Committee on Medical Aspects of Radiation in the Environment (COMARE)

Twentieth report

Risks of cardiovascular disease from exposure to ionising radiation

Chair: Professor J D Harrison

Table of contents

Preface

i. The Committee on Medical Aspects of Radiation in the Environment (COMARE) is a Department of Health and Social Care (DHSC) expert committee that provides independent expert advice to the UK Government on the health effects of radiation. Over the 40 years of its existence, the committee has provided advice on a range of issues from childhood cancer clusters in the vicinity of nuclear installations to risks of skin cancer caused by UV from sunbeds and the significance and control of radiation doses resulting from the use of computed tomography (CT) in the UK.

ii. The aim of this report is to provide advice to the DHSC on the cardiovascular health implications for the UK population of exposure to ionising radiation, considering diseases including coronary or ischaemic heart disease and cerebrovascular disease. The report reviews the available evidence of an association between radiation exposure and cardiovascular diseases, from epidemiological and biological studies, and reaches conclusions on possible risks at both high doses, as are received by normal tissues during radiotherapy, and particularly for low doses or low dose rates, as received in medical diagnostic imaging and occupational exposures.

Lay summary

Background

S.1 The Department of Health and Social Care asked COMARE to review the cardiovascular health implications for the UK population resulting from exposure to ionising radiation, focussing on the evidence for risks at low doses (<100 mGy[1] low-LET[2] radiation) or low dose-rates (<5 mGy/h low-LET radiation). COMARE established the Cardio-/Cerebro-vascular Effects Subcommittee for this work, with the terms of reference:

> *"to advise COMARE on the available evidence of a causal association between cardiovascular and cerebrovascular disease and low-level radiation exposure, and to inform COMARE of the health implications for the UK population and further research priorities."*

S.2 In producing this report, the subcommittee reviewed the available evidence of an association between radiation exposure and cardiovascular disease (CVD), considering diseases including coronary or ischaemic heart disease (IHD) and cerebrovascular disease (CeVD). Substantial evidence is now available from epidemiological studies of medical, occupational and environmental exposures and there is also a growing understanding of the mechanisms of radiation action in cells and tissues.

S.3 The subcommittee focussed on the potential risks of low dose and low dose rate exposures, but in doing so also considered data for high doses (>1 Gy), particularly where these might facilitate extrapolation to low doses and dose rates.

Conclusions

S.4 The Committee interprets the evidence from the Life Span Study (LSS) of Japanese A-bomb survivors as providing ***Strong evidence*** with respect to higher dose exposures (above about 0.5 Gy) but ***Limited evidence*** of risks of CVD from low to moderate doses (0.1 to 0.5 Gy) (received following a single radiation exposure).

S.5 The Committee concludes that radiotherapy studies of persons treated for cancer provide ***Medium evidence*** with respect to very high doses (>10 Gy) as a risk factor for IHD and CeVD but ***No evidence*** on risks below about 10 Gy; however, studies of persons receiving radiotherapy for non-cancer disease suggest that there is risk at <10 Gy.

S.6 The Committee interprets the evidence from epidemiological studies of occupational populations as providing ***Medium evidence*** that low dose or low dose rate radiation is a risk factor for IHD and CeVD, with some evidence of excess risk in the dose range 0.1 to 0.5 Gy, but only providing ***Limited evidence*** in support of quantitative estimations of the dose-response association at low dose or

[1] Gray (Gy) - the international unit of radiation dose, which measures the amount of energy absorbed per unit mass of tissue.
[2] Linear Energy Transfer - a measure of energy transfer to tissue as a charged particle moves through it.

low dose rates. There are some indications in these populations that dose-response associations may not be linear.

S.7 Epidemiological studies of environmentally exposed populations provided ***Limited Evidence*** supporting findings from occupational populations.

S.8 Overall, the epidemiological data provide evidence of increasing risk of CVD with increasing dose at high doses (>1 Gy) and some evidence at moderate doses (0.1 to 1 Gy), with no direct evidence of risks at low doses (<0.1 Gy) and low dose rates. No firm conclusions can be drawn regarding the possible existence of dose thresholds, below which there would be no or minimal effect.

S.9 The conclusions from the epidemiological evidence are to some degree supported by mechanistic evidence. Cell killing will be an important factor at high doses and may also be of importance at lower doses. However, while high doses have been shown to increase inflammation and cell senescence within blood vessels, moderate doses may be anti-inflammatory and have the potential to slow the process of plaque formation. At low doses, potential effects could involve non-targeted as well as targeted effects, with damage to DNA and other cellular molecules.

S.10 The biological data do not support clear conclusions on dose-response relationships and possible thresholds of effect for CVDs. Unlike cancer, for which there is a clearly understood mutational basis which operates in linear proportion to dose, mutation is not a strong feature of CVD. The current understanding of mechanisms is insufficient to draw conclusions regarding the extent of risk at low doses.

S.11 Based on the evidence reviewed in this report, COMARE has made a number of recommendations (Chapter 8) and key points are summarised below.

Key points of COMARE's recommendations

1. COMARE recommends that further epidemiological research is carried out on radiation-exposed populations to improve the understanding of CVD risks at moderate and low doses and low dose rates.
2. COMARE recommends that further research is undertaken into the biological mechanisms of radiation action in CVD.
3. COMARE recommends that clinicians continue to minimise radiation exposures of critical vasculature while maintaining effective clinical outcomes in radiotherapy procedures.
4. COMARE recommends that the relevant authorities consider initiatives to improve population health by reducing risks that may act multiplicatively with radiation.
5. COMARE recommends that government, the devolved administrations, and relevant agencies collaborate to ensure that adequate dataset and research governance arrangements are shared throughout the UK in respect of datasets and cohorts used in these types of analyses.

Chapter 1. Introduction

1.1 Cardiovascular diseases (CVDs) or diseases of the circulatory system are a leading cause of death in the UK and worldwide[3]. They include:

- coronary heart disease, also known as ischaemic heart disease (IHD), affecting the blood vessels supplying the heart muscle
- cerebrovascular disease (CeVD) affecting the blood vessels supplying the brain
- peripheral arterial disease affecting blood vessels supplying the arms and legs
- congenital heart disease arising as birth defects that affect the normal development and functioning of the heart
- deep vein thrombosis and pulmonary embolism in which blood clots in leg veins can dislodge and move to the heart and lungs.

Heart attacks (myocardial infarction (MI)) and strokes (ischaemic) are acute events caused by blockages that prevent blood from flowing to the heart and brain. A less common form of stroke is haemorrhagic, resulting from the rupture of a blood vessel. The underlying cause in the majority of cases of coronary heart disease, cerebrovascular diseases and peripheral arterial disease is atherosclerosis (HPA (2010); see Chapter 5).

1.2 The main risk factors for CVD that have been consistently identified are age, smoking, diabetes mellitus, hypertension, obesity, increased total and low density lipoprotein cholesterol, decreased high density lipoprotein cholesterol, as well as a heritable genetic component for heart disease specifically (Little et al, 2023).

1.3 It has also long been recognised that exposure of patients to ionising radiation during radiotherapy (RT) can damage the heart and blood vessels such as the carotid and coronary arteries (UNSCEAR, 2008; HPA, 2010). Mean doses to the heart from X-ray RT to the breast, which is one of the more common treatments, are 2 to 9 Gray (Gy) with some patients receiving over 20 Gy, although the doses are delivered in a number of fractions to minimise tissue damage (McGale and Darby, 2005; Jacobse et al, 2019; Boekel et al, 2020; Kearney et al, 2022). Delivery of RT has vastly improved in recent years as exemplified by treatment for mediastinal Hodgkin's lymphoma in which the median heart dose of older mantle RT was 25 to 30 Gy, but with modern techniques a median heart dose of <10 Gy is often achieved (Bergom et al, 2021). Similarly, in breast cancer, median heart dose of <1 Gy can be achieved compared to 5 to 15 Gy in older regimens (Taylor et al, 2007).

1.4 The International Commission on Radiological Protection (ICRP), which recommends a system of protection that is adopted in the UK and worldwide (ICRP, 2007), distinguishes between (1) tissue reactions occurring above dose thresholds with increasing severity and (2) stochastic effects for which the probability increases with increasing dose and a linear non-threshold (LNT) dose-response model is assumed for protection purposes. The stochastic effects

[3] WHO Global Health Observatory

considered are cancer in exposed individuals and hereditary effects arising in their descendants. ICRP (2012b) has regarded the effects of radiation on the circulatory system as effectively a tissue reaction, occurring above a threshold of dose. From their review of evidence from radiotherapeutic experience and epidemiological studies, ICRP concluded that a threshold dose of 0.5 Gy should be applied to all CVDs (ICRP, 2012b). However, it should be noted that this threshold dose was not defined in the conventional sense (assuming no excess risk below the threshold), but as the dose for around 1% incidence obtained using an estimate of excess relative risk (ERR) assuming a linear dose-response (ICRP, 2012b). The point was made that it was "unclear whether there is a dose below which the risk of circulatory disease is not increased and, if so, what this dose might be". It was further concluded that the evidence did not allow distinction between doses delivered acutely, and fractionated and chronic exposures, and so the 0.5 Gy threshold was assumed to apply to all exposures (ICRP, 2007). Although ICRP assessed a possible threshold in response, it did not address the other defining characteristic of tissue reactions, namely the variation of severity of effect with dose above the threshold. Although there is evidence that, for example, severity of tissue fibrosis increases with administered dose, usually of >30 Gy (Geara et al, 1998; Rosen et al, 2001; Oh et al, 2012; Verginadis et al, 2025), there is little evidence of such increasing severity for any type of CVD.

1.5 The ICRP (ICRP, 2007, 2021) expresses stochastic risks in terms of "health detriment", in which cancer incidence estimates are adjusted to take account of the severity of disease in terms of lethality, quality of life, and years of life lost. The primary source of information on cancer caused by radiation is the Life Span Study (LSS) of the Japanese survivors of the atomic bombings at Hiroshima and Nagasaki in 1945. Estimates of lifetime risks of cancer incidence derived from studies of these populations, supplemented by other epidemiological data, are transferred and averaged across Asian and Western populations, adjusted for fatality, morbidity and years of life lost, and summed with a component of estimated risk of hereditary effects to provide overall stochastic detriment values. For the purposes of radiological protection, a LNT dose response model is assumed to apply to stochastic effects at low doses or low dose rates. Recent results demonstrate relationships at doses below 100 mGy of low linear energy transfer (LET) radiation (Lubin et al, 2017; Little et al, 2018; Hauptmann et al, 2020) with little evidence of the existence of a threshold. In a review of all relevant epidemiological studies, the United States National Council on Radiation Protection and Measurements (NCRP) concluded that current epidemiological data support the continued use of a LNT dose–response model for radiological protection purposes, with no other model representing a more pragmatic interpretation (NCRP, 2018). A recent review of biological mechanisms relevant to the inference of risk of cancer from low dose and low dose rate radiation also concluded that there remains good justification for the use of a non-threshold model for risk inference for radiological protection purposes (UNSCEAR, 2021).

1.6 Table 1.1 shows the ICRP values of stochastic detriment as severity-weighted risk coefficients per sievert (Sv) of effective dose (see Chapter 2 for dose quantities), calculated as age-, population- and sex- averaged values for both the whole population (public) and the working age population, with somewhat higher

estimated lifetime detriment for the whole population because of the inclusion of children.

Table 1.1: Severity-adjusted nominal risk coefficients (detriments) per effective dose (10^{-2} Sv^{-1}) (ICRP, 2007)

Exposed population	Cancer	Hereditary effects	Total
Whole	5.5	0.2	5.7
Adult*	4.1	0.1	4.2

*working age population, 18 to 64y

1.7 Following from the use of a LNT dose-response model for stochastic health effects, it is internationally accepted that protection should be optimised by keeping doses as low as reasonably achievable, taking economic and societal factors into account (ICRP, 2007; IAEA, 2014). This ALARA principle (as low as reasonably achievable) is applied in the UK (IRR, 2017) as ALARP (as low as reasonably practicable), the terms being largely similar.

1.8 Presently, the ICRP framework for stochastic effects does not include specific considerations of diseases other than cancer and hereditary effects because these were not considered to be related to low doses (<100 mGy of low LET radiation) or low dose-rates (<0.1 mGy/min of low LET radiation averaged over 1 hour) (UNSCEAR, 2012).

1.9 Diseases of the circulatory system, in particular IHD and stroke, are the leading causes of premature death globally (Khan et al, 2020; GBD, 2021) (2nd in the UK[4]). They are also the second ranking (after neonatal disorders) cause of disability adjusted life-years in all ages and the highest in those aged 50 years and over (GBD, 2020). Even a small proportional increase in risk as a result of low doses of radiation, therefore, could have a meaningful impact on population health. There have been suggestions that inclusion of circulatory disease in low dose risk estimation could approximately double the 'total' risk coefficients shown in Table 1.1.

1.10 Contemporary radiation exposures are significantly different from those experienced by the 1945 residents of Hiroshima and Nagasaki, and, with the exception of doses to normal tissues received during RT, are almost exclusively of low-dose and low-dose rate. It is therefore important to look beyond the atomic bomb survivor studies to evaluate whether radiation exposures in contemporary exposure situations might also increase the risk of circulatory disease.

1.11 In particular, this is important in relation to IHD and CeVD as these have the highest population prevalences (Khan et al, 2020; GBD, 2021).

1.12 The current report aims to provide a summary review of the current evidence on a causal association between radiation exposure and IHD and CeVD disease risk. It does not aim to provide an exhaustive systematic review and assessment of all available peer-reviewed and grey literature.

[4] Trends in the epidemiology of cardiovascular disease in the UK

Chapter 2. Exposure assessment

Dose quantities and measurements

2.1 The 2 main quantities in general use to quantify exposures of human organs and tissues to ionising radiation are absorbed dose and effective dose (ICRP, 2007; ICRU, 2020; ICRP, 2021).

2.2 Absorbed dose, D, is a basic physical dose quantity, with the unit Gy, where 1 Gy = 1 J kg^{-1} in SI base units. When using the quantity absorbed dose for radiological protection purposes, doses are averaged over tissue volumes. It is assumed that the mean value of absorbed dose averaged over a specific organ or tissue can be correlated with radiation effects, either tissue reactions or stochastic effects. A difficulty encountered in the assessment of risks of circulatory diseases is that the target tissues and organs are not well understood.

2.3 Effective dose, E, with the unit Sv, is the main quantity used in the control and optimisation of protection against stochastic effects, principally cancer (ICRP, 2021), and it is also widely used in assessing radiation exposures. It is calculated as the sum of doubly weighted absorbed doses to organs / tissues:

$$E = \sum_T w_T \sum_R w_R D_{T,R}$$

where E is the effective dose in Sv, w_T is the tissue weighting factor, w_R is the radiation weighting factor, and $D_{T,R}$ is the mean absorbed dose in Gy for organ or tissue, T, and radiation type, R. Tissue weighting factors are fractions (total = 1) that represent the contribution of the individual organs and tissues to overall stochastic risks. Radiation weighting factors are multipliers that account for the different effectiveness per Gy of different radiation types in causing cancer and hereditary effects (for example, 1 for gamma rays and beta particles, 20 for alpha particles). Radiation weighting factors are simplified values based largely on experimental data on the relative biological effectiveness (RBE) of different radiation types. An intermediate quantity, equivalent dose, H_T (Sv), can be calculated for individual organs and tissues in which just radiation weighting for the effectiveness of different radiations is considered:

$$H_T = \sum_R w_R D_{T,R}$$

2.4 For the purposes of optimisation of radiological protection, ICRP introduced an additional dose quantity, collective dose (ICRP, 1977, 1991, 2007). Collective effective dose takes account of the group of persons exposed to radiation and the period of exposure as the sum of all individual doses from a source over a specified time period. The special name used for the collective dose quantity is the ‘man sievert’. ICRP (2021) advises that the use of collective effective dose to predict potential/possible health effects should be treated with caution, put into context and judged in relation to background morbidity rates.

2.5 Because absorbed dose in organs and tissues and effective dose are not directly measurable, additional quantities are used to measure exposures. In medicine,

these quantities include incident air kerma (IAK, K_i), entrance surface air kerma (ESAK, K_e) or kerma-area product (KAP, P_{KA}) for radiography and fluoroscopy, and CT dose index ($CTDI_{vol}$) and dose-length product (DLP) for computed tomography (CT). Dose coefficients are available for the calculation of organ / tissue doses and effective doses from these measured quantities (Jones and Wall, 1985; Hart et al, 1994; Rannikko et al, 1997; Kramer et al, 2004; Lee et al, 2011; Wall et al, 2011; Lee et al, 2012; Ding et al, 2015; Shrimpton et al, 2016).

2.6 For the control of occupational and environmental exposures to external radiation, operational quantities are used for measurement and instrument calibration (ICRU, 1985, 1988, 1993). For individual monitoring, the operational quantity is the personal dose equivalent, $H_p(d)$, which is the dose equivalent in ICRU (International Commission on Radiation Units and Measurements) (soft) tissue at an appropriate depth, d, below a specified point on the human body. The specified point is normally taken to be where the individual dosemeter is worn. For the assessment of effective dose from measurement of personal dose equivalent, d = 10 mm and $H_p(10)$ has been chosen and if the dosemeter is worn in a position on the body that is representative of whole-body exposure, it is assumed that the value of $H_p(10)$ provides a reasonable estimate of effective dose. For the assessment of the dose to the skin and to the extremities, the personal dose equivalent, $H_p(0.07)$, with a depth d = 0.07 mm, is recommended for use as an operational quantity. For the case of monitoring the dose to the lens of the eye, a depth d = 3 mm has been used (ICRP, 2010, 2012b; Bolch et al, 2015).

2.7 In some situations, in which individual monitoring is not carried out, an assessment of effective dose may be performed by area monitoring applying the quantity ambient dose equivalent, $H^*(10)$. Organ / tissue doses and effective doses from intakes of radionuclides by inhalation and ingestion can be calculated using ICRP dose coefficients and bioassay data and ICRP also provides data for the calculation of doses for administered radiopharmaceuticals (ICRP, 2012a, 2015, 2021).

2.8 Table 2.1 shows UNSCEAR (2012) descriptions of dose levels from very high to very low which are used here. In terms of averaged absorbed dose to the whole body or individual organs, UNSCEAR (2012) considered low doses to be below 100 mGy of low LET radiation, with doses below 10 mGy classed as very low.

2.9 The biological effects of radiation are also affected by dose rate, with lower dose rates generally being less effective to an extent that depends on the endpoints under consideration. Low dose rate was defined by UNSCEAR (2012) as less than 0.1 mGy low LET radiation per minute averaged over about 1 hour. ICRP (2021) has used the same description of low doses (<100 mGy) and specified low dose rate as <5 mGy per hour.

2.10 It should be noted that these terms are applied to low LET radiation and differences in biological effectiveness need to be taken into account when considering high LET radiations, including from radionuclides that emit alpha particles. RBE values of high compared to low LET radiations are generally lower when considering tissue reactions than for stochastic effects (for example, ICRP (2003, 2012b)). The relationship between localised tissue dose (Gy) and biological effects is particularly challenging in cases such as the increasing use of alpha emitters and protons in RT (Terry et al, 2019).

Table 2.1: Terminology for levels of radiation dose (based on UNSCEAR (2012))

Description of dose	Range of absorbed dose for low LET radiation	Example scenarios of exposure
Very high	Greater than about 10 Gy	Normal tissue doses in radiotherapy
High	About 1 Gy to about 10 Gy	Worker doses after severe accidents
Moderate	About 100 mGy to about 1 Gy	Worker doses for around 100,000 individuals after the Chornobyl accident; multiple CT scans; cumulative doses to early nuclear workers
Low	About 10 mGy to about 100 mGy	CT scans, annual occupational exposure of a small proportion of workers
Very Low	Less than about 10 mGy	Annual doses received by most people from all sources; doses from conventional radiology

Radiotherapy exposures

2.11 Patients treated with X-ray RT often receive doses to the heart, brain or other parts of the cardiovascular system of many Gy. Patients treated for cancers of the breast and lung commonly have received doses over 5 Gy to the heart (Darby et al, 2013; Mulrooney et al, 2020; Shrestha et al, 2021), but most planning algorithms for the breast now include dose limits for the heart which should reduce exposures (RCR, 2016). Patients receiving radiation treatment for Hodgkin lymphoma have in the past received doses of 20–30 Gy to the heart (van Nimwegen et al, 2016), but this treatment is now seldom used (RCR, 2019). Patients treated for head and neck cancers often receive over 5 Gy to the brain or carotid arteries (Haddy et al, 2011; El-Fayech et al, 2017; Huang et al, 2019; Lee et al, 2020; van Aken et al, 2021).

Medical imaging exposures

2.12 Medical X-ray imaging exposures are an important contributor to the radiation doses received by the UK population. The heart and vasculature are exposed in diagnostic and interventional imaging procedures, although the doses are much lower than those involved in RT. However, individual patients can undergo repeated imaging for certain conditions. Doses from imaging procedures are generally reported either in terms of measurable dose quantities, which are not comparable directly to doses to individual organs and tissues, or effective dose. CT is the diagnostic procedure that delivers the largest proportion of the doses to the population from diagnostic procedures (Hart et al, 2012), while interventional cardiology and radiology procedures deliver the highest doses from single procedures. A small proportion of patients, usually less than 1%, receive effective doses over 100 mSv from repeated CT scans, with data available from the USA (Rehani and Nacouzi, 2020; Rehani et al, 2020), Europe (Brambilla et al, 2020),

and the UK (Martin and Barnard, 2022). However, a greater number receive doses above 100 mGy to individual organs or tissues that may be at risk. In a study of cumulative doses to the heart and brain from CT scans that was carried out in a group of UK hospitals over a period of 5½ years, 9.5% of patients having head CT scans received over 100 mGy to the brain and 3.7% of patients having body CT scans received over 100 mGy to the heart (Martin and Barnard, 2021).

CT scans

2.13 Patient doses from CT scanning are reported in terms of the volume averaged CT dose index ($CTDI_{vol}$), dose length product (DLP), or effective dose. The limited available data on doses to the heart from CT scans of the thorax give values between 10 and 20 mGy per procedure. The $CTDI_{vol}$ represents an average dose to tissues within a patient represented by a standard phantom. The mean value of $CTDI_{vol}$ reported for CT scans of the thorax in the UK is 11 mGy (Shrimpton et al, 2014) and third quartile values from the distribution of UK dose survey results are 8.5 mGy for chest scans, 9.1 mGy for CT chest pulmonary angiography (CTPA) and 6 to 20 mGy for CT angiography (CTA) (Castellano et al, 2017; UKHSA, 2022).

2.14 The UK study of cumulative doses to the heart, brain and carotid artery from multiple CT scans mentioned above (Martin and Barnard, 2021) included 105,757 patients who received CT scans at 3 hospitals within 1 hospital group over a period of 5½ years, 65,394 having body scans and 58,430 having head scans. Absorbed doses to the heart were >100 mGy for 2.4% of patients, >200 mGy for 0.3%, and >500 mGy for only 5 patients, less than 0.01%. Conversely, 97.6% received doses to heart of <100 mGy, with 3.8% receiving 50 – 100 mGy and 31.3% 20 – 50 mGy. Patients receiving doses to the heart of over 200 mGy were predominantly between 50 and 90 years of age.

2.15 CT examinations of the head are performed frequently. The dose distribution within the head is reasonably uniform and $CTDI_{vol}$ can be taken as an approximate measure of dose to the brain. Values of $CTDI_{vol}$ for different scanning techniques from a UK survey gave median values of 56 to 62 mGy and third quartile values 61 to 68 mGy (Shrimpton et al, 2014). The national diagnostic reference level (DRL) based on the third quartile values from recent surveys for the $CTDI_{vol}$ is 47 mGy (UKHSA, 2022). $CTDI_{vol}$ values for children were 20 to 40 mGy for those under 5 years and 40 to 60 mGy for those over 5 years (Shrimpton et al, 2014). The study mentioned in 2.12 and 2.14 of cumulative doses in a group of UK hospitals reported that absorbed doses to the brain were >100 mGy for 5,609 patients, 9.5% of the total having brain scans (Martin and Barnard, 2021). Brain doses >500 mGy were received by 79 patients, 0.08% of the total receiving head scans, and 42% of these patients were under 50 years of age. About 90% of the group having head CT scans received doses <100 mSv, with 19.5% receiving 50 to 100 mGy and 43.8% receiving 20 to 50 mGy.

2.16 Martin and Barnard (2021) further reported that 1.3% of all the CT scan patients received an absorbed dose of >100 mGy to the thyroid, which was used as a surrogate to estimate doses received by the carotid artery, but none received doses >500 mGy.

2.17 CT doses to the brain from multiple head scans for patients included in epidemiological studies were up to about 350 mGy (Pearce et al, 2012; Berrington de Gonzalez et al, 2016).

Nuclear medicine

2.18 Exposures from radiopharmaceuticals are measured in terms of the activities administered, but there are well established models used to calculate absorbed radiation doses to individual organs and tissues (ICRP, 2015). Nuclear medicine examinations of the heart using ^{99m}Tc pharmaceuticals result in doses of 1 to 2 mGy to the heart wall, while earlier examinations using ^{201}Tl gave doses of 15 to 22 mGy. Radiopharmaceuticals for brain imaging deliver doses of the order of 10 mGy to the brain. Positron emission tomography (PET) scans that have become increasingly important in the last decade use 400 MBq of ^{18}F labelled fluorodeoxyglucose ([^{18}F] FDG) for myocardial and tumour imaging. These scans give doses of 29 to 35 mGy to the heart wall and 16 to 17 mGy to the brain, based on the latest dosimetry models (Quinn et al, 2016).

Interventional procedures

Interventional cardiology

2.19 Procedures include coronary angiography, coronary graft angiography, cardiac ablations, and insertion of stents. Doses depend on the type and complexity of the procedure and are mostly reported as either KAP or effective dose. Median KAP values are in the range 20 to 40 Gy cm^2 (Hart et al, 2012; Sciahbasi et al, 2017) with doses to a few patients extending up to several hundred Gy cm^2 (Neil et al, 2010). The UK DRL for coronary angiography is 31 Gy cm^2, based on the third quartile of the distribution, and for coronary graft angiography 47 Gy cm^2 (PHE, 2019). It is estimated that these values correspond to doses to the heart of 30 to 100 mGy, but doses to individuals may extend up to 300 mGy for multiple complex procedures on a few patients. The same patients are also likely to have undergone CT scans and possibly nuclear medicine examinations which could make an additional contribution.

2.20 Other interventional radiology procedures can also give high doses to the heart. Endovascular aortic aneurysm repair (EVAR) is a life-sparing procedure that can involve particularly high dose levels. Brambilla et al (2015) found that the median cumulative effective dose for EVAR procedures was 224 mSv with median doses to thoracic and abdominal organs in the range 190 to 270 mGy and Harbron et al (2020) reported a UK study with median heart doses for thoracic EVAR of 84 mGy, with some cases reaching several hundred mGy.

2.21 Paediatric interventional procedures can give rise to higher doses than for adults. A study in a UK paediatric hospital reported typical doses to the heart of 20 to 40 mGy per procedure with doses for some procedures of several hundred mGy (Keiller and Martin, 2015). The same authors reported doses of several hundred mGy for paediatric cardiology procedures based on analysis of dose measurements for the upper 90th percentile of cases in data published by the National Council on Radiation Protection and Measurements (NCRP), with doses over 1 Gy for some patients in the 70 to 85 kg weight range (NCRP, 2010). Harbron et al (2016) reviewed data for 5 studies reported in terms of KAP in groupings of weight or age ranges (France, Canada and the USA). KAP values for

the majority of studies of children under 10 years, or less than 40 kg, were in the range 1 to 20 Gy cm^2, while KAP values for those over 15 years of age extended from 20 up to 200 Gy cm^2. There is no straightforward link between KAP values and heart dose for paediatric patients because there are large variations in body size and in the X-ray projections used during a procedure. Results from analysis of available data (Appendix B) indicate that there is likely to be a proportion of older paediatric patients and young adults who receive doses to the heart of several hundred mGy from interventional cardiology procedures.

Neuroradiology procedures

2.22 Brain doses from cerebral angiography procedures on adults are in the order of 100 mGy and those for cerebral embolization are 150 to 500 mGy or greater (Sanchez et al, 2014). The highest brain dose from embolization procedures in this study were 800 to 1600 mGy. The mean KAP for cerebral angiography in a UK survey was 69 Gy cm^2 (Hart et al, 2012), but values can be as high as 200 Gy cm^2 for coronary angiography and several hundred Gy cm^2 for cardiac ablations (Neil et al, 2010). A KAP of 1 Gy cm^2 equates to a dose to the brain of about 1.9 mGy (Sanchez et al, 2014), so doses from neuroradiology procedures will typically result in doses to the brain of over 100 mGy , with some doses of several hundred mGy. Brain doses from paediatric procedures when optimized should be less than 100 mGy per procedure, but if large fields are used doses could be of the order of 500 mGy (Thierry-Chef et al, 2008).

Summary of medical imaging exposures

2.23 The mean absorbed doses from single diagnostic CT imaging are in the ranges 10 to 20 mGy for the heart and 50 to 70 mGy for the brain, but individual patients with specific conditions may receive multiple CT examinations over several years that may involve doses of over 200 mGy to the heart and 500 mGy to the brain. Interventional cardiology procedures typically give doses of 30 to 100 mGy to the patient's heart, but some procedures, especially on paediatric patients may involve doses of several hundred mGy. Single radionuclide PET procedures give doses of around 30 mGy to the heart. Doses to the brain from neuroradiology procedures may range from 100 mGy to 1 Gy. It should be remembered that medical imaging procedures play a vital part in the management of patients, many of whom have life-threatening conditions. Optimisation of radiological protection associated with these procedures is important to ensure that dose levels are commensurate with the intended purpose (ICRP, 2024).

Public and worker doses

Public and worker doses in planned and existing exposure situations

2.24 There are several distinct scenarios in which people can get exposed to radiation. These can be classified as planned, existing or emergency situations (ICRP, 2007). A planned exposure is the controlled use of a source, as in the industrial or medical use of radiation. Existing situations are distinguished as sources of exposure that are occurring when action is considered, such as exposures to natural sources and legacy contamination from earlier occurrences. Emergency situations involve loss of control of sources of exposure.

2.25 Doses are generally assessed as effective dose for the purposes of radiological protection and to ensure compliance with dose limits and other dose control criteria. While the use of effective dose facilitates comparisons and can give an approximate indication of possible overall risk (ICRP, 2021), it can conceal very different distributions of dose between organs and tissues. For example, while doses from terrestrial gamma rays or from ingested caesium-137 result in similar doses to all organs, iodine-131 inhalation or ingestion results in doses mainly to the thyroid and inhalation of radon results in doses mainly to the lungs. A further complication in the context of this report is that the target tissues for the induction of circulatory diseases are not well understood.

2.26 The average (non-medical) annual effective dose to members of the UK population results mainly from exposure to existing natural sources of radiation, with an average total annual effective dose estimated as 2.3 mSv (Oatway et al, 2011). The main contributors to this average dose are inhalation of radon gas and its radioactive progeny in homes (1.3 mSv), ingestion of radionuclides in foods (0.3 mSv), terrestrial gamma rays from radionuclides in rocks, soils and building materials (0.4 mSv), and cosmic radiation from space (0.3 mSv). Radon levels and gamma ray exposures are variable around the UK, with the highest levels in Cornwall with an average annual effective dose to members of the public estimated as 6.9 mSv (although for individuals this can be significantly higher).

2.27 Exposure of the public from planned routine discharges from nuclear facilities and other users of radioactive sources are generally very low, with an estimated average effective dose to individuals of <1 μSv per year (Oatway et al, 2011). Annual surveys in the UK over many years have shown the highest doses to be due to discharges from the Sellafield nuclear fuel reprocessing plant on the Cumbrian coast (RIFE, 2021, 2025). The most recent estimate of the annual effective dose to the Representative Person (ICRP, 2007) in Cumbria was 0.20 mSv for 2024, down from 0.24 mSv in 2020. This dose related mainly to the consumption of shellfish and fish, together with external dose from sediments. The main contributor to this dose was enhanced levels of natural polonium-210 in shellfish, resulting from past operations of a phosphate processing works at Whitehaven, near Sellafield, rather than Sellafield discharges. Similar doses to the Representative Person have been estimated for the Capenhurst uranium enrichment plant in Cheshire, with values of 0.22 mSv for 2024, increased from 0.15 mSv for 2023, and due largely to external radiation from the site (RIFE, 2025).

2.28 Planned occupational exposures are controlled and regulated, with employers applying dose constraints, usually set at 6 mSv per year, below the legal limit of an annual effective dose of 20 mSv per year. The UK Health Security Agency (UKHSA) maintains a UK database of monitoring results for classified workers who receive the highest occupational doses. As reported by Oatway et al (2011), the Central Index of Dose Information (CIDI) showed that average doses for the thousands of classified workers in the nuclear and defence industries were in the range of 0.1 to 1 mSv per year. However, a relatively small proportion of workers received higher doses. CIDI records indicated a total of 3,152 workers having recorded doses in the range of 1 to 6 mSv per year, a few receiving doses of up to 15 mSv per year, and none exceeding the 20 mSv per year dose limit.

2.29 Medical staff may also incur similar doses to those received in the nuclear industry. Oatway et al (2011) recorded a total of 913 staff with annual effective doses in

2009/10 of 1 to 6 mSv and 109 workers with doses exceeding 6 mSv per year in the UK. In France, the highest doses (0.36 mSv (0.33 to 0.39)) were reported for nuclear medicine radiographers and technicians (Baudin et al, 2023).

2.30 Occupational exposures to existing sources occur in mining and offshore gas and oil operations (Oatway et al, 2011). Small numbers of workers in small, poorly ventilated, mines in the UK have received annual effective doses, mainly from radon and progeny, of up to 20 mSv per year, with an average of 6 mSv in 2010 (30 miners with 6 to 20 mSv in 2010). For larger mines, doses were lower, with an average for 2010 of 0.6 mSv. Gas and oil extraction releases naturally occurring radionuclides, principally isotopes of radium, lead and polonium. Annual effective doses recorded for 2010 averaged 0.2 mSv, with 33 workers receiving 1 to 6 mSv and 1 in the 6 to 20 mSv range.

2.31 Average annual effective doses in the US from occupational exposures were reported for 2003 to 2006 by NCRP (NCRP, 2009) to be 0.81 to 0.93 mSv (industry and commerce), 0.54 to 0.72 mSv (education and research), 3.07 mSv in aviation, and 0.50 to 0.73 mSv (defence and military). A survey carried out from 2012 to 2014 showed that over time, annual doses to US radiologic technologists working in general radiology decreased from an average of 0.6 mSv to below the limits of detection over a 36 year period of time, but doses for nuclear medicine/PET imaging workers remained at 1 to 2 mSv (Villoing et al, 2021). The majority of occupational exposure in nuclear medicine/PET imaging is due to irradiation from patients and is difficult to protect against (Zeff and Yester, 2005). It is noted that the use of average dose estimates conceals differences between individual workers and doses could be significantly higher for some individuals.

Public and worker doses in accidents

2.32 Emergency situations can lead to very high and widespread doses, with the most notable examples being the accidents occurring at the nuclear power plants at Chornobyl in 1986 and Fukushima Daiichi in 2011.

2.33 UNSCEAR (2020) has evaluated exposures of the Japanese public and workers after the Fukushima accident. The average effective doses to the public who were not evacuated and to those evacuated from the most contaminated areas averaged between about 0.1 and 10 mSv in the first year after the accident, mostly due to external exposures from contaminating caesium isotopes. Doses reduced to an average of up to about 1 mSv per year for the following 10 years and subsequently to an average of 0.3 – 0.4 mSv. Average absorbed doses to the thyroid from ingested iodine isotopes were estimated in the range from about 1 to 30 mGy in the first year. The total collective effective dose to the population was estimated as 12,000 man Sv (the cumulative dose (in Sv) per person summed over all members of the cohort) in the first year and 32,000 man Sv over the first 10 years.

2.34 For the over 20,000 workers involved in responding to the Fukushima accident, the average first year effective dose was 13 mSv. Six workers received doses greater than 250 mSv, with the highest being 679 mSv, largely due to inhalation of radioiodine. A further 168 workers received effective doses in the range of 100 to 250 mSv. From April 2013, all worker doses were below 50 mSv and by 2018 the maximum was reduced to 20 mSv. The average annual effective dose to 10,708 workers reduced to 3 mSv. The highest thyroid doses ranged from 5 to 32 Gy.

2.35 Compared to the Fukushima Daiichi accident, the earlier Chornobyl accident resulted in substantially greater doses to larger numbers of people (UNSCEAR, 2000, 2011). For example, the average first year effective dose for 530,000 recovery operation workers was estimated as 120 mSv, with the majority in the range of 20 to 500 mGy whole-body dose. Recorded doses for 134 of the 600 workers on site on the first day, both nuclear plant workers and emergency responders, were in the range of 0.8 to 16 Gy; they suffered acute radiation syndrome, and 28 workers died in the first 3 months. The first year average effective dose for 115,000 evacuated members of the public was 30 mSv, with maximum doses more than an order of magnitude higher. The average absorbed dose to the thyroid of evacuees, largely from consumption of milk containing iodine-131, was estimated to be about 500 mGy, with individual values ranging from <50 mGy to >5 Gy (UNSCEAR, 2018), with particularly high thyroid doses, >35 Gy, recorded in groups of exposed children in Ukraine and Belarus (Little et al, 2014; Little et al, 2015).

Summary of public and occupational exposures

2.36 Effective dose is the main quantity used to assess radiation exposures because it facilitates comparisons between different exposures to external and internal sources. However, it may conceal large differences in absorbed doses to particular organs and tissues. In the context of this report, target organs and tissues are not well understood.

2.37 With these caveats, it is clear that doses to all organs and tissues are low or very low in the case of planned or existing exposures of workers and members of the public (not considering doses received as medical patients). Emergency situations have resulted in moderate doses to members of the public and high doses to workers.

Chapter 3. Epidemiology

3.1 Potential impacts on human health from radiation exposures are studied using a variety of different epidemiological study designs, most notably observational studies which are not based on the deliberate (randomised) exposure allocation by the research team (randomised controlled trials (RCTs)).

3.2 RCTs are considered to have the strongest potential to make unbiased inferences about the causal effect of an exposure on an outcome of interest, at least in theory. However, in most situations of radiation exposure, with the exception of those in medical settings, they cannot be implemented.

3.3 Alternative observational epidemiological designs, including cohort studies and case-control studies, can provide estimates of risk similar to those from RCTs, but inferences are more difficult as these study designs are highly susceptible to issues of bias and confounding that may impact on the validity of the study.

3.4 Epidemiological studies of radiation exposure are susceptible to all forms of bias that also hamper observational studies in other settings. In particular, there are concerns around (exposure) measurement error or bias, selection bias such as the healthy worker effect, and related issues of collider bias, recall bias, loss-to-follow-up bias, and issues of residual confounding as a result of specific information not being available (UNSCEAR, 2017; Berrington de Gonzalez et al, 2020; Daniels et al, 2020; Gilbert et al, 2020; Hauptmann et al, 2020; Linet et al, 2020; Schubauer-Berigan et al, 2020).

3.5 Nonetheless, the benefit of conducting such studies is that they can provide information on comparatively large populations under non-contrived “real-world” settings, benefitting the external validity of findings, and the ability to study effects following long-term exposure or to study the effects from exposures following long latencies.

3.6 Epidemiological evidence of CVD risks from low dose or low dose rate radiation exposures comes from observational epidemiological studies of the Japanese atomic bomb survivors, medical exposures, occupationally exposed populations, and environmental exposures.

3.7 In these epidemiological studies, people exposed to radiation are compared to populations that are not exposed, or which have different levels of exposure, with respect to an outcome, and the differences are expressed as relative measures of association (Relative Risks (RR), Excess Relative Risks (ERR), Hazard Ratios (HR), or others depending on study design), and sometimes also as absolute differences (that is, the number of additional, or fewer, people with the outcome, for example expressed as Excess Absolute Risk (EAR)).

3.8 Relative measures of association centre around 1 (no difference) with a higher number indicating an excess risk and a number between 0 and 1 indicating a risk reduction (with ERR expressed as RR-1), and sometimes these measures are expressed per unit exposure or dose to describe linear associations between exposure/dose and risk, or at a particular dose, for example, 1 Gy, if a linear association is not assumed.

3.9 A specific measure of association used in studies of exposed populations is the Standardized Mortality Ratio (SMR), in which the outcome is compared between workers and a comparable (in terms of sex and age distribution) group from the general population. Related measures include Standardised Incidence Ratios (SIR) or Standardised Registration Ratio (SRR). Although a useful measure for initial comparison, particularly for a large number of outcomes, this measure is particularly susceptible to various biases. In particular, because workers are generally healthier on average than the normal population, a common observation is 'healthy worker selection bias' (Vrijheid et al, 2007a). SMRs also have the limitation that they do not provide information on quantitative associations with the level of radiation exposure. Therefore, although SMRs may be reported in this report in places for reference, they will not be further discussed.

Evidence from the Japanese atomic bomb survivors

3.10 The impact of a single radiation exposure has been studied in the Life Span Study (LSS) of Japanese A-bomb survivors (Ozasa et al, 2018); a cohort of 120,321 people followed from the 1950s, with dose-response assessed for mortality from heart diseases in 86,600 members of the cohort with individual dose estimates (Takahashi et al, 2017). About 45% of the exposed cohort received a radiation dose (weighted absorbed colon dose based on DS02R1 estimations) of <5 mGy, and 6.4% received >500 mGy (Cullings et al, 2017).

3.11 The LSS has provided evidence of a dose-related excess risk of circulatory disease mortality (Preston et al, 2003; Yamada et al, 2004; Shimizu et al, 2010; Ozasa et al, 2012) with ERR/Gy (dose estimates for the colon) of 0.11 [0.05, 0.17][5] (Ozasa et al, 2012). There was some indication that risk might be higher in women (0.14 [0.06, 0.23]) than in men (0.07 [–0.001, 0.16]).

3.12 For all heart disease, an ERR/Gy of 0.14 [0.06, 0.23] was observed (Shimizu et al, 2010). A linear model best fitted the data, with ERR/Gy of 0.14 [0.04, 0.25], 0.18 [0.03, 0.33] and 0.20 [–0.05, 0.45] for dose ranges under 2 Gy, 1 Gy, and 0.5 Gy, respectively, without evidence of a threshold, although subsequent work highlighted methodological issues suggesting that the likelihood ratio test is probably invalid in this context (Little, 2013). A significant dose response for heart failure over the 0 to 0.4 Gy dose range was reported (Takahashi et al, 2017).

3.13 The heart disease risks were greatest for hypertensive heart disease, rheumatic heart disease and heart failure. For IHD specifically (n=3,556; 3,079 with weighted absorbed colon dose <200 mGy) there was no excess risk across the complete dose range (ERR/Gy 0.03 [–0.08, 0.15]). However, the authors reported that there was some indication that IHD risk increased only in the higher dose categories (Takahashi et al, 2017).

3.14 Takahashi et al (2017) also reported an ERR/Gy of 0.02 [–0.13, 0.20] for MI, 0.04 [–0.12, 0.22] for other ischemic heart diseases, and 0.21 [0.07, 0.37] for heart failure, among other endpoints.

3.15 ERR/Gy for stroke, based on 9,622 cases, was 0.09 [0.01, 0.17]. Although there were indications of upward curvature in the dose-response, there was no evidence that the linear-quadratic model significantly improved the fit over the linear model (p=0.17). There were weak suggestions of smaller effects at lower doses, with

[5] In this report, figures in square brackets are 95% confidence intervals (CI). Thus, in this case, 0.11 is the mean value, and lower and upper confidence intervals on this mean value are 0.05 and 0.17

ERR/Gy of 0.03 [–0.10, 0.16] for the dose range 0 to 1 Gy and –0.07 [–0.28, 16] for 0 to 0.5 Gy (Shimizu et al, 2010), but the uncertainties in these estimates are considerable.

3.16 Similarly, for cerebrovascular infarction (ERR/Gy 0.04 [–0.10, 0.20]) and cerebral haemorrhage (ERR/Gy 0.05 [–0.06, 0.17]) there was no excess risk observed across the dose range (Shimizu et al, 2010).

3.17 Shimizu et al (2010) reported minimal confounding from smoking, alcohol, education, occupation, obesity or diabetes.

3.18 There have been reports also of excess CVD incidence in the Adult Health Study (AHS), a (biennially clinically examined) subset of the LSS, in particular hypertension (Yamada et al, 2004), although there was no significant dose response for peripheral artery disease (Takahashi et al, 2018).

3.19 Although the LSS provides important information on cancer and non-cancer effects from moderate to high doses received following a single radiation exposure, more or less uniform to the whole body, the relevance of risk estimates to low dose or low dose rate, protracted exposures is unclear. A large proportion, 74,444 of 86,611 (~86.0%) survivors received doses of <50 mGy, and so most received low dose (<100 mGy). Nevertheless, almost all exposures were received at high dose rate within a period of <10 seconds (Rühm et al, 2018). In addition, Ozasa et al (2016) advised that these results should be treated with caution because of changes in disease classification and other possible factors influencing risk in this population.

Evidence from radiotherapy

Long-term cardiovascular risk associated with radiotherapy for cancer

3.20 Greater risks of cardiac events occurring following radiotherapy (RT) treatments have been reported among individuals with hypertension and pre-existing cardiac disease (Darby et al, 2013; Dess et al, 2017).

3.21 A large number of observational studies and randomised controlled trials have investigated the long-term effects of RT treatment of cancer and non-malignant diseases. These studies report a long-term increase in risk of CVD (up to 40 years after treatment for lymphoma). Many of these studies have investigated the effects of RT for breast cancer and there have been many studies estimating risks in relation to heart doses resulting from standard breast cancer RT regimens (Darby et al, 2013; Jacobse et al, 2019; Boekel et al, 2020; Killander et al, 2020; Baaken et al, 2022).

3.22 Other cancers within the thorax and abdomen that are treated with RT have a lower incidence in the population or have a lower rate of long-term survival during which cardiovascular effects might be manifest. A few studies have been carried out in more depth over many decades for patients with Hodgkin lymphoma and for paediatric RT for a variety of malignancies (Cutter et al, 2015; Haddy et al, 2016; van Nimwegen et al, 2016; van Nimwegen et al, 2017; Mulrooney et al, 2020; Shrestha et al, 2021). These studies have grouped patients in terms of the dose received by the heart and so can provide an indication of dose dependence. Data on patients receiving <10 Gy to the heart are limited, but those studies that do present their results separately do not indicate increased CVD risks.

3.23 Other cancers in the region of the heart treated with radiation are those of the lungs and oesophagus. For these cancer types, doses are higher and, despite the shorter survival times, cardiovascular effects have been observed within about 2 years (Dess et al, 2017; Atkins et al, 2019).

3.24 Risks of CVD can be increased by several fold in patients treated with RT for cancers in the thorax. Breast cancer and lymphoma are of particular importance because of the potential for curative treatment and long-term survival.

3.25 There have also been a number of studies of CVD in persons treated for non-malignant disease (Little et al, 2012a; Adams et al, 2018; Sadetzki et al, 2021) or receiving radiation for diagnostic purposes (Tran et al, 2017).

Breast Cancer radiotherapy exposures

3.26 Darby et al (2013) reported a population-based case control study of 2,168 women with a mean heart dose of 4.9 Gy (range, 0.03 to 27.7 Gy) which demonstrated a linear increased incidence of major coronary events, with an ERR/Gy of 0.074 [0.029, 0.145] using mean heart dose. There was some evidence of excess risk for those receiving 5 to 9 Gy heart dose.

3.27 van den Bogaard et al (2021) published a study of 910 women receiving RT at a single institution following breast-conserving therapy. They reported an ERR/Gy for MI of 0.117 [–0.098, 0.383] among patients with atherosclerotic plaque in the left anterior descending (LAD) artery, and 0.161 [–0.034, 0.395] among patients without atherosclerotic plaque in the LAD artery, using mean heart dose. The authors suggested that for persons with atherosclerotic plaque, it was dose to the plaque that was most predictive of radiation-associated MI.

3.28 Taylor et al (2017) pooled the data from dosimetry studies of breast cancer RT regimens in the 1980s to estimate radiation doses to the heart (average dose to the whole heart 6 Gy) and the effect of radiation on long-term cardiac mortality. The study included 75 trials involving 40,781 women with median age 56 years. The meta-analysis yielded a risk ratio for cardiac mortality at 10 years after RT (n=1,253) of 1.30 [1.15, 1.46]. The ERR/Gy of cardiac mortality in relation to mean heart dose was assessed to be 0.04 [0.02, 0.06]. The authors concluded that, based on available data, a clear relationship exists between whole-heart dose and risk of cardiac events following RT for breast cancer, with a significant increase in risk for left-sided breast cancer patients. A history of ischaemic heart disease and smoking were identified as confounding factors for risk of cardiac death. The study has quite significant limitations resulting from use of grouped estimates of dose for each component regimen, so that there is the potential for ecological bias.

Hodgkin Lymphoma radiotherapy studies

3.29 van Nimwegen et al (2016) carried out a case-control study of 325 cases diagnosed with coronary heart disease as their first cardiovascular event after receiving RT for treatment of Hodgkin lymphoma (HL) and who were matched to 4 patient controls each. The mean heart dose was assessed using the percentage of cardiac volume within the field as 22.0 Gy for cases and 20.4 Gy for controls. A linear radiation dose-response relationship best described the data, with a regression line estimate of ERR/Gy of 0.07 [0.03, 0.15].

3.30 Another case-control study (with 89 cases, 200 controls) nested within the same Dutch cohort of patients following RT treatment for Hodgkin lymphoma showed a 1.4% increase in valvular heart disease among those receiving 20 or 30 Gy to the heart (Cutter et al, 2015). Heart failure has also been assessed in a case-control study (with 91 cases, 278 controls) nested within this cohort, with HR of 1.27 [0.86, 1.89]; 1.65 [0.98, 2.77]; 3.84 [1.97, 7.47] and 4.39 [2.00, 9.65] in groups receiving mean left ventricular doses of 1 to 15 Gy, 16 to 20 Gy, 21 to 25 Gy and ≥26 Gy, respectively (van Nimwegen et al, 2017).

3.31 Maraldo et al (2015) conducted a pooled analysis of 9 European randomized clinical trials of persons with Hodgkin lymphoma, assessing several cardiovascular outcomes. An excess HR/Gy of 0.015 [0.006, 0.024] for all cardiovascular event incidence, and 0.019 [0.009, 0.028] for major cardiovascular event incidence was observed in relation to mean heart dose.

Childhood cancer survivor studies

3.32 RT related cardiac risks have also been assessed in the Childhood Cancer Survivors Study (CCSS) of 24,214 patients, of whom 11,960 had received RT (59.7% also received the chemotherapy drug, anthracycline), from the United States and Canada recruited in 1970 to 1999 (Shrestha et al, 2021). Paediatric cancer survivors originally diagnosed with leukaemia, brain cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, renal tumours, neuroblastoma, soft tissue sarcomas, or bone sarcomas diagnosed prior to 21 years of age (median 7 years) and with a minimum of 5 years survival post RT were assessed for cardiac disease.

3.33 The study showed a cumulative incidence of cardiac disease 30 years after cancer diagnosis of 4.8%, substantially higher than among siblings (Mulrooney et al, 2020), and doses of 5.0 to 19.9 Gy to volumes >50% of the heart were associated with an increased rate of cardiac disease, RR of 1.6 [1.1, 2.3] (Bates et al, 2019).

3.34 Further analysis of only patients with conditions graded 3 to 5 (grade 3 - severe or disabling, grade 4 - life-threatening, and grade 5 - fatal), indicated 2 to 7 fold excess risks of cardiac disease, coronary heart disease or heart failure from ≥10 Gy to the heart (Shrestha et al, 2021).

3.35 The 20 year cumulative incidence of heart failure in this study has declined with time, being 0.69% for those treated in the 1970s, 0.74% for those treated in the 1980s, and 0.54% for those treated in the 1990s (Mulrooney et al, 2020). The incidence of coronary artery disease has also declined with time, being 0.38%, 0.24%, and 0.19%, in the groups treated in the 1970s, 1980s and 1990s, respectively. The decrease was particularly marked among survivors of Hodgkin lymphoma.

3.36 Haddy et al (2016) reported on 3,162 patients from the French part of the same cohort. Results described increasing risk of cardiac disease among 5 year survivors of childhood cancer with increasing mean heart doses for all grades of cardiac disease and grades ≥ 3. The cumulative incidence of any type of cardiac disease at 40 years of age (n=156) was 7.4% [6.2, 8.9] for cardiac disease of grade ≥3. The mean heart dose was 7.5 Gy for all patients, 17.2 Gy for patients with cardiac disease, and 19.7 Gy for patients with a cardiac disease of grade ≥3. For patients who had received anthracycline, the risk of radiation-induced cardiac

disease increased markedly with attained age. The ERR/Gy was 0.26 [0.06, 0.82] up to 20 years and 0.87 [0.28, 3.46] at >40 years of age, but there was no increase in ERR/Gy with attained age in patients who had received anthracycline. Patients who received a mean heart dose <0.1 Gy and anthracycline had a comparable RR (compared to no RT and no anthracycline) of 18.4 [7.1, 48.0] to those receiving 15 to 30 Gy without anthracycline (with same reference group), RR of 18.9 [7.1, 50.2].

Lung and oesophagus cancer studies

3.37 Studies in patients with breast cancer or lymphoma have demonstrated that radiation-induced cardiac disease often occurs many years after RT. However, patients receive greater radiation exposure of the heart for treatment of cancer of the lung or oesophagus. Although the shorter survival of these patients means that they are less likely to be affected by long term cardiac changes, the higher doses can lead to effects within the first 2 years.

3.38 Dess et al (2017) reported an incidence of a grade 3 cardiac event within 24 months of 11% [5%, 16%] among 125 patients with non-small cell lung cancer receiving a median cardiac dose of 11 Gy (range 0.3 to 46 Gy). An ERR/Gy (in relation to mean heart dose) of 0.07 [0.02, 0.13] was assessed. Atkins et al (2019) reported a 5.8% [4.3%, 7.7%] cumulative incidence of a major cardiac event over a 2 year period among 748 patients receiving a mean heart dose of 12.3 Gy (range 6 to 19 Gy) while being treated for a similar condition. In later analysis of the same data, Atkins et al (2021) estimated an ERR/Gy of 0.03 [0.00, 0.06] for major adverse cardiac events in relation to mean heart dose.

3.39 In a study of 479 patients treated with RT for oesophageal cancer, who received between 5 and 50 Gy to the heart, 18% experienced a severe cardiac event (G3+) within the 76 month follow-up, with a median time of 7 months (Wang et al, 2020). The number of events was lower in those receiving a mean heart dose less than 15 Gy. An ERR/Gy of 0.034 [0.006, 0.062] in relation to mean heart dose was determined.

Studies of persons treated for non-malignant disease or subject to diagnostic exposures

3.40 Sadetzki et al (2021) reported increased risks of vascular disease with RR=1.19 [1.09, 1.29], stroke RR=1.35 [1.20,1.53], carotid artery stenosis RR=1.32 [1.06, 1.64], and IHD RR=1.12 [1.01, 1.26] in a cohort of 17,734 persons who were treated for tinea capitis in childhood in Israel, 7,408 of whom received RT with mean doses of 1.5, 0.09, 0.78, or 0.017 Gy to the brain, thyroid, salivary gland, or breast, respectively. The doses tended to be low relative to those in groups treated for cancer. Efrati et al (2009) reported on a study of 145 individuals receiving RT and 150 matched controls with no history of RT in this cohort and noted a significant increase in carotid intima media thickness (IMT) and increased prevalence of carotid stenosis in the exposed group, with adjusted OR=5.36 (2.78, 10.33), but no such increase in femoral IMT or prevalence of femoral stenosis. However, no individual doses were used in this analysis.

3.41 Adams et al (2018) analysed persons treated for enlarged thymus with X-rays in early infancy, comparing risk among an irradiated group with non-irradiated siblings, and reported a non-significantly increased risk of coronary heart disease with ERR/Gy of 0.08 [–0.01, 0.20]. The doses in this group were moderate to high,

with median cumulative heart dose of 1.41 Gy (range 0.17 to 20.2) in the irradiated group.

3.42 Little et al (2012a) reported dose-dependent excess risks in a US cohort of 3,719 peptic ulcer patients, 1,859 of whom were treated with X-rays, with heart doses in the range 0 to 6.20 Gy. There were 1,469 deaths from all circulatory disease, with an ERR/Gy of 0.08 [0.03, 0.14] and 1,003 deaths from IHD, with an ERR/Gy of 0.10 [0.04, 0.17].

3.43 Tran et al (2017) analysed a pooled cohort of 77,275 persons who received multiple fluoroscopic X-rays as part of their air-collapse treatment for tuberculosis and reported a dose-dependent excess risk for all circulatory disease for exposure <0.5 Gy, with ERR/Gy of 0.246 [0.036, 0.469], and also for IHD with ERR/Gy of 0.267 [0.003, 0.552]. However, over the full dose range, with doses up to 27.8 Gy, the dose response was null.

Long-term cerebrovascular risk

3.44 The effects of RT on the brain can either be due to direct cerebral irradiation or irradiation of blood vessels supplying the brain. Meta-analyses of data from around the world on patients treated with RT for head and neck cancer (30 to 80 Gy) show risks of cerebrovascular disease (CeVD) and stroke to be approximately doubled on average, but the relative risk may be up to 5.6 in groups receiving higher doses (Plummer et al, 2011; Huang et al, 2019). A systematic review of all available studies of radiation exposure, 93 of them informative, with about half assessing risks from medical RT, found evidence of excess risk of CeVD, with an ERR/Gy of 0.188 [0.093, 0.283] (Little et al, 2023).

3.45 A retrospective analysis of a prospective study cohort of 750 head and neck cancer patients in the Netherlands treated with definitive (chemo) RT calculated dose–volume parameters for the carotid arteries in the treatment plans (van Aken et al, 2021). Twenty-seven patients experienced an ischaemic cerebrovascular event during follow-up (mean 3.4 years) with a cumulative risk of 4.6% and excess risk, HR/Gy mean carotid dose, of 0.03 [0.00, 0.07].

3.46 Haddy et al (2011) conducted a cohort study of 4,590 2 year survivors of childhood malignant neoplasms (other than leukaemia) treated in 1985 or before in one of eight cancer centres in France or the UK, and of which 4,227 were still alive 5 years after diagnosis. RT had been received by 2,947 of these patients and 724 had died during follow-up, 23 from CeVD. Radiation dose to the brain was 10.5 to 49.2 Gy (mean 25.3 Gy) for those treated for CNS cancers and 1.9 to 6.7 Gy (mean 3.4 Gy) for those treated for other cancers. Cumulative CeVD mortality was 1.3% at 40 years after diagnosis for all patients, and 1.7% [1.0%, 2.8%] for those who received RT. There was no significant association (p=0.5) with average brain dose, but a linear dose-response when considering dose to the prepontine cistern, with an ERR/Gy of 0.22 [0.01, 0.44]. A RR of 24.2 [5.1, 115] was observed for patients who had received 50 Gy or more compared with patients who did not receive RT. It is noted that the prepontine cistern is very close to the circle of Willis, a vascular network that provides all the terminal vasculature to the brain (Haddy et al, 2011).

3.47 Mueller et al (2013) reported on the Childhood Cancer Survivor Study, a retrospective cohort of 14,358 5 year survivors of childhood cancer, with 4,023

selected siblings as controls, and showed that after 23.3 years of follow-up RT increased CeVD risk with a HR of 5.9 [3.5, 9.9] for 30 to 49 Gy and 11.0 [7.4, 17.0] for >50 Gy.

3.48 In the same cohort, Fullerton et al (2015) reported 72 cases of recurrent stroke among 271 persons with a first stroke, estimating a HR of 4.4 [1.4, 13.7] for patients who received cranial RT doses of ≥50 Gy.

3.49 El-Fayech et al (2017) analysed a cohort of 3,172 5 year survivors of childhood cancer, 2,202 of whom received RT. Median follow-up was 26 years, during which 54 experienced a stroke (39 of which were ischaemic). Patients not receiving RT had a stroke risk similar to that of the general population, whereas those who received RT had an 8.5-fold (95% CI [6.3, 11.0]) increased risk. The ERR/Gy was 0.24 [0.11, 0.53] for all stroke, and 0.42 [0.16, 1.20] for ischaemic stroke.

3.50 Sadetzki et al (2021) assessed risk of CeVD in a cohort of 17,734 persons in Israel treated for tinea capitis in childhood (with sibling controls), 7,408 of whom were treated with X-rays. There were 1,089 incident cases of CeVD and brain doses of 0 to 6 Gy were received, yielding an ERR/Gy of 0.20 [0.12, 0.29].

3.51 In a US cohort of 3,719 persons treated for peptic ulcer, 1,859 of whom were treated with X-rays, there were 226 deaths from stroke, with thyroid doses of 0 to 0.46 Gy, with a non-significant ERR/Gy of 0.422 [–1.455, 3.039] (Little et al, 2012a).

Summary of radiotherapy and diagnostic radiation exposure risk

3.52 Cardiovascular effects have been reported following RT treatments where the heart or brain have received doses of a few Gy or greater. A clear relationship exists between mean heart dose and risk of cardiac events following RT for breast cancer with typical doses of several Gy or more. The risks are reported to be significantly higher among individuals with pre-existing cardiac disease.

3.53 Several studies demonstrate a linear relationship between cardiovascular effects and mean heart dose. An example is the relative risk of heart disease among patients receiving RT of between 14 Gy and 36 Gy during childhood (Shrestha et al, 2021). However, few of these studies enable an extrapolation with any degree of accuracy down to doses of less than 10 Gy. Doses tend to be substantially lower in groups treated with RT for non-malignant disease, or given radiation for diagnostic reasons, and studies have shown excess risk at <6 Gy (Sadetzki et al, 2021), or indeed <0.5 Gy (Tran et al, 2017).

3.54 Organ doses in RT studies are highly non-uniform, so that if the target tissue is incorrectly specified then doses will be substantially biased. Even if the correct target tissue is chosen, organ doses are often determined many years after the event, and often rely on treatment plans – so if these are slightly out, or the organ position is not correctly ascertained then doses will be inaccurate. Another serious issue with all RT studies is that of selection – the people who receive a certain treatment (and in particular receive a specific radiation dose) could do so because of some underlying medical condition, which may well determine the subsequent disease status.

3.55 Strengths of the medical RT cohorts are that they frequently have very rich data on medical/environmental risk factors, particularly those known to be associated with

CVD. As detailed in the analysis of Little et al (2024), there is little evidence that making adjustments for such factors results in significant changes to radiation risk estimates.

Evidence from occupational populations

3.54 An important source of evidence of low-dose or low dose rate exposure and ischemic heart disease (IHD) and cerebrovascular disease (CeVD) risk are large occupational population (worker) cohorts which, because of long follow-ups, offer an increasingly important data source on the effects of protracted low dose-rate exposure to external sources of radiation (Wakeford, 2009, 2021).

3.55 These observational studies have important strengths, notably their direct relevance to human health, their size, the length of follow-up, and often good exposure assessments.

3.56 However, there are weaknesses that limit their ability for causal inference inherent to all observational epidemiology, including for example sampling or follow-up bias and missing information on confounders. They may also have insufficiently large populations, hampering subgroup analyses and hampering interpretation of findings.

3.57 There are several large national occupational radiation worker cohorts, and for several decades extensive work has been done to pool data from some of these cohorts to improve statistical power, initially at a national level and then internationally. An overview of the main occupational cohorts or pooled cohorts with information on cardiovascular outcome data is provided below.

International Agency for Research on Cancer 15-country study of nuclear industry workers

3.58 The 15-country study was a multinational retrospective cohort study of the mortality of nuclear industry workers employed in the production of nuclear power, manufacturing of nuclear weapons, enrichment and processing of nuclear fuel, production of radioisotopes or reactor or weapons research, but not uranium mining, including workers from 15 countries (Australia, Belgium, Canada, Finland, France, Hungary, Japan, Lithuania, Slovakia, South Korea, Spain, Sweden, Switzerland, UK, US) (Cardis et al, 2005; Vrijheid et al, 2007a).

3.59 The 15-country study assessed associations between radiation exposure and non-cancer outcomes including CVDs, as well as the main focus on cancer, although not including the Japanese cohort, US-Idaho National Laboratory and Canada-Ontario Hydro cohorts because of missing information on non-cancer mortality or socio-economic status (Vrijheid et al, 2007b). These analyses were based on a total of 275,312 workers and 4,067,861 person-years of follow-up from 1943 to 2000.

3.60 In these analyses, the main study population included workers with at least 1 year in a facility and who had been monitored for external radiation exposure, with doses resulting predominantly from higher energy photon radiation. Workers were excluded who had the potential for substantial (>10% of whole-body dose) from neutrons and/or internal contamination with radionuclides other than tritium that were not adequately measured (Cardis et al, 2007). External radiation exposure

data were obtained from facility records and/or national registries. Doses to specific organs were included, with colon doses used for all non-respiratory diseases. Errors in dose assessments were evaluated to obtain bias factors for use in the epidemiological analyses; these were generally close to 1, but with varying magnitude of uncertainty, particularly in the earlier years (Thierry-Chef et al, 2007).

3.61 The average cumulative dose (Hp(10)) in the population was 20.7 mSv, with <0.1% of workers having received cumulative doses >500 mSv. Average colon dose and lung dose were estimated at 16.9 mSv and 17.9 mSv, respectively.

3.62 The study included 8,412 circulatory disease deaths, of which 5,821 were from IHD and 1,224 from CeVD.

3.63 The overall finding for circulatory diseases, with doses lagged by 10 years, was a small, non-significant, dose-response association with an ERR/Sv of 0.09 [–0.43, 0.70] (Vrijheid et al, 2007b). Effects were stronger with increasing lag time up to 15 years and were stronger for men than for women.

3.64 A limitation of the 15-country study is that information on factors such as smoking habits, alcohol intake and diet was not available.

3.65 Furthermore, subsequent work showed that there were important errors in the exposure assessment of the Canadian cohort which, once corrected as best as possible, resulted in reduced cancer mortality risks (Zablotska et al, 2014b). The impact of these errors on CVD incidence or mortality risks is not known but may also affect the 15-country study pooled results.

UK National Registry for Radiation Workers (NRRW)

3.66 The NRRW includes workers from a wide range of industrial employer organisations in the UK but principally from the Ministry of Defence, the Atomic Weapons Establishment (AWE), the UK Atomic Energy Authority (UKAEA), the sites formerly managed by British Nuclear Fuels plc (BNFL), and UK nuclear power generation sites. It includes workers who started being monitored for exposure to external radiation during 1940 to 1999, and to date has had 3 analyses (Muirhead et al, 2009a), as well as extended analyses of the third (NRRW-3) analysis (Haylock et al, 2018; Zhang et al, 2019a; Hunter et al, 2022).

3.67 In addition to external radiation dose, primarily from gamma rays and X-rays but with smaller contributions from beta particles and neutrons, records were kept of internal exposure, primarily to uranium, plutonium and tritium (Zhang et al, 2019a).

3.68 NRRW-3 included about 23,600 of workers (14%) who started work before 1960 when higher exposures occurred resulting in these workers contributing 41% of the overall collective dose and with 19% of this group having accumulated lifetime occupational external doses >100 mSv (Muirhead et al, 2009b). Overall, 6% of the workers included in NRRW-3 had working lifetime doses >100 mSv.

3.69 Muirhead et al (2009a) reported an ERR/Sv for all circulatory disease of 0.25 [–0.01, 0.54] and of 0.16 [–0.42, 0.91] for CeVD. They also reported an ERR/Sv of 0.28 [–0.19, 0.85] for all circulatory diseases not strongly related to smoking. It was noted that risks for exposure to external radiation were greater in workers who were not also monitored for potential intakes of radionuclides.

3.70 The extended NRRW-3 analyses added a further ten years of follow-up to the end of 2011, by which time 21% of the workers had died. External doses >100 mSv over a working lifetime were recorded for 13% of all workers who had died, and 62% of these workers had started work before 1960 (Haylock et al, 2018).

3.71 The most recent non-cancer (extended) NRRW 3rd analyses (NRRW-3) were based on 167,003 workers (56% industrial workers) with 3,684,391 person years of follow-up (mean length of follow-up was 32 years) of whom 34,995 were deceased by the end of follow-up (Haylock et al, 2018; Zhang et al, 2019a).

3.72 Mean and median doses from external radiation were 62.1 mSv and 17.1 mSv, respectively (Haylock et al, 2018).

3.73 Analysis of mortality from heart disease specifically was based on 174,541 subjects, which included 11,014 deaths from heart disease, including 9,814 from IHD (Zhang et al, 2019a).

3.74 The updated analyses reported excess mortality from heart disease with an ERR/Gy of 0.37 [0.11, 0.65], and confirmed excess IHD mortality, with an ERR/Gy of 0.32 [0.04, 0.61] (Zhang et al, 2019b). Significant inter-facility heterogeneity was noted, but exclusion of outliers did not materially change the summary dose-response slope (Zhang et al, 2019a).

3.75 Hinksman et al (2022) updated the CeVD mortality analyses based on a study cohort of 166,812 nuclear workers (3,665,413 person-years), including 3,219 deaths from ischaemic stroke, haemorrhagic stroke and other/ill-defined CeVD. They reported an ERR/Sv of 0.57 [0.00, 1.31], with increased mortality rates being observed above 10 to 20 mSv (Hinksman et al, 2022).

3.76 A study was done on a subset of the NRRW cohort consisting of installations previously operated by British Nuclear Fuels Limited (BNFL) (McGeoghegan et al, 2008). Analysis of mortality patterns among male employees up to 2006 indicated a raised ERR/Gy estimate[6] for CVD mortality with respect to cumulative external dose of 0.65 [0.30, 1.04]. This was mainly attributable to the ERR/Gy for deaths from IHD, with an ERR/Gy of 0.70 [0.26, 1.19].

3.77 Significant heterogeneity of CVD mortality ERR/Gy estimates was observed between industrial ("blue collar") and non-industrial ("white collar") workers and between workers monitored only for exposure to external radiation or also for potential exposure to internally deposited radionuclides.

3.78 Nested within the McGeoghegan cohort, a matched case control study of IHD mortality was also established among male industrial workers at Sellafield and the BNFL Springfields uranium processing plant (after Sellafield, the largest BNFL installation), originally set up to study associations with occupational noise and shift work but with external radiation dose and internal exposure added later (de Vocht et al, 2020). This study took account of confounding by socio-economic status, occupational noise, shift work, and pre-employment blood pressure, body mass index, and tobacco smoking.

[6] McGeoghegan et al. (2008) used a 15 year lag period and reported 90% confidence intervals that have here been converted to 95% confidence intervals (assuming a Normal distribution) for consistency with results for other studies.

3.79 The study of de Vocht et al (2020) consisted of 1,220 matched worker pairs. Cumulative external doses were in the range 0 to 1,656 mSv and cumulative internal doses to the liver were 0.004 to 5,732 mSv. Median external doses were 69.1 and 64.8 mSv for cases and controls, respectively, at Sellafield, and 7.1 and 8.6 mSv, respectively, at Springfields. Corresponding median internal doses were 164 mSv and 139 mSv at Sellafield and 2.2 mSv and 2.7 mSv at Springfields. The association between IHD mortality and external dose was confirmed, and a log-linear increase in risk per 100 mSv of 2% (95% CI [-4%, 8%]) was observed for unlagged external dose and 5% (95% CI [-2%, 11%]) for 15 year lagged dose. There was no evidence of excess risk in relation to internal sources of radiation. However, heterogeneity between various groups of workers was significant, in particular between those monitored for internal emitters or not.

3.80 de Vocht et al (2020, 2021) conducted a quantitative assessment of biases in the same nested case-control study and concluded that confounding from pre-employment tobacco smoking, BMI, blood pressure, or from socio-economic status or occupational exposures to noise and shiftwork, or patterns of missing data, were unlikely to explain the observed association between external radiation exposure and IHD risk. Their analyses further provided some indication that, in this population, the dose-response association may be non-linear with the risk plateauing at about 43% (7 to 92%) excess risk from about 400 mSv.

3.81 Zhang et al (2024) investigated the shape of the dose-response curve in the complete NRRW cohort and observed the same downwardly curving linear-quadratic shape as de Vocht et al (2021). However, further work indicated that this shape may result from a study population artefact with the smaller risk per unit at doses >0.4 Sv driven by workers who started employment before 30 years of age and those who were employed for over 30 years.

International Nuclear WORKers Study (INWORKS)

3.82 The INWORKS pooled cohort study consisted of nuclear industry workers from France, the UK and US employed for at least 1 year who had dosimetry records for external radiation exposure, and was set up as a follow-up to the 15-Country Study (Hamra et al, 2016; Gillies et al, 2017).

3.83 French workers were from Commissariat à l'Energie Atomique (CEA), AREVA Nuclear Cycle (AREVA) and Electricité de France (EDF) and had follow-up from 1968 to 2004 (Metz-Flamant et al, 2013). UK workers were those included in the NRRW with follow-up to 2001 (Muirhead et al, 2009b). US workers included Department of Energy's Hanford site, Idaho National Laboratory, Oak Ridge National Laboratory, Savannah River site and the Portsmouth Naval Shipyard with follow-up to 2005 (Schubauer-Berigan et al, 2015).

3.84 INWORKS included 308,297 workers with 8.2 million person-years of follow-up. Mean dose ranged from 8.6 to 94.6 mSv. Sixty-six percent of the cohort received less than 10 mSv cumulative dose but 6.4% (almost 20,000 workers) accrued more than 100 mSv, with more than 1,000 workers receiving lifetime doses in excess of 500 mSv (Hamra et al, 2016). The study is of particular importance because it includes workers employed at early nuclear weapons facilities (Hanford, USA; Sellafield, UK; Marcoule, France), with a large proportion having received annual doses in these early years that would not be acceptable today (Wakeford, 2021). Unlike the 15-Country Study, INWORKS did not exclude workers with internal and

neutron exposures (Wakeford, 2021).

3.85 INWORKS recorded 27,848 deaths attributed to circulatory diseases, including 17,463 IHD and 4,444 CeVD deaths. Linear dose-response associations were reported for all circulatory disease mortality with an ERR/Sv of 0.22, 90% CI [0.08, 0.37], IHD mortality with an average ERR/Sv of 0.18, 90% CI [0.004, 0.36] and for CeVD mortality with an ERR/Sv of 0.50, 90% CI [0.12, 0.94] (Gillies et al, 2017). When the dose range was limited to 0 to 100 mSv, significant linear association point estimates were similar to that for the whole dose range for circulatory disease mortality, ERR/Sv 0.14, 90% CI [–0.45, 0.76], but very different for IHD, ERR/Sv –0.56, 90% CI [<0, 0.19] and CeVD, ERR/Sv 2.07, 90% CI [0.43, 3.80]. For the range 0 to 500 mSv, however, IHD mortality, ERR/Sv 0.23, 90% CI [0.01, 0.47] and CeVD mortality, ERR/Sv 0.86, 90% CI [0.35, 1.43] were comparable with estimates for the whole dose range. For CeVD, the ERR/Sv point estimate increased with lower doses from 0.50 for the full dose range to 2.32 for <50 mSv, which was not observed for IHD. This increase in ERR/Sv at lower doses is consistent with the significant (p=0.017) downward curvature in the dose response for CeVD.

3.86 Significant heterogeneity in ERR by workforce was observed, with excess risks largely attributable to the combined Sellafield and Chapelcross sites in England, with a CVD mortality ERR/Sv[f] for UK workers of 0.38 [0.15, 0.64]; IHD of 0.33 [0.06, 0.64] and CeVD of 0.51 [–0.05, 1.18] (Wakeford, 2022). Considering just the Sellafield workforce, ERR/Sv estimates for CVD, IHD and CeVD were 0.53 [0.23, 0.88]; 0.49 [0.13, 0.90] and 0.62 [–0.04, 1.47], respectively. Exclusion of this population from the pooled cohort resulted in a reduction of the ERR/Gy for CVD mortality to an unexceptional 0.06 [–0.14, 0.21]. In contrast, exclusion of other sites, in particular UKAEA, Portsmouth Naval Shipyard, or Idaho National Laboratory, resulted in increased summary risks. Excluding each of these sites and Sellafield resulted in an aggregate risk estimate comparable to that for the whole pooled cohort, ERR/Sv 0.27 [90% CI: 0.05, 0.50], and residual heterogeneity was no longer significant (p>0.5) (Gillies et al, 2017).

3.87 Such heterogeneity between countries and facilities was much smaller, and did not reach traditional statistical significance, for IHD or CeVD individually (Gillies et al, 2017).

3.88 Various possible explanations have been put forward for the observed heterogeneity and include artifacts from differences in ERR of different outcomes and distributions of cases between cohorts and facilities, but also potentially variations in lifestyle factors between sites. No association was observed in the INWORKS study for COPD (ERR/Sv of –0.07, 90% CI [–0.45, 0.38]), which is a much stronger marker for tobacco smoking, indicating residual confounding by smoking was probably not a major factor.

3.89 Risks (for exposure to external sources of radiation) were found to be greater in UK workers who were not also monitored for potential intakes of radionuclides, whereas results for the INWORKS combined cohort show the opposite effect, with greater risks appearing in those workers who were also monitored for internal exposure (Gillies et al, 2017; Zhang et al, 2019a; Hinksman et al, 2022). However, these differences were only statistically significant (p=0.03) for CeVD in the UK workers (Hinksman et al 2022).

Million Person Study (MPS)

3.90 The study of a Million U.S. Radiation Workers and Veterans, also known as the Million Person Study of Low-Dose Health Effects (MPS), includes over 30 individual radiation cohorts. The MPS cohort of 1,065,703 workers includes nuclear power plant workers (n=135,193) with follow-up from 1957 to 2011, first monitored before 1984 (Boice et al, 2022a). Also included are medical radiation workers (n>109,019), Los Alamos National Laboratory workers (n=26,328) (Boice et al, 2022b), industrial radiographers (n=123,556) (Boice et al, 2022c), nuclear submariners and other navy personnel (n>200,000), and radium dial painters (n=3,276) (Boice et al, 2022d).

3.91 The MPS includes individualized and annualized dosimetry. The final study population of 135,193 nuclear power plant workers included all workers with a cumulative dose >10 mSv and a 10% sample of workers with a cumulative dose <10 mSv.

3.92 The nuclear power plant worker cohort in the MPS included 7,561 heart disease cases, comprising 5,410 IHD and 1,078 CeVD cases. There was no evidence of excess IHD risk (p for trend 0.70) with an ERR at 100 mGy of –0.01 [–0.06, 0.04] (Boice et al, 2022a).

3.93 Results do not show an excess IHD risk in US nuclear power plant workers compared to the general population (SMR 0.80 [0.78,0.82]) (Boice et al, 2022d), or for other occupational groups included in the MPS: industrial radiographers (SMR 0.80 [0.78, 0.83]), Los Alamos National Laboratory workers (SMR 0.60 [0.58, 0.63]) (Boice et al, 2022b), medical workers (SMR 0.53 [0.51, 0.56]) (Boice et al, 2023), and Mallinckrodt Chemical Works workers (0.92 [0.84,1.00]) (Golden et al, 2022). There was also no excess risk for all heart disease in Mound workers (0.81 [0.75, 0.87]) (Boice et al, 2014; Schöllnberger et al, 2022).

3.94 Boice et al (2022d) describe differences in IHD risk among the different MPS cohorts, with a general absence of excess risk, although some evidence of excess risk was noted for uranium workers employed at the Mallinckrodt Chemical Works cohort with an ERR at 100 mGy of 0.13 [–0.01, 0.28].

3.95 The MPS has a number of important limitations that affect inferences on causality. In particular, other occupational factors, including uranium processing operations also involving high levels of airborne dust exposures, and lack of information on lifestyle and other potential confounding factors, make interpretation of the results difficult. The link to excess risk for kidney disease observed by Golden et al (2022) in the Mallinckrodt cohort suggests that other occupational factors that are not accounted for may play an important role.

3.96 Some of the results of the MPS do not triangulate well with those from other occupational cohort studies. No excess risks were observed for either lung cancer or leukaemia, when, in particular, a clear excess leukaemia risk would have been expected (UNSCEAR, 2006). However, there are weak indications of a trend for leukaemia (ERR / Gy of 1.5 [–0.01, 3.1], p>0.1) in the nuclear power plant workers (Boice et al 2022a). It is noted that the statistical power of the individual MPS studies is generally quite low.

Mayak worker cohort

3.97 The Mayak nuclear installation, located in the Southern Urals, was the first and largest Russian nuclear enterprise, and includes facilities for weapons-grade plutonium production. It commenced operations in 1948 to produce plutonium for nuclear weapons for the former USSR.

3.98 The Mayak Worker Cohort (MWC) consists of 22,377 nuclear workers first employed between 1948 and 1982 at one of the main facilities. The end-of-follow-up for this cohort for the study reported by Azizova et al (2018) was 31st December 2008 for workers who resided in Ozyorsk (the dormitory town for Mayak) or 31st December 2005 for all workers who moved away (or date of migration with loss of follow-up). In total the cohort included 842,538 person-years of follow-up.

3.99 Worker exposures to external radiation and plutonium in the MWC were higher than those in other cohorts, particularly before 1960. Cumulative external doses were of the order of 0.1 Sv for 35% of cohort members and over 1 Sv for 17% (Azizova et al, 2018).

3.100 Of those who died, 5,123 (44.8%) died from circulatory disease, and of these deaths from circulatory disease, 2,905 (57%) were from IHD and 1,610 (31%) were from CeVD (Azizova et al, 2018).

3.101 A recent mortality study of the Mayak worker cohort (Azizova et al, 2022a) extended follow-up by 10 years to 2018, resulting in 890,132 person-years of follow-up with mean duration of employment of 18.1 years. After exclusion of cases of acute radiation syndrome, the study included 22,334 workers of whom 14,328 had a known cause of death, including 6,019 cases of diseases of the circulatory system, 3,481 IHD and 1,808 CeVD cases.

3.102 Radiation doses were lagged by 10 years and reported dose-response associations in ERR/Gy of cumulative liver absorbed doses from external radiation exposure were 0.07 [–0.02, 0.18] for IHD mortality and –0.02 [–0.12, 0.11] for CeVD mortality. There was also no excess risk observed in the resident subcohort or the migrant subcohort (either in males or females) considered separately.

3.103 A joint study of CVD mortality among workers from Mayak and nearly 23,500 workers from Sellafield, the equivalent nuclear establishment in the UK, was conducted by Azizova et al (2018), showing a difference between the Sellafield worker cohort with an ERR/Gy for IHD mortality of 0.53 [0.14, 1.00] and Mayak workers with a much smaller excess risk of 0.06 [0.01, 0.13]. Mean cumulative external dose at Mayak (520 mGy) was much higher than at Sellafield (70 mGy).

3.104 Limiting the dose range in the cohorts to <2 Sv, <1 Sv, <0.5 Sv, and <0.3 Sv showed increased ERR/Sv for IHD with the lower doses in the Sellafield cohort ranging from 0.52 [0.14, 1.00] for <2 Sv to 1.15 [0.20, 2.31] for <0.3 Sv. This was not observed in the Mayak cohort, where no significant excess risks were observed at doses <2 Sv (Azizova et al, 2018). These findings may relate to the significant linear-quadratic curvature in dose-response observed for the Sellafield cohort, in contrast to the absence of such curvature for the Mayak workers. A similar pattern was observed for all circulatory disease, but not for CeVD for which no significant excess risks were observed in either cohort.

3.105 Azizova et al (2023b) also explored the effect of dose rate, expressed as Gy/year, on IHD mortality. They observed that although excess risks increased with increasing dose rates of 0.005 to 0.050 Gy/year, this increase may have been driven by when the exposure occurred rather than dose rate.

3.106 Azizova et al (2023a) assessed associations between subtypes of heart disease incidence and radiation exposure in the MWC, which included 7,722 IHD cases (5,432 in men and 2,290 in women) of which 2,185 were acute MIs and 3,976 angina pectoris, 4,939 cases of heart failure, 3,689 cases of cardiac arrhythmia and conduction disorders, and 559 cases of chronic rheumatic heart disease. They reported statistically significant excess incident risks with 10 year lagged cumulative liver-absorbed external gamma doses for IHD (ERR/Gy 0.19 [0.12 to 0.26]), angina pectoris (ERR/Gy 0.20 [0.11 to 0.30]), heart failure (ERR/Gy 0.27 [0.18 to 0.38]) and cardiac arrhythmia and conduction disorders (ERR/Gy 0.23 [0.14 to 0.34]), but not chronic rheumatic heart disease or acute MI. Adjustments for smoking, alcohol consumption, body mass index, hypertension, and diabetes mellitus influenced the magnitude of observed incidence risks, but not whether associations existed. Associations were notably stronger when adjustments for alpha dose were not included.

3.107 Azizova et al (2022b) assessed CeVD and types of stroke incidence risk in the Mayak cohort of 22,377 workers followed up until the end of 2018. There were 9,469 cases of CeVD, of which 2,078 were stroke including 262 cases of haemorrhagic stroke. CeVD incidence (10 year lagged) was statistically significantly associated with cumulative liver absorbed dose of external radiation exposure with an overall ERR/Gy of 0.39 [0.31, 0.48]; 0.37 [0.27, 0.47] in men and 0.47 [0.31, 0.66] in women. Estimates were similar when analyses were restricted to those employed longer than 1 year. Comparable associations were observed for cumulative internal alpha radiation dose with ERR/Gy of 0.31 [0.11, 0.59] in men and 0.32 [0.11, 0.61] in women. In contrast, no associations were observed for stroke, or haemorrhagic or ischemic stroke, considered separately.

3.108 Excess risk estimates were only minimally impacted by adjustment for smoking and alcohol consumption, but were increased in men after adjustment for BMI. However, excess risks reduced from ERR/Gy 0.90 [0.59, 1.33] to –0.06 [–0.28, 0.32] with increased effect modification by attained age from <50 years of age to over 80 years.

3.109 A strength of the Mayak cohort is that it has extensive data on important confounding factors including smoking, alcohol consumption, BMI, hypertension and diabetes, but there are also several important limitations that complicate inferences. One puzzling and unexplained feature remains the much lower (and often non-significant) ERR in the mortality analysis compared with that for incidence. It has been shown that mortality rates for Ozyorsk residents and Mayak workers in the years 1998 to 2010 were much lower than those elsewhere in Russia (Deltour et al, 2015). Mayak workers who carried on living in Ozyorsk city would be part of a surveillance programme with access to a high-quality health care system while migrants living in other regions would have varying, generally lower, quality health care systems (Azizova et al, 2015), and there was also an extensive post-mortem programme in place for residents. In addition, there have been marked differences in disease coding practices for mortality across the country (Wasserman and Värnik, 1998; Danilova et al, 2016), resulting in

differential diagnosis for resident workers and those having moved elsewhere (Wakeford, 2022), which has been reported to be as high as around 41% of the cohort by the end of 2005 (Azizova et al, 2015). Differences in dose-responses between these groups have been reported for IHD (Azizova et al, 2015) and CeVD (Moseeva et al, 2014).

Chornobyl recovery workers

3.110 A cohort study of 53,772 Russian liquidators who worked in the Chornobyl accident zone within the first year following the accident (1986 to 1987), and who had individual doses of 0.0001 to 1.42 Gy (mean whole-body dose 0.16 Gy), reported a high incidence of 27,456 CVD (other than CeVD) cases, 22,220 of which were IHD and 14,720 other non-IHD (and non-CeVD) CVD cases, in the 1986 to 2012 follow-up period (Kashcheev et al, 2017).

3.111 Excess risk was reported for incidence of CVD (other than CeVD) with an average ERR/Gy of 0.47 [0.31, 0.63] assuming no latency period. The highest excess risk was observed for those who worked only during the first 6 weeks after the accident with an ERR/Gy of 0.80 (0.53,1.08), reducing to 0.17 [0.11, 0.47] for those who worked for longer than 12 weeks; mean daily doses were 20.9 mGy and 7.7 mGy, respectively (Kashcheev et al, 2017). These results were in agreement with previous studies of the liquidators (Ivanov et al, 2006).

3.112 The same authors also studied 23,264 CeVD cases in the same cohort and reported an ERR/Gy of 0.45 [0.28, 0.62], with a higher estimate for those leaving the zone within 6 weeks (0.64 [0.38, 0.93]) (Kashcheev et al, 2016). These results were also in agreement with the earlier analysis of the cohort (Ivanov et al, 2006).

3.113 There are, however, difficulties in the interpretation of this study, and there remain concerns of cohort selection, diagnosis confirmation and dose information (Wakeford, 2022; Little et al, 2023). The study population has a much higher incidence, but not mortality, of CVD and CeVD than would reasonably be expected, with 40 to 50% diagnosed with IHD or CeVD (Schöllnberger et al, 2022).

3.114 There is also no information on potential lifestyle and other confounding factors in this cohort, including smoking, alcohol consumption, excessive weight, hypercholesterolemia, and socio-economic factors. The authors also note the harder working conditions of those arriving in the first year compared to others.

3.115 Tapio et al (2021) pointed out that, as is common in many cohorts, the SIR risk estimates that can be derived from this study are almost certainly misleading, since the general Russian population (and Ukrainian population) is very likely not representative of the Chornobyl recovery workers because of the healthy-worker selection effect.

Uranium miners and millers

3.116 Uranium underground miners are primarily exposed to internal ionizing radiation from radon decay products via inhalation, and to a lesser extent to uranium ore dust and external gamma radiation. Doses from inhaled radon and its radioactive progeny deliver alpha particle doses confined very largely to the lungs.

3.117 A study of mortality for a pooled cohort of 118,329 male uranium miners from Canada, the Czech Republic, France, Germany and the USA, employed from 1942 to 1996 with follow-up until 2013 with 4,125,533 person-years of follow-up (pooled

within the PUMA study), included 16,921 deaths from circulatory diseases (SMR 0.88 [0.86, 0.89]), of which 9,457 were from IHD (SMR 0.92 [0.91, 0.94]) (Richardson et al, 2020). The study did not include information on exposures that would have allowed for internal dose-response analyses.

3.118 A French cohort study of 5,086 uranium miners followed up from 1946 to 2007 included a post-1955 sub-cohort of 3,377 miners with records of external gamma-ray exposures, with 110,548 person-years of follow up (Rage et al, 2015). The study reported SMRs for circulatory diseases of 0.93 [0.84, 1.02], IHD of 0.92 [0.79, 1.07], and CeVD of 0.96 [0.79, 1.17] in the main cohort and SMRs of 0.90 [0.77, 1.04]; 0.89 [0.70, 1.13] and 0.91 [0.66, 1.24], respectively, in the post-1955 sub-cohort. Exposure to cumulative external gamma rays was not associated with circulatory diseases (p=0.69) or IHD (p=0.15), but a positive association was observed with CeVD (p=0.05). Analyses of dose-response associations with external gamma rays in the post-1955 sub-cohort gave estimates of ERR/100 mGy of –0.02 [–0.14, 0.17] for all circulatory disease, –0.10 [<–1, 0.22] for IHD and 0.33 [–0.07, 1.25] for CeVD.

3.119 A case-control study of 76 circulatory disease deaths (including 26 from IHD and 16 from CeVD) and 237 controls nested within the above French cohort was set up to further explore the impact of circulatory disease risk factors (Drubay et al, 2015). The authors concluded that adjustment for weight, hypertension, diabetes, hypercholesterolemia and smoking status would not have materially changed the results obtained.

3.120 A German cohort of 58,982 former uranium miners, the WISMUT cohort, included 9,039 deaths from CVDs, 4,613 deaths from IHD and 2,073 CeVD deaths (Kreuzer et al, 2013). Mean cumulative gamma dose of exposed (86%) miners was 47 mSv, with maximum cumulative dose of 909 mSv. No excess risk was observed for CVD (ERR/Sv –0.13 [–0.38, 0.12]), IHD (–0.03 [–0.38, 0.32]) or CeVD (0.44 [–0.16, 1.04]). There was little impact of lagging exposure by 2 to 15 years. The cohort did not have complete individual information on potential confounding factors, including smoking, cholesterol, blood pressure, or diabetes, or on occupational confounders such as arsenic and dust, or on medical radiation exposure.

3.121 A pooled cohort of 7,431 uranium milling, refining and processing workers from Canada and Germany (270,201 person years of follow-up; at least 20 years) was conducted to explore differences between uranium underground miners and nuclear reactor workers (Zablotska et al, 2018). Mean, median, and range of lifetime gamma-ray doses were 61.5 mSv, 13.8 mSv, and 0 to 5,098.8 mSv, respectively.

3.122 No significant excess risks were observed in male workers for mortality from CVD (ERR/Sv 0.13 [–0.11, 0.48]), IHD (0.21 [–0.13, 0.71]), or stroke (–0.19 [–1.12, 0.50]). Women had lower dose compared to men and similarly no excess risks were observed for mortality from CVD (ERR/Sv –0.69 [–3.12, 3.58]) or IHD (1.20 [–3.52, 11.9]); there were insufficient stroke cases to estimate ERR.

Recent Reviews

3.123 Tapio et al (2021) conducted a narrative review of the available evidence on CVD risks, including that from occupationally exposed groups. They concluded that there is strong evidence in support of a causal association between acute high-dose and chronic low-dose radiation exposure and most types of circulatory disease, in particular IHD and CeVD. The data indicate increasing dose-related

trends for morbidity and mortality from IHD and CeVD, although they highlighted that the significant trends are largely driven by occupational cohorts in the UK and Russia.

3.124 A recent large and comprehensive systematic review and meta-analysis of the epidemiological evidence of radiation associated risks of CVD in groups exposed to radiation with individual radiation dose estimates was conducted by Little et al (2023). The results of this study are presented in this section, while noting that it includes data published up to October 2022 of groups who were occupationally and environmentally exposed as well as results from the Life Span Study and therapeutically and diagnostically exposed cohorts.

3.125 The meta-analysis was based on 93 studies (of an initially identified database of 15,098 articles), and reported a meta-analytic summary dose-response ERR/Gy of 0.11 [0.08, 0.13] for all CVD, as well as estimates for subgroups: IHD (0.08 [0.05, 0.12]), other (non-IHD) heart disease (0.04 [0.02, 0.05]), CeVD (0.19 [0.09, 0.28]), and all other CVDs (0.17 [–0.03, 0.37]).

3.126 However, these summary dose-response associations rely on inclusion of data for exposures at higher doses and the assumption that they are applicable at lower doses. Little et al (2023) interpreted the results of their review and meta-analysis as providing evidence supporting a causal association between radiation exposure and CVD at high dose, and to a lesser extent at low dose.

3.127 Little et al (2023) also reported significant interstudy heterogeneity, in agreement with previous studies and reviews, which they attributed to unmeasured confounding or effect modification. They did note, however, that studies looking specifically at this issue reported the effect of possible modifying effects of lifestyle, medical and environmental factors, particularly smoking, obesity, diabetes, hypertension and hypercholesterolaemia, is likely to be small.

3.128 Little et al (2023) noted that the observed heterogeneity was reduced significantly when only higher quality studies were included, or if the analyses were restricted to studies with moderate doses (below 0.5 Gy) or low dose rates of less than 5 mGy/hr; the latter gave an ERR/Gy of 0.23, [0.11, 0.34] for IHD and 0.31, [0.13, 0.49] for CeVD. When the Mayak worker data were removed the heterogeneity between the low dose-rate studies was much reduced, and generally only borderline significant ($0.03<p<0.05$).

3.129 A difficulty in the interpretation of the summary risk estimates from this review is that studies of mortality and incidence were combined for some analyses, despite the potential for different issues of bias and confounding. Separate estimates of risks for mortality and incidence gave ERR/Gy values of 0.342 [0.043, 0.641] and 0.154 [–0.023, 0.332], respectively. However, Little et al (2023) noted that sensitivity analyses showed that exclusion of some subsets of data, in particular the Mayak cohort data, made little difference to summary risk estimates, and the same applied to the inclusion of 2 other groups (Los Alamos workers, Rochester thymus cohort) that were found adventitiously (but were not in the systematic review dataset).

3.130 Peters et al (2023) also conducted a systematic review and meta-analysis of occupational low-dose radiation exposure and ischaemic heart disease and concluded that occupational exposure to low-dose (<0.5 Gy) ionising radiation is

associated with increased IHD mortality risk. Cohorts included nuclear energy workers, nuclear laboratory workers, medical radiation workers, uranium workers, millers, or miners, and fluorspar miners. The review included 26 studies, none of which were in the lowest risk of bias category. Overall, the risk of bias was judged as moderate and was mostly due to control of confounders and quality of exposure assessment.

3.131 Fourteen studies reported SMRs with a summary SMR of 0.81 [0.74, 0.89], in line with other studies reporting a reduced risk compared with the general population, indicating healthy-worker bias (Peters et al, 2023).

3.132 Ten studies reported internal comparisons with a summary ERR/Sv for 10 year lagged external exposure of 0.10 [0.01, 0.20] and low between-study heterogeneity. Corresponding 5 year lagged results were 0.09 [–0.05, 0.23], N=3, 15 year lagged results 0.23 [0.06, 0.41], N=3, and 20 year lagged results 0.14 [0.07, 0.21], N=2 (Peters et al, 2023). There was no significant inter-study heterogeneity (p=0.28).

Summary of occupational risks

3.133 There is evidence from larger population studies, in particular based on studies from the nuclear power industry, of an excess IHD and CeVD risks in relation to external radiation dose.

3.134 The most comprehensive systematic review on the topic (Little et al, 2023) reported summary risk estimates, ERR/Gy, for all CVD of 0.11 [0.08, 0.13], and specifically for IHD of 0.08 [0.05, 0.12] and for CeVD of 0.19 [0.09, 0.28] based on studies of occupational and other populations. Consistent results for IHD were obtained in an independent systematic review and meta-analysis by Peters et al (2023), which included only evidence from occupational settings and reported a summary ERR/Sv of 0.10 [0.01, 0.20] with low between-study heterogeneity.

3.135 However, for a variety of reasons, the interpretation of results from studies of worker populations is difficult, not least because of the lack of information on lifestyle and other confounding factors as well as limitations in the assessment of exposure.

3.136 Results show significant heterogeneity in risk estimates for IHD as well as for CeVD which require further investigation. These are of the same order as observed in other syntheses of epidemiological studies, but limit conclusions regarding causality.

Radiation and the environment

Environmental exposures from nuclear facilities

Chornobyl residents

3.137 Slusky et al (2017) investigated the incidence of chronic diseases and mortality amongst individuals who were resident in areas contaminated by the Chornobyl disaster and subsequently emigrated to Israel. Compared to less exposed adults (n=480), those from the more exposed group (n=359) had elevated odds of ischaemic heart disease with OR = 2.01 [0.97, 4.20], although this increase was

not statistically significant. This small study is uninformative on CVD risk as there were no recorded radiation doses.

The Techa River Cohort

3.138 Krestinina et al (2019) analysed circulatory disease mortality for 60,205 individuals born before 1950 who form the Techa river cohort, of whom 14,830 died from circulatory diseases during the period 1950 to 2015, assessing the relationship with radiation dose. The population received external and internal exposures as a result of waterborne releases from the Mayak nuclear facility in the Russian Federation, and detailed individual exposure information is available. The analysis included individualized estimates of total absorbed doses to organs and tissues, and dose to muscle was used in most analyses. For the period 1950 to 2015, there were 1,836,203 person years at risk. Doses spanned the range 0 to 0.995 Gy.

3.139 The estimated ERR/Gy for mortality with 15 year lag period was 0.30 [0.08, 0.52] for all circulatory diseases, 0.92 [0.54, 1.35] for ischaemic heart disease and 0.34 [–0.07, 0.82] for CeVD. A linear ERR model provided the best fit. Analyses with lag periods of 0, 2, 5 or 10 years from start of exposure did not reveal any significant risk of mortality for any endpoint.

3.140 A weakness of the cohort is that there is little information on medical/environmental risk factors, only ethnic group (Slav versus Tartar/Bashkir). However, the dosimetry, which is based on residential history, is of reasonably high quality. There is bio-dosimetric validation for a sample of dose estimates using electron paramagnetic resonance (EPR) measurements on tooth enamel and fluorescence in situ hybridization (FISH) chromosome studies using peripheral blood lymphocytes (Degteva et al, 2015).

The Semipalatinsk Cohort

3.141 Grosche et al (2011) conducted a study of exposed populations near the Semipalatinsk Nuclear Test Site (SNTS) in Kazakhstan where there were over 450 atmospheric and underground nuclear weapons tests in the period 1949 to 1989, before the dissolution of the USSR (in 1991). Data for residents of this area and from six control villages several hundred km to the east/southeast of the SNTS were assembled and doses estimated. External whole-body doses were in the range 0 to 0.63 Gy. The resulting cohort of 19,545 persons was followed for CVD mortality for the period 1960 to 1999 (Grosche et al, 2011).

3.142 There were 1,498, 878 and 453 deaths from all CVD, heart disease and stroke, respectively, in the part of the exposed group with dose estimates, and 1,358, 843 and 386 deaths from all CVD, heart disease and stroke, respectively, in the control group. The aggregate RR (exposed versus control) estimates were 2.27 [2.10, 2.45]; 2.23 [2.02, 2.46] and 2.30 [2.00, 2.65] for all CVD, heart disease and stroke, respectively, suggesting substantial non-radiation related differences between the exposed settlements and the controls. There is little other information on environmental/medical risk factors, only for ethnic group (Kazakh versus Russian).

3.143 Grosche et al (2011) derived ERR/Gy estimates of 0.02 [–0.32, 0.37] for all CVD, 0.06 [–0.39, 0.52] for heart disease and –0.06 [–0.65, 0.54] for stroke, restricting to the exposed settlements only, based on external whole-body doses.

3.144 A weakness of the study is the dosimetry, which is based on fallout deposition maps, combined with questionnaire-derived individual estimates of residential locations for the subjects; the questionnaires were only completed many years after the period of exposure. The study used only fallout data for the 11 tests in the period August 29th 1949 to September 25th 1962 that were thought to contribute doses of more than 5 mSv. Only 17,303 out of the cohort of 19,545 people had usable dose estimates.

Fukushima Daiichi nuclear accident

3.145 Toda et al (2017) assessed the medium-term impact of the 2011 Fukushima nuclear accident on CVD risks, attempting to identify whether risk factors for CVD changed after the accident. The participants were 563 residents aged 40 to 74 years participating in public health check-ups during the period 2009 to 2012, administered by Minamisoma City, which is located 10 to 40 km from the nuclear plant. No exposure data are available. The outcome measure was the sex-specific Framingham CVD risk score used to evaluate individuals' risk for developing a CVD event, and which incorporates age, HDL cholesterol level, systolic blood pressure, use of medicines for hypertension, smoking status and fasting glucose level, which was compared before (2009 to 2010) and after (2011 to 2012) the accident.

3.146 Multivariable regression was used for the analysis. Data were obtained from 563 persons (60.2% women) aged 40 to 74 years. After adjusting for covariates, no statistically significant changes were identified in CVD risk score post-accident in both sexes. The study concluded that there was no obvious increase in CVD risk (Toda et al, 2017). However, this small study yields very little quantitative or qualitative evidence on CVD risk after radiation exposure, as there are no individual measures of radiation dose.

Non-nuclear background radiation

3.147 Two cohort studies have examined the effect of high background radiation on mortality in Yangjiang, Guangdong Province China. One of these studies (Sun et al, 2002), followed up a cohort of 78,614 subjects from 1987 to 1995 who were resident in a high background radiation area, together with 27,903 subjects who were resident in a nearby control area. There was a non-significant elevated risk for deaths from diseases of the circulatory system, with RR = 1.07 [0.98, 1.17]. This study has very little quantitative information on CVD risk, being without data on individual radiation doses. In the second study (Tao et al, 2012), a cohort of 31,604 men and women aged 30 to 74 years was followed up during the period 1979 to 1998. There was found to be no increase in non-cancer mortality related to cumulative high background radiation dose.

Summary of Environmental risks

3.148 There was limited evidence available on CVD risks from environmental sources, derived from a small number of studies, mostly without individual estimates of radiation dose. Only 2 environmental studies incorporate individual radiation doses. Both studies have little information on other medical/environmental risk factors. Only one of these 2 studies found increased risks for all circulatory diseases and for ischaemic heart disease.

Chapter 4. Dose response and population impact

Dose response

4.1 Several studies demonstrate a linear relationship between cardiovascular effects and high tissue doses from medical exposures. Examples are for the incidence of coronary heart disease following treatments for Hodgkin lymphoma between 4 Gy and 30 Gy (van Nimwegen et al, 2016), cardiac mortality following breast RT between 2 Gy and 14 Gy (Taylor et al, 2017), and the relative risk of heart disease among patients receiving RT during their childhood between 14 Gy and 36 Gy (Shrestha et al, 2021). However, none of these studies enable an extrapolation with any degree of confidence down to doses of less than 10 Gy.

4.2 For non-medical exposures, most studies have fitted or assumed a linear model. In the MWC, a linear fit appeared generally appropriate (Azizova et al, 2015; 2022a; 2022b; 2023b) for mortality and incidence for IHD and CeVD (with some exceptions noted below). Takahashi et al (2017) also report a linear best fit for heart disease mortality overall in atomic bomb survivors.

4.3 In contrast, others reported a sublinear (downwardly curving) association with smaller risks per unit exposure at higher compared to lower doses. For example, recent work in UK nuclear fuel workers aimed at evaluating the shape of the dose-response association observed indications of a linear response plateauing at an excess risk of 43% around 400 mSv (de Vocht et al, 2021), although with high uncertainty (95% CI: 7% to 92%). Sublinearity was also observed by Zablotska et al (2018) in analysis of uranium processing workers, with a similar linear response with increasing risk up to about 350 mSv and then a flattening of the curve. Similar observations were made by Zhang et al (2024) for IHD mortality in the updated NRRW-3 cohort study, although the NRRW results for lower risks per dose at higher doses may be associated with workers who started employment at earlier age or who worked for more than 30 years in the industry.

4.4 Gillies et al (2017) reported that in the INWORKS study, the dose responses for circulatory diseases and for IHD specifically were best described by a linear model, while for CeVD the data were best fitted by a linear-exponential model curving downwards.

4.5 Hinksman et al (2022) in their analysis of CeVD mortality in the extended NRRW-3 cohort also reported that data were best fitted by a linear-exponential dose-response rather than a linear model. They further reported that increased CeVD mortality rates were observed from doses as low as 10 to 20 mSv.

4.6 Azizova et al (2022b) also reported non-linear shapes to better fit the data than the linear model for CeVD in the MWC in women but not men. However, when workers exposed above 2 Gy were excluded, a linear model fitted the data best for both sexes.

4.7 Although a linear ERR dose-response model fits the data for CeVD in the Chornobyl recovery operation workers cohort reasonably well, there was similarly an indication of a linear-exponential model which was however not explicitly tested (Kashcheev et al, 2016).

4.8 Little et al (2023) in their systematic review and meta-analysis observed differences in the ERR/Gy for IHD and all CVD between studies grouped by maximum dose, with higher risks per dose for studies with lower maximum doses, ranging from 0.31 [0.08, 0.54] for maximum dose <0.5 Gy to 0.07 [0.03, 0.10] for studies with maximum dose >5Gy. Similarly, higher risks per dose, ERR/Gy, were observed for studies with lower maximum dose rates <5 mGy/hr (0.24 [0.18, 0.31]) than for studies with higher dose rates ≥5 mGy/hr in a single dose (0.14 [0.06, 0.22]) or fractionated doses of ≥5 mGy/hr (0.07 [0.03, 0.11]).

Age at first exposure

4.9 Zhang et al (2024) modelled the IHD mortality dose-response in the extended NRRW-3 cohort by age-at-first exposure, considering variation in risk across 3 groups, <30, 30–45, and 45+ years old. They observed that a linear dose-response shape fitted the data best for workers with age-at-first exposure of 30+ years. There was no evidence of variation in the ERR/Sv estimates across the categories ($p>0.5$). Analysis of the variation in ERR/Sv with time since first exposure also did not provide evidence of increased risk during the first 20 years after first radiation exposure, but thereafter the excess risk point estimate rose to a peak value for the 30–45 year group before declining again. For those with age-at-first exposure below 30 years of age, however, evidence of excess risk was only observed for radiation doses between 0.1 Sv and 0.4 Sv, but not for lower or higher doses. For those who received 0.1 to 0.4 Sv, excess risk was only observed for those younger than 35 years of age or those 50+ years of age.

4.10 Although not significant ($p>0.5$), there was a general tendency both for all CVD and CeVD for ERR/Sv to reduce with increasing age-at-first exposure in the INWORKS data as analysed by Gillies et al (2017), and as the authors remarked “there was a general pattern for the point estimate of ERR/Sv associated with the dose received before age 50 to be higher than the ERR/Sv associated with doses received at older ages for IHD”.

4.11 Zablotska et al (2014a) in a study of IHD mortality in a Canadian fluoroscopy cohort reported a reduction in ERR/Gy from 0.817 [<–0.194, 8.605] to 0.144 [–0.153, 0.608], and 0.175 [0.006, 0.403] for age-at-first exposure categories 0 to 9, 10 to 19, and 20 to 87 years of age, respectively.

4.12 Although not statistically significant, there was a progressive reduction of ERR/Gy for MI incidence with increasing age at exposure in the Adult Health Study (AHS) data of Yamada et al (2004).

4.13 In the LSS mortality analysis of Shimizu et al (2010) and Little et al (2012b), which were essentially of the same data as for the analysis of Takahashi et al (2017), there was little evidence of age at exposure modifications of heart disease. In contrast, there are non-significant indications of reductions in ERR for CeVD mortality with increasing age at exposure in the LSS (Shimizu et al, 2010), and highly significant reductions in ERR with increasing age at exposure based on

analysis of both contributing and underlying cause of death[7] (Little et al, 2012b).

4.14 Zablotska et al (2018) did not observe an interaction between CVD mortality and age-at-first exposure in a pooled cohort of Canadian and German uranium processing workers.

Population impact

4.15 The population impact of CVD risk from low dose or dose rate radiation exposures has been considered principally by Little et al (2023).

4.16 Little et al (2023) estimated the population based excess lifetime CVD mortality risks based on data from Canada, England and Wales, France, Germany, Japan and the USA. Although they combine incidence and mortality studies from different settings and dose ranges, their summary risk estimates for IHD are comparable to those of Peters et al (2023), who only included worker studies.

4.17 Little et al (2023) reported a range in absolute risk estimates for mortality ranging from 2.32% per Gy [1.68%, 2.96%] for England and Wales to 3.64% per Gy [2.63%, 4.64%] for Germany, depending on underlying CVD mortality rates in the different populations, and which largely resulted from CeVD (with a range of 0.83 to 1.26%/Gy) and IHD (with a range of 0.34 to 1.37%/Gy). The estimate for England and Wales used background mortality rates for 2021; using data for 2003 gave a risk estimate of 3.91% per Gy [2.83, 4.99], reflecting the higher proportion of deaths from CVD in earlier years. These estimates corresponded to years of life lost per Gy of 0.20 [0.14, 0.25] using England Wales 2021 rates and 0.32 [0.23, 0.40] using England Wales 2003 rates.

4.18 Little et al (2023) comment that their risk estimates for a UK population for lifetime risk of mortality from CVD of 2.3% per Gy for a 2021 population and 3.9% per Gy for a 2003 population, are slightly lower, but of similar magnitude to risks estimated for cancer mortality which for a 2003 population were in the range of 4.4 to 5.2% per Gy (UNSCEAR, 2008). ICRP (2007) refers to a lifetime fatal cancer risk of about 5% per Sv for a composite world population averaged over sex and age-at-exposure.

4.19 Little et al (2023) pointed out that doses of 10 to 20 Gy that might be received by the heart in some types of RT treatment could result in lifetime risks of CVD that exceed 50%, but that in general treatments will be justified despite such risks. They also referred to possible risks following the much lower doses received in CT diagnostic scanning. For the example of doses of 0.5 to 15 mGy to the heart, they suggested that a group of 10,000 people each receiving 10 scans might incur between 0.2 and 15 excess deaths due to ischaemic heart disease over a lifetime. However, caution is needed in interpreting these results, especially given the heterogeneity in the underlying data, for example between the high dose and low dose/low dose-rate studies, and the degree of extrapolation in the level of assumed dose.

[7] The underlying cause of death is the disease or injury that initiated the causal chain that led to death, while a contributing cause of death is one that, while not directly causing death, played a significant role in the outcome

4.20 Martin et al (2024a) estimated excess numbers of deaths from CVD, including CeVD, from CT scans to the body and head performed on 105,574 patients in England using the summary risk estimates of Little et al (2023). Applying dose thresholds of 200 mGy or 50 mGy, below which it was assumed that there is no risk, Martin et al estimated excess deaths from CeVD as 7 to 26 per 100,000 patients, and deaths from CVD excluding CeVD as <1 to 7 per 100,000 patients, using the dose distribution from the study of 105,574 patients. However, as pointed out by the authors, these estimates are subject to substantial uncertainties. Commenting on the paper, Harbron (2024) raised a number of concerns, including the use of arbitrary thresholds, and concluded that, at this stage, estimates of CVD related to CT scans appear to be premature and, as also stated by (Martin et al, 2024b), need to be interpreted with caution.

Summary of dose response and population impact

4.21 A clear and consistent conclusion cannot be drawn from the literature on the shape of dose-response relationships over the full dose-range. Linear relationships have been reported or have been obtained by specifying the model structure, while both supralinear and sublinear associations have also been reported.

4.22 The data provide some indications of a reduction in risk per dose with increasing age at exposure, although this is not consistently observed across studies.

4.23 Estimates of population impact remain difficult and dependent on important assumptions and should therefore be interpreted as indicative only of the possible extent of risks.

Chapter 5. Mechanisms

Introduction

5.1 Ionising radiation deposits energy within the body and its constituent cells in the form of highly structured tracks of ionisation and excitation events correlated in space and time (Hill, 2020). These tracks vary significantly for different qualities of radiation which ultimately results in the modulation of their biological efficiency. In addition to producing damage directly in macromolecules such as DNA, the majority of interactions in the cases of low LET radiations (including X-rays and gamma rays) occur in the surrounding water. These interactions result in the production of reactive species along the track, most notably the highly reactive hydroxyl radical (·OH). These reactive species subsequently diffuse and interact with each other or surrounding macromolecules. Due to the highly reactive environment within the cell, the lifetime of hydroxyl radicals is approximately 4 to 9 x 10^{-9}s, with an associated maximum diffusion distance of 6 to 9 nm, so any resulting damage produced is in close proximity to the original radiation track (Roots and Okada, 1975).

5.2 In most circumstances, the damage done by ionising radiation to DNA and other macromolecules is significantly smaller than that resulting from endogenous processes. For example, endogenous damage results in ~50,000 DNA lesions per cell per day as a result of normal metabolic processes of the cell (De Bont and van Larebeke, 2004; Swenberg et al, 2011). In comparison, 1 Gy of low-LET ionising radiation will produce just over 2,000 base damages (BD), ~1,000 DNA single strand breaks (SSB) and ~40 DNA double-strand breaks (DSB) for both acute and chronic exposures (Hall and Giaccia, 2019).

5.3 However, while endogenous DNA damage is typically repaired quickly with high fidelity by a range of DNA repair mechanisms, this is not the case with radiation-induced lesions. What makes ionising radiation so biologically effective is that it causes clustered DNA lesions (defined as 2 or more lesions within a distance of approximately 2 helical turns) at a biologically relevant frequency as a result of correlation of energy deposition, and therefore damage sites, in space and time along the radiation track. Studies have shown that for low-LET radiation, such as photons, ~20 to 50% DSB are complex by virtue of additional strand breaks and/or base damage within 10 base pairs (Nikjoo et al, 2002; Goodhead, 2006). The frequency and complexity of these complex DSB increases with increasing LET, with up to 90% or more of DSB being complex for high LET α-particles (Nikjoo et al, 2001). Increasing complexity of these clustered lesions has been shown to result in an increase in lesion lifetime and a reduction in the probability and fidelity of repair, corresponding to an increase in their biological effectiveness.

5.4 In addition to DSB, ionising radiation can also efficiently produce non-DSB clustered lesions, consisting of 2 or more lesions (such as BD or strand break within ~ 10 base pairs) but not including a DSB. For X-rays these are produced at a frequency of around 4 to 8 times that of DSB (Eccles et al, 2011). The subsequent repair of individual sites of damage in the cluster is significantly impaired by the proximity of neighbouring sites of damage. This results in an increased likelihood

that these breaks will still be present during replication, resulting in replication-induced breaks from stalled replication forks which can result in an enhanced mutation frequency (Gulston et al, 2002; Malyarchuk et al, 2009; Georgakilas et al, 2013). For alpha particle irradiation, there remain unknowns around the production of damage but in general DNA damage is more complex and more difficult to repair (UNSCEAR, 2000; Pouget and Constanzo, 2021).

5.5 The number of DNA lesions (as well as damage to other macromolecules) initially produced by ionising radiation will increase linearly with dose (Rothkamm and Löbrich, 2003). Close proximity of DSB may also result in illegitimate repair between these, resulting in chromosomal rearrangements. At low dose and dose-rates, this will be restricted to correlated sites of damage along a single track. However, at high dose and dose-rates associated with RT exposures, the density of DSB is such that chromosomal rearrangements between DSB produced by independent tracks increases, resulting in a quadratic increase in chromosomal rearrangements with dose (Savage, 1998).

5.6 There have been extensive studies and reviews of the biological basis for cancer induction by radiation, recognising mutation of DNA as a primary initiating event but also considering the role of radiation in tumour progression (for example, (UNSCEAR, 2006, 2012, 2021)). Stem cells and early progenitor cells are considered to be the main targets from which cancers arise, with their long life-spans allowing sufficient time for the accumulation of multiple alterations required to convert normal cells into pre-malignant cells (Prise and Saran, 2011; López-Lázaro, 2015). Studies modelling cancer incidence over time indicate that, for leukaemias, 1 or 2 genetic alterations are required while a number in the range of 5 to 7 is required for solid cancers (Martincorena et al, 2017). UNSCEAR (2021) concluded that the mechanisms affecting cancer risk have been shown to operate at least down to 10 mGy and that mutational mechanisms resulting from energy deposition events in or very near (for example, within the diffusion range of short-lived radiolysis products) to genomic DNA (Shuryak and Brenner, 2021) imply dose-risk relationships that are linear with dose at low doses without a dose threshold. DSBs in DNA are induced in linear proportion to doses down to at least 1 mGy (UNSCEAR, 2021).

5.7 Ionising radiation has been shown to also initiate a range of processes in which biological effects can be observed in locations removed in space (for example, beyond the irradiated cell) and in time (for example, in the progeny of the irradiated cell population) from the initial damage and are commonly referred to as ‘non-targeted’ effects (Morgan and Sowa, 2007; Hei et al, 2008; Prise and O'Sullivan, 2009; Kadhim et al, 2013). A characteristic of these non-targeted effects is that their dose responses are generally non-linear, with effects observed to increase with dose at very low to moderate doses but become saturated typically at doses significantly less than 1 Gy. For example, studies have shown perturbation of intra- and inter-cellular signalling processes at doses as low as 2 mGy with the response saturating at around 25 mGy (Portess et al, 2007). As a result, above the saturation dose it is unlikely for a given effect to affect the shape of the dose response and direct effects are likely to dominate. There is experimental evidence that non-targeted effects may operate in the case of high LET exposures as in RT

with alpha-emitting radionuclides as well as for low LET radiation (Pouget et al, 2022).

5.8 Non-targeted effects typically involve the perturbation of multiple signalling pathways forming part of the natural communication that exists between cells within tissues (Hei et al, 2008). A range of studies have shown evidence for a key role for cytokines, including interleukin 6 (IL-6), IL-8, transforming growth factor-β1 (TGFβ1) and TNFα, as well as reactive oxygen species (ROS), reactive nitrogen species (RNS) and extracellular vesicles. Such signalling can also result in changes in gene expression, inflammatory and immune related responses and epigenetic changes. Effects are not only observed in the irradiated cells but also in surrounding non-irradiated cells (bystander effect) and tissue elsewhere in the body (abscopal effect) (Buonanno et al, 2023). Rather than transient effects, these signalling feedback loops, associated oxidative stress and epigenetic regulation of the cell, may last for hours, days and even extend to subsequent cell generations.

5.9 Additionally, effects can also be observed in the progeny of the irradiated cell population (both irradiated and unirradiated bystander cells) (Kadhim et al, 2013). Radiation-induced genomic instability is associated with an increased rate of genetic alterations including cytogenetic rearrangements, mutations, gene amplification, transformation and cell death, multiple generations after the parental cell population have been irradiated. These are heterogeneous in nature arising non-clonally within the decedent population and occur at a higher frequency than can be explained by a specific gene mutation.

5.10 These non-targeted effects may include responses that can ultimately be either beneficial (for example, enhanced removal of precancerous cells via intercellular induction of apoptosis) or detrimental (for example, increase in genomic instability) to the individual, with the overall impact dependent on the relative balance of the various non-targeted effects induced. UNSCEAR (2012, 2021) have noted the variability of responses observed and concluded that there is as yet no indication of a causal association of non-targeted phenomena with radiation-related disease and that some may not operate at low doses (<100 mGy) in vivo.

5.11 There is some evidence of involvement of clonal haematopoiesis (CH) in CVD, although the evidence for radiation exposure inducing CH (and possibly thereby CVD) is not strong. Jaiswal et al (2017) suggested a link between CH and CVD, but there are at least 3 larger studies that do not (van Zeventer et al, 2021; Kar et al, 2022; Kessler et al, 2022). In addition, there is only weak evidence that radiation may be associated with CH. The only moderately strong evidence for this comes from the study of Bolton et al (2020) which suggests that X-ray therapy might cause CH but the results must be regarded as equivocal (Crants et al, 2022). A study of a single NASA astronaut (and their ground-based twin) suggested elevated CH after prolonged spaceflight (Mencia-Trinchant et al, 2020), but there are multiple stressors associated with spaceflight (for example, microgravity, noise, abnormal day-night cycle) and the link of CH with radiation exposure is therefore unclear; there is also no assessment of CVD. Animal studies have also suggested links between radiation exposure and CH (Hirabayashi et al, 2015; Yoshida et al, 2022), but these do not assess CVD.

5.12 Although effects of radiation on the heart were reported as early as 2 years after the discovery of X-rays (Sabrazes and Riviere, 1897; Seguy and Quenisset, 1897),

progress in understanding the underlying mechanisms has been slow. This is owed in particular to the emphasis on radiation-induced cancers and the incompatibility between the identified mechanisms of radiation-induced cancers and the pathogenesis of CVD. While cancers are associated with random accruement of mutations that endow cells with autonomy from the control of their surrounding tissues and environment, this is not the likely biological basis of CVD. Uncontrolled cellular proliferation, which characterises cancer is a feature that is distinctly absent in CVD.

Radiation and types of cardiovascular disease

5.13 Initial reports from animal experiments were mostly on the consequence of high doses of radiation on the muscle of the heart, the cardiomyocytes, leading to irregular heartbeats and palpitations (Seguy and Quenisset, 1897). Such manifestations, however, were not observed in humans, although a possible explanation was that the radiation doses, post-radiation time and other parameters could not be compared with those of the early animal experiments. Importantly, application of what was then the new technology of ECG, which measures heart muscle function, were unequivocal in concluding that there are no detrimental effects of radiation on the heart (Senderoff et al, 1959; BMJ, 1976). This engendered the spurious notion that the heart is radio-resistant. Despite this, reports on cardiovascular effects after exposure to radiation continued to surface, mainly pericarditis and cardiomyopathy.

5.14 Pericarditis pertains to the inflammation of the double membrane sac that encompasses the entire heart. It is the earliest form of radiation effect on the heart and is characterised by the accumulation of exudate (protein-rich solution) in the pericardial sac (Fajardo and Stewart, 1970). Acute pericarditis is observed after a few days to weeks of high doses of radiation (>50 Gy to the heart) but is presently very rare due to efforts to minimise exposures of the heart to radiation. This acute form is characterised by a porous pericardium, presumably due to cell death, and is generally limited in time. It can however, in some instances progress to deposition of fibrin, which thickens the pericardium and leads to chronic constrictive pericarditis. Chronic pericarditis can be caused by somewhat lower doses of radiation (for example, 20 to 40 Gy to the heart), with onset times of an average of a year, but ranging from 3 months to over a decade (for example, Zhuang et al (2017) and Marinko (2019)). This pathology is characterised by fibrous thickening of the pericardium and the deposition of collagen. In severe cases, this can lead to chronic constrictive pericarditis. The cellular cause of this bears similarities to cardiomyopathies.

5.15 Cardiomyopathies are pathologies of the heart muscle of which cardiac fibrosis and myocardial necrosis are the 2 that are most commonly associated with exposure to radiation. The former is a consequence of increased deposition of collagen in the heart muscle and proliferation of the cardiomyocytes. The latter is caused by death of cardiomyocytes. These effects are seen at high doses of radiation (>15 Gy) (Lauk et al, 1985), and feature fibrosis, inflammation and effacement of the peri-myocyte endothelium, which is consistent with injury to the micro-vessels at the site of radiation. Although the outcome is abnormality of the heart muscle, the cause is damage to blood vessels as well as heart muscle, both of which are underpinned by the process of inflammation. Thickening and fibrosis of blood

vessel walls can reduce the heart's compliance, resulting in diastolic dysfunction. The risk of developing radiation-induced fibrosis has been reported to be affected by the epigenetic state of the promoter of diacylglycerol kinase alpha (DGKA) (Weigel et al, 2016).

5.16 Atherosclerosis emerged later as another condition which radiation exposures can cause or promote (Gold, 1962; Wolffe and Siegal, 1962). Atherosclerotic changes and plaque formation in the arteries are the underlying causes of coronary artery and cerebrovascular diseases and so are central as the causes of vascular disease mortality and morbidity (HPA, 2010; ICRP, 2012b). The formation of atherosclerotic plaques is a slow process and is not accompanied by any overt manifestation of ill health. Their presence is often only known when they rupture, releasing their blood-clotting contents into the blood stream. This causes blockage of blood flow and deprivation of oxygen to the heart muscle (ischaemia), resulting in the cessation of heart contraction and function (a heart attack) in the case of blockage in the coronary artery – and to the brain leading to stroke in the case of blockages in carotid or cerebral arteries. Less severe blockage of the coronary artery resulting from ischaemic disease can result in angina, which has also been linked with radiation exposure (Little et al, 2023).

Mechanisms underlying atherosclerosis

5.17 Atherosclerotic plaques form within the wall of the artery. The processes that lead to this development are highly complex, with the 2 major components of the plaques being monocytes (a type of white blood cells) and cholesterol in the initial form of low-density lipoprotein (LDL). These components must penetrate the wall of the blood vessel to initiate the formation of a plaque (Ahmed et al, 2023). In normal and healthy blood vessels, plaque formation does not happen, largely because the inner lining of the blood vessel, the endothelium, is intact and functions to prevent the entrapment and entry of monocytes and LDL. In unhealthy or aged blood vessels, the integrity of the endothelium is compromised. This is often initiated by increased adhesiveness of the endothelial cells which constitute the endothelium (Poston et al, 2022).

5.18 Several factors can lead to endothelial cell adhesiveness, including damage to the endothelium. When the integrity of the endothelial layer is compromised, LDL, a normal constituent of the blood, readily adheres within the vessel wall and becomes trapped and the breach of the endothelium is eventually healed by proliferation of the surrounding endothelial cells (Torzewski, 2021). The encapsulated LDL, through complex processes, causes the overlying endothelium to become inflamed. One of the features of this inflammation is high adhesiveness of their apical surface (towards the blood stream) (Cerutti and Ridley, 2017; Jiang et al, 2022). Monocytes, a constituent of the blood, which normally roll along the endothelium within the blood stream, become adhered to the top of activated endothelial cells. The continuously flowing blood stream flattens the adhered monocytes, easing their passage between the walls of adjacent endothelial cells.

5.19 Another feature of activated endothelial cells is the deterioration of the integrity of their cell-cell junction, further easing the passage of monocytes through the endothelium (Lampugnani, 2012; Moore et al, 2013). These features of inflamed endothelial cells allow monocytes access into the blood vessel wall, where they transform into macrophages to remove trapped cholesterol. Plaques develop as

macrophage egress to the bloodstream fails and trapped cells accumulate, transforming to foam cells as they engulf cholesterol (Clarke et al, 2020; Popa-Fotea et al, 2023). Plaques can increase in size to occlude arteries, and with further decline in the integrity of their endothelial covering, rupture can release the puss-like contents that are extremely pro-thrombotic (ability to trigger blood clotting).

Potential mechanisms of radiation action

5.20 The ability of ionising radiation to increase the risk of atherosclerosis has been demonstrated in extensive studies using mice (Yamamoto et al, 2021). There are many points in the entire process of atherogenesis that could be triggered or enhanced by ionising radiation. These will be discussed in sequential order of the atherogenic process.

5.21 Ionising radiation has been reported to increase the membrane adhesiveness of different cell types, including human umbilical cord endothelial cells (Colden-Stanfield et al, 1994; Gaugler et al, 1997), aorta endothelial cells (Khaled et al, 2012), coronary artery endothelial cells (Voisard et al, 2007; Lowe and Raj, 2014), dermal microvascular endothelial cells (Quarmby et al, 2000; Prabhakarpandian et al, 2001; Rousseau et al, 2011), and cerebral vessel endothelial cells (Wood et al, 2005). Human coronary artery endothelial cells showed increased adhesion of monocytes and release of pro-inflammatory cytokines (Interleukin-6 and IL-8) at a dose of 2 Gy X-rays (Baselet et al, 2017b). Exposure of human umbilical vein endothelial cells to X-rays (>2 Gy) resulted in increased expressions of the membrane protein, ICAM-1, partially mediated by TGF-β1 (Kiyohara et al, 2011). Lower X-ray doses (0.125 to 0.5 Gy) have also been shown to result in increases in ICAM-1 expression and enhanced adhesion in peripheral blood mononuclear cells (Cervelli et al, 2014). Baselet et al (2017a) used human coronary artery cells exposed to X-ray doses of 0.05, 0.1, 0.5 or 2 Gy to show a dose-dependent increase in pro-atheromatous processes. Cells underwent G1 arrest, compensated by subsequently increased proliferation, at higher doses of 0.5 or 2 Gy. A dose-dependent increase in the cellular senescence marker, β-galactosidase, was observed from 0.05 Gy but significant increases of pro-inflammatory markers, IL-6 and CCL2 were confined to doses of 0.5 and 2 Gy.

5.22 Radiation-induced adhesiveness has been found to result from increased expression of membrane proteins that mediate monocyte attachment including ICAM-1 (Quarmby et al, 2000; Prabhakarpandian et al, 2001; Voisard et al, 2007; Kiyohara et al, 2011), VCAM-1 and E-selectin (Hallahan et al, 1995; Hallahan et al, 1996; Hallahan et al, 1997; Prabhakarpandian et al, 2001). The expression of these adhesive membrane proteins is augmented as part of cellular responses in the context of inflammation. Inflammation is a normal response of healthy tissue to infections and damage and is meant to potentiate the removal of dead cells and initiate the process of repair and healing (Medzhitov, 2010). When macrophages interact with dead cells, they release molecules that are anti-inflammatory such as IL-10 and TGF-β which inhibit the production of pro-inflammatory proteins such as IL-1 and TNF-α by these cells (Chung et al, 2006). However, conditions such as those in developing arterial plaques can overwhelm the ability of macrophages to remove damaged cells and this can result in prolonged inflammatory signalling (Rock and Kono, 2008). The induction of inflammation by radiation at high doses is

well documented (Bours et al, 2000; Najafi et al, 2018). However, lower doses in the range of 0.1 to 1 Gy may result in the down-regulation of monocyte adhesion to the endothelium and an anti-inflammatory effect as shown in vitro (Kern et al, 2000; Hildebrandt et al, 2002; Roedel et al, 2002)) and in vivo (Arenas et al, 2006). Large et al (2015) reported an anti-inflammatory effect at 0.5 Gy in primary human dermal microvascular endothelial cells. Consistent with this, radiation doses of 0.025 to 0.05 Gy conferred protection against development of atherosclerotic plaques in ApoE-/- mice, which spontaneously develop such plaques (Mitchel et al, 2011). This perceived benefit of radiation is being used therapeutically, particularly in Germany, for the treatment of non-malignant inflammatory and degenerative diseases (Trott, 1994; Ott et al, 2015).

5.23 A further cellular response to radiation at high doses (>1 Gy) is senescence (Lowe and Raj, 2014; Wang et al, 2016; Yamamoto et al, 2021). Cell senescence can be triggered in a number of ways, including by the continued and prolonged presence of damaged DNA (Wang et al, 2016). Irradiated endothelial cells that become senescent, augment the expression of adhesive proteins such as ICAM-1, E-selectin and CD44 (Kim et al, 2014; Lowe and Raj, 2014). In the case of CD44, senescence is reported to involve loss of epigenetic regulation of the CD44 gene in which cytosine molecules in the CD44 promoter that are normally methylated lose their methyl group leading to gene activation (Lowe and Raj, 2014). In addition to changes in DNA methylation, irradiated cells can also undergo another form of epigenetic change which involves the loss of histone proteins (Lowe et al, 2020), which function to regulate the accessibility of DNA to transcription factors (proteins that trigger expression of genes). Hence loss of histones increases the accessibility of promoters and deregulated expression of genes.

5.24 The passage of monocytes across the endothelium into the vessel wall can occur in several ways, of which the best-described is entry between the junctions of adjacent endothelial cells. The adjacent cell membranes of these cell-cell junctions are held together very tightly by specialised proteins that physically interact with each other. The opening and closing of these junctions regulate the movement of monocytes and plasma components into the vessel wall. Cells that become senescent as a result of radiation exposure express significantly reduced levels of VE-cadherin, Claudin 5, ZO-1, Occludin and Connexin 4 (Kabacik and Raj, 2017; Wang et al, 2019), which are all cell junction proteins. These changes increase the permeability of the endothelium to monocytes, LDL and other constituents of the blood. The reduced expression of these proteins is another consequence of inflammatory response of the endothelium involving NF-κB (Wang et al, 2019; Wijerathne et al, 2021) which favours the entry of immune cells into the vessel wall to remove damaged or dead cells or foreign bodies.

Mechanisms and dose-response

5.25 At very high radiation doses (>10 Gy), such as those that may be received during RT, tissue reactions occur and it is likely that the resulting inactivation of a large number of cells and associated functional impairment of the irradiated cells and tissue will dominate the response due to direct damage to the structures of the heart and associated blood vessels. Such damage is accompanied by inflammatory responses. Resulting effects include fibrotic damage, especially in the pericardium and myocardium, pericardial adhesions, microvascular damage, along

with stenosis of the valves and coronary arteries (Schultz-Hector and Trott, 2007; Kadhim et al, 2013; Tapio, 2016).

5.26 While high doses (>1 Gy) have been shown to be pro-inflammatory and also increase endothelial cell senescence, moderate doses (0.1 to 1 Gy) have been suggested to be anti-inflammatory and may therefore have the potential to slow the development of atherosclerosis. Although cell killing will be substantially less than at higher doses, it may nevertheless be of importance at lower doses. For example, Little et al (2009) proposed a model in which monocyte killing could result in an almost linear dose-response over the range from 0 – 4 Gy and risks consistent with observations from studies of nuclear workers. Simonetto et al (2017) have proposed a stochastic model for atherosclerosis which features the uptake of monocytes into the arterial wall, their proliferation as macrophages and transition to foam cells. Such models are potentially informative and help bring together epidemiological findings and possible mechanistic steps in disease progression, but currently rely on assumptions that are yet to be validated.

5.27 At low doses associated with typical human exposures (<0.1 Gy), potential effects could involve non-targeted as well as targeted effects, with damage to DNA and other cellular molecules. Unlike carcinogenesis, for which there is a clearly understood mutational basis which operates in linear proportion to dose down to 1 mGy at least (UNSCEAR, 2021), mutation is not a feature in the progression of atherosclerosis. While the vascular smooth muscle cells that provide the fibrous cap of atherosclerotic plaques have been found to be monoclonal, this has been shown to be a feature of the normal vessel wall, rather than the result of mutation and clonal expansion associated with plaque formation (HPA, 2010).

Summary of mechanisms

5.28 At very high doses (>10 Gy) to the heart, cell killing will cause direct damage, leading to or contributing to pericarditis and cardiomyopathy. The experimental evidence indicates that the progression of atherosclerosis can be increased at high doses (>1 Gy), with associated elevation of inflammation, but anti-inflammatory responses at moderate doses (100 mGy to 1 Gy) may be taken to suggest that dose-response may not be linear. However, a plausible model of monocyte killing suggested by Little et al (2009) is compatible with approximate linearity from very low doses (0 to 4 Gy).

5.29 Although much has been established about potential mechanism of radiation action in atherogenesis, involving inflammation and cell senescence as well as other effects, the current understanding of mechanisms is insufficient to draw conclusions regarding the extent of risk at low doses. Any estimate of such risks will remain speculative, pending a firmer understanding of the complex interactions involved in atherogenesis and the role of radiation in its causation, promotion, or indeed, inhibition.

Chapter 6. Evidence synthesis

6.1 Chapters 1 to 5 review the biological and epidemiological evidence for associations between low dose or low dose rate radiation exposure and CVD risk, particularly for IHD and CeVD. Based on that review, this chapter summarises and appraises the evidence to determine the strength of evidence and whether associations could be causal.

6.2 There are various related frameworks provided to determine the strength of a body of evidence. This report uses the framework described in Guidance Note *Assessing the Strength of Evidence*, published by the UK Department for International Development in 2014[8]. The framework is provided in Table 6.1, and is revised to extend beyond clinical trials:

Table 6.1: Framework for assessing the strength of evidence (amended for the purpose of this report)

Categories of evidence	Quality + size + consistency + context	Typical features of the body of evidence	What it means for a proposed intervention
Very Strong	High quality body of evidence, large in size, consistent, and contextually relevant.	Research questions aimed at isolating cause and effect (for example, what is happening) are answered using high quality experimental and quasi-experimental research designs, sufficient in number to have resulted in production of a systematic review or meta-analysis. Research questions aimed at exploring meaning (for example, why and how something is happening) are considered through an array of structured qualitative observational research methods directly addressing contextual issues.	The Committee are very confident that the exposure either does or does not have the effect anticipated. The body of evidence is very diverse and highly credible, with the findings convincing and stable.
Strong	High quality body of evidence, large or medium in size, highly or moderately consistent, and contextually relevant.	Research questions aimed at isolating cause and effect (for example, what is happening) are answered using high quality quasi-experimental research designs and/or quantitative observational studies. They are sufficient in number to have resulted in the production of a systematic review or meta-	The Committee are confident that the exposure either does or does not have the effect anticipated. The body of evidence is diverse and credible, with the findings convincing and stable.

[8] How to Note: Assessing the Strength of Evidence

		analysis. Research questions aimed at exploring meaning (for example, why and how something is happening) are considered through an array of structured qualitative observational research methods directly addressing contextual issues	
Medium	Moderate quality studies, medium size evidence body, moderate level of consistency. Studies may or may not be contextually relevant.	Research questions aimed at isolating cause and effect (for example, what is happening) are answered using moderate to high-quality quantitative observational designs. Research questions aimed at exploring meaning (for example, why and how something is happening) are considered through a restricted range of qualitative observational research methods addressing contextual issues.	The Committee believe that the exposure either may or may not have the effect anticipated. The body of evidence displays some significant shortcomings. There are reasons to think that contextual differences may unpredictably and substantially affect outcomes.
Limited	Moderate-to-low quality studies, medium size evidence body, low levels of consistency. Studies may or may not be contextually relevant.	Research questions aimed at isolating cause and effect (for example, what is happening) are answered using moderate to low-quality quantitative observational studies. Research questions aimed at exploring meaning (for example, why and how something is happening) are considered through a narrow range of qualitative observational research methods addressing contextual issues.	The Committee believe that the exposure either may or may not have the effect anticipated. The body of evidence displays very significant shortcomings. There are multiple reasons to think that contextual differences may substantially affect outcomes
No evidence	No/few studies exist.	Neither cause and effect, nor meaning is seriously interrogated. Any available studies are of low quality and are contextually irrelevant.	There is no plausible evidence that the exposure does/does not have the effect indicated.

Evaluation of evidence

Evidence from the LSS study

6.3 The LSS of Japanese A-bomb survivors provides important information on cancer and non-cancer effects from moderate to high doses received following a single event, but its relevance to low dose or low dose rate, protracted exposures is much less clear. The Committee interprets the evidence for the LSS cohort as providing

Strong evidence with respect to moderate to high doses (0.5 to 5 Gy) from a single event, but ***Limited evidence*** with respect to low to moderate doses (<0.5 Gy).

Evidence from Radiotherapy

6.4 RT doses to target tissues are generally of the order of several Gy.

6.5 There is strong evidence for an increase in risk of CVD at very high (>10 Gy) absorbed doses, especially in relation to breast cancer RT. There is little evidence in studies of persons treated for RT of excess risk at doses <10 Gy. However, for persons treated for non-cancer disease or those receiving diagnostic exposures there is evidence of excess risk at doses <10 Gy.

6.6 Evidence from meta-analyses indicated increased risk for IHD, heart failure and heart valve disease. There is some evidence of increased risk of cerebrovascular effects.

6.7 Extrapolation of observed dose-response relationships might indicate increased risks extending to lower doses of the order of several 100 mSv, but with the relatively small numbers of patients in individual clinical studies, the evidence of any risk below a dose of 5 Gy is not statistically significant among persons receiving RT for cancer. Variations in study endpoints preclude combining of data from different reports as is done with worker studies.

6.8 The Committee interprets the evidence from RT as providing ***Medium evidence*** with respect to high doses (>10 Gy) as a risk factor for IHD and CeVD.

6.9 The Committee interprets the evidence from RT as providing ***No evidence*** with respect to the quantitative estimation of the dose-response association at low dose or low dose-rate radiation as a risk factor for IHD and CeVD, as these are based on downwards extrapolation from high doses.

Evidence from Occupational and Environmental Epidemiology

6.10 There is evidence from studies of larger occupationally exposed populations, in particular based on studies from the nuclear industry, of an excess CVD risk, both for IHD and CeVD, in relation to external radiation dose.

6.11 In these cohorts, linear relationships often showed best fit to the data (or were forced by the model structure), but both supralinear and sublinear associations have also been reported.

6.12 The INWORKS study of US, UK and French workers explicitly explored effects of dose ranges, and whereas increased excess risk for CeVD per unit exposure was observed when the dose range was restricted to 100 mSv or lower compared to the full range, there was no evidence of excess risk for IHD for this low dose range. The Mayak worker cohort showed no excess mortality at doses <2 Sv.

6.13 Evidence of excess risks in the nuclear industry are mostly based on data from the UK fuel cycle and the Russian Mayak cohort, with data from elsewhere (most notably the US and France) showing lower excess risks, if any.

6.14 Both for IHD and CeVD, evidence of excess risk is not consistent across studies and populations, and this heterogeneity, observed in observational epidemiological studies generally, would benefit from further investigation. A possible reason for heterogeneity is the absence of information on lifestyle confounders and other occupational exposures in many of the occupational studies. However, data from different sources indicates that these confounders are unlikely to appreciably modify risk.

6.15 Data from studies of Chornobyl recovery workers provide evidence of excess IHD and CeVD risk, but these high risks do not align with expected risks from other data and there are significant uncertainties with these studies.

6.16 Findings from other occupational groups, in particular medical workers and radiographers, with prolonged exposure to low dose radiation, only provide weak evidence of excess risks.

6.17 There is some evidence from the Techa river cohort that environmental external radiation exposure might be associated with increased IHD mortality risk, but not of CeVD mortality. The available evidence in relation to the Fukushima Daichii event did not indicate evidence of increased CVD risks but was of low quality.

6.18 The Committee interprets the evidence from occupational populations as providing ***Medium evidence*** with respect to low dose or low dose rate radiation as a risk factor for IHD.

6.19 The Committee interprets the evidence from occupational populations as providing ***Medium evidence*** with respect to low dose or low dose rate radiation as a risk factor for CeVD.

6.20 The Committee interprets the data from occupational populations as providing ***Limited evidence*** with respect to the quantitative estimation of the dose-response association at low dose or low dose rate radiation as a risk factor for IHD and CeVD. It further interprets the evidence from occupational exposures as indicating that a summary dose-response association may not be linear.

6.21 The Committee interprets the results from environmentally exposed populations as providing ***Limited evidence*** with respect to supporting findings from occupational populations.

6.22 The Committee interprets the results from environmentally exposed populations as providing ***Limited evidence*** with respect to the quantitative estimation of the dose-response association at low dose or low dose rate radiation as a risk factor for IHD and CeVD.

Mechanistic data

6.23 At high doses typically associated with therapeutic exposures, biological effects are dominated by the direct, targeted effects of radiation on the irradiated cells and tissue. Observed effects will be attributable to gross cell killing and tissue impairment, leading to direct damage to the structures of the heart and blood vessels. On this basis, it can be concluded that the data provide ***Strong evidence*** in support of observed effects at high doses.

6.24 At moderate doses (0.1 to 1 Gy), dominant mechanisms are less clear, with the possibility of anti-inflammatory effects that could slow the development of diseases and influence dose-response relationships. In addition, non-targeted effects within cells may also contribute to the biological response due to long term perturbation in intra- and intercellular signalling and are also associated with non-linear dose-response relationships. However, it should also be noted that plausible models have been proposed that invoke stochastic responses that could conform to a linear dose-response. Overall, the data can be judged to provide ***Medium evidence*** in support of effects being observed but ***No evidence*** in direct support of assumptions regarding dose-response and quantitative estimates of risk.

6.25 At low doses (<0.1 Gy) a number of potential mechanisms of radiation action have been discussed involving inflammation and cell senescence as well as other effects. Nonetheless, the current understanding of mechanisms is insufficient to draw conclusions regarding the extent of risk at low doses. The situation is unlike that for cancer for which there is a good understanding of cellular events that can lead to stable unrepaired DNA damage passing on proliferative advantage, and which may lead to malignant disease. Thus, while mechanistic data provide support for the assumption of a non-threshold dose-response relationship for cancer, the same is not the case for CVD. Estimates of cardiovascular risks at low dose will remain speculative pending a firmer understanding of the complex interactions involved in atherogenesis and the role of radiation in its causation, promotion, or possible inhibition. The data do not support firm judgements on the possibility of a threshold (or thresholds) of response. Overall, it is concluded that the data provide ***Limited evidence*** that effects may occur at low doses and ***No evidence*** in support of any dose-response relationship.

Chapter 7. Summary and conclusions

7.1 Cardiovascular diseases (CVDs) are a leading cause of death in the UK and worldwide. The main types are coronary heart disease, also known as ischaemic heart disease (IHD), and cerebrovascular disease (CeVD). Heart attacks (a form of IHD) and strokes (a form of CeVD) are acute events caused by blockages that prevent blood from flowing to the heart and brain. The underlying cause in the majority of cases of coronary heart disease, cerebrovascular diseases and peripheral arterial disease is atherosclerosis.

7.2 The main risk factors for CVD that have been consistently identified are age, smoking, diabetes mellitus, hypertension, obesity, increased total and low-density lipoprotein cholesterol, decreased high density lipoprotein cholesterol, as well as a heritable genetic component for heart disease specifically.

7.3 Substantial information is now available on risks of radiation-associated CVDs from a variety of epidemiological studies of human populations and there is also growing understanding of the mechanisms of radiation action in cells and tissues.

7.4 The Committee interprets the evidence from the Life Span Study (LSS) of Japanese A-bomb survivors as providing ***Strong evidence*** of risks of CVD, including CeVD, from moderate to high doses (received following a single radiation exposure), but ***Limited evidence*** with respect to low to moderate doses (<0.5 Gy).

7.5 RT studies are judged by the Committee to provide ***Medium evidence*** that very high (>10 Gy) absorbed doses cause or amplify the risk of CVD, with increased risk of IHD, heart failure and heart valve diseases, and some evidence of increased risk of CeVD. Studies are weakened by the potential for substantial selection bias. The data do not inform on risks below about 10 Gy, although studies of persons receiving RT for non-cancer disease suggest that there is risk at <10 Gy.

7.6 Evidence from epidemiological studies of occupational exposures at moderate doses (0.1 – 1 Gy) and above are judged to provide ***Medium evidence*** in demonstrating excess risk of CVD, mainly IHD and CeVD. Important information comes from the UK National Registry of Radiation Workers (NRRW), US Million Person Study (MPS), the International Nuclear Worker Study (INWORKS) of radiation workers in the USA, UK and France, and studies of the Russian Mayak workforce.

7.7 The data show statistically significant excesses in risk from the order of 0.1 Gy, but no firm conclusions can be drawn regarding possible thresholds of effect, although there are a number of studies suggesting excess risk at <0.5 Gy, implying that any threshold dose would have to be somewhat below this level.

7.8 The data from epidemiological studies of occupational populations was evaluated as providing ***Medium evidence*** of the possibility that low dose or low dose rate radiation is a risk factor for IHD and CeVD, but only providing ***Limited evidence*** in support of quantitative estimations of the dose-response association at low dose or low dose rates. There are some indications in these populations that dose-response associations may not be linear.

7.9 Epidemiological studies of environmentally exposed populations provided ***Limited evidence*** supporting findings from occupational populations.

7.10 The above conclusions from the epidemiological evidence are to some degree supported by mechanistic evidence. At high and very high radiation doses, such as those that may be received during RT, it is likely that the inactivation of a large number of cells and associated functional impairment of the irradiated cells and tissue will dominate the response due to direct damage to the structures of the heart and associated blood vessels. While high doses (>1 Gy) have been shown to be pro-inflammatory and also increase endothelial cell senescence, moderate doses (0.1 to 1 Gy) have been suggested to be anti-inflammatory and may therefore have the potential to slow the development of atherosclerosis.

7.11 Although cell killing will be substantially less than at higher doses, it may nevertheless be of importance at lower doses. For example, a model has been proposed in which monocyte killing could result in an almost linear dose-response over the range from 0 to 4 Gy with risks consistent with observations from occupational studies. In addition, a stochastic model for atherosclerosis has been proposed which features the uptake of monocytes into the arterial wall, their proliferation as macrophages and transition to foam cells.

7.12 At low doses associated with typical human exposures (<0.1 Gy), potential effects could involve non-targeted as well as targeted effects, with damage to DNA and other cellular molecules. Unlike carcinogenesis, for which an important mechanism is mis-repair of double-strand breaks in DNA which are induced in linear proportion to dose down to 1 mGy at least, mutation is not a feature in the progression of atherosclerosis. Although much has been established about potential mechanism of radiation action in atherogenesis, the current understanding of mechanisms remains insufficient to draw conclusions regarding the extent of risk at low doses.

7.13 Data on biological responses do not allow comment on possible thresholds of effect for CVDs. While there are data suggesting that the severity of fibrosis is dependent on the level of dose (above about 30 Gy), there is no evidence that severity of CVD is dose dependent. CVD does not appear to be a tissue reaction, in the sense defined by ICRP, but while plausible stochastic mechanisms have been proposed, they remain to be validated.

7.14 The large meta-analysis of epidemiological data conducted by Little and colleagues in 2023 gave an overall ERR/Gy estimate for CVD of 0.11 [0.08, 0.13]. They further derived an excess absolute risk coefficient for CVD mortality in England and Wales of 2.3% per Gy, on which basis the consideration of CVD with cancer at low doses would add substantially to the overall low-dose risk. However, estimates of this type should be treated as indicative of possible risks in the absence of direct evidence at low doses and limited information on biological mechanisms.

Chapter 8. Recommendations

8.1 This report considers the available evidence of an association between radiation exposure and CVDs. The aim of the report is to provide advice to DHSC on health implications for the UK population from the exposure of ionising radiation. The following recommendations should be reviewed and developed as more evidence becomes available.

Recommendation 1

8.2 COMARE recommends that further research is carried out to improve understanding of CVD risks at low and moderate doses and from doses received at a low dose rate, focusing on epidemiological studies for populations with the greatest potential to be informative.

8.3 Epidemiological studies with the greatest potential are those of the Japanese atomic bomb survivors and studies of radiation workers. Worker studies need to apply due emphasis on exposure and dose assessments, and the accuracy of diagnoses. To address issues of individual-level characterisation and lifestyle factors, nested case-control studies within cohort studies could be considered. Given the evidence from a number of studies of non-linearity of dose-response, further studies should include modelling of different dose-response relationships.

8.4 In the UK, the NRRW is an impressive resource that should be fully utilised. Questions raised by previous studies should be addressed in further follow-up, including heterogeneity between constituent workforces. The observation of higher CVD risks for the Sellafield workforce is an obvious candidate for further analysis, including the unexplained difference between groups of workers according to whether they were monitored for internal exposure.

Recommendation 2

8.5 COMARE recommends that further research is undertaken on biological studies of mechanisms of radiation action in CVD in order to develop a more coherent picture of the steps involved in atherogenesis and how radiation might act to initiate and/or accelerate the process. Thought should be given in experimental design to the applicability of results to low doses and low dose rates.

Recommendation 3

8.6 COMARE recognises the need for optimising protocols for dose reduction, wherever possible. Considering current protection practices, the Committee recommends that clinicians using radiation therapeutically at very high doses continue to minimise radiation exposures of critical vasculature while maintaining effective clinical outcomes.

8.7 Although the Committee concludes that the evidence of CVD risks at low doses is insufficient to provide quantitative estimates with any confidence, the possibility that CVD adds to low-dose risk cannot be dismissed. Those responsible for the implementation and regulation of protection should be aware of this possibility. However, our current understanding indicates that current practices to control risks

of cancer at low doses and low dose rates by dose and risk optimisation, should be adequate in also protecting from any additional risk from CVD.

Recommendation 4

8.8 Because radiation may act multiplicatively with other CVD risk factors, COMARE recommends that the relevant authorities give consideration to initiatives to improve population health by reducing these risks (including from smoking, obesity, diabetes, hypertension, diet, elevated cholesterol, physical inactivity); thereby also reducing radiation risks.

Recommendation 5

8.9 COMARE recognises the value of workforce cohorts and other cohorts for epidemiological analyses. The Committee recommends that government, the devolved administrations, and relevant agencies collaborate to ensure that adequate dataset and research governance (access/analysis) arrangements are shared throughout the UK in respect of such datasets. Care should be exercised to prevent data loss when new procedures or IT systems are introduced.

References

Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al: Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 109:1878-1886, 2007

Adams, M. J., Fisher, S. G., Lipshultz, S. E., et al. (2018). "Risk of Coronary Events 55 Years after Thymic Irradiation in the Hempelmann Cohort." Cardiooncology 4.

Ahmed, M. E., Hakim, D. and Stone, P. H. (2023). "The plaque hypothesis: understanding mechanisms of plaque progression and destabilization, and implications for clinical management." Curr Opin Cardiol 38(6): 496–503.

Arenas, M., Gil, F., Gironella, M., et al. (2006). "Anti-inflammatory effects of low-dose radiotherapy in an experimental model of systemic inflammation in mice." Int J Radiat Oncol Biol Phys 66(2): 560–567.

Atkins, K. M., Rawal, B., Chaunzwa, T. L., et al. (2019). "Cardiac Radiation Dose, Cardiac Disease, and Mortality in Patients With Lung Cancer." J Am Coll Cardiol 73(23): 2976–2987.

Atkins, K. M., Bitterman, D. S., Chaunzwa, T. L., et al. (2021). "Statin Use, Heart Radiation Dose, and Survival in Locally Advanced Lung Cancer." Pract Radiat Oncol 11(5): e459–e467.

Azizova, T. V., Grigoryeva, E. S., Haylock, R. G., et al. (2015). "Ischaemic heart disease incidence and mortality in an extended cohort of Mayak workers first employed in 1948-1982." Br J Radiol 88(1054): 20150169.

Azizova, T. V., Batistatou, E., Grigorieva, E. S., et al. (2018). "An Assessment of Radiation-Associated Risks of Mortality from Circulatory Disease in the Cohorts of Mayak and Sellafield Nuclear Workers." Radiat Res 189(4): 371–388.

Azizova, T. V., Bannikova, M. V., Grigoryeva, E. S., et al. (2022a). "Mortality from various diseases of the circulatory system in the Russian Mayak nuclear worker cohort: 1948-2018." J Radiol Prot 42(2).

Azizova, T. V., Moseeva, M. B., Grigoryeva, E. S., et al. (2022b). "Incidence risks for cerebrovascular diseases and types of stroke in a cohort of Mayak PA workers." Radiat Environ Biophys 61(1): 5–16.

Azizova, T. V., Bannikova, M. V., Briks, K. V., et al. (2023a). "Incidence risks for subtypes of heart diseases in a Russian cohort of Mayak Production Association nuclear workers." Radiat Environ Biophys 62(1): 51–71.

Azizova, T. V., Grigoryeva, E. S. and Hamada, N. (2023b). "Dose rate effect on mortality from ischemic heart disease in the cohort of Russian Mayak Production Association workers." Sci Rep 13(1): 1926.

Baaken, D., Merzenich, H., Schmidt, M., et al. (2022). "A nested case-control study on radiation dose-response for cardiac events in breast cancer patients in Germany." Breast 65: 1–7.

Baselet, B., Belmans, N., Coninx, E., et al. (2017a). "Functional Gene Analysis Reveals Cell Cycle Changes and Inflammation in Endothelial Cells Irradiated with a Single X-ray Dose." Front Pharmacol 8: 213.

Baselet, B., Azimzadeh, O., Erbeldinger, N., et al. (2017b). "Differential Impact of Single-Dose Fe Ion and X-Ray Irradiation on Endothelial Cell Transcriptomic and Proteomic Responses." Front Pharmacol 8: 570.

Bates, J. E., Howell, R. M., Liu, Q., et al. (2019). "Therapy-Related Cardiac Risk in Childhood Cancer Survivors: An Analysis of the Childhood Cancer Survivor Study." J Clin Oncol 37(13): 1090–1101.

Baudin, C., Vacquier, B., Thin, G., et al. (2023). "Occupational exposure to ionizing radiation in medical staff: trends during the 2009-2019 period in a multicentric study." Eur Radiol 33(8): 5675–5684.

Bergom, C., Bradley, J. A., Ng, A. K., et al. (2021). "Past, Present, and Future of Radiation-Induced Cardiotoxicity: Refinements in Targeting, Surveillance, and Risk Stratification." JACC CardioOncol 3(3): 343–359.

Berrington de Gonzalez, A., Salotti, J. A., McHugh, K., et al. (2016). "Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions." Br J Cancer 114(4): 388–394.

Berrington de Gonzalez, A., Daniels, R. D., Cardis, E., et al. (2020). "Epidemiological Studies of Low-Dose Ionizing Radiation and Cancer: Rationale and Framework for the Monograph and Overview of Eligible Studies." J Natl Cancer Inst Monogr 2020(56): 97–113.

Black, D. (1984). "Investigation of the possible increased incidence of cancer in West Cumbria. Report of the Independent Advisory Group. HMSO, London.".

BMJ (1976). "Editorial: Radiotherapy and the heart in Hodgkin's disease." British Medical Journal 1(6022): 1360–1360.

Boekel, N. B., Duane, F. K., Jacobse, J. N., et al. (2020). "Heart failure after treatment for breast cancer." Eur J Heart Fail 22(2): 366–374.

Boice, J. D., Jr., Cohen, S. S., Mumma, M. T., et al. (2014). "Mortality among mound workers exposed to polonium-210 and other sources of radiation, 1944-1979." Radiat Res 181(2): 208–228.

Boice, J. D., Jr., Cohen, S. S., Mumma, M. T., et al. (2022a). "Mortality from leukemia, cancer and heart disease among U.S. nuclear power plant workers, 1957-2011." Int J Radiat Biol 98(4): 657–678.

Boice, J. D., Jr., Cohen, S. S., Mumma, M. T., et al. (2022b). "Mortality among workers at the Los Alamos National Laboratory, 1943-2017." Int J Radiat Biol 98(4): 722–749.

Boice, J. D., Jr., Ellis, E. D., Golden, A. P., et al. (2022c). "Sex-specific lung cancer risk among radiation workers in the million-person study and patients TB-Fluoroscopy." Int J Radiat Biol 98(4): 769–780.

Boice, J. D., Jr., Quinn, B., Al-Nabulsi, I., et al. (2022d). "A million persons, a million dreams: a vision for a national center of radiation epidemiology and biology." International Journal of Radiation Biology 98(4): 795–821.

Boice, J. D., Jr., Cohen, S. S., Mumma, M. T., et al. (2023). "Mortality among medical radiation workers in the United States, 1965-2016." Int J Radiat Biol 99(2): 183–207.

Bolch, W. E., Dietze, G., Petoussi-Henss, N., et al. (2015). "Dosimetric models of the eye and lens of the eye and their use in assessing dose coefficients for ocular exposures." Ann ICRP 44(1 Suppl): 91–111.

Bolton, K. L., Ptashkin, R. N., Gao, T., et al. (2020). "Cancer therapy shapes the fitness landscape of clonal hematopoiesis." Nat Genet 52(11): 1219–1226.

Bours, V., Bonizzi, G., Bentires-Alj, M., et al. (2000). "NF-kappaB activation in response to toxical and therapeutical agents: role in inflammation and cancer treatment." Toxicology 153(1-3): 27–38.

Brambilla, M., Cerini, P., Lizio, D., et al. (2015). "Cumulative radiation dose and radiation risk from medical imaging in patients subjected to endovascular aortic aneurysm repair." Radiol Med 120(6): 563–570.

Brambilla, M., Vassileva, J., Kuchcinska, A., et al. (2020). "Multinational data on cumulative radiation exposure of patients from recurrent radiological procedures: call for action." Eur Radiol 30(5): 2493–2501.

Buonanno, M., Gonon, G., Pandey, B. N., et al. (2023). "The intercellular communications mediating radiation-induced bystander effects and their relevance to environmental, occupational, and therapeutic exposures." Int J Radiat Biol 99(6): 964–982.

Cardis, E., Vrijheid, M., Blettner, M., et al. (2005). "Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries." Bmj 331(7508): 77.

Cardis, E., Vrijheid, M., Blettner, M., et al. (2007). "The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Estimates of Radiation-Related Cancer Risks." Radiation Research 167(4): 396–416, 321.

Castellano, I. A., Nicol, E. D., Bull, R. K., et al. (2017). "A prospective national survey of coronary CT angiography radiation doses in the United Kingdom." J Cardiovasc Comput Tomogr 11(4): 268–273.

Cerutti, C. and Ridley, A. J. (2017). "Endothelial cell-cell adhesion and signaling." Exp Cell Res 358(1): 31–38.

Cervelli, T., Panetta, D., Navarra, T., et al. (2014). "Effects of single and fractionated low-dose irradiation on vascular endothelial cells." Atherosclerosis 235(2): 510–518.

Chung, E. Y., Kim, S. J. and Ma, X. J. (2006). "Regulation of cytokine production during phagocytosis of apoptotic cells." Cell Res 16(2): 154–161.

Clarke, J. D., Duarte Lau, F. and Zarich, S. W. (2020). "Determining the Significance of Coronary Plaque Lesions: Physiological Stenosis Severity and Plaque Characteristics." J Clin Med 9(3).

Colden-Stanfield, M., Kalinich, J. F. and Gallin, E. K. (1994). "Ionizing radiation increases endothelial and epithelial cell production of influenza virus and leukocyte adherence." J Immunol 153(11): 5222–5229.

Crants, S. A., Olson, S. S., Li, Y., et al. (2022). "Radiation Therapy and Subsequent Clonal Hematopoiesis: An Analysis of a Biorepository of 89,782 Patients." International Journal of Radiation Oncology*Biology*Physics 114(3, Supplement): e504.

Cullings, H. M., Grant, E. J., Egbert, S. D., et al. (2017). "DS02R1: Improvements to Atomic Bomb Survivors' Input Data and Implementation of Dosimetry System 2002 (DS02) and Resulting Changes in Estimated Doses." Health Physics 112(1): 56–97.

Cutter, D. J., Schaapveld, M., Darby, S. C., et al. (2015). "Risk of valvular heart disease after treatment for Hodgkin lymphoma." J Natl Cancer Inst 107(4).

Daniels, R. D., Kendall, G. M., Thierry-Chef, I., et al. (2020). "Strengths and Weaknesses of Dosimetry Used in Studies of Low-Dose Radiation Exposure and Cancer." J Natl Cancer Inst Monogr 2020(56): 114–132.

Danilova, I., Shkolnikov, V. M., Jdanov, D. A., et al. (2016). "Identifying potential differences in cause-of-death coding practices across Russian regions." Popul Health Metr 14: 8.

Darby, S. C., Ewertz, M., McGale, P., et al. (2013). "Risk of ischemic heart disease in women after radiotherapy for breast cancer." N Engl J Med 368(11): 987–998.

De Bont, R. and van Larebeke, N. (2004). "Endogenous DNA damage in humans: a review of quantitative data." Mutagenesis 19(3): 169–185.

de Vocht, F., Hidajat, M., Martin, R. M., et al. (2020). "Ischemic Heart Disease Mortality and Occupational Radiation Exposure in a Nested Matched Case-Control Study of British Nuclear Fuel Cycle Workers: Investigation of Confounding by Lifestyle, Physiological Traits and Occupational Exposures." Radiat Res 194(4): 431–444.

de Vocht, F., Martin, R. M., Hidajat, M., et al. (2021). "Quantitative Bias Analysis of the Association between Occupational Radiation Exposure and Ischemic Heart Disease Mortality in UK Nuclear Workers." Radiation Research 196(6): 574–586, 513.

Degteva, M. O., Shagina, N. B., Shishkina, E. A., et al. (2015). "Analysis of EPR and FISH studies of radiation doses in persons who lived in the upper reaches of the Techa River." Radiat Environ Biophys 54(4): 433–444.

Deltour, I., Tretyakov, F., Tsareva, Y., et al. (2015). "Mortality of populations potentially exposed to ionising radiation, 1953-2010, in the closed city of Ozyorsk, Southern Urals: a descriptive study." Environ Health 14: 91.

Dess, R. T., Sun, Y., Matuszak, M. M., et al. (2017). "Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non-Small-Cell Lung Cancer." J Clin Oncol 35(13): 1395–1402.

Ding, A., Gao, Y., Liu, H., et al. (2015). "VirtualDose: a software for reporting organ doses from CT for adult and pediatric patients." Phys Med Biol 60(14): 5601–5625.

Drubay, D., Caër-Lorho, S., Laroche, P., et al. (2015). "Mortality from Circulatory System Diseases among French Uranium Miners: A Nested Case-Control Study." Radiation Research 183(5): 550–562, 513.

Eccles, L. J., O'Neill, P. and Lomax, M. E. (2011). "Delayed repair of radiation induced clustered DNA damage: friend or foe?" Mutat Res 711(1-2): 134–141.

Efrati, S., Sadetzki, S., Zaretsky, M., et al. (2009). "Carotid atherosclerotic disease following childhood scalp irradiation." Atherosclerosis 204(2): 556–560.

El-Fayech, C., Haddy, N., Allodji, R. S., et al. (2017). "Cerebrovascular Diseases in Childhood Cancer Survivors: Role of the Radiation Dose to Willis Circle Arteries." Int J Radiat Oncol Biol Phys 97(2): 278–286.

Fajardo, L. F. and Stewart, J. R. (1970). "Cardiovascular radiation syndrome." N Engl J Med 283(7): 374.

Fullerton, H. J., Stratton, K., Mueller, S., et al. (2015). "Recurrent stroke in childhood cancer survivors." Neurology 85(12): 1056–1064.

Gaugler, M. H., Squiban, C., van der Meeren, A., et al. (1997). "Late and persistent up-regulation of intercellular adhesion molecule-1 (ICAM-1) expression by ionizing radiation in human endothelial cells in vitro." Int J Radiat Biol 72(2): 201–209.

GBD (2020). "Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019." Lancet 396(10258): 1204–1222.

GBD (2021). "Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019." Lancet Neurol 20(10): 795–820.

Geara, F. B., Komaki, R., Tucker, S. L., et al. (1998). "Factors influencing the development of lung fibrosis after chemoradiation for small cell carcinoma of the lung: evidence for inherent interindividual variation." Int J Radiat Oncol Biol Phys 41(2): 279–286.

Georgakilas, A. G., O'Neill, P. and Stewart, R. D. (2013). "Induction and repair of clustered DNA lesions: what do we know so far?" Radiat Res 180(1): 100–109.

Gilbert, E. S., Little, M. P., Preston, D. L., et al. (2020). "Issues in Interpreting Epidemiologic Studies of Populations Exposed to Low-Dose, High-Energy Photon Radiation." J Natl Cancer Inst Monogr 2020(56): 176–187.

Gillies, M., Richardson, D. B., Cardis, E., et al. (2017). "Mortality from Circulatory Diseases and other Non-Cancer Outcomes among Nuclear Workers in France, the United Kingdom and the United States (INWORKS)." Radiat Res 188(3): 276–290.

Gold, H. (1962). "Atherosclerosis in the rat. Effect of x-ray and a high fat diet." Proc Soc Exp Biol Med 111: 593–595.

Golden, A. P., Ellis, E. D., Cohen, S. S., et al. (2022). "Updated mortality analysis of the Mallinckrodt uranium processing workers, 1942–2012." International Journal of Radiation Biology 98(4): 701–721.

Goodhead, D. T. (2006). "Energy deposition stochastics and track structure: what about the target?" Radiat Prot Dosimetry 122(1-4): 3–15.

Grosche, B., Lackland, D. T., Land, C. E., et al. (2011). "Mortality from cardiovascular diseases in the Semipalatinsk historical cohort, 1960-1999, and its relationship to radiation exposure." Radiat Res 176(5): 660–669.

Gulston, M., Fulford, J., Jenner, T., et al. (2002). "Clustered DNA damage induced by gamma radiation in human fibroblasts (HF19), hamster (V79-4) cells and plasmid DNA is revealed as Fpg and Nth sensitive sites." Nucleic Acids Res 30(15): 3464–3472.

Haddy, N., Mousannif, A., Tukenova, M., et al. (2011). "Relationship between the brain radiation dose for the treatment of childhood cancer and the risk of long-term cerebrovascular mortality." Brain 134(Pt 5): 1362–1372.

Haddy, N., Diallo, S., El-Fayech, C., et al. (2016). "Cardiac Diseases Following Childhood Cancer Treatment: Cohort Study." Circulation 133(1): 31–38.

Hall, E. J. and Giaccia, A. J. (2019). Radiobiology for the radiologist, Wolters Kluwer.

Hallahan, D., Clark, E. T., Kuchibhotla, J., et al. (1995). "E-selectin gene induction by ionizing radiation is independent of cytokine induction." Biochem Biophys Res Commun 217(3): 784–795.

Hallahan, D., Kuchibhotla, J. and Wyble, C. (1996). "Cell adhesion molecules mediate radiation-induced leukocyte adhesion to the vascular endothelium." Cancer Res 56(22): 5150–5155.

Hallahan, D. E., Kuchibhotla, J. and Wyble, C. (1997). "Sialyl Lewis X mimetics attenuate E-selectin-mediated adhesion of leukocytes to irradiated human endothelial cells." Radiat Res 147(1): 41–47.

Hamra, G. B., Richardson, D. B., Cardis, E., et al. (2016). "Cohort Profile: The International Nuclear Workers Study (INWORKS)." Int J Epidemiol 45(3): 693–699.

Harbron, R. W., Dreuil, S., Bernier, M. O., et al. (2016). "Patient radiation doses in paediatric interventional cardiology procedures: a review." J Radiol Prot 36(4): R131–r144.

Harbron, R. W., Abdelhalim, M., Ainsbury, E. A., et al. (2020). "Patient radiation dose from x-ray guided endovascular aneurysm repair: a Monte Carlo approach using voxel phantoms and detailed exposure information." J Radiol Prot 40(3): 704–726.

Harbron, R. W. (2024). "Estimates of cardiovascular disease risk from CT scans may be premature." Journal of Radiological Protection 44(2): 024503.

Hart, D., Jones, D. G. and Wall, B. F. (1994). Estimation of effective dose in diagnostic radiology from entrance dose and dose-area product measurement. Chilton, Oxfordshire. NRPB-R262.

Hart, D., Hillier, M. C. and Shrimpton, P. C. (2012). Doses to Patients from Radiographic and Fluoroscopic X-ray Imaging Procedures in the UK - 2010 review. HPA, Chilton. HPA-CRCE-034.

Hauptmann, M., Daniels, R. D., Cardis, E., et al. (2020). "Epidemiological Studies of Low-Dose Ionizing Radiation and Cancer: Summary Bias Assessment and Meta-Analysis." J Natl Cancer Inst Monogr 2020(56): 188–200.

Haylock, R. G. E., Gillies, M., Hunter, N., et al. (2018). "Cancer mortality and incidence following external occupational radiation exposure: an update of the 3rd analysis of the UK national registry for radiation workers." Br J Cancer 119(5): 631–637.

Hei, T. K., Zhou, H., Ivanov, V. N., et al. (2008). "Mechanism of radiation-induced bystander effects: a unifying model." J Pharm Pharmacol 60(8): 943–950.

Hildebrandt, G., Maggiorella, L., Rödel, F., et al. (2002). "Mononuclear cell adhesion and cell adhesion molecule liberation after X-irradiation of activated endothelial cells in vitro." Int J Radiat Biol 78(4): 315–325.

Hill, M. A. (2020). "Radiation Track Structure: How the Spatial Distribution of Energy Deposition Drives Biological Response." Clin Oncol (R Coll Radiol) 32(2): 75–83.

Hinksman, C. A., Haylock, R. G. E. and Gillies, M. (2022). "Cerebrovascular Disease Mortality after occupational Radiation Exposure among the UK National Registry for Radiation Workers Cohort." Radiat Res 197(5): 459–470.

Hirabayashi, Y., Tsuboi, I., Nakachi, K., et al. (2015). "Experimentally induced, synergistic late effects of a single dose of radiation and aging: significance in LKS fraction as compared with mature blood cells." J Appl Toxicol 35(3): 230–240.

HPA (2010). Circulatory Disease Risk. Report of the independent Advisory Group on Ionising Radiation. . Documents of the Health Protection Agency. RCE-16.

Huang, R., Zhou, Y., Hu, S., et al. (2019). "Radiotherapy Exposure in Cancer Patients and Subsequent Risk of Stroke: A Systematic Review and Meta-Analysis." Front Neurol 10: 233.

Hunter, N., Haylock, R. G. E., Gillies, M., et al. (2022). "Extended analysis of solid cancer incidence among the Nuclear Industry Workers in the UK: 1955–2011." Radiation Research 198(1): 1–17, 17.

IAEA (2014). Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards, IAEA Safety Standards Series No. GSR Part 3. Vienna.

ICRP (1977). "Recommendations of the International Commission on Radiological Protection. ICRP Publication 26." Ann. ICRP 1(3).

ICRP (1991). "Recommendations of the International Commission on Radiological Protection. ICRP Publication 60." Ann. ICRP 21(1-3).

ICRP (2003). "Relative Biological Effectiveness (RBE), Quality Factor (Q), and Radiation Weighting Factor (wR). ICRP Publication 92." Ann. ICRP 33(4).

ICRP (2007). "The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103." Ann.ICRP 37(2-4): 1–332.

ICRP (2010). "Conversion Coefficients for Radiological Protection Quantities for External Radiation Exposure. ICRP Publication 116." Ann. ICRP 40(2-5).

ICRP (2012a). "Compendium of Dose Coefficients based on ICRP Publication 60. ICRP Publication 119." Ann. ICRP 41(S).

ICRP (2012b). "ICRP Statement on Tissue Reactions / Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context. ICRP Publication 118." Ann. ICRP 41(1-2).

ICRP (2015). "Radiation Dose to Patients from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances. ICRP Publication 128." Ann. ICRP 44(2S).

ICRP (2021). "The Use of Dose Quantities in Radiological Protection. ICRP Publication 147." Ann. ICRP 50(1).

ICRP (2024). "Optimisation of Radiological Protection in Digital Radiology Techniques for Medical Imaging. ICRP Publication 154." Ann. ICRP 52(3).

ICRU (1985). Determination of dose equivalents resulting from external radiation sources. ICRU Report 39. Bethesda, MD, USA.

ICRU (1988). Determination of dose equivalents from external radiation sources – Part II. ICRU Report 43. Bethesda, MD, USA.

ICRU (1993). Quantities and Units in Radiation Protection Dosimetry. ICRU Report 51. Bethesda, MD, USA.

ICRU (2020). Operational Quantities for External Radiation Exposure. . ICRU Report 95. Bethesda, MD, USA.

IRR (2017). The Ionising Radiations Regulations 2017, UK Government.

Ivanov, V. K., Maksioutov, M. A., Chekin, S. Y., et al. (2006). "The risk of radiation-induced cerebrovascular disease in Chernobyl emergency workers." Health Phys 90(3): 199–207.

Jacobse, J. N., Duane, F. K., Boekel, N. B., et al. (2019). "Radiation Dose-Response for Risk of Myocardial Infarction in Breast Cancer Survivors." Int J Radiat Oncol Biol Phys 103(3): 595–604.

Jaiswal, S., Natarajan, P. and Ebert, B. L. (2017). "Clonal Hematopoiesis and Atherosclerosis." N Engl J Med 377(14): 1401–1402.

Jiang, H., Zhou, Y., Nabavi, S. M., et al. (2022). "Mechanisms of Oxidized LDL-Mediated Endothelial Dysfunction and Its Consequences for the Development of Atherosclerosis." Front Cardiovasc Med 9: 925923.

Jones, D. G. and Wall, B. F. (1985). Organ doses from medical x-ray examinations calculated using Monte Carlo techniques. Chilton, Oxon. NRPB-R186.

Kabacik, S. and Raj, K. (2017). "Ionising radiation increases permeability of endothelium through ADAM10-mediated cleavage of VE-cadherin." Oncotarget 8(47): 82049–82063.

Kadhim, M., Salomaa, S., Wright, E., et al. (2013). "Non-targeted effects of ionising radiation--implications for low dose risk." Mutat Res 752(2): 84–98.

Kar, S. P., Quiros, P. M., Gu, M., et al. (2022). "Genome-wide analyses of 200,453 individuals yield new insights into the causes and consequences of clonal hematopoiesis." Nat Genet 54(8): 1155–1166.

Kashcheev, V. V., Chekin, S. Y., Maksioutov, M. A., et al. (2016). "Radiation-epidemiological Study of Cerebrovascular Diseases in the Cohort of Russian Recovery Operation Workers of the Chernobyl Accident." Health Phys 111(2): 192–197.

Kashcheev, V. V., Chekin, S. Y., Karpenko, S. V., et al. (2017). "Radiation Risk of Cardiovascular Diseases in the Cohort of Russian Emergency Workers of the Chernobyl Accident." Health Phys 113(1): 23–29.

Kearney, M., Keys, M., Faivre-Finn, C., et al. (2022). "Exposure of the heart in lung cancer radiation therapy: A systematic review of heart doses published during 2013 to 2020." Radiother Oncol 172: 118–125.

Keiller, D. A. and Martin, C. J. (2015). "Radiation dose to the heart in paediatric interventional cardiology." J Radiol Prot 35(2): 257–264.

Kern, P. M., Keilholz, L., Forster, C., et al. (2000). "Low-dose radiotherapy selectively reduces adhesion of peripheral blood mononuclear cells to endothelium in vitro." Radiother Oncol 54(3): 273–282.

Kessler, M. D., Damask, A., O'Keeffe, S., et al. (2022). "Common and rare variant associations with clonal haematopoiesis phenotypes." Nature 612(7939): 301–309.

Khaled, S., Gupta, K. B. and Kucik, D. F. (2012). "Ionizing radiation increases adhesiveness of human aortic endothelial cells via a chemokine-dependent mechanism." Radiat Res 177(5): 594–601.

Khan, M. A., Hashim, M. J., Mustafa, H., et al. (2020). "Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study." Cureus 12(7): e9349–e9349.

Killander, F., Wieslander, E., Karlsson, P., et al. (2020). "No Increased Cardiac Mortality or Morbidity of Radiation Therapy in Breast Cancer Patients After Breast-Conserving Surgery: 20-Year Follow-up of the Randomized SweBCGRT Trial." Int J Radiat Oncol Biol Phys 107(4): 701–709.

Kim, K. S., Kim, J. E., Choi, K. J., et al. (2014). "Characterization of DNA damage-induced cellular senescence by ionizing radiation in endothelial cells." Int J Radiat Biol 90(1): 71–80.

Kiyohara, H., Ishizaki, Y., Suzuki, Y., et al. (2011). "Radiation-induced ICAM-1 expression via TGF-β1 pathway on human umbilical vein endothelial cells; comparison between X-ray and carbon-ion beam irradiation." J Radiat Res 52(3): 287–292.

Kramer, R., Vieira, J. W., Khoury, H. J., et al. (2004). "MAX meets ADAM: a dosimetric comparison between a voxel-based and a mathematical model for external exposure to photons." Phys Med Biol 49(6): 887–910.

Krestinina, L. Y., Silkin, S., Degteva, M., et al. (2019). "Risk analysis of the mortality from the diseases of the circulatory system in the Ural cohort of emergency-irradiated population for the years 1950–2015." Radiacionnaâ Gigiena 12: 52–61.

Kreuzer, M., Dufey, F., Sogl, M., et al. (2013). "External gamma radiation and mortality from cardiovascular diseases in the German WISMUT uranium miners cohort study, 1946-2008." Radiat Environ Biophys 52(1): 37–46.

Lampugnani, M. G. (2012). "Endothelial cell-to-cell junctions: adhesion and signaling in physiology and pathology." Cold Spring Harb Perspect Med 2(10).

Large, M., Hehlgans, S., Reichert, S., et al. (2015). "Study of the anti-inflammatory effects of low-dose radiation: The contribution of biphasic regulation of the antioxidative system in endothelial cells." Strahlenther Onkol 191(9): 742–749.

Lauk, S., Kiszel, Z., Buschmann, J., et al. (1985). "Radiation-induced heart disease in rats." Int J Radiat Oncol Biol Phys 11(4): 801–808.

Lee, C., Kim, K. P., Long, D., et al. (2011). "Organ doses for reference adult male and female undergoing computed tomography estimated by Monte Carlo simulations." Med Phys 38(3): 1196–1206.

Lee, C., Kim, K. P., Long, D. J., et al. (2012). "Organ doses for reference pediatric and adolescent patients undergoing computed tomography estimated by Monte Carlo simulation." Med Phys 39(4): 2129–2146.

Lee, J. Y., Kim, Y. A., Kim, H. S., et al. (2020). "Radiotherapy can increase the risk of ischemic cerebrovascular disease in head and neck cancer patients: A Korean population-based cohort study." Radiother Oncol 142: 85–91.

Linet, M. S., Schubauer-Berigan, M. K. and Berrington de González, A. (2020). "Outcome Assessment in Epidemiological Studies of Low-Dose Radiation Exposure and Cancer Risks: Sources, Level of Ascertainment, and Misclassification." J Natl Cancer Inst Monogr 2020(56): 154–175.

Little, M. P., Gola, A. and Tzoulaki, I. (2009). "A model of cardiovascular disease giving a plausible mechanism for the effect of fractionated low-dose ionizing radiation exposure." PLoS Comput Biol 5(10): e1000539.

Little, M. P., Kleinerman, R. A., Stovall, M., et al. (2012a). "Analysis of dose response for circulatory disease after radiotherapy for benign disease." Int J Radiat Oncol Biol Phys 84(5): 1101–1109.

Little, M. P., Azizova, T. V., Bazyka, D., et al. (2012b). "Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks." Environ Health Perspect 120(11): 1503–1511.

Little, M. P. (2013). "A review of non-cancer effects, especially circulatory and ocular diseases." Radiat Environ Biophys 52(4): 435–449.

Little, M. P., Kukush, A. G., Masiuk, S. V., et al. (2014). "Impact of uncertainties in exposure assessment on estimates of thyroid cancer risk among Ukrainian children and adolescents exposed from the Chernobyl accident." PLoS One 9(1): e85723.

Little, M. P., Kwon, D., Zablotska, L. B., et al. (2015). "Impact of Uncertainties in Exposure Assessment on Thyroid Cancer Risk among Persons in Belarus Exposed as Children or Adolescents Due to the Chernobyl Accident." PLoS One 10(10): e0139826.

Little, M. P., Wakeford, R., Borrego, D., et al. (2018). "Leukaemia and myeloid malignancy among people exposed to low doses (<100 mSv) of ionising radiation during childhood: a pooled analysis of nine historical cohort studies." Lancet Haematol 5(8): e346–e358.

Little, M. P., Azizova, T. V., Richardson, D. B., et al. (2023). "Ionising radiation and cardiovascular disease: systematic review and meta-analysis." Bmj 380: e072924.

Little, M. P., Boerma, M., Bernier, M. O., et al. (2024). "Effects of confounding and effect-modifying lifestyle, environmental and medical factors on risk of radiation-associated cardiovascular disease." BMC Public Health 24(1): 1601.

López-Lázaro, M. (2015). "Stem cell division theory of cancer." Cell Cycle 14(16): 2547–2548.

Lowe, D. and Raj, K. (2014). "Premature aging induced by radiation exhibits pro-atherosclerotic effects mediated by epigenetic activation of CD44 expression." Aging Cell 13(5): 900–910.

Lowe, D. J., Herzog, M., Mosler, T., et al. (2020). "Chronic irradiation of human cells reduces histone levels and deregulates gene expression." Sci Rep 10(1): 2200.

Lubin, J. H., Adams, M. J., Shore, R., et al. (2017). "Thyroid Cancer Following Childhood Low-Dose Radiation Exposure: A Pooled Analysis of Nine Cohorts." J Clin Endocrinol Metab 102(7): 2575–2583.

Malyarchuk, S., Castore, R. and Harrison, L. (2009). "Apex1 can cleave complex clustered DNA lesions in cells." DNA Repair (Amst) 8(12): 1343–1354.

Maraldo, M. V., Giusti, F., Vogelius, I. R., et al. (2015). "Cardiovascular disease after treatment for Hodgkin's lymphoma: an analysis of nine collaborative EORTC-LYSA trials." Lancet Haematol 2(11): e492–502.

Marinko, T. (2019). "Pericardial disease after breast cancer radiotherapy." Radiology and Oncology 53(1): 1–5.

Martin, C. J. and Barnard, M. (2021). "Potential risks of cardiovascular and cerebrovascular disease and cancer due to cumulative doses received from diagnostic CT scans?" J Radiol Prot 41(4).

Martin, C. J. and Barnard, M. (2022). "How much should we be concerned about cumulative effective doses in medical imaging?" J Radiol Prot 42(1).

Martin, C. J., Barnard, M. and de Vocht, F. (2024a). "Evaluation of risks of cardiovascular disease from radiation exposure linked to computed tomography scans in the UK." Journal of Radiological Protection 44(1): 011513.

Martin, C. J., Barnard, M. and de Vocht, F. (2024b). "Authors' response to 'Estimates of cardiovascular disease risk from CT scans may be premature' (Harbron, 2024)." Journal of Radiological Protection 44(2): 024502.

Martincorena, I., Raine, K. M., Gerstung, M., et al. (2017). "Universal Patterns of Selection in Cancer and Somatic Tissues." Cell 171(5): 1029–1041.e1021.

McGale, P. and Darby, S. C. (2005). "Low doses of ionizing radiation and circulatory diseases: a systematic review of the published epidemiological evidence." Radiat Res 163(3): 247–257.

McGeoghegan, D., Binks, K., Gillies, M., et al. (2008). "The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946-2005." Int J Epidemiol 37(3): 506–518.

Medzhitov, R. (2010). "Inflammation 2010: new adventures of an old flame." Cell 140(6): 771–776.

Mencia-Trinchant, N., MacKay, M. J., Chin, C., et al. (2020). "Clonal Hematopoiesis Before, During, and After Human Spaceflight." Cell Rep 33(10): 108458.

Metz-Flamant, C., Laurent, O., Samson, E., et al. (2013). "Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers." Occup Environ Med 70(9): 630–638.

Mitchel, R. E., Hasu, M., Bugden, M., et al. (2011). "Low-dose radiation exposure and atherosclerosis in ApoE$^{-/-}$ mice." Radiat Res 175(5): 665–676.

Moore, K. J., Sheedy, F. J. and Fisher, E. A. (2013). "Macrophages in atherosclerosis: a dynamic balance." Nat Rev Immunol 13(10): 709–721.

Morgan, W. F. and Sowa, M. B. (2007). "Non-targeted bystander effects induced by ionizing radiation." Mutat Res 616(1-2): 159–164.

Moseeva, M. B., Azizova, T. V., Grigoryeva, E. S., et al. (2014). "Risks of circulatory diseases among Mayak PA workers with radiation doses estimated using the improved Mayak Worker Dosimetry System 2008." Radiat Environ Biophys 53(2): 469–477.

Mueller, S., Fullerton, H. J., Stratton, K., et al. (2013). "Radiation, atherosclerotic risk factors, and stroke risk in survivors of pediatric cancer: a report from the Childhood Cancer Survivor Study." Int J Radiat Oncol Biol Phys 86(4): 649–655.

Muirhead, C. R., O'Hagan, J. A., Haylock, R., et al. (2009a). Third Analysis of the National Registry for Radiation Workers: Occupational Exposure to Ionising Radiation in Relation to Mortality and Cancer Incidence. Chilton, Health Protection Agency. HPA-RPD-062.

Muirhead, C. R., O'Hagan, J. A., Haylock, R. G., et al. (2009b). "Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers." Br J Cancer 100(1): 206–212.

Mulrooney, D. A., Hyun, G., Ness, K. K., et al. (2020). "Major cardiac events for adult survivors of childhood cancer diagnosed between 1970 and 1999: report from the Childhood Cancer Survivor Study cohort." Bmj 368: l6794.

Najafi, M., Motevaseli, E., Shirazi, A., et al. (2018). "Mechanisms of inflammatory responses to radiation and normal tissues toxicity: clinical implications." Int J Radiat Biol 94(4): 335–356.

NCRP (2009). Ionizing Radiation Exposure of the Population of the United States. Report No. 160. Bethesda, MD.

NCRP (2010). Radiation Dose Management for Fluoroscopically-Guided Interventional Medical Procedures. Report No. 168. Bethesda, MD.

NCRP (2018). Implications of Recent Epidemiologic Studies for the Linear-Nonthreshold Model and Radiation Protection. Commentary No. 27. . Bethesda, MD.

Neil, S., Padgham, C. and Martin, C. J. (2010). "A study of the relationship between peak skin dose and cumulative air kerma in interventional neuroradiology and cardiology." J Radiol Prot 30(4): 659–672.

Nikjoo, H., O'Neill, P., Wilson, W. E., et al. (2001). "Computational approach for determining the spectrum of DNA damage induced by ionizing radiation." Radiat Res 156(5 Pt 2): 577–583.

Nikjoo, H., Bolton, C. E., Watanabe, R., et al. (2002). "Modelling of DNA damage induced by energetic electrons (100 eV to 100 keV)." Radiat Prot Dosimetry 99(1-4): 77–80.

Oatway, W. B., Jones, A. L., Holmes, S., et al. (2011). Ionizing Radiation Exposure of the UK Population: 2010 Review. . PHE-CRCE-026.

Oh, Y. T., Noh, O. K., Jang, H., et al. (2012). "The features of radiation induced lung fibrosis related with dosimetric parameters." Radiother Oncol 102(3): 343–346.

Ott, O. J., Niewald, M., Weitmann, H. D., et al. (2015). "DEGRO guidelines for the radiotherapy of non-malignant disorders. Part II: Painful degenerative skeletal disorders." Strahlenther Onkol 191(1): 1–6.

Ozasa, K., Shimizu, Y., Suyama, A., et al. (2012). "Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overview of cancer and noncancer diseases." Radiat Res 177(3): 229–243.

Ozasa, K., Takahashi, I. and Grant, E. J. (2016). "Radiation-related risks of non-cancer outcomes in the atomic bomb survivors." Ann ICRP 45(1 Suppl): 253–261.

Ozasa, K., Grant, E. J. and Kodama, K. (2018). "Japanese Legacy Cohorts: The Life Span Study Atomic Bomb Survivor Cohort and Survivors' Offspring." J Epidemiol 28(4): 162–169.

Pearce, M. S., Salotti, J. A., Little, M. P., et al. (2012). "Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study." Lancet 380(9840): 499–505.

Peters, C. E., Quinn, E. K., Rodriguez-Villamizar, L. A., et al. (2023). "Exposure to low-dose radiation in occupational settings and ischaemic heart disease: a systematic review and meta-analysis." Occup Environ Med 80(12): 706–714.

PHE (2019). National Diagnostic Reference Levels (NDRLs) from 19 August 2019, Public Health England.

Plummer, C., Henderson, R. D., O'Sullivan, J. D., et al. (2011). "Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review." Stroke 42(9): 2410–2418.

Popa-Fotea, N. M., Ferdoschi, C. E. and Micheu, M. M. (2023). "Molecular and cellular mechanisms of inflammation in atherosclerosis." Front Cardiovasc Med 10: 1200341.

Portess, D. I., Bauer, G., Hill, M. A., et al. (2007). "Low-Dose Irradiation of Nontransformed Cells Stimulates the Selective Removal of Precancerous Cells via Intercellular Induction of Apoptosis." Cancer Research 67(3): 1246–1253.

Poston, R. N., Chughtai, J., Ujkaj, D., et al. (2022). "Monocytic Cell Adhesion to Oxidised Ligands: Relevance to Cardiovascular Disease." Biomedicines 10(12).

Pouget, J. P. and Constanzo, J. (2021). "Revisiting the Radiobiology of Targeted Alpha Therapy." Front Med (Lausanne) 8: 692436.

Pouget, J. P., Santoro, L., Piron, B., et al. (2022). "From the target cell theory to a more integrated view of radiobiology in Targeted radionuclide therapy: The Montpellier group's experience." Nucl Med Biol 104-105: 53–64.

Prabhakarpandian, B., Goetz, D. J., Swerlick, R. A., et al. (2001). "Expression and functional significance of adhesion molecules on cultured endothelial cells in response to ionizing radiation." Microcirculation 8(5): 355–364.

Preston, D. L., Shimizu, Y., Pierce, D. A., et al. (2003). "Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997." Radiat Res 160(4): 381–407.

Prise, K. M. and O'Sullivan, J. M. (2009). "Radiation-induced bystander signalling in cancer therapy." Nat Rev Cancer 9(5): 351–360.

Prise, K. M. and Saran, A. (2011). "Concise review: stem cell effects in radiation risk." Stem Cells 29(9): 1315–1321.

Quarmby, S., Hunter, R. D. and Kumar, S. (2000). "Irradiation induced expression of CD31, ICAM-1 and VCAM-1 in human microvascular endothelial cells." Anticancer Res 20(5b): 3375–3381.

Quinn, B., Dauer, Z., Pandit-Taskar, N., et al. (2016). "Radiation dosimetry of 18F-FDG PET/CT: incorporating exam-specific parameters in dose estimates." BMC Med Imaging 16(1): 41.

Rage, E., Caër-Lorho, S., Drubay, D., et al. (2015). "Mortality analyses in the updated French cohort of uranium miners (1946-2007)." International archives of occupational and environmental health 88(6): 717–730.

Rannikko, S., Ermakov, I., Lampinen, J. S., et al. (1997). "Computing patient doses of X-ray examinations using a patient size- and sex-adjustable phantom." Br J Radiol 70(835): 708–718.

RCR (2016). Postoperative radiotherapy for breast cancer: UK consensus statements.

RCR (2019). Radiotherapy dose fractionation - Chapter 8 Hodgkin lymphoma.

Rehani, M. M. and Nacouzi, D. (2020). "Higher patient doses through X-ray imaging procedures." Phys Med 79: 80–86.

Rehani, M. M., Yang, K., Melick, E. R., et al. (2020). "Patients undergoing recurrent CT scans: assessing the magnitude." Eur Radiol 30(4): 1828–1836.

Richardson, D. B., Rage, E., Demers, P. A., et al. (2020). "Mortality among uranium miners in North America and Europe: the Pooled Uranium Miners Analysis (PUMA)." International Journal of Epidemiology 50(2): 633–643.

RIFE (2021). Radioactivity in Food and the Environment, 2020, EA, FSA, FSS, NRW, NIEA, SEPA. 26.

RIFE (2025). Radioactivity in Food and the Environment, 2024, EA, FSA, FSS, NRW, NIEA, SEPA. 30.

Rock, K. L. and Kono, H. (2008). "The inflammatory response to cell death." Annu Rev Pathol 3: 99–126.

Roedel, F., Kley, N., Beuscher, H. U., et al. (2002). "Anti-inflammatory effect of low-dose X-irradiation and the involvement of a TGF-beta1-induced down-regulation of leukocyte/endothelial cell adhesion." Int J Radiat Biol 78(8): 711–719.

Roots, R. and Okada, S. (1975). "Estimation of life times and diffusion distances of radicals involved in x-ray-induced DNA strand breaks of killing of mammalian cells." Radiat Res 64(2): 306–320.

Rosen, II, Fischer, T. A., Antolak, J. A., et al. (2001). "Correlation between lung fibrosis and radiation therapy dose after concurrent radiation therapy and chemotherapy for limited small cell lung cancer." Radiology 221(3): 614–622.

Rothkamm, K. and Löbrich, M. (2003). "Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses." Proc Natl Acad Sci U S A 100(9): 5057–5062.

Rousseau, M., Gaugler, M. H., Rodallec, A., et al. (2011). "RhoA GTPase regulates radiation-induced alterations in endothelial cell adhesion and migration." Biochem Biophys Res Commun 414(4): 750–755.

Rühm, W., Azizova, T., Bouffler, S., et al. (2018). "Typical doses and dose rates in studies pertinent to radiation risk inference at low doses and low dose rates." J Radiat Res 59(suppl_2): ii1–ii10.

Sabrazes, J. and Riviere, P. (1897). "Recherches sur l'action biologique des rayons X." Compt. Rendu. Acad. Sci. 124: 979.

Sadetzki, S., Chetrit, A., Boursi, B., et al. (2021). "Childhood Exposure to Low to Moderate Doses of Ionizing Radiation and the Risk of Vascular Diseases." Am J Epidemiol 190(3): 423–430.

Sanchez, R. M., Vano, E., Fernández, J. M., et al. (2014). "Brain radiation doses to patients in an interventional neuroradiology laboratory." AJNR Am J Neuroradiol 35(7): 1276–1280.

Savage, J. R. (1998). "A brief survey of aberration origin theories." Mutat Res 404(1-2): 139–147.

Schöllnberger, H., Dauer, L. T., Wakeford, R., et al. (2022). "Summary of Radiation Research Society Online 67th Annual Meeting, Symposium on “Radiation and Circulatory Effects”." International Journal of Radiation Biology: 1–10.

Schubauer-Berigan, M. K., Daniels, R. D., Bertke, S. J., et al. (2015). "Cancer Mortality through 2005 among a Pooled Cohort of U.S. Nuclear Workers Exposed to External Ionizing Radiation." Radiat Res 183(6): 620–631.

Schubauer-Berigan, M. K., Berrington de Gonzalez, A., Cardis, E., et al. (2020). "Evaluation of Confounding and Selection Bias in Epidemiological Studies of Populations Exposed to Low-Dose, High-Energy Photon Radiation." J Natl Cancer Inst Monogr 2020(56): 133–153.

Schultz-Hector, S. and Trott, K.-R. (2007). "Radiation-induced cardiovascular diseases: Is the epidemiologic evidence compatible with the radiobiologic data?" International Journal of Radiation Oncology*Biology*Physics 67(1): 10–18.

Sciahbasi, A., Ferrante, G., Fischetti, D., et al. (2017). "Radiation dose among different cardiac and vascular invasive procedures: The RODEO study." Int J Cardiol 240: 92–96.

Seguy, G. and Quenisset, F. (1897). "Action des rayons X sur le coeur.1897." Compt. Rendu. Acad. Sci. 124: 790.

Senderoff, E., Kavee, D. J., Johnson, J. R., et al. (1959). "Survival following acute coronary artery ligation subsequent to irradiation of canine heart." Proc Soc Exp Biol Med 100(1): 1–3.

Shimizu, Y., Kodama, K., Nishi, N., et al. (2010). "Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003." BMJ (Clinical research ed.) 340: b5349–b5349.

Shrestha, S., Bates, J. E., Liu, Q., et al. (2021). "Radiation therapy related cardiac disease risk in childhood cancer survivors: Updated dosimetry analysis from the Childhood Cancer Survivor Study." Radiother Oncol 163: 199–208.

Shrimpton, P. C., Hillier, M. C., Meeson, S., et al. (2014). Doses from Computed Tomography (CT) Examinations in the UK – 2011 Review. PHE Report. Chilton, PHE. PHE-CRCE-013

Shrimpton, P. C., Jansen, J. T. and Harrison, J. D. (2016). "Updated estimates of typical effective doses for common CT examinations in the UK following the 2011 national review." Br J Radiol 89(1057): 20150346.

Shuryak, I. and Brenner, D. J. (2021). "REVIEW OF QUANTITATIVE MECHANISTIC MODELS OF RADIATION-INDUCED NON-TARGETED EFFECTS (NTE)." Radiation Protection Dosimetry 192(2): 236–252.

Simonetto, C., Azizova, T. V., Barjaktarovic, Z., et al. (2017). "A mechanistic model for atherosclerosis and its application to the cohort of Mayak workers." PLoS One 12(4): e0175386.

Slusky, D. A., Cwikel, J. and Quastel, M. R. (2017). "Chronic diseases and mortality among immigrants to Israel from areas contaminated by the Chernobyl disaster: a follow-up study." Int J Public Health 62(4): 463–469.

Sun, Q., Zou, J., Akiba, S., et al. (2002). "Noncancer mortality (1987–1995) in high background radiation area of Yangjiang, China." International Congress Series 1225: 277–282.

Swenberg, J. A., Lu, K., Moeller, B. C., et al. (2011). "Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology, and risk assessment." Toxicol Sci 120 Suppl 1(Suppl 1): S130–145.

Takahashi, I., Shimizu, Y., Grant, E. J., et al. (2017). "Heart Disease Mortality in the Life Span Study, 1950-2008." Radiat Res 187(3): 319–332.

Takahashi, I., Cologne, J., Haruta, D., et al. (2018). "Association Between Prevalence of Peripheral Artery Disease and Radiation Exposure in the Atomic Bomb Survivors." J Am Heart Assoc 7(23): e008921.

Tao, Z., Akiba, S., Zha, Y., et al. (2012). "Cancer and non-cancer mortality among Inhabitants in the high background radiation area of Yangjiang, China (1979-1998)." Health Phys 102(2): 173–181.

Tapio, S. (2016). "Pathology and biology of radiation-induced cardiac disease." J Radiat Res 57(5): 439–448.

Tapio, S., Little, M. P., Kaiser, J. C., et al. (2021). "Ionizing radiation-induced circulatory and metabolic diseases." Environ Int 146: 106235.

Taylor, C., Correa, C., Duane, F. K., et al. (2017). "Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials." J Clin Oncol 35(15): 1641–1649.

Taylor, C. W., Nisbet, A., McGale, P., et al. (2007). "Cardiac exposures in breast cancer radiotherapy: 1950s-1990s." Int J Radiat Oncol Biol Phys 69(5): 1484–1495.

Terry, S. Y. A., Nonnekens, J., Aerts, A., et al. (2019). "Call to arms: need for radiobiology in molecular radionuclide therapy." Eur J Nucl Med Mol Imaging 46(8): 1588–1590.

Thierry-Chef, I., Marshall, M., Fix, J. J., et al. (2007). "The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Study of Errors in Dosimetry." Radiation Research 167(4): 380–395, 316.

Thierry-Chef, I., Simon, S. L., Land, C. E., et al. (2008). "Radiation dose to the brain and subsequent risk of developing brain tumors in pediatric patients undergoing interventional neuroradiology procedures." Radiat Res 170(5): 553–565.

Toda, H., Nomura, S., Gilmour, S., et al. (2017). "Assessment of medium-term cardiovascular disease risk after Japan's 2011 Fukushima Daiichi nuclear accident: a retrospective analysis." BMJ Open 7(12): e018502.

Torzewski, M. (2021). "The Initial Human Atherosclerotic Lesion and Lipoprotein Modification-A Deep Connection." Int J Mol Sci 22(21).

Tran, V., Zablotska, L. B., Brenner, A. V., et al. (2017). "Radiation-associated circulatory disease mortality in a pooled analysis of 77,275 patients from the Massachusetts and Canadian tuberculosis fluoroscopy cohorts." Sci Rep 7: 44147.

Trott, K. R. (1994). "Therapeutic effects of low radiation doses." Strahlenther Onkol 170(1): 1–12.

UKHSA (2022). National Diagnostic Reference Levels (NDRLs) from 13 October 2022.

UNSCEAR (2000). Sources and effects of ionizing radiation. Volume II. . UNSCEAR 2000 Report to the General Assembly, with scientific annexes. U. N. S. C. o. t. E. o. A. Radiation.

UNSCEAR (2006). Effects of Ionizing Radiation Volume I. . UNSCEAR 2006 Report to the General Assembly, with scientific annexes. U. N. S. C. o. t. E. o. A. Radiation.

UNSCEAR (2008). Sources, Effects and Risks of Ionizing Radiation. Volume I: Sources. UNSCEAR 2008 Report to the General Assembly, with scientific annexes. U. N. S. C. o. t. E. o. A. Radiation.

UNSCEAR (2011). Sources, Effects and Risks of Ionizing Radiation. Vol II: Effects. Annex D: Health effects due to radiation from the Chernobyl accident. UNSCEAR 2008 Report to the General Assembly, with scientific annexes. U. N. S. C. o. t. E. o. A. Radiation.

UNSCEAR (2012). Sources, Effects and Risks of Ionizing Radiation. . UNSCEAR 2012 Report to the General Assembly, with scientific annexes. U. N. S. C. o. t. E. o. A. Radiation.

UNSCEAR (2017). Sources, Effects and Risks of Ionizing Radiation. Annex A: Principles and criteria for ensuring the quality of the Committee's reviews of epidemiological studies of radiation exposure. UNSCEAR 2017 Report to the General Assembly, with scientific annexes. U. N. S. C. o. t. E. o. A. Radiation.

UNSCEAR (2018). Evaluation of data on thyroid cancer in regions affected by the Chernobyl accident. U. N. S. C. o. t. E. o. A. Radiation.

UNSCEAR (2020). Sources, Effects and Risks of Ionizing Radiation. Annex B: Levels and effects of radiation exposures due to the accident at the Fukushima Daiichi Nuclear Power Station: implication of information published since the UNSCEAR 2013 Report. UNSCEAR 2020 Report to the General Assembly, with scientific annexes. U. N. S. C. o. t. E. o. A. Radiation.

UNSCEAR (2021). UNSCEAR 2020/21 Report Vol III. Sources, Effects and Risks of Ionizing Radiation. Annex C: Biological mechanisms relevant for the inference of cancer risk from low-dose and low-dose-rate radiation. UNSCEAR 2021 Report to the General Assembly, with scientific annexes. U. N. S. C. o. t. E. o. A. Radiation.

van Aken, E. S. M., van der Laan, H. P., Bijl, H. P., et al. (2021). "Risk of ischaemic cerebrovascular events in head and neck cancer patients is associated with carotid artery radiation dose." Radiother Oncol 157: 182–187.

van den Bogaard, V. A. B., Spoor, D. S., van der Schaaf, A., et al. (2021). "The Importance of Radiation Dose to the Atherosclerotic Plaque in the Left Anterior Descending Coronary Artery for Radiation-Induced Cardiac Toxicity of Breast Cancer Patients?" Int J Radiat Oncol Biol Phys 110(5): 1350–1359.

van Nimwegen, F. A., Schaapveld, M., Cutter, D. J., et al. (2016). "Radiation Dose-Response Relationship for Risk of Coronary Heart Disease in Survivors of Hodgkin Lymphoma." J Clin Oncol 34(3): 235–243.

van Nimwegen, F. A., Ntentas, G., Darby, S. C., et al. (2017). "Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines." Blood 129(16): 2257–2265.

van Zeventer, I. A., Salzbrunn, J. B., de Graaf, A. O., et al. (2021). "Prevalence, predictors, and outcomes of clonal hematopoiesis in individuals aged ≥80 years." Blood Adv 5(8): 2115–2122.

Verginadis, II, Citrin, D. E., Ky, B., et al. (2025). "Radiotherapy toxicities: mechanisms, management, and future directions." Lancet 405(10475): 338–352.

Villoing, D., Borrego, D., Preston, D. L., et al. (2021). "Trends in Occupational Radiation Doses for U.S. Radiologic Technologists Performing General Radiologic and Nuclear Medicine Procedures, 1980-2015." Radiology 300(3): 605–612.

Voisard, R., Wiegmann, D., Baur, R., et al. (2007). "Low-dose irradiation stimulates TNF-alpha-induced ICAM-1 mRNA expression in human coronary vascular cells." Med Sci Monit 13(5): Br107–111.

Vrijheid, M., Cardis, E., Blettner, M., et al. (2007a). "The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Design, Epidemiological Methods and Descriptive Results." Radiation Research 167(4): 361–379, 319.

Vrijheid, M., Cardis, E., Ashmore, P., et al. (2007b). "Mortality from diseases other than cancer following low doses of ionizing radiation: results from the 15-Country Study of nuclear industry workers." Int J Epidemiol 36(5): 1126–1135.

Wakeford, R. (2009). "Radiation in the workplace-a review of studies of the risks of occupational exposure to ionising radiation." J Radiol Prot 29(2a): A61–79.

Wakeford, R. (2021). "Overview of epidemiological studies of nuclear workers: opportunities, expectations, and limitations()." J Radiol Prot 41(4).

Wakeford, R. (2022). "Risk of diseases of the circulatory system after low-level radiation exposure-an assessment of evidence from occupational exposures." J Radiol Prot 42(2).

Wall, B. F., Haylock, R., Jansen, J. T., et al. (2011). Radiation Risks from Medical X-ray Examinations as a Function of the Age and Sex of the Patient. HPA-CRCE-028.

Wang, H., Segaran, R. C., Chan, L. Y., et al. (2019). "Gamma Radiation-Induced Disruption of Cellular Junctions in HUVECs Is Mediated through Affecting MAPK/NF-κB Inflammatory Pathways." Oxid Med Cell Longev 2019: 1486232.

Wang, X., Palaskas, N. L., Yusuf, S. W., et al. (2020). "Incidence and Onset of Severe Cardiac Events After Radiotherapy for Esophageal Cancer." J Thorac Oncol 15(10): 1682–1690.

Wang, Y., Boerma, M. and Zhou, D. (2016). "Ionizing Radiation-Induced Endothelial Cell Senescence and Cardiovascular Diseases." Radiat Res 186(2): 153–161.

Wasserman, D. and Värnik, A. (1998). "Reliability of statistics on violent death and suicide in the former USSR, 1970-1990." Acta Psychiatr Scand Suppl 394: 34–41.

Weigel, C., Veldwijk, M. R., Oakes, C. C., et al. (2016). "Epigenetic regulation of diacylglycerol kinase alpha promotes radiation-induced fibrosis." Nat Commun 7: 10893.

Wijerathne, H., Langston, J. C., Yang, Q., et al. (2021). "Mechanisms of radiation-induced endothelium damage: Emerging models and technologies." Radiother Oncol 158: 21–32.

Wolffe, J. B. and Siegal, E. I. (1962). "X-ray of the abdominal aorta in detection of atherosclerosis." Clin Med (Northfield) 69: 401–406.

Wood, K., Jawahar, A., Smelley, C., et al. (2005). "Exposure of brain to high-dose, focused gamma rays irradiation produces increase in leukocytes-adhesion and pavementing in small intracerebral blood vessels." Neurosurgery 57(6): 1282–1288; discussion 1282–1288.

Yamada, M., Wong, F. L., Fujiwara, S., et al. (2004). "Noncancer disease incidence in atomic bomb survivors, 1958-1998." Radiat Res 161(6): 622–632.

Yamamoto, Y., Minami, M., Yoshida, K., et al. (2021). "Irradiation Accelerates Plaque Formation and Cellular Senescence in Flow-Altered Carotid Arteries of Apolipoprotein E Knock-Out Mice." J Am Heart Assoc: e020712.

Yoshida, K., Satoh, Y., Uchimura, A., et al. (2022). "Massive expansion of multiple clones in the mouse hematopoietic system long after whole-body X-irradiation." Sci Rep 12(1): 17276.

Zablotska, L. B., Little, M. P. and Cornett, R. J. (2014a). "Potential increased risk of ischemic heart disease mortality with significant dose fractionation in the Canadian Fluoroscopy Cohort Study." Am J Epidemiol 179(1): 120–131.

Zablotska, L. B., Lane, R. S. and Thompson, P. A. (2014b). "A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data." Br J Cancer 110(1): 214–223.

Zablotska, L. B., Fenske, N., Schnelzer, M., et al. (2018). "Analysis of mortality in a pooled cohort of Canadian and German uranium processing workers with no mining experience." International archives of occupational and environmental health 91(1): 91–103.

Zeff, B. W. and Yester, M. V. (2005). "Patient self-attenuation and technologist dose in positron emission tomography." Med Phys 32(4): 861–865.

Zhang, W., Haylock, R. G. E., Gillies, M., et al. (2019a). "Mortality from heart diseases following occupational radiation exposure: analysis of the National Registry for Radiation Workers (NRRW) in the United Kingdom." J Radiol Prot 39(2): 327–353.

Zhang, W., Haylock, R. G. E., Gillies, M., et al. (2019b). "Reply to comment on 'Mortality from heart disease following occupational radiation exposure: analysis of the national registry for radiation workers (NRRW) in the United Kingdom'." J Radiol Prot 39(4): 1132–1135.

Zhang, W., Haylock, R. G. E., Gillies, M., et al. (2024). "Shape of radiation dose response relationship for ischaemic heart disease mortality and its interpretation: analysis of the national registry for radiation workers (NRRW) cohort." Journal of Radiological Protection 44(2): 021502.

Zhuang, X. F., Yang, Y. M., Sun, X. L., et al. (2017). "Late onset radiation-induced constrictive pericarditis and cardiomyopathy after radiotherapy: A case report." Medicine (Baltimore) 96(5): e5932.

Appendix A. Abbreviations and glossary

Acronym	Meaning
AHS	Adult Health Study
ALARA	as low as reasonably achievable
ALARP	as low as reasonably practicable
AWE	Atomic Weapons Establishment
BD	base damages
BNFL	British Nuclear Fuels Limited
CEA	French Alternative Energies and Atomic Energy Commission
CeVD	cerebrovascular disease
CH	clonal haematopoiesis
CI	confidence interval
CIDI	Central Index of Dose Information
CT	Computed tomography
CTA	CT angiography
CTDI	CT dose index
CTPA	CT chest pulmonary angiography
CVD	cardiovascular disease
DAMPs	damage-associated molecular patterns
DCS	diseases of the circulatory system
DGKA	diacylglycerol kinase alpha
DHSC	Department for Health and Social Care
DLP	dose length product
DNA	deoxyribonucleic acid
DRL	diagnostic reference level
DSB	double strand breaks
EAR	excess absolute risk
ECG	electrocardiogram
ERR	excess relative risk
ESAK	entrance surface air kerma
EVAR	endovascular aortic aneurysm repair
Gy	gray
HR	hazard ratio
HUVEC	human umbilical cord endothelial cells
IAK	incident air kerma

Acronym	Meaning
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
IHD	ischemic heart disease
IQR	interquartile range
KAP	kerma-area product
LDL	low density lipoprotein
LET	linear energy transfer
LNT	Linear no threshold
LSS	Life Span Study
MI	myocardial infarction
MOD	Ministry of Defence
MWC	Mayak Worker Cohort
NCRP	National Council on Radiation Protection and Measurements
NRRW	National Registry for Radiation Workers
ORNL	Oak Ridge National Laboratory
PET	positron emission tomography
RBE	relative biological effectiveness
RCT	randomised controlled trials
RIFE	radioactivity in food and the environment
RNA	ribonucleic acid
RNS	reactive nitrogen species
ROS	reactive oxygen species
RR	relative risk
RT	radiotherapy
SASP	senescence-associated secretory phenotype
SI	international unit
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SRR	standardized registration ratio
SSB	single strand breaks
Sv	sievert
UKAEA	UK Atomic Energy Authority
UKHSA	UK Health Security Agency
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation

ABSORBED DOSE The quantity of energy imparted by ionising radiation to a unit mass of matter such as tissue. Absorbed dose has the units of joules per kilogram (J kg^{-1}) and the specific name gray (Gy), where 1 Gy = 1 J kg^{-1}.

COMPUTED TOMOGRAPHY (CT) A special radiographic technique that uses a computer to assimilate multiple X-ray images into a two-dimensional cross-sectional image.

DOSE A measure of the amount of radiation received. More strictly it is related to the energy absorbed per unit mass of tissue (*see Absorbed Dose*). Doses can be estimated for individual organs or for the body as a whole.

DOSIMETER A device used to measure an absorbed dose of ionising radiation.

EFFECTIVE DOSE Effective dose is the sum of the weighted equivalent doses in all the tissues and organs of the body. It takes into account the biological effectiveness of different types of radiation and variation in the susceptibility of different organs and tissues to radiation damage. Thus, it provides a common basis for comparing exposures from different sources. Unit = sievert (Sv).

EPIDEMIOLOGY The study of factors affecting health and illness of populations, regarding the causes, distribution and control.

GRAY (Gy) The international (SI) unit of absorbed dose. One gray is equivalent to one joule of energy absorbed per kilogram of matter such as body tissue.

ICRP International Commission on Radiological Protection. It consists of experts in radiology, genetics, physics, medicine and radiological protection from a number of countries. Established in 1928 it meets regularly to consider the research on the effects of radiation and publishes recommendations on all aspects of radiation protection including dose limits to man.

INCIDENCE This is the number of new cases of a disease arising in a population over a specific period of time, usually 1 year.

IONISING RADIATION Radiation that is sufficiently energetic to remove electrons from atoms in its path. In human or animal exposures ionising radiation can result in the formation of highly reactive particles in the body which can cause damage to individual components of living cells and tissues.

IRRADIATION The process by which an item is exposed to radiation, either intentionally or accidentally.

JUSTIFICATION	Consideration that a medical exposure shall show a sufficient net benefit, weighing the total potential diagnostic or therapeutic benefits it produces, including the direct health benefits to an individual and the benefits to society, against the individual detriment that the exposure might cause, taking into account the efficacy, benefits and risks of available alternative techniques having the same objective but involving no or less exposure to ionising radiation.
LINEAR NO-THRESHOLD (LNT) MODEL	The model used in radiation protection to estimate the long-term, biological damage caused by ionising radiation, which assumes that the damage is directly proportional ('linear') to the dose of radiation, at all dose levels and that any radiation exposure is always considered harmful with no safety threshold.
PAEDIATRIC	Of, or relating to, the medical care of children.
PATIENT DOSE	The ionising radiation dose to a patient or other individual undergoing a medical exposure.
RADIONUCLIDE	A type of atomic nucleus that is unstable, and which may undergo spontaneous decay to another atom by emission of ionising radiation (usually alpha, beta or gamma).
RADIOSENSITIVITY	The relative susceptibility of cells, tissues, organs, organisms, or any other substances to the effects of radiation.
RISK	The probability that an event will occur, for example that an individual will become ill or die before a stated period of time or age. This is also a non-technical term encompassing a variety of measures of the probability of a (generally) unfavourable outcome.
SIEVERT (Sv)	The international (SI) unit of effective dose obtained by weighting the equivalent dose in each tissue in the body with the ICRP-recommended tissue weighting factors and summing over all tissues. Because the sievert is a large unit, effective dose is commonly expressed in millisieverts (mSv) – that is one-thousandth of 1 sievert. The average annual radiation dose received by members of the public in the UK is 2.7 mSv.
STOCHASTIC	Stochastic effect or 'chance effect' is a classification of radiation effects that refers to the random, statistical nature of the damage. The severity is independent of dose. Only the probability of an effect increases with dose.
X-RAY	An image obtained using high energy radiation with waves shorter than those of visible light. X-rays possess the properties of penetrating most substances to varying extents, of acting on a photographic film or plate (permitting radiography), and of causing a fluorescent screen to give off light (permitting fluoroscopy). In low doses X-rays are used for making images that help to diagnose disease, and in high doses to treat cancer.

Appendix B. Heart dose in paediatric cardiology

B.1 Harbron et al (2016) reviewed data for 5 studies reported in terms of KAP in groupings of weight or age ranges (France, Canada and the USA (3)). KAP values for the majority of studies of children under 10 y, or less than 40 kg, were in the range 1 to 20 Gy cm^2, while KAP values for the over 15 y age groups extended from 20 up to 200 Gy cm^2. There is not a straightforward link between KAP values and heart dose for paediatric patients, because there are large variations in body size and in the X-ray projections used during a procedure.

B.2 As an approximate indication, a KAP value of 1 Gy cm^2 is likely to represent a dose to the heart of 5 to 10 mGy for an infant, but only 1 to 3 mGy for a 15 y old (Keiller and Martin, 2015). An exponential fit of the limited data of heart dose per unit KAP against age gave a coefficient:

$$\text{Heart dose/KAP} = 7.731 \times e^{-0.087 \times \text{Age}} \text{ mGy/Gy cm}^2$$

B.3 This was used to estimate heart doses from median KAP values and those representing either the maximum doses or the third quartile included in the review by Harbron et al (2016) and these together with heart dose data from Keiller and Martin (2015) are plotted in Figure B1 against age. Results from surveys together with the plot would indicate that there is likely to be a proportion of older paediatric patients and young adults who receive doses to the heart of several hundred mGy from interventional cardiology procedures.

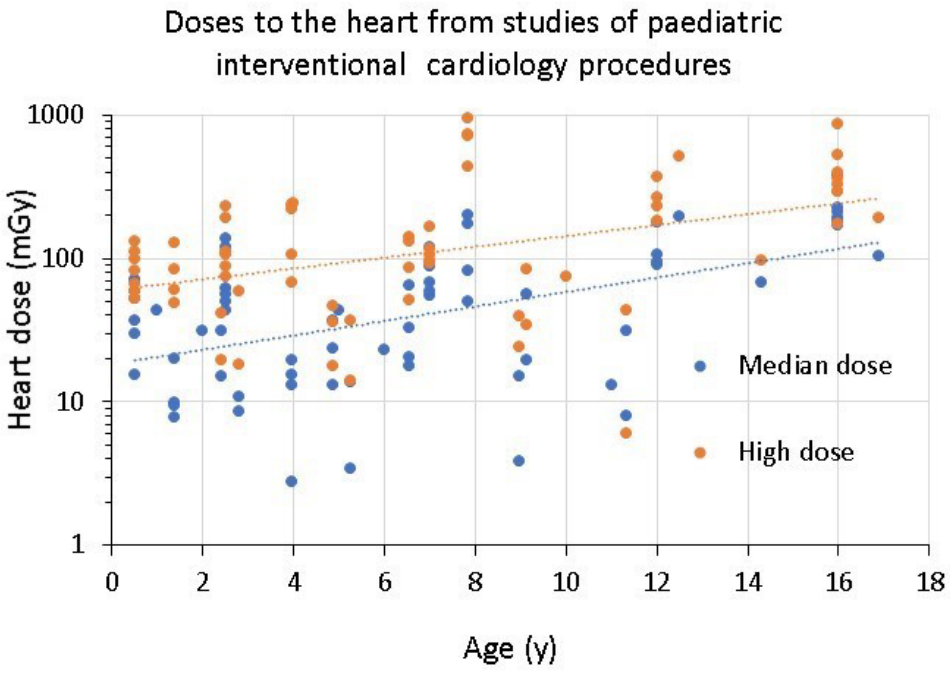

Figure B1: Heart doses per procedure for paediatric cardiology, predicted from KAP data using the derived conversion factor, plotted against patient age. (N.B. All doses over 400 mGy are from the high dose reports in North American data sets.)

Appendix C. The Committee on Medical Aspects of Radiation in the Environment

C.1 The Committee on Medical Aspects of Radiation in the Environment (COMARE) was established in November 1985 in response to the final recommendation of the report of the Independent Advisory Group chaired by Sir Douglas Black (Black, 1984). COMARE's terms of reference are:

> "*to assess and advise government and the devolved administrations on the health effects of natural and human-made radiation and to assess the adequacy of the available data and the need for further research*"

C.2 In the course of providing advice to Government and the devolved authorities for forty years, COMARE has published twenty major reports and many other statements and documents. This is the 20th report; previous reports are listed below. Reports and statements, as well as other committee information, can be found on the COMARE page of GOV.UK.

C.3 Each major report is prepared by a subcommittee, prior to consideration and agreement by the full committee. Once agreed by the committee, the report is submitted to DHSC for agreement to publish. DHSC ensures the appropriate involvement of the devolved administrations.

COMARE reports

Nineteenth report	Radiation doses in interventional radiology: issues for patients and staff within the UK, PHE, Chilton, August 2021
Eighteenth report	Medical radiation dose issues associated with dual-energy X-ray absorptiometry (DXA) scans for sports performance assessments and other non-medical practices, PHE, Chilton, July 2019.
Seventeenth report	Further consideration of the incidence of cancers around the nuclear installations at Sellafield and Dounreay. PHE, Chilton, September 2016
Sixteenth report	Patient radiation dose issues resulting from the use of CT in the UK. PHE, Chilton, August 2014
Fifteenth report	Radium contamination in the area around Dalgety Bay. PHE, Chilton, May 2014
Fourteenth report	Further consideration of the incidence of childhood leukaemia around nuclear power plants in Great Britain. HPA, Chilton, May 2011
Thirteenth report	The health effects and risks arising from exposure to ultraviolet radiation from artificial tanning devices. HPA, Chilton, June 2009
Twelfth report	The impact of personally initiated X-ray computed tomography scanning for the health assessment of asymptomatic individuals. HPA, Chilton, December 2007
Eleventh report	The distribution of childhood leukaemia and other childhood cancer in Great Britain 1969–1993. HPA, Chilton, July 2006
Tenth report	The incidence of childhood cancer around nuclear installations in Great Britain. HPA, Chilton, June 2005
Ninth report	Advice to Government on the review of radiation risks from radioactive internal emitters carried out and published by the Committee Examining Radiation Risks of Internal Emitters (CERRIE). NRPB, Chilton, October 2004
Eighth report	A review of pregnancy outcomes following preconceptional exposure to radiation. NRPB, Chilton, February 2004
Seventh report	Parents occupationally exposed to radiation prior to the conception of their children. A review of the evidence concerning the incidence of cancer in their children. NRPB, Chilton, August 2002
COMARE and RWMAC* joint report	Radioactive contamination at a property in Seascale, Cumbria. NRPB, Chilton, June 1999
Sixth report	A reconsideration of the possible health implications of the radioactive particles found in the general environment around the Dounreay nuclear establishment in the light of the work undertaken since 1995 to locate their source. NRPB, Chilton, March 1999
Fifth report	The incidence of cancer and leukaemia in the area around the former Greenham Common Airbase. An investigation of a possible

* Radioactive Waste Management Advisory Committee.

	association with measured environmental radiation levels. NRPB, Chilton, March 1998
Fourth report	The incidence of cancer and leukaemia in young people in the vicinity of the Sellafield site, West Cumbria: further studies and an update of the situation since the publication of the report of the Black Advisory Group in 1984. Department of Health, London, March 1996
COMARE and RWMAC* joint report	Potential health effects and possible sources of radioactive particles found in the vicinity of the Dounreay nuclear establishment. HMSO, London, May 1995
Third report	Report on the incidence of childhood cancer in the West Berkshire and North Hampshire area, in which are situated the Atomic Weapons Research Establishment, Aldermaston and the Royal Ordnance Factory, Burghfield. HMSO, London, June 1989
Second report	Investigation of the possible increased incidence of leukaemia in young people near the Dounreay nuclear establishment, Caithness, Scotland. HMSO, London, June 1988
First report	The implications of the new data on the releases from Sellafield in the 1950s for the conclusions of the Report on the Investigation of the Possible Increased Incidence of Cancer in West Cumbria. HMSO, London, July 1986

* Radioactive Waste Management Advisory Committee.

COMARE membership

Chair

Professor J D Harrison BSc PhD FSRP
Faculty of Health, Science and Technology, Oxford Brookes University

Present members

Professor A Berrington de Gonzalez BSc MSc DPhil
The Institute of Cancer Research, London

Professor R Foster PhD, DSc, CBE, FRSB, FMedSci, FRS
The Sir Jules Thorn Sleep & Circadian Neuroscience Institute and Nuffield Laboratory of Ophthalmology, University of Oxford

Dr G Heyes BSc MSc PhD
University Hospitals Birmingham NHS Foundation Trust

Dr M A Hill BSc MSc PhD FIPEM FSRP MInstP CRadP CPhys
Department of Oncology, University of Oxford

Dr R V Kemp BA MSc PhD MRTPI(Rtd) SIRM
Independent Risk Communication Consultant

Professor M P Little MA DPhil CRadP
Feinberg School of Medicine, Northwestern University, Evanston, IL, USA & Faculty of Health, Science and Technology, Oxford Brookes University

Dr S McCready-Shea BA PhD DipHS CRadP FSRP CMIOSH

Dr R McNally BSc MSc DIC PhD
Population Health Sciences Institute, Newcastle University

Professor D Read DSc PhD BSc FRSC FGS FSRP

Professor G Smith BSc ARCS
Clemson University, S.C., and GMS Abingdon Ltd

Professor J Smith
University of Portsmouth

Professor M Sperrin
Medical Physicist, IPEM

Professor D Sutton BSc MSc PhD CSci CRadP FIPEM FSRP FBIR
University of Dundee

Dr S Y A Terry BSc PhD FHEA
King's College London

Professor M Toledano BA MSc PhD DLSHTM DIC FHEA
School of Public Health, Imperial College

Dr C Westcott MA PhD

Former members who served during preparation of this report

Dr J Barrett BSc MB ChB FRCP FRCPE FRCR OBE
Clinical oncologist

Professor F de Vocht BSc Ir MSc PhD
Population Health Sciences, Bristol Medical School, University of Bristol

Dr C Martin BSc PhD FinstP FIPEM FSRP CRadP
University of Glasgow

Professor S Martin BSc MSc PhD PGCAP FHEA FRSB FRCPath HonMRCR
University of Nottingham

Professor P Pharoah BM BCh PhD DPH MFPH FRCP
Cambridge Cancer Centre, University of Cambridge

Dr T C Oh
Lancashire Teaching Hospitals NHS Trust

Professor L E Rhodes BSc MB BS MD FRCP FRSB
Faculty of Biology Medicine & Health, University of Manchester

Professor R Taylor MA FRCPE FRCP FRCR
College of Medicine, Swansea University

Secretariat

Dr S Mann BSc DPhil CEng MIET (Scientific)

Dr E Petty BSc PhD (Scientific)

Mrs S Watson BSc MMedSci MSRP CRadP (Minutes)

Assessors in attendance representing the following organisations

Department for Energy Security and Net Zero
Department for Levelling Up, Housing and Communities
Department of Health and Social Care
Department of Health, Social Services and Public Safety (Northern Ireland)
Environment Agency
Food Standards Agency
Food Standards Scotland
Health and Safety Executive
NHS Scotland
Nuclear Decommissioning Authority
Office for Nuclear Regulation
Public Health Scotland
Scottish Environment Protection Agency
Scottish Government
UK Health Security Agency
Welsh Government

COMARE Cardio-/Cerebrovascular Effects Subcommittee membership

Chair	**Professor F de Vocht** BSc Ir MSc PhD Population Health Sciences, Bristol Medical School, University of Bristol
Members	**Dr J Barrett** BSc MB ChB FRCP FRCPE FRCR OBE Clinical oncologist
	Professor J D Harrison BSc PhD FSRP Faculty of Health, Science and Technology, Oxford Brookes University
	Dr M A Hill BSc MSc PhD FIPEM FSRP MInstP CRadP CPhys University of Oxford
	Professor M P Little MA DPhil CRadP Feinberg School of Medicine, Northwestern University, Evanston, IL, USA & Faculty of Health, Science and Technology, Oxford Brookes University
	Dr C Martin BSc PhD FinstP FIPEM FSRP CRadP University of Glasgow
	Dr R McNally BSc MSc DIC PhD Population Health Sciences Institute, Newcastle University
	Professor P Pharoah BM BCh PhD DPH MFPH FRCP Cambridge Cancer Centre, University of Cambridge
	Dr K Raj UK Health Security Agency
Assessors	**DHSC**
Secretariat	**Dr E Petty** BSc PhD
External reviewers	**Professor Richard Wakeford** BSc PhD CSci CPhys FInstP CStat CEng MNucl CRadP HonFSRP Institute of Population Health, University of Manchester
	Dr Sophie Jacob PhD Institut de Radioprotection et de Sûreté Nucléaire (IRSN)

Produced by UK Health Security Agency for the Committee on Medical Aspects of Radiation in the Environment

Publications number: GOV-20686