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A Proposed Change to Astronaut Exposures Limits Is a Giant Leap Backwards for Radiation Protection

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Opinion/Position paper

A proposed change to astronaut exposures limits is a giant leap backwards for radiation protection

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ABSTRACT

Addressing the uncertainties in assessing health risks from cosmic ray heavy ions is a major scientific challenge recognized by many previous reports by the National Academy of Sciences (NAS) and the National Council on Radiation Protection and Measurements (NCRP) advising the National Aeronautics and Space Administration (NASA). These reports suggested a series of steps to pursue the scientific basis for space radiation protection, including the implementation of age and sex dependent risk assessments and exposure limits appropriate for a small population of radiation workers, the evaluation of uncertainties in risk projections, and developing a vigorous research program in heavy ion radiobiology to reduce uncertainties and discover effective countermeasures. The assessment of uncertainties in assessing risk provides protection against changing assessments of risk, reveals limitations in information used in space mission operations, and provides the impetus to reduce uncertainties and discover the true level of risk and possible effectiveness of countermeasures through research. However, recommendations of a recent NAS report, in an effort to minimize differences in age and sex on flight opportunities, suggest a 600 mSv career effective dose limit based on a median estimate to reach 3% cancer fatality for 35-year old females. The NAS report does not call out examples where females would be excluded from space missions planned in the current decade using the current radiation limits at NASA. In addition, there are minimal considerations of the level of risk to be encountered at this exposure level with respect to the uncertainties of heavy ion radiobiology, and risks of cancer, as well as cognitive detriments and circulatory diseases. Furthermore, their recommendation to limit Sieverts and not risk in conjunction with a waiver process is essentially a recommendation to remove radiation limits for astronauts. We discuss issues with several of the NAS recommendations with the conclusion that the recommendations could have negative impacts on crew health and safety, and violate the three principles of radiation protection (to prevent clinically significant deterministic effects, limit stochastic effects, and practice ALARA), which would be a giant leap backwards for radiation protection.

1. Introduction

A recent US National Academy of Science (NAS) report (National Academy of Sciences 2021) advocates the implementation of a simplified effective dose limit of 600 mSv for all astronauts, withdrawing from the age and specific limits used since 1990 at NASA. The objective of this recommendation is stated as a means to allow equivalent flight opportunities for males and females of different ages. However, there is minimal discussion of what flight limitations in the current framework and in the near-term exist for female astronauts or what new possibilities are opened for females by the proposed change. The stated charge to the NAS listed in the report (National Academy of Sciences 2021) suggests that non-cancer risks should not be considered, however, we discuss extensive evidence that risk limits for cancer fatality likely have a large bearing on the occurrence of radiation induced non-cancer risks. In this report we caution several of the recommendations in the NAS report and describe extensive over-sights in relation to crew safety by their recommendations.

In space astronauts are exposed to high energy protons and heavy ions that make up the galactic cosmic rays (GCR), trapped protons and

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electrons in low EARTH orbit (LEO), and infrequent solar particle events (SPE) comprised largely of medium energy protons. Secondary radiation, including high linear energy transfer (LET) recoil nuclei from neutrons are produced in shielding and tissues. NASA currently uses a radiation limit of 3% cancer fatality risk evaluated at the 95% confidence interval as a limit to career exposures. In addition, limits are used to avoid clinically significant deterministic or non-cancer effects to the skin, lens of the eye, central nervous system (CNS) and the circulatory system (See discussion below for details).

Cancer risk varies with age at exposure, health history, ethnicity, lifestyle choices, and sex. This leads to a difference in effective doses to reach an equal projection of lifetime risk for individuals or, equivalently, to different lifetime risks for a given dose. The risks of breast, ovarian and uterine cancer coupled with a known higher risk of radiation-induced lung cancer found in epidemiology studies, increases the risk of females compared to males in projection models (Cucinotta et al., 2013a; Cucinotta et al., 2013b; Cucinotta, 2014; Cucinotta, 2015; Cucinotta et al., 2015; Cucinotta et al., 2016; Cacao et al., 2016; Cucinotta et al., 2017; Cucinotta and Cacao, 2017; Cucinotta et al., 2018; Cucinotta et al., 2020a; Cucinotta et al., 2020b). In addition, the longer lifespan for females compared to males leads to an additional lifetime radiation risk of about 10% for never-smokers independent of tissue sensitivity to radiation. Furthermore, past occupational radiation exposures (space missions, aviation, medical exposures related to flight duties) will also post a difference by affecting future space mission assignments. This last difference reduces the importance of an equivalent dose limit independent of age and sex. For example, two female astronauts of the same age, one with a prior International Space station (ISS) mission and the another without, would have different limits for a lunar or Mars mission.

The NAS committee recommended 600 mSv effective dose limit is based on a 2012 NASA Space Cancer Risk (NSCR) model developed by Cucinotta (Cucinotta et al., 2013a; Cucinotta et al., 2013b; Cucinotta, 2014) of the median estimate of the dose for a 3% risk of exposure induced death (REID) from cancer for 35-year old females. In-fact, the more recent versions of NSCR model suggest the possibility of a much higher risk than 3% fatality at 600 mSv for 35-y old females (Cucinotta, 2015; Cucinotta et al., 2015; Cucinotta et al., 2016; Cacao et al., 2016; Cucinotta et al., 2017; Cucinotta and Cacao, 2017; Cucinotta et al., 2018; Cucinotta et al., 2020; Cucinotta et al., 2020). As described in this present report the NAS commitee also did not consider heavy ion and high LET neutron experiments that suggest important contributions from non-targeted effects (NTE), which include bystander effect, genomic instability and tissue microenvironment changes, in cancer risk, a large relative risk (RR) or relative biological effectiveness (RBE) for breast cancers compared to gamma-rays, and evidence for radiation risks of circulatory diseases and cognitive detriments. The NSCR-2012 model does not account for qualitative differences between high- and low-LET radiation that result due to increased complexity of DNA damage and oxidative stress at high LET, and the resulting differences in biochemical signaling in relation to disease development and progress. The large number of open radiobiology issues are largely minimized or not discussed in the NAS report (National Academy of Sciences 2021), which relies almost entirely on discussion of gamma-ray and X-ray epidemiology studies. It is well known that microscopic energy deposition from heavy ions leads to both quantitative and qualitative differences in biological effects compared to gamma-rays and X-rays (see discussion below).

The NAS report suggests that a waiver process should be developed for space exploration missions that would exceed the recommended effective dose limit (National Academy of Sciences 2021). A main conclusion of our critique of the NAS report is that we find that the recommendations of a 600 mSv limit, irrespective of the corresponding risk and its uncertainty, when combined with a waiver process has the effect of removing radiation limits for astronauts. The NAS recommendation contradicts substantially past NAS (NAS 1970; NAS 1996; NRC 2008; NRC 2012; NAS-IOM 2001; NRC 1998) and NCRP recommendations (NCRP 1989; NCRP 2000; NCRP 2006; NCRP 2014; NCRP 1997; NCRP 2010) as described below. An unstated assumption made in the recommendation of waivers is that they are issued by NASA. Our opinion is that this is fundamentally unethical, since it allows NASA to decide that an astronaut may be exposed to any quantity of radiation, in other words, it creates a mechanism whereby NASA can potentially allow significant harm to an employee. The only ethical way to proceed with a waiver is if it is granted by an authority independent of the employer and the employee that has examined the interest of all individuals affected, as is done by Institutional Review Boards.

Space missions have a low aggregate risk for loss of crew (LOC), as estimated by NASA to be less than 1 in 270 (Cucinotta et al., 2013b; Aerospace Safety Advisory Panel 2013). The actual so-called accident occurrences in the Apollo and Space Transportation System (STS) (space shuttle) programs have led to an astronaut mortality of ~1.2% for all NASA programs to-date, with the International Space Station (ISS) incurring no accidents since its start in 1998. The average life-loss for an astronaut of 40-y age at exposure from a radiation induced cancer is estimated at about 15 years for gamma-rays and expected to be higher for heavy ions based on animal studies (Cucinotta, 2014; Cucinotta et al., 2020a), or about 2.5 times less than an estimated ~40 life-loss years for a during mission LOC. Using the ratio for differences in average life-loss and considering a 4–6- person crew size, suggests that a comparable risk basis for a during-mission LOC design criteria to REID limit would be a 1–10 ratio. On this basis, the 1 in 270 aggregate risk for during mission LOC is then quite similar to the current 1 in 33 radiation cancer fatality limits at NASA, while an aggregate risk of 1 in 750 suggested to be achievable through smart investments recommended by the Aerospace Safety Advisory Panel (ASAP) (Aerospace Safety Advisory Panel 2013) would suggest a lower limit on acceptable radiation fatality risks. These arguments suggest a lower radiation limit should be a future goal for space radiation protection. NCRP Report No. 98 (NCRP 1989) noted that radiation risks should not be ignored, but should be limited because of a high LOC risk. Other considerations are the additional radiation non-cancer mortality and morbidity risks (2–3-fold higher than mortality risk), and the ethical consideration that values life at all ages, as opposed to considerations of LOC during the mission alone.

The NAS recommendation to set limits based on the highest-risk sensitive individual means that older astronauts, who would incur a lower risk for exposure to the same quantity of radiation, would be eventually excluded from renewed participation in missions. The exclusion of experienced astronauts would seem to significantly increase the risk to mission objectives, as well as to the safety of crew members on such missions.

In this Commentary, the authors evaluated the main recommendations of the recent NAS report (1) through the following eight targeted questions:

Q1) *Is the premise that female astronauts are limited in mission opportunities compared to male astronauts valid in the current decade?*

Q2) *Is there valid new information to suggest radiation induced lung cancer risk is not higher in females than males? Do low dose and low dose-rate reactor worker studies have any relevance for predicting radiation risk to astronauts?*

Q3) *Issues in estimating the risks of breast, ovarian, and uterine cancers from heavy ions were not discussed in the NAS Report, along with the sex dependence of RBE for radiation-induced lung cancer. How could this information influence a limit or waiver process?*

Q4) *Should uncertainties in space radiation risk assessments be downplayed or ignored before risks limits are set and sufficient knowledge of heavy ion radiobiology effects on cancer, cognition and circulatory diseases are obtained? Are the limits for non-cancer effects violated by the NAS Recommendation?*

Q5) *The NAS Report did not consider differences in risk estimates between the 2012 version of the NSCR (Cucinotta et al., 2013a; Cucinotta*

et al., 2013b; *Cucinotta, 2014*), *and more recent versions of NSCR (Cucinotta, 2015*; *Cucinotta et al., 2015*; *Cucinotta et al., 2016*; *Cacao et al., 2016*; *Cucinotta et al., 2017*; *Cucinotta and Cacao, 2017*; *Cucinotta et al., 2018*; *Cucinotta et al., 2020a and 2020b*). *What are the implications of these differences?*

Q6) *What would be alternate solutions for near and mid-term goals for equality of flight opportunities for astronauts of different ages and sex in-light of anti-discriminatory government legislation, such as HIPAA* privacy laws, and GINA** regulating the use of individual personal information?*

Q7) *Is a waiver process necessary when NASA management has the authority to increase limits to higher risk or exposure level? Is it ethical for a waiver to be issued by an employer that permits an employee to incur potentially life-threatening risks?*

Q8) *What are risk communication processes, especially for missions involving large radiation health risks?*

**Health Insurance Portability and Accountability Act of 2000 and its Modifications*

***Genetic Information Non-Discrimination Act of 2018.*

2. Discussion of NAS recommendation #1

Recommendation #1: NASA should proceed with the proposed approaches to revising the space radiation health standard. As proposed by NASA, the agency should:

- **Apply a single space radiation standard to all astronauts;**
- **Utilize the most protective approach in setting the space radiation standard;**
- **Set the standard as a dose limit; and**
- **Utilize the mean value of the risk distribution based on 3% risk of exposure-induced death.**

Q1) Is the premise that female astronauts are limited in mission opportunities compared to male astronauts valid in the current decade?

We find very few scenarios where female astronauts are limited in mission opportunities compared to male astronauts with the current risk limits at NASA, with none likely in the next 10–15 years. State-of-the-art uncertainty analysis, has shown that female astronauts can participate on several ISS Missions with a total duration of 2-years if their first mission is at age 35 years (Cucinotta, 2014). Also, lunar missions of up to 6-months would be within the current standards (Cucinotta et al., 2018), and certainly a combination of an ISS and a lunar mission both of up to 6-month is possible. Some assumptions are needed on the balance of number and length of missions (ages, between missions, etc.). ISS missions are limited in the number of persons on-board with twelve persons participating in 6-month missions per year or six persons on 12-month missions or some combination. Crew assignments are divided between NASA and other national space agencies with NASA enjoying typically 2 crew persons per crew rotation. We also need to consider how many years of training are involved between missions, which is typically 3–5 years. Under the assumption of radiation risk declining with age of exposure, ISS durations longer than 2 years are possible. Timelines for lunar missions and their potential durations are often modified, however at this time we expect the first lunar missions would be of short duration (< 30 days) and no earlier than 2028. No funding for a lunar base needed for a long-stay has been allocated by US Congress, and a lunar base would likely delay a Mars mission by many years because of financial constraints.

Therefore, in the current decade there are no limitations for female astronauts until total times on ISS missions longer than 2 years are considered, which has not occurred in the past for either male of female astronauts, and female astronauts would likely be able to participate in ISS missions and several short lunar missions. Another scenario is a deep-space mission such as a 1-year Mars swing-by mission. Here there are possible limitations for female compared to male astronauts, especially if past ISS or lunar missions had occurred for an individual. However, the blood forming organ (BFO) limit could limit both male and female astronauts depending on shielding and SPE considerations. For a Mars mission projected at 900–1100 days, the current limit system and the proposed 600 mSv limit would likely exclude both male and female astronauts until risk projection uncertainties are significantly reduced and effective countermeasures are discovered.

Q2) Is there valid new information to suggest radiation induced lung cancer risk is not higher in females than males? What impact do low dose and low dose-rate reactor worker studies have for predicting radiation risk to astronauts?

The NAS Report describes studies besides the Japanese Life Span Study of atomic bomb survivors (LSS) (Brenner et al., 2018; Grant et al., 2017) that provide differential results on lung cancer risks between males and females, with the main so-called "new" findings based on the International Study of Reactor Workers (INWORKS) (Leuraud et al., 2015; Richardson et al., 2015; Richardson et al., 2018). The LSS study provides information on breast, ovarian and uterine cancer risks and demonstrated a higher risk of lung cancer in females compared to males. Older studies on medical patients exposed at much high doses were considered earlier in NAS and NCRP reports advising NASA on radiation risks. The average organ doses in the LSS are about 250 mSv, while in the INWORKS the average organ doses are estimated at 20 mSv, but for chronic irradiation often over more than 10 years of employment. We find that the INWORKS study of cancer deaths in reactor workers in the US, Canada and Europe provides useful information for other exposed groups at lower doses of low LET radiation, but not for astronauts and is much less useful than the LSS for the following reasons:

1) The doses in the INWORKS are predominantly far below a single ISS mission dose (~90% of the INWORKS population) with less than 3% of the population studied near the NAS recommended dose limit of 600 mSv (**Table 1**). In contrast the LSS has a significant number of persons with organ doses above 100 mSv (> 50%) of relevance to ISS or lunar missions, and in the region of the recommended effective dose limit (Table 1).
2) The low doses of the INWORKS are such that on average a worker received an additional single electron track per cell per year from a penetrating gamma-ray, which has almost no relevance to heavy ion exposures where all the cells in the path of a single heavy ion simultaneously receive large doses (0.1 to several Gy dependent on Z and E) within 10^{-16} s. In contrast the LSS cohort received larger doses (many with doses of 0.1 to several Gy) almost instantaneously (< 1 s), albeit the spatial distribution of ionizations within a cell would be very different compared to ions (**Fig. 1**). The types of DNA damage events (Goodhead and Nikjoo, 1989) would be similar in the INWORKS and LSS. However, the number of such events at the lower doses of the INWORKS presents statistical limitations relative to

Table 1
Comparison of doses in INWORKS to LSS. The INWORKS study is only 9% female while the LSS is 60% female and doses more distributed near 600 mSv (Grant et al., 2017; Brenner et al., 2018; Leuraud et al., 2015; Richardson et al., 2015; Richardson et al., 2018).

Dose range, mSv	*Number persons*	*% of cohort*	*Approximate %- females*
	INWORKS (reactor workers)		
< 10	115,915	70%	7%
10–50	36,470	21	2.1
50–100	10,029	5.8	0.58
> 100	10,667	6.2	0.62
	LSS (Japanese A-bomb survivors)		
< 5	35,978	44.9%	26.9%
5 to 500	39,031	48.7	29.2
500 –1000	3136	3.9	2.3
> 1000	2060	2.6	1.5

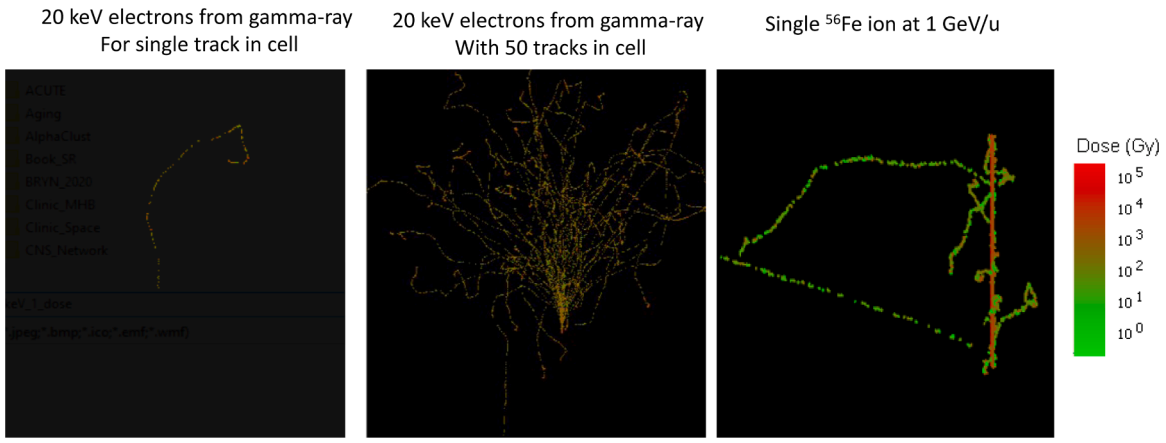

Fig. 1. Dose deposited in 20 nm voxel representative of a small segment of DNA with several hundred base-pairs from (left panel) 20 keV electron produced by gamma-rays at ~1 mGy, (center panel) 20 keV electrons from gamma-rays at ~50 mGy, and (right panel) single ^{56}Fe ion at 1 GeV/u. Calculations are made with the RITRACKS code (Plante and Cucinotta, 2008). For the average worker dose of 20 mGy in the INWORKS, single electrons would occur in each cell about once per year. Each heavy ion creates 100 s or more electrons in a directly traversed cell through ionization along its path nearly instantaneously ($< 10^{-16}$ s). For LSS, 10 to several 100 electrons could occur in each cell almost instantaneously (< 1 s), which is more representative of ions although important differences in the spatial distribution of ionizations occur. The track core of the ion traversal produces a much higher voxel dose (10^5 Gy) than gamma-rays, even for absorbed doses of gamma-rays as large as several hundred Gy (> 100,000 mGy) leading to qualitative differences in damage denoted as clustered DNA damage (Goodhead and Nikjoo, 1989). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

background cancer rates, and the presence of multiple DNA damage events simultaneously in LSS exposures is suggested to lead to differential biochemical reactions in response to this damage compared to INWORKS, with such reactions more reflective of the burst of damage in cells following heavy ion traversals.

3) The INWORKS study is less than 9% females compared to the LSS study which has ~60% females.
4) The number of persons in the INWORKS is larger than the LSS, however the number of person-years (PY) used in statistical analysis is similar in both studies (~2.5 million).
5) The NSCR model uses cancer incidence data for its low LET radiation baseline, while INWORKS reports only cancer mortality data. The LSS reports both incidence and mortality. Cancer mortality rates continue to decline (Siegel et al., 2021) in the U.S., and the NSCR model uses the most up-to-date information to convert incidence to mortality based on the current U.S. population as recommended by the NAS BEIR VII Report (BEIR, 2006), and provides a tool to explore this conversion for high LET radiation and healthy workers.
6) The LSS and INWORKS both must consider birth cohort effects; however, these effects are more straight-forward in the LSS study because of the single exposure date, while in the INWORKS study persons of the same age at exposure often have different birth years separated by years to several decades.
7) The LSS provides important information on age at exposure, attained age or latency for tissue specific cancers not provided by INWORKS at this time, allowing investigation of both excess additive risk (EAR) and excess relative risk (ERR) models using the LSS data.
8) The INWORKS does not provide accurate information on a dose-rate modifier (e.g. dose and dose-rate reduction effectiveness factor (DDREF)) because the chronic exposures involved both low dose-rate and protraction effects, and there is no appropriate comparison group with acute exposures. In contrast DDREF estimates, although somewhat uncertain, have been made from the LSS through study of the shape of the dose response curves (BEIR, 2006; Hoel, 2015), with values estimated in the range of 1.2–3, which are considered in the NSCR model's Bayesian analysis (Cucinotta et al., 2017). Protraction effects would not be important for space missions because of their limited duration and dose-rate effects distinct from low LET radiation (Cucinotta et al., 2016; Schimmerling and Cucinotta, 2006) due to small number of heavy ion traversals per cell (Cucinotta et al., 1998).

Q3) Issues in estimating the risks of breast, ovarian, and uterine cancers from heavy ions were not discussed in the NAS Report, along with the possible sex dependence of RBE for lung cancer. How would this information influence a Sievert limit or waiver process for females?

The NAS report makes no discussion of issues related to assessing risks of female specific cancers (breast, ovarian and uterine corpus) and differences in RBE observed in male and female mice. These issues are important for understanding uncertainties for heavy ions and other high LET radiation. Storer et al. (Storer et al., 1988) examined gamma-ray exposures in 6 strains of mice, and showed that relative risk (RR) estimates adequately represented the RR in the atomic bomb survivors for several types of cancer, including lung, mammary (breast), liver and leukemia. This study along with matching the tumor types in mice and humans provides important justification for exploring RBEs in mice for several tissues. We next summarize published studies that suggest there are important open issues related to understanding risks and RBE's for female astronauts exposed to high LET radiation.

Secondary neutrons in space or on the Martian surface have a broad energy range (Kim et al., 2014; Kim et al., 2015). Older studies of neutron effects at high LET provide some information of relevance to NASA. Fission neutrons ($E < 2$ MeV) do not adequately represent neutron energies in space, however they provide information on the largest RBE's observed. Cyclotron neutrons with energies up to 20 MeV are more representative of neutrons to be encountered in space. Coggle (Coggle, 1988) studied the RBE for lung adenomas and adenocarcinoma in 3-month-old male and female SAS/4 albino outbred mice and found that the RBE for cyclotron neutrons (mean neutron energy 7.5 MeV) were 2-fold higher in female mice compared to male mice with an estimated RBE for females and males compared to higher X-rays doses of 8.6 ± 3.6 (female) and 4.7 ± 1.8 (male). RBE estimates against a lower dose of X-rays (0.1 Gy) were estimated as 86 for females and 47 for males. Of note is that the RBE for cyclotron neutrons is found as 4-times lower than fission neutrons in other studies. Unfortunately, NASA has not funded studies of RBE for lung cancer comparing male to female mice with identical fluences of heavy ions. In contrast, we note that funding by the National Institutes of Health (NIH) for animal research requires nearly all studies to use both male and female animals. Exceedingly large RBE's are reported for fission neutron induced lung tumors in female RFM and Balb/C mice of > 283 and 60, respectively (Ullrich et al., 1976; Ullrich et al., 1977), however no comparisons to male mice were made.

In Balb/c mice (Ullrich et al., 1977) the RBE for low dose fission neutrons was estimated at 33 for mammary tumors. Several studies of mammary tumors in rats estimated RBEs as large as 100 (Fry, 1981; NCRP 1990). These values are much larger than the average RBE across various solid tumors in mice. However, the fraction of adenocarcinomas in different strain of rats is generally < 15%, with a much larger fraction of benign fibroadenomas occurring, which are less useful for considering risks in humans.

An important issue in understanding the risks of mammary cancers after high LET radiation is the influence of damage, including cancer induction, to the mouse ovary. Ovarian tumors in mice are believed to occur when extensive oocyte cells are killed which results in elevated release of gonadotrophins from the perturbed pituitary-gonad axis (NCRP 1990). A clear threshold dose for induction of ovarian tumors by gamma-rays occurs at about 100 mGy. Damage to the ovary, including changes to hormonal regulation, is suggested to reduce mammary tumor induction at higher doses of fission neutrons potentially reducing RBE estimates because of the downward curvature introduced at higher doses (Ullrich et al., 1977; Fry, 1981; NCRP 1990).

Because no human data for cancer risk from heavy ions exists, experimental findings on mechanisms for heavy ions and elucidating both qualitative and quantitative differences with low LET radiation are vital to space radiation risk assessment. Non-targeted effects (NTE) are an important issue in estimating low dose space radiation cancer risks because they alter the shape of the dose response for tumor induction, which increases RBE estimates, and suggest a mechanism for tumor induction distinct from DNA damage and mutation. Barcellos-Hoff and coworkers in a series of elegant experiments with a chimera model of mammary tumor induction by radiation (Illa-Bochaca et al., 2014; Omene et al., 2020) has demonstrated NTE, including differences in the protective immune infiltration of myeloid cells between low LET and heavy ions. Protective myeloid cells are shown to be inhibited with heavy ions, a mechanism not observed in gamma-ray irradiation, leading to rapid progression of tumors. Spaceflight has been shown to have differential inflammatory effects on crew and experimental systems in missions of duration of few months (Akiyama et al., 2020; Gueguinou et al., 2009), and thus the influence of NTE related to immune response and synergies with other flight factors should be a concern for long-term missions.

The risk for ovarian and uterine cancers for heavy ions has not been well studied, with no estimates of RBE's reported. A recent report using 12-week-old C57BL/6 exposed to 0.5 Gy Fe particles (Mishra et al., 2018) shows a large increase risk of ovarian cancers, which were diagnosed as tubular adenomas or mixed tubular adenoma/granulosa cell tumors.

Q4) Should uncertainties in space radiation risk assessments be downplayed or ignored before risks limits are set and sufficient knowledge of heavy ion radiobiology effects on cancer, cognition and circulatory diseases are obtained? Are the limits for non-cancer effects violated by the NAS Recommendation?

Permissible exposure limits are based on the principle of limiting stochastic risks to a level that it accepted based on ethical considerations, and the societal value of the endeavor leading to risk (Schimmerling, 2010). There are many open questions and large uncertainties in our ability to predict the GCR risk at a larger exposure level of 600 mSv or similar levels, which suggest that it's premature to accept such a limit, and as noted above the current limit system poses no barriers for multiple missions by female astronauts in this decade and perhaps longer into the future. Here we point out several areas that suggest the risk is poorly defined and requires further investigation to i) decide if the fatality risk for exploration missions is below 3% and ii) the level of morbidity risk for cancer, circulatory diseases and cognitive detriments at this exposure level. The goal of our summary is not to make an extensive review, but to point out several major questions that been identified through research but have not be adequately addressed.

NTEs include bystander effects where cells traversed by heavy ions transmit oncogenic signals to nearby cells, genomic instability in the progeny of irradiated cells and tissue microenvironment changes related to cancer development. NTE have been shown to impact initiation, promotion and progression stages of tumorigenesis at low doses of high LET radiation (Illa-Bochaca et al., 2014; Omene et al., 2020; Maxwell et al., 2008; Kadhim et al., 2013; Lorimore et al., 2003; Barcellos-Hoff and Mao, 2016; Hada et al., 2014; Nagasawa and Little, 1992; Belyakov et al., 2005; Chang et al., 2016). Initiation processes impacted by NTEs include chromosomal exchanges, sister chromatid exchanges, gene mutation, and neoplastic transformation, and shown to lead to a supra-linear dose response at low doses when less than one ion traverses a cell nucleus. A similar functional response provided an optimal global fit to the Harderian gland tumor study with several heavy ions (Chang et al., 2016; Cucinotta et al., 2018). Mechanistic studies of NTE's and dose response studies with heavy ions and high LET radiation at low fluence, where particle traversals are less than one particle per cell, suggest a deviation from linearity and increase in RBE which are important implications for GCR cancer risk assessments. A deviation from linearity would reduce the effectiveness of shielding.

As noted by Cucinotta et al. (Cucinotta et al., 2015) several studies (Fry, 1981; Fry et al., 1985; Alpen et al., 1993; Weil et al., 2009; Weil et al., 2014; Grahn et al., 1992; Imaoka et al., 2007; Trani et al., 2010; Datta et al., 2013; Wang et al., 2015) have suggested that high charge and energy (HZE) particles and neutrons could produce more aggressive and lethal tumors compared to tumors produced by low LET radiation or background tumors, which is a qualitative difference not accounted for in current risk estimates. **Table 2** summarizes these findings from animal studies with HZE particle beams or fission neutrons. For low LET radiation there is an implicit assumption made by epidemiology models that the tumors induced by radiation are similar to background tumors in a population. This assumption is consistent with the relative (multiplicative) risk model, and also based on lack of information to make an alternative assumption. Using the sensitivity analysis method described in recent reports (Cucinotta, 2014; Cucinotta et al., 2015), suggests that increases in tumor lethality for HZE particle and neutrons compared to background or low LET tumors as suggested by animal studies could substantially increase REID and uncertainty estimates. These are important findings on more aggressive tumors produced by high LET radiation, while not conclusive at this time, these possibilities based on current evidence still need to be understood before long-term exploration missions are conducted.

The NAS recommendation (National Academy of Sciences 2021)

Table 2
Summary of qualitative differences in tumor response for HZE particles compared to γ-rays or control tumors in mice.

Tumor model	Qualitative difference observed
Harderian Gland Tumors in B6CF1 female mice (Chang et al., 2016; Fry et al., 1985; Alpen et al., 1993)	Dose response for Fe particles was qualitatively different from γ-rays.
Hepatocellular carcinoma in male C3H/HeNCrl mice (Weil et al., 2009; Weil et al., 2014)	Dose response for Si and Fe particles was qualitatively different from γ-rays. Incidence of metastatic tumors significantly increased with Si and Fe particles compared to γ-rays or simulated solar protons.
Lung tumor in C57BL/6 mice (Wang et al. 2015)	More aggressive lung tumors observed for Si particles compared to low LET or control tumors.
Mammary tumors (Illa-Bochaca et al., 2014; Omene et al., 2020; Imaoka et al., 2007)	Differences in mammary tumor types comparing heavy ions to low LET radiation with more aggressive tumors observed. Heavy ions inhibit protective myeloid cells leading to rapid progression of tumors.
Intestinal tumors in APC $^{Min/+}$ mice (Datta et al., 2013)	Heavy ions increased tumor multiplicity and grade compared to protons or γ-rays.

does not consider the impacts of a 600 mSv limit on the risks of deterministic effects (tissue reactions) from GCR and SPEs. NASA has implemented a preliminary dose limit to the CNS for heavy ions and other high LET radiation of 100 mGy. CNS risks would be deterministic in nature, and therefore risks are to be avoided and not limited under a fundamental principle of radiation protection. The 100 mGy limit was based on earlier studies of cognitive risks, while investigators continue to document cognitive detriments at lower doses, including several studies at 50 mGy (Britten et al., 2017; Cucinotta and Cacao, 2019; Parihar et al., 2016; Parihar et al., 2015; Parihar et al., 2020; Raber et al., 2016). The possibility that the CNS limit should be lowered to 50 mGy or even lower for heavy ions and high LET secondary radiation would lead to the possibility that a 600 mSv limit would lead to either in-mission or post-mission cognitive detriments. CNS risks would include in-flight detriments of cognition, such as memory and performance detriments, and late effects, including advancement of the age of Alzheimer's disease (Liu et al., 2018) or increases in the incidence of Parkinson's disease (Azizova et al., 2020). Differential results are reported for differences in male and female cognitive responses in mice after heavy ion irradiation, with B6D2F1 mice showing higher sensitivity for females (Raber et al., 2016) and C57Bl/6 mice showing higher sensitivity for males (Parihar et al., 2020).

The translation of various experimental observations of cognitive detriments in rodent models exposed to heavy ions to human risk is complex. In a simplified approach the "Sievert" is the result after conversion of physical organ doses to biological equivalent organ doses, and this conversion varies with health risk as described below for various types of cancer. For CNS risks if a threshold dose of more than 100 mGy of heavy ions occurs, the "Sievert" for space radiation is essentially zero for space missions, including a Mars mission. However, if the threshold is below ~50 mGy the threshold is likely exceeded. Therefore, the value of a "Sievert" for cognitive risks is undefined until threshold doses and RBE's are determined (or alternative biophysical approaches to risks assessment are created), and could be greatly above 600 mSv based on several experiments reported recently (Britten et al., 2017; Cucinotta and Cacao, 2019; Parihar et al., 2016; Parihar et al., 2015; Parihar et al., 2020; Raber et al., 2016).

Circulatory risks from low dose radiation including to those in Russian radiation workers (Little et al., 2012) and the LSS (Takahashi et al., 2017) suggest a no threshold dose response model for overall risks with differential results for the various components of the risk. However, RBE values and DDREFs for circulatory risks have been sparsely studied. Cucinotta and co-workers used the meta-analysis results for ischemic heart disease (IHD) and cardiovascular disease (CVD) with the deterministic RBE model to estimate organ Gy-Eq dose and predicted that circulatory disease risk would add 15–35% (dependent on age at exposure and sex) of the total lifetime fatality risk over the cancer risk alone (Cucinotta et al., 2017; Cucinotta et al., 2013b; Cucinotta et al., 2020). For the LSS studies higher RR are found for females compared to males (Little et al., 2012), however the meta-analysis of Little et al. (Takahashi et al., 2017) did not consider sex differences on RR estimates. Using identical RR factors for males and females results in a higher prediction for males for the U.S. population because of differences in background rates of age specific IHD and CVD for males and females.

Other lifetime risks to be considered are the increased risks of death from non-cancer respiratory diseases found in the LSS study (Pham et al., 2013) for doses of 1000 mSv and higher, which could be approached if the RBE from GCR for this endpoint was high. Also, the results of low GCR dose studies of cataract in astronauts (Cucinotta et al., 2001; Chylack et al., 2009) suggest vision impairing opacities cannot be excluded from occurring within a long mission (> 1 year) at higher lens GCR doses than past Apollo, Skylab and STS missions. For a deep space mission near solar minimum, the 600 mSv would allow some possibility of exceeding the annual blood forming organ (BFO) limit of 500 mGy-Eq.

Q5) The NAS Report did not consider differences in risk estimates between the 2012 version of the NSCR developed by Cucinotta et al. (*Cucinotta* et al., *2013a*; Cucinotta et al., 2013b; *Cucinotta, 2014*), *and more recent versions of NSCR* (*Cucinotta, 2015*; Cucinotta et al., 2015; Cucinotta et al., 2016; Cacao et al., 2016; Cucinotta et al., 2017; Cucinotta and Cacao, 2017; Cucinotta et al., 2018; Cucinotta et al., 2020; *Cucinotta* et al., *2020*). *What are the implications of these differences?*

Since 2012 several new versions of the NSCR model have been developed and published by Cucinotta et al. (Cucinotta, 2015; Cucinotta et al., 2015; Cucinotta et al., 2016; Cacao et al., 2016; Cucinotta et al., 2017; Cucinotta and Cacao, 2017; Cucinotta et al., 2018; Cucinotta et al., 2020; Cucinotta et al., 2020). Uncertainties considered in the NSCR-2012 model include the physics of environments and radiation transport in predicting organ exposures, low LET epidemiology, quality factor (QF) and dose-rate modifiers represented by the DDREF, while more recent versions consider the role of NTEs on QFs and higher lethality of tumors at high LET. A review of some of the changes were supported by the NASA external Research and Clinical Advisory Panel (RCAP) in 2015 (NASA 2015) comprised of several of the members of the NAS and NCRP review panels for the NSCR-2012 (NRC 2012; NCRP 2014). The main developments were:

i Replacing risk estimates based on RBE_{max} (RBE relative to low dose or chronic gamma-rays) with estimates based on RBE_{acute} (RBE relative to acute gamma-rays for doses near 1 Gy). This reduced uncertainties due to error avoidance from low dose or chronic gamma-ray exposures, which are often ineffective, and from using sparse gamma-ray data to estimate RBE_{max} that were reported in heavy ion experiments. In this approach the QF has two terms representing the so-called core and penumbra of ionizations along an ions path. The core term because it involves very large energy depositions from individual ions, is assumed not to be modified by a DDREF.

ii Refining the NSCR Quality Factor (QF) to consider objective determination of model parameters as recommended by NAS in 2012 (NRC 2012), and introducing a correlation of the QF and DDREF using similar experimental data for QF parameter analysis and revised Bayesian analysis of the probability distribution function (PDF) of the DDREF.

iii Updating parameter estimates from heavy ion experiments published after 2012 (Chang et al., 2016; Suman et al., 2016) and re-evaluation of cell (Cacao et al., 2016) and fission neutron experiments (Cucinotta et al., 2017) in QF parameter estimates.

iv Sensitivity study of higher lethality for high Z–high LET tumors in conversion of incidence to fatality risk (Cucinotta, 2014; Cucinotta et al., 2017).

v Predictions of circulatory disease risk in combination with cancer risk using meta-analysis from Little et al. (Little et al., 2012) for circulatory risks and RBE for non-cancer risks from NCRP recommendations (NCRP 2000).

vi Introducing QF model with non-targeted effects for solid cancer risks (Cucinotta and Cacao, 2017; Cucinotta et al., 2018; Cucinotta et al., 2020a).

vii Updates to US population data for life-table and tissues specific cancer risks to most recent (2018) available data from the Center of Disease Control and Prevention (CDC).

The NSCR-2012 model developed an average QF for all solid cancers and a separate QF for leukemia risk, with a resulting lower QF for leukemia compared to solid cancers. However, the development of tissue specific QF for various solid cancer types and between males and females was not addressed because of insufficient experimental data for heavy ions.

The definition of a "Sievert" is distinct in the NSCR-2012 model from that recommended by the NCRP (NCRP 2000). NSCR-2012 and more recent versions use a track structure-based approach, with different

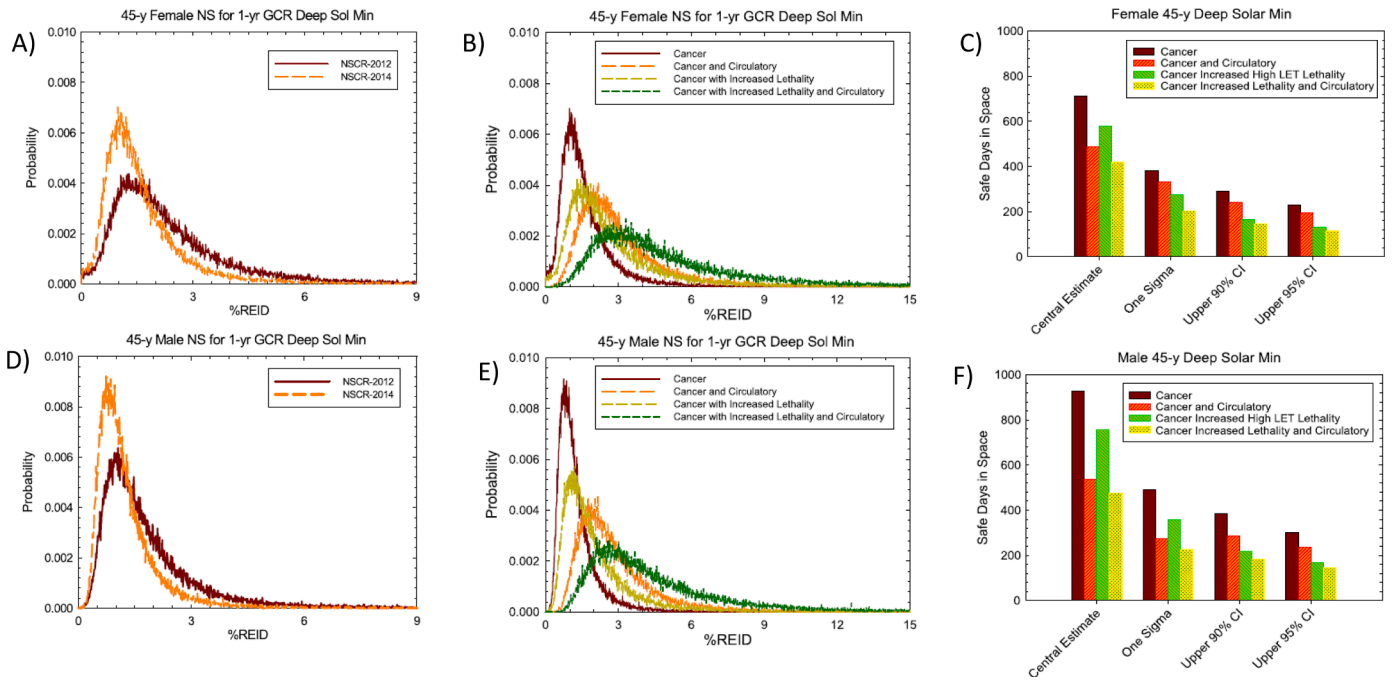

Fig. 2. Panel A/D, probability distribution functions for fatal cancer for females (A), and males (D) comparing the older NSCR-2012 to the NSCR-2014 predictions (Cucinotta et al., 2015). **Panel B/E**, probability distribution functions for REID by fatal cancer or with addition of circulatory disease risks and increased fatality from high LET particles for females (B) and males (E). **Panel C/F**, predictions of the number of "safe days" in space to be below career exposure limits for REID for females (C) and for males (F) using different assumptions on allowable uncertainties in the NSCR-2014 model without or with additional fatal risk contributors. . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

parameter estimates for the QF for solid cancer and leukemia risk. The NCRP recommends the use of radiation weighting factors or LET dependent quality factors with no distinction between solid cancer and leukemia risks. There are also different definitions in the NSCR-2012 definition compared to NSCR-2018, where the latter couples the QF to the DDREF model and the underlying probability distributions for model parameters. Thus, the duration of an exposure to GCR or SPEs leading to 600 mSv effective dose (i.e., Sieverts) is, to some extent arbitrary until a specific definition of how to convert particle fluence to risk is made.

Risk estimates were made for ISS crew on 6-month followed by 1-year missions near solar minimum (Cucinotta, 2014). These analyses show a dependence on age for each mission length and solar cycle conditions. Furthermore, several missions, including 1-year mission, carry risks for female astronauts within the current radiation limits. As such, with current limits, significant ISS opportunities will be likely for female crew even with the assumptions of circulatory risk and increased tumor lethality (Cucinotta, 2014).

For deep space missions the NSCR-2014 model made predictions compared to NSCR-2012 and with the additional assumptions of increased circulatory risk and higher tumor lethality estimates as shown in Fig. 2. These estimates made for 1-year missions near solar minimum with 20 g/cm^2 aluminum shielding are relevant for lunar missions. On the surface of the moon the GCR are reduced by 1/2, and detailed analysis including estimates of NTE, shows female crews can participate in several short duration lunar missions or a combination of 6-month ISS mission and a short duration lunar mission.

For long-stay lunar missions that might occur in the next decade (2030′s) more detailed analyses would be needed for both female and male astronauts.

For a Mars mission the cancer and circulatory disease risks could be quite high as shown by predictions near average solar minimum conditions in Table 3 (reproduced from (Cucinotta et al., 2020a)). The upper 95% confidence levels exceed 10% for both females and males of different ages, and the morbidity risk for cancer above 20% in several cases. The current NAS Recommendation is to allow these potentially high risks through NASA using a waiver process.

Another factor not considered in the NAS report is that there is a difference in the probability distribution of the %REID for different types of space radiation exposures (trapped radiation, solar particle events, solar minimum GCR, solar maximum GCR, GCR in LEO versus deep space due to EARTH magnetic shielding, Mars surface), and for different shielding materials. Heavy ions have a larger uncertainty compared to solar protons. Heavy ion biological effectiveness peaks at kinetic energies of few hundred MeV/u, which is an energy region

Table 3
Predictions of mean and 95% confidence intervals for cancer and circulatory disease risks for a 900-day Mars mission near solar minimum (Cucinotta et al., 2020a).

Age at exposure, y	%REIC (cancer morbidity)	%REID (cancer death)	%REID (circulatory disease death)	%REID (combined probability of death)
	Females U.S. average population			
20	20.9 [7.04, 51.4]	9.74 [2.71, 21.9]	1.16 [0.48, 2.26]	10.9 [3.45, 22.5]
40	13.2 [3.65, 35.5]	7.59 [2.03, 20.3]	1.2 [0.51, 2.37]	8.8 [2.78, 21.0]
60	8.63 [2.22, 26.0]	5.91 [1.44, 17.8]	1.23 [0.53, 2.49]	7.17 [2.3, 18.7]
	Males U.S. average population			
20	12.7 [4.97, 29.3]	6.1 [1.96, 14.1]	1.48 [6.3, 2.93]	7.58 [3.38, 15.6]
40	9.28 [3.13, 22.4]	4.94 [1.18, 12.2]	1.54 [0.66, 3.05]	6.49 [2.58, 13.6]
60	6.26 [1.82, 16.0]	3.82 [0.89, 9.69]	1.62 [0.69, 3.19]	5.44 [2.06, 11.3]

reduced substantially at solar maximum due to solar modulation, or in LEO due to the EARTH's magnetic field. Secondary neutrons carry a large REID uncertainty and are produced in higher amounts for aluminum shielding compared to water or polyethylene, and more frequently on the lunar or Mars surface due to albedo neutrons. The use of a 600 mSv limit does not consider the variation in uncertainty with the specifics of the different kinds of space radiation exposure.

Q6) What would be alternate solutions to the NAS Recommendation for a goal for equality of flight opportunities for astronauts of different ages and sex, in-light of anti-discriminatory government legislation, such as HIPAA privacy laws, and GINA regulating the use of individual personal information?

An important issue in minimizing space radiation risk is the conundrum of ignoring the science, which suggests higher risks for females, large uncertainties in predicting risks, and a variety of factors that would possibly enable medical staff to identify astronauts of low or high radiation sensitivity. The major part of the solution to the conundrum is to complete research studies needed to fully understand radiobiology of the issues identified above including risks of breast, ovarian and uterine, lung and other cancers, the role of non-targeted effects, the quality of HZE particle tumors compared to low LET radiation, cognitive risks, and circulatory disease risk.

There are several areas of risk prediction that could be pursued on an individual basis through a medical program, including those related to family history of cancer and genetic screening (NCRP 2010; Locke and Weil, 2016), however the science in these areas is incomplete at this time. The NIH maintains a policy that sex as a biological variable (SABV) is of utmost importance in clinical care and research (Clayton, 2018;). In the LSS (Brenner et al., 2018) the age of menarche is shown to have a profound effect on radiation breast cancer risk in women with a 3-fold decrease in risk for exposures at age 30 between ages of menarche of 12 and 18 years. The study of tumor induction in mice (Storer et al., 1988) following gamma-ray radiation suggests susceptibility is inherently tied to predisposition to specific types of cancer. However, two limitations occur here. First as described above high LET radiation has been shown to use distinct mechanisms of cancer initiation and progression compared to low LET radiation. Secondly, there are a large number of cancer types that contribute to overall radiation cancer risks, including lung, breast, liver, stomach, colon, bladder, brain, and leukemias. Family history for one specific cancer type may have only a small impact on overall risks. The science of genetic factors that may increase or reduce radiation risks from heavy ions and other high LET radiation is incomplete at this time, while tissue specific factors may have only a small impact on overall risk. Genetic factors related to DNA damage and immune responses and several other hallmark processes that span several tissues should be a focus of research studies on genetic susceptibility with heavy ions.

We have argued that the current radiation limits, which are based on a 3% fatality risk and assessment of uncertainties in the projection at the 95% confidence level, is sufficient to allow most flight opportunities for female astronauts in the current decade and possibly well into the next decade. The basic conundrum of balancing opportunity and risk for individuals is illustrated in Fig. 3, which illustrates the problem of finding simultaneous equality of mission opportunities and risk limits for women and men. We can offer several possible alternative approaches to the NAS recommendation that would ensure safety and health of individual and that uncertainties and open science issues are not ignored, while ensuring significant and equal opportunity:

- Limit crew independent of age and sex to 3 space missions made-up of ISS increments and short duration lunar missions. This would also reduce the individual's cumulative risk of flight related LOC and allow flight opportunities for a greater number of persons independent of age and sex or other factors.
- Use the up-to-date NSCR model to evaluate sex-averaged risks and uncertainties thereby keeping the age dependence of risks, but not ignoring uncertainties in risk projections. The age dependence of risk includes components related to finite lifespan due to all cause of death in a population (e.g. the U.S. population), and age dependent radiation sensitivity found in epidemiological studies.
- The preceding approach could be implemented within the NSCR approach with or without consideration of risk probability distributions as illustrated in **Fig. 3**. Here by applying the same principles used for the joint distribution of males and females to separate risk probabilities for males and females, such as the ones shown in **Fig. 2 above**. Let rM be the most probable risk for males, and rF be the most probable risk for females, with σM and σF the corresponding 95% width of each distribution. Then, without violating current approaches, NASA could set separate limits for rM and rF, using the different widths for permissible exposure.

3. Discussion of NAS recommendation #5

Recommendation #5: NASA should develop a protocol for waiver of the proposed space radiation standard that is judicious, transparent, and informed by ethics. To avoid the perception that an exception to the standard is built into the space radiation standard itself, NASA should follow the ethics decision framework in developing a waiver protocol and it should provide supporting analysis and explanation justifying any waiver to the standard.

Q7) Is a waiver process necessary when NASA management has the authority to increase limits to higher risk or exposure level? Is it ethical for a

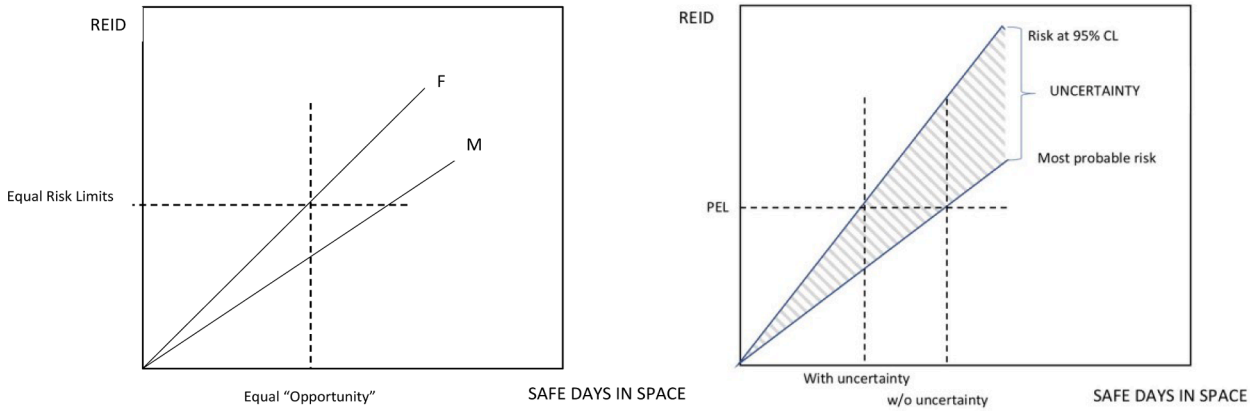

Fig. 3. Illustration of differences in considerations of the risk of exposure induced death (REID) versus opportunities for females and males. The left panel illustrates a consideration with uncertainties ignored, while the right panel shows considerations with uncertainty bands displayed. Opportunities are represented as "Safe Days in Space". NASA and NAS are considering approaches to balance this conundrum of competing view-points on astronaut risks.

waiver to be issued by an employer that permits an employee to incur life-threatening risks?

The current NAS report suggests a waiver process should be developed for space exploration missions that would exceed the recommended effective dose limit. Our main concerns with this recommendation are that the NCRP Report 167 (NCRP 2010) has stated a waiver process is prohibited under U.S. Law, and we suggest the combination of the proposed effective dose limit and a waiver process is equivalent to NASA withdrawing from radiation limits for astronauts.

The NCRP Report 167 stated that the "assumption of risk" defense is barred by the U.S. Federal Employment Compensation Act (FECA), and is not needed as NASA management is authorized to modify the dose (or risk) limit for specific missions. Notably the NAS report (National Academy of Sciences 2021) does not discuss NCRP Report 167 findings with respect to a potential waiver process. Quoting from NCRP Report 167 (NCRP 2010):

> *As a matter of public policy, most courts have reasoned that an employee's expressed or implied assumption of risk will not be given effect because of the unequal bargaining power between the employer and employee and the economic necessity under which the employee is required to assume the risk. Therefore, an employee is protected against an unreasonable employment contract and against any harm resulting from his or her employer's negligence. Consent by an employee to continue working on a task made dangerous by an employer's negligence is commonly called "assumption of risk." In employer and employee relationships, the assumption of risk defense is barred by most Workmen's Compensation Acts, such as FECA.*

We note that if there is indeed an exception to the U.S. labor laws noted by NCRP as applied to astronauts, it is not described in the NAS Report (National Academy of Sciences 2021). If in contrast to the NCRP Report 167 discussion on illegality (NCRP 2010), that waivers are possible, we point out an ethical problem if they were to be issued by NASA. This is fundamentally unethical because it creates a mechanism whereby NASA may inadvertently decide to subject an employee to potentially serious harm. The ethical way to proceed with a waiver is it should be granted by an authority independent of the employer and the employee, that has examined the interests of all individuals affected (including family, friends, and the public). This is typically done by properly functioning Institutional Review Boards

4. NAS recommendation #6

Recommendation #6: NASA should conduct research to develop evidence-based risk communication and the agency should develop a radiation risk communication research agenda to fill knowledge gaps such as (1) what information astronauts want; (2) how astronauts process risk information; and (3) who/what are the most effective sources of information for astronauts. In addition, NASA should carry out research to examine and improve the effectiveness of its current and proposed risk communication strategies and materials.

Q8) What are risk communication processes, especially for missions involving large radiation health risks?

One other observation that we were concerned with involves the discussion in the NAS Reports on risk communication and training of astronauts. We agree with the NAS Report (National Academy of Sciences 2021) discussion that the use of a stop-light to inform astronauts of their radiation risks is severely over-simplified compared to the level of potential risk to be encountered for several mission scenarios. In this area we have a comparison to researchers that traveled to the Department of Energy's, Brookhaven National Laboratory (BNL) to conduct experiments with heavy ions at the Alternating Gradient Synchrotron (AGS) and the NASA Space Radiation Laboratory (NSRL). Researchers are required to follow strict safety procedures, undergo extensive training in radiation safety, and pass written tests that must be renewed every 2 years. During their work near the accelerator beam-lines all researchers wear dosimeters. In the 25 years since NASA funded research began at BNL not a single person has received a dose over 1 mSv per year, which is a negligible dose compared to a single ISS mission where average doses are 80 mSv per 6-month mission (Cucinotta et al., 2008). In fact, the population dose for all NASA funded researchers to BNL (typically ~50 persons per year) over many years is likely lower than the average ISS mission dose for a single astronaut, while the number of hours of training is many orders or magnitude larger.

We recommend that training on radiation protection, including knowledge of heavy ion radiation biology, heavy ion physics and epidemiology, with administration of a written test be part of the astronaut candidate selection process. Rather than updated training for crew on specific missions, we recommend that training of all astronauts with information on the most recent radiobiology findings occur every 2-years. This level of training would increase awareness throughout the astronaut community, and it would be beneficial if adult family and loved ones of astronauts were allowed to receive the identical information presented in training lectures and written material developed.

5. Comparisons to past NAS/NRC and NCRP recommendations

The recent NAS report (National Academy of Sciences 2021) diverges substantially from past recommendations to NASA by the NCRP or the NAS, National Research Council (NRC). Cucinotta summarized major recommendations in several publications (Cucinotta, 2014; Cucinotta et al., 2015) which we list here. He notes, "Key recommendations with respect to NASA's regulatory framework for radiation limits, levels of acceptable risk, and approaches to manage uncertainties in risks estimates were delivered in several NCRP and NAS reports of the past. In 1989 the NCRP (NCRP 1989) discussed three types of comparisons of space radiation risks to other risks to form the basis for an acceptable lifetime risk level for space radiation exposure: 1) to limits for ground-based radiation workers, 2) to accidental deaths in the 'safe', 'less-safe', and 'hazardous' occupations, and 3) to other accidental fatality risks faced by crew-members. Ground-based radiation workers have lifetime radiation risks no greater than risks experienced on average in the 'safe industries', which was estimated as 0.5% in 1989 (NCRP 1989). However, the dose limits for ground-based radiation workers were similar to the accidental deaths probability in the "less--safe industries" where life-time risks of up to 3% were estimated at that time. The NCRP noted that because astronauts face other occupational fatality risks, comparison of radiation limits to life-time fatality risks in 'hazardous industries' was not appropriate. Based on these observations, the NCRP recommended NASA use a 3% lifetime fatality risk as the basis for dose limits, and for the use of epidemiology based models to estimate age at exposure and sex specific dose limits for astronauts working in LEO (NCRP 1989). NASA implemented the NCRP recommended sex and age-at-exposure specific dose limits in 1990."

In summarizing NCRP Report 132 published in 2000 (NCRP 2000), Cucinotta notes, "Within a decade of the publication of NCRP Report No. 98, the NCRP reported that the comparison of space radiation risks to the 'less-safe industries' no longer supports a 3% fatality risk as a basis for radiation dose limits, because of the improvements in safety leading to lower fatality rates in ground-based occupations. The comparison to less-safe industries would lead to a lower acceptable risk level and stated (NCRP 2000): *The NCRP now considers the comparison with lifetime risk associated with the occupational exposure limits recommended for workers on the ground to be the most direct and the most valid. Consequently, the NCRP recommends that the excess lifetime fatal cancer risk due to the radiation exposure of space workers for missions in LEO be limited to 3% excess mortality and that this be the basis for career limits.* Indeed improvements in ground-based occupational safety since 1989 have occurred with average lifetime fatality risks in most less-safe industries now below 1% (National Safety Council 2011)."

The Institute of Medicine (IOM) of NAS noted in their 2001 Safe Passage report (NAS-IOM 2001) and re-affirming an earlier SSB report (NCRP 1998), "Until the radiation hazards to astronauts can be controlled or otherwise mitigated by physical shielding, a 1998 National Research Council report states, *'long-duration space travel should be postponed (SSB and NRC, 1998)'. Even if an effective physical radiation shield is developed, it in no way diminishes the need for clinical study, including monitoring of crewmembers' exposures, long-term medical follow-up, and the development of preventive medical treatments to make astronauts more resistant to deep space-induced radiation damage*". In reviewing the NASA Permissible Exposure Limits (PELs), which stated the career radiation limit of 3% Risk of Exposure Induced Death (% REID) at the 95% confidence level (CL), the NRC noted (NRC 2008), *"The committee strongly recommends that the permissible exposure limits specified in the current NASA radiation protection standards not be violated to meet engineering resources available at a particular level of funding."* Cucinotta notes, "These external safety recommendations to NASA were focused on deep space missions, however it is shown in this report that similar concerns hold for multiple or long-term (1 year or longer) ISS missions especially for missions near solar minimum were dose-rates dominated by GCR can approach 1 mSv/day and about 2-fold higher than missions near solar maximum for similar ISS altitudes."

The NCRP Commentary-23 (NCRP 2014) published in 2014, supported the use of the NSCR model for evaluation of risks for both ISS and short-term lunar missions. The principle of as low as reasonably achievable (ALARA) is applied after radiation limits are already projected to be met to further reduce exposures and risk. ALARA is in essence a call for an ongoing negotiation prior and during a mission to reduce radiation exposure; a negotiation between health and safety experts with mission directors and engineers controlling a mission, who have potential competing conflicts of interest. A large focus of the NCRP Commentary was on possible efforts to implement ALARA, however we suggest ALARA efforts would have a reduced effectiveness with a waiver process eliminating radiation limits in-place at NASA.

6. Conclusions

In conclusion, we find that the NAS Report under-values or ignores information that suggests risks could be quite high and takes a giant leap backwards through a proposed effective dose limit, and a waiver process that is likely to lead to violation of each of the three principles of radiation protection.

The current radiation limits would not prevent female astronauts from participating in largely all missions planned for the current decade, while sufficient investments in the near-term could help to more completely understand risks for missions in the next decade. We also recommend that the relative level of investments in radiation protection and radiobiology be comparable to other flight safety issues being analyzed in-light of the similar fatality risk that could be allowed by NASA and should be openly reported to the public.

Considering uncertainties in projection models of GCR suggests both male and female astronauts could exceed a 3% fatality risk for a 600 mSv effective dose, and possibly incur clinically significant deterministic effects (tissue reactions). Therefore, we disagree with the NAS recommendation to ignore uncertainties in risk projections, which would also contradict earlier recommendations by the NCRP and NAS. Uncertainty analysis has progressed in recent years in that we can focus on specific issues that need to be addressed; non-targeted effects, the possible higher lethality of tumors produced by high LET radiation, tissue specific risk assessments, cognitive detriments, circulatory diseases, and possibility of leukemia's and vision impairing cataracts during long space missions. NASA should make sufficient investments to understand risks and reduce uncertainties in these areas, while discovering possible countermeasures. The knowledge to understand these aspects of space radiation risks would logically not only lead to approaches to reduce uncertainties and develop counter-measures, but also to the determination of the level of countermeasures needed to obtain acceptable risk levels for exploration mission female and male crew.

We support the notion that men and women should have the same opportunities for professional advancement, and each should understand clearly what is scientifically known about the potential combined hazards in their mission, and what levels of risk uncertainties exist in their estimation. However, it is a fundamental fact of nature that men and women, exposed to the same quantity and/or quality of radiation, do not always incur the same risks, or the same combined risks (e.g., to microgravity and radiation) to each tissue type or physiological system in the body. The NAS report, while concurring with the equal opportunity requirement, fails to address the consequence of their recommendations that leads to unequal risks for men and women and that, therefore, NASA risk management has to accept different limits or, if they exist, compensating countermeasures for each.

It is necessary to emphasize that limits on radiation exposure are calculated **predictions** for any given mission and that a waiver would have to be issued prior to any mission for which the predicted risk exceeds accepted limits. If radiation exposure **during a mission** exceeds the calculated risk for that mission, such as might be caused by an unexpected solar event during an extra-vehicular activity (EVA), the rationale for aborting or not the mission needs to be documented, and the unplanned radiation incident (or accident) needs to be investigated by proper procedures, but should not be dismissed with a waiver.

In addition, due to HIPAA privacy rules, both the NASA and the NAS report ignore individual differences among females of the same age, such as ethnic background, sexual activity, childbearing history, as well as other differences that apply to both men and women such as, body mass, muscle tone, medical history, lifestyle choices such as smoking, alcohol or drug use, and other factors leading to possibly large inter-individual differences in the risks incurred by exposure to radiation in space. More generally, the use of a generic "35-year old female" to replace consideration of the individual risk of every astronaut is a critical break with well-established risk management practices that have been vetted by responsible international advisory groups for many decades.

Based on NCRP Report No. 167 (NCRP 2010) it is not clear that employees such as astronauts can sign waivers to assume risks such as severe morbidity or death due to radiation exposure under current U.S. Labor Laws. Beyond this potential barrier, an unstated assumption made in the discussion of waivers is that they may be issued by NASA. This is fundamentally unethical, since it allows NASA to decide that an astronaut may be exposed to any quantity of radiation and violates the assumption of risk constraints. The only ethical way to proceed with a waiver is if it is granted by an authority independent of the employer and the employee, that has examined the interests of all individuals affected (including family, friends, and the public) as is done by properly functioning Institutional Review Boards. By recommending that NASA "develop a protocol for waivers" the NAS panel has relinquished its duty to provide solid ethical guidance with oversight, regardless of the qualification that it be "judicious, transparent, and informed by ethics."

Declaration of Competing Interest

None.

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