, and to the opening of the atomic age.

Biological effects of neutrons were of almost immediate interest; reports on these were beginning to emerge already by 1935 (Zirkle 1947). Due to the concurrent discovery of the neutron and development of the cyclotron at the University of California at

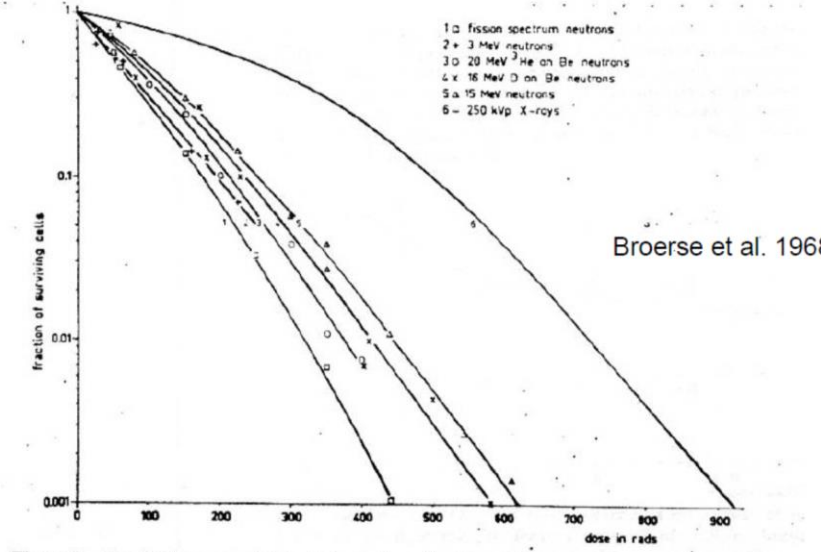
were made for enhancement of therapy by the capture of slow neutrons by the loading of tumors with selected nuclei that have a very high neutron capture probability, such as ^{10}B (Locher 1936). The discovery of nuclear fission in 1938 added further interest regarding the biological effects of neutrons – as well as considerable concern!

In the first volume of the International Journal of Radiation Biology, in 1959, Gerald ('Gerry') Neary and his coworkers published three back-to-back papers with results of their experiments on biological effects of neutrons (Evans et al. 1959; Neary, Evans et al. 1959; Neary, Tomkinson, et al 1959). By that time there was already a significant literature on the topic, but very many scientific and practical questions remained to be answered.

The present article aims to give a feel of the state of knowledge of neutron radiobiology by 1959, summarize some key features of the three Neary papers of 1959 and, then in the final section, indicate how the field has progressed in several areas of current relevance to human exposures and radiobiology research

Neutron Radiobiology: an old story

Neutron Survival Curves



Broerse et al. 1968

Figure 3. Survival curves obtained for cultured cells of human origin irradiated with different beams of fast neutrons and with 250 kVp x-rays.

Neutron: Energy dependence of RBE

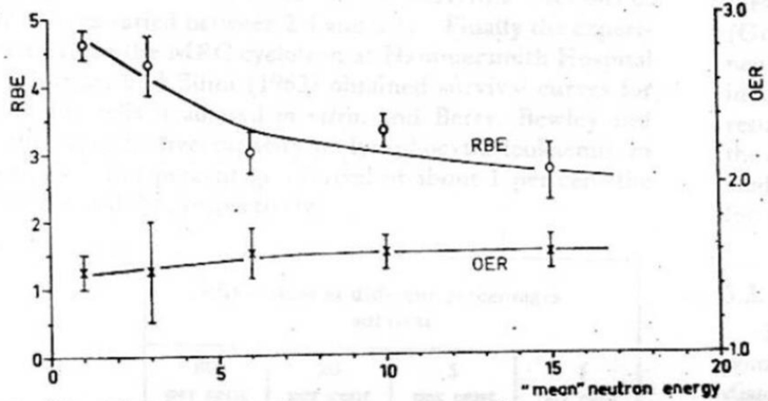


Figure 5. The RBE and OER of fast neutrons as a function of mean neutron energy, for impairment of the proliferative capacity of cultured human cells. The RBE-values correspond to doses producing 50 per cent cell killing.

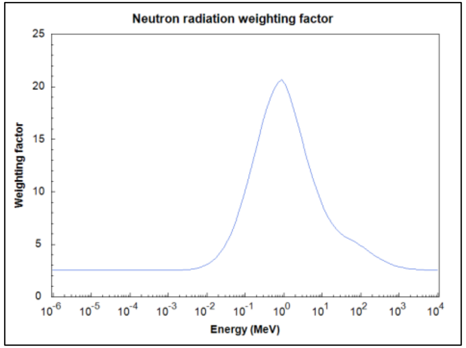
Neutron Radiobiology: weighting factor

Radiation weighting factor wR (ICRP) used for cancer risk estimations. Introduced for **radiation protection** purposes in order to account for the relative detriment of different types of radiation

- **Pooling RBE data** from different experiments
- Absorbed dose (Gy) to equivalent dose H (Sv)

$$H = w_R * \mathrm{D}$$

- Depends on energy: **maximum of 20 around 1 MeV**.
- Mean quality factor decreases with increasing neutron energy to values of **< 5 for neutrons > 20 MeV**: **continuous functions used by ICRP**

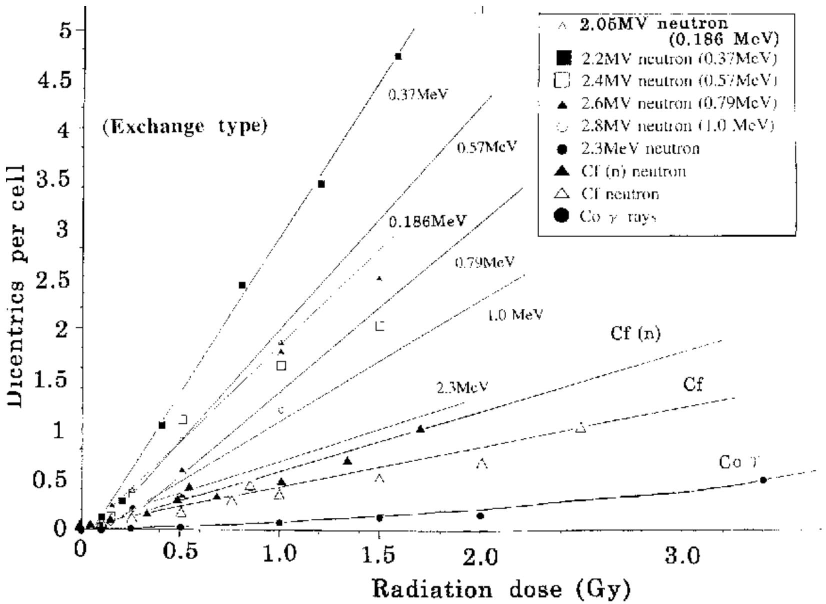


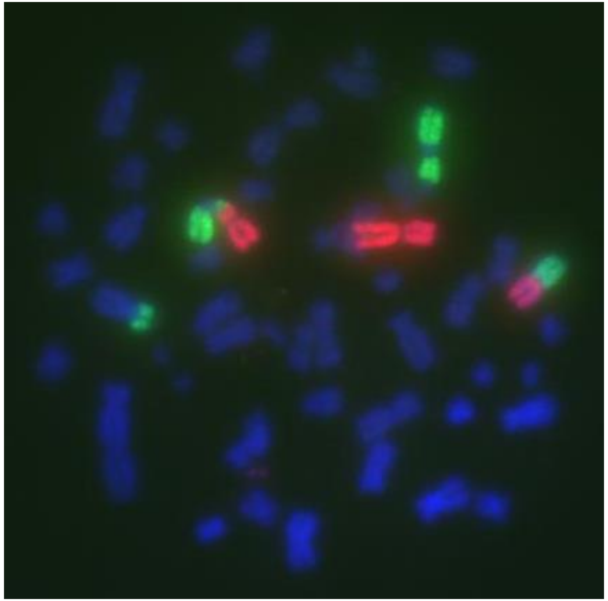
Radiation Type	Energy	W (ICRP-60)	W (ICRP-92)
Photons	all	1	1
Electrons, muons	all	1	1
Neutrons	<10 keV	5	function
Neutrons	10-100 keV	10	function
Neutrons	>100 keV- 2Mev	20	function
Neutrons	>2 -20 MeV	10	function
Neutrons	>20Mev	5	function
Protons	<2 MeV	5	2
α-particles, fission fragments	all	20	20

$$w_R = \begin{cases} 2.5 + 18.2e^{-[\ln(E_n)]^2/6}, & E_n < 1\ \mathrm{MeV} \\ 5.0 + 17.0e^{-[\ln(2E_n)]^2/6}, & 1\ \mathrm{MeV} \leqslant E_n \leqslant 50\ \mathrm{MeV} \\ 2.5 + 3.25e^{-[\ln(0.04E_n)]^2/6}, & E_n > 50\ \mathrm{MeV} \end{cases}$$

Neutron Radiobiology: an old story

Chromosomal aberrations





Tanaka et al. – J Rad Res 1999

Neutron Radiobiology: an old story

Chromosomal aberrations

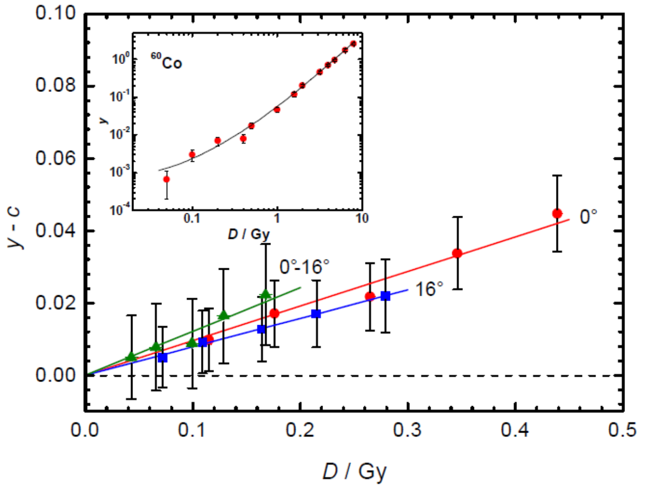


Fig. 3 Yield y of dicentric chromosomes observed for the 0° (circles) and 16° (squares) beams and the (0°-16°) difference spectrum (up triangles). Linear functions $y = \alpha \cdot D$ were fitted to the experimental data. The insert shows the yield curve for ^{60}Co γ-radiation which was used as reference.

Table 2 Linear yield coefficients α for the irradiations at 0° and 16° as well as for the (0°-16°) difference spectrum. The type-A and type-B uncertainties $u_\alpha^{(A)}$ and $u_\alpha^{(B)}$ of α and the total uncertainties u_{RBE} of the RBE_M values are indicated for a coverage factor $k = 1$. The linear yield coefficient for ^{60}Co γ-radiation is $\alpha_{ref} = (0.0106 \pm 0.003)$ Gy^{-1}.

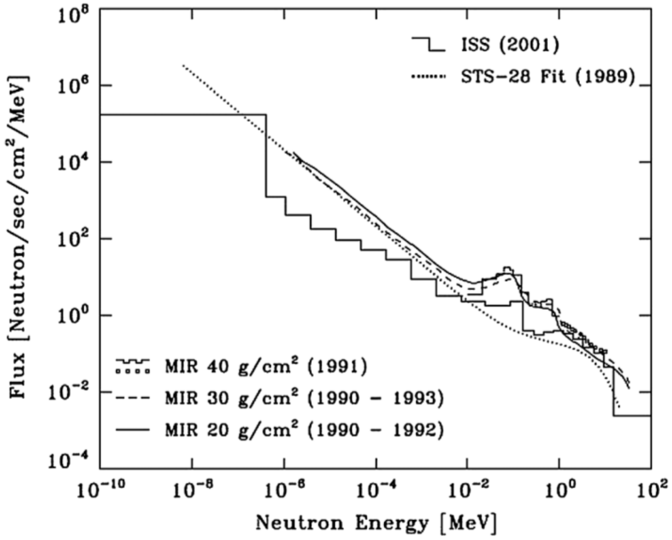
	α / Gy^{-1}	$u_\alpha^{(A)}$ / Gy^{-1}	$u_\alpha^{(B)}$ / Gy^{-1}	RBE_M	u_{RBE}
0°	0.096	0.004	0.020	9.0	2.0
16°	0.0787	0.0014	0.016		
0°-16°	0.121	0.008	0.025	11.4	2.5

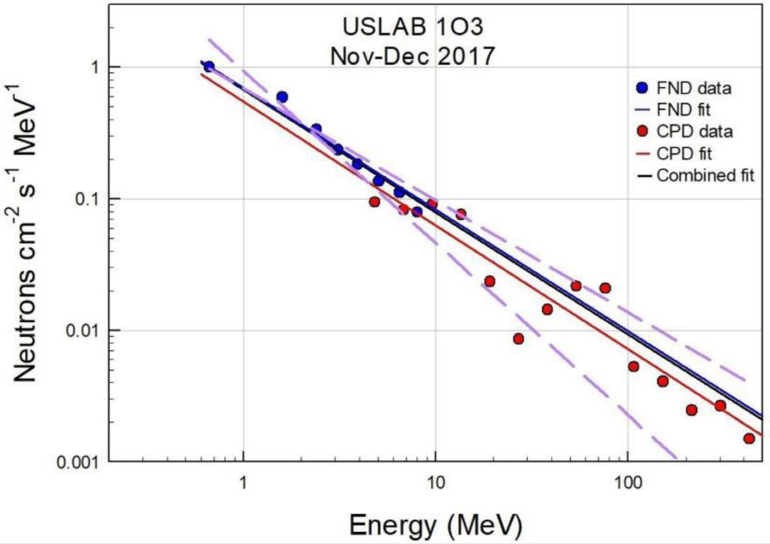
One of the few experiments conducted with high-energy neutrons using a relevant biological endpoint for cancer risk estimations

Nolte et al. – 2006

Neutrons on ISS:

- Neutrons of high energy contribute significantly to the ambient dose equivalent of the crew on the International Space Station (ISS)





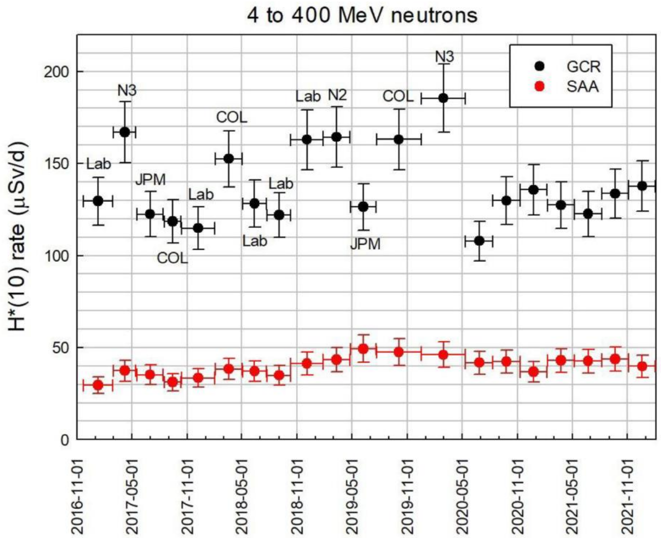
Zeitlin et al. – Life Sci Sp Res 2023

Neutrons in Space

Neutrons on ISS:

- Neutrons of high energy contribute significantly to the ambient dose equivalent of the crew on the International Space Station (ISS)

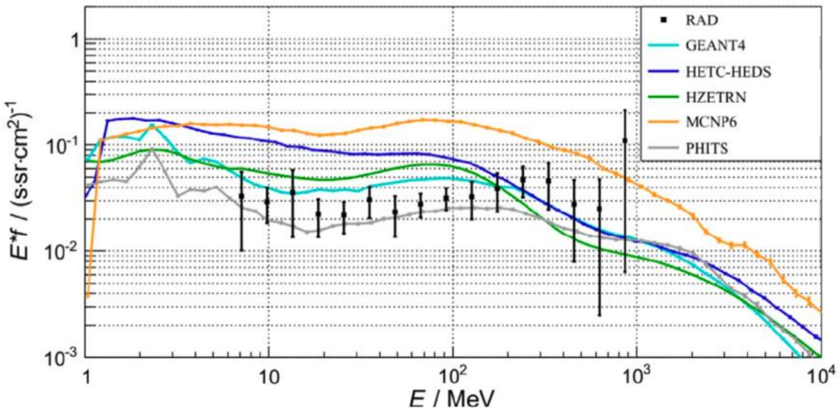
Mission	Altitude (km)	Neutron dose rate (μGy/day)	Charged particle dose rate (μGy/day)	Neutron equivalent dose rate (μSv/day)	Charged particle equivalent dose rate (μSv/day)
STS-55	302	5.9	57.2	52.0	120.1
STS-57	470	25.3	461.9	220.0	859.4
STS-65	306	11.0	75.2	95.0	157.8
STS-94	296	3.7	101.5	30.8	213.9



Durante & Cucinotta – Rev Mod Phys 2011 /Zeitlin et al. – Life Sci Space Res 2023

Neutrons on Mars:

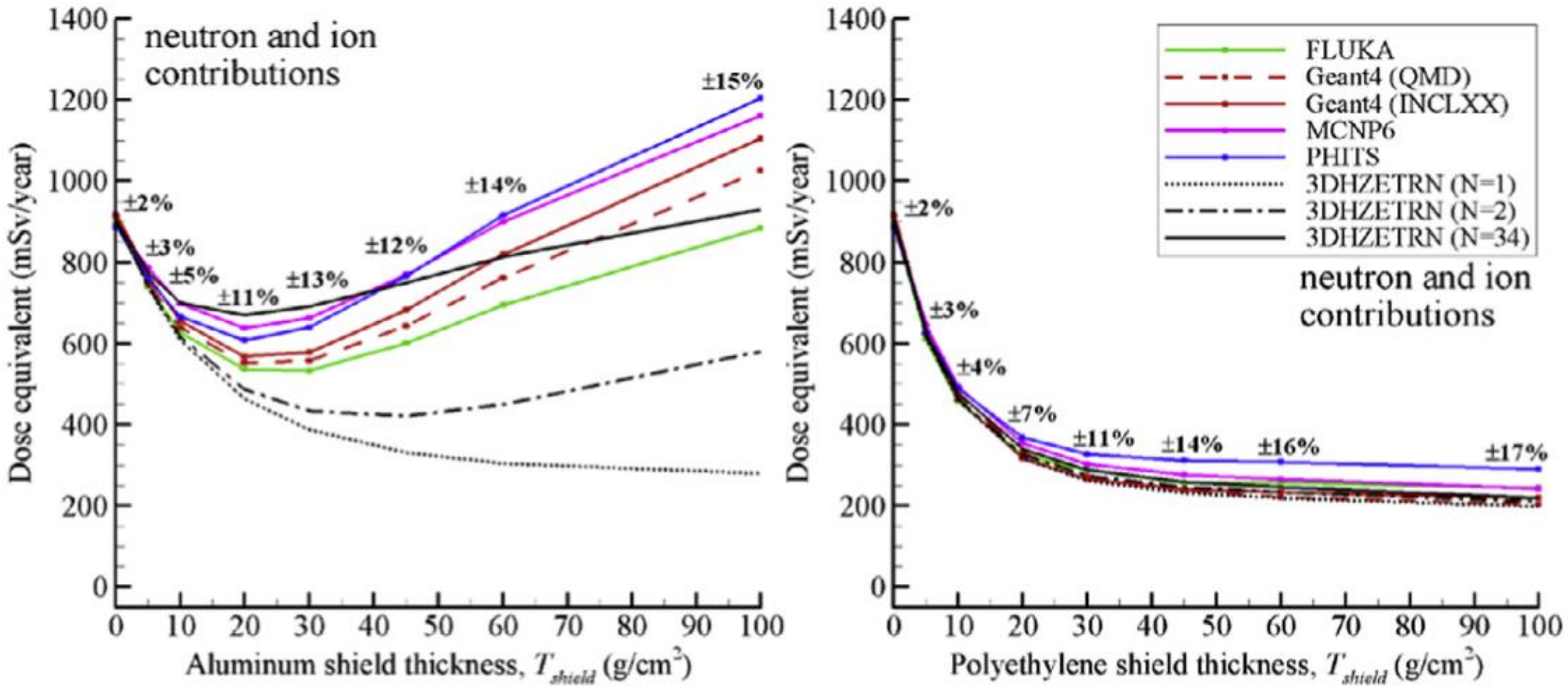
- The Radiation Assessment Detector (RAD) onboard the Mars Science Laboratory (MSL):
  - Neutron dose rate between 7 and 740 MeV of 5.1 ± 1.0 µGy/d (2.2% of the total surface dose rate)
  - Dose equivalent rate of 23.6 ± 4.1 µSv/d (3.8% of the total surface dose equivalent rate)
  - Extrapolation to 1 - 1000 MeV range: neutrons 5% contribution to the charged particle dose equivalent rate



Matthiä et al. – Life Sci Space Res 2017

Neutrons in Space

Neutrons and shielding:



Slaba et al. – Life Sci Space Res 2017

Research Gap

What do we need to improve neutron radiation risk estimations for space:

- Limited RBE data for neutrons above 20 MeV leads to high uncertainties in radiation risk estimations
- Lack of RBE data on relevant biological endpoints and *in vivo* data (e.g. cardiovascular risks, central nervous system decrements, ..)
- Facilities to perform radiobiology experiments using high-energy neutrons:
  - Field size of at least 5 x 5 cm^2
  - Uniform dose distribution
  - Simulation/calculation of absorbed dose (Gy)
  - Possibility to perform rodent experiments?

Research Gap

Example of a recent *in vivo* CNS experiments with neutrons:

Int J Mol Sci. 2021 Apr 1;22(7):3668. doi: 10.3390/ijms22073668

Chronic Low Dose Neutron Exposure Results in Altered Neurotransmission Properties of the Hippocampus-Prefrontal Cortex Axis in Both Mice and Rats

Balaji Krishnan [1,*], Chandramouli Natarajan [1], Krystyn Z Bourne [1], Leila Alikhani [2], Juan Wang [3,4], Allison Sowa [5], Katherine Groen [3], Bayley Perry [3,4], Dara L Dickstein [3,4], Janet E Baulch [2], Charles L Limoli [2], Richard A Britten

Int J Mol Sci. 2021 Aug 21;22(16):9020. doi: 10.3390/ijms22169020.

Acute, Low-Dose Neutron Exposures Adversely Impact Central Nervous System Function

Peter M Klein [1], Yasaman Alaghband [2], Ngoc-Lien Doan [2], Ning Ru [2], Olivia G G Drayson [2], Janet E Baulch [2], Enikö A Kramár [3], Marcelo A Wood [3], Ivan Soltesz [1], Charles L Limoli [2]

- Columbia University Radiological Research Accelerator Facility (RARAF)
- Primarily neutrons with a broad spectrum of energies (0.2–9 MeV), ~19% consisted of inherent γ-rays
- Mice were slowly rotated at a rate of 0.5 rotations/min around the neutron beam, providing isotropic irradiation


Thank you for your attention!
Questions?
Contact: C.Vandevoorde@gsi.de