In vitro approach för att öka förståelse av mekanismer och risk av strålinducerad cancer

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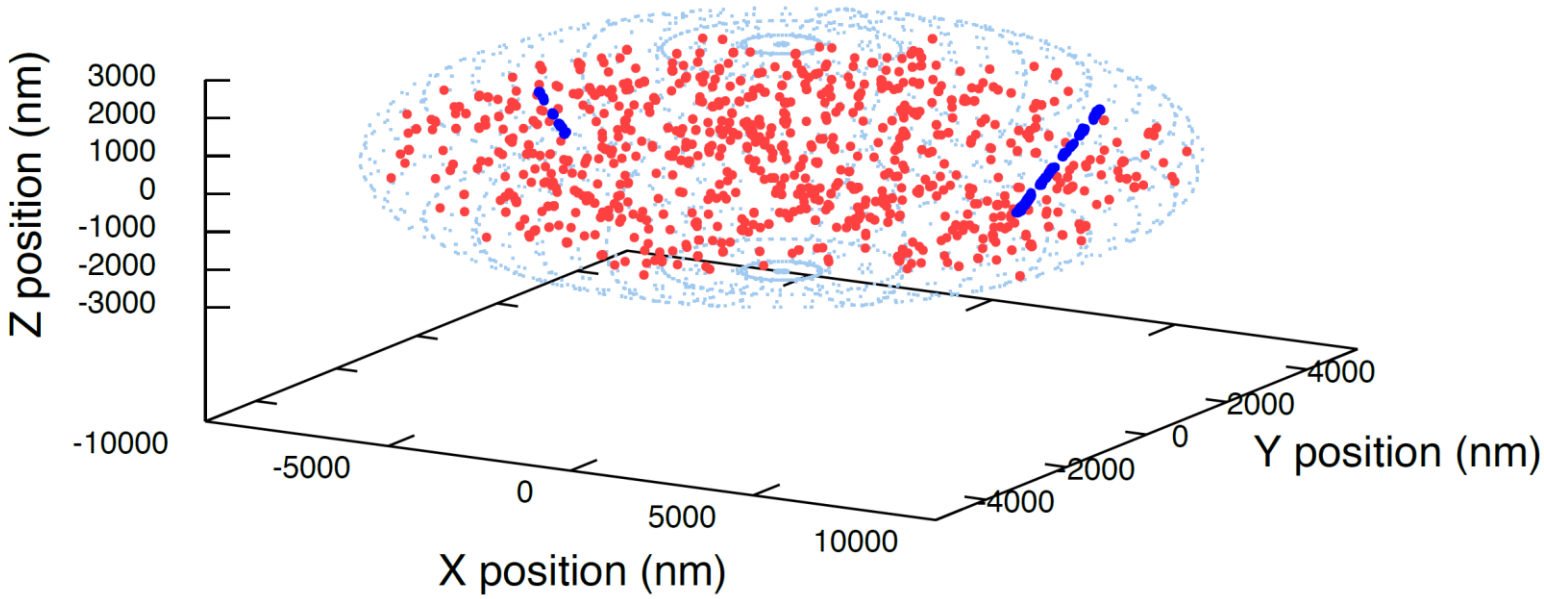

What is the radiogenic cancer risk from flying at 10 km?

(dose rate at 10 km: ca 5 µSv/h including the neutron component)

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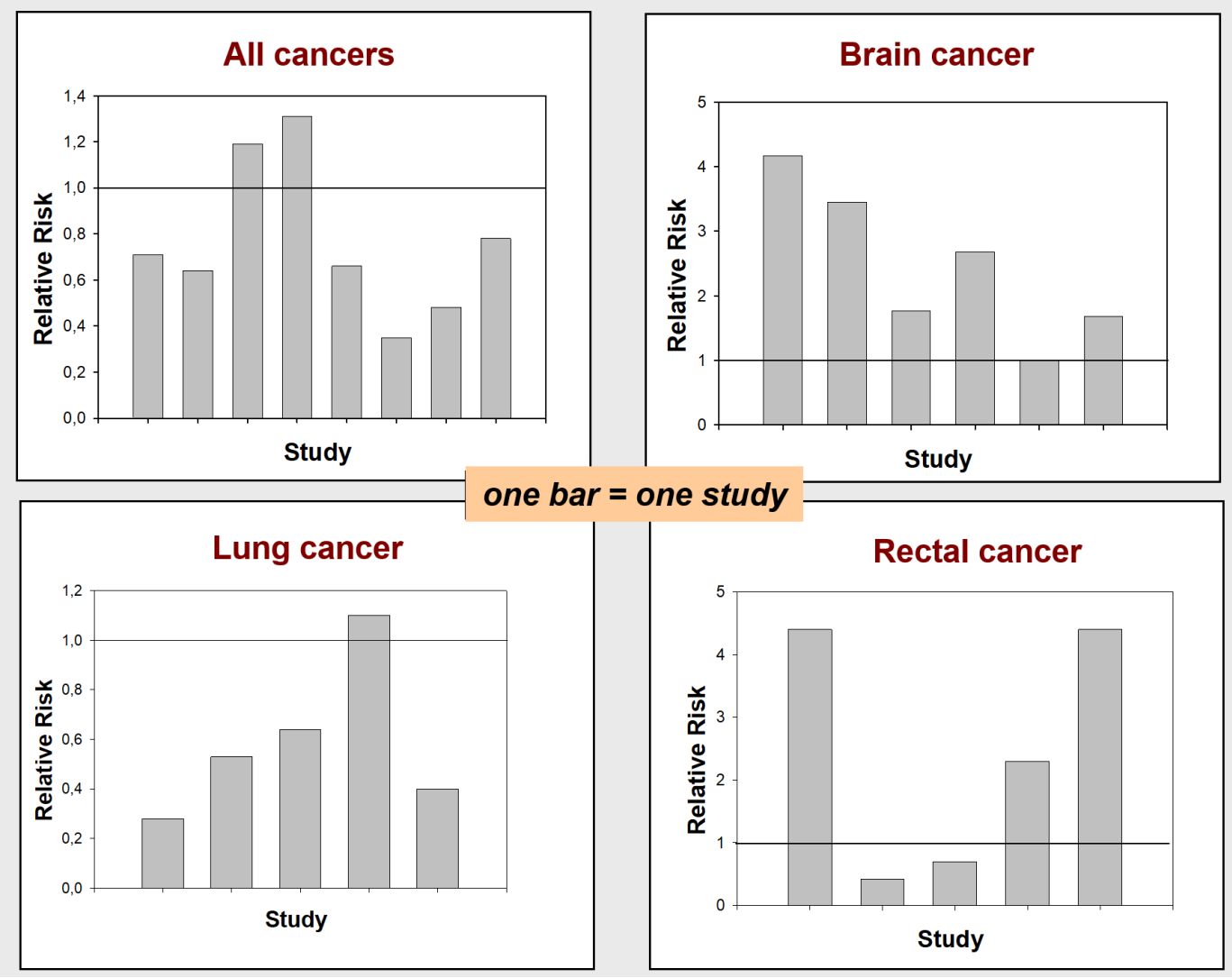
40x

Relative risk of cancer among civilian and military pilots
Results of selected epidemiological studies
(average annual effective dose of a pilot: 5 µSv/h * 1000h = 5 mSv)



The radiation protection dilemma
What is the level of risk after low radiation doses?

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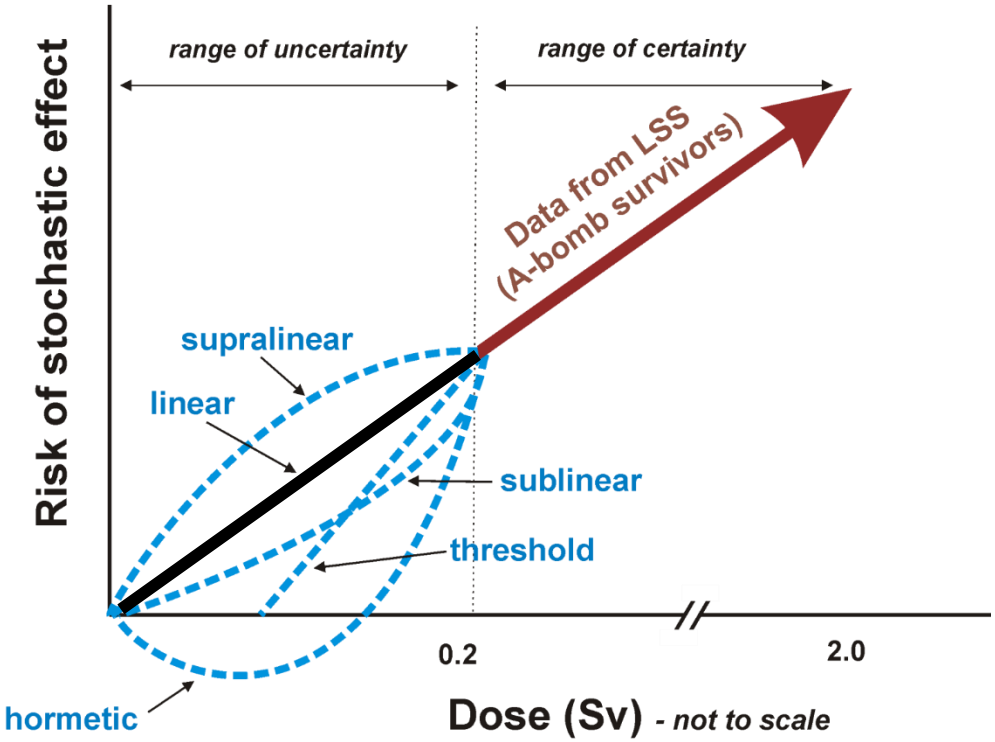
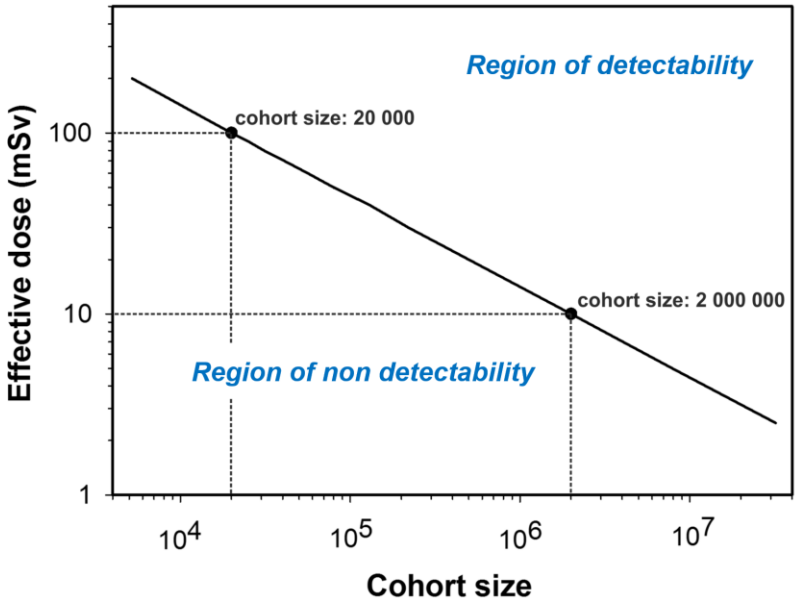
The current radiation protection policy is based on the assumption that the risk of radiation-induced cancer increases linearaly with dose

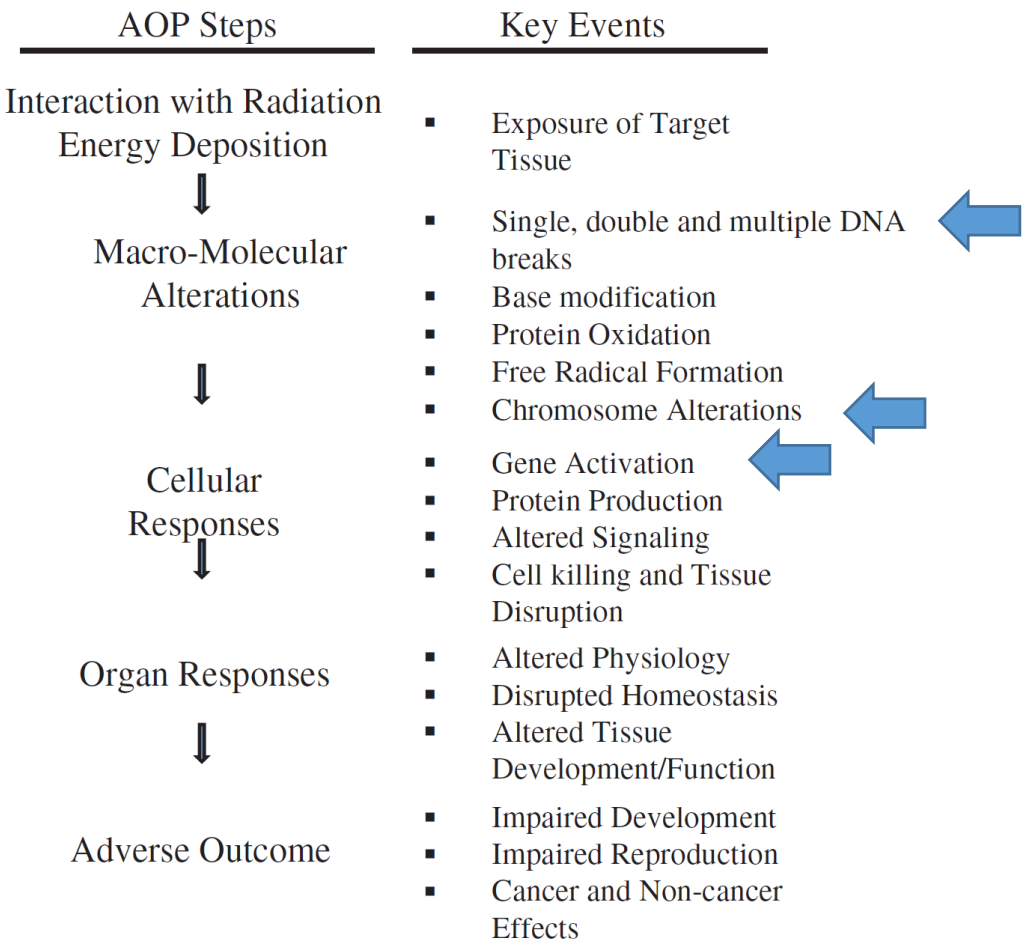


Epidemiological studies lack statistical power to detect low dose – related cancer effects in adults



According to UNSCEAR, a low dose is that below 100 mGy and low dose-rates are those of 0.1 mGy min^{-1} or less for low LET radiation, or one- track traversal per cell per hour for high LET radiations.

The adverse outcome pathway (AOP) approach is a conceptual construct that represents a linkage between a molecular initiating event and an adverse outcome (e.g. cancer) at a biological level of organization relevant to risk assessment. Key initiating events can be studies as biomarkers of cancer induction



Source: R. Julian Preston IJRB 93, NO. 10, 2017

Some research at the Centre for Radiation Protection Research (Stockholm University) where the AOP approach is applied to better understand cellular effects of radiation related to cancer risk

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Cellular effects of low doses of mixed fields (gamma and alpha) delivered under low dose rates

Why? Because natural and occupational exposures are chronic and often mixed. Is the risk of stochastic effects of low dose rate exposure same as after acute exposure? Are mixed field effects different? Is there a DDREF?

Cellular effects of high doses of mixed fields (gamma and alpha) delivered under high dose rate

Why? Very often people are exposed to mixed beams of low and high LET radiation (high natural background, air travel, LSS). Are the effects of the different radiation qualities additive or synergistic?

Cellular effects of changing dose rate (second derivative of dose)

Why? In many exposure situations the dose rate is changing during irradiation. Does the effect of a radiation dose depend on the second derivative of dose?

Cellular effects of low mixed field doses delivered under low dose rates

Low and high dose rate exposure facilities at the CRPR

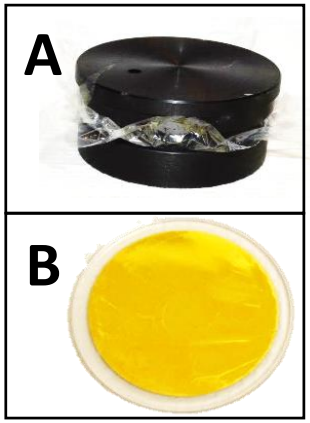
Low dose rate

1 mGy/h

1.6 mGy/h

8 mGy/h

12 mGy/h



1 mGy/h

^{241}Am alpha source

High dose rate

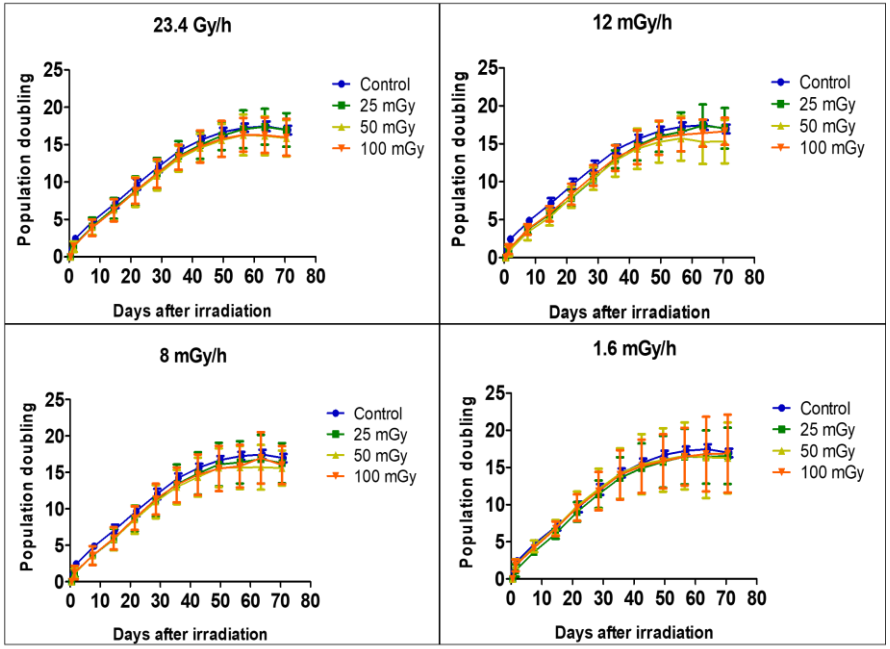
0.8 Gy/min

^{137}Cs gamma sources

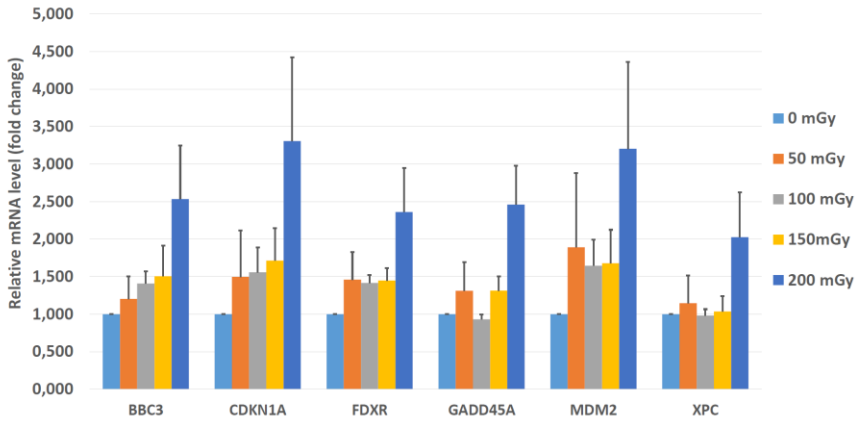
Cellular effects of low mixed field doses delivered under low dose rates

Some preliminary results

Cell viability results of VH10 cells after high and low dose rate exposure to a dose of 100 mGy. Cell viability was determined based on five independent experiments using the MTT assay. Bars represent standard deviations.



Relative mRNA levels of DNA damage-responsive genes in human VH10 fibroblasts after alpha particle exposure (1mGy/h) at different final doses (0, 50, 100, 150 and 200 mGy). Bars represent mean results from 3 independent experiments. Error bars represent standard deviations.



Results from ongoing PhD project of Milagrosa Lopez-Riego

The high dose rate mixed field exposure facility at the Centre for Radiation Protection Research

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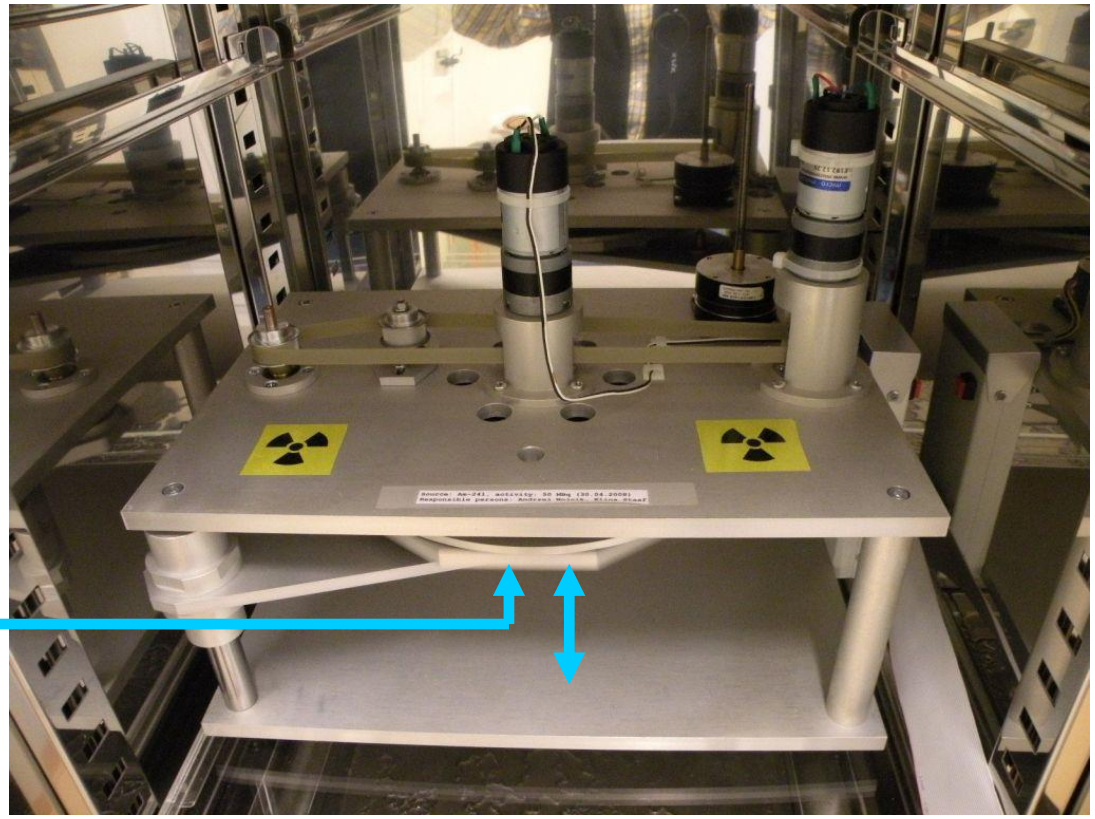
The ^{241}Am alpha irradiation facility – dose-rate: 0.21 Gy/min

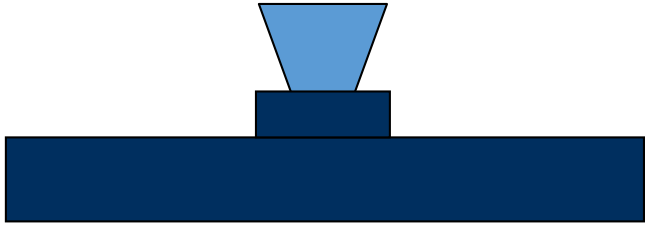


The exposure dish covered by 1.5 µm Mylar

X-ray tube 190 kV
(peak at 80 keV)

0.052 Gy/min

0.068 Gy/min



Some results…

In human peripheral blood lymphocytes the effect of mixed beams on gene expression is individually variable

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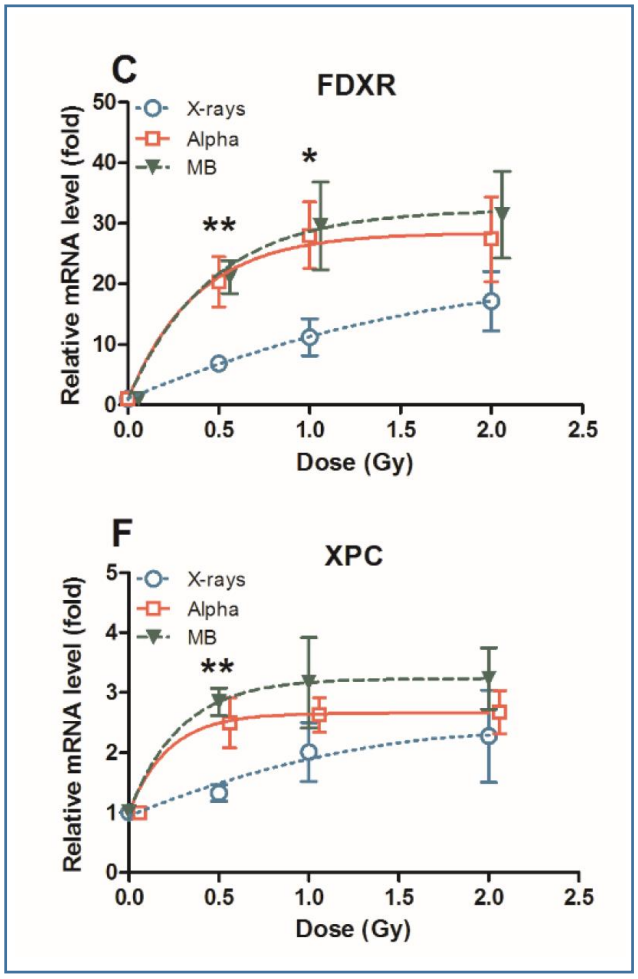
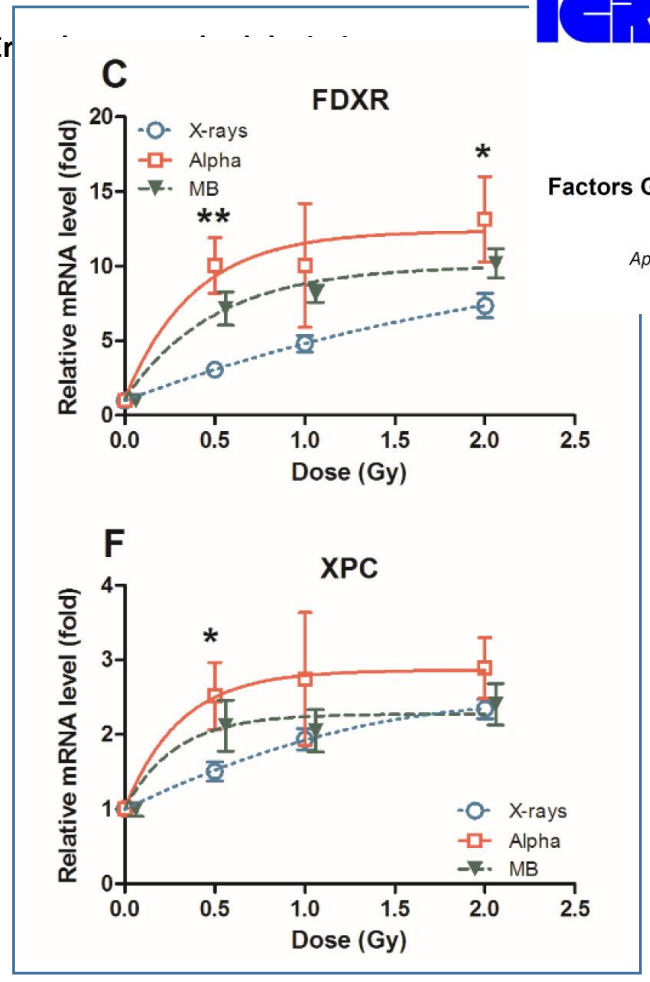
Donor 1



Donor 2



Relevant for:

ICRP INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

ICRP ref 4842-3301-8489

Terms of Reference for ICRP Task Group 111

Factors Governing the Individual Response of Humans to Ionising Radiation

Approved by the ICRP Main Commission on 15 October 2018

A Joint Task Group of ICRP Committees 1 and 3

We are now looking at the impact of mixed fields on alternative splicing

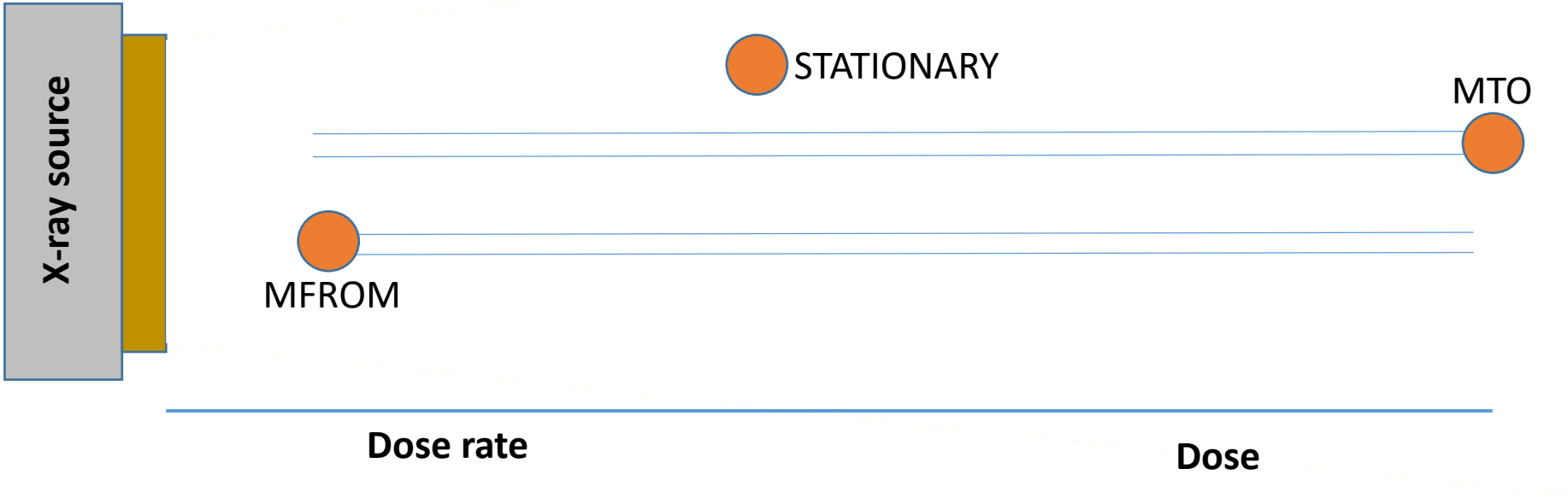
Peripheral blood lymphocytes from 2 donors, 3 independent experiments per donor

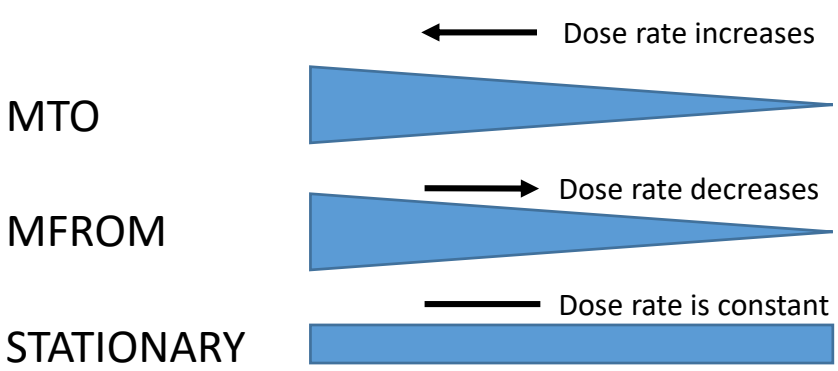
Results from defended PhD project of Lei Chang. Submitted for publication.

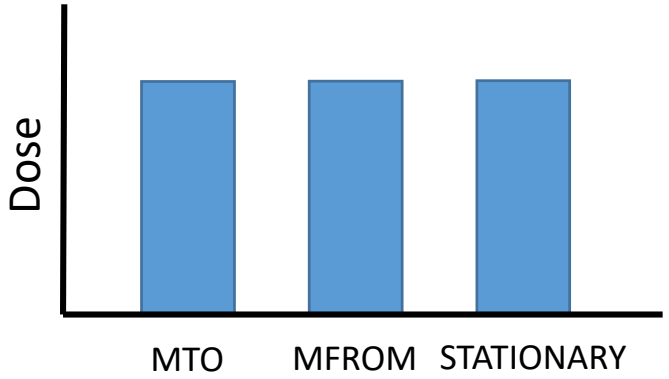
Cellular effects of changing dose rate

Motion experiment to test the impact of the second derivative of dose

Cell sample; MTO = moving to source, MFRO = moving from source







The total dose is the same in all samples.

Filter experiment to test the impact of the second derivative of dose

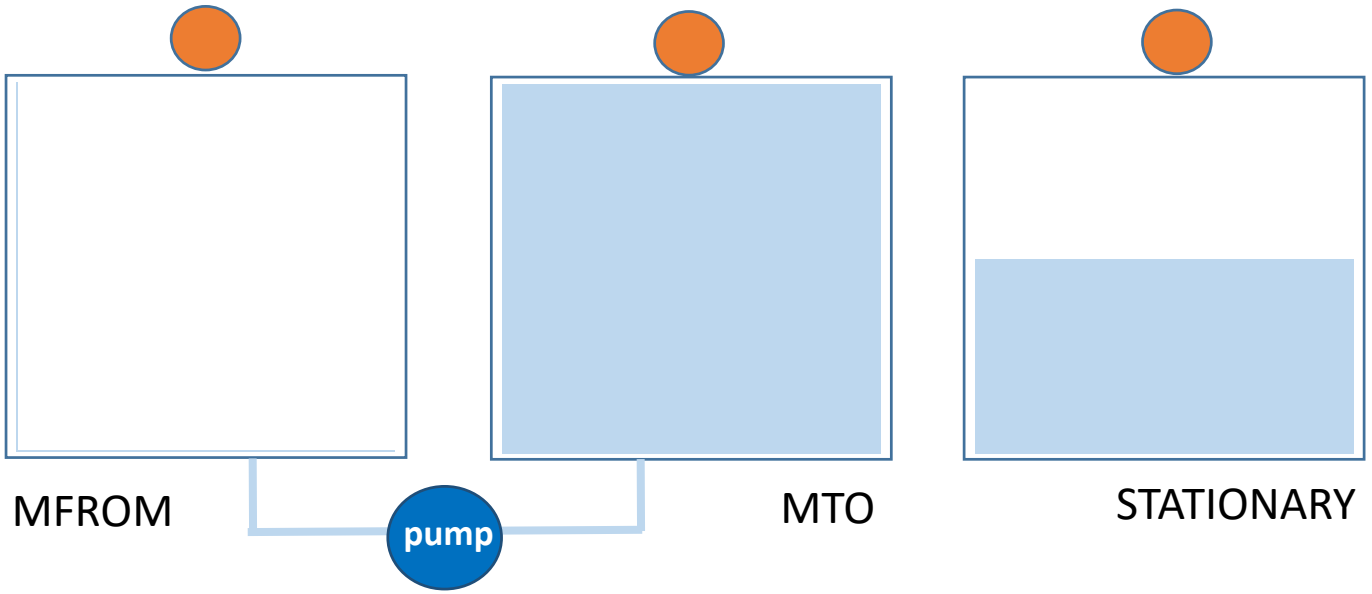
= Cell sample

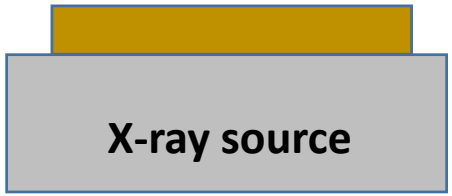
MTO = dose rate increases
MFRO = dose rate decreases

= $BaCl_2$

The total dose is again the same in all samples

What about the biological effect?





Changing dose rate exposure facilities at the CRPR

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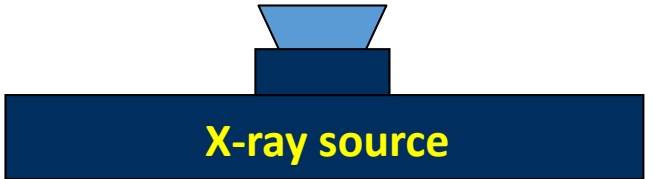
0.15 Gy/min - 0.0042 Gy/min

0.11 Gy/min - 0.0027 Gy/min



Some results…

Micronuclei in cells exposed under conditions of changing dose rates

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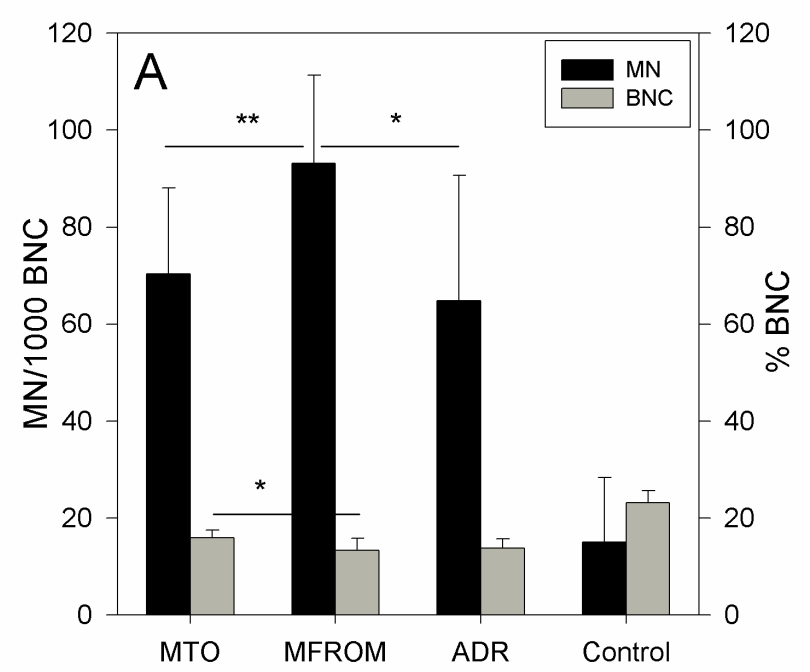
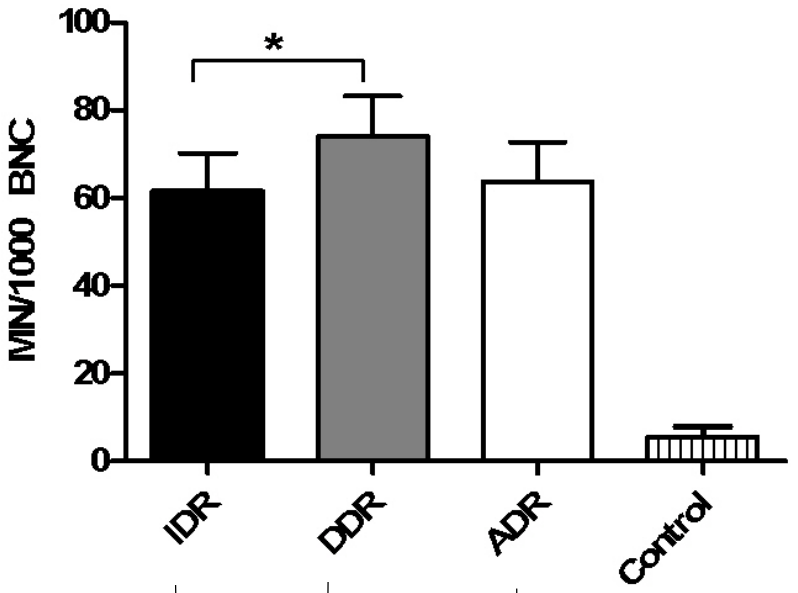
The highest biological effect is always seen in cells which are exposed under conditions of a decreasing dose rate

The effect has nothing to do with the adaptive response

TK6 cells are irradiated in movement



CHO cells are irradiated through a dynamic $BaCl_2$ filter



Increasing dose rate

Decreasing dose rate

Stationary - avarage dose rate

Results from defended PhD project of Karl Brehwens. Published in Rad. Res. (2010) and Int. J. Radiat. Biol. (2014)

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