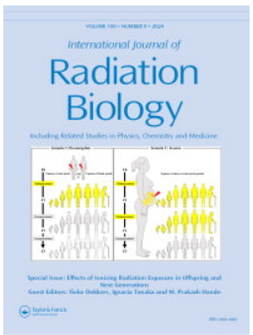

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REVIEW

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A systematic review of human evidence for the intergenerational effects of exposure to ionizing radiation

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ABSTRACT

Purpose: To provide a synthesis of the published evidence pertaining to the intergenerational health effects of parental preconceptional exposure to ionizing radiation in humans.

Methods: The study populations are the descendants of those who were exposed to ionizing radiation prior to conception. A Boolean search identified publications for review in accordance with Office of Health Assessment and Translation guidelines. Initially, a risk of bias assessment was conducted for each published study and relevant data extracted. Information was organized into adverse health outcome groups and exposure situations. To make an assessment from the body of evidence within each group, an initial confidence rating was assigned, before factors including inconsistencies between studies, magnitude of effect, dose response and confounders were considered. From this, 'an effect', 'no effect' or whether the evidence remained 'inadequate' to determine either effect or no effect, was ascertained. This assessment was based primarily upon the author's conclusions within that evidence-base and, by binomial probability testing of the direction of effect reported.

Results: 2441 publications were identified for review which after screening was reduced to 127. For the majority of the adverse health groups, we find there to be inadequate evidence from which to determine whether the health effect was, or was not, associated with parental preconceptional radiation exposure. This was largely due to heterogeneity between individual study's findings and conclusions within each group and, the limited number of studies within each group. We did observe one health grouping (congenital abnormalities) in occupationally exposed populations, where an increase in effect relative to their controls or large magnitude of effects, were reported, although it is noted that the authors of these studies interpreted their findings as most likely not to be associated with parental radiation exposure.

Conclusions: We find there to be a lack of evidence to enable the formal assessment of radiation-related adverse effects in offspring of exposed humans. This is not the same as there being no clear evidence that effects may occur but does infer that if adverse health effects do arise in children of exposed parents, then these effects are small and difficult to reproducibly measure. Inconsistencies in designing studies are unavoidable, however we highlight the need for an element of standardization and, more sharing of primary datasets as part of open access initiatives, in order for future reviews to make reasonable conclusions. Overall, there is a need for future work to ensure comparable measures between studies where possible.

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Ionizing radiation; transgenerational; intergenerational; health effect; preconception; hereditary; offspring

Introduction

The intergenerational effects of parental radiation exposure before conception in humans remain poorly understood and controversial. It was the major concern after the Japanese atomic bombings and more broadly, after Gardner et al (1990) reported a raised incidence of leukemia and non-Hodgkin's lymphoma among children living near the Sellafield nuclear facility which they associated with paternal exposure to radiation before conception. This became known as the 'Gardner hypothesis'. The current consensus from epidemiological studies however suggests human health not to be significantly affected (UNSCEAR 2001; ICRP 2007; Little et al. 2013; Boice 2020). By contrast, the evidence gained from cellular and animal studies generally support the presence of detrimental outcomes in unexposed offspring as a result of parental exposure

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to radiation, particularly when males are irradiated with ≥1Gy (UNSCEAR 2001).

Systematic reviews, previously more common in clinical settings, are now being used in academia. Given the process includes pre-defined inclusion and exclusion criteria as set out in a protocol, the potential for any selection bias is reduced as all studies which meet the criteria are included regardless of the results. Various regulatory bodies have published recommendations on how to effectively conduct a systematic review. One of these is the Office of Health Assessment and Translation (NTP-OHAT 2015), who provide detailed guidelines for reviews primarily within the field of toxicology i.e. for assessing the evidence regarding an exposure type and the adverse health effects surrounding this (Rooney et al. 2014).

A considerable number of studies have been published in the years since the publication of the reviews noted above, with the UNSCEAR review published in 2001. There is a need therefore to systematically gather all studies over this, and previous decades, to understand if anything new can be drawn from the literature using this approach. For this, the consequences of preconceptional exposure to all types and doses of ionizing radiation, including low linear energy transfer (LET) X-rays, beta-particles and gamma-rays and, high-LET alpha- particles and neutrons were examined. The exposure situations covered include occupational, A-bomb survivors, medical exposure excluding the treatment of cancer and environmental. Additionally, a broad range of health parameters are considered; pregnancy outcomes, genomic anomalies, solid cancers, non-solid cancers, non-cancer diseases and mortality. Our overall objective is to conduct a systematic review of the published evidence pertaining to the intergenerational health effects of parental preconceptional exposure to ionizing radiation in humans. This review covers the period from 1988–2018 and is extended from 2018–2022 by Amrenova et al (published in this Special Issue).

Methods

Guidelines for systematic reviews in environmental and toxicology research from the Office of Health Assessment and Translation/National Toxicology (OHAT/NT) were followed (NTP-OHAT 2015). OHAT guidelines integrate concepts from GRADE (Schünemann et al. 2008) and Cochrane (Higgins et al. 2023). The protocol is published in the international prospective register of systematic reviews (PROSPERO) under registration number 123237 in line with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) (Page et al. 2021).

Search strategy

A Boolean search construct was used across three databases: PubMed, Scopus and Web of Science. The key words focused around three areas relating to 'inheritance', 'ionizing radiation' and 'readout of the health effects'. The following search construct was used; (Transgenerational OR Trans-generational OR Transgeneration OR Trans-generation OR Intergeneration OR Inter-generation OR Hereditary OR Offspring OR Off-spring OR Preconception OR Pre-conception OR Preconceived OR Pre-conceived OR Descendant) AND (Radiation OR Irradiation OR 'Ionizing radiation' OR 'Ionizing radiation') AND (Instability OR 'health effect' OR Genetic OR Genomic OR Bystander OR By-stander OR Epidemiology OR Epidemiological OR non-targeted OR non-targeted). The original search was carried out on 20/03/2018 and included all articles from January 1988 through to March 2018. The follow up search was carried out on 19/02/2019 and the original cutoff date of 1988 was used with 'stillbirth' and 'congenital' added. All 'hits' were imported into a reference manager and 'duplicates' removed. Titles and abstracts were screened for eligibility by two independent reviewers and reference lists of all studies screened for any additional relevant studies. Authors were contacted to request full texts if articles were not available open access.

Inclusion/exclusion criteria

All study types where the study population were the offspring of exposed person(s), were included (Table 1). All types of ionizing radiation were considered, across all dose ranges and dose rates. Research published as original articles and peer reviewed in English since 1988 to 2018 (companion review includes studies published from 2018–2022, Amrenova et al. 2023) were considered eligible. When identified, companion and follow-up studies were treated as a single study and the most recent results synthesized within

Table 1. PECO Statement.

PECO Element	Evidence
Participants/ population	The human offspring or cellular material (excluding in vitro and ex vivo studies), and/or member(s) of subsequent generations, of a parent or parents exposed to ionizing radiation prior to conception of the relevant offspring.
Intervention(s), exposure(s)	All types of ionizing radiation including X-rays, Beta-particles, Gamma-rays, alpha-particles, and neutrons, for which exposure is documented as being prior to conception.
Comparator(s), control	The offspring or cellular material, and/or member(s) of subsequent generations, of unexposed parent or parents. For studies which only include a dose response model, the offspring or cellular material, and/or member(s) of subsequent generations of the lowest-dose-exposed parents prior to conception of the relevant offspring. In case-control risk assessment studies, where the control subjects do not meet the inclusion criteria of the relevant case, the comparator is the control.
Outcome(s)	Endpoints may be genetic and/or phenotypic, but must have a heritable component, thus a broad range of health outcomes are relevant. These include pregnancy outcomes, genomic anomalies, solid cancer, non-solid cancer, non-cancer diseases and mortality.

The PECO statement represents population (the exposure group of interest), exposure (the exposure situation of interest), comparator (the group of which the exposed are being compared), and outcome (study outcomes in relation to the exposure) (NTP-OHAT 2015).

Table 2. Risk of bias domains and question.

Number	Question	Bias domain
1	**Did the study design or analysis account for important confounding and modifying variables?**	Confounding Bias
2	**Can we be confident that parents were exposed before but not after conception?**	Detection Bias
3	**Were appropriate comparison groups used?**	Selection Bias
4	Were appropriate inclusion/exclusion criteria used?	Selection Bias
5	Are the reported exposures reliably without bias? Is dose information sufficiently detailed as to avoid bias?	Detection Bias
6	Were outcome data complete without attrition or exclusion from analysis?	Attrition/Exclusion Bias
7	Is the experimental design robust?	Detection Bias
8	Is data analysis, collation and interpretation rigorous?	Detection Bias
9	Is the evaluation consistent with the findings reported?	Detection Bias
10	Are the statistical methods used appropriate?	Other sources of Bias
11	Is there any evidence of publication bias?	Other sources of Bias

Questions 1–3 include 'key questions' that held higher weighting within the determination of tier allocation for quality assessment and confidence assessments.

Table 3. Scoring criteria for risk of bias.

RoB	Description
1	Definitely low risk of bias: There is direct evidence of low risk of bias practices. (May include specific examples of relevant low risk of bias practices).
2	Probably low risk of bias: There is indirect evidence of low risk of bias practices OR it is deemed that deviations from low risk of bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias
3	Probably high risk of bias: There is indirect evidence of high risk of bias practices OR there is insufficient information provided about relevant risk of bias practices.
4	Definitely high risk of bias: There is direct evidence of high risk of bias practices (may include specific examples of relevant high risk of bias practices).

the confidence assessments and statistical analyses. Reviews, viewpoint articles, non-peer reviewed sources including grey literature (defined as research produced by organizations outside of the traditional commercial or academic publishing) and conference papers, were excluded. Studies were excluded if it was reported that offspring were exposed prenatally or after birth. Studies were also excluded if either parent had been exposed to radiation for cancer treatment to minimize bias of genetic effects that may be related to the parental disease.

Data extraction strategy

For each study, data on the subject matter, parental exposure, experimental design, findings and conclusions, and other relevant data was extracted. The criteria for data extraction and risk of bias assessment were independently tested using a subset of references, scores were crosschecked, and criteria optimized to ensure consistency. Any disagreements were resolved by discussion with additional reviewer. Only data from those categories pertaining to human evidence was collected for this review.

Assessment of internal validity

Flaws in the experimental design and procedures, data analysis and reporting of observations and other relevant information can lead to over- or under-estimating reporting of an effect. Therefore, for each individual study, a series of questions were asked, designed to assess studies for potential sources of bias (Table 2) and a bias rating applied (Table 3). Bias domains included confounding bias, detection bias, selection bias, attrition/exclusion bias and 'other' sources of bias (statistical tests used appropriately, evidence of publication bias). As shown in Table 2, questions 1–3 were key questions which held higher weighting. The most important of these with respect to this review was question 2 on the 'timing of parental exposure' whereby, according to OHAT, a probable RoB relates to 'suspected' postconceptional exposure whereas, high RoB is where the study provides 'evidence' that this is the case. The bias questions were adapted from OHAT guidelines and all risk of bias scores were crosschecked by an independent reviewer for consistency and accuracy. No re-analysis of the statistical tests carried out by the original authors was performed.

Confidence in the body of evidence

The next step involved assessing the confidence in the body of evidence from studies in each group before drawing overall conclusions. Studies were grouped according to health outcome; pregnancy outcomes, genomic anomalies, solid cancers, non-solid cancers, non-cancer diseases and mortality and, exposure situation (occupational, non-cancer associated medical, A-bomb survivors and environmental).

Making an initial assessment

An initial confidence rating was assigned based around three key study design features (Risk of bias (RoB) question 1, 2 and 3, Table 2), these being confounding variables, exposure timing (before or after conception) and appropriate comparison groups. Studies were initially rated in a tier approach, with tier 1 holding the lowest overall bias rating and tier 3 the highest bias rating. Tier 1 studies must be rated as 'definitely low' or 'probably low' RoB for key criteria and, all other RoB questions rated as 'definitely low' or 'probably low' RoB. Tier 2 studies meets neither the criteria for tiers 1 or 3. Tier 3 studies are rated as 'definitely high' or 'probably high' RoB for the key elements and where most other questions answered, 'definitely high' or 'probably high' RoB. Tier 3 studies and those assigned a high RoB for key

question 2 were removed from any subsequent analysis including narrative, confidence assessment and statistical analysis (Supplementary material)

Downgrading of confidence

Five key areas were assessed to establish if downgrades in the confidence in the body of evidence should be made, these were; RoB across the studies, unexplained inconsistency, indirectness, imprecision, publication bias (Figure 1). For example, confidence in a body of evidence was downgraded if a substantial RoB across multiple studies was evident, or if large variability in the direction or magnitude of effect estimates in individual studies could not be explained. Any inconsistencies judged to be due to differences in the type of study design did not contribute to any decision to downgrade a body of evidence. Judgements were made in accordance with OHAT guidance (NTP-OHAT 2015).

Upgrading of confidence

Four aspects were used to establish if upgrades in the confidence in the body of evidence should be made, these were; large magnitude of effect, dose response, plausible confounding and consistency across study designs (Figure 1). As examples, an upgrade would be appropriate if a dose-response pattern was observed within or across studies, if residual confounding or bias would underestimate an association (bias toward the null) or, if a consistent result is observed between dissimilar populations (factors such as time, location, exposure) and study types (cohort, case-control). Again, judgements were made in accordance with OHAT guidance (NTP-OHAT 2015).

Synthesis of body of evidence

The confidence in the body of evidence was rated and conclusions made. This conclusion is based upon the authors conclusions of the individual studies which comprise that body of evidence and, the direction of any effect reported in the majority of the studies. In order to translate into 'no effect', high confidence in the body of evidence has to be reached. Where there is no majority in the author's conclusions, and large inconsistencies in the direction of effect, then this is translated into inadequate evidence. Where confidence assessments have not been carried out, this is due to lack of studies within small groups.

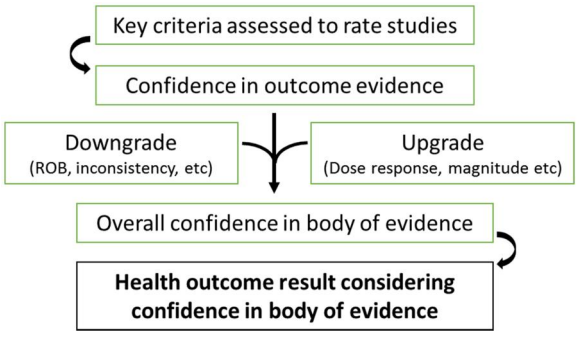

Figure 1. Flow diagram of key steps involved for assessing confidence in the body of evidence (NTP-OHAT 2015). The confidence assessment approach begins with an initial confidence assessment that is downgraded or upgraded to reach a final overall confidence rating for the body of evidence. This was performed per health outcome grouping with exposure scenarios taken into consideration. RoB = risk of bias.

Statistical analysis

Vote counting based on the direction of effect was performed using a binomial probability test following guidelines from Cochrane (Higgins et al. 2023). For each study, the effect is categorized as 'an effect' or 'no effect' based on the effect sizes reported. The two-sided P value from the binomial probability test was performed in Microsoft Excel using the function =2*BINOM.DIST. The syntax requires the smaller of the 'number of effects favoring the intervention' or 'the number of effects favoring the control' to be inserted into the function.

Structure of review

The findings from each study were grouped into health outcomes consisting of (i) pregnancy outcomes, (ii) genomic anomalies, (iii) solid and non-solid cancer, and (iv) other non-cancer diseases and mortality. For each health outcome, studies were further grouped by exposure situations. These include occupational exposure, non-cancer associated medical exposure, exposure to radiation from atomic bombs, and environmental exposure. A confidence assessment in the body of evidence was performed for sub-groups that contained more than three studies. Study identification numbers are in squared brackets [] throughout the document. Summary tables showing details pertinent to the studies design, findings and conclusions are provided in the body of the text with accompanying RoB heatmaps in Supplementary materials.

Results

The search term identified 2441initial hits of which 198 remained after title and abstract screening. After detailed examination, 72 studies remained and an additional 55 studies were identified through reference lists of the eligible studies. The high number of studies identified through reference list screening of eligible studies can be explained by many studies not including key words in the title and abstract (Figure 2).

What is the evidence for increased adverse pregnancy outcomes?

Pregnancy outcomes include congenital abnormalities, fetal death/perinatal mortality, birth weight and 'other' pregnancy outcomes such as sex ratio and twinning.

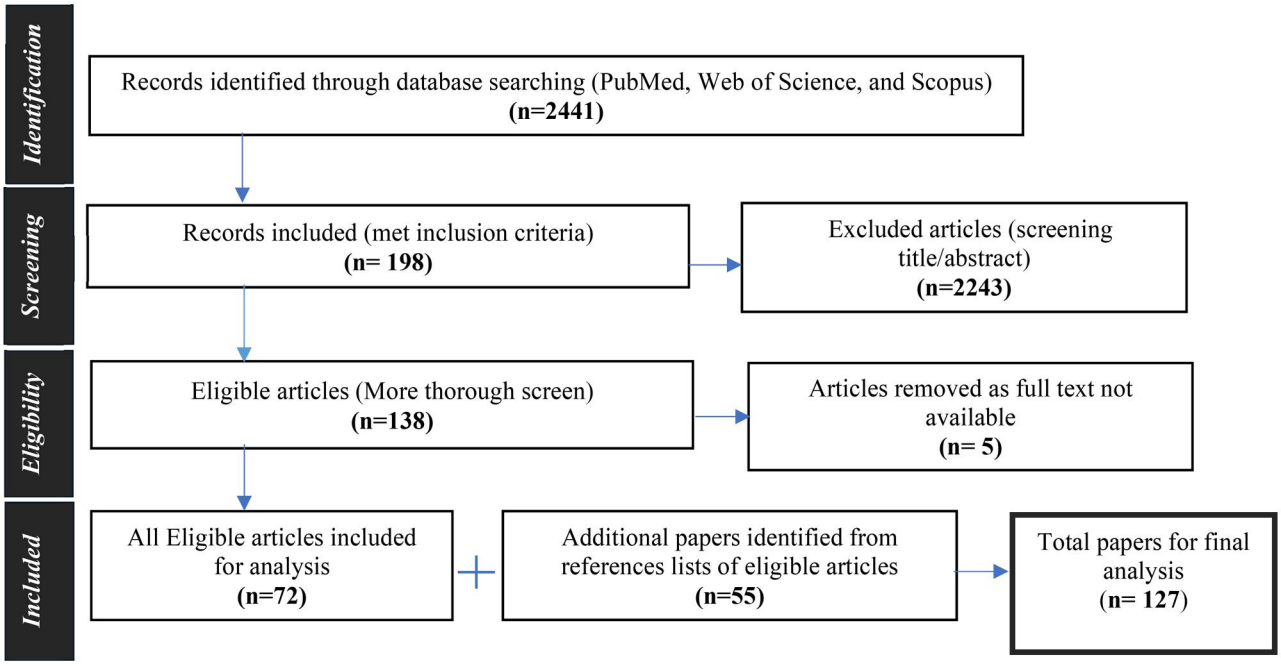

Figure 2. Flow diagram showing literature search and screening process.

Congenital abnormalities

Congenital abnormalities are defined as structural or functional abnormalities that occur during intrauterine life (World Health Organization 2023). As shown in Supplementary Table 1, the RoB rating excluded 6 studies [190, 201, 254, 94, 102, 262] rated as tier 3 and 10 studies [117, 155, 103, 104, 134, 244, 235, 267, 268, 92] as high RoB for question 2. Of the remaining 21 studies investigating congenital abnormalities, the terminology varied with 'congenital anomalies', 'congenital malformations', 'birth defects', 'sentinel anomalies' and 'new-born diseases' all being used. Some studies report results for individual congenital anomalies such as Down syndrome, neural tube defects (NTDs) and cleft palate, whereas other studies do not. Populations include occupational (nuclear workers, healthcare professionals, veterinarians), offspring of A-bomb survivors, non-cancer associated medical exposed (skin hemangioma patients) and environmentally exposed populations (Table 4).

Occupational exposure

Studies that show an effect. A number of studies investigating congenital abnormalities in offspring born to occupationally exposed populations report an effect. One of the earlier studies was by Roman et al (1996) [290] who researched the health of children born to medical radiographers in England. Among 9208 pregnancies, a borderline excess of chromosomal anomalies (other than Down's syndrome) was reported in the children of female (but not male) radiographers (RR (Relative Risk) 3.9, 95% CI 1.3–9.0), although this is based on only five observations. Parker et al (1999) [47] undertook a case-control study of Sellafield workers (doses of 0.01–33 mSv in the 90 days before conception, and 0.01–911 mSv total preconceptional dose, according to film badge measurements) which included two control groups: non-radiation workers in Sellafield and a non-Sellafield cohort. Birth registration documents were primarily used with the focus on stillbirth rates, however, stillbirths with a congenital abnormality were also included. They reported a statistically significantly raised Odds Ratio (OR) (1.43, 0.93–1.94, $p = .047$) for all congenital abnormalities, and an OR of 1.69 (1.10–2.32, $p = .011$) for neural tube defects (NTDs) (Parker et al. 1999). A recognized limitation includes cause of death only being recorded on the registration documents from 1961 onwards. Furthermore, although confounders including year of birth, paternal age and paternal preconceptional irradiation were adjusted for, maternal age was not. A second study (Sever et al. 1988a) [153] on radiation workers also found an increase in congenital abnormalities. The study group included nuclear workers at the Hanford site with recorded external (gamma) whole-body exposures (dose groups 0–9.9, 10–49.9, and >50 mSv), with 37% of fathers exceeding 10 mSv. Sever et al found associations between congenital dislocation of the hip and tracheoesophageal fistula, with employment of the parents at Hanford ($p = .08$), but not with parental radiation exposure. NTDs by contrast did show a significant association with parental preconception exposure (OR for 10 mSv; 1.46 (CI 0.981, 4.5) and 100 mSv; 5.6 (0.81,36), $p = .02$. No other associations were found in the eleven other defined defects, including Down syndrome. To conclude, Sever et al state that due to the lack of a genetic effect being seen in A-bomb studies, it is likely their reported positive findings are false positives. A small group of female veterinarians, exposed to X-rays during their work, were assessed for congenital abnormalities in their offspring. The details on dose information was limited, however, an elevated rate of self-reported birth defects among the veterinarians, as compared to the control group was observed (RR 4.2, CI 1.2–15.1) (Schenker al. 1990) [227]. A four-fold increase in congenital abnormality amongst offspring of

Table 4. Studies investigating congenital abnormalities in the offspring of radiation exposed parents.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
47	Parker et al. (1999)	Nuclear industry workers, UK	9078 total livebirths	Stillbirth with a congenital anomaly Stillbirth with neural-tube defects	**OR (95% CI)** 1·43 (0·93–1·94) 1·69 (1·10–2·32)	Effect reported
48	Doyle et al. (2000)	Nuclear industry workers, UK	27,262 offspring	Any major malformation	**OR (95% CI)** Reported by men= 1.0 (0.8–1.2)	No effect
75	Irgens et al. (2003)	Commercial aircrew, Norway	Control= 1,621,186 Pilot= 2367 Cabin attendant= 3716	Birth defects Total Cleft (Lip and palate) Hypospadias Down syndrome	**OR (95% CI), Total exposure** Male pilots = 1.10 (0.70–1.16) Male pilots= 0.90 (0.29–2.81) Male pilots= 0.32 (0.04–2.26) Male pilots= 1.24 (0.46–3.30)	No effect
153	Sever et al. (1988a)	Nuclear industry workers, US	Control= 977 Cases= 672	All malformations Neural tube defects	**OR (95% CI)** 10mSv = 1.08 (0.977, 1.29) 100mSv = 1.78 (0.77, 3.9) 10mSv = 1.46 (0.98, 4.5) 100mSv = 5.6 (0.81, 36)	Effect reported[a]
191	Wiesel et al. (2016)	Healthcare professions, Germany	Control = 154	Congenital abnormality	**Incidence** Case= 8 (30%) Control= 60 (6.2%)	Effect reported
227	Schenker et al. (1990)	Veterinarians, US	Control= 794 pregnancies Test= 537 pregnancies	Infant with any reported defect	**RR (95% CI)** 3.8 (2.0–7.3)	Effect reported
285	Green et al. (1997)	Electric power workers, Canada	Control= 300 Test= 246	Congenital anomaly	**RR (95% CI)** 0.72 (0.55–0.95)	No effect
290	Roman et al. (1996)	Medical radiographers, UK	3882 pregnancies	Congenital abnormalities	**Observed/ expected Ratio (95% CI)** 1.0 (0.6–1.5)	Effect[f]
294	Métneki & Czeizel (2005)	Children born in Hungary	4,139,205 births	Down syndrome	Birth prevalence of 1.17 per 100 in the 1970s increased to 1.50 per 100 between 1989 and 1999 with a maximum 1.77 in 1992.	Effect
197	Yoshimoto and Mabuchi (1991)	A-bomb survivors, Japan	Control= 41,069 Case= 31,159	New-born diseases	**Excess RR** 0.030, p= 0.711	No effect
215	Otake et al. (1990)	A-bomb survivors, Japan	55,303 pregnancy terminations	Congenital abnormality	**Regression coefficient** Joint parental exposure= 0.00099 (S.E. 0.00184) Birth order of child= 0.00087* (S.E. 0.00042) Year of birth= 0.00120** (S.E. 0.00032)[b]	Non-significant increase
257	Källén et al. (1998)	Radiotherapy for skin hemangioma, Sweden	19,494	Anencephaly Encephalocele Esophageal atresia Anal atresia Hypospadias Severe kidney malformation Positional foot defect Unstable hip Syndactyl Limb reduction Hemangioma	**RR (95% CI)** 1.4 (0.6–2.9) 1.5 (0.4–4.1) 1.1 (0.4–2.5) 1.4 (0.6–2.9) 1.5 (1.0–2.1) 1.7 (0.8–3.1) 1.4 (1.1–1.7) 1.2 (1.0–1.3) 1.9 (1.4–2.5) 1.5 (0.9–2.3) 1.7 (1.3–2.1)	Effect[e]
305	Goldberg et al. (1998)	Radiography for adolescent idiopathic scoliosis, US	1,292	Congenital malformations	**OR (95% CI)** 1.20 (0.78–1.84)	Effect
40	Czeizel (1991)	Residents after Chernobyl, Hungary	2,323,018	Sentinel anomalies	**Total birth prevalence** 4.08/10,000	No effect
239	Sperling et al. (2012)	Seven European countries after Chernobyl	5,315,400	Down Syndrome	**OR from 1987 vs. before 1987** Total OR= 1.17 (1.11,1.23)	Effect reported
240	Sperling et al. (1994)	Residents West Berlin after Chernobyl, Germany	190 073	Down Syndrome	**Prevalence per 1000 livebirths** All cases= 1.56 1980 = 1.44, 1981 = 1.42, 1982 = 1.53, 1983 1.59, 1984 = 1.38, 1985 = 1.56, **1986 = 1.35,** 1987 = 2.11 1988 = 1.77, 1989 = 1.38	Effect reported
264	Burkart et al. (1997)	Berlin and Bavaria after Chernobyl, Germany	Bavaria= 11,9000 Northern Bavaria= 52000 Nuremberg/Fuerth/ Erlangen. = 6400 West-Berlin= 19000	Down syndrome	**Mean prevalence per 1000 births** Bavaria= 1.08 Northern Bavaria= 0.94 West Berlin= 1.56	No effect[c]
158	Siffel et al. (1996)	Vicinity to nuclear power plant, Hungary	26 893 total births	Congenital abnormalities Down syndrome	**Rate per 1000 births** Before operation of nuclear plant= 63.79/ 1000 After operation of nuclear plant= 51.2/1000 Before operation of nuclear plant= 0.89/ 1000 After operation of nuclear plant= 1.39/1000	No effect
208	Mangones et al. (2013)	Vicinity to nuclear power plant, India	328,124 total Zone 1 = 35,038 Zone 2 = 49,313 Zone 3 = 140,017 Zone 4 = 103,756	All defects	**Rate for 1000 births; rate ratios for comparison to zone 1** (zone 1 closest), Zone 1 = 2.25/1000 Zone 2 rate ratio= 0.86 (0.64–1.16) Zone 3 rate ratio= 1.02 (0.80–1.30) Zone 4 rate ratio= 0.86 (0.66–1.11).	No effect

(*continued*)

Table 4. Continued.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
221	Queisser-Luft et al. (2011)	Vicinity to nuclear power plants, Germany	2423	Birth defects	**RR** 0.94	No effect
234	Sever et al. (1988b)	Vicinity of Hanford site, US	23,319 total 40 12 12	Neural tube defect Cleft lip with/without cleft palate Cleft palate	**Prevalence rate** at birth/1000 total births 1.72 (1.22–2.34) 0.51 (0.26–0.89) 0.51 (0.26–0.89)	Effect[d]
247	Wang et al. (2010)	Vicinity to nuclear power plants, Taiwan	4,491	Congenital abnormalities	**OR (95% CI)** 1.58 (0.85–2.93)	No effect

[a]Two defects, congenital dislocation of the hip and tracheoesophageal fistula, showed statistically significant associations with employment of the parents at Hanford, but not with parental radiation exposure. NTD showed a significant association with parental preconception exposure on the basis of a small number of cases. Eleven other defects, including Down syndrome, for which an association with radiation was considered most likely, showed no evidence of such an association.
[b]Significant levels: *($p < .05$), **($p < .01$).
[c]Clusters observed but concluded not related with exposure.
[d]Effect reported but authors state cannot be explained by employment at Hanford.
[e]Effect reported for NTDs, authors state possibly a chance result of multiple statistical testing. Statistics were also reported for the following health outcomes: Spina bifida; RR= 0.9 (0.5–1.6), Hydrocephaly; RR = 1.0 (0.4–1.8), Microcephaly; RR= 0.4 (0.0–2.2), An/microphthalmia; RR= 0.8 (0.1–2.8), Severe ear malformation; RR= 0.9 (0.3–1.9), Cleft lip/palate; RR= 0.5 (0.3–0.8), Isolated cleft palate; RR= 0.7 (0.4–1.2), Congenital heart defect; RR = 1.0 (0.6–1.4), Other gut atresia; RR= 0.7 (0.1–2.7), Polydactyly; RR = 1.0 (0.6–1.5), Chondrodystrophy; RR = 0.3 (0.0–1.6), Craniosynostosis; RR= 0.6 (0.1–2.3) and Down syndrome; 0.9 (0.6–1.3).
[f]Maternal results (reported in text) show an effect.
OR: Odds Ratio; RR: Relative Risk; 95% CI: 95% Confidence Interval; SE: Standard Error; NTD: Neural Tube Defect.

healthcare personnel who were exposed to radiation was reported by Wiesel et al in 2016 [191]. This finding, derived from self-reported information, is based upon only thirty pregnancies with eight out of 27 infants being diagnosed with a congenital abnormality (30%), as compared to 6.2% of the comparison group (total 154 offspring) (Wiesel et al. 2016).

Studies that do not show an effect. Three studies showed no increase in congenital abnormalities. Doyle et al [48] investigated offspring born to UK nuclear industry workers reporting an OR of 1.0 (CI 0.8–1.2) for congenital abnormalities amongst offspring of exposed fathers, with no relationship found where dose received before conception was monitored for, and an OR of 1.4 (CI 0.9–2.1) for those reported by exposed mothers (Doyle et al. 2000). Irgens et al [75] investigated the effects of cosmic radiation on pregnancy outcomes in male airline pilots and female cabin attendants. A median dose of 51.0 mSv accumulated in the year before birth, and a median of 204 mSv accumulated over all years before birth (estimated via number of flight hours). No increased risks were observed for the offspring of male pilots, either for the year before birth or ever for any adverse outcomes, except for Down syndrome (OR 1.41, 95% CI 0.53–3.76). Regarding exposure during the year before birth (n = 2512), offspring of female cabin attendants had a higher incidence of Down syndrome (OR 1.44, 95% CI 0.60–3.47) (Irgens et al. 2003).

Lastly, Green et al (1997) [285] researched congenital anomalies in children of parents occupationally exposed to low level ionizing radiation at a Canadian electric power plant. The results showed that employment was not associated with an increased risk of congenital anomalies in the offspring with risk estimates of 1.75 (95% CI 0.86 to 3.55 for mothers and 0.84 (95% CI 0.68 to 1.05) for fathers.

Confidence assessment for occupational exposure. When all [47, 48, 75, 153, 191, 227, 285, 290] studies are considered (excluding study 190 as tier 3 and 117, 155 as high RoB for question 2, Supplementary Table 1), the evidence for congenital abnormalities in occupationally exposed parents can be translated into *high confidence for an effect* due to the majority (five of eight) of the studies showing an increase relative to their controls. However, the binomial test did not show significance; p value= 0.36). Specifically, the initial confidence rating of *moderate* was upgraded due to the large magnitude in effect reported across most studies, although inconsistencies in the magnitude of effect is seen, this can be explained by the variation of populations studied. No downgrades were warranted although it is noted that study [48] has a low sample size and study [227] lacks information on exposure. No evidence of a dose effect was seen across any of the studies.

When only those studies with *good-high* rating that parent(s) were only exposed preconceptionally (question 2) were considered [47, 48, 75, 153, 285], one upgrade was warranted due to the large magnitude in effect (studies 47, 48 and 153 all reporting OR greater than 2), however this could not be translated into a health effect due to inconsistencies in the authors conclusions. This conclusion of *inadequate evidence for congenital abnormalities* is supported by the binomial test where two studies reported in the direction of an increasing effect and three studies report a decreasing effect ($p = .81$).

Atomic-bomb survivors

Two studies were captured that included analysis of congenital abnormalities in offspring born to A-bomb survivors. Yoshimoto and Mabuchi (1991) [197] investigated mortality and new-born diseases amongst 31,159 offspring born to parents with a combined gonadal dose of 0.405 Sv (0.047 Sv

neutron and 0.358 Sv gamma). A control group of 41,069 offspring were used for comparison. When those diagnosed with new-born diseases were investigated, a linear relative risk model showed no statistically significant increase following parental exposure, the excess relative risk being 0.030 (+/- 0.046) per Sv based on the Dosimetry System 1986 (DS86) doses (Relative Biological effectiveness (RBE) of neutrons = 20) (p value= 0.711) (Yoshimoto and Mabuchi 1991). An assumption is made here that this category included neonatal deaths from congenital disorders, however no information on this or on the occurrence of congenital abnormalities in livebirths, is given. The second study (Otake et al. 1990) [215] investigated pregnancy outcomes in A-bomb survivors, represented 70,073 livebirths, stillbirths, and medical terminations. A standard linear model assuming a neutron RBE of 20 resulted in the estimated increase per Sv in the predicted frequency of untoward outcomes as 0.00354 (±0.00343). After adjustment for concomitant sources of variation, the estimated increase per Sv in the proportion of such births is 0.00422 (±0.00342). Important confounders including city, sex, mean age of both parents, birth order and birth year were all accounted for, and although dose information was presented, the more recent DS86 doses could not be estimated for 14,770 of the parents included.

Non-cancer associated medical exposure

Källén et al (1998) [257] examined reproduction outcome in women irradiated in their infancy to treat skin hemangioma. Information on radiation quality and mean reported ovarian dose was given, ranging from 0.06 Gy to 8.55 Gy. Women who received an ovarian dose of <0.01 Gy were used as the control population and all mothers included in the study were exposed before the age of 18 months. This relatively large study involving 19,494 progenies from 17,393 women found a significant trend between NTDs and ovarian dose (p = .02). For all malformations, a slight excess was reported (RR of 1.08, 95% CI 1.02–1.15), although no dose-response was seen (p = .52) (Källén et al. 1998). Goldberg et al. 1998 [305] investigated adverse reproductive outcomes among women exposed to low levels of IR from diagnostic radiography for adolescent idiopathic scoliosis. A regression model analysis revealed an OR of 1.20 (95% CI = 0.78–1.84) for congenital malformations, interpreted by the authors as an increase.

Environmental exposure studies

Studies that show an effect. Birth defects in offspring of people living near the Hanford site (plutonium nuclear weapons production facility) were increased according to Sever et al [234]. Approximately 6% of all infants with a birth defect had a parent with a cumulative exposure exceeding 10.0 mSv due to employment at Hanford or, an estimated annual local resident (between 1977- 1982) dose of 0.0001 mSv to 0.0004 mSv. Hospital records were used to identify 454 malformation cases among 23,319 births (19.6 per 1,000 births), which when compared against controls, showed a statistically significant elevated rate of NTDs (1.72 per 1,000 births vs. 0.99 per 1,000). In contrast to this, the incidence of cleft lip was significantly lower at 0.59 per 1,000 vs. 1.17 per 1,000. Sever et al concluded that due to a lack of any dose response (from individual monitoring of external dose), the observed increase in NTDs could not be explained by either employment of the parents at Hanford or, by the impact of plant emissions on the local population (Sever et al. 1988b). Sperling et al [240] reported a cluster of 12 Down syndrome cases in West Berlin in January 1987, which was higher than expected, concluding this to be "causally related" to radiation exposure from the Chornobyl disaster (Sperling et al. 1994). Métneki and Czeizel (2005) [294] also reported an increase in the recorded total (birth + fetal) prevalence rate of Down syndrome using information in the Hungarian Congenital Abnormality Registry. The birth prevalence of 1.17 per 100 in the 1970s increased to 1.50 per 100 between 1989 and 1999 with a maximum of 1.77 in 1992. The study concludes that the increase is due to the higher proportion of prenatally diagnosed fetuses with Down syndrome and an increasing number of women aged over 35, however also comment that environmental factors cannot be excluded. A large-scale follow-up study to [240] assessed the underlying time trends in Down Syndrome occurrence to investigate whether there were any significant changes after Chornobyl [239]. This included populations in countries affected by fallout from Chornobyl including Bavaria and West Berlin in Germany, Belarus, Hungary, the Lothian Region of Scotland, Northwest England, and Sweden, involving a total of 6,173 cases of trisomy 21 among 5,315,400 live births. Estimated ovarian doses in Belarusian and West Berlin regions within the first two weeks were not likely to exceed 5mSv. The study showed a significant increase: OR 1.17 (1.07–1.27), $P < 0.0003$, which remained significant when the Belarus and Berlin data (where individuals had a higher likelihood of exposure) were excluded: OR 1.10 (1.00–1.21), $P = 0.0495$ (Sperling et al. 2012).

Studies that do not show an effect. By contrast, Burkart et al [264] found the Down syndrome clusters detected in Germany after the Chornobyl accident not to be associated with parental exposure to the gonads (dose estimates= 0.1–0.55mSv), concluding the cluster in cases was unlikely to be due to radiation contamination (Burkart et al. 1997). Further, Czeizel [40] examined 2,323,018 offspring from the Hungarian congenital abnormality register in the years before and after the accident (1980–1989) (Czeizel 1991). The results showed no increase in rates after the disaster, however the statistical analysis was limited and lacked detail. Congenital abnormalities were examined in children born within a 30 km radius of the Pak's nuclear power plant, Hungary [158]. This study included 26,893 offspring in 55 settlements: occurrences of congenital abnormalities corresponded to the expected baseline rate, with the exception of one group. Of the 55 settlements, eight had spatial clusters which Siffel et al state could be from overdiagnosis or chance (Siffel et al. 1996). A separate vicinity study also

showed no increase of malformations [208]. This study included children from mother's resident within a 20-mile radius of the Indian Point nuclear power plant between 1992–2001. The principal finding was 702 major malformations in 666 children from a total of 328,124 live births, yielding an incidence of 2.1 per 1000, which was no greater than that reported for the State of New York (5.9 per 1000 births for the same malformations) (Mangones et al. 2013). Similarly, no increase in birth defects of infants to mothers living within a radius of 10 km around two selected nuclear power plants (Biblis and Philippsburg) was observed [221]. The dose from natural exposure is reported to be 2.1mSv/year, with an additional anthropogenic dose of 1.9mSv/year. The rate of birth defects was found to be 4.5% in the study region and 4.7% in the control region (RR= 0.94), and when adjusted for potential cofounders, the risk remained comparable (RR= 0.90, lower 95% CL 0.73). Neither exposure to pesticides at beginning of pregnancy, maternal medical radiation or paternal occupational exposure proved to be a risk factor for birth defects (Queisser-Luft et al. 2011) [221]. The incidence of congenital abnormalities in offspring born to women living in the vicinity of nuclear power plants in Taiwan were assessed [247]. In total 5,679 individuals were included in the analyses, with 4,491 in the 'plant-vicinity' group, and 1,188 in the 'non-plant-vicinity' group. The results showed no differences after accounting for confounding variables (OR= 1.58, 95% CI = 0.85–2.93), with Wang et al concluding that residence in the vicinity of this nuclear power plant to not be a significant factor for abnormal health situations during pregnancy (Wang et al. 2010).

Confidence assessment for environmental exposure. When the confidence assessment was performed on environmentally exposed populations, all included studies [158, 208, 221, 234, 239, 240, 247, 264, 294] had a potential risk of exposure after conception. Studies 201, 254, 94, 102, and 262 were excluded as tier 3's and studies 103, 104, 134, 244, 235, 267, 268 and 92 excluded as high RoB for question 2 regarding exposure after conception, supplementary Table 1. Study 40 was excluded as study 294 is a more recent follow-up. No downgrades or upgrades were warranted based on OHAT's guidelines, giving a *low-moderate* rating. Due to inconsistencies in the direction of effect reported, this translated into *inadequate evidence* for congenital abnormalities in environmentally exposed populations.

Confidence assessment for 'all' exposures situations. When only those studies with good-high rating that parent(s) were only exposed (any exposure situation) preconceptionally (question 2) were considered [47, 48, 75, 153, 215, 257, 305, 285], one upgrade was warranted due to the large magnitude in effect (studies 47, 48 and 153 all reporting OR greater than 2), however this could not be translated into a health effect due to inconsistencies in the results. This is supported by the binomial test where five studies reported in the direction of an increasing effect and three studies report a decreasing effect for congenital (p = .36).

In summary, occupationally and medically exposed populations, for which there is greater confidence in the timing of exposure, show mostly *an effect for congenital abnormalities*, however the small number of studies available for analysis limits the strength of this finding. When 'all' exposure situations are considered, the evidence is rated as *inadequate* due to inconsistencies in the effects reported.

Fetal death/perinatal mortality

In total, 12 studies report data on fetal death/perinatal mortality, of which six are occupational (commercial aircrew, nuclear industry workers, medical workers and veterinarians), two non-cancer associated medical exposure, and four environmental exposure studies (Table 5). Outcomes categorized include miscarriages, stillbirths and fetal death at any stage before birth. The RoB rating excluded three studies from further analysis [190,138,254] rated as tier 3 and three studies as high RoB for question 2 [244,247,267] (supplementary Table 2).

Occupational exposure

Studies that show an effect. A small reproductive survey of female veterinarians who performed radiology X-ray examinations reported stillbirths to occur at approximately 4 times the rate (0.9%), as compared to control law school graduates (0.2%) (Schenker et al. 1990) [227]. Here, instead of dose measurements, the number of X-ray examinations per week was reported. A much larger study involving two comparison groups; non-radiation workers in Sellafield (1089 livebirths and 21 stillbirths) and non-Sellafield cohort (231,848 livebirths and 3468 stillbirths) and, a Sellafield radiation worker cohort of 9078 livebirths and 130 stillbirths was carried out by Parker et al (1999) [47]. With individualized dose monitoring, a significant association between a father's total exposure to external radiation before conception and stillbirth rates were reported (adjusted OR per 100 mSv = 1.24 [95% Cl 1.04–1.45], p = 0·009). This association was higher for stillborn offspring with congenital abnormalities, in particular those with NTDs. However, no effect was seen when total preconceptional internal dose or exposure to numerous types of radionuclides were considered (Parker et al. 1999). A similar study into fetal death amongst offspring of nuclear industry workers showed a borderline increased risk in early miscarriage. Among pregnancies reported by women, there was evidence of a small increase in risk of early miscarriage in mothers who had been monitored before conception (OR= 1.3, CI 1.0–1.6, p = .05), but the risk did not increase with dose (p = .25). The risk of late miscarriage was not associated with preconceptional monitoring (p = .53). For stillbirth, the odds ratio was again raised in mothers monitored for dose (OR= 2.2, CI 1.0–4.6, p = .05). When exposed fathers were preconceptionally monitored for dose, there was little evidence of an increase in risk with increasing dose (OR= 1.1, CI 0.9–1.4, p = .13 for early miscarriage, OR= 0.7, CI 0.5–1.1, p = .46 for late miscarriage, OR= 1.4, CI 0.9–2.4, p = .09 for stillbirth)

Table 5. Studies investigating fetal death/perinatal mortality in the offspring of radiation exposed parents.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
47	Parker et al. (1999)	Nuclear industry workers, UK	Stillbirths = 130 Livebirths = 9078	Stillbirth	**OR (95% CI)** 1·24 (1·04–1·45)	Effect reported
48	Doyle et al. (2000)	Nuclear industry workers, UK	27,261 pregnancies	Stillbirth	**Reported by men: OR (95% CI)** 0–2·49mSv= 1·1 (0·7–1·8) 2·50–9·99 = 0·9 (0·6–1·4) 10·0–19·99 = 0·8 (0·4–1·3) 20·0–49·99 = 1·2 (0·8–1·8) ≥50·00 = 1·3 (0·9–2·0) ≥100 mSv= 1·4 (0·9–2·4)	No effect
75	Irgens et al. (2003)	Commercial aircrew, Norway	Control= 1,621,186 Pilot= 2367 Cabin attendant= 3716	Perinatal mortality	**OR (95% CI)** **Year proceeding birth** Male pilots = 0.78 (0.54–1.13) **Ever** Male pilots = 0.85 (0.61–1.18)	No effect
227	Schenker et al. (1990)	Female veterinarians, US	Subjects = 537 Controls = 794	Fetal death	**RR (95% CI)** 0.9 (0.67–1.29) No. of radiographic examinations performed per week >5 1.81 (1.01–3.24)	Borderline effect[a]
288	Pearce et al. (2002)	Sellafield male radiation workers, UK	Cases= 9208	Stillbirths	**OR (95% CI)** 1.24 (1.04–1.45)	Effect
290	Roman et al. (1996)	Medical radiographers, UK	3882 pregnancies	Miscarriages Stillbirth Rarer spontaneous adverse events (ectopic pregnancy, blighted ovum, and hydatidiform mole).	2% 1% 1%	No effect
257	Källén et al. (1998)	Radiotherapy for skin hemangioma, Sweden	19,494	Stillbirth	**RR (95% CI)** 1.21, (1.06–1.39), P = 0.26	No effect[b]
305	Goldberg et al. (1998)	Radiography for adolescent idiopathic scoliosis, US	1,292	Stillbirth	**OR (95% CI)** 0.38 (0.15–0.97)	No effect
40	Czeizel (1991)	Residents after Chernobyl, Hungary	All pregnancy outcomes 231,048 230,912 228,971 230,213 229,906 231,048 230,912 228,971 230,213 229,906	Ectopic pregnancies Spontaneous abortions	***Incidence (%)*** 1985 = 0.8% 1986 = 0.9% 1987 = 0.8% 1988 = 0.9% 1989 = 0.9% 1985 = 11.3% 1986 = 11.5% 1987 = 11.5% 1988 = 11.7% 1989 = 11.6%	No effect
230	Scherb et al. (1999)	European residents after Chernobyl	Total livebirths= 11,739,194 Total stillbirths= 74,739	Stillbirth	There is a marked differential effect in the long-term stillbirth time trends between Western Europe, Central Europe and Eastern Europe.	Effect[c]
258	Dummer et al. (1998)	Residents in vicinity of Sellafield nuclear installation, UK	Total livebirths= 256,066 Total stillbirths= 4034	Stillbirth	**OR (95% CI)** 0.66 (0.30–1.49)	No effect
237	Slama et al. (2008)	Vicinity to nuclear, Beaumont- Hague, France	Control= 215 livebirths. Case= 611 livebirths	Miscarriage	**OR (95% CI)** Reference area= 1 Beaumont-Hague= 0.86 (0.55- 1.33)	No effect

[a]Borderline statistical significance of findings with radiographic examination.
[b]No effect, with the possible exception of NTDs.
[c]Effect reported although authors state could be other causes.
OR: Odds Ratio; RR: Relative Risk; 95% CI: 95% Confidence Interval.

(Doyle et al. 2000) [48]. Shortly after, Pearce et al (2002) [288] researched stillbirths among the offspring of male radiation workers at the Sellafield and reported a significant positive association between the total paternal preconceptional exposure to external radiation and the risk of stillbirth (after adjustment for year of birth, social class, birth order and paternal age, odds ratio at 100 mSv 1.24 (95% confidence interval 1.04–1.45)).

Studies that do not show an effect. In addition to reporting congenital outcomes above, two studies also reported no effect on fetal death. Roman et al (1996) [290] who researched the health of 9208 pregnancies born to medical radiographers in England reported 83% to be livebirths, 12% to be miscarriages (gestational age < 20 weeks), 1% to be stillbirths (gestational age > 20 weeks), and 1% were other rarer spontaneous adverse events (ectopic pregnancy, blighted ovum, and hydatidiform mole). It is noted that this is based on small sample sizes. Irgens et al. 2003 [75] also reported perinatal death to not be affected in offspring of male pilots.

Confidence assessment for occupational exposure. This evidence, based upon six occupational studies [47, 48, 75, 227, 288, 290], translated into *inadequate evidence* for an effect on fetal death. Specifically, the initial confidence assessment

of *moderate* was upgraded once for large magnitude in effects seen, however inconsistencies within the results exists (binomial test; p value = 0.34). No dose effect was observed.

Non-cancer associated medical exposure

Two non-cancer associated medically exposed studies were captured which reported fetal death. Kallen et al [257] observed an excess of perinatal deaths in women irradiated for skin hemangioma during infancy (RR = 1.21, 95% CI 1.06–1.39), although no relationship with dose was found contributing to the authors conclusions of no effect (Källén et al. 1998). While Goldberg et al. 1998 [305], who investigated adverse reproductive outcomes among women exposed as a consequence of diagnostic radiography for adolescent idiopathic scoliosis, found fewer stillbirths in the exposed group compared to the control group; OR of 0.38 (95% CI = 0.15–0.97).

Environmental exposure

Four studies examined stillbirth/neonatal death in environmentally exposed populations (Table 5). The studies examined residents in the vicinity of nuclear installations and residents in potentially contaminated areas.

Studies that show an effect. Scherb et al. (1999) [230] carried out a time trend analysis to assess stillbirth rates in European countries (categorized as Western Europe, Central Europe and Eastern Europe) before and after the Chornobyl accident using data collected from national registries. The researchers found eastern European (with estimated higher exposures) countries to exhibit an estimated absolute excess in stillbirth from 225 (36–419) in 1986 to 364 (168–568) in 1987, before reducing to 210 (16–413) over the period of 1988–1992. This was in contrast to the Western and Central European trends (Scherb et al. 1999). Various issues with regards to incomplete datasets and reporting in some countries were identified meaning some data was excluded from the analysis, additionally, the estimated average doses lacked detail on localized areas of contamination.

Studies that do not show an effect. In total, three studies were identified which showed no effect. A study of Hungarian residents, potentially exposed from the Chornobyl accident, reported no difference in annual pregnancy outcomes between 1985–1989 (Czeizel 1991) [40]. Miscarriages were measured in populations living in the vicinity of a nuclear waste reprocessing plant in Beaumont-Hague [237] (no dose estimations), and no effect was observed (OR of 0.86, 95% CI 0.55- 1.33) (Slama et al. 2008). Dummer et al [258] investigated whether proximity to the Sellafield nuclear installation increased the risk of stillbirths and found no evidence to support this. Using data collected from the UK Office for National Statistics (1950–1989), Dummer et al identified 4034 stillbirths and found no association between those mothers residing within or out with a distance of 25 km from Sellafield (Dummer et al. 1998).

Confidence assessment for environmental exposure. The confidence assessment for the environmentally exposed populations [230, 258, 40, 237], all of which had a potential risk of exposure after conception, was *low-moderate*. No downgrades were warranted however an upgrade was made for [258 and 237] reporting effect sizes above 2. Due to inconsistencies in the direction of effect reported by the authors, this translated into *inadequate evidence* for fetal death as OHAT states that high confidence must be reached in order to translate into no effect.

Confidence assessment for 'all' exposures situation. When only those studies examining fetal/perinatal death with good-high rating that parent(s) were only exposed (any exposure situation) preconceptionally (question 2) were considered [47, 48, 257, 288, 305], one upgrade was warranted due to the large magnitude in effect (studies 47, 48 reporting OR greater than 2), however this cannot be translated into a health effect due to inconsistencies in the results. This was supported by the binomial test (p = .19), where four of the five studies were in the direction of an increasing effect.

Birth weight

Ten studies were identified which reported birth weight (Table 6). These included two occupational studies involving commercial aircrew and, fathers working in biomedical laboratories and also, three non-cancer associated medical studies examining diagnostic X-ray of men and, women previously treated for skin hemangioma. All environmental studies involved populations living in the vicinity of nuclear installations. A combination of high and low birth weight was investigated.

Occupational exposure

Magnusson et al [115] analyzed the birth weights of offspring born to male biomedical research scientists who had been exposed to a range of agents, including 434 children born to researchers exposed to radioisotopes. A borderline association between exposure to radioactive isotopes and high birth weight (OR 1.8; CI 1.0–3.2) was reported. Linear regression showed an adjusted increase in birth weight to 54 g when working with radioactive isotopes (CI 9–117 P = 0.09) (Magnusson et al. 2006). However, detail on exposures, including on confounders such as organic and carcinogenic compounds, was missing. Irgens et al. [75] examined the effects of cosmic radiation on pregnancy outcomes in male airline pilots and female cabin attendants. No difference was reported for male pilots for when total exposure was investigated (RR 0.91) or exposure in the year proceeding birth (RR 0.88) (Irgens et al. 2003).

Non-cancer associated medical exposure

Studies that show an effect. The relationship between paternal preconceptional exposure to diagnostic x-rays and altered birth weight in offspring was studied in the Avon Longitudinal Study of Parents and Children (Shea and Little

Table 6. Studies investigating birth weight in the offspring of radiation exposed parents.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
115	Magnusson et al. (2006)	Fathers working in biomedical laboratories, Sweden	laboratory employees= 2840 non-laboratory employees = 1909	Birth weight	**OR (95% CI)** Low birth weight= 0.6 (0.2–1.8) High birth weight= 1.8 (1.0–3.2) Small for gestational age= 0.8 (0.2–3.0) Large for gestational age= 2.1 (0.5–8.4) Pre-term birth= 1.3 (0.5–3.1) Post-term birth= 1.2 (0.6–2.6)	Effect reported
75	Irgens et al. (2003)	Commercial aircrew, Norway	Control= 1,621,186 Pilot= 2367 Cabin attendant= 3716	Low birth weight	**OR (95% CI)** **Year proceeding birth** Male pilots = 0.88 (0.72–1.08) **Ever** Male pilots = 0.91 (0.76–1.10)	No effect
154	Shea and Little (1997)	Diagnostic X- rays, UK	Exposed= 164 Controls= 7146	Birth weight	Exposed fathers= 3315g Unexposed fathers= 3388g; P value= 0.064	Effect reported
257	Källén et al. (1998)	Radiotherapy for skin hemangioma, Sweden	Cases= 19494	Birth weight <1500g <2500g 2500g +	**Number** Total= 116, Expected= 118 Total= 500, Expected = 732 Total= 17,337, Expected= 17,105	No effect
305	Goldberg et al. (1998)	Radiography for adolescent idiopathic scoliosis, US	1,292	Low birth weight	**OR (95% CI)** 0.84 (95% CI = 0.59–1.21)	No effect
40	Czeizel (1991)	Residents after Chernobyl, Hungary	1,309,583	Liveborn under 2500g	% 1980 = 11.0, 1981 = 10.2, 1982 = 9.9, 1983 = 9.8 1984 = 10.1, 1985 = 9.9, 1986 = 9.8, 1987 = 9.6 1988 = 9.4, 1989 = 9.2	No effect
70	Gong et al. (2017)	Vicinity to nuclear facilities in Texas, US	92,526 297 188 111 106 16	Low birth weight	**OR (95% CI) for Proximity (Km)** >50 = 1.00 (referent) 40–50 = 0.91 (0.81–1.03) 30–40 = 0.98 (0.84- 1.13) 20–30 = 0.95 (0.79- 1.15) 10–20 = 0.86 (0.70- 1.04) 0–10 = 0.98 (0.59–1.61)	No effect
208	Mangones et al. (2013)	Vicinity to nuclear power plant, India	328,124 total live births Zone 1 = 35,038 Zone 2 = 49,313 Zone 3 = 140,017 Zone 4 = 103,756	Low birth weight	**Rate ratios (95% CI) for comparison to zone 1 (Zone 1 closest to radius, zone 4 furthest)** Zone 1=- Zone 2 = 0.97 (0.92–1.03) Zone 3 = 0.87 (0.83–0.92) Zone 4 = 1.13 (1.07–1.18)	No effect
247	Wang et al. (2010)	Vicinity to Nuclear Power Plant, Taiwan	5679	Low birth weight	**OR (95% CI)** 1.04 (0.79–1.37)	No effect
237	Slama et al. (2008)	Vicinity to nuclear waste reprocessing plant, Beaumont-Hague, France	245 737	Birth weight	Change in mean birth weight (g) (95% CI) Reference area= 0 Beaumont-Hague= −10 (-86–66)	No effect

OR: Odds Ratio; RR: Relative Risk; 95% CI: 95% Confidence Interval.

1997) [154]. A reduced mean birth weight of 3358 g (n = 172) was seen in offspring amongst exposed fathers (mean gonadal dose of 4.40mGy (exposure to the hip/pelvis) and 0.07 mGy (lumbar spine imaging), compared to a mean of 3437 g (n = 7546) in the unexposed group (p = .055) and, a reduction in intrauterine growth (3374 g and 3437 g) for exposed and unexposed respectively (p = .078). When adjusted for the offspring's sex and parental variables including age, height, race, education, occupational exposure, parity, and maternal smoking, a downward trend in birth weight and fetal growth was still present.

Studies that do not show an effect. Kallen et al [257] investigated offspring's birth weight in a population of women irradiated for skin hemangioma in infancy. Data was collected from Swedish health registries on the delivery outcome for 19,494 infants, where the number of infants with a birth weight less than 1500 g was comparable to expected numbers calculated from the total population of Swedish women of reproductive age (RR = 0.93, 95% CI 0.79–1.10) (Källén et al. 1998). As such, it was concluded that birth weights were not reduced. Similarly, Goldberg et al. 1998 [305] reported an OR of 0.84 (95% CI = 0.59 − 1.21) for low birth weight, indicating no increase in offspring born with low birth weight in women previously exposed to diagnostic radiation, compared to the control group.

Environmental exposure

All five studies that examined low birth weights in parental populations living in the vicinity of nuclear power plants showed no effect.

No effect was seen in a Hungarian population potentially exposed by the Chornobyl accident (Czeizel 1991) [40], similarly, those in the vicinity of nuclear waste reprocessing plant in Beaumont- Hague (Slama et al. 2008) [237] showed no effect when compared with an unexposed reference group. Populations in the vicinity of nuclear power plants in Taiwan also showed no effect (Wang et al. 2010) [247]. Wang et al analyzed pregnancy outcomes in 5,679 individuals, of which 4,491 were in the "plant-vicinity" group, and 1,188 in the "non-plant-vicinity" group (OR 1.04 (95% CI =

0.79–1.37)). Mangones et al [208] investigated birth weight amongst people living in the vicinity of Indian Point nuclear power plant. The results showed an increase in risk of low birth weight over time, but this was in zones 3 and 4 (furthest) compared to zone 1 (closest) to the nuclear installation (Mangones et al. 2013). Lastly, a case-control study of maternal residential proximity to nuclear facilities in Texas and the relationship with low birth weight in offspring revealed no statistically significant differences [70]. Compared with the reference group (50 km from a nuclear facility), the exposed groups (0–10 km away) showed no increase in low birth-weight risk (adjusted odds ratio OR 0.98 (CI 0.59, 1.61) (Gong et al. 2017). The sample size was limited to two nuclear power plants and no directly measured data on radiation exposure were available.

Confidence assessment for birth weight. In summary, there are an insufficient number of occupationally and medically exposed studies to perform an assessment, meaning there is *inadequate evidence* to determine if there is an effect on birth weight. When the confidence assessment was performed on environmentally exposed populations, all [40, 70, 208, 237, 247] studies had a potential risk of exposure after conception. No downgrades were warranted however an upgrade was made for consistency within results as all studies concluded no effect. This translated into *moderate-high confidence for no effect* on birth weight.

Confidence assessment for 'all' exposure situation

When only those studies with *good-high* rating that parent/s were exposed (all exposure situation) preconceptionally only (question 2) were considered [115, 154, 257, 305], one upgrade was warranted due to the large magnitude in effect, however this cannot be translated into an effect on birth weight due to inconsistencies in the results (binomial test; p value = 0.93).

'Other' pregnancy outcomes

Other pregnancy outcomes have also been identified in eight studies (Table 7). These include sex ratio, twinning and preterm birth. One study was excluded due to a tier 3 risk of bias rating [146] and two studies excluded due to a high RoB for question 2 [127,229] (Supplementary material, Table 4).

Occupational exposure

Studies that show an effect. Dickinson et al. [284] researched the sex ratio of children born to male nuclear workers at Sellafield in Cumbria, northern England with approximate 90-day preconceptional doses of either <10 mSv or >10 mSv. The study included 260,060 singleton births between 1950 and 1989. Findings showed the sex ratio among children of men employed at any time at Sellafield was 1.094 (95% CI: 1.060, 1.128), significantly higher than

Table 7. Studies investigating 'other pregnancy outcomes' in the offspring of radiation exposed parents.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
75	Irgens et al. (2003)	Commercial aircrew, Norway	Control= 1,621,186 Pilot= 2367 Cabin attendant= 3716	Preterm birth	**OR (95% CI)** **Year proceeding birth** Male pilots = 0.78 (0.54–1.13) **Ever** Male pilots = 0.85 (0.61–1.18)	No effect
114	Maconochie et al. (2001)	Nuclear industry workers, UK	>46 000	Sex Ratio	Total livebirths reported by male workers Sex Ratio= (1·06) **OR (95% CI)** = 1·00 (0·98–1·02)	No effect
284	Dickinson et al. (1996)	Sellafield male radiation workers, UK	260,060 births	Sex Ratio	**Sex Ratio (95% CI)** Sellafield= 1.094 (1.060 1.128) Other Cumbrian children= 1.055 (1.046, 1.063)	Effect[b]
257	Källén et al. (1998)	Radiotherapy for skin hemangioma, Sweden	19,494	Sex ratio twinning	**Sex ratio (95% CI)** 1.06 (0.91–1.89)	No effect
208	Mangones et al. (2013)	Vicinity of nuclear power plant, India	328,124 total Zone 1 = 35,038 Zone 2 = 49,313 Zone 3 = 140,017 Zone 4 = 103,756	Prematurity	**Rate ratios (95% CI) for comparison to zone 1 (Zone 1 closest to radius, zone 4 furthest)** Zone 2 = 1.02 (0.98- 1.06) Zone 3 = 0.88 (0.85–0.91) Zone 4 = 1.10 (1.06–1.13)	No effect
237	Slama et al. (2008)	Vicinity of nuclear waste reprocessing plant in Beaumont-Hague, France	1057 202	Infertility	**RR (95% CI)** Reference area = 1 Beaumont-Hague= 0.99 (0.64–1.55)	No effect
247	Wang et al. (2010)	Proximity to Nuclear Power Plant, Taiwan	5679	Premature birth	**OR (95% CI)** 1.21 (0.95–1.53)	No effect
128	Mudie et al. (2010)	Nuclear Testing in Kazakhstan	***11,605 deliveries*** 33 36 48 24 33 36 48 24	Different sex twining Same sex twinning	**OR (95% CI)** >20.0 = 1 20–39.9mSv= 0.93 (0.41- 2.13) 40–59.9mS= 1.95 (0.87- 3.94) ≥60.0mS= 0.68 (0.26- 1.80) >20.0mS= 1.00 20–39.9mS= 1.57 (0.87- 2.81) 40–59.9mS= 1.48 (0.81- 2.68) ≥60.0mS= 1.32 (0.69- 2.51)	No effect[a]

[a]Weak evidence with no dose response, authors suggest no significant effect and interpret with caution.
[b]The sex ratio among children of men employed at any time at Sellafield was significantly higher than that among other Cumbrian children.
OR: Odds Ratio; RR: Relative Risk; 95% CI: 95% Confidence Interval.

that among other Cumbrian children, 1.055 (95% CI: 1.046, 1.063). This was more pronounced in the 345 children whose fathers were estimated from annual dose estimates to have received more than 10 mSv of external radiation in the 90 days preceding conception (1.396 (95% CI: 1.127, 1.729)), although no significant linear trend between sex ratio and preconceptional dose was found.

Studies that do not show an effect. Maconochie et al [114] found no significant difference in sex ratio amongst 46,000 children born to UK nuclear industry workers when compared to the general population in England and Wales. Self-reported information was linked to dose at the time of conception and total parental external dose, principally based on film badge measurements (Maconochie et al. 2001). While Irgens et al [75] who examined a number of different pregnancy outcomes, similarly, reported no increase in risk of preterm birth in male pilots (RR 0.85) (Irgens et al. 2003).

Non-cancer associated medical exposure

A normal sex ratio of 1.07 (expected 1.06) and twinning 382 (expected 344) was reported in the non-cancer associated medically (skin hemangioma) exposed individuals (Källén et al. 1998) [257].

Environmental exposure

Studies that show an effect. The only study which showed an effect in this health outcome grouping was that reported by Mangones et al [208]. They showed an increase in premature births amongst people living in the vicinity of Indian Point nuclear power plant. Specifically, 2.1 major malformations per 1000 births, including premature births, were reported over a 10-year period although there was no relationship to proximity to the nuclear power plant (Mangones et al. 2013).

Studies that do not show an effect. In contrast to this, a vicinity study around nuclear power plants in Taiwan (Wang et al. 2010) [247]) reported the adjusted OR for premature birth to be 1.21 (95% CI = 0.95–1.53), p = .121. No difference in prevalence ratio of 12-month involuntary infertility was found in populations living in the vicinity of a nuclear waste reprocessing plant in Beaumont-Hague (0.99, 95% CI 0.64 to 1.55), compared to a reference area (Slama et al. 2008) [237]. Mudie et al [128] examined twinning in offspring of parents chronically exposed to radioactive iodine, 137-Cs and 90-Sr from nuclear testing in Kazakhstan reporting an absence of any effect. Overall, the same-sex twinning rate was 7.85 per 1000 and the opposite-sex twinning rate was 4.45 per 1000, with no differences between radiation exposure categories, parental age at radiation exposure, or year of birth. Different-sex, but not same-sex, twinning increased with maternal age (P(trend) = 0.04) and increased soon after radiation exposure (OR = 4.08) for births within 5 years compared with 20 years after exposure (Mudie et al. 2010). However, this effect was similar in low and high radiation exposure areas and is based on low numbers.

In summary, although the majority of studies examined show no effect on other pregnancy outcomes, the varying categories of health outcome prevented any confidence assessment being performed.

Summary of findings for pregnancy outcomes.

- The largest health outcome category based on number of studies within this pregnancy outcomes group was congenital abnormalities.
- A variation in results reported is observed between differently exposed populations. For occupationally and medically exposed populations, for which there is greater confidence in the timing of exposure, most studies show *an effect for congenital abnormalities*, however the small number of studies available for analysis limits the strength of this finding. Indeed, for occupationally exposed parents with a *good-high* rating that parent(s) were exposed preconceptionally only, no conclusions could be drawn due to inconsistencies in the results.
- There is some evidence to suggest an increase in NTDs amongst offspring of exposed populations.
- For A-bomb survivor studies, which represent the largest cohort studied, a non-significant increase in new-born diseases is seen.
- No evidence of a dose effect was seen across any of the studies.
- Environmentally exposed populations represent the majority of studies whereby a mixture of effects/no effects were reported; however, these studies all lack critical information on the timing of exposure in relation to conception.

What is the evidence for increased genomic anomalies?

A total of seventeen studies were identified investigating genetic alterations (mutations and/or chromosome aberrations) in offspring of exposed individuals (Table 8). This consisted of nine studies involving occupational exposure, six Atomic bomb studies, and two environmental studies. Studies excluded from analysis included [102] as tier 3 and [63, 277, 265, 278, 299, 300, 301, 302] due to *high* risk of bias relating to post-conception exposure (Supplementary table 5).

Occupational exposure

Studies that show an effect. Multiple studies examined DNA mutations and chromosome aberrations in offspring of Chornobyl Nuclear Power Plant clean-up workers. Aghajanyan and Suskov [5] quantified unstable chromosome aberrations in children of exposed parents from the Chornobyl nuclear accident. The study included two groups; group 1 (average effective dose of 231 mSv; individual doses 50–480 mSv over 2 weeks – 6 months) consisted of fathers who were liquidators and mothers living in non-contaminated areas, whereas group 2 consisted of fathers, mothers

Table 8. Studies investigating genomic anomalies in the offspring of radiation exposed parents.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
5	Aghajanyan and Suskov (2009)	Chernobyl, Ukraine	Children of liquidators: 79 Children from contaminated areas: 80 Controls: 12	Chromatid type Chromosomal type Chromatid type Chromosomal type Chromatid type Chromosomal type	**Frequency** 1.62 ± 0.13 0.17 ± 0.03 1.63 ± 0.12 0.22 ± 0.02 1.05 ± 0.12 0	Effect reported
6	Aghajanyan et al. (2011)	Chernobyl, Ukraine	Case= 39 offspring Control= 12 offspring	Single fragments Chromatid exchanges Dicentrics All aberrant cells Single fragments Chromatid exchanges Dicentrics All aberrant cells	**Frequency** Children of liquidators 2.67 ± 0.26 1.67 ± 0.26 0.10 ± 0.04 2.67 ± 0.26 Controls 1.03 ± 0.12 0 0 1.13 ± 0.12	Effect reported
85	Kiuru et al. (2003)	Chernobyl clean- up workers, Ukraine	148 born after accident	Minisatellite Mutations	**OR (95% CI)** 1.33 (0.80–2.20)	Effect reported[a]
160	Slebos et al. (2004)	Chernobyl clean- up workers, Ukraine	72	Minisatellite mutations	**Mutation frequency** (%) Born before = 1.62 Born after = 2.46; p = 0.18 MiniS 33.15 probe Born before = 1.5 born after = 1.01. p= 0.81	No effect[b]
188	Weinberg et al. (2001)	Chernobyl liquidators, Ukraine	41 born after 22 born before 28 from uncontaminated regions	Microsatellite mutations	Sevenfold increase in the number of bands for children conceived after parental exposure when compared to children conceived before P= <10–6	Effect reported
189	Weinberg et al. (1997)	Chernobyl liquidators, Ukraine	13 families[d]	Microsatellite-mutations	**Total new bands** RADP PCR new bands No.= 38 Inter-SRR PCR new bands No.= 10	Effect reported
202	Livshits et al. (2001)	Chernobyl clean-up Workers, Ukraine	Control= 163 Case= 183	Minisatellite mutation	**Mutation rate per band** Total = 0.06 (p = 0.64)	No effect
256	Furitsu K et al. (2005)	Chernobyl liquidators, Ukraine	Control= 69 Case= 61	Microsatellite mutations	**No. of mutations (mutation rate × 10 − 3)** **Autosomal** Control= 18 (8.5) Case= 11 (5.9) **X-linked** Control = 0 Case= 0 **Y-linked** Control= 3 (2.1) Case= 4 (2.9)	No effect
173	Tawn et al. (2015)	Sellafield nuclear workers, UK	Control = 103 offspring and 10 grandchildren Exposed = 152 offspring and 13 grandchildren	Minisatellite mutations	**Mutation rate** % Control: Paternal= 5.3%, Mean mutation rate: Paternal= 5.4%, Exposed: Paternal = 5.8, Paternal: 1.16 (95% CI 0.76–1.80) p = 0.53 Dose estimate groups 50–175mSv = 1.20 (95% CI 0.72–2.00) p = 0.53 >175 mSv = 1.13 (95% CI 0.68–1.88) p = 0.63	No effect
86	Kodaira et al. (2004)	A-bomb survivors, Japan	61 born to exposed parents 58 born to unexposed	Minisatellite mutations	**Mutation in paternal alleles** (%); Total in exposed= 4.6% Total in control= 4.7% Difference (95% CI) = −0.07% (-2.89, 3.36%)	No effect
74	Horai et al. (2018)	A-bomb survivors, Japan	3 family trios including 3 offspring 1 control family including 1 control	SNVs and indels	A-bomb survivors (paternal exposure) = 62, 81, and 42 de novo germline SNVs Control= 48 de novo germline SNVs	No effect
87	Kodaira et al. (2010)	A-bomb survivors, Japan	66 born to exposed parents 63 born to unexposed	Microsatellite mutations	**Mutation rate** (%) Exposed= 0.25 × 10 − 2 Control= 0.35 × 10 − 2	No effect
224	Satoh et al. (1996)	A-bomb survivors, Japan	64 born to exposed parents 60 born to unexposed	Minisatellite mutations Microsatellite mutations	**Mutation rates in 6 loci per locus per gamete** Exposed= 1.5% Control= 2.0% (p = 0.37) Exposed= 0% Control= 0.5%	No effect
261	Kodaira et al. (1995)	A-bomb survivors, Japan	64 born to exposed parents 60 born to unexposed	Six minisatellite mutations	**Mutation rates for different loci** Exposed= 1.5% Control= 2.0% (p = 0.37)	No effect
263	Asakawa et al. (2004)	A-bomb survivors, Japan	66 born to exposed parents 62 born to unexposed	Mutations	**Mutation rate** (%) Exposed = 0, Control = 1.8 × 10–5	No effect
12	Arruda et al. (2008)	Goiania accident, Brazil	7 children and 2 grandchildren	Mutations in AZFa loci.	sY84 and sY86 showed a duplication in 75% (12/16) of the exposed group.	Effect reported[c]
41	da Cruz et al. (2008)	Goiania accident, Brazil	Control= 300 Case= 17	Microsatellite mutations	**Mutation rate in 12 loci** Exposed= 2x10–^{2} Control= 6.9 × 10–^{4}	Effect reported

[a]Effect reported above > 20cSv.
[b]No increase germline minisatellite mutations but suggest a modest increase in germline mutations in tetranucleotide repeats.
[c]Some children had the same AZFa duplication as their parent.
[d]Exact number of offspring not reported.
OR: Odds Ratio; RR: Relative Risk; 95% CI: 95% Confidence Interval; SNV: Single nucleotide variant.

and children living in cesium-137 contaminated areas (135 – 688 kBq/m^2). The 12 offspring controls were non-irradiated residents residing in non-contaminated areas of similar ages. Group 1 included 79 children (41 boys and 38 girls) and group 2 had 80 children (47 boys and 33 girls). The results reported a similar frequency of unstable chromosome aberrations in children of liquidators and those who lived continuously in contaminated regions, both of which were higher than controls (aberrant cells for children of group 1 = 2.28+/-0.17, group 2 = 2.22+/-10.15, control 1.13+/-0.12) (Aghajanyan and Suskov 2009). Aghajanyan et al. [6], similarly studied the presence of unstable aberrations in the offspring of (Chornobyl liquidator) fathers. The average effective paternal dose was reported as 266 mSv with 70% of the liquidator's doses ranging from 50 to 460 mSv, however in one-third of liquidators the doses are unknown. The families lived in uncontaminated land with the ages of the children (n = 39) ranging from 1 month to 18 years. The controls (n = 12) were non-exposed residents of non-contaminated areas of similar ages. Results showed significantly increased aberrant genomes frequencies not only in exposed parents (n = 106, $p < .01$), but also in their children born after the accident (n = 159, $p < .05$) which Aghajanyan et al suggest relates to parental exposure leading to genomic instability in the offspring. Similar to the previous study, the frequency of aberrant cells in children of liquidators was 2.67+/-0.26 compared with 1.13+/1–0.12 in the control ($p < .05$) (Aghajanyan et al. 2011). One of the earliest studies investigated germline mutations in liquidators and their families who had emigrated to Israel from the Chornobyl disaster area [189]. A total of 47 individuals from 13 families (both parents and one or two children), who are now living in Israel, were included. The exact offspring number is not stated, neither is the time of emigration or any statistical analysis, however, Weinberg et al report new bands representative of *e novo* mutations only in children born to the liquidators and, only in the children born after the accident (Weinberg et al. 1997). A follow-up study to this consisted of 28 children from 14 families conceived before any exposure and an exposed group (modal dose of 50–200mGy) of 41 children born after the accident [188]. Using the observed frequency of 0.27 *e novo* bands per individual from the internal control, a spontaneous mutation rate of $4.5 \times 10^{-10}/1.2 \times 10^{-8}$ was obtained, which was considered to fit well with expectation, and a mutation rate of $3.4 \times 10^{-9}/9.0 \times 10^{-8}$ per bp in the exposed group; sevenfold higher than the background (Weinberg et al. 2001). Hereditary minisatellite mutation rates were compared in groups of offspring born to Chornobyl clean-up workers (from Estonia) either before (n = 198) or after (n = 148) the accident (Kiuru et al. 2003) [85]. Paternal doses ranged between 43mSv and 300mSv. In total, 94 *e novo* paternal minisatellite mutations were found at eight tested loci showing a non-significant increase in mutation rate among children born after the accident (0.042 (52 mutations)) compared to 0.036 (42 mutations) for those born before (OR 1.33, 95% CI 0.80– 2.20). Kiuru et al also reported an increased mutation rate among offspring born to workers who had received doses of 200mSv or above (OR 3.0, 95% CI 0.97–9.30), with no association with father's age (OR 1.04, 95% CI 0.94– 1.15) or, the sex of the child (OR 0.95, 95% CI 0.50– 1.79). Although it may be reasonable to assume the family of the liquidator remained in Estonia at the time of the accident or subsequent, the lack of details means this cannot be verified.

Studies that do not show an effect. A number of studies showed no effect. For instance, Livshits et al [202] compared mutations in minisatellite alleles in 183 offspring of Chornobyl clean-up workers with that in children born to fathers residing in unexposed regions, finding no significant differences between the two groups. Dose estimates for the liquidators, based upon duration and work activity, varied from 0.048 to 1.2 Sv, with a gonadal dose estimated to be below 150 mSv. The study population included children who were conceived whilst their fathers were working at the facility or, up to 2 months later (subgroup 1, n = 88) and children who were conceived at least 4 months after their fathers had stopped working at the site (subgroup 2, n = 95). Although an increase in mutation frequencies was seen for the majority of loci (e.g. 1.44 times higher for CEB1) in subgroup 1 compared to subgroup 2, this was not statistically significant ($p = .31$), with the authors acknowledging the potential for somatic mutations in the children (Livshits et al. 2001). Similarly, Slebos et al [160] found no difference in the germline mutation rate in children born to clean-up workers before and after the Chornobyl accident. Information on the father's recorded dose, their time in zone and the work performed, was provided for 36 tetrad families with both a 'before' and an 'after' child (72 children altogether), and 44 triad families, five with a 'before' child only and 39 with an 'after' child (Slebos et al. 2004). Similarly, no increase in microsatellite mutation rate was observed by Furitsu et al [256] in their study examining offspring (n = 61) of Chornobyl liquidators (estimated mean dose 39 mSv). Thirty-one autosomal, one X-linked and 40 Y-linked chromosomal loci were used. Mutation rates of 2.9×10^{-3} and 2.1×10^{-3} (Y-linked loci) and, 5.9×10^{-3} and 8.5×10^{-3} (autosomal loci) in the children of exposed and control parents, respectively were reported (Furitsu et al. 2005). This difference is not statistically significant. Furitsu et al state that likely exposures were low in dose, and therefore could be a reason to why no increases in mutation rates due to radiation could be found. More recently, Tawn et al [173] found no evidence of any elevation in germline mutation frequencies in children of male workers occupationally exposed to radiation at the Sellafield nuclear facility. Individual dose records were used to estimate chronic exposures of 51–764 mSv in the exposed group (152 offspring and 13 grandchildren) who were compared with a control group (103 offspring and 10 grandchildren) selected from workers with doses <50 mSv. Tawn et al s reported a non-statistically significant paternal mutation rate ratio of 1.16 (95% CI 0.76–1.80, $p = .53$) and no difference for the maternal mutation rate ratio (1.04, 95% CI 0.48– 2.28, p = 1.00) (Tawn et al. 2015).

Confidence assessment for occupational exposure. Overall, seven studies [6, 85, 160, 188, 202, 256, 173] were considered (studies 5 and 189 removed due to high likelihood in overlap of populations) resulting in an initial confidence assessment of *moderate*. Inconsistencies in the direction of effect can be explained by differing study populations, meaning no downgrade was made. Two of the seven [160, 202] had potential issues with indirectness, due to small sample size and/or inappropriate controls, while most of the studies did not report confidence intervals or a measure of precision. Thus, based on OHAT, no upgrades were warranted. Although a final confidence rating of *moderate* remains, due to the inconsistency in results reported by the authors, this translates into *inadequate evidence* in either direction for genomic anomalies (Binomial test; p value = 0.5).

When only those studies with *good-high* rating that parents were exposed preconceptionally only (question 2) were considered [6, 85, 160, 188, 256, 173], one upgrade was warranted due to the large magnitude in effect (studies 47, 48 and 153 all reporting OR greater than 2), however this cannot be translated into a health effect due to inconsistencies in the results (Binomial test; p value = 0.36).

Atomic-bomb survivors

A total of six studies investigated DNA anomalies/mutations amongst offspring of the atomic-bomb survivors, all of which show the absence of an effect.

One of the earliest papers, analyzed tandem-repetitive elements in germ cells in families with paternal and maternal gonadal doses of $0.711-5.460$ Sv and $>$ 0.01 Sv, respectively (Kodaira et al. 1995) [261]. The 50 test families included at least one parent who was exposed (64 children) was compared to 50 unexposed families (60 children). An insignificant mean mutation rate of 1.5% and 2.0% were observed in the six minisatellite loci of exposed and control parents, respectively. Following this, a second pilot study used a genome scanning approach to assess the genetic effects in mice and humans (paternal and maternal mean gonadal doses of 1.7 Sv) (Asakawa et al. 2004) [263]. Unexpectedly, no mutations were identified in the exposed families, whereas the control group had 1.8×10^{-5} ($P < 0.05$), which is considerably lower than estimated by previous publications. Technical limitations regarding spot analysis were recognized and false-negative rates were estimated. A follow-up study from this, again, found no evidence of increased mutation rates at minisatellite loci in the offspring of the A-bomb survivors (Kodaira et al. 2010) [87]. A very similar sample size to study [263] of 49 exposed (66 offspring) and 51 control families (63 offspring) were examined using a panel of 40 microsatellite loci. The study found seven mutations in the exposed alleles and 26 in the unexposed alleles, which does not indicate an effect from parental exposure to radiation. Satoh et al [224] in a follow-up to study to [261] also reported no effect in mutation rates. The mean mutation rates per locus per gamete in the six minisatellite loci were the same as previously reported (1.5%) for exposed gametes, mean parental gonadal dose 1.9 Sv and, 2.0% for unexposed gametes (p = .37). They also reported no difference in rates for the five microsatellite loci examined (0% for the exposed gametes and 0.5% for the unexposed gametes) (Satoh et al. 1996). Kodaira et al [86] similarly found no evidence of any increase due to parental exposure (paternal and maternal mean dose 1.61 Sv and 1.34 Sv respectively). The authors analyzed mutations at eight hypervariable minisatellite loci in 61 exposed families and 58 unexposed, again reporting the mean mutation rates in the exposed group to be marginally lower than in the control group (0.07% for the paternal alleles and 0.08% for the maternal alleles) (Kodaira et al. 2004). Some concerns are noted regarding the inability to analyze some samples due to occasional failures of PCR amplification. Lastly, Horai et al. examined e novo single-nucleotide variants in the germline of survivors, by whole-genome sequencing [74]. The limited study of three survivor family trios and one control family showed similar frequencies of e novo single nucleotide variants. No additional in-depth analysis was performed, however self-reported effects on health and paternal distance from the epicenter (~1.5 km) were used to estimate paternal doses of between 2.0 and 8.6 Gy (Horai et al. 2018).

Environmental exposure

Studies that show an effect. Two studies examined mutation frequencies in children of parents who were accidentally exposed to cesium-137 in Goiania after an abandoned radiotherapy unit was dismantled and dispersed among the community as scrap. Men and women were exposed over two weeks to 0.2–7 Gy prior to conception. DNA duplications were found in tagged sequences at a single locus (AZFa on the Y chromosome) in 75% (12/16) of offspring born to exposed individuals (Arruda et al. 2008) [12]. The sample consisted of eight sons of exposed fathers and one son of an exposed father and an exposed grandfather. Two families showed duplications of sY84 and sY86, in both fathers and their sons, whereas in four other families, only the sons had a duplication in the AZF region. A second larger study was carried out by da Cruz et al [41]. Microsatellite mutations in the offspring of exposed parents (10 exposed families and 17 children) were compared with a control group comprising 300 children, 19 years after the accident. An increase in the number of new alleles in the offspring of the exposed individuals were detected, with a mutation rate of 2×10^{-2} and a doubling dose for germline mutations of 0.03 per gene per Gy, whereas the spontaneous mutation rate in the control group was 6.9×10^{-4}. Chi-square tests showed that neither mother's age nor father's age both in control or exposed groups had an association with germline mutation frequency (p = .16 and p = .17, respectively) (da Cruz et al. 2008).

Confidence assessment for 'all' exposure situation. The confidence assessment on all eligible studies irrespective of exposure type [6, 74, 85, 160, 188, 256, 173 and 41] (excluding those which had follow-up studies, companion studies with smaller sample sizes, high RoB for postconceptional

exposure, rated as tier 3, (Supplementary table 4) translated into *inadequate evidence* for genomic anomalies due to four studies reporting an effect and four reporting no effect (binomial test; p value = 0.5).

Other' genetic anomalies

Other genomic anomalies included two occupational studies examining hypermethylation status and one environmental study investigating genetic differences in HLA genes (Table 9). The environmental study [89] was categorized as a tier 3 and two additional environmental studies [303, 304] were rated high risk of bias for exposure after conception and therefore all were removed from analysis (Supplementary table 6).

No differences in hypermethylation status were seen in the offspring (n = 16) of 83 Chornobyl clean-up workers (compared to a control group; 103 unirradiated volunteers (22 offspring) (Kuzmina et al. 2014) [101]. The same authors, Kuzmina et al [100] went on to examine hypermethylation of gene promoters in 74 unexposed offspring born to 124 irradiated subjects involving Chornobyl Nuclear Power Plant clean-up workers, nuclear workers, residents of territories with radioactive contamination with recorded individual doses of between 30 to 480 mSv of varying radiation quality. No differences were found between this population and an undefined control group comprising unexposed volunteers; however, it was acknowledged that larger offspring sample sizes are required (Kuzmina et al. 2016).

Summary of findings for genomic anomalies

- A moderate confidence rating for the body of evidence from DNA mutation and cytogenetic occupational studies translated into inadequate evidence in which to make any conclusions due to inconsistencies with the authors conclusions (four studies reported an effect and four reported no effect).
- All A-bomb survivor studies report no effect in the unexposed offspring.
- A confidence assessment could not be performed on environmentally exposed populations due to the majority having a high RoB for exposure post conception. Studies [12] and [41] were considered at low risk for this and did report an effect, although both were within the same population.
- Two studies reported no effect in methylation of specific genes of interest in offspring of Chornobyl workers.

What is the evidence for increased cancer rates?

A total of 36 studies were identified as investigating various types of solid cancer and non-solid cancer amongst offspring of exposed individuals (Table 10). Four studies were excluded as tier 3's [43, 42, 91, 138] and two additional exclusions wwere made due to issues around timing of exposure [68, 295]. Many studies report on both solid and non-solid cancers.

Occupational exposure

Studies that show an effect. A number of studies show an increase in cancer risk (solid and non-solid) amongst offspring of occupationally exposed parents. The first of these, Gardner et al [276], examined the incidence of leukemia and lymphoma among young (< 25 years) people living near the Sellafield nuclear plant in West Cumbria. The study included cases of leukemia (n = 52), non-Hodgkin's lymphoma (n = 22) and Hodgkin's disease (n = 23) in those born and diagnosed between 1950–85 for comparison with 1001 matched controls. The findings showed RRs for leukemia and non-Hodgkin's lymphoma (NHL) to be higher in children born near Sellafield, specifically, in those born to fathers employed at the plant at time of conception (2.44 (1.04–5.71)), and in those born to fathers who received a total preconceptional dose of ≥100 mSv (6.42 (1.57–6.3)) (Gardner et al. 1990). From this, Gardner et al proposed that childhood leukemia and NHL may be associated with fathers' exposure to ionizing radiation before conception asserting that this association might be causal. This was soon followed by an investigation of parental occupations of children with leukemia in west Cumbria, north Humberside and Gateshead (McKinney et al. 1991) [209]. No specific doses were stated, instead, parents were categorized as 'certain, likely and uncertain' to have been exposed. Although this study includes all exposure categories including gestational, data on cases exposed before conception only are recorded. From this, a total of 15 offspring born to exposed parents and 10 control cases were included. Significant associations were found between the incidence of childhood leukemia and reported preconception ionizing and non-ionizing radiation exposure of fathers; OR = 3.23 (95%CI= 1.36- 7.72). The authors do note a geographical

Table 9. Studies investigating 'other' genomic anomalies in the offspring of radiation exposed parents.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
101	Kuzmina et al. (2014)	Chernobyl liquidators and nuclear specialists, Ukraine	Control = 22 Test = 21	Methylation status of 4 genes (p16/CDKN2A, p14/ARF, RASSF1A, GSTP1A)	**Number of offspring** Control 0/22 Test 1/21 (GSTP1 gene)	No effect
100	Kuzmina et al. (2016)	Chernobyl clean-up workers, nuclear workers, residents in contaminated areas, Ukraine	Control = 282 Case = 124	Hypermethylation for a set of 5 genes (p16/INK4A, p14/ARF, RASSF1A, GSTP1, RARB)	No significant difference for control or case subjects (no statistics reported)	No effect

Table 10. Studies investigating solid and non-solid cancers in the offspring of radiation exposed parents.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
45	Dickinson et al. (2002)	Sellafield radiation workers, UK	Workers = 9859 Control= 256,851	All solid tumors Hodgkin's disease Brain and spinal tumors Other non-gender specific cancers 	**RR (95% CI)**, age in years 0–6 yrs= 1.4 (0.6–3.0) P value= 0.42 7–25 yrs= 1.6 (0.8–2.7) P value= 0.14 0–24 yrs= 1.5 (0.9–2.4) P value= 0.09 7–25 yrs= 1.4 (0.4- 3.9) P value= 0.55 0–24 yrs= 1.4 (0.3- 3.8) P value= 0.59 7–25 yrs= 1.7 (0.4- 4.5) P value= 0.42 0–24 yrs= 0.9 (0.2- 2.5) P value= 0.90 0–6 yrs= 2.2 (0.9- 4.7) P value= 0.09 7–25 yrs= 1.6 (0.6- 3.4) P value= 0.28 0–24 yrs= 1.9 (1.0–3.3) P value= 0.05	Effect[a]
81	Johnson et al. (2008)	Radiologists, US	81,262 born to females 24,678 born to males	Solid tumors Leukemia Lymphoma	**Hazard Ratio (95% CI)** 0 mGy= 1.0 0.0–0.17 mGy = 1.0 (0.6–1.6) 0.18–1.0 mGy = 0.9 (0.6–1.5) 1.01–12.6 mGy= 1.2 (0.5–3.1), P trend= 0.44 0 mGy = 1.0 >0- 0.17 mGy = 1.1 (0.6–2.0) 0.18- 1.0 mGy = 0.9 (0.5–1.8) 1.01- 12.6 mGy = 1.1 (0.3–3.7) P-trend= 0.72 0 mGy = 1.0 >0- 0.17 mGy = 2.3 (1.1- 4.9) 0.18- 1.0 mGy = 1.8 (0.9–3.9) 1.01- 12.6 mGy = 2.7 (0.9–8.7) P-trend= 0.32	No effect
120	Meinert et al. (1999)	Childhood Cancers, Germany	Controls= 2588 Cases= 2358 Cases= 1184	Solid tumours[b] Leukemia[c]	**OR (95% CI)** Paternal occupational exposure before conception In year before pregnancy= 1.20 (0.80–1.81) Involving dosimetry= 1.04 (0.30–3.62) Paternal occupational exposure before conception In year before pregnancy= 1.20 (0.83–1.73) Involving dosimetry= 1.80 (0.71- 4.58)	No effect for solid tumors, effect for Leukemia
139	Roman et al. (1999)	Nuclear industry, UK	39 557 children of male employees and 8883 children of female employees	All malignancies except leukemia and non-Hodgkin's lymphoma Leukemia and non-Hodgkin's lymphoma	**Rate ratio (95% CI)** Before employment and monitoring= 1.0 After employment and monitoring= 1.7 (0.9 to 3.3) Monitored (All) = 1.3 (0.7 to 2.2) External radiation only= 1.3 (0.7 to 2.4) External and internal= 1.2 (0.6 to 2.5) Before employment and monitoring= 1.00 After employment and monitoring= 1.0 (0.3 to 3.6) Monitored (All)= 1.8 (0.7 to 4.4) External radiation only= 1.5 (0.5 to 4.2) External and internal= 2.3 (0.8 to 6.6)	No effect
162	Sorahan et al. (1995)	Radiation workers, UK	Case= 35,949 Control= 38,323	All Childhood cancers Leukemia	**Odds ratio (95% CI)**, pre-employment and post- employment Dental surgeons Pre= 1.27 (0.61–2.68) Post= 1.50 (0.76–3.02) Veterinary surgeons Pre= 0.86 (0.24- 2.98) Post= 1.50 (0.48- 5.13) Radiologists Pre= 0.26 (0.00- 2.42) Post= 0.33 (0.01–4.16) Surgeons and anesthetists Pre= 1.00 (0.43–2.34) Post= 1.07 (0.48–2.40) Nuclear industry worker Pre= 1.86 (1.08- 3.29), p< 0.05 Post= 2.19b (1.28- 3.86), B = p< 0.01 Industrial radiographer Pre= 0.25 (0.01- 2.53) Post= 0.50 (0.08- 2.34) Dental surgeons Pre= 2.00 (0.43 to 12.37) Post= 1.75 (0.45 to 8.15) Veterinary surgeons Pre= 1.00 (0.19 to 5.36) Post= 2.00 (0.43 to 12.37) Surgeons and anesthetists Pre= 0.50 (0.11 to 1.87) Post= 0.63 (0.16 to 2.17) Nuclear industry worker Pre= 2.22 (0.97 to 5.54) Post= 3.14 (1.30 to 8.72), p< 0.01	No effect
164	Draper et al. (1997)	Radiation workers, UK	Case= 35,949 Control= 38,323	All cancers excluding leukemia and non-	**RR (95% CI)** Radiation exposure of fathers before the	No effect[b]

(*continued*)

Table 10. Continued.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
				Hodgkins lymphoma	child's conception Non-radiation worker= 1.00	
				Leukemia and non-Hodgkin lymphoma	Total preconception dose < mSv: <0.1 = 0.49 (0.01 to 9.48) 0.1–49.9 = 0.95 (0.54 to 1.68) 50.0–99.9 = 0.99 (0.13 to 7.41) >100.0 = 1.00 (0.07 to 13.77) Radiation worker total= 0.94 (0.56 to 1.58) Radiation worker total, not monitored= 0.89 (0.48 to 1.62) Non- radiation worker= 1.0 Total preconception dose < mSv): <0.1 = 8.17 (1.18 to ∞) 0.1–49.9 = 1.47 (0.81 to 2.68) 50.0–99.9 = 4.49 (0.60 to 51.98) >100.0 = 0.46 (0.01 to 5.17)	
238	Sorahan et al. (2003)	Radiation workers, France	Cases= 35,949	Cancers other than leukemia and non-Hodgkin's lymphoma[a] Leukemia and non-Hodgkin's lymphoma	**RR (95% CI)** Paternal employment at facilities participating in the National Registry for Radiation Workers Left employment before conception No= 1.0, Yes= 0.85 (0.38–1.89) Employed at the date of conception No = 1.0, Yes= 0.91 (0.51- 1.65) Employed in the year of diagnosis No= 1.0, Yes= 0.88 (0.44- 1.77) Paternal preconception dose categories: updated national data set excluding for LNHL 'Gardner cases' and their controls Non-radiation worker= 1.00 <0.01 = 1.00 (0.01- 78.50) 0.1–49.9 = 0.93 (0.52- 1.64) 50.0–99.9 = 0.99 (0.13–7.38) 100.0+ = 1.00 (0.07–13.80) left employment before conception No= 1.00 Yes= 1.04 (0.46–2.35) Employed at the date of conception No= 1.00 Yes= 2.34 (1.31–4.18), P< 0.01. Employed in the year of diagnosis No= 1.00 Yes= 2.26 (1.22–4.19), P< 0.01. Total preconception dose Non-radiation worker= 1.0 <0.01 = 6.73 (0.92–∞) 0.1–49.9 = 1.53 (0.85–2.77) 50.0–99.9 = 3.83 (0.42–47.67) 100.0+ = 0.86 (0.07–6.57)	Effect
287	Parker et al. (1993)	Children of Sellafield male radiation workers, UK	Cases= 9256	Leukemia	7% (38 person-Sv) of the collective total preconceptional dose and 7% (3 person-Sv) of the collective dose for the six months before conception were associated with children born in Seascale- The distribution of the paternal preconceptional radiation dose is statistically incompatible with this exposure providing a causal explanation for the cluster of childhood leukaemias in Seascale.	No effect
289	Roman et al. (1993)	West Berkshire and North Hampshire health districts-workers of nuclear industry, UK	Cases= 54 Control= 324	Leukemia or non-Hodgkin's lymphoma	**RR (95% CI)** 2.5 (0.6–9.0)	Effect
290	Roman et al. (1996)	Children born to medical radiographers, England	3882 pregnancies	All malignancies	**RR (95% CI)** 2.7 (0.9–6.5)	Effect
293	Bunch et al. (2009)	Cancer in the offspring of female radiation workers: a record linkage study,	Cases= 52,612 Control= 52,612	Leukemia or non-Hodgkin's lymphoma All cancers excluding Leukemia or non-Hodgkin's lymphoma	**RR (95% CI)** 1.20 (0.31, 4.97) 2.60 (0.87, 9.32)	No effect[h]
84	Kinlen (1993)	Young people, Scotland	Cases= 1369 Controls= 4107	Leukemia Leukemia and non-Hodgkin's lymphoma	**OR (95% CI)** Paternal exposure Before conception= 1.00 0–01–49–99 mSv= 1–32 (0.58 – 3.02) ≥50mSv= 1–04(0.21- 5.17), p = 0.81 Paternal exposure	No effect

(*continued*)

Table 10. Continued.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
					Before conception= 1.00 0 01–49 99 mSv= 1–14 (0.51- 2.54) ≥50mSv= 1 02 (0.20- 5.06)	
119[d]	Mclaughlin et al. (1993)	Regions of Ontario, Canada, with an operating nuclear facility.	Case= 112 Control= 890	Leukemia	**OR (95% CI)** Paternal radiation exposure Total whole-body dose (external plus internal due to tritium) (mSv): Before conception: 0 = 1.00 0.1–1.49 = 0.80 (0.26- 2.47) ≥50 = 1.09 (0.21- 5.55), P value= 0.91 During 6 months before conception: 0 = 1.00 0.1–4.9 = 0.73 (0.16- 3.31) ≥5 = 1.25 (0.32- 4.75), P value= 0.85 External whole-body dose before conception (mSv): 0 = 1.00 0.1–49 = 0.77 (0.25- 2.36) ≥50 = 1.29 (0.23- 7.00), P value= 0.37 Radon dose (internal dose to lung) before conception (working level months): 0 = 1.00 0.1–49 = 1.89 (0.21- 17.3) ≥50 = 5.14 (0.48- 55.2), P value= 0.39	No effect
209	Mckinney et al. (1991)	Children with leukemia in West Cumbria and Gateshead, UK	Case= 15 Control= 19	Leukemia and non-Hodgkin's lymphoma	**OR (95% CI)** 3.23 (1.36- 7.72)	Effect but interpret with caution
9	Amemiya et al. (1993)	A-bomb survivors, Japan	Cases= 7 offspring	Retinoblastoma	**Frequencies** Japan= 1:16,391 Nagasaki Prefecture= 1:16,053, City= 1: 14,144 Hiroshima Prefecture= 1:18,219, City= 1: 19,352	No effect
76	Izumi et al. (2003)	A-bomb survivors, Japan	40,487 total offspring	Solid tumors Hematopoietic tumors	**Risk ratio (95% CI)** Paternal Exposure (mSv) age 1–9 years 0–4 (reference)= 1.00 P= 0.78 5–49 = 0.80 (0.17–3.68) >50-= none reported Continuous dose (100 mSv) = 1.03 (0.84–1.14) P value = 0.66 Paternal Exposure (mSv) 20+ years old 0–4 (reference)= 1.00 P value= 0.60 5–49 = 0.99 (0.63–1.49) 50–149 = 0.89 (0.55–1.35) 150–499 = 1.09 (0.71–1.63) 500–4000 = 0.68 (0.39–1.10) Unknown = 1.12 (0.76–1.61) Continuous dose (100 mSv) = 0.96 (0.92–1.00) P value = 0.07 Paternal Exposure (mSv) age 1–9 years 0–4 (reference)= 1.00 P value= 0.47 5–49 = 1.07 (0.36–3.13) >50–149= non reported Continuous dose (100 mSv) = 0.97 (0.73–1.09) P value= 0.70 Paternal Exposure (mSv) 20+ years old 0–4 (reference)= 1.00 P value= 0.86 5–49 = 1.68 (0.37–5.60) 50–149 = 0.58 (0.03–3.06) 150–499 = 1.10 (0.17–4.21) 500–4000 = 0.63 (0.03–3.28) Unknown = Not estimated Continuous dose (100 mSv) = 0.91 (0.03–3.28) P value= 0.36	No effect3
77	Izumi et al. (2003)	A-bomb survivors, Japan	41,010 A-bomb offspring	All cancers excl leukemia Leukemia	**Mortality raw numbers** =279 =35	No effect
196	Yoshimoto et al. (1990)	A-bomb survivors, Japan	67,574 children	All cases (including Leukemia)	Linear Multiple Regression Analysis of incidence < 20 years, by Conjoint Parental Dose = −.000081	No effect
71	Grant et al. (2015)	A-bomb survivors, Japan	75,327 offspring	Cancer mortality	**HR (95% CI)** for continuous dose response (1Gy) Fathers' exposure= 0·815 (0·614–1·083)	No effect
10	Andersson et al. (1994)	Thorotrast patients, Denmark, UK	369 offspring total	Lung Testis Melanoma of skin Thyroid gland All other All sites and types (including non-solid cancer) Total cancer incidence	**SMR ratio[b] (95% CI)** = 7.3 (0.2–40.5) =2.8 (0.1–15.3) =5.9 (0.7–21.2) =16.8 (0.4–93.5) = 0.0 (0–1.2) = 1.3 (0.5–2.9) By dose SMR ratio (95% CI)	No effect

(*continued*)

Table 10. Continued.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
				Non-Hodgkin's lymphoma Leukemia	0–749mSv = 1.1 (0.2–3.2) 750- 1499mSv= 1.9 (0.2–6.9) ≥1500mSv= 2.3 (0.1–12.8) All= 1.3 (0.5–2.9) = 0.0 (0–35) =0.0 (0–21.2)	
17	Bailey et al. (2010)	Acute lymphoblastic leukemia in children, Australia	Cases= 416 Controls= 1361	Acute Lymphoblastic Leukemia[f]	**OR (95% CI)** Any diagnostic X-rays Paternal= 1.17 (0.88–1.55)	Effect
107	Linabery et al. (2006)	Medical test irradiation, US and Canada	Cases= 158 Controls= 173	Acute lymphoblastic leukemia and Acute myeloid leukemia combined	**OR (95% CI)** Paternal preconception irradiation Any exposure No= 1.00 Yes= 0.92 (0.57–1.47) No. of exposures 0 = 1.00 1 = 1.30 (0.69- 2.47) ≥2 = 0.75 (0.43- 1.31), P trend= 0.41	No effect
157	Shu et al. (1994)	Children with leukemia, US and Canada	Cases= 382 Controls= 511	Leukemia[g]	**OR (95% CI)** Paternal X-ray exposure Never= 1.0 Ever (prior to conception= 1.08 (0.42- 2.81) More than a year= 0.95 (0.36- 2.52) Within a year= 1.32 (0.49- 3.54) Within a month= 2.56 (0.67- 9.75)	Effect
90	Kossenko, (1996)	Techa river residents, Russia	Case= 17000	Leukemia Solid Cancer	The leukemia risk, estimated on the basis of the linear model of absolute risk, was 0.85 per 10, 000 person-y Gy of the dose accumulated in red bone marrow. Solid cancer risk (except osteosarcoma), estimated using linear model of relative risk, was 0.65 per Gy of dose accumulated in soft tissues.	No effect
212	Michaelis et al. (1992)	Vicinity to nuclear plant, West Germany	30 143 274 19 82 152	Acute leukemia	**RR (95% CI)** 0–14 years <5km= 1.44 (0.81 – 2.79) P value= 0.143 <10km= 1.00 (0.78- 1.31) P value= 0.523 <15km= 1.06 (0.88- 1.28) P value= 0.285 0–4 years <5km= 3.01 (1.25–10.31) P value= 0.015 <10km= 1.18 (0.84- 1.73) P value= 0.199 <15km= 1.28 (0.99- 1.69) P value= 0.037	Slight increase[d]
210	Mclaughlin et al. (1993)	Born to mothers residing in the vicinity of Ontario (Canada) nuclear facilities	4 14 4 63 3 88	Leukemia	Ratio of the observed: expected number of childhood leukemia deaths or incident cases. Leukemia mortality for Ontario, Canada regions containing a nuclear facility (within a 25 km radius), according to child's residence at birth or at death Research and development= 0.56 (0.15–1.4) Uranium refinery= 1.32 (0.72–2.2) Uranium mines and mill= 0.87 (0.23–2.2) Power station—Pickering= 1.09 (0.84–1.4) Power station—Bruce= 1.35 (0.27–4.0) All Ontario facilities= 1.07 (0.86–1.3)	Slight increase[e]
219	Pobel and Viel (1997)	Leukemia among young people near La Hague nuclear reprocessing plant, France	25 1 1 0	Leukemia	**RR (95% CI)** Fathers' exposures (mSv) From conception[†] to birth: Reference= 1.00 0.1–0.99 = 1.13 (0.02 to 11.09) 1–3.99 = 1.19 (0.03 to 11.09) ≥ 4= -	No effect
260	Kaatsch et al. (1998)	Vicinity to nuclear power plants, Germany		Acute leukemia Lymphoma	**RR (95% CI)** 0–4 years <5 km= 1.39 (0.69–2.57) 0–14 years <15 km= 0.88 (0.53–1.49) <10 km= 1.15 (0.64–2.06)	Slight increase[f]
276	Gardner et al. (1990)	Young people near Sellafield nuclear plant, West Cumbria, UK	52 Cases of leukemia, 22 of non-Hodgkin's lymphoma, and 23 of Hodgkin's Controls= 1001	Leukemia Leukemia and non-Hodgkin's lymphoma	**RR (95% CI)** for fathers timing of parental employmentBefore conception= 1.39 (0.53–3.65) At conception= 2.07 (0.69–6.14) At birth= 1.92 (0.66–5.56) Before diagnosis= 0.89 (0.36- 2.18) Ever= 1.22 (0.54- 2.74) 6 months before conception 1–4mSv= 1.10 (0.25–4.91) 5–9mSv= 3.04 (0.28–32.61) More than 10 = 8.21 (1.62–41.73) Before conception= 1.08 (0.47- 2.52) At conception= 1.48 (0.59- 3.75) At birth= 1.26 (0.48- 3.28) Before diagnosis= 0.64 (0.28- 1.45)	Effect

(*continued*)

Table 10. Continued.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
					Ever= 0.81 (0.39- 1.69) 6 months before conception 1–4mSv= 0.97 (0.28–3.41) 5–9mSv= 1.12 (0.13–9.93) More than 10 = 5.01 (1.13–22.24)	
280	Bithell JF et al. (1994)	Populations residing near nuclear installations, England and Wales.	Cases= 1945	Leukemia and non-Hodgkin's lymphoma	**Observed/expected ratio** All sites= 0.99, p value= 0.223	No effect[g]
286	Kinlen et al. (1995)	Children living in the vicinity of large rural construction sites and Sellafield, UK	Offspring of over 1000 work men, exact number not given	Leukemia and non-Hodgkin's lymphoma	**Observed/expected ratio (95% CI)** 1.37 (1.15–1.63)	No effect
291	Sharp et al. (1996)	Vicinity of nuclear sites, Scotland	Dounreay= 3527 Chapelcross= 10908 Hunterston= 43236 Torness= 7894 Faslane= 45250 Holy Loch= 47595 Rosyth= 197015	Leukemia and non-Hodgkin's lymphoma	**Observed/expected ratio (95% CI)** Dounreay= 1.99 (0.91–3.77) Chapelcross= 1.08 (0.60–1.78) Hunterston= 0.84 (0.61–1.14) Torness= 0.90 (0.41–1.72) Faslane= 0–90 (0.41–1.72) Holy Loch= 0.85 (0.62–1.13) Rosyth= 1.02 (0.90–1.16)	No effect
292	Wakeford and Parker, (1996)	Young persons resident in small areas of West Cumbria, UK	Cases= 41	Leukemia and non-Hodgkin's lymphoma	**Incidence rate ratio (95% CI)** West Cumbria (including Seascale= 1.01 (0.72- 1.41) West Cumbria (excluding Seascale= 0.87 (0.60- 1.24) Copeland (including Seascale)= 1.62 (1.13–2.31) Copeland (excluding Seascale)= 1.37 (0.90–1.99)	No effect
294	Hoffmann et al. (2007)	Geesthacht nuclear establishments near Hamburg, Germany	14 cases	Leukemia	**Standardized incidence ratios (SIRs), (95% CI)** 3.5 (1.9–5.9)	Effect
295	Kendall et al. (2013)	Natural background radiation, UK	Cases= 27,447 Controls= 36,793	Leukemia	**Excess relative risk (ERR), (95% CI)** 12% ERR (3–22); two-sided P = 0.01, per millisievert of cumulative red bone marrow dose	Effect
296	Urquhart et al. (1991)	Dounreay nuclear installation, Scotland	Cases= 14 Controls= 55	Leukemia and non-Hodgkin's lymphoma	**OR (95% CI)** Father employed in nuclear industry at conception 0.38 (0,06- 2.34)	No effect
297	Bunch et al. (2014)	Vicinity of Sellafield and Dounreay, UK	122, 980 individuals within Allerdale and Copeland Districts and 213,760 individuals within the remainder of Cumbria	All malignancies	**Standardized incidence ratios (SIRs), (95% CI)** Seascale = 3.58 (1.54- 7.05) Copeland and Allerdale county districts= 0.94 (0.80–1.09) Remainder of Cumbria= 0.96 (0.86- 1.08)	No effect
298	Craft et al. (1993)	Vicinity of Seascale, UK	Cases= 6686	Brain tumors	**Poisson probability** p = 0*000009	Effect

[a]Effect but authors conclude unlikely from radiation.
[b]No effect from radiation, any increase may be a chance finding or from another factor.
[c]No effect, although due to the small sample size, an effect cannot be ruled out at this time.
[d]A slight non-significant increase in acute leukemia in the installation regions when compared to non-installation regions was seen.
[e]Childhood leukemia is slightly, but not significantly increased.
[f]Children <5yo with acute leukemia living within 5 km of the nuclear installation did show an increased tendency (RR = 1.39), but this was based on 12 children. 4 of which were living close to the Krummel nuclear power plant (near Hamburg) [Associated with leukemia already. The remaining 19 did not show an increased incidence. Apart from the Krummel power plant, there were no significant RR for all malignancies or acute leukemia at any of the nuclear installation sites compared to controls.
[g]In none of the 25 km circles around the installations was the incidence ratio significantly greater than 10. The only significant results for the linear risk score test were for Sellafield (P = 0.00002) and Burghfield (P = 0.0031).
[h]Authors conclude no effect, although state that a weak association was observed between maternal exposure and cancer in the offspring however this was based on low sample sizes∞ Conditional maximum likelihood estimate is not available because the sufficient statistic is at one extreme of its range. The median unbiased point estimate is shown.
OR: Odds Ratio; RR: Relative Risk; 95% CI: 95% Confidence Interval; SMR: Standardized Mortality Ratio; HR: Hazard Ratio.

overlap with the Gardner study however, identifying four matches (representing control and test) which are included in both studies. Shortly after, Roman et al (1993) [289] published a case-control study of leukemia and NHL among children aged 0–4 years living in West Berkshire and North Hampshire health districts. The results showed five (9%) of the 54 cases and 14 (4%) of the 324 controls had fathers or mothers, or both, who had been employed by the nuclear industry (RR 2.2, 95% CI 0.6 to 6.9). The RR of those fathers who had been monitored for exposure before their child was conceived was 9.0, 95% CI 1.0 to 107.8, although none had accumulated a recorded dose of more than 5 mSv and none had been monitored at any time in the four years before conception. Further, no dose-response was evident among fathers who had been monitored. Roman et al (1996) [290] also reported increased risks of cancer in the children

of male radiographers (RR 2.7, 95% CI 0.9–6.5,). However, it is noted that the findings are based on small samples sizes.

Draper et al aimed to test the 'Gardner hypothesis' examining 38,323 control and 35,949 offspring of radiation workers. Measured paternal doses (n = 82) were between 0.1 and >100mSv and maternal total preconception doses (n = 15), 0.1 - 50 mSv. After cases studied by Gardner et al were excluded, it is reported that fathers of children with leukemia or NHL were significantly more likely than fathers of controls to have been radiation workers (RR 1.77, 95% CI 1.05 – 3.03). However, no dose-response relationship was seen, indeed the risk was not increased for fathers with a lifetime preconception dose of 100 mSv or more, or for those who had a dose in the six months before conception of 10 mSv or more. Draper et al interpret the observed associations as chance findings or to have resulted from exposure to infective or other agents (Draper et al. 1997) [164].

Dickinson et al [45] examined cancer rates in offspring of male Sellafield workers who were assessed for pre-conceptional internal exposure (via urine analysis) from plutonium, fission products, and natural uranium, as well as external monitoring by film badge (although details of dose were not reported). The control group included 256,851 children of the non-Sellafield cohort while the cases included 9859 children of radiation workers. Children of radiation workers had an increased risk of all solid tumors (0–24 years, RR = 1.5, 95% CI: 0.9–2.4, p = .09) when compared to the non-Sellafield controls, which when further examined showed this largely related to 'other non-gender-specific cancers' (0–24 years, RR = 1.9, 95% CI: 1.0–3.3, p = .05). However, when adjusted for demographics (parental migration/community population mixing), the overall excess among children (0–24) was no longer statistically significant (RR = 1.7, 95% CI: 0.8–3.2, p = .50). Fathers monitored for pre-conceptional exposure to internal radionuclides did not show any increased risk of cancer (Dickinson et al. 2002). Sorahan et al [238] examined the incidence of leukemia and NHL showing statistically significantly increases with paternal employment on the date of conception (RR 2.34, 95% CI 1.31, 4.18) and, for paternal employment on the date of diagnosis (RR 2.26, 95% CI 1.22, 4.19). In contrast, the RR for those whose employment ceased before conception was close to one (RR 1.04, 95% CI 0.46, 2.35). For all cancers excluding leukemia and NHL, the RR was 0.94 (95% CI 0.56, 1.58). Sorahan et al discuss the lack of an association with paternal pre-conception doses and support the idea the increased risks observed relate to infective agent exposure due to high levels of population mixing (Sorahan et al. 2003). Lastly, Meinert et al [120] investigated cancer incidence in the offspring of healthcare providers in Germany. Data on 2358 cases (1184 leukemia's, 234 NHLs, 399 central nervous system tumors, 160 neuroblastomas, 147 nephroblastoma's, 97 bone tumors, and 137 soft tissue sarcomas) and 2588 controls were analyzed. A non-significant OR of 1.80 (95% CI: 0.71–4.58) was reported for those working whilst under dosimetry surveillance before conception of the child however radiation doses were mostly unknown or below the level of detection, and no dose exceeded 30 mSv. X-ray examinations of the father (but not of the mother) were significantly related to childhood leukemia (OR= 1.33; 95% CI 1.10–1.61) (Meinert et al. 1999).

Studies that do not show an effect. Urquhart et al (1991) [296] examined whether the observed excess of childhood leukemia and NHL in the area around the Dounreay nuclear installation was associated with established risk factors, with factors related to the plant or, with parental occupation in the nuclear industry. The study included 14 cases in children (<15 years of age) who were diagnosed between 1970 and 1986 and, 55 controls born in the area matched for sex and date of birth. No increase in relative risks for maternal exposure to x rays, social class of parents, employment at Dounreay before conception or diagnosis or, father's dose of ionizing radiation before conception were found. The authors conclude the raised incidences of childhood leukemia and NHL in this small study cannot be explained by paternal occupation at Dounreay or, by paternal exposure to external ionizing radiation before conception. No association between childhood leukemia and occupational exposure of fathers to ionizing radiation before the time of conception was identified (OR = 0.87, 95% CI 0–32–2.34) in the offspring of nuclear workers in Ontario (103–112 mSv lifetime dose) (McLaughlin et al. 1993) [119]. The study included fathers working in the nuclear industry, mothers living in the vicinity (at the time of the childbirth), and children with (n = 112)/without (n = 890) leukemia identified from the Ontario Cancer Registry. The mother's exposure was not considered as a potential risk factor and therefore residence within the vicinity was selected for both case and controls. Similarly, Kinlen et al [84] found no relationship between paternal preconceptional radiation exposure in the nuclear industry and non-solid cancers in young people in Scotland. The study included fathers of children with leukemia or NHL since nuclear operations began (in 1958) with lifetime average accumulated doses (350mSv) and, the fathers of randomly chosen controls (1369 cases matched to 4107 controls). Maternal doses were not mentioned. No significant excess was observed in any subgroup (Kinlen 1993). Around the same time, Parker et al (1993) [287] published results of a study examining the leukaemic clusters in the small village of Seascale (close to Sellafield). A total of 9256 children born to fathers who had been exposed to radiation due to employment at Sellafield before the child's conception were involved, including 7318 with fathers who were exposed in the six months before conception. Overall, they found 7% of the collective total (and 6 months before conception) preconceptional dose to be associated with children born in Seascale, with the mean individual doses before conception being consistently lower in Seascale than in the rest of West Cumbria which showed no excess in leukemia's.

Cancer incidence in children in England, Wales, and Scotland over the period 1953–81 was examined by Sorahan et al [162]. Radiation workers from a number of different occupations were studied, including radiologists, clinical, veterinary and dental surgeons, nuclear industry workers

and industrial radiographers. 35,949 children with cancer were included in the study together with 38,323 control children born to non-radiation workers with no indication that preconception employment in any of the occupations studied being more important than post-conception employment for risk of all childhood cancers or, all childhood leukemia's (Sorahan et al. 1995). A total of 39,557 children of male and 8,883 children of female nuclear workers were found to include 111 cancers (28 leukemia) by Roman et al [139]. The estimated standardized incidence ratio was 98/100 (95% CI 73 -129) and 96/100 (50 to 168) for all malignancies and, 109/100 (61 to 180) and 95/100 (20 to 277) for leukemia, for children born to male and females respectively. Although the leukemia rate in children whose fathers had accumulated a pre-conceptional dose of >100 mSv was 5.8 times that in children who were conceived before their fathers' employment in the nuclear industry (95% confidence interval 1.3 to 24.8), this was based on only three exposed cases and no significant trends were detected between increasing paternal dose and leukemia (Roman et al. 1999). Bunch et al (2009) [293] conducted a record linkage study involving cancer in the offspring of female radiation workers. Pooled analyses included 52,612 cases and their matched controls. The reported results provided no evidence of an increased risk of childhood cancer associated with maternal preconception radiation work. Childhood cancer in offspring born in 1921–1984 to US radiologic technologists with a total paternal and maternal preconception dose estimation of 6.9–51 mSv and 0–9.3 mSv, respectively, were studied [81]. Annual ovary and testes organ dose estimates were used with dose details gathered from a range of sources including literature and dose records. The sample included 81,262 and 24,678 offspring of female and male technologists respectively, although control groups were not stated/included. Johnson et al reported leukemia's (n = 63) and solid tumor's (n = 115) in offspring not to be associated with preconception radiation exposure. However, paternal preconception exposure to estimated cumulative doses >82 mGy (n = 6 cases) was found to be associated with a non-significant risk of childhood cancer of 1.8 (95% CI 0.7–4.6) (Johnson et al. 2008).

Confidence assessment for occupational exposure situation. In summary, studies [45,81,120,139,164,238] (good-high rating that parent(s) were only exposed preconceptionally (question 2) examined solid cancer in offspring born to occupationally exposed workers (excluded 42, 43 as tier 3 and 162 as companion study to 290 with likely overlapping populations) (supplementary Table 7). An initial confidence assessment of *low-moderate* was assigned. No downgrades were warranted however a double upgrade was made for a large magnitude in effect as all studies reported RR's above five. This resulted in a final confidence assessment of *high*, however as only studies 45 and 238 reported an effect based on the authors conclusions, this translated into *inadequate* evidence. The binomial test supports this where two studies report effect sizes in the direction of an increasing effect and four studies report effect sizes in the direction of a decreasing effect (p = .34).

Non-solid cancer amongst occupationally exposed populations was assessed in studies [81, 84, 119, 120 139, 164, 209, 238, 276 287] (excluding study 162 as above, 289 excluded as potential overlap with 287 and, 296 excluded due to possible overlap with study 84). An initial confidence assessment of *low-moderate* was downgraded for imprecision in the results reported, although a double upgrade was warranted because all studies reported large magnitude of effects. This resulted in a final confidence rating of *moderate*, however for studies [81, 84, 119, 139] the authors conclude no effect despite the large magnitudes for an effect being reported. This subsequently translates into *inadequate* evidence. However, the binomial test included seven studies to be in the direction of an increasing risk (p = .17).

Atomic-bomb survivors

All studies show no effect. Cancer in the offspring of the A-bomb survivors has been studied in five studies in this review, all of which report no effect/no increase in incidence. One of the early studies, conducted by Yoshimoto et al [196] investigated malignant tumors before age 20 years in offspring born to parents with joint parental dose ranges of 0.01–0.09, 0.10–0.49, 0.50–0.99, 1.00- 2.49 and 2.50+ Sv. The data set consisted of (1) a population of 31,150 live-born children where one or both parents received >0.01 Sv (average conjoint gonad exposure 0.43 Sv) and, (2) two suitable comparison groups totaling 41,066 children. Altogether, 43 and 49 malignant tumors were identified in the children of exposed and control parents, respectively, with multiple linear regression analysis showing no differences (Yoshimoto et al. 1990). A follow-up study by Izumi et al [76] reported median doses of 143 mSv for 15,992 exposed fathers and 133 mSv for 10,066 exposed mothers. The sample population includes a subset of the F1 mortality population: 40,487 Japanese offspring (20,743 men and 19,744 women) born from 1 May 1946 through 31 December 1984. The results showed cancer incidence was not higher for subjects with exposed parents than for the reference subjects (0–4 mSv), nor did the incidence rates increase with increasing dose. For 3568 subjects with two exposed parents, the adjusted risk ratio for all cancers was 0.97 (95% CI 0.70– 1.36) (Izumi et al. 2003). A companion paper by Izumi et al [77] investigated cancer-related mortality among offspring of atomic bomb survivors (median doses; paternal 143 mSv (n = 12,722) and maternal 132 mSv (n = 7,726). During the half century follow-up, 314 cancer deaths occurred (mean age of living subjects was 45.7 years) which were no higher than observed for reference subjects (0–4 mSv), and mortality did not increase with increasing dose. For subjects with both parents exposed, the adjusted hazard ratios for cancer deaths was 0.96 (95% CI 0.59–1.55) (Izumi et al. 2003). An update on this to 2010 was published by Grant et al [71] which also updated weighted gonadal doses as 0, 1–49, 50–149, 150–500 and ≥500mGy for 4643 mothers and 2764 fathers. A total of 75,327 (mean age 53.1yrs) offspring born to exposed parents were included (38,590 males and 36,737

females. No association was found between paternal (0·815, 95% CI 0.614–1.083; p = 0·14) or maternal (0.891, 95% CI 0.693–1.145; p = .36) exposure and risk of death caused by cancer. Age or time between parental exposure and delivery similarly showed no effect on risk of death (Grant et al. 2015). Lastly, Amemiya et al [9] investigated retinoblastoma in offspring of A-bomb survivors using information taken from the Committee on the National Registry of Retinoblastoma and identifying those whose parents were, and were not, exposed. Although the results showed seven of the 42 retinoblastoma patients to have parents or grandparents who were exposed, family history was thought to be the dominant factor (Amemiya et al. 1993).

Non-cancer associated medical exposure

Studies that show an effect. Studies have also been conducted to ascertain cancer incidence in the offspring of non-cancer related medically exposed individuals, for example the incidence of leukemia in infants born to parents who had received diagnostic X-ray's [157]. Cases (n = 382) were identified through registration in North American clinical trials with controls (n = 743) randomly selected and matched by year of birth, telephone area code. Infant leukemia was found to be associated with paternal preconceptional exposure, specifically, acute lymphoblastic leukemia and found to be related to two or more X-rays of the lower gastrointestinal tract and lower abdomen (OR= 3.78, 95% CI, 1.49–9.64, trend test, P < 0.01), although the lack of information on dose or the underlying diseases that necessitated the diagnostics is noted (Shu et al. 1994). Bailey et al. (2010) [17] also examined parental exposure to diagnostic radiological procedures and the risk of childhood acute lymphoblastic leukemia as part of the Aus-ALL study. Case families were identified and recruited through all 10 pediatric oncology Centers in Australia giving two main populations, (1) mothers exposed whilst pregnant (not considered in this review) and, (2) fathers exposed before conception (clinical CT-scans and X-rays) (416 offspring). Controls for the study were recruited by random digit dialing (between 2003 -2006) and were frequency-matched by age, sex, and state of residence (n = 1361 families). Increased risks were reported for any paternal abdominal X-ray before conception (OR 1.17, 95% CI, 0.88–1.55), for more than one X-ray (OR 1.47, 95% CI, 0.98–2.21) and, for any paternal intravenous urinary tract X-ray before conception (OR 3.56, 95% CI, 1.59–7.98) (Bailey et al. 2010). All results were based on self-reported exposures however, although where uncertainty was evident, the authors removed these from analysis.

Studies that do not show an effect. Andersson et al [10] reported on the effects of preconception irradiation on cancer in the offspring of patients treated with thorotrast (alpha particle emitter). The paternal mean estimated accumulated α-particle dose to the testis at conception was 62.7 mGy, corresponding to 941 mSv, with approximately half of the offspring fathered by men with a dose of <750mSv. After a median follow-up of 40 years, 226 children of exposed fathers passed away from cancer (Standardized Mortality Rate of 1.3; 95% CI of 0.5- 2.9) (Andersson et al. 1994). The relationship between medical exposure and acute leukemia among children with Down Syndrome was assessed, as part of the Children's Oncology Group (COG) [107]. The paper includes parental preconception and n utero exposure, but for this review only preconception data was extracted. Children with Down syndrome (controls; n = 173) were frequency-matched on age to children with Down syndrome and leukemia (cases; n = 158), diagnosed at ages 0 to 19 years during the period 1997–2002. No association was observed between any paternal preconception irradiation and acute leukemia (OR: 0.92; 95% CI: 0.57–1.47), nor was there an association among subjects with ALL or AML when analyzed separately (Linabery et al. 2006).

Confidence assessment for non-cancer associated medical exposure. For medical parental exposure and non-solid cancer, all studies described [17, 107, 157 and 10] were considered. No downgrades were made, and one upgrade was given because large effect sizes were reported [17, 107,157]. However, as the authors conclusions are inconsistent with two reporting an effect and two reporting no effect, this translates into *inadequate* evidence. This is supported by the binomial test that included two studies in the direction of an increasing effect and two studies in the direction of a decreasing effect (p = 1.375).

Environmental exposure

Studies that show an effect. Craft et al (1993) [298] investigated the excess of childhood leukemia and lymphoma identified in Seascale, Cumbria, UK. In total, 6686 cases of malignant disease in young people diagnosed before their 25th birthday (between 1968 and 1985) who were identified from three regional cancer registries, were allocated to a census ward on the basis of 'usual place of residence'. Wards were ranked by cancer incidence and Poisson probability. Based on this, the Seascale ward was found to be the most highly ranked for ALL, but not NHL, for the time periods 1968–85 or 1968–76. When ALL and NHL incidence were combined, a higher rank for Seascale was seen. The authors conclude that the incidence of ALL and NHL in the Seascale ward remains high when put into a wider geographical context. Hoffmann et al (2007) [294] published a study on childhood leukemia in the vicinity of the Geesthacht nuclear establishments near Hamburg, Germany. All incident cases (< 15 years of age) reported during 1990–2005 within a 5-km radius of the Krümmel nuclear power plant were included. 14 cases were found whereas four were expected based on national rates (1990–2005: SIR = 3.5; 95% confidence interval (CI), 1.9–5.9), which was larger for children 0–4 years of age (SIR = 4.9; 95% CI, 2.4–9.0). The authors conclude that the incidence of childhood leukemia in this region is significantly higher than that for Germany as a whole.

Studies that do not show an effect. Michaelis et al [212]) reported on the incidence of childhood malignancies of

residents living in the vicinity of West German nuclear power plants. A total of 18 nuclear power plants were included and exposed cases consisted of people living within 15 km (12 study subject parents had worked at nuclear installations), where all exposed subjects had a maximum cumulative dose of 100mSv. A slight non-significant increase in acute leukemia (RR 1.06) in the installation regions when compared to non-installation regions was seen, for lymphomas, the RR was 1.67 (p = .017), neuroblastoma 1.11 (p = .36) and, Wilms' tumor 1.3 (p = .12). No trend across time was seen, however the highest RR's were associated with all installations set up before the 1970s (Michaelis et al. 1992). A follow up study (1991–95) which included additional background on the individual's family history and regions from three additional nuclear installations, was carried out by Kaatsch et al [260]. This resulted in an additional 1046 children being included. Overall, the follow-up time period did not confirm the results seen in the original study whereby no increase in acute leukemia was observed in children <5yrs living within 5 km of the nuclear installation (Kaatsch et al. 1998).

Sharp et al. (1996) [291] also investigated the incidence of childhood leukemia and non-Hodgkin's lymphoma in the vicinity of nuclear sites in Scotland during 1968–93. More cases were observed than expected in the study zones around Rosyth naval base, Chapelcross electricity generating station, and Dounreay reprocessing plant. However, the maximum likelihood ratio test reached significance only for Dounreay (p = .030), further, the linear risk score test did not indicate a trend in risk with distance from any of the seven sites, including Dounreay. The relationship between childhood leukemia and living in the vicinity of Canadian nuclear facilities including uranium refinery and nuclear power generators, was carried out by McLaughlin et al [210]. The study included children from 0–14 years old who died from leukemia between 1950–1987 (n = 1894), or who were diagnosed between 1964–1986 and whose mothers were resident, at the time of birth, within 25 miles from one of 5 nuclear facilities'. The overall ratio of childhood leukemia deaths, from pooled observed and expected numbers, was 1.17 (O = 54, E = 46.1). Of those born near nuclear power stations it was 1.4 (O = 36, E = 25.7) (Mclaughlin et al. 1993). Overall, the reported occurrence of childhood leukemia was slightly, but not significantly increased, at the five regions, however the authors state that some of the high ratios were seen at sites with small sample sizes and conclude no trend is seen.

Similar studies have been carried out on other populations living in the vicinity of nuclear power plants. A case-control study examined leukemia among young people near La Hague nuclear reprocessing plant and included both mothers living in the vicinity and fathers employed at the plant [219]. Twenty-seven cases of leukemia were diagnosed during the period 1978–93 in people aged under 25 years and matched with 192 controls for sex, age, place of birth, and residence at time of diagnosis. No association was found between the incidence of leukemia with fathers' occupational exposure however an association was seen with the regular use of local beaches by children and mothers (RR 2.87; 95% CI 1.05 to 8.72 and RR 4.49 (1.52 to 15.23) ($P \leq 0.01$) for more or less than once a month respectively (Pobel and Viel 1997). Cancer malignancy and mortality were studied in offspring of people exposed to discharges of radioactive waste into the Techa River in the South Urals. Kossenko et al [90] examined health records and self-reported information of 28,000 exposed residents and 17,000 F1 offspring born between 1953 and 1990. In comparison with matched control groups living in uncontaminated areas, no increased incidence of malignant neoplasms was observed among the exposed population. The leukemia risk, estimated on the basis of the linear model of absolute risk, was 0.85 (0.24- 1.45) per 10,000 person-y Gy of the dose accumulated in RBM, and solid cancer risk (except osteosarcoma), estimated using linear model of RR, was 0.65 (CI 95% 0.27–1.03) per Gy of dose accumulated in soft tissues (Kossenko 1996). Bithell et al (1994) [280] investigated childhood leukaemias and NHLs near nuclear installations in England and Wales using the linear risk score test based on vicinity. The study included 11,283 cases of leukemia and NHL registered in children under the age of 15 and found none of the 25 km circles around the installations to have an incidence ratio significantly greater than 10, although significance was detected for Sellafield ($P = 0.00002$) and Burghfield ($P = 0031$). Soon after, Wakeford and Parker (1996) [292] published a study on leukemia and NHL in young person's resident in West Cumbria. They found forty-one cases diagnosed in people under 25 years during 1968–85 were resident in the 49 electoral wards (West Cumbria and the adjacent ward of Broughton) giving raised incidence rate ratios (two-sided $P < 0.01$) for ALL among those aged 0 -14 years in the Seascale ward and, for those aged 0–24 years in the Egremont North ward. Apart from Seascale, none of the electoral wards had a father of an affected child linked to an occupational dose of radiation recorded before conception, nor were the excesses noted above associated with recorded doses of radiation received occupationally by fathers. Bunch et al (2014) [297] investigated cancer excesses in individuals born or resident in the vicinity of Sellafield and Dounreay, UK. The authors conclude that individuals born close to the installations from 1950 to 2006 were not shown to be at any increased risk of cancer during the period 1971 to 2006.

Confidence assessment for environmental exposure. When the confidence assessment was performed on environmentally exposed populations, all [90, 210, 212, 219, 260, 280, 291, 294, 297] had a potential risk of exposure after conception. Studies 298 and 292 removed as possible overlap with 297. One downgrade was made due to three of the nine studies highlighted for indirectness [210, 219, 260]. One upgrade was made for a large magnitude in effect [219 and 294]. Therefore, based on authors conclusions this translates into low-moderate confidence. From this, four of the nine studies report increases. Due to inconsistencies within the results, this again translates into inadequate evidence.

Confidence assessment for 'all' exposures situation. When only those studies with good-high rating that parent(s) were only exposed (any exposure situation) preconceptionally were

considered for solid-cancers and, potentially overlapping populations removed, a *moderate* confidence in the body of evidence [45, 81, 139, 164, 120, 238, 71, 10, 293] was given (supplementary Table 7). After one upgrade for large magnitude of effect, a final confidence of *moderate-high* was determined. Although the majority (seven out of nine) of the studies report no effect, OHAT guidelines state that a *high* confidence rating is required before a conclusion of no effect overall can be reached. Given the upgrade was applied due to a high magnitude of effect, it is not justifiable to conclude high confidence for no effect, accordingly, the conclusion on the evidence for solid cancers remains *inadequate*. This is supported by the binomial test where two studies were in the direction of an increasing effect and seven studies were in the direction of a decreasing risk ($p = .08$).

When only those studies with good-high rating that parent(s) were only exposed (any exposure situation) preconceptionally were considered for non-solid cancers and, potentially overlapping populations removed, the confidence assessment was rated as *moderate* [81, 84, 119, 120, 139, 164, 238, 76, 17,107,157, 10, 280, 287, 291, 293, 294, 295, 297]. A double upgrade for large magnitude of effect was warranted and gave a final confidence of high. Based on the author's conclusions showing inconsistency in results however, this translated into *inadequate* evidence overall. It is noted that although 14/18 studies concluded no effect (binomial; $p = .01$), three of these reported some association with paternal preconceptional exposure.

Summary of findings for solid cancer.

- A final evidence confidence rating of *high* was given for those studies examining solid cancer amongst offspring of occupationally exposed individuals however this translated to *inadequate* evidence due to inconsistencies in the authors conclusions. This included where authors interpreted observed effects as being unlikely to be as a consequence of parental radiation exposure.
- Solid cancer in offspring of A-bomb survivors was investigated in five studies, all of which showed no effect, however there is high likelihood of overlap in populations between studies.
- The confidence in the body of evidence based on 'all' exposure situations combined was *moderate*, however due to inconsistent results based on authors conclusions, this translated into *inadequate* evidence.

Summary of findings for non-solid cancer.

- The confidence in the body of evidence for non-solid cancers in occupational exposure studies was *moderate*. Inconsistencies in the reported conclusions translated into *inadequate* evidence. When this was repeated with all exposure situations combined, a final confidence rating of high was given, however again this was translated into *inadequate evidence* due to inconsistencies in the authors conclusions.

What is the evidence of increased non-cancer diseases and mortality rates?

Non-cancer diseases and mortality rates were assessed in three atomic bomb survivor studies (Table 11). Two of these investigated multifactorial diseases including hypertension, diabetes mellitus, hypercholesterolemia, ischemic heart disease and stroke, and one study reported non-cancer mortality incidence. Two additional environmental exposure studies were captured which considered mortality in the offspring of individuals living near the Techa River and, multiple non-cancer diseases in the offspring of British Nuclear Test Veterans however these were both excluded as tier 3 [138] or issues around timing of exposure [92].

No effect in mortality and non-cancer-related diseases amongst offspring was observed in any of the studies examined. Fujiwara et al [65] researched the prevalence of adult-onset multifactorial diseases among 11,951 offspring (range= 19–59 years) of survivors exposed to 0.005 Gy-1.0 Gy. They found no association between the prevalence or risk of multifactorial diseases (OR per Gy of paternal dose was 0.91, (CI 0.81–1.01, P = 0.08) (Fujiwara et al. 2008). Following on from this, and perhaps a re-analysis of the same dataset, came a study evaluating the radiation risk of individual multifactorial diseases in offspring [171]. For male offspring, the mean paternal dose was 0.121 (range 0–3.76) Gy with mean gonadal doses of 0.138 (range 0–2.76) Gy, for female offspring, corresponding values were 0.144 (range 0–3.92) Gy with mean gonadal dose of 0.161 (range 0–3.05) Gy of which approximately 8.9% of mothers had

Table 11. Studies investigating non-cancer diseases and mortality in the offspring of radiation exposed parents.

ID	Author	Population	Sample size (offspring)	Abnormality	Risk estimate/test statistic	Authors conclusion
65	Fujiwara et al. (2008)	A-bomb survivors, Japan	11,951 offspring	Multifactorial disease	**OR (95% CI)** adjusted for parental dose at 1Gy Fathers' dose Male offspring= 0.76 (0.65–0.89) Female offspring= 1.04 (0.90–1.21)	No effect
171	Tatsukawa et al. (2013)	A-bomb survivors, Japan	11,951 offspring	Multifactorial disease	**OR (95% CI)** adjusted for parental dose at 1Gy Fathers dose= 0.93 (0.86–1.01) Conjoint dose= 0.96 (0.90–1.03)	No effect
71	Grant et al. (2015)	A-bomb survivors, Japan	75,327 offspring	Non-cancer mortality	**HR (95% CI)** for continuous dose response (1Gy) Fathers' exposure= 1.103 (0.979–1.241)	No effect

OR: Odds Ratio; HR: Hazard Ratio; 95% CI: 95% Confidence Interval.

gonadal doses ≥ of 0.5 Gy. Overall, Tatsukawa et al reported no statistically significant association between parental radiation exposure and any of the multifactorial disease endpoints examined (OR = 0.84, CI 0.75–0.94) (Tatsukawa et al. 2013). For both studies, it was noted that the offspring are too young to have experienced most of their morbidity from diabetes, heart disease and stroke (mean age males 49.1 ± 7.3, mean age females 48.1 ± 7.9). Mortality risk among children of A-bomb survivors over a 50 and 62 year follow up was published by Izumi et al [77] and Grant et al [71], respectively. The latter report updates the radiation risks of death caused by non-cancer diseases up to 2010 includes 75,327 (mean age 53.1yrs) offspring born to exposed parents. Grant et al report paternal exposure to have no effect on deaths caused by non-cancer diseases (1·103, CI 0·979– 1·241; p = 0·12) (Grant et al. 2015).

Summary of findings for non-cancer disease and mortality

None of the studies examined showed any association between non-cancer disease incidence and mortality in offspring born to exposed parents. No studies assessing non-cancer diseases and mortality within offspring of occupationally or medically exposed parents were identified in this review.

Discussion

The purpose of this research was to provide a synthesis of the published evidence from 1988- 2018 pertaining to the intergenerational health effects of parental preconceptional exposure to ionizing radiation in humans (For an update from 2018–2022 please see Amrenova et al., in this Special Issue). Adverse health outcomes were grouped according to condition e.g. specific pregnancy outcomes such as congenital abnormalities, and then further organized according to radiation exposure situations. From this, the available evidence was considered to ascertain 'an effect', 'no effect' or whether the evidence remained 'inadequate' to determine either effect or no effect. This assessment was based primarily upon the authors conclusions within that evidence-base and, by binomial probability testing of the direction of effect reported (Higgins et al. 2023). Overall, we find that for the majority of the adverse health groups there was inadequate evidence from which to determine whether the health effect was, or was not, associated with parental preconceptional radiation exposure. This was largely due to the heterogeneity between individual study's findings and conclusions within each group and, the limited number of studies within each group.

Many papers included in this review do not necessarily pose the research question of examining adverse effects in unexposed offspring born to radiation exposed parents. Some investigate health effects in children born in the vicinities of nuclear facilities or in contaminated areas. Although the parents of these children may have been exposed to radiation, the potential for postconceptional exposure cannot be excluded. This is particularly true for those studies collectively grouped as 'environmental' exposure, and some smaller occupational studies. The approach taken here was to describe these studies as they make up a large proportion of research into intergenerational effects on offspring and are part of the scientific and media discourse, however, to exclude them from the analysis when drawing overall conclusions. Indeed, other reviews examining this question also consider environmental studies, albeit with similar qualifiers as noted here (Boice 2020). By employing the structured methods of OHAT, the body of work can be examined, minimizing (although not excluding) the potential for evidence to be left out, whilst highlighting potential areas of bias. For instance, the key RoB question on the timing of parental exposure (question 2) was the main determinant for description and analysis whereby, according to OHAT, a probable RoB relates to 'suspected' postconceptional exposure whereas, high RoB is where the study provides 'evidence' that this is the case. Consistency in assigning such RoB assessment was challenging, however generally aligned to rationales such as e.g. A-bomb studies and those examining the effects post-Chornobyl in distant countries could be argued to reflect potentially 'brief' postconceptional exposure, and treated differently to studies who examine effects in residents stated as living in contaminated regions. Further, efforts were made to identify those studies which discriminated populations into before conception and possible post-conception exposure, and/or those which reported paternal exposure separately to maternal data.

As stated above, studies were grouped based on health outcome and additionally, by exposure situation. This was to enable the synthesis of the evidence from similar studies, assess the RoB consistently, and to draw reasonable conclusions on similar endpoints. An important exposure situation excluded from this review was parents who had previously been treated by radiation for cancer. This was to minimize potential bias of any effects in their children being related to the parental disease. However, such studies are important not least because they represent a large and ever-increasing body of work but also, because the dose and exposure information, including timing of the exposures and associated chemotherapeutic interventions, are documented in detail. It is not within the scope of this current review to summarize (in a nonsystematic manner) the current literature for this population, however it is worthy to note that many of the studies performed thus far show no relationship with preconceptional exposure and increases in adverse pregnancy outcomes or risks of cancer (for reviews see (NCRP 2013; Nielsen et al. 2018; Boice 2020). It is recommended therefore that a similar systematic process to that carried out here is performed for the literature on this large cancer survivor population.

In assessing the confidence in the body of evidence, all 'tier 3′ studies (definitely high RoB) and studies with a high bias score relating to the key question 2 (potential for exposure after conception), were removed from the confidence assessment. Similarly, when obvious, companion or studies which had been superseded by follow-up studies, were also removed. Using this process, all of the groups had

'inadequate' evidence from which to formulate a conclusion. The only exception to this was the 'high confidence for an effect' for congenital abnormalities effects observed in occupationally exposed groups. This was based upon eight studies, two of which involved small sample sizes and where postconceptional exposure could not be excluded. When these studies were removed from the confidence analysis and/or, where 'all' exposure situations were considered, then no overall conclusion could be reached. This, similar to many of the other groupings assessed in this review, was due to the inconsistencies in the authors conclusions for 'an effect' or 'no effect'. Pertinent here, are the number of studies which report positive effect sizes for congenital abnormalities, particularly for NTDs, but which are concluded by the authors not to be associated with parental radiation exposure. A lack of a dose response, incompatibility with A-bomb cohort findings, in addition to lack of confounder information are generally cited as justification for these interpretations. Given this and the recent re-appraisal of earlier A-bomb data which concluded that parental exposure to radiation is (mostly non-significantly) associated with increased risks of major congenital abnormalities and perinatal death (Yamada et al. 2021), further consideration into the evidence surrounding congenital abnormalities should be examined.

The clusters of childhood leukemia's identified in the village of Seascale, within the geographic locale of Sellafield nuclear plant, UK, led to Gardner [276] hypothesizing their causal association with paternal preconceptional radiation exposure (Gardner et al. 1990). Many of the studies undertaken to test or examine this hypothesis are included in this review, also, see the series of comparative reviews by Little et al. (1994, 1996), Little (1992, 1993, 1999). Overall, there was inadequate evidence in which to formulate a conclusion for both solid and non-solid cancers. However, as noted above, this is based upon the authors conclusions with a number of studies reporting statistics showing an effect or non-significant increase, but where these findings are interpreted as being unlikely to relate to radiation exposure and most likely related to some other factor, such as infection. For instance, Kinlen et al (1995) found an excess of childhood leukemia and NHL near large rural construction sites, which was greater at times when construction workers and operating staff overlapped (Kinlen et al. 1995). Indeed, population mixing was found to be a significant risk factor for ALL/NHL and an explanation for the leukaemic clusters in the vicinity of Sellafield (Dickinson and Parker 1999). A high magnitude in effect, defined as a RR or OR above two, increases the confidence in the finding as being less likely to be a chance effect. For the solid cancer grouping, study [45] is the only study to report a high magnitude of effect. In contrast to this, a total of eight [81, 84, 119, 120, 139, 164, 209, 238] studies reported either a RR or OR of two or above for non-solid cancers. For occupationally exposed populations, the majority reported magnitudes of effects in the direction of an increasing risk. Given many authors conclude this not to be associated to parental radiation exposure as stated above, further mechanistic understanding into the complex interactions of multiple stressors and more detailed knowledge of the multiplicity of exposures (confounders) or exposome in the periods preceding conception, is needed.

The assessment for consistency and uncertainty highlighted limitations in the bodies of evidence in addition to an insufficient number of eligible studies from which to fully assess the question posed in this review. For example, details on exposure types and doses were often estimates for the population as a whole, rather than individualized. Where estimates of parental dose were provided, this was variably categorized into specified periods before conception, however lacked consistency meaning pooled examination was limited. Furthermore, although it is not always feasible to gather specific information relating to lifestyle and confounding details, often such data was not reported. Similarly, the collective grouping of health outcomes, data from maternal and paternal exposures and, data of preconceptional, in-utero and postconceptional exposures, rather than separately, reduced the confidence in which the question of preconceptional exposure could be formally addressed. Indeed, the lack of standardization between studies made it difficult to perform any meaningful analysis of the body of evidence. So, although a vast amount of research has been published over many decades there is large heterogeneity in the design of the studies and, in the reporting of the results. These issues are not unique to this review, nor is the call to improve study design and reporting for future studies (Rooney et al. 2014; Walker et al. 2018).

Conclusion

In conclusion, we find there is a lack of sufficient detail in the available evidence to enable the formal assessment of radiation-related adverse effects in unexposed human offspring after parental exposure. This is distinct from a conclusion of there being no clear evidence that effects may occur but does infer that if adverse health effects do arise in children of exposed parents, then these effects are small and difficult to reproducibly measure. Of those studies which do report some effect most show no evidence of any dose effect, and although it is recognized this is more difficult in human populations as there are many variables in dose estimations that cannot always be accounted for, this may contribute to how the findings are evaluated. Further understanding of the mechanistic processes which may be associated with intergenerational effects should serve to determine the importance of dose in this regard. Inconsistencies in designing studies are unavoidable in terms of the populations and exposures, however there is a need for an element of standardization across the field and, more sharing of primary datasets as part of open access initiatives, in order to make reasonable conclusions, especially to enable the pooling of statistical data for meta-analysis. Statistical power improves with larger sample numbers and as shown many radiation effects are relatively small, therefore pooling of data in the future is needed. Overall, there is a need for future work to address this to ensure comparable measures between studies where possible.

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Author contributions

RA conceptualized the study and supervised the work; RA, JS, ES and AM devised the methodology; JS and ES performed the screening and JS, ES, AM, KC and RA conducted data extraction and risk of bias assessments; JS, FD and RA performed all assessment and analysis; JS and RA wrote the manuscript with some contribution from KC, AM and FD.

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