



Dose-Effects Models for Space Radiobiology: An Overview on Dose-Effect Relationship

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Space radiobiology is an interdisciplinary science that examines the biological effects of ionizing radiation on humans involved in aerospace missions. The dose-effect models are one of the relevant topics of space radiobiology. Their knowledge is crucial for optimizing radioprotection strategies, the risk assessment of the health hazard related to human space exploration, and reducing damages induced to astronauts from galactic cosmic radiation. Dose-effect relationships describe the observed damages to normal tissues or cancer induction during and after space flights. They are developed for the various dose ranges and radiation qualities characterizing the actual and the forecast space missions.

Based on a Pubmed search including 53 papers reporting the collected dose-effect relationships after space missions or in ground simulations, 7 significant dose-effect relationships (e.g., eye flashes, cataract, **central nervous systems**, cardiovascular disease, cancer, chromosomal aberrations, and biomarkers) have been identified.

For each considered effect, the absorbed dose thresholds and the uncertainties/limitations of the developed relationships are summarized and discussed. The current knowledge on this topic can benefit from further in vitro and in vivo radiobiological studies, an accurate characterization of the quality of space radiation, and the numerous experimental dose-effects data derived from the experience in the clinical use of ionizing radiation for diagnostic or treatments with doses like those foreseen for the future space missions.

The growing number of pooled studies could improve the prediction ability of dose-effect relationships for space exposure and reduce their uncertainty level. Novel research in the field is of paramount importance to reduce damages to astronauts from cosmic radiation before Beyond Low Earth Orbit exploration in the next future.

In that sense **an innovative approach could come from state of the art instrumentation and detectors operating in space**, built for astroparticle measurements, allows for the estimation of GCR properties and absorbed dose with a greater accuracy, **thanks to the recent availability of the Alpha Magnetic Spectrometer (AMS) detector, installed on the International Space Station, that measures charged components of cosmic rays since 2011 and is approved to be operative for all the life cycle of the ISS.**

Outline

- ◇ AMS INFN Roma Sapienza Research Group
- ◇ Space Radiation Environment
- ◇ Part I: Dose Effects Relationship (DER)
 - ◇ The Overview
 - ◇ CNS DER
 - ◇ Possible improvements strategies
- ◇ Part II : Target Effects vs Non Target Effects

INTRODUCTION

Alpha Magnetic Spectrometer (AMS)

INFN ROMA SAPIENZA RESEARCH GROUP



The AMS SPRB collaboration was created in 2017 by the synergy of the AMS INFN Roma Sapienza (Italy) group led by Alessandro Bartoloni with the medical physics research group led by Lidia Strigari currently at IRCCS university Hospital of Bologna (Italy)

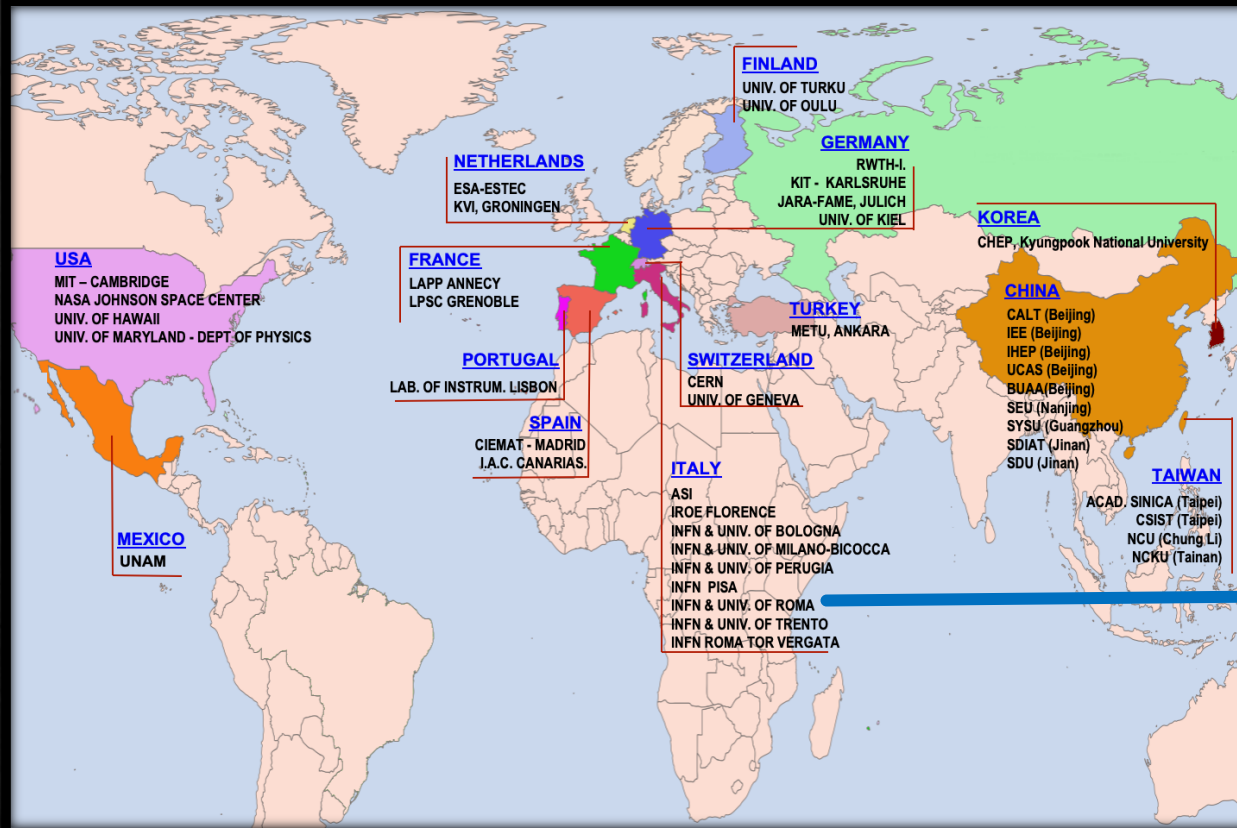
Alpha Magnetic Spectrometer AMS02

AMS is a particle detector measuring Galactic Cosmic Ray fluxes.
It was installed on the International Space Station (ISS) on May 19, 2011



A. Bartoloni - RAD 10 Summer Edition





The AMS collaboration

(<http://ams02.space>)

An international collaboration made of 44 Institutes
from America, Asia and Europe

A. Bartoloni - RAD 10 Summer Edition



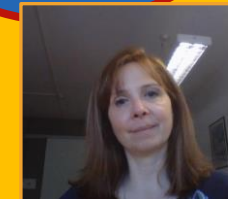
Silvia Strolin



Miriam Santoro



Lidia Strigari



Aboma Negasa Guracho



Alessandro Bartoloni



Giuseppe Della Gala



Giulia Paolani



The AMS02 detector has collected so far more than **200 billion** Cosmic Rays events.

More Info in the AMS-02 webpage:

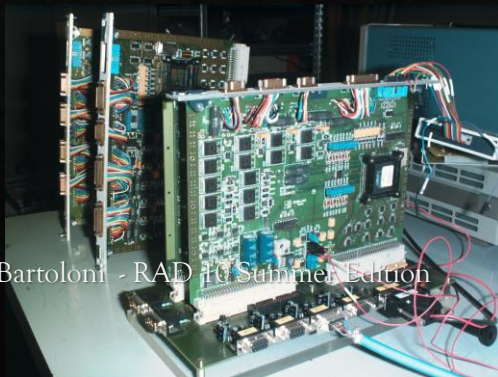
<https://ams02.space>

27/7/2022

The INFN Roma and the Sapienza university joined the AMS collaboration in 2001.

The group has taken part to the construction of the **Transition Radiation Detector (TRD)**, having as main task the responsibility to develop the slow control electronics of the GAS System of the TRD (UG-Crate).

The UG-CRATE was part of a safety-critical system and the group took care of all the phases of the development (Design-Test-Integrate-Fly) following the NASA requirements.



A. Bartoloni - RAD 10 Summer Edition





At INFN Roma AMS group, led by **Alessandro Bartoloni**, the primary activity is the use of the AMS measurements of cosmic rays to improve the space radiobiology knowledge with a primary emphasis on ***the space radiation relevance and risk for human space exploration.***

In this topic, there is a strong collaboration and participation to the Roma group of the Medical Physics department of the IRCCS University Hospital of Bologna, led by **Lidia Strigari**.



Dr. Lidia Strigari

Medical Physics Department

IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy

A. Bartoloni - RAD 10 Summer Edition



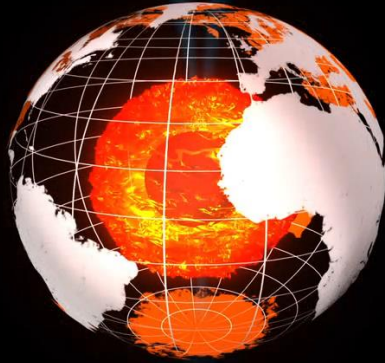
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SPACE RADIATION & ASTRONAUT SAFETY

«To fully understand the relationship between ionizing radiation and biology, and to solve problems in this field, researchers incorporate fundamentals of **biology, physics, astrophysics, planetary science, and engineering**» *(credit : NASA)*

(credit : ESA)

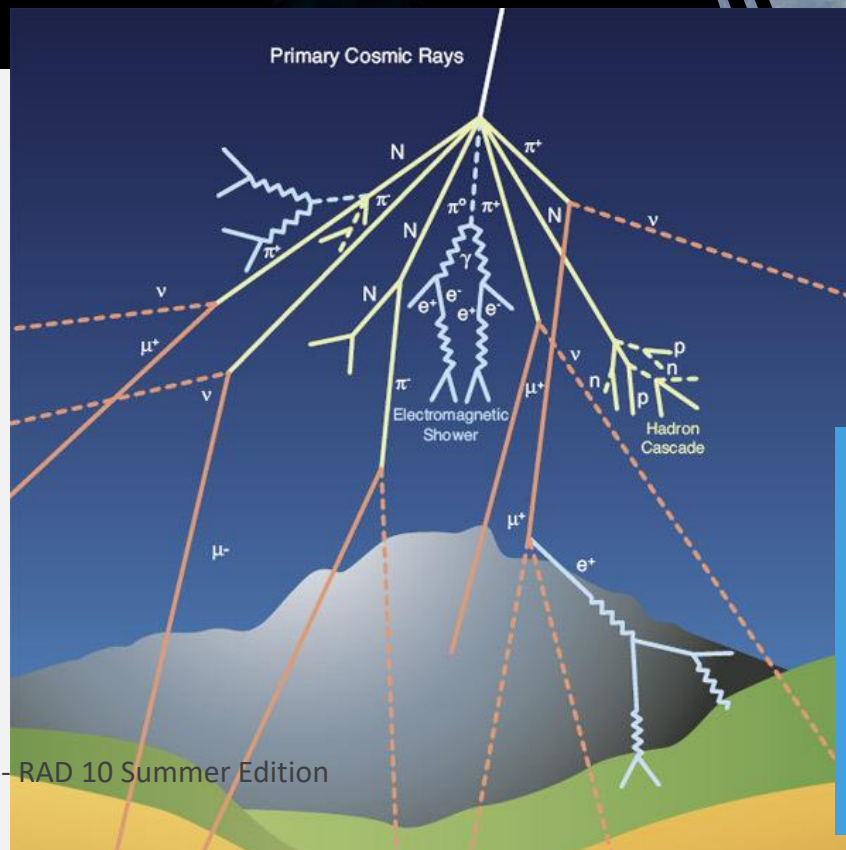


Cosmic Rays Interactions with the geo-magnetosphere

Earth is a cocoon !!!

Magnetosphere stops/deflects 99.9% of charged particles

the Earth Atmosphere is equivalent to a metal shielding 1 meter thick



The annual cosmic ray “dose” at sea level is around **0.27 mSv**

<10% of “background radiation”
(Radon, Soils, Foods, Medical,..)

Origin of Space Radiation and Consequent Risk

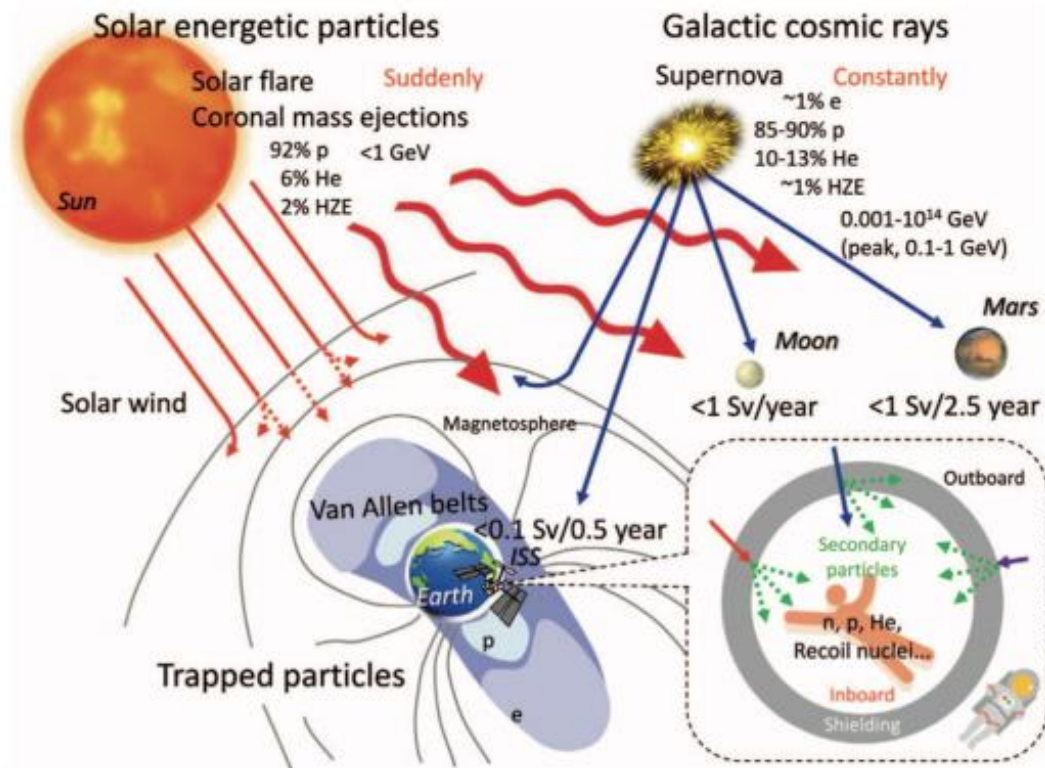
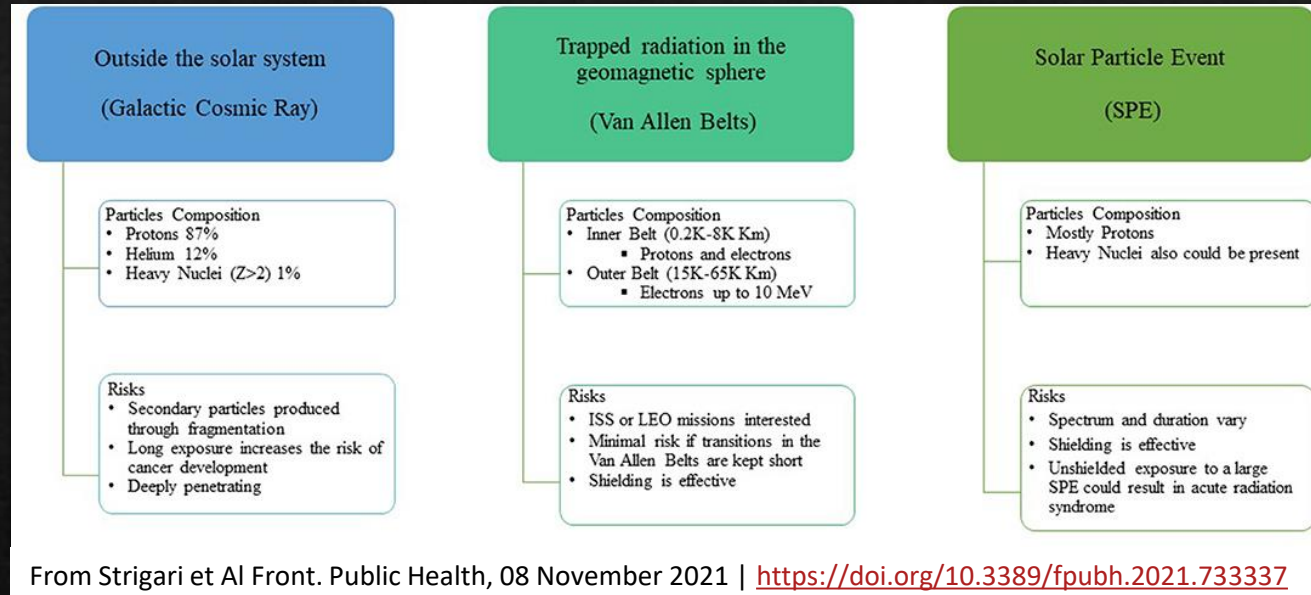


Image courtesy of European Space Agency (ESA)



From Strigari et Al Front. Public Health, 08 November 2021 | <https://doi.org/10.3389/fpubh.2021.733337>

Space Radiation composition

- Galactic Cosmic Rays (GCR)
- Particle emitted by the Sun (SEP) during isolated events
- Particle trapped in Earth's magnetic field (Radiation Belt)

None of the 3 components is constant in time, mainly due to the solar activity

Human Space activities must cope with the high radiation environment of outer space.

Limits and concerns

The manned spaceflight especially the one beyond the LEO could represent a concern for the health of astronauts.

The limit in carrying out the missions are due to health effects

- short-term (<hours)
- acute effects (<months)
- late effects including severe toxicity

Radioprotection in space is a difficult jobs due to the presence of different species of particle and nuclei that present different characteristics in penetrating the barrier and shielding

x150-200

x300-400

x250 (x750)

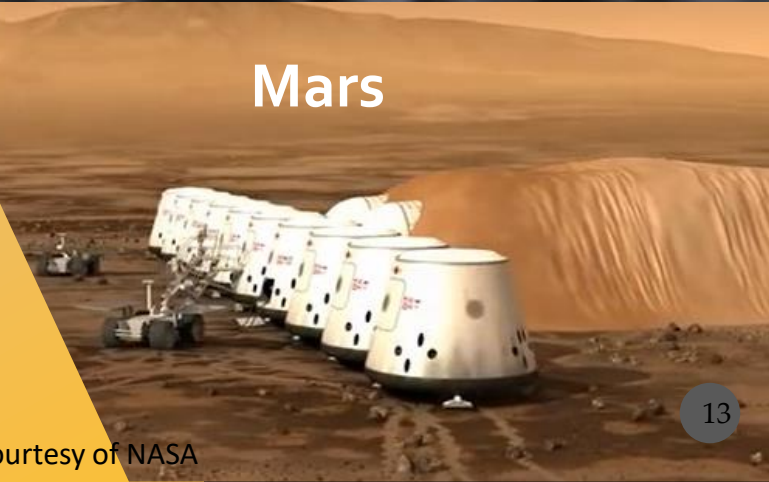
LEO-ISS



Moon



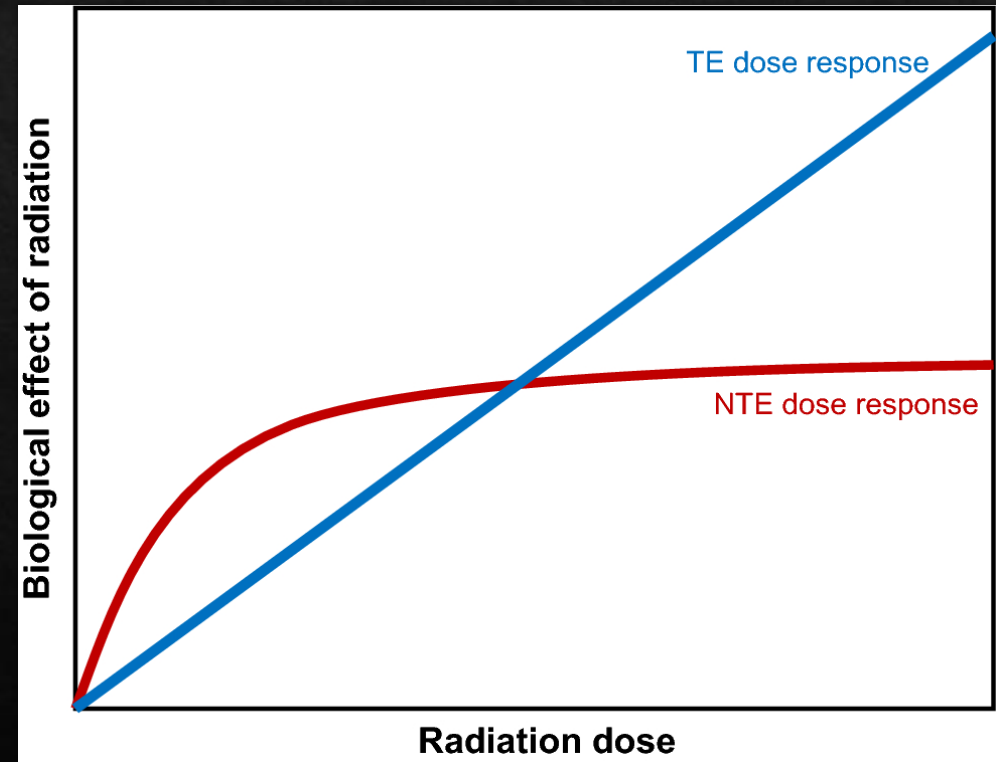
Mars



Part I: Dose Effects Relationship (DER)

Dose-Effect Relationship

Crucial point to predict the toxicity of the space radiation expected for the astronauts/space workers is the creation of reliable mathematical models that describe the correlation between the exposition to IR and the possible damages to the organ at risk



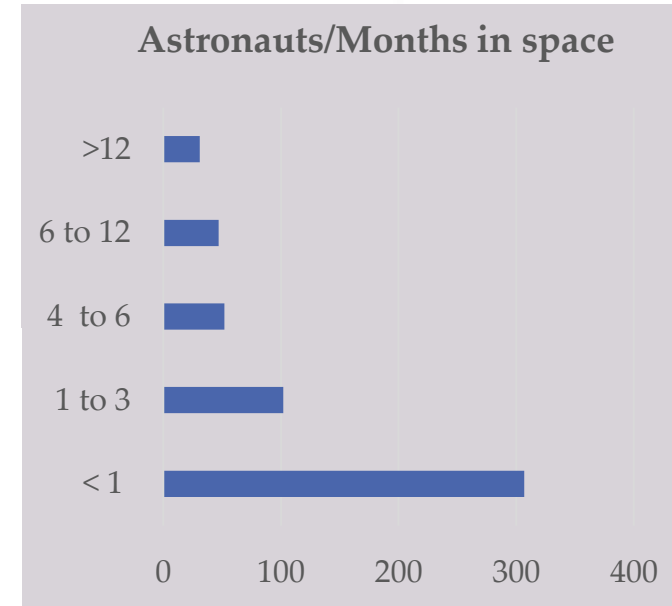
Dose-Effects Relationship

The known dose-effect relationships are
based on a limited number of
astronauts
(hundreds)

Total Space Radiation Dose (mGy)	<0.2	0.2–1.99	2–3.99	4–10.99	≥11	Total
# Astronauts	14	19	11	15	14	73
# Cancer Deaths	2	2	1	0	2	7
# Cardiovascular Disease Deaths	1	4	1	1	0	7
# Accident Deaths	6	5	0	0	1	12
# Other Deaths	1	0	1	0	1	3
# Unknown Deaths	1	0	0	3	1	5
Mean Medical Dose (SD)	2.4 (6.4)	27.7 (13.6)	34.4 (20.8)	29.1 (15.6)	32.5 (21.7)	25.1 (19.4)
Mean Year at Birth (SD)	1932.6 (4.1)	1931.7 (5.2)	1931.6 (2.5)	1932.2 (4.4)	1931.5 (3.3)	1931.9 (4.1)
Mean Age at Entry into Astronaut Corps (SD)	31.6 (2.7)	32.2 (3.4)	33.0 (2.5)	31.8 (2.8)	32.5 (2.2)	32.2 (2.8)
Mean Follow up Time (SD)	29.3 (23.6)	40.3 (15.0)	46.4 (12.9)	50.7 (7.8)	48.1 (7.5)	42.8 (16.1)
Total Group Person Years	409.9	766.5	510.1	760.8	673.4	3120.8
Mean Age at Death (SD)	57.7 (23.8)	65.7 (15.9)	64.5 (14.9)	78.2 (19.9)	74.9 (10.2)	65.2 (19.1)
Mean Current Age of Living Astronauts (SD)	79.9 (2.9)	82.1 (3.9)	84.9 (3.1)	83.6 (3.6)	83.8 (2.3)	83.4 (3.4)

Table 1. Early astronaut cohort demographics binned by total space radiation dose category. SD = standard deviation.

Radiation Exposure and Mortality from Cardiovascular Disease and Cancer in
Early NASA Astronauts S.Robin et Al - 2018



Needs of improvements

We made and publish in 2021
an extensive review of the
existent literature to use as
starting point for improvements
this research areas

<https://doi.org/10.3389/fpubh.2021.733337>

REVIEW article

Front. Public Health, 08
November 2021
Sec. Radiation and Health
<https://doi.org/10.3389/fpubh.2021.733337>

This article is part of the Research Topic
Medical Application and Radiobiology Research of
Particle Radiation
[View all 16 Articles >](#)

Dose-Effects Models for Space Radiobiology: An Overview on Dose- Effect Relationships



Lidia Strigari¹,



Silvia Strolin¹,



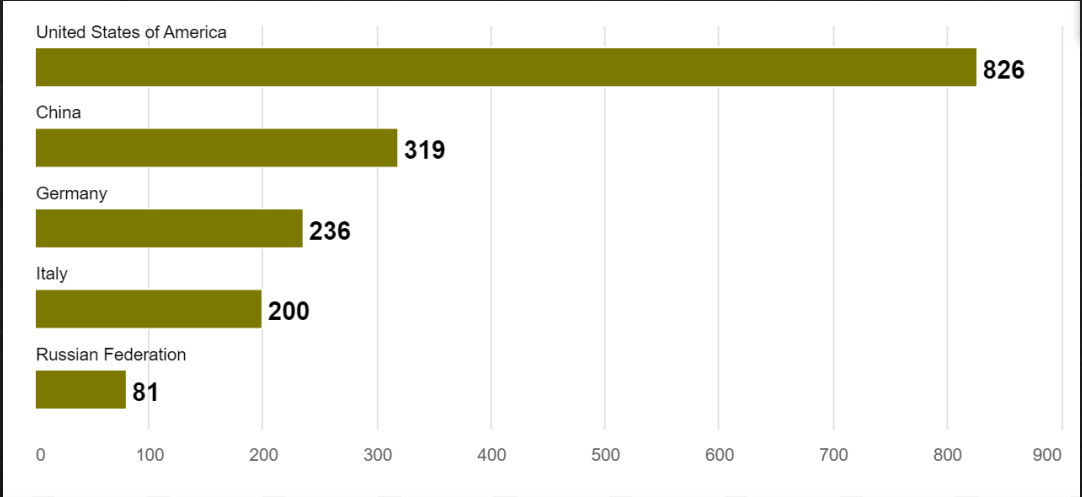
Alessio Giuseppe Morganti² and



Alessandro Bartoloni^{3*}

Model	Study Type	Dose Range/Threshold or LET	#Papers	Reliability	Priority
Eye Flashes	Spaceflight	LET>5-10 KeV/μm	4	****	*
Cataract	Spaceflight	8 mSv	5	***	***
CNS	Ground/Simulations	100-200 mGy	11	**	*****
CVD	Spaceflight	1000 mGy	4	*	***
	Ground/Simulations	0.1-4,500 mSv	8		
Cancer	Spaceflight	< 100 mGy	2	***	*****
	Ground/Simulations	< 100 mGy	9		
Biomarkers or Chromosomal Aberrations	Spaceflight	<5-150 mGy	11	***	*****
	Ground /Simulations	< 10,000 mGy	4		
Other Risks	Ground/Simulations	2,000 mGy	2	*	***

*= Very Low, **=Low, ***=Medium, **** = High, ***** = Very High.



Article Statistics (June 2022)



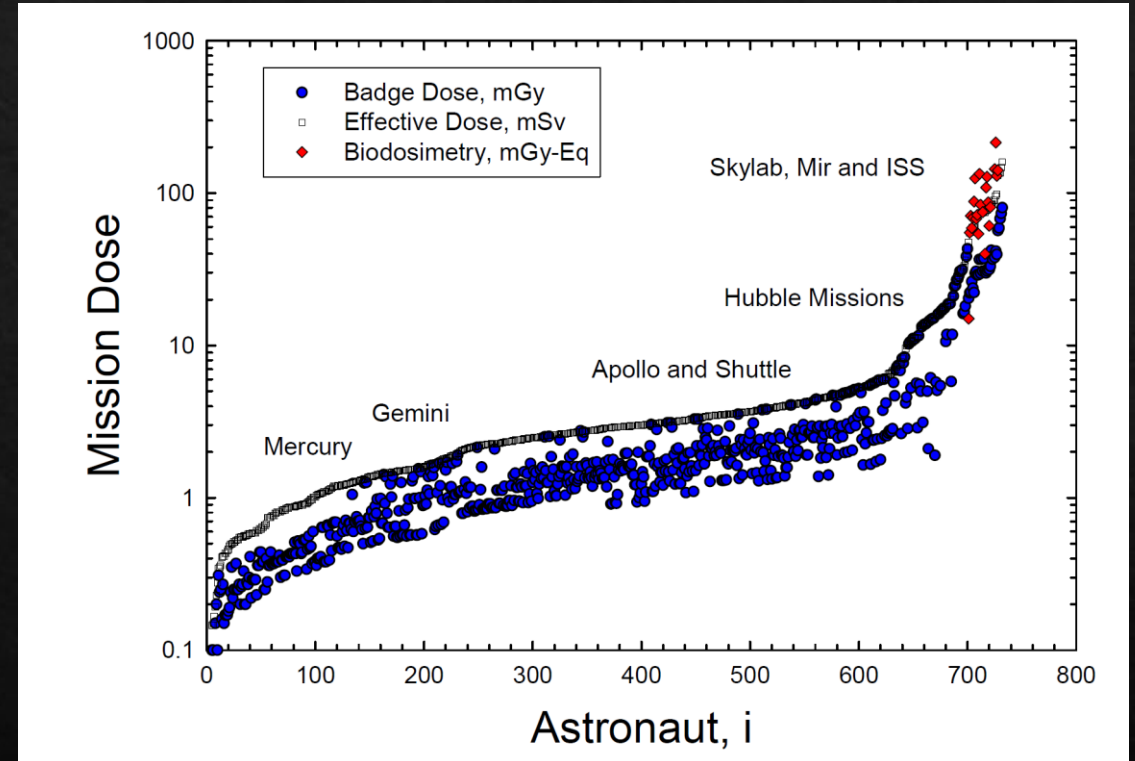
RISK for the CNS due to IR

Space Radiation effects on CNS

The potential acute and late risk from GCR and SPEs for astronauts on board the ISS are not considered a major concern.

Instead, deep space exploration and long term (>1 year) mission are under consideration.

On exploratory BLEO missions' astronauts will be exposed to a variety of particles (HZE) which differ in terms of particle energy and particle linear energy transfer (LET)

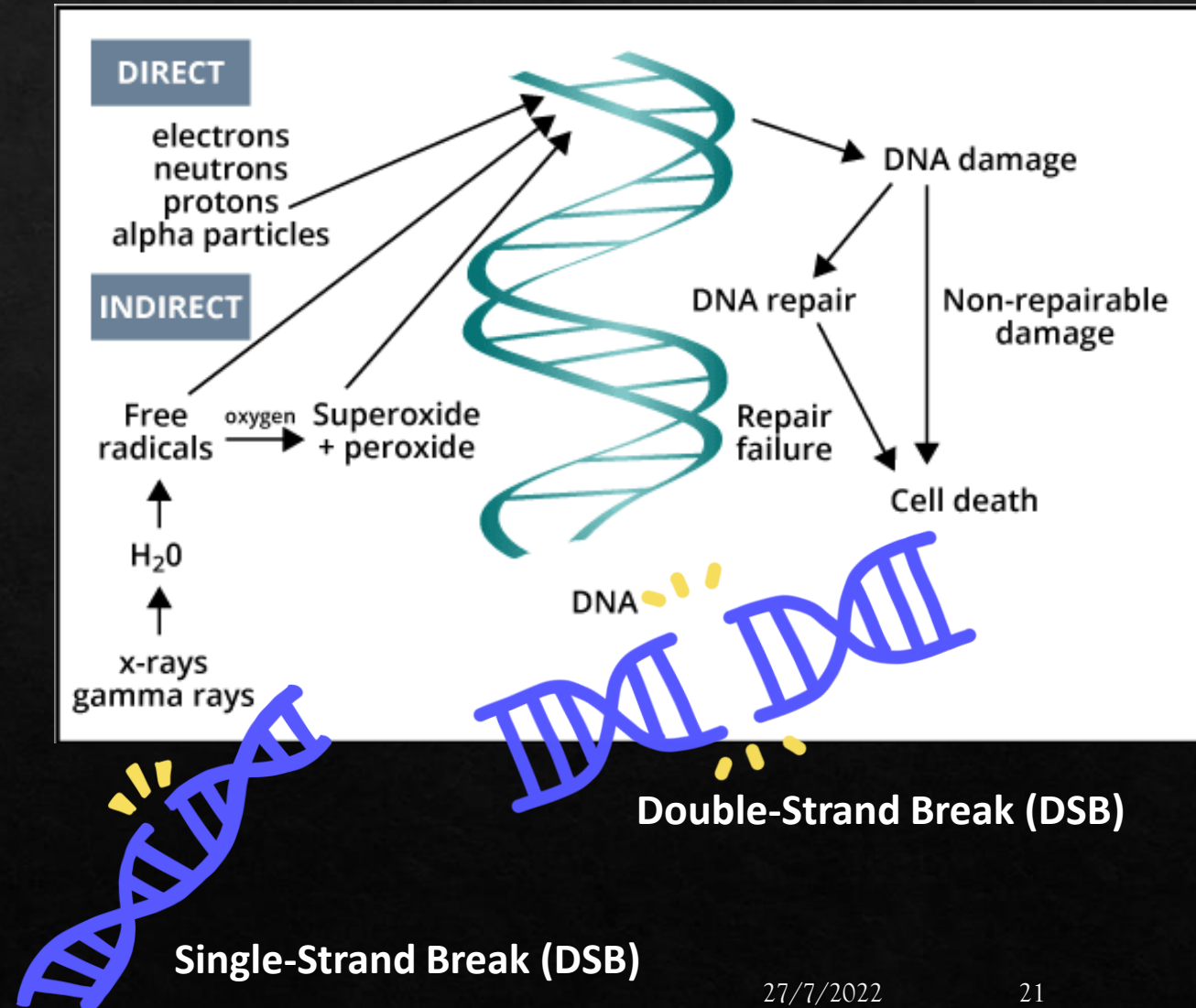


Summary of mission personnel dosimetry from all past NASA crew (Cucinotta et al. 2008).

Ionizing Radiation risk for CNS

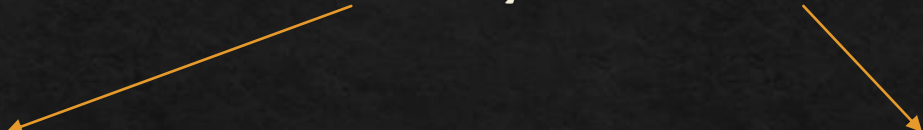
Ionizing radiation particles have in the physical ability to generate free radicals that may cause direct or indirect DNA damage

also provide a source of metabolic stress to which the central nervous system (CNS) is particularly susceptible as compared to other tissue types.



Space Radiation effects on CNS

Early vs Late

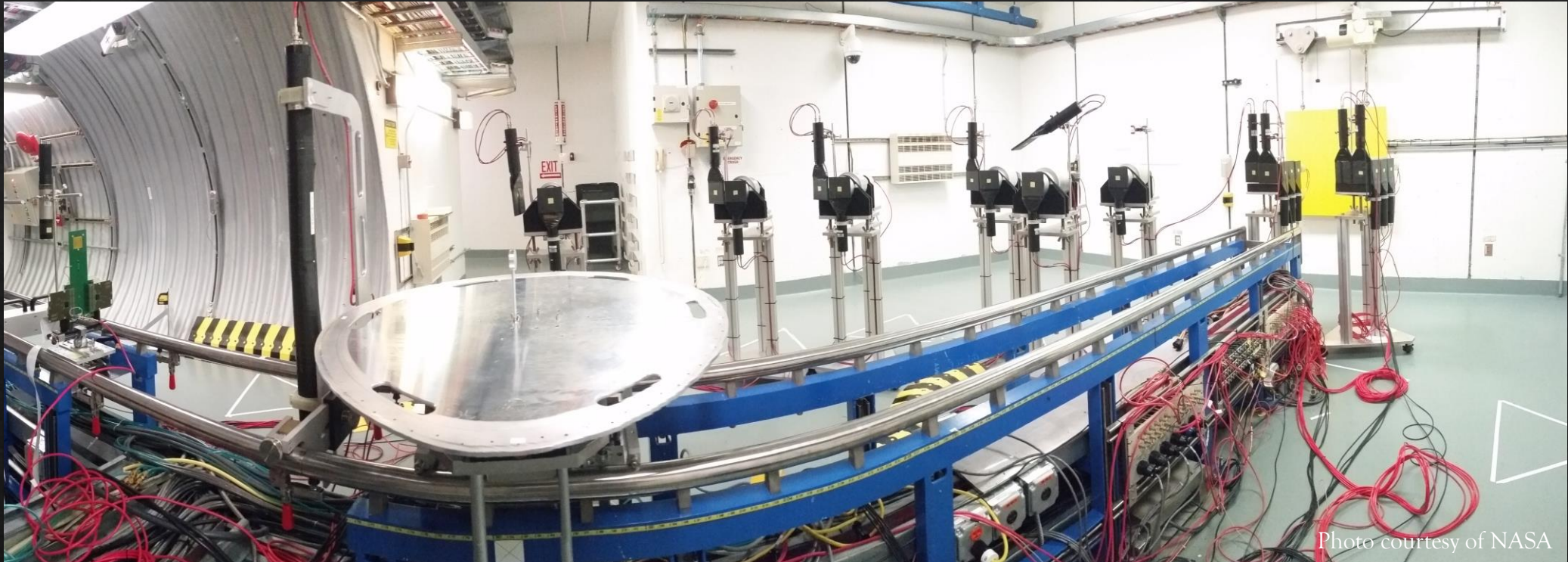


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graph TD; A[Space Radiation effects on CNS] --> B[Early]; A --> C[Late];
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- ◇ **Neurocognitive deficit**
- ◇ **Operant reactions**
- ◇ **Short Term memory detriments**
- ◇ **Altered motor function**

- ◇ *Neurocognitive deficit*
- ◇ *Operant reactions*
- ◇ *Short Term memory detriments*
- ◇ *Altered Motor function*
- ◇ **Altered Neuro Genesis**
- ◇ **Oxidative DNA Damage**
- ◇ **Alzheimer Disease**

Dose Effects Relationship for CNS



Galactic Cosmic Ray Simulator & Particle Accelerator facilities

Studies on the effects of radiation on CNS has been done only on ground at the accelerator facility or through simulations

Dose effects relationship investigations

Particles used are a mixing of heavy-ion and protons to provide evidence for the CNS health risk for missions outside of LEO.

The doses used in experimental studies have been much higher than the annual GCRs dose.

Solar modulation is taken in account

Microgravity effects are also to be considered.

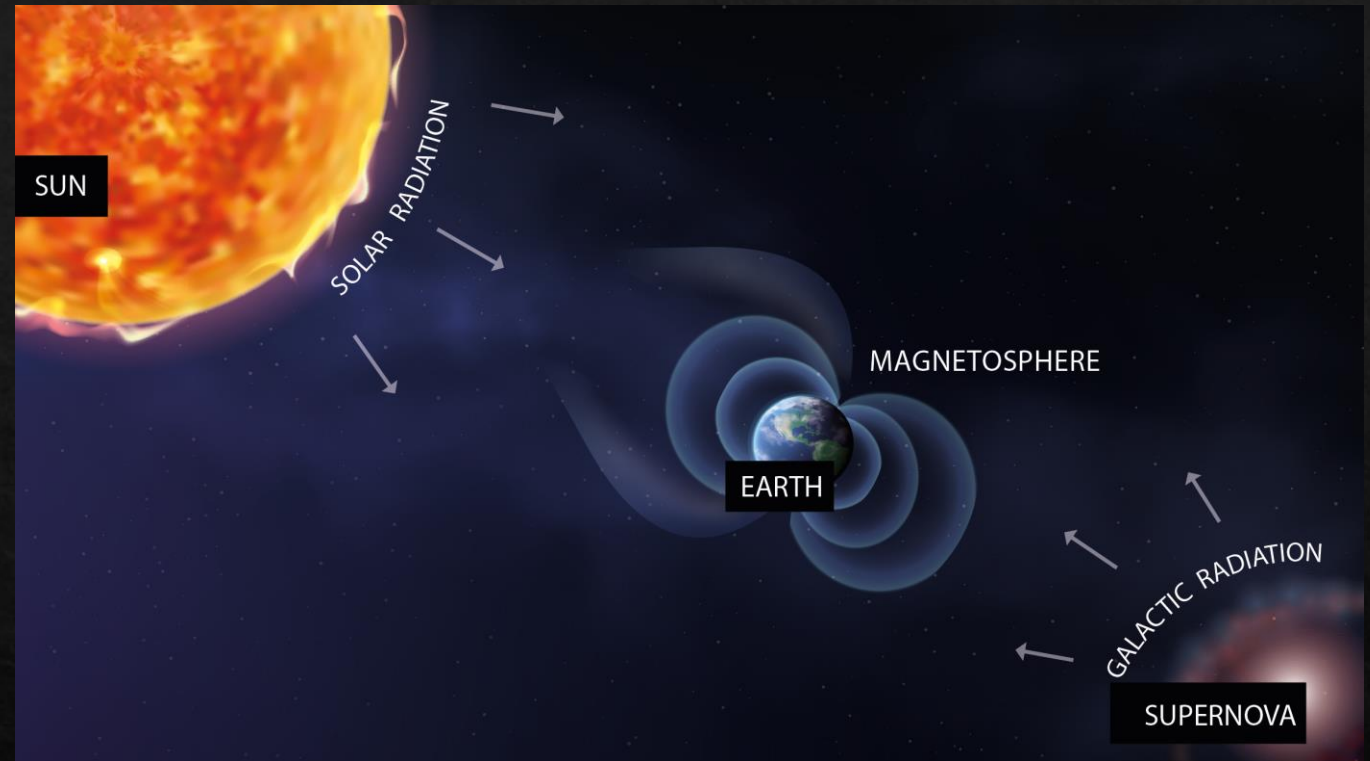


Image courtesy of IAEA

Dose effects relationship

There are evidence that :

- ◇ doses **as low as 20 cGy** of simulated GCR radiation can **significantly impair learning and memory** in a rodent model
- ◇ proton radiation caused marked **neurocognitive deficits** at doses as low as **25 cGy**.
- ◇ exhibition of significant changes in proteins associated with dopamine receptors and transporters in the brain at mission-relevant doses and dose rates. Further investigation is still mandatory to elucidate the impact of **dopamine changes** as a predictor for the CNS morbidity of the astronauts.
- ◇ Individual **radio susceptibility** should be considered in dose-effect models predicting the radiation-induced CNS changes.
- ◇ CNS effects depend on multiple mechanisms leading to synapse changes, in fact the average lifetime of synapses varies in different brain regions and depends on the exposure time.
- ◇ Observations in mice revealed a dependence on **radiation quality and absorbed dose**, suggesting that microscopic energy deposition plays an important role.

Further investigation are required to produce dose-effects models that will allows to predict the risk of CNS damage due to radiation during the space exploration

❖ **Computer Simulation of interactions of IR with biological matter**

Simplified 3D neuron models with properties equivalent to realistic neuron morphology have been developed using GEANT4 to describe the effect observed in rats after a dose from 0.1 to 2 Gy delivered to the hippocampus. Of note, the changes to synapses are one aspect to be considered.

❖ **Synergy with the Clinical Field :**

The possible risks to astronauts chronically exposed to space radiation could prevent astronauts from performing complex executive functions which are to be deeply investigated after radiotherapy for brain cancers.

❖ **Mathematical Modelling :**

Cacao E and Cucinotta FA in 2016 reported a predictive mathematical model of radiation-induced changes to neurogenesis for various radiation types after acute or fractionated irradiation, extending a mouse model of impaired neurogenesis in the hippocampal dentate gyrus after exposure to low-LET radiation to heavy ion irradiation.

❖ **Quantitative Meta Analysis**

recently, the first quantitative meta-analysis of the dose-response for proton and heavy-ion rodent studies has been published based on the widely used novel object recognition test, which estimates detriments in recognition or object memory (27). The log-normal model predicts a heavy-ion dose threshold of ~0.01 Gy for novel object recognition-related cognitive detriments.

❖ **Radioprotectors effects in models :**

One of the most promising ways to prevent and mitigate the acute effects of CNS and the neurocognitive impairment during long-term spaceflight is based on the use of substances (e.g., Dammarane Sapogenins)

❖ **Synergy with the Astroparticle experiments**

A synergy with Astroparticle researches

Part II : Target Effects vs Non Target Effects



Target Effects vs. Non-Target Effects in Estimating the Carcinogenic risk due to Galactic Cosmic Rays in Exploratory Space Missions.

L. Strigari^{1,2}, A.N. Guracho², A. Bartoloni²

¹Department of Medical Physics, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

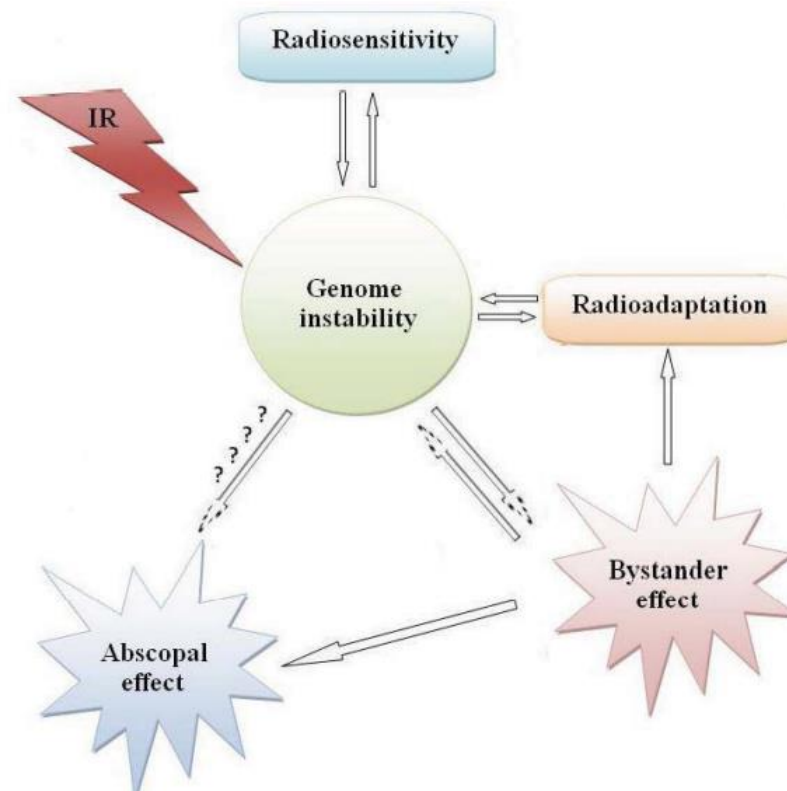
² Istituto Nazionale di Fisica Nucleare (INFN) Rome-Sapienza Division, Rome, Italy

Work in progress at Roma AMS group (*A.Bartoloni, A.N. Guracho, L.Strigari*)

•“The scarcity of data with animal models for tissues that dominate human radiation cancer risk, including lung, colon, breast, liver and stomach , suggest that **studies of NTEs in other tissues are urgently needed** prior to long-term space missions outside the protection of the Earth’s geomagnetic sphere”

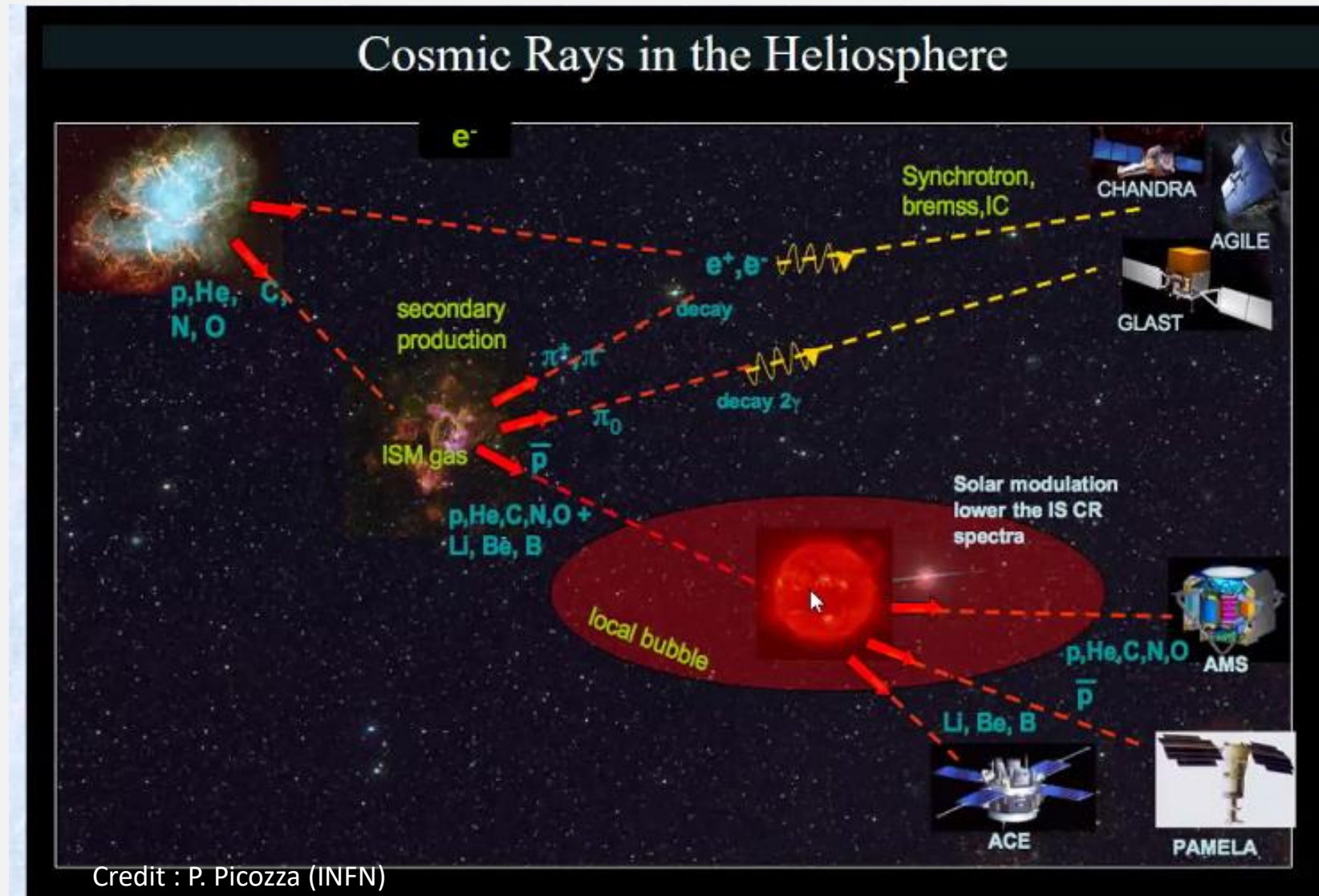
Non-Targeted Effects Models Predict Significantly Higher Mars Mission Cancer Risk than Targeted Effects Models

E.Cucinotta, Eliedonna E. Cacao • Published 12 May 2017 • Biology, Physics • Scientific Reports



“A **cosmic-ray** observatory is a scientific installation built to detect high-energy-particles coming from space called **cosmic rays**.

This typically includes photons (high-energy light), electrons, protons, and some heavier nuclei, as well as antimatter particles.



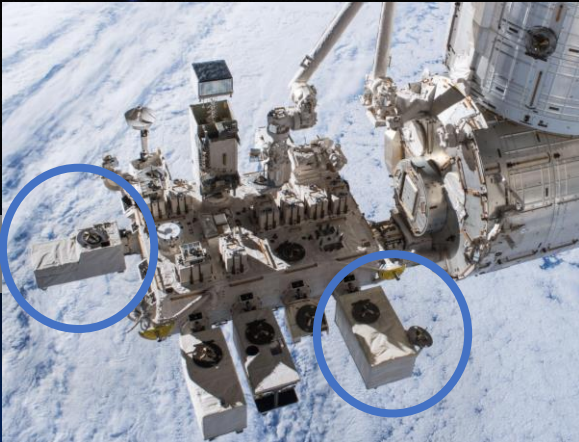
Principal Operating Cosmic Ray Space Detectors

International Space Station based



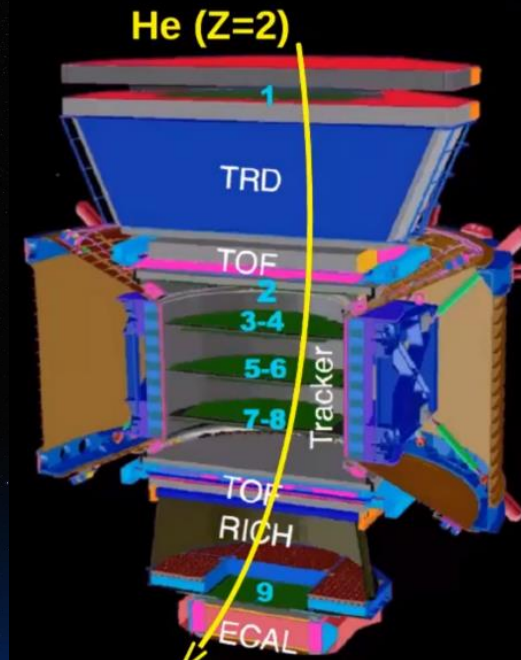
AMS02 – 2011

CALET - 2015



ISS-CREAM – 2017-2019

an ensemble of instruments
each one designed to
capture and measure the
cosmic ray particles



Satellite Based

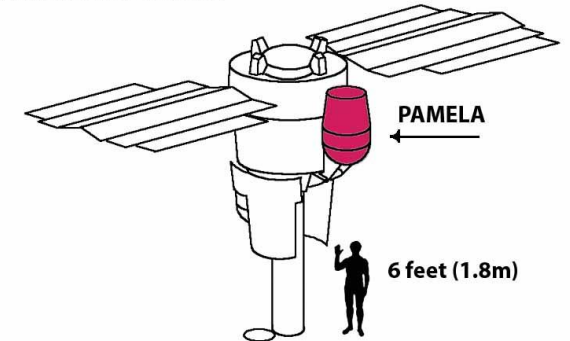


ACE - 1997



DAMPE - 2017

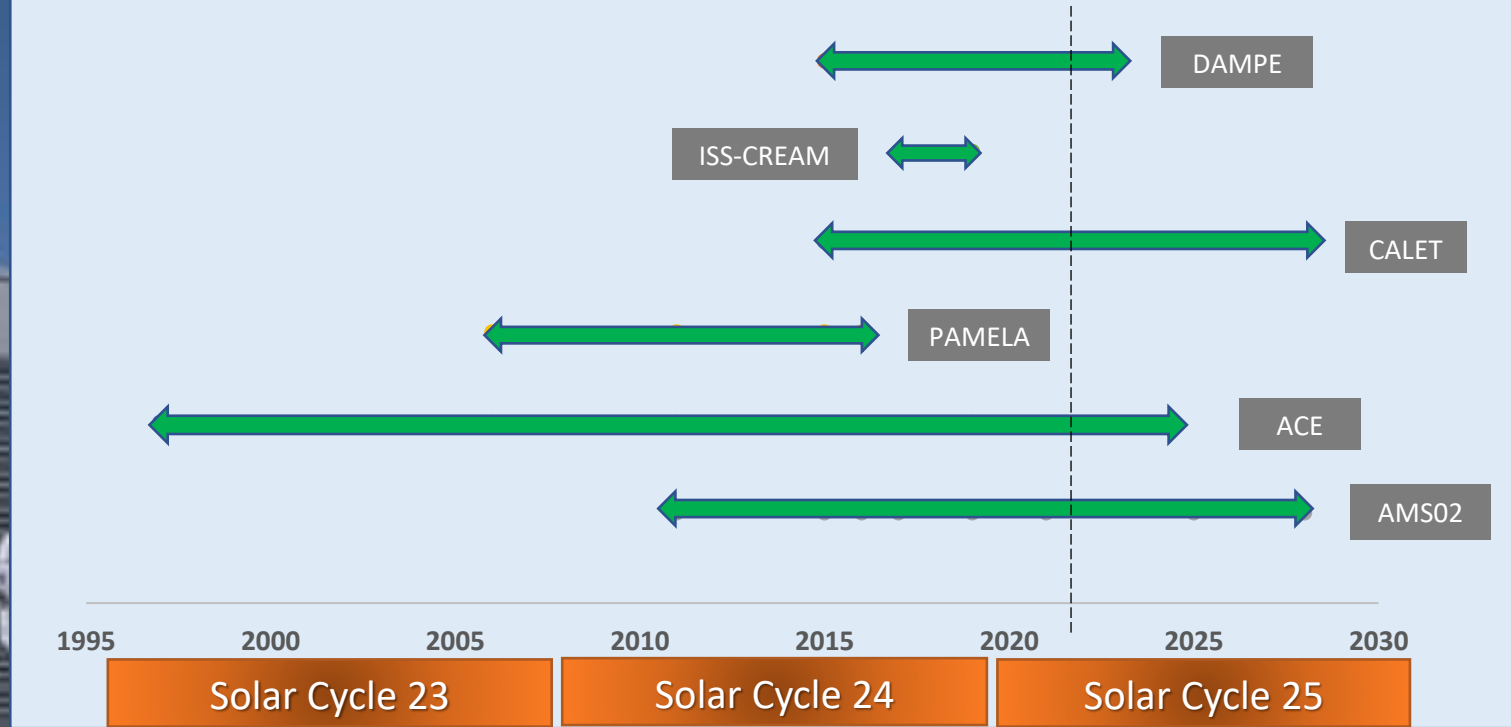
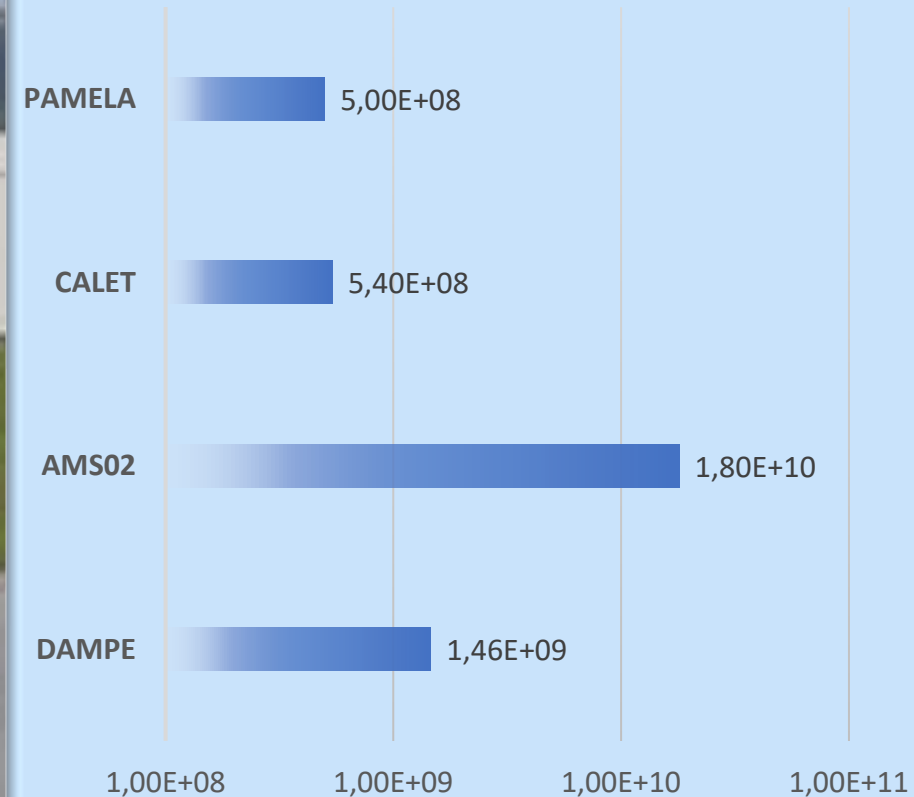
Resurs-DK
Reconnaissance Satellite



PAMELA – 2006-2016

Missions Operations

CR EVENTS/YEAR (BILLION)



Cosmic Ray Components Identification

e^+, e^- ✓ ALL

p^+, p^- ✓ ALL

D, He ✓ ALL

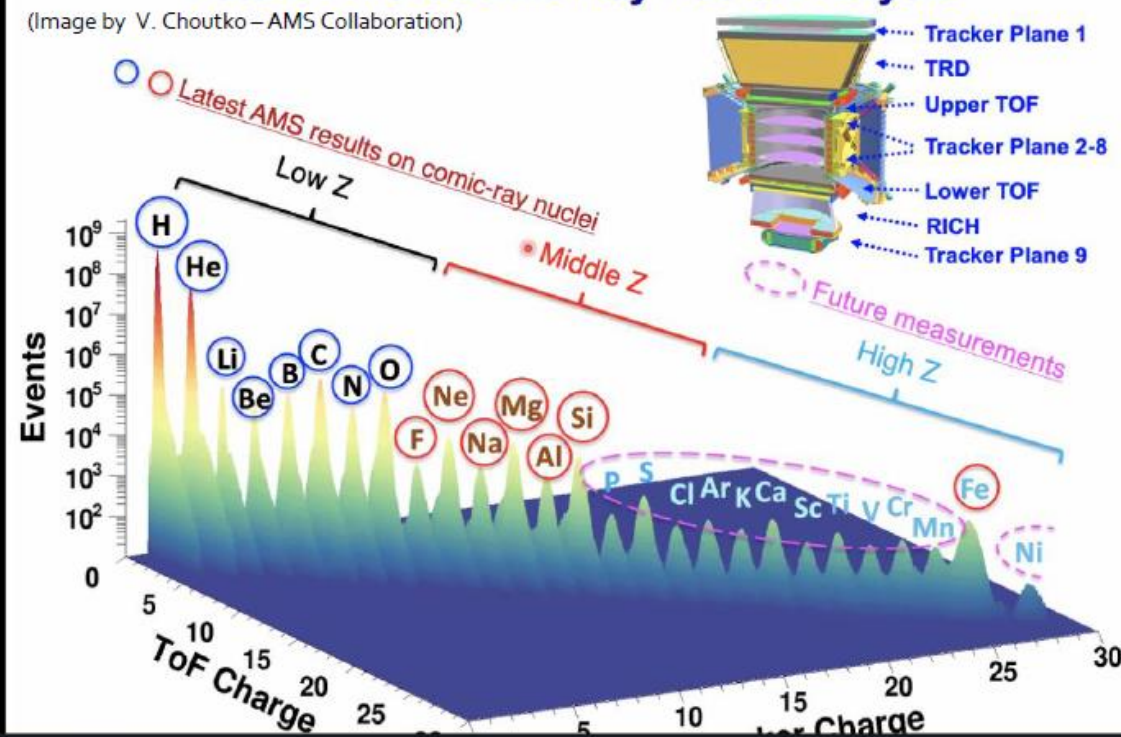
Low-Z (≤ 8) ✓ ALL (PAMELA up to $Z=6$)

Middle-Z ✓ AMS02, CALET, ISS-CREAM, ACE, DAMPE

High-Z (>14) ✓ AMS02, CALET, ISS-CREAM, ACE, DAMPE

Future AMS Cosmic-Ray Nuclei Analysis

(Image by V. Choutko – AMS Collaboration)



Properties of Iron Primary Cosmic Rays: Results from the Alpha Magnetic Spectrometer

AMS Collaboration • M. Aguilar (Madrid, CIEMAT) et al. (Jan 29, 2021)

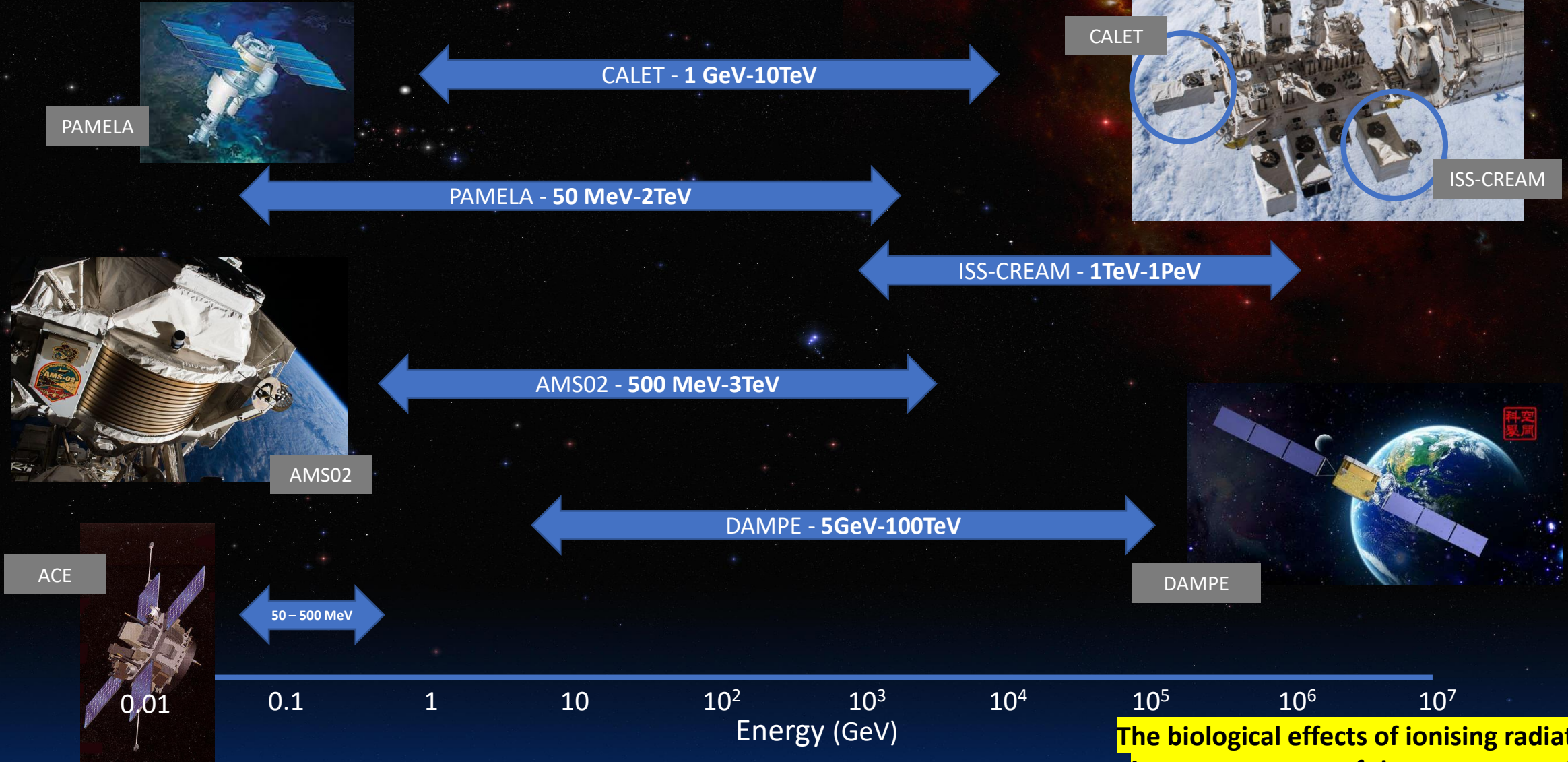
Published in: *Phys.Rev.Lett.* 126 (2021) 4, 041104

Properties of Heavy Secondary Fluorine Cosmic Rays: Results from the Alpha Magnetic Spectrometer

AMS Collaboration • M. Aguilar (Madrid, CIEMAT) et al. (Feb 25, 2021)

Published in: *Phys.Rev.Lett.* 126 (2021) 8, 081102

HEP-APE Energy Range



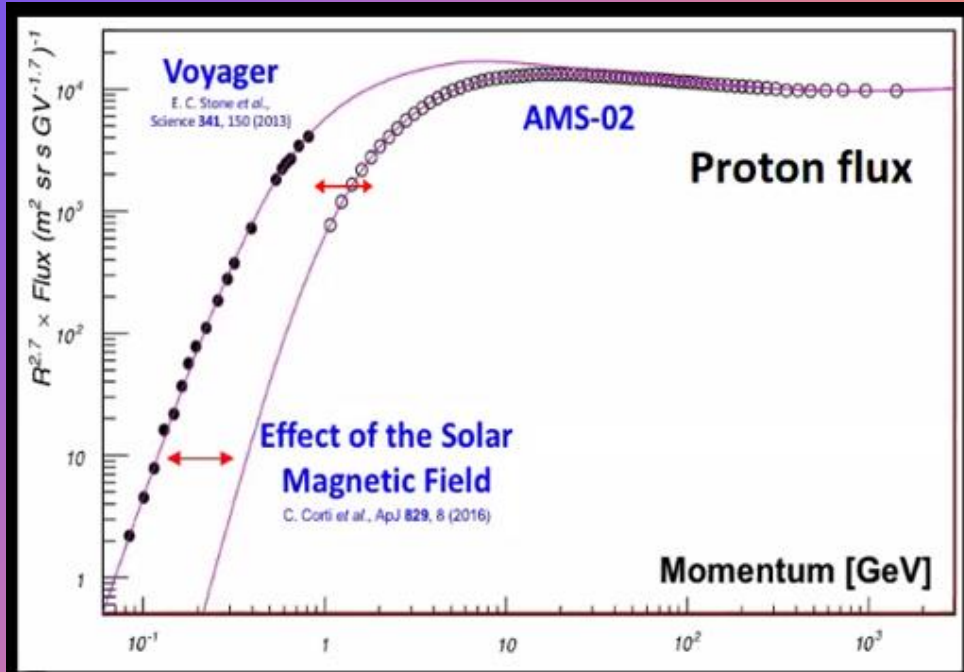
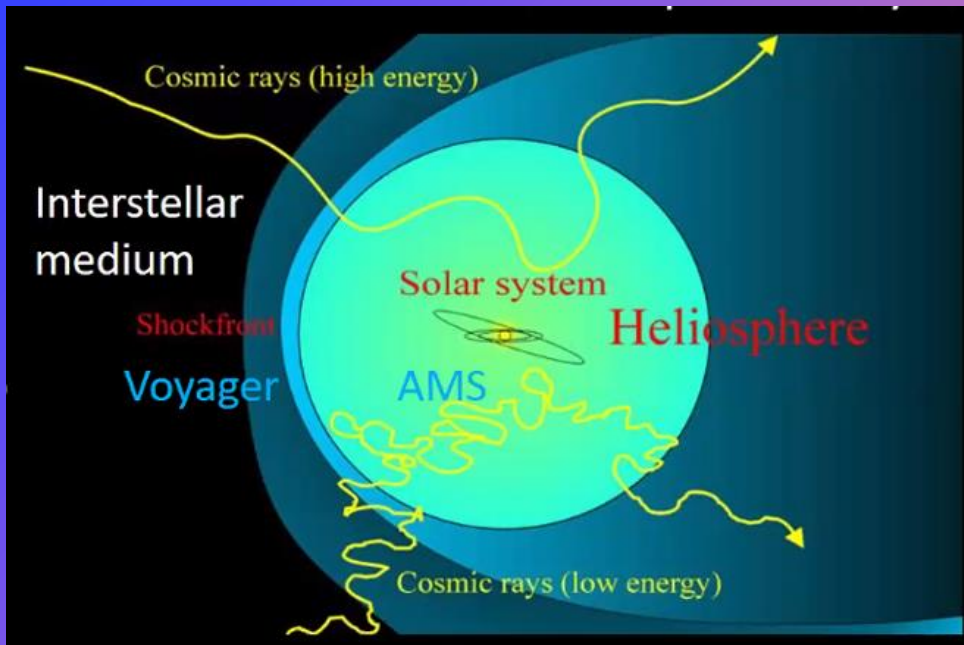
The biological effects of ionising radiation is a consequence of the energy transfer by ionization and excitation to body cells

Cosmic Rays Solar Modulation

Cosmic rays from interstellar medium are
«screened» by the Heliosphere.

This effect is particularly visible at low energies

Measurements of time evolution of cosmic ray
fluxes of different particles over an extended
period of time is very valuable



Credit S.Ting & AMS Collaboration

NTE in Tumor Prevalence (TP) of HGT in rodent model

- **Prevalence** is the number of people/cell with a specific disease or condition in each population at a specific time. This measure includes both newly diagnosed and pre-existing cases of the disease.
- **Tumor prevalence (TP)** is described by a Hazard function, H , which is dependent on radiation type for γ -rays or particles with charge number Z and kinetic energy per atomic mass unit (u), E and fluence F , the energy per unit area contained in the particles with which a cell is irradiated

$$TP = 1 - e^{-H(Z,E,F)}$$

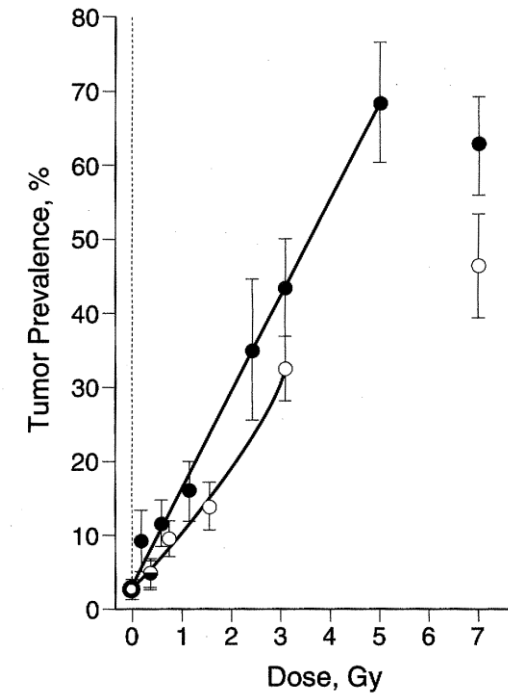


FIG. 1. Tumor prevalence for mice irradiated with 228A MeV helium ions (●) in the plateau of the Bragg curve, or ^{60}Co γ rays (○). The mice received pituitary isografts. The curve is the fitted regression. The error bars indicate the standard deviation of the prevalence.

Tumorigenic Potential of High-Z, High-LET Charged-Particle Radiations

E. L. Alpen; P. Powers-Risius; S. B. Curtis; R. DeGuzman

Radiat Res (1993) 136 (3): 382–391.

<https://doi.org/10.2307/3578551>

Hazard Functions for Gamma & Target Effects (TE)

Non-Targeted Effects Models Predict Significantly Higher Mars Mission Cancer Risk than Targeted Effects Models

F. Cucinotta, E. Eliedonna, E. Cacao • Published 12 May 2017 • Biology, Physics • Scientific Reports

Hazard Function for Tumor Prevalence:

For γ -rays we used the following form for the Hazard function:

$$H_{\gamma} = H_0 + [\alpha_{\gamma}D + \beta_{\gamma}D^2] * S(D)$$

Where, H_0 represents the background prevalence ($D=0$)

α_{γ} and β_{γ} are the linear and quadratic coefficient with dose Induction terms, and $S(D)$ the cell survival probability.

For particles it is considered a track structure model that extrapolates to low doses (or low fluence) the functional form used in the NASA cancer risk assessment.

$$H_{TE}(Z, E, F) = [H_0 + \Sigma F + \beta D^2] * S$$

Hazard Function for Non-Target Effects (NTE)

The NTE model assumes a non-linear type response in addition to the linear dose term at low doses.

$$H_{NTE}(Z, E, F) = [H_0 + \Sigma F + \beta D^2 + \eta] * S$$

the η function that represents the NTE contribution, which is parameterized as a function of LET, L by:

$$\eta = \eta_0 L e^{-\eta_1 L} [1 - e^{-N_{Bys}}]$$

Models to evaluate the NTE contributions using the AMS data

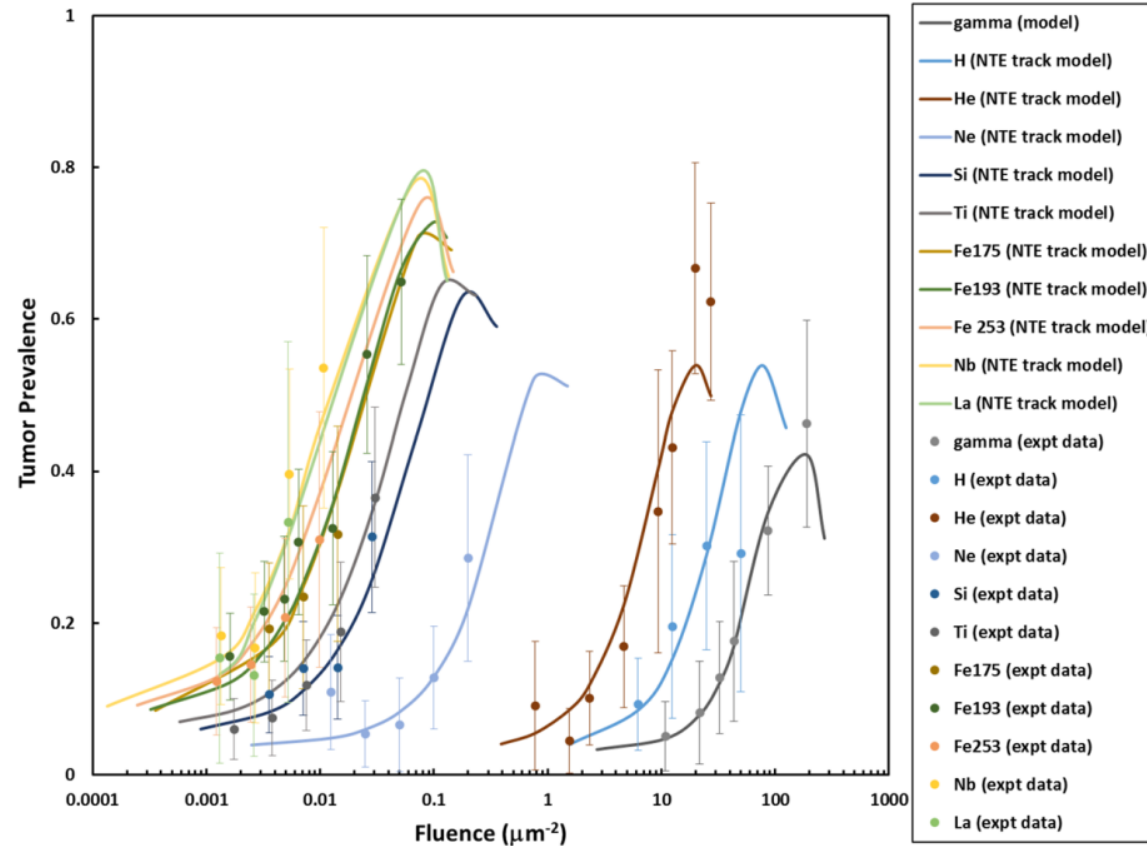
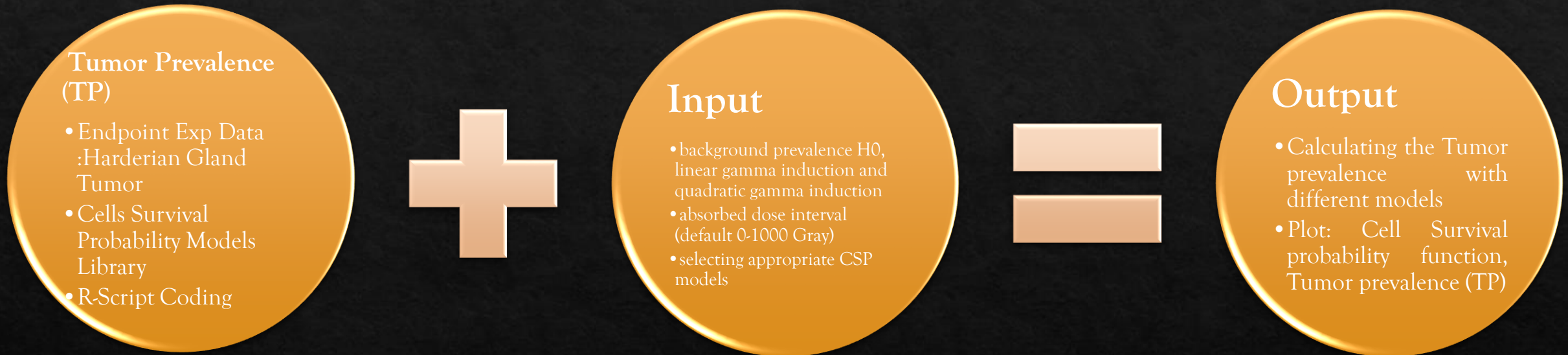


Figure 3. Comparison of the non-targeted effects (NTE) model of the percent Harderian gland tumor prevalence versus particle fluence to experiments of Alpen *et al.*^{12, 13} and Chang *et al.*¹⁴. Error bars represent standard errors in the experiments.

Tool for NTE components evaluation



Tumor Prevalence (TP)

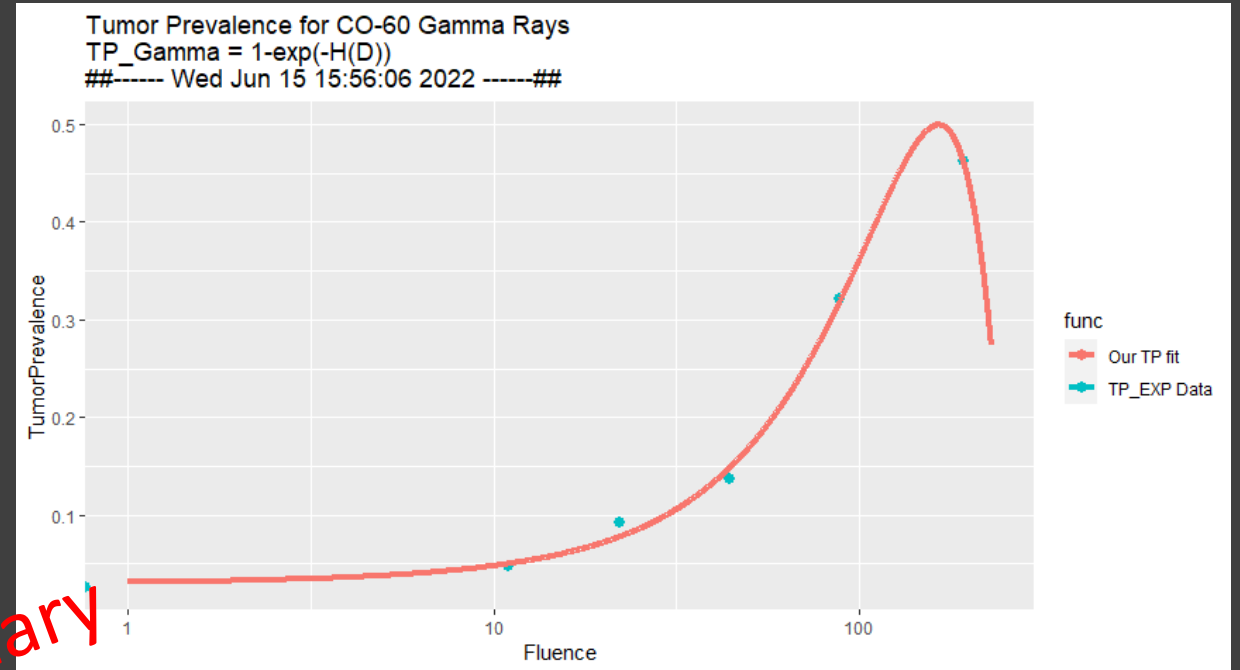
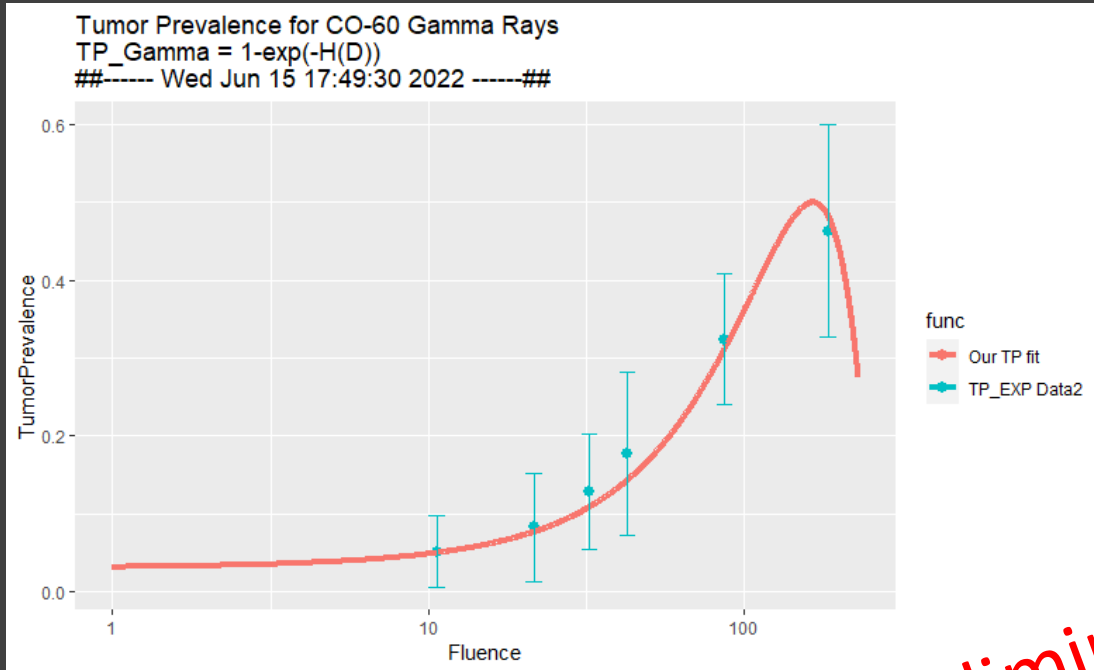
- *Experimental Data taken from Alpen et al 1997*
- *60-Co Gamma Source*
- *Ions according to the table 1*
- *Exposition time in between 60 sec. to 120 sec.*
- *Range in water are max.*
- *LET precision is few % of the vales.*
- *Irradiation field is 3 x 5 cm².*

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TABLE I
Nominal Energies, LET_∞,^a and Maximum Ranges in Water

Ion	Energy (A MeV)	Entrance LET _∞ (keV/μm)	Range in water (cm)
Hydrogen, ¹ ₁ H	250	0.4	35
Helium, ⁴ ₂ He	228	1.6	26
Neon, ²⁰ ₁₀ Ne	670	25	31
Iron, ⁵⁶ ₂₆ Fe	600	193	9.7
Iron, ⁵⁶ ₂₆ Fe	350	253	2.5
Niobium, ⁹³ ₄₃ Nb	600	464	4.8

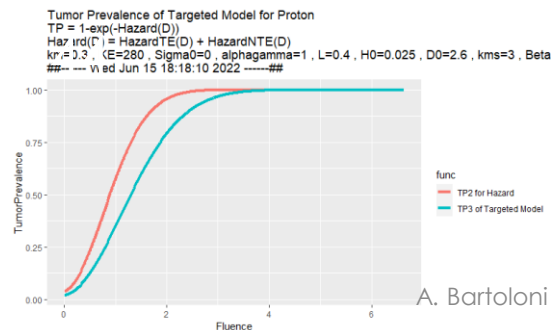
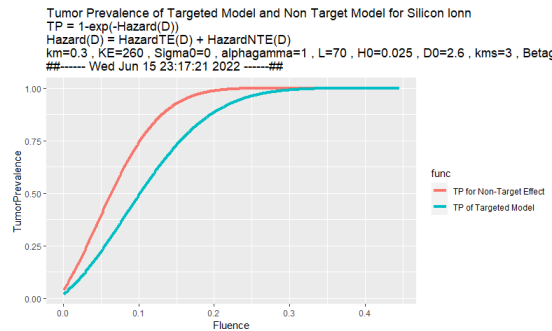
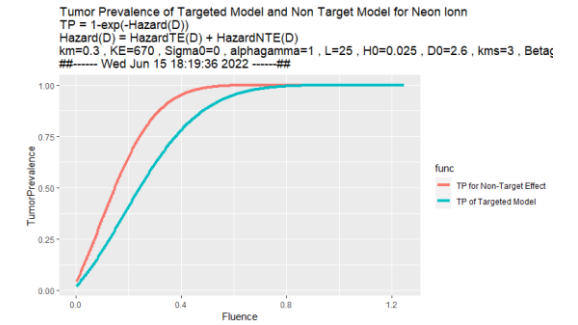
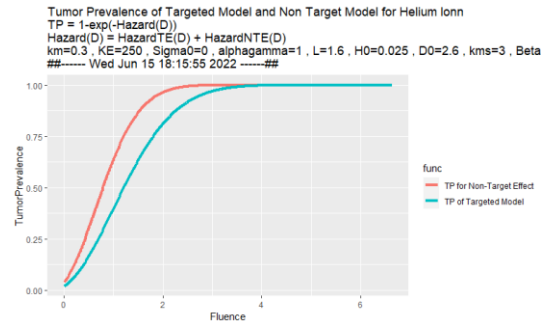
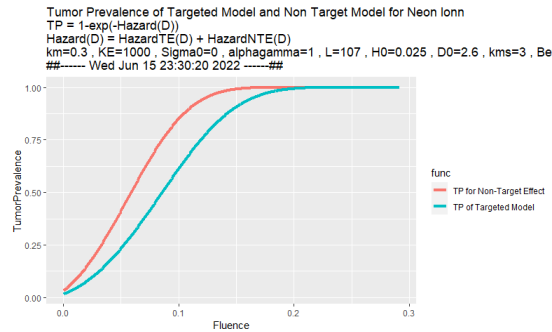
^a The values are for dose-averaged LET; however, at the zero absorber position in the plateau region of the Bragg curve, dose-averaged LET and track-averaged LET are essentially the same.



Preliminary

Gamma Rays

- $TP = 1 - e^{-H(Z,E,F)}$
- $H_\gamma = H_0 + [\alpha_\gamma D + \beta_\gamma D^2]S(D)$



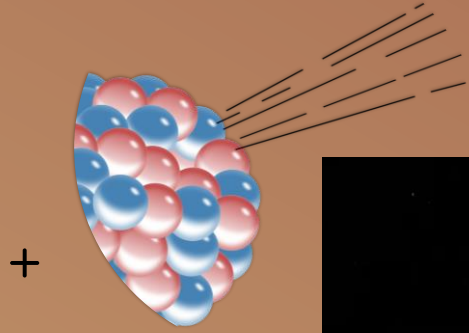
Preliminary

TE vs NTE

In the plots the percentage of tumors prevalence is used to investigate the effects of Non-Target Effects (NTE) in predictions of chronic GCR exposure risk.

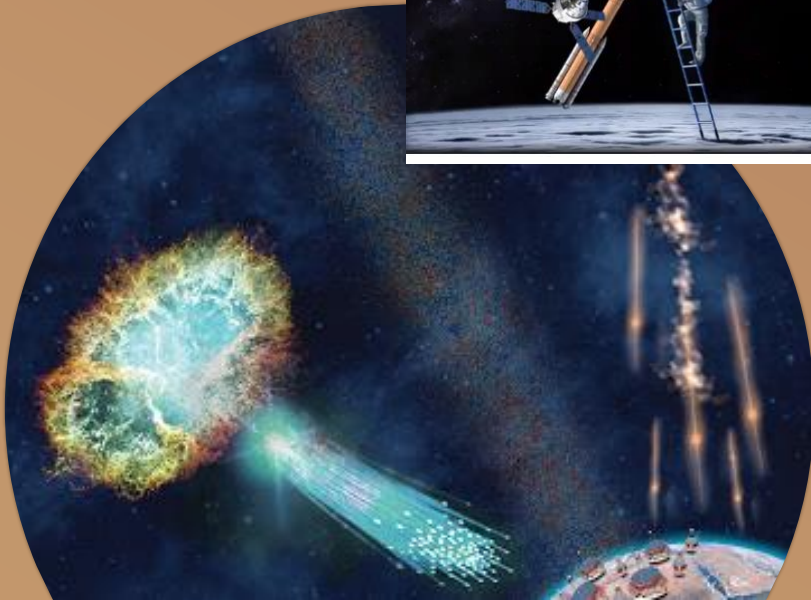
The expected contribution of the NTE is an increase of radiation risk 2-fold higher compared to a TE model.

detrimental effects of ionizing radiation are not restricted only in the irradiated cells but also to non-irradiated bystanders or even distant cells manifesting various biological effects.



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THANKS FOR THE ATTENTION !

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25th WRMISS in Mons, Belgium

September 6 -8, 2022

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Part I references

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BACKUP SLIDE