PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing the health effects associated with occupational radiation exposure in Korean radiation workers: protocol for a prospective cohort study
AUTHORS	Seo, Songwon; Lim, Wan Young; Lee, Dal Nim; Kim, Jung Un; Cha, Eun Shil; Bang, Ye Jin; Lee, Won; Park, Sunhoo; Jin, Young Woo

VERSION 1 – REVIEW

REVIEWER	Robert Daniels National Institute for Occupational Safety and Health, USA
REVIEW RETURNED	08-May-2017

GENERAL COMMENTS	A significant limitation of the current study is that the planned collection of self-reported information appears limited to a baseline survey; therefore, longitudinal information on coexposures and other risk factors will not be available. This is in stark contrast to the authors' claim of obtaining: "…comprehensive information on potential confounding variables …" The collection of these data are only possible using a prospective designs, as proposed by the authors, and would be a marked improvement on existing data on radiation health effects in the workplace; therefore, it is unclear why the use of periodic questionnaires is excluded in the proposed study. Another advantage of periodic follow-up is the ability to prospectively recruit newly hired radiation workers into the study cohort. It is unclear why this was not considered given the prospective design. Specific Comments: Lines 90-108. The introduction is confusing. It seems to suggest that the large pooled studies are less informative than single country studies, which is clearly not the case. Line 95. Misspelling of the word: "countries". Line 116. Suggest revising the Sentence to: "For Korean radiation workers …" given that there are many studies of workers from other nations. Also, I assume you are referring to healthy worker selection into the cohort (i.e., the "hire effect"), which is typically seen as a deficit in risk in an occupational cohort compared to an external referent population (i.e., SIRs and SMRs <1). Contrary to the author's claim, the healthy worker hire effect was not evident for cancer incidence among radiation workers in Jeong et al. (2010), who reported cancer SIRs above unity for all but liver cancer.

	However, the bias was clearly evident in SMRs reported by Ahn et al. (2008). This was not unexpected for a cancer mortality study with mean followup less than 8 years. Line 117. The phrase, “predominantly retrospective” is somewhat confusing. First, as worded, it seems to suggest that a retrospective study is most vulnerable to “healthy worker effects and provide limited evidence of radiation-related cancer risk due to short follow-up and limited information on confounding variable.” Of course these limitations also apply to prospective designs. Furthermore, excluding the previous contribution to the 15 country study, there have been 2 studies of Korean radiation workers (Ahn et al., 2008; Jeong et al., 2010). Ahn et al., is clearly a historical cohort study (i.e., retrospective). However, the most recent study (Jeong et al., 2010) recruited participants from a questionnaire and clinical health survey conducted during the followup period (1992-2005). This is similar to the design proposed for the current study and by definition a prospective study. Thus there seems to be one of each study design type. Consider replacing the sentence with: For Korean radiation workers, sparse information is available from two studies that are limited by short follow-up and sparse information on confounding variables.[18, 19]” Line 157. The periodicity of the self-administered questionnaire is not defined. Is this questionnaire only used at baseline? If so, then there is no longitudinal information on comorbidities, coexposures, and potential confounders, which is a significant limitation. Line 221. Please be more explicit on the list of variables to be compared in validation studies. The term “some items” is not informative. Line 231. Specific outcomes of a priori interest should be listed. What hypotheses are being tested? Currently the authors point only toward “ … incidence of cancer or non-cancer diseases (such as cataracts and circulatory disease), and mortality.” Line 233. Specific hypotheses related to particular biomarkers in the NHISS should be stated. As currently written, biomarkers appear to be an afterthought that the authors will consider at a later date. Which biomarkers will be used for what outcomes and why? Line 237. The term “dose” is ambiguous. Do you mean effective, equivalent or absorbed dose? Do you mean cumulative dose or annual dose? Here I assume you mean the cumulative dose (sievert) from summing annual total effective doses both from external and internal exposures, as reported by the National Dose Registry. Line 241. The exposure metric planned for analysis should be clearly stated. For example the term “organ dose” could represent absorbed dose or equivalent dose. For epidemiologic purposes, absorbed dose is preferred. At a minimum, some discussion on the expected contribution from high-LET radiations (e.g., neutrons) should be provided. Line 249. It is not clear whether data collection by subsequent questionnaires will also occur at each follow-up interval. If not, then there is no longitudinal information on important confounders. Thus, prospective data collection appears limited to periodic linkages with the National Cancer Registry, National Vital Statistics Registry, and the NHISS.

REVIEWER	LEURAUD Klervi IRSN, France
REVIEW RETURNED	23-May-2017

GENERAL COMMENTS	This paper presents the protocol of a new cohort of radiation workers in the Republic of Korea. It is overall informative, even if some important information is missing, notably on the period of follow-up and the way in which the duration of employment will be addressed. The manuscript would gain in clarity in re-organizing the content of the sub-sections. INTRODUCTION The rationale for setting up the cohort is well explained. Line 90-91: The authors use “radiation workers” to refer to medical radiation workers (given references [7] and [8] cited line 98) and to nuclear-related workers (given references [4-6] and [9-12] line 98). Later, the term “radiation workers” is dedicated to nuclear-related workers (line 113). The terminology should be streamlined. Line 95: the argument given line 95 should be tempered. I do not agree that “results from most studies were inconsistent across counties”. Instead, it appears that in general results are consistent among the different national studies (except few ones). Line 98: it is surprising that the NRRW study (Muirhead et al. 2009) and the recent U.S. study of a pooled nuclear worker cohort (Schubaueur-Berigan et al. 2015) are not cited; they should be. Line 104: I do not agree that the “heterogeneity of baseline risk” in INWORKS could question the validity of the results in the very low-dose range. The heterogeneity of baseline risks, if any, was handled for by an appropriate stratification. Line 119: the authors should precise what “non-destructive testing” means (what type of occupation). METHODS AND ANALYSIS This section would gain in clarity in being better organized, with a section to describe the study population, a section to describe the survey questionnaire, a section to describe the dosimetry data with sources, a section to describe the health outcomes with sources, a section to describe the statistical analysis plan, a section with the limits of the study, and finally the discussion on the potential impact and future work. Study population Workers registered in the NSSC on the 2016-2017 period are eligible for the study. It should be informative to know when nuclear activities started in the Republic of Korea and which part of the overall population of radiation workers the selected population represents. Moreover, is there any idea of the proportion of women in the selected population? Line 143: use of future tense is no more suitable. Line 148-155: this information should not be given at this stage but later once the sources and types of data have been introduced. Line 149: the terminology “secondary health data” is not common, it is not obvious why this data is secondary.

	Survey questionnaire Is it planned that this questionnaire will be administered again to participants in the future or is a unique questionnaire? In the “occupational history” category (Table 1), “calendar year of entry” should be replaced by “calendar year of hiring” to avoid confusion with entry in the study. Information on duration of employment from the questionnaire is truncated at the date of the survey. Consequently, it cannot be used in the analyses if no further data is available in the future to update this variable. How do the authors conceive the way to take account of duration of employment in the future analyses? Duration of employment is an important variable to partially control for the healthy worker survivor effect. Sample size calculation This section should be moved after the description of sources of data and linkage; it concerns the statistical methods section. The method is not clear and should be explained more explicitly: what is the model (effect of dose) applied? Analysis plan The description of data linkage has nothing to do with the description of the analyses. A section should be devoted to all dosimetry aspects (sources of data, types of radiation, calculation of absorbed organ doses found lines 242-244). Some details could be provided on the way exposure to ionizing radiation has been measured since 1984. Line 202-212: It is not explained how health events that occurred before 1991 will be known. Does it mean that the follow-up will begin in 1991? This must be clarified. Lines 232-235: will the biomarkers be used as outcomes or adjustment variables? Lines 236-240: the external analysis (SIR, SMR) should be presented first and then, after, the internal analysis. Lines 243-244: the description of how the organ doses will be estimated is unclear. Line 246: explain ERR and EAR, not defined beforehand The description of the analyses lacks precision; for example, we do not know when the follow-up begins and we do not know how the problem of lost to follow-up will be treated. The limits of the study could be gathered in a devoted section.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment: A significant limitation of the current study is that the planned collection of self-reported information appears limited to a baseline survey; therefore, longitudinal information on coexposures and other risk factors will not be available. This is in stark contrast to the authors' claim of obtaining: "…comprehensive information on potential confounding variables …" The collection of these data are only possible using a prospective designs, as proposed by the authors, and would be a marked improvement on existing data on radiation health effects in the workplace; therefore, it is unclear why the use of periodic questionnaires is excluded in the proposed study.
Another advantage of periodic follow-up is the ability to prospectively recruit newly hired radiation workers into the study cohort. It is unclear why this was not considered given the prospective design.

Response: Thanks for the comment. We plan to use self-administered questionnaire surveys at five-year intervals to update information on existing study subjects and recruit newly hired workers. Following your comment, we have included more details about the study design and methods, and have reorganized subsections to give a better explanation of our study protocol.

Comment: Lines 90-108. The introduction is confusing. It seems to suggest that the large pooled studies are less informative than single country studies, which is clearly not the case.

Response: Thanks for raising this point. We agree that large pooled studies provide more information than single-nation studies. We wanted to highlight the necessity of a single-nation study for obtaining risk estimates that reflect each country's own characteristics. To clarify this, we have added a statement about the advantage of large pooled studies and modified the sentences in order to avoid any misunderstanding as follows [lines 103-113]: "Although these international efforts have been able to accumulate scientific evidence of health effects in occupationally exposed populations and provided more precise dose-response estimates than single-nation studies, findings from these studies at low-dose ranges, particularly <100 mSv, should be still interpreted with caution due to wide confidence intervals for risk estimates and limited information on confounders. Moreover, given that baseline risks possibly differ from nation to nation, generalizations of the findings to other populations should be made with caution. Thus, to supplement international collaborative studies, it is important to evaluate the health effects of low-dose ionizing radiation in national studies reflecting the characteristics of the particular country, including comprehensive information on confounding factors."

Comment: Line 95. Misspelling of the word: "countries".

Response: Thank you for pointing out the typo. We have revised this sentence since another reviewer pointed out that the sentence "findings from most studies were inconsistent across countries" might be somewhat subjective and controversial. Hence, in order to avoid any misunderstanding, we have modified this sentence with more specific terms, and the modified sentence does not include the word "countries" [lines 95-97].

Comment: Line 116. Suggest revising the Sentence to: "For Korean radiation workers …" given that there are many studies of workers from other nations. Also, I assume you are referring to healthy worker selection into the cohort (i.e., the "hire effect"), which is typically seen as a deficit in risk in an occupational cohort compared to an external referent population (i.e., SIRs and SMRs <1). Contrary to the author's claim, the healthy worker hire effect was not evident for cancer incidence among radiation workers in Jeong et al. (2010), who reported cancer SIRs above unity for all but liver cancer. However, the bias was clearly evident in SMRs reported by Ahn et al. (2008). This was not unexpected for a cancer mortality study with mean followup less than 8 years.

Response: We agree with your comment. Accordingly, we have modified this sentence as follows [lines 121-123]: “For Korean radiation workers, sparse information is available from two studies that are limited by short follow-up and sparse information on confounding variables.”

Comment: Line 117. The phrase, “predominantly retrospective” is somewhat confusing. First, as worded, it seems to suggest that a retrospective study is most vulnerable to “healthy worker effects and provide limited evidence of radiation-related cancer risk due to short follow-up and limited information on confounding variable.” Of course these limitations also apply to prospective designs. Furthermore, excluding the previous contribution to the 15 country study, there have been 2 studies of Korean radiation workers (Ahn et al., 2008; Jeong et al., 2010). Ahn et al., is clearly a historical cohort study (i.e., retrospective). However, the most recent study (Jeong et al., 2010) recruited participants from a questionnaire and clinical health survey conducted during the followup period (1992-2005). This is similar to the design proposed for the current study and by definition a prospective study. Thus there seems to be one of each study design type. Consider replacing the sentence with: For Korean radiation workers, sparse information is available from two studies that are limited by short follow-up and sparse information on confounding variables.[18, 19]”

Response: We agree with your comment. Accordingly, we have modified this sentence as shown in the reply to the previous comment.

Comment: Line 157. The periodicity of the self-administered questionnaire is not defined. Is this questionnaire only used at baseline? If so, then there is no longitudinal information on comorbidities, coexposures, and potential confounders, which is a significant limitation.

Response: Thanks for raising this point. As stated in our reply to comment #1, our description of the study design was not explicit. We have clearly stated the periodicity of the self-administered questionnaire survey in the revised manuscript as follows [lines 158-161]: “We will continue to conduct the self-administered questionnaire survey at five-year intervals to update information on existing study participants, recruit newly hired workers, and evaluate the association between radiation dose and health effects on long-term follow-up.”

Comment: Line 221. Please be more explicit on the list of variables to be compared in validation studies. The term “some items” is not informative.

Response: We appreciate your comment. We now provide a list of variables in the revised manuscript [lines 229-231].

Comment: Line 231. Specific outcomes of a priori interest should be listed. What hypotheses are being tested? Currently the authors point only toward “ … incidence of cancer or non-cancer diseases (such as cataracts and circulatory disease), and mortality.”

Response: The primary purpose of the study is to evaluate the association between occupational exposure and cancer incidence among Korean radiation workers, since cancer is expected to be the most frequent radiation-induced health outcome and to provide more statistically relevant results (this is a typical endpoint in radiation epidemiology).We have specified the primary outcome in the revised manuscript [line 241]. In addition, since health effects from protracted low dose exposure are still poorly known, we plan to explore the association between exposed dose and all available health outcomes, which is a common approach in radiation epidemiological studies.

Comment: Line 233. Specific hypotheses related to particular biomarkers in the NHISS should be stated. As currently written, biomarkers appear to be an afterthought that the authors will consider at a later date. Which biomarkers will be used for what outcomes and why?

Response: Due to the nature of the health outcomes (e.g., cancer and circulatory disease) and young cohort, long-term follow-up will be necessary to draw firm conclusions about radiation-induced diseases. Therefore, we plan to use laboratory biomarkers (i.e., laboratory test items in the NHISS) as surrogate endpoints for health outcomes. Similar to the reply to the previous comment, we plan to look into all available laboratory test items in order to explore possible health effects from radiation exposure. Because we are not able to access this database at this stage, the information we can provide is limited. Following your comment, we now provide specific laboratory test items in Table 2, and include an example explaining the rationale and the use of laboratory test items in the revised manuscript [Table 2, lines 246-249].

Comment: Line 237. The term “dose” is ambiguous. Do you mean effective, equivalent or absorbed dose? Do you mean cumulative dose or annual dose? Here I assume you mean the cumulative dose (sievert) from summing annual total effective doses both from external and internal exposures, as reported by the National Dose Registry.

Response: Thanks for highlighting this point. The control group will consist of workers whose effective doses have not exceeded 0.1 mSv/quarter for external exposure and 0.1 mSv/year for internal exposure during their employment according to the National Dose Registry. We have added this information to the revised manuscript [lines 253-256].

Comment: Line 241. The exposure metric planned for analysis should be clearly stated. For example the term “organ dose” could represent absorbed dose or equivalent dose. For epidemiologic purposes, absorbed dose is preferred. At a minimum, some discussion on the expected contribution from high-LET radiations (e.g., neutrons) should be provided.

Response: We appreciate your comment. Accordingly, we have changed “organ dose” to “absorbed organ dose” [lines 204-205].
In terms of high-LET radiation (e.g., neutrons), we have very limited information because relevant data have not been reported to the National Dose Registry. Based on the limited number of companies working with high-LET radiation and empirical knowledge from regulatory experts, the number of workers exposed to high-LET would be expected to be less than 5% of all Korean radiation workers. We have mentioned this point in the section on dosimetry data as follows [lines 193-198]: “It might be challenging to ensure the inclusion of radiation doses from high-Linear Energy Transfer (LET) exposure in the current Korean dose reporting system; however, since the proportion of workers with potential high-LET exposure is expected to be less than 5%, the impact of high-LET exposure on risk estimates would be minimal”.

Comment: Line 249. It is not clear whether data collection by subsequent questionnaires will also occur at each follow-up interval. If not, then there is no longitudinal information on important confounders. Thus, prospective data collection appears limited to periodic linkages with the National Cancer Registry, National Vital Statistics Registry, and the NHISS.

Response: As in our answer to comment #1, we realized that our description of the study design was not explicit. We plan to conduct the self-administered surveys subsequently and long-term follow-up of health status on a regular basis. We now clearly state the periodicity of the self-administered survey in the revised manuscript [lines 158-161].

Reviewer: 2

Comment: This paper presents the protocol of a new cohort of radiation workers in the Republic of Korea. It is overall informative, even if some important information is missing, notably on the period of follow-up and the way in which the duration of employment will be addressed. The manuscript would gain in clarity in re-organizing the content of the sub-sections.

Response: We thank you for your thoughtful critique of the manuscript. We have reorganized the content of the sub-sections as per your suggestion and addressed all your comments below.

INTRODUCTION
The rationale for setting up the cohort is well explained.

Comment: Line 90-91: The authors use “radiation workers” to refer to medical radiation workers (given references [7] and [8] cited line 98) and to nuclear-related workers (given references [4-6] and [9-12] line 98). Later, the term “radiation workers” is dedicated to nuclear-related workers (line 113). The terminology should be streamlined.

Response: Workers in radiation-related occupations except those in medical diagnostics are officially termed “radiation workers” in Korean law. To clarify between the use of the term “radiation workers” as a general term and as a descriptor for our study population, we now use the phrase ‘workers in radiation-related occupations’ as the general term [lines 90, 114].

Comment: Line 95: the argument given line 95 should be tempered. I do not agree that “results from most studies were inconsistent across counties”. Instead, it appears that in general results are consistent among the different national studies (except few ones).

Response: Thanks for raising this issue. We agree that, in general, results are consistent among different national studies. In order to avoid an misunderstanding due to our statement about “inconsistency of results from different studies”, we have modified the sentence as follows [lines 93-97]: “Due to large uncertainties inherent in low-dose radiation studies, including incomplete information on radiation dose, limited sample size, and lack of information on confounders, the evidence for an association with radiation, particularly for organ-specific risks, was weak in most studies and more precise risk estimates should be obtained.”

Comment: Line 98: it is surprising that the NRRW study (Muirhead et al. 2009) and the recent U.S. study of a pooled nuclear worker cohort (Schubaueur-Berigan et al. 2015) are not cited; they should be.

Response: Thanks for your recommendation. We have incorporated these articles as references [lines 100-101] in the revised manuscript.

Comment: Line 104: I do not agree that the “heterogeneity of baseline risk” in INWORKS could question the validity of the results in the very low-dose range. The heterogeneity of baseline risks, if any, was handled for by an appropriate stratification.

Response: Thanks for your comment. We did not mean to question the validity of the INWORKS results. We wanted to describe the uncertainty of results in low-dose ranges. To avoid misleading our readers, we have deleted the phrase “heterogeneity of baseline risk”. In addition, we have noted the issue of generalizing findings from one study population to another to explain the necessity of single-nation studies [lines 105-110].

Comment: Line 119: the authors should precise what “non-destructive testing” means (what type of occupation).

Response: To avoid any confusion, we have changed “non-destructive testing” to “industrial radiography”, and “non-destructive testing worker” to “industrial radiographer” in the revised manuscript.

METHODS AND ANALYSIS
Comment: This section would gain in clarity in being better organized, with a section to describe the study population, a section to describe the survey questionnaire, a section to describe the dosimetry data with sources, a section to describe the health outcomes with sources, a section to describe the statistical analysis plan, a section with the limits of the study, and finally the discussion on the potential impact and future work.

Response: Following your very valuable comment, we have reorganized the suggested sections. We have described statistical analysis methods separately according to analytical purpose e.g. validity and reliability of self-administered questionnaires, and health risk associated with ionizing radiation exposure are described separately.

Study population
Comment: Workers registered in the NSSC on the 2016-2017 period are eligible for the study. It should be informative to know when nuclear activities started in the Republic of Korea and which part of the overall population of radiation workers the selected population represents.
Moreover, is there any idea of the proportion of women in the selected population?

Response: As the beginning of nuclear activities in Korea, a research reactor was first introduced at1962, and the first nuclear power plant opened in 1978. The study population includes all radiation workers except those working with medical diagnostics. The proportion of women is expected to be less than 10%. This additional information is now included in the study limitations of the revised manuscript [lines 285-288, 293-296].

Comment: Line 143: use of future tense is no more suitable.

Response: We have changed the future tense to the present tense as suggested [line 149].

Comment: Line 148-155: this information should not be given at this stage but later once the sources and types of data have been introduced.

Response: Thanks for pointing this out. We absolutely agree with you, but to facilitate the reader’s understanding of the study, it would be more appropriate to provide this information in the study design section. We have deleted all redundant information in the later sections.

Comment: Line 149: the terminology “secondary health data” is not common, it is not obvious why this data is secondary.

Response: Secondary data refers to data collected by someone else for a purpose different from that of our study. In other words, it involves the re-use of data, which were collected through previous research or surveys (please refer to http://www.esrc.ac.uk/news-events-and-publications/news/news-items/new-impacts-from-old-data/).

In our study, data in the national cancer registry, the national vital statistics registry, and the national health insurance sharing service were originally collected for administrative purposes, and not for research purpose. Therefore, we used the term “secondary health data”. Following your comment, to avoid confusion with a general understanding of “secondary”, we have deleted “secondary” in the sentence.

Survey questionnaire
Comment: Is it planned that this questionnaire will be administered again to participants in the future or is a unique questionnaire?

Response: Indeed, the survey questionnaire will be administered at five-year intervals. We have explained this plan more explicitly at the end of the section on the Study population and design [lines 158-161].

Comment: In the “occupational history” category (Table 1), “calendar year of entry” should be replaced by “calendar year of hiring” to avoid confusion with entry in the study.

Response: We have changed “calendar year of entry” to “calendar year of hiring” [Table 1].

Comment: Information on duration of employment from the questionnaire is truncated at the date of the survey. Consequently, it cannot be used in the analyses if no further data is available in the future to update this variable. How do the authors conceive the way to take account of duration of employment in the future analyses? Duration of employment is an important variable to partially control for the healthy worker survivor effect.

Response: Thanks for your query. Once radiation workers are recruited to the cohort, we are able to continuously follow up their employment from the Central Registry for Radiation Worker Information. Thus, we can get information on the duration of employment after the date of the survey.

Sample size calculation
Comment: This section should be moved after the description of sources of data and linkage; it concerns the statistical methods section.
The method is not clear and should be explained more explicitly: what is the model (effect of dose) applied?

Response: We have moved this section to the end of “METHOD AND ANALYSIS”. Regarding estimating a detectable effect size, for the purpose of simplicity, we used a Poisson regression model comparing the incidence of all cancers combined between two groups (exposed group and control group). In general, this approach is statistically conservative, possibly increasing statistical power when a continuous value of radiation dose is applied for a dose-response analysis. However, we have decided to delete this description in the revised manuscript because this calculation concerns only this year’s study population, and may create confusion about the periodicity of the self-administered questionnaire and continuous enrollment of workers in the cohort [line 273].

Analysis plan
Comment: The description of data linkage has nothing to do with the description of the analyses.

Response: We have deleted the section title “Analysis plan”, and reorganized the following sections for more details: Dosimetry data and health outcomes, Validity and reliability of self-administered questionnaires and Health risk associated with ionizing radiation exposure

Comment: A section should be devoted to all dosimetry aspects (sources of data, types of radiation, calculation of absorbed organ doses found lines 242-244). Some details could be provided on the way exposure to ionizing radiation has been measured since 1984.

Response: We have reorganized this section, specifying sources of dosimetry data and health outcomes. Because we are not able to access the dosimetry database at this stage, the information we can provide is limited. Following your comment, we have now included some details about dose measurements based on relevant published articles [lines 191-198, 203-209].

Comment: Line 202-212: It is not explained how health events that occurred before 1991 will be known. Does it mean that the follow-up will begin in 1991? This must be clarified.

Response: To analyze the dose-response relationship for cancer incidence, the follow-up starting date is the first exposure date or 1 January 1992, whichever occurred later. This is because the national cancer registry did not fully ascertain cancer incidence for all cities in Korea until 1991. We have corrected 1991 to 1992 in the sentence [line 214], and clarify the follow-up in the revised manuscript [lines 264-268].

Comment: Lines 232-235: will the biomarkers be used as outcomes or adjustment variables?

Response: The laboratory biomarkers (i.e., laboratory test items) from the NHISS databases will be mainly used as surrogate endpoints for health outcomes. However, they could be used as adjustment (independent) variables as well for a sensitivity analysis (e.g., interaction effect between radiation exposure and indicators of metabolic syndrome with regard to cardiovascular disease) [lines 246-249].

Comment: Lines 236-240: the external analysis (SIR, SMR) should be presented first and then, after, the internal analysis.

Response: We have changed the order of the external and internal analyses in that sentence [lines 251-256].

Comment: Lines 243-244: the description of how the organ doses will be estimated is unclear.

Response: Thanks for your comment. We have described this more specifically with relevant references in the section on dosimetry and health outcomes as follows [lines 205-209]: “Absorbed organ dose is estimated based on methods using the ICRP 116 organ dose conversion coefficients and irradiation geometry factors,[30] considering information about work practices, such as use of protective devices and badge location, from the nationwide survey as suggested by the Million Worker Study (MWS)[31] and the USRT study.[32]”

Comment: Line 246: explain ERR and EAR, not defined beforehand

Response: We have explained ERR and EAR in the revised manuscript as follows [lines 256-260]: “Risk estimates for radiation exposure are typically presented as excess relative risk (ERR) and excess absolute risk (EAR). The ERR is the relative risk minus 1.0, which refers to the magnitude of the radiation risk relative to the baseline. The EAR refers to the difference between the rate in an exposed and an unexposed population.”

Comment: The description of the analyses lacks precision; for example, we do not know when the follow-up begins and we do not know how the problem of lost to follow-up will be treated.

Response: We have added more details about calculating person-years and latency periods [lines 264-271]. Considering that the national health registries cover the whole Korean population and the completeness of cancer incidence for 2012 was 97.7% (Jung et al., 2015), loss to follow-up of health status would be minimal.

Comment: The limits of the study could be gathered in a devoted section.

Response: Thanks for your recommendation. We now have a separate section on study limitations for more details including limited information about female workers and workers whose exposed dose is not available from the electronic National Dose Registry [lines 278, 285-288, 293-296].

VERSION 2 – REVIEW

REVIEWER	Robert Daniels National Institute for Occupational Safety and Health (NIOSH). USA
REVIEW RETURNED	05-Jul-2017

GENERAL COMMENTS	The authors have adequately addressed my comments following review of the previous draft. I have also reviewed the changes made in response to comments made by other reviewers and all seem appropriate. I have no further comments on the revised manuscript.

REVIEWER	LEURAUD Klervi IRSN, France
REVIEW RETURNED	26-Jul-2017

GENERAL COMMENTS	The manuscript is now better organized than in its former version. My concern is about the definition of doses. The description of doses is unclear and I need to be convinced that suitable quantities will be used in the dose-response analyses. Effective doses are indeed not appropriate to derive health risk estimates. Line 93-97 : This sentence (from “Due to…” up to “… obtained”) disrupts the logical sequence of arguments, i.e., nuclear worker studies have been performed (lines 90-93), these studies – either national or international – have provided certain results (lines 97-102), however these studies have limitations due to limited information on confounders, etc. (lines 103-110), thus it is important to conduct national studies focusing on confounding factors (lines 103-110). So, I would delete this sentence as it is a somewhat redundant (limited power and limited information on confounders) with lines 105-108. Line 97: Reference 3 does not seem appropriate. Line 124: A word is missing after (NDT). Line 125: I am not sure the phrasing is correct (“to account” instead of “accounts”?) Line 143: the nature of the dose should be specified.

	Line 149: “visited” instead of “visit”? Line 151: the authors could add “(described below)” after “informed consent” to inform the reader that this survey is going to be described. Line 185: The section about dosimetry data and the section about health outcomes should be separated. Lines 185-209: Dosimetry data: this section must be clarified. First, the authors state that “external and internal doses are collected” in the National Dose Registry. Regarding internal doses, more information is needed on, for example, the nature of doses in the registry and the completeness of data. Are all workers regularly monitored in regards to risk of radionuclide intake? In summary, the reader needs information allowing assessing the potential of this data. It is well known that calculating doses due to radionuclides intake is a real challenge, especially on a large scale, and worker studies are sometimes hampered by lack of data on internal contamination. Moreover, I do not think it is feasible to estimate organ absorbed doses from committed effective doses, so how do the authors consider handling internal doses in the estimation of health risks? Second, regarding external exposure: in ref 28, the authors describe “personal dose equivalents” measured by individual dosimeters and in the manuscript, the authors mention “effective doses”. The authors should clearly precise the nature of doses and the type of radiation (photons?). It is not clear why doses due to neutrons are not taken into account: is it because they cannot be separated from the photon doses or because they are not reported in the registry? And if the doses cannot be estimated, would it be possible to identify the workers with neutron doses to conduct sensibility analyses? Regarding organ absorbed doses, they are estimated from operational quantities such as personal dose equivalents (Hp(d)), not from effective doses. I think it is important to accurately describe the type of available data. Line 204: “organ absorbed dose”, instead of “absorbed organ dose” (ICPR) Line 226: I am not sure the phrasing is correct. Lines 233-236: these two sentences could be combined in a way that avoids repetitions. What will be the approach if the comparison shows that the answers to the self-questionnaire differ from information in the national databases? Line 253: Effective doses are not the quantities to be used to derive risk estimates in epidemiological studies, they “serve as the basis for the contractual relationship in the regulatory framework” (ICRP). Lines299-301: is it planned that retired workers will be included in the study in the future (the phrasing suggests it)?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Robert Daniels
Institution and Country: National Institute for Occupational Safety and Health (NIOSH), USA
Competing Interests: None declared

Comment: The authors have adequately addressed my comments following review of the previous draft. I have also reviewed the changes made in response to comments made by other reviewers and all seem appropriate. I have no further comments on the revised manuscript.

Response: Thank you very much for your time and effort for the review of the manuscript.

Reviewer: 2
Reviewer Name: LEURAUD Klervi
Institution and Country: IRSN, France
Competing Interests: None declared

Comment: The manuscript is now better organized than in its former version. My concern is about the definition of doses. The description of doses is unclear and I need to be convinced that suitable quantities will be used in the dose-response analyses. Effective doses are indeed not appropriate to derive health risk estimates.

Response: As we described in the dosimetry section (Dosimetry data and health outcomes in the previous manuscript), organ absorbed dose will be used for the dose-response analyses. Effective dose will only be used to determine the control group (≤0.1mSv) for the internal comparison using SIRs or SMRs. To clarify this, we have changed “radiation dose” to “organ absorbed dose” in the section of Health risk associated with ionizing radiation exposure [line 269].

Comment: Line 93-97 : This sentence (from “Due to…” up to “… obtained”) disrupts the logical sequence of arguments, i.e., nuclear worker studies have been performed (lines 90-93), these studies

– either national or international – have provided certain results (lines 97-102), however these studies have limitations due to limited information on confounders, etc. (lines 103-110), thus it is important to conduct national studies focusing on confounding factors (lines 103-110).
So, I would delete this sentence as it is a somewhat redundant (limited power and limited information on confounders) with lines 105-108.

Response: We have deleted this sentence.

Comment: Line 97: Reference 3 does not seem appropriate.

Response: Thank you for pointing this out. There was an error when we used a software tool for managing the citations. We have deleted the reference.

Comment: Line 124: A word is missing after (NDT).

Response: We have added “technologies” after NDT to make it more grammatically correct [line 124].

Comment: Line 125: I am not sure the phrasing is correct (“to account” instead of “accounts”?)

Response: Thank you for pointing this out. We have corrected the phrasing [line 125].

Comment: Line 143: the nature of the dose should be specified.

Response: The nature of the dose is the effective dose, which is the sum of the external dose (Hp(10)) and the committed effective dose. The nature of the dose is now more explicit [lines 143-144 and 147].

Comment: Line 149: “visited” instead of “visit”?

Response: Thank you for pointing this out. We have corrected it as you have indicated [line 150].

Comment: Line 151: the authors could add “(described below)” after “informed consent” to inform the reader that this survey is going to be described.

Response: As per the reviewer’s suggestion, we have added the phrase to inform the readers that details on the survey are described in the following section, “Survey questionnaire and informed consent form” [lines 152-153].

Comment: Line 185: The section about dosimetry data and the section about health outcomes should be separated.

Response: Thank you for your suggestion. We have separated these descriptions in the revised manuscript.

Comment: Lines 185-209: Dosimetry data: this section must be clarified.
First, the authors state that “external and internal doses are collected” in the National Dose Registry. Regarding internal doses, more information is needed on, for example, the nature of doses in the registry and the completeness of data. Are all workers regularly monitored in regards to risk of radionuclide intake? In summary, the reader needs information allowing assessing the potential of this data. It is well known that calculating doses due to radionuclides intake is a real challenge, especially on a large scale, and worker studies are sometimes hampered by lack of data on internal contamination. Moreover, I do not think it is feasible to estimate organ absorbed doses from committed effective doses, so how do the authors consider handling internal doses in the estimation of health risks?

Response: Thank you for your comments. The radiation doses in the national dose registry are effective doses, which are the sum of the external dose (Hp(10)) and the committed effective dose. In Korea, reporting internal doses applies only to workers whose annual committed effective dose is likely to exceed 2 mSv/year. Because we are not able to access the dosimetry database for all radiation workers, we do not know the exact percentage of workers reporting their internal doses, but according to the empirical knowledge from regulatory experts based on the number of workers working for facilities at risk of radionuclide intake, the percentage of workers reporting their committed effective doses would be expected to be about 10% of all Korean radiation workers. Regarding estimating organ absorbed doses from committed effective doses, it is not feasible because we do not know details about the internal exposure such as exposure time and types of radionuclide. Thus, we are unable to use internal dose to estimate organ absorbed dose; however, it will be considered for sensitivity analyses for dose-response estimates (e.g., an adjusted analysis and stratified analysis using continuous or binary/categorical values of internal exposure). We have explained this usage of internal dose more explicitly in the revised manuscript [lines 201-203, 209-210, and 272-274].

Comment: Second, regarding external exposure: in ref 28, the authors describe “personal dose equivalents” measured by individual dosimeters and in the manuscript, the authors mention “effective doses”. The authors should clearly precise the nature of doses and the type of radiation (photons?). It is not clear why doses due to neutrons are not taken into account: is it because they cannot be separated from the photon doses or because they are not reported in the registry? And if the doses cannot be estimated, would it be possible to identify the workers with neutron doses to conduct sensibility analyses?

Response: Effective dose from external exposure in this study is personal dose equivalent, Hp(10), mostly from photon exposure. From the current national dose registry, we are not able to identify those who were exposed to neutrons because only Hp(10) are reported without distinguishing exposure to neutrons from exposure to photons [lines 198-199]. We may conduct a sensitivity analysis for workers whose facilities are related to neutrons, but there are also workers who were not exposed to neutrons among the workers working for neutron-related facilities. Since currently we are not able to distinguish between them, unfortunately, we are unable to assess the association between health risk and neutron doses at this stage; however, as per your valuable comments, we will consider adding a survey question about potential exposure to neutrons to future survey questionnaires for a sensitivity analysis.

Comment: Regarding organ absorbed doses, they are estimated from operational quantities such as personal dose equivalents (Hp(d)), not from effective doses. I think it is important to accurately describe the type of available data.

Response: Yes, we absolutely agree with your comments. The type of available data for estimating organ absorbed doses has been rewritten to be more explicit [lines 189-190 and 193-194].

Comment: Line 204: “organ absorbed dose”, instead of “absorbed organ dose” (ICPR)

Response: Thank you for pointing this out. We have corrected this accordingly.

Comment: Line 226: I am not sure the phrasing is correct.

Response: We have had a professional native English-speaking editor check the phrasing to ensure it is correct. We have changed one word (“has” to “contains”) on that line [line 236].

Comment: Lines 233-236: these two sentences could be combined in a way that avoids repetitions. What will be the approach if the comparison shows that the answers to the self-questionnaire differ from information in the national databases?

Response: Thank you for your suggestions. Validity and reliability will be conducted with different purposes and methods, although analysis methods are the same (i.e., external comparison for validity, and internal comparison for reliability in this study). Thus, we believe it is more appropriate that these two sentences be separated. Regarding the same items of the self-questionnaire and information in the national databases, we will basically use the information in the national databases because the national data would be more accurate in terms of incomplete memory recall or recall bias. The purpose of examining the discrepancy between the survey data and the national data is to explain (estimate) levels of validity in using the information from the self-questionnaire that do not belong to the national data.

Comment: Line 253: Effective doses are not the quantities to be used to derive risk estimates in epidemiological studies, they “serve as the basis for the contractual relationship in the regulatory framework” (ICRP).

Response: We absolutely agree with your comments. Effective doses will not be used for dose-response analyses for risk estimates per unit dose. The purpose of using effective dose in this study is to determine a control group for overall comparisons of SIR or SMR.

Comment: Lines299-301: is it planned that retired workers will be included in the study in the future (the phrasing suggests it)?

Response: Currently, there is no specific plan to include retired workers in this study, but we would possibly consider this for a future study [line 310].

VERSION 3 – REVIEW

REVIEWER	LEURAUD Klervi IRSN, France
REVIEW RETURNED	21-Aug-2017

GENERAL COMMENTS	No further comments