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Acute Hematological Effects in Mice Exposed to the Expected Doses, Dose-rates, and Energies of Solar Particle Event-like Proton Radiation

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Abstract

NASA has funded several projects that have provided evidence for the radiation risk in space. One radiation concern arises from solar particle event (SPE) radiation, which is composed of energetic electrons, protons, alpha particles and heavier particles. SPEs are unpredictable and the accompanying SPE radiation can place astronauts at risk of blood cell death, contributing to a weakened immune system and increased susceptibility to infection. The doses, dose rates, and energies of the proton radiation expected to occur during a SPE have been simulated at the NASA Space Radiation Laboratory, Brookhaven National Laboratory, delivering total body doses to mice. Hematological values were evaluated at acute time points, up to 24 hrs. post-radiation exposure.

1.0 Introduction

Cells with rapid turnover are most susceptible to the adverse effects of ionizing radiation, e.g., gastrointestinal cells, hematopoietic cells and reproductive cells. Hematopoietic cells are of interest because decreased blood cell counts leave irradiated individuals susceptible to infection and decreased immunity. Crew members during space flight are also at risk of developing problems from reduced numbers of peripheral blood cells caused by exposure to space radiation. Space radiation consists of particles trapped in the Earth's magnetic field, particles (primarily protons) originating from our Sun and galactic cosmic rays, which are high-energy protons and heavy ions from outside our solar system. The amount of space radiation an astronaut receives depends on several factors, including the location of the astronaut in the altitude above the Earth where shielding from the magnetic field is weaker.

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During a Solar Particle Event (SPE), significant spikes in the energy and fluence of solar particles increase the risk of astronaut exposure to higher doses of ionizing radiation.

SPEs are unpredictable, with more frequent events at the height of the 11 year solar cycle. SPEs, consisting of flares and coronal mass ejections, eject large amounts of high-energy protons at different dose rates. The dose-rates during an SPE are expected to vary from 10 to 50 cGy per hour (dependent on shielding). The August 1972 SPE is usually referred to as a worst-case scenario, with an omnidirectional proton fluence of 5.00×10^9 protons/cm² at energies above 30 MeV. If astronauts had been exposed to radiation from this SPE during extravehicular activity, the estimated total dose to the blood forming organs from this particular SPE would have been up to 1.38 Gy-Eq (Hu et al. , 2009). It is important to note that SPE radiation is predicted to produce a highly inhomogeneous dose distribution in humans with external doses that are significantly higher than internal doses (Wilson et al., 1997). This raises several issues when attempting to model SPE-like radiation in mice in that the dose distribution (external > internal), energy/fluence and linear energy transfer (LET) spectrum cannot be simultaneously matched due to the relative size of humans and mice (Cengel et al., 2010).

Previous reports on blood cell counts after proton radiation exposure include 1 GeV proton exposures, resulting in decreased white blood cell (WBC) and lymphocyte counts 24 hours after exposure (Wambi et al. , 2009, Ware et al. , 2010), as well as 24 hours after 70 MeV proton exposure (Maks et al. , 2011) and 36 hours after 70 MeV proton exposure (Gridley et al. , 2011, Luo-Owen et al. , 2012). Blood cell counts in mice remained decreased 4 days and 21 days after exposure to 230 MeV protons (Gridley et al. , 2008). In the present study we investigated the effect of simulated SPE proton radiation, producing an inhomogeneous dose distribution, in the mouse model. A homogenous spread out Bragg peak proton beam was also utilized in this study to compare the effects of inhomogeneous simulated SPE proton radiation to homogenous proton radiation on hematologic toxicity in the mouse model. The effect on hematopoietic cells at acute time points of 24 hours and as early as 4 hours after a single exposure to protons were evaluated, since the biological effects of exposure to significant doses of radiation are expected to manifest within hours of radiation exposure.

2.0 Materials/Methods

2.1 Animals

Female ICR mice (5-7 weeks of age) were purchased from Taconic Farms, Inc. (Germantown, NY). Mice were housed 4 per cage under standard husbandry conditions with *ad lib* access to normal rodent chow and water. Upon arrival, the animals were acclimated for 7 days in the Brookhaven National Laboratory (BNL) Animal Facility. All protocols in the experiment were approved by the Institutional Animal Care and Use Committees (IACUCs) of the University of Pennsylvania and BNL.

2.2 Physics and Dosimetry

Proton irradiations were performed at the NASA Space Radiation Laboratory (NSRL) at BNL. To deliver a dose distribution with consistent linear energy transfer, 8 different

energies were chosen between 30.63 MeV and 74.62 MeV (referred to as 30-74 MeV throughout) to produce eight individual Bragg curves, which add up to an approximation of a flat dose distribution. The maximum proton energy of 74.62 MeV has a projected range in water of 4.57 cm; this energy was chosen to ensure that the dose to the mouse was homogeneous regardless of mouse orientation within the radiation chamber. To equalize the dose received by the animals during the irradiation and avoid any positional effect, the exposure was divided into 12.5 cGy segments in which the beam scrolled through the 8 different energies while delivering a total dose of 12.5 cGy. The mice were rotated 180 degrees and the process repeated until the required dose was delivered. Experiments and results from this proton radiation beam will be referred to as 30-74 MeV proton beam.

A separate experiment simulating an SPE was also performed at NSRL. The mouse SPE proton protocol required “scaling down” of the typical energies of an estimated SPE exposure. The energy distribution of the generic SPE is proportional to $e^{(-T/75)}$, where T is the beam kinetic energy expressed as MeV. The energy distribution of the mouse SPE is proportional to $e^{(-(T-21.5)/19)}$. Energies ranging from 30 MeV to 150 MeV were delivered using 13 separate setup files, with each file programming the appropriate thickness of degrader filter to generate the 13 different energies. The files were called up automatically, each with the calculated dose fraction to deliver a dose with an energy distribution approximating the scaled down mouse SPE. The energies, dose fraction, cutoff error and error fraction are listed in Table 1. Normalization values were calculated at the ionization chamber measurement point (depth=1.27 mm) which was used at NSRL to calibrate each filtered beam component. Experiments and results relating to this proton radiation beam will be referred to as the scaled SPE proton beam.

2.3 Radiation exposure

Animals were placed in aerated radiation chambers (7.3 cm × 4.1 cm × 4.1 cm). Non-anesthetized mice were exposed to total body irradiation (TBI) in a single fraction at doses of 25, 50 cGy, 75 cGy, 100 cGy or 200 cGy at either a low dose rate (LDR) of 50 cGy/h or high dose rate (HDR) of 50 cGy/min. A separate experiment was performed using a very low dose rate of 0.28 cGy/min (17 cGy/h) at doses of 50, 75, or 100 cGy. For all proton radiation experiments, the mouse cages were rotated 180 degrees every ¼ of the total dose at the low dose rate and ½ of the total dose at the high dose rate.

To adequately compare the LDR data to the HDR data or the extremely low dose rate data to the HDR data, all animals were confined in the radiation chamber for the complete LDR exposure time. For example, the group of animals exposed to the 25 cGy dose at the HDR were only exposed for 0.5 min., but remained in the radiation chamber for a complete confinement time of 30.0 min., which mimics the 25 cGy LDR exposure time. Additionally, the non-irradiated control groups were also confined in the irradiation chambers for the longest duration of the radiation exposure times (4 hours total). Separate sham-irradiated control groups remained in the irradiation chamber for approximately 3, 4.5, or 6 hours to mimic the radiation exposure time of the mice exposed to the very low dose rate (0.28 cGy/min) at doses of 50, 75, or 100 cGy. To eliminate diurnal variation in the hematology analyses, the exposure start times were staggered so that all dose groups were removed from

the beam at the same time and post-radiation procedures were performed all together at the appropriate time point(s).

2.4 Hematopoietic cell count analyses

At 4 or 24 hours after completion of the exposure, 8-12 mice irradiated at each radiation dose and dose rate were euthanized by CO₂ asphyxiation followed by cardiac puncture to collect blood. For the exposures at the very low dose rate of 0.28 cGy/min, blood was collected only at the 24 hour time point. The blood from each animal was collected and placed into a lavender top blood collection tube containing EDTA and stored at ambient temperature. The blood samples were analyzed by a Bayer Advia 120 Hematology Analyzer (Antech Diagnostics, Lake Success, NY) and a complete blood cell count with differential was performed within 24 hours of blood collection.

2.5 Statistical analyses

The average counts of white blood cells (WBCs), neutrophils, and lymphocytes were determined in the sham-irradiated controls as baseline values. The blood cell counts obtained in animals at different time points were divided by the respective baseline values and expressed as fractions of control for statistical analyses. Histograms were generated using GraphPad Prism software (Version 5) and data analyzed by the Student's T test, comparing each dose point to the 0 cGy controls or comparing the results obtained from each dose-rate experiment at the same dose point.

The dose effect on the blood cell counts was determined by variance analyses using a general linear model, which was performed using a Minitab statistical software, release 15 (Minitab Inc., State College, PA). The relationship between the dose and blood cell count was determined by fitting the data to a linear quadratic model, $y = \exp(-\alpha D - \beta D^2)$, where y is blood cell count expressed as a fraction of the pre-irradiation baseline value, D stands for radiation dose (Gray or Gy), and α and β are the fitted coefficients for the linear and quadratic components of the linear quadratic model.

3.0 Results

3.1 Blood cell count changes after exposure to the scaled SPE

Peripheral WBC counts are decreased as soon as 4 hours post-exposure and remained decreased at 24 hours post-exposure at both the HDR and LDR (Fig. 1A & B). Lymphocyte counts followed a similar trend at all doses and dose rates (Fig. 1E & F). For both the WBCs and lymphocytes, the cell counts were significantly different at the 25 cGy dose when comparing the high dose rate to the low dose rate results (***, Fig. 1A, B, E, & F) at both the 4 and 24 hour time points. Dose rate differences were observed, but not in a consistent manner when the WBC and lymphocyte counts were evaluated at the different doses and time points. Lastly, neutrophil counts were not significantly different from the control (0 cGy) group at any of the doses, time point, and dose rates investigated (Fig. 1C & D).

3.2 Blood cell count changes 4 and 24 hours after exposure to protons (30-74 MeV)

Total WBC counts are decreased in a dose-dependent manner, with a similar trend observed in the lymphocyte count shortly after the radiation exposure. Proton radiation resulted in a significant decrease in total WBC and lymphocyte counts at 4 and 24 hours post-radiation at all doses (25 – 200 cGy) and at both dose rates of 50 cGy/min (HDR, Fig. 2A, B, E, F, * indicates $p < 0.05$, compared to the 0 Gy dose) and 50 cGy/h (LDR, Fig. 2A, B, E, F, ** indicates $p < 0.05$, compared to the 0 Gy dose). Dose rate differences were only observed in the 25 and 50 cGy dose groups at 4 hours post-radiation (Fig. 2A and 2E, *** indicates $p < 0.05$, when comparing the HDR to the LDR). At 24 hours post-radiation, the dose response curves were nearly identical between the groups irradiated at HDR and the groups irradiated at LDR for WBCs (Figure 2B) and lymphocytes (Figure 2F). The neutrophil counts at 4 hours post-radiation decreased significantly in the 50, 100 and 200 cGy groups irradiated at HDR (Fig. 2C) but increased significantly in the 200 cGy group irradiated at LDR (Fig. 2C). The change in neutrophil count between the HDR and LDR in the 200 cGy dose group was different, in a statistically significant manner (Fig. 2C). At 24 hours post-irradiation, the low dose rate radiation exposure resulted in a significant reduction in neutrophil counts at the 25 and 200 cGy doses while the high dose rate resulted in a significant reduction in neutrophil counts at the 50 cGy dose, compared to the counts at the 0 Gy dose.

3.3 Blood cell count changes from proton exposure at 0.28 cGy/min (30-74 MeV proton beam)

The effect of the proton radiation at a very low dose rate (0.28 cGy/min) on blood cell counts at 24 hours post-exposure was similar to the effect of the proton radiation at the HDR (50 cGy/min) on the blood cell counts at the same time point. The WBC, neutrophil and lymphocyte counts of the 50, 75, and 100 cGy groups irradiated at the 0.28 cGy/min dose rate were significantly lower than the results in the corresponding control groups but not significantly different from the results in the corresponding dose groups irradiated at the 50 cGy/min dose rate (data not shown).

3.4 Effective doses to produce 10%, 50%, and 90% reductions after proton radiation exposure

Effective dose (ED) of proton radiation required to reduce total WBC, neutrophil or lymphocyte counts by 10% (ED_{10}), 50% (ED_{50}) or 90% (ED_{90}) was calculated based on the data obtained 24 hours after exposure. The ED_{10} , ED_{50} and ED_{90} values for WBCs and lymphocytes of the animals irradiated with simulated SPE proton radiation were comparable to the corresponding ED_{10} , ED_{50} and ED_{90} values of the animals irradiated with 30-74 MeV protons, regardless of the dose rate (Table 2).

4.0 Discussion

Limited data are available to predict the human hematopoietic response to SPE radiation exposure. We and others have extensively studied the murine hematopoietic response to a variety of radiation forms, including gamma rays, high energy protons and HZE particles, all of which produce a relatively homogeneous dose distribution in mice. The effects of the

unique inhomogeneous characteristics of SPE-like radiation on the hematopoietic radiation response have not been extensively evaluated and are incompletely understood. The data presented here indicate that total body proton radiation (homogenous and inhomogeneous), delivered at different dose rates and energies, result in comparably reduced circulating blood cell counts, specifically total white blood cell and lymphocyte counts, as early as 4 hours after exposure. The doses investigated were based on the estimated doses to the blood forming organs (BFO) that could have resulted if astronauts had been exposed to SPE radiation during three large SPEs; the estimates ranged from 19.29-46.25 cGy-Eq inside the spacecraft to 37.87-138.40 cGy-Eq during extravehicular activity (EVA) (Hu, Kim, 2009).

The results from the total WBC and lymphocyte counts are strikingly similar at all the dose rates, doses, and energies utilized in these studies. The 30-74 MeV proton beam resulted in average WBC counts that were comparable at all three dose-rates investigated, 50 cGy/min, 50 cGy/h, and 0.28 cGy/min, at the 24 hour time point. Further, when the ED values for decreased WBC and lymphocyte counts are compared, the simulated SPE and the 30-74 MeV proton beam exposures resulted in similar values. Taken together, the proton radiation utilized in these studies did not result in dose-rate or energy distribution specific effects on WBC and lymphocyte counts.

The total WBC count results in these studies (in response to either the simulated SPE proton beam or the 30-74 MeV scrolling proton beam) are in agreement with previous results reported 24 hours after exposure to 70 MeV protons (Maks et al., 2011). Interestingly, the reduction in total WBC counts at 24 hours after exposure to 1 GeV protons (2 Gy dose), previously reported by Ware et al. (Ware et al., 2010), was less than the observed reduction in total WBC counts reported here and by Maks et al. Specifically, 1 GeV protons produced about a 2.5 fold decrease in total WBC counts while the lower energy protons (used in this study and by Maks et al.) produced about a 5 fold decrease in total WBC counts at 24 hours after exposure. The SPE proton beam used in this study (with 92% of dose at 30 MeV, Table 1) also resulted in approximately a 5 fold decrease in total WBC counts at 24 hours after exposure, suggesting that the lower energy protons may be more deleterious than the high energy protons and that the unpredictable energies of SPE radiation could be a major concern for hematopoietic toxicity.

The absolute neutrophil counts (ANC) were significantly reduced at 4 and 24 hours after proton radiation with the 30-74 MeV beam (although not in a consistent manner). The ANC in the non-irradiated mice in these experiments were > 800. After exposure to 50 cGy at the HDR, the ANC at 4 hours post-exposure was 667 ± 382 (average $\pm$ standard deviation), and 707 ± 88 at 24 hours post-exposure, respectively, which by clinical parameters is categorized as moderate neutropenia (ANC 500-1000). Interestingly the ANC was not altered in a statistically significant fashion after the SPE simulation experiment, at either of the time points (4 or 24 hours post-exposure), doses, or dose rates investigated. The dose-depth profile of a 30 MeV proton beam is considered superficial (< 1 cm), while the 30-74 MeV proton beam dose-depth profile deposits a mostly uniform dose to a depth of approximately 4 cm. It is hypothesized that a greater dose will be absorbed by the blood forming organs and the bone marrow compartments (i.e., spine and pelvic areas) from the 30-74 MeV beam, and less of a uniform dose to these areas from the scaled SPE beam,

suggesting that an inhomogeneous dose distribution to various bone marrow compartments (and the lymphatic vasculature) may result in hematological changes that are distinct from those resulting from a homogeneous dose distribution.

The majority of protons in an SPE are at or below 50 MeV, although historical large SPEs that have been documented include proton energies >60 MeV (Wilson, 1997). The present experiments establish that, in mice, using proton irradiation conditions designed to match the linear energy transfer and approximate energy of an SPE, compared to a relatively homogeneous dose distribution (30-74 MeV proton beam) provides similar results for total WBC counts, specifically lymphocyte counts. Moreover, there was no significant dose rate effect from 50 cGy/min to 17.5 cGy/h (0.29 cGy/min). Not only are blood cell counts used for early indicators and dose estimates of exposure (Flidner et al. , 2007), but adequate numbers of circulating WBCs are critical for immune responses and fighting infection. Lymphocytes are the most radiosensitive blood cell type (Neff and Cassen, 1968). Neutrophils are the first responders during an infection. Protection against neutropenia in patients receiving radiotherapy is through treatment with growth factor granulocyte-colony stimulating factor (G-CSF), commercially known as Neupogen® or Neulasta® (pegylated G-CSF). Treatment for radiation-induced lymphopenia is not yet available. Although SPE radiation is unpredictable, the development of radiation countermeasures to prevent or mitigate the acute lymphocyte reduction should be developed to avoid both acute and late radiation injuries.

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References

- Flidner TM, Graessle D, Meineke V, Dorr H. Pathophysiological principles underlying the blood cell concentration responses used to assess the severity of effect after accidental wholebody radiation exposure: an essential basis for an evidence-based clinical triage. *Experimental hematology*. 2007; 35:8–16. [PubMed: 17379081]
- Gridley DS, Freeman TL, Makinde AY, et al. Comparison of proton and electron radiation effects on biological responses in liver, spleen and blood. *International journal of radiation biology*. 2011; 87:1173–81. [PubMed: 22035456]
- Gridley DS, Rizvi A, Luo-Owen X, et al. Variable hematopoietic responses to acute photons, protons and simulated solar particle event protons. *In Vivo*. 2008; 22:159–69. [PubMed: 18468399]
- Hu S, Kim MH, McClellan GE, Cucinotta FA. Modeling the acute health effects of astronauts from exposure to large solar particle events. *Health physics*. 2009; 96:465–76. [PubMed: 19276707]
- Luo-Owen X, Pecaut MJ, Rizvi A, Gridley DS. Low-dose total-body gamma irradiation modulates immune response to acute proton radiation. *Radiation research*. 2012; 177:251–64. [PubMed: 22149957]
- Maks CJ, Wan XS, Ware JH, et al. Analysis of white blood cell counts in mice after gamma- or proton-radiation exposure. *Radiation research*. 2011; 176:170–6. [PubMed: 21476859]
- Neff RD, Cassen B. Relative radiation sensitivity of circulating small and large lymphocytes. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 1968; 9:402–5.

- Wambi CO, Sanzari JK, Sayers CM, et al. Protective effects of dietary antioxidants on proton total-body irradiation-mediated hematopoietic cell and animal survival. *Radiation research*. 2009; 172:175–86. [PubMed: 19630522]
- Ware JH, Sanzari J, Avery S, et al. Effects of proton radiation dose, dose rate and dose fractionation on hematopoietic cells in mice. *Radiation research*. 2010; 174:325–30. [PubMed: 20726731]
- Wilson, J.; Cucinotta, FA.; Tai, H.; Simonsen, LC.; Shinn, JL.; Thibeault, SA.; Kim, MY. Nasa Technical Paper 3682. National Aeronautics and Space Administration; USA: 1997. Galactic and solar cosmic ray shielding in deep space.

Figure 1.

Blood cell counts are decreased 4 and 24 hours after a single total body exposure to a simulated SPE proton beam. Total WBC counts are statistically different in all dose groups examined after exposure to an SPE at the HDR (left panel), compared to the control (0 Gy dose) group (A). SPE exposure at 4 and 24 hours post-exposure resulted in similar changes in total WBC counts (A & B) and lymphocyte counts (E & F). There was no statistically significant - changes observed in the neutrophil counts (C & D). Analyses performed using the unpaired Student's T test resulted in statistically significant differences in which $p < 0.05$

is indicated by the following symbols: * the differences between the results for the high dose rate (HDR) dose group compared to the results for the control (0 Gy dose) group were statistically significant; ** the differences between the results for the LDR group compared to the results for the control group were statistically significant; *** the differences between the results for the HDR dose group compared to the results for the LDR dose group were statistically significant.

Figure 2.

Blood cell counts are decreased 4 and 24 hours after a single exposure to scrolling 30-74 MeV proton energy radiation. 8 Bragg peaks at scrolling proton energies were designed to produce a homogenous proton dose distribution in mice resulting in decreased peripheral white blood cell (WBC, A & B), neutrophil (C & D), and lymphocyte (E & F) counts (mean $\pm$ standard deviation). Analyses performed using the unpaired Student's T test resulted in statistically significant differences in which $p < 0.05$ is indicated by the following symbols: * the differences between the results for the high dose rate (HDR) dose group compared to

the results for the control (0 Gy dose) group were statistically significant; ** the differences between the results for the LDR group compared to the results for the control group were statistically significant; *** the differences between the results for the HDR dose group compared to the results for the LDR dose group were statistically significant.

Table 1

Energy distribution and energy degrader filter settings of the simulated SPE exposure with an overall error from cutoff less than 1%.

MeV	Filter Setting (cm)	Dose Fraction (%)	Cutoff Error (%)	Error Fraction
30	14.325	92.3480	1	.0092
40	13.75	3.6400	1	.000036
50	13.05	1.8131	2	.000036
60	12.225	0.9882	5	.00049
70	11.275	0.5203	10	.0005
80	10.20	0.2997	10	.0003
90	9.050	0.1646	10	.0002
100	7.775	0.0997	10	.0001
110	6.400	0.0536	10	.00005
120	4.925	0.0295	10	.00003
130	3.375	0.0181	10	.00002
140	1.725	0.0103	10	.00001
150	0.000	0.0061	10	.000006

Table 2

Effective doses of protons to decrease blood cell count by 10% (ED₁₀), 50% (ED₅₀) and 90% (ED₉₀).

Cell Type	Radiation	Dose Rate	Effective dose (and 95% CI)		
			ED ₁₀	ED ₅₀	ED ₉₀
WBCs	Simulated SPE	0.5 Gy/min	0.16 (0.14 – 0.18)	1.05 (0.92 – 1.18)	3.48 (3.03 – 3.93)
		0.5 Gy/h	0.15 (0.13 – 0.18)	1.01 (0.87 – 1.15)	3.35 (2.88 – 3.83)
	30 – 74 MeV	0.5 Gy/min	0.15 (0.13 – 0.18)	1.00 (0.84 – 1.17)	3.33 (2.79 – 3.88)
		0.5 Gy/h	0.15 (0.13 – 0.18)	1.00 (0.84 – 1.16)	3.32 (2.78 – 3.85)
Neutrophils	Simulated SPE	0.5 Gy/min	1.03 (0.68 – 1.39)	2.65 (1.74 – 3.55)	4.82 (3.17 – 6.48)
		0.5 Gy/h	0.44 (0.18 – 0.71)	2.38 (0.97 – 3.78)	5.90 (2.42 – 9.38)
	30 – 74 MeV	0.5 Gy/min	0.74 (0.13 – 1.36)	4.89 (0.85 – 8.93)	16.23 (2.82 – 29.66)
		0.5 Gy/h	0.45 (0.25 – 0.66)	2.98 (1.64 – 4.32)	9.91 (5.45 – 14.36)
Lymphocytes	Simulated SPE	0.5 Gy/min	0.14 (0.12 – 0.16)	0.92 (0.80 – 1.04)	3.06 (2.66 – 3.45)
		0.5 Gy/h	0.13 (0.11 – 0.15)	0.87 (0.75 – 0.99)	2.88 (2.49 – 3.28)
	30 – 74 MeV	0.5 Gy/min	0.13 (0.11 – 0.15)	0.87 (0.73 – 1.02)	2.90 (2.42 – 3.38)
		0.5 Gy/h	0.14 (0.12 – 0.16)	0.92 (0.77 – 1.06)	3.05 (2.55 – 3.54)